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The authors of the plenary and poster abstracts as presented in this supplement express their personal and professional opinion and these are not necessarily those of the European Association for Clinical Pharmacology and Therapeutics.
MORPHINE DECREASES TICAGRELOR
CONCENTRATIONS BUT NOT ITS EFFECTS:
A RANDOMIZED, DOUBLE-BLIND,
PLACEBO-CONTROLLED TRIAL
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Background: This study examines possible drug-drug interactions between ticagrelor and morphine. Our recent drug interaction trial with clopidogrel shows that morphine decreases the concentrations and effects of clopidogrel, which could lead to treatment failure in susceptible individuals. We hypothesized that the pharmacodynamic consequences of drug-drug interactions would be less between morphine and ticagrelor.

Material and Methods: Twenty-four healthy subjects received a loading dose of 180 mg ticagrelor together with placebo or 5 mg morphine intravenously in a randomized, double-blind, placebo-controlled, cross-over trial. Pharmacokinetics were determined by liquid chromatography tandem mass spectrometry, and ticagrelor effects were measured by platelet function tests.

Results: Concomitant i.v. injection of morphine slows drug resorption of ticagrelor and its active metabolite (P < 0.05) by one hour and decreases plasma levels of ticagrelor and its active metabolite (by 25%–31%; P < 0.03) and the drug exposure (area under the curve by 22%–23%; P < 0.01). Importantly, however, the effects of ticagrelor on platelet aggregation in whole blood, platelet plug formation, and vasodilator-stimulated phosphoprotein (VASP) phosphorylation are not affected by morphine.

Conclusions: Morphine co-administration moderately decreases ticagrelor plasma concentrations but does not inhibit its effects. Therefore, a 180 mg loading dose of ticagrelor appears to provide consistent and reliable platelet inhibition when morphine has to be given for pain relief.

PREGNANCY OUTCOME FOLLOWING MATERNAL EXPOSURE TO PREGABALIN: A REASON FOR CONCERN? A COLLABORATIVE ENTS AND MOTHERISK STUDY
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Background: While animal studies have shown reproductive toxicity of pregabalin, data on pregnancy outcomes in women exposed to this drug are lacking, despite accepted use in women of childbearing potential. In this study, we primarily investigated the rate for major birth defects and other pregnancy outcomes following maternal use of pregabalin.

Material and Methods: This is a multicenter, observational prospective cohort study comparing pregnancy outcomes in women exposed to pregabalin with matched controls (exposed neither to any medications known to be teratogenic nor to any antiepileptic drugs). Data were systematically collected by Teratology Information Services between 2004 and 2013.

Results: We obtained data from 173 exposed pregnancies and 692 controls. After exclusion of chromosomal syndromes, major birth defects were reported more frequently in pregnancies exposed to pregabalin during 1st trimester of pregnancy than in the control group (6.6% vs 2.0%; odds ratio 3.5, 95% confidence interval 1.2–9.7, P = 0.004). Moreover, the rate of live births was lower in the pregabalin group (71.1% vs 85.4%, P = 0.001), primarily due to a higher rate of both elective (10.4% vs 4.8%, P = 0.01) and medically indicated (5.2% vs 1.7%, P = 0.02) pregnancy-terminations. The crude rate of spontaneous abortion (15.8% vs 8.7%, P = 0.001) was also higher in the pregabalin group.

Conclusions: This study raises a signal for a possible increase in the rate of major birth defects and spontaneous abortion after first trimester exposure to pregabalin. These results call for further confirmation through independent studies.

SELF-REPORTED CONFIDENCE IN PRESCRIBING SKILLS CORRELATES POORLY WITH ASSESSED COMPETENCE IN FOURTH-YEAR MEDICAL STUDENTS
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Introduction: The objective of this study was to investigate the relationship between students’ self-reported confidence and their objectively assessed competence in prescribing.

Material and Methods: We assessed the competence in several prescribing skills of 403 fourth-year medical students at the VU University Medical Center, the Netherlands, in a formative simulated examination on a 10-point scale (1 = very low; 10 = very high). Afterwards, the students were asked to rate their confidence in performing each of the prescribing skills on a 5-point Likert scale (1 = very unsure; 5 = very confident). Their assessments were then compared with their self-confidence ratings.

Results: Students’ overall prescribing performance was adequate (7.0 ± 0.8), but they lacked confidence in two essential prescribing skills. Overall, there was a weak positive correlation (r = 0.2; P < 0.01; 95% CI, 0.1–0.3) between reported confidence and actual competence.

Conclusions: This study suggests that self-reported confidence is not an accurate measure of prescribing competence, and that students lack insight into their own strengths and weaknesses in prescribing. Future studies should focus on developing validated and reliable instruments so that students can assess their prescribing skills.

ADHERENCE TO DABIGATRAN AMONG NEW ZEALAND PATIENTS
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Background: Dabigatran, a direct thrombin inhibitor, is the only drug funded in New Zealand for stroke prevention in patients with atrial fibrillation. A previous small New Zealand cohort study suggested an adherence rate of 70% after a median follow-up of eight
on the implanted prosthesis were found between cohorts, although the period from admission to surgery (median [IQR]) (7 [4-9] and 5 [2-7] days) and that of hospital stay (16 [12-20] and 13 [10-17] days) were longer in those treated with antithrombotics. No statistically differences in the haemorrhagic events were observed between cohorts (68.2% and 60.3, P = 0.09), although a higher percentage of thromboembolic events (12.1 and 4.8, P = 0.004) and mortality (20.5% and 13.6%, P = 0.05) were described in those treated with antithrombotics.

Conclusions: Patients presented with hip fracture treated with antithrombotics had a higher mortality and frequency of thromboembolic events than those not treated with antithrombotics, but the frequency of haemorrhagic events was not higher. Thus, in patients treated with antithrombotics, careful attention has to be paid not only to the haemorrhagic events but also to the thromboembolic ones.

**NEOADJUVANT CHEMOTHERAPY SCHEME CUSTOMIZED BY BRCA1 LEVELS IN HER-2 NEGATIVE PRIMARY BREAST CANCER PATIENTS: A RANDOMIZED CLINICAL TRIAL. BERNAQ STUDY**

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Introduction: Neoadjuvant chemotherapy (NAC) is increasingly used for early-stage operable breast cancer to improve complete response rates and increase survival. BReast Cancer 1 (BRCA1) plays a crucial role in DNA repair, and its expression has been associated to sensitivity to platinum and/or resistance to taxanes. Complete response rates with NAC may thus be improved using BRCA as a biomarker to predict a better response by individualized breast cancer care.

Material and Methods: BERNAQ is an investigator-driven, open-label, multicenter, randomized controlled trial (RCT). The study was designed to compare the efficacy and tolerability of NAC customized by BRCA1 levels versus a standard chemotherapy, with pathological response as the primary end point. The study is publicly funded (PI-0233-2012) and is being conducted in 7 public reference hospitals. We describe the design, network established, organization of clinical teams, and general management support to effectively carry out an investigator-driven RCT in a public system setting.

Results: Women with primary Her-2 negative breast cancer (n = 30) are randomized 1:1 to receive standard FEC therapy (5-fluorouracil + epirubicin + cyclofosfamide) (arm 1) or a chemotherapy scheme customized by BRCA1 levels (arm 2). Patients with low expression will receive ECF therapy (epirubicin + cisplatin + 5-fluorouracil); patients with levels of BRCA1 will be treated with eight cycles of docetaxel + cyclofosfamide. Definitive surgery will be performed within 4 weeks after the last chemotherapy cycle. An independent general management team was built for handling regulatory affairs, data and safety monitoring, pharmacovigilance tasks, and daily trial operational activities during trial implementation.

Conclusion: Trial implementation requires a coordinated, multidisciplinary team of people with a solid commitment to support the organization, design, and implementation of study procedures in compliance with regulatory and ethical requirements for investigator-driven RCTs. The challenge of pragmatic design reflecting real practice is fully performed with independent resources.

EudraCT No.: 2011-005843-28 (09/01/2013 registered).
CARDOVASCULAR RISK AND ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES (METADTCR)

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Introduction: Androgen deprivation therapy (ADT) is the cornerstone therapy in advanced prostate cancer management. Currently, to study cardiovascular risk, many studies pooled ADT modalities, sometimes with orchietomy. Our objective was to compare the coronary and cerebrovascular risk (myocardial infarction, ischemic stroke) and the cardiovascular and overall mortality across the different ADT modalities.

PROSPERO Registration: CRD42014010598

Methods: We performed a literature search of randomized controlled trials (RCTs) and observational studies using MEDLINE and Embase since 1930 to July 28, 2014, without language restriction provided that they gave data on prostate cancer patients comparing one ADT modality to another or radiotherapy or total prostatectomy or placebo. ADT modalities were GnRH agonists, GnRH antagonists, antiandrogens (steroidal or nonsteroidal), and newer drugs (ibarabera, enzalutamide). Orchietomy was the relevant alternative. For observational studies pooling several ADT modalities, details on each ADT group were requested to the author. We will also perform a network meta-analysis including RCTs.

Results: Among 3614 abstracts, 47 cohorts fulfilled inclusion criteria and 8 provided sufficient data to be analysed. One study gave details on cardiovascular death and 2 on only coronary and cerebrovascular risk, but cardiovascular events definition were too heterogeneous to be pooled (one study added arrhythmia and heart failure to ischemic heart disease). For the 6 other studies, as they did not compare the same modalities of ADT, they were not meta-analysed for overall survival. A total of 153 abstracts mentioning RCT fulfilled inclusion criteria, and data analysis is ongoing.

Conclusions: Data from observational studies did not support consistent evidence that any particular ADT modality may increase cardiovascular risk or overall survival. We are conducting a nationwide population-based prospective cohort of 4 years thanks to the French Health Reimbursement Agency database, which allowed us to investigate more in depth the association between different ADT modalities and cardiovascular risk.

CARNIVOY LEKERASE 1 C.628G>A SINGLE NUCLEOTIDE VARIATION REDUCES HYDROLYSIS OF CLOPIDOGREL AND ENALAPRIL, BUT NOT THAT OF QUINAPRIL

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Background: Carboxylesterase 1 (CES1) hydrolyzes about 90% of the prodrug clopidogrel to inactive carboxylic acid metabolite and about 40% to 60% of the prodrugs quinapril and enalapril to their active metabolites. In vitro studies have shown that the CES1 c.628G>A (p.G143E, rs71647871) single-nucleotide variation (SNV) can markedly affect metabolism of clopidogrel and ACE inhibitors.

Materials and Methods: We studied pharmacokinetics and pharmacodynamics of 600-mg oral clopidogrel, 10-mg oral quinapril, and 10-mg oral enalapril in 10 carriers and 12 noncarriers of the CES1 c.628G>A SNV. Clopidogrel, its carboxylic acid acetyl-β-D-glucuronide, and active cis 5-thiol metabolite plasma concentrations and platelet aggregation were measured for up to 12 hours. Quinapril and quinaprilat plasma concentrations were measured for up to 24 hours and those of enalapril and enalaprilat for up to 48 hours.

Results: Clopidogrel carboxylic acid to clopidogrel area under the curve (AUC) ratio was 53% smaller in CES1 c.628G>A carriers than in noncarriers (P = 0.009), indicating impaired hydrolysis of clopidogrel. Consequently, AUC of clopidogrel and its active cis 5-thiol metabolite were 12.3% (P = 0.004) and 67% (P = 0.009) larger in c.628G>A carriers than in noncarriers. Consistent with pharmacokinetics, average inhibition of P2Y12-mediated platelet aggregation 0-12 h after clopidogrel intake and maximum observed platelet inhibition were 19 percentage points higher in c.628G>A carriers than in noncarriers (P = 0.036 and P = 0.041, respectively). AUC of enalaprilat was 20% lower in CES1 c.628G>A carriers than in noncarriers (P = 0.049). The CES1 c.628G>A genotype had no significant effect on quinapril pharmacokinetics.

Conclusions: The CES1 c.628G>A SNV increased clopidogrel active metabolite concentrations and antplatelet effects by reducing hydrolysis of parent clopidogrel to inactive metabolites. Therefore, the CES1 c.628G>A allele may increase clopidogrel efficacy and bleeding risk. The CES1 c.628G>A SNV decreased active enalaprilat concentrations by reducing the hydrolysis of enalapril, but had no observable effect on quinapril pharmacokinetics.
Conclusions: Plasma concentrations of risperidone and 9-OH-risperidone after single i.m. injections of risperidone ISM® were well described by a population PK model. The predictive performance was successfully qualified so that this model can be further used for simulations aiding to provide a dosing rationale for risperidone ISM®.

INFECTIOUS RISK OF BIOLOGICAL DRUGS VERSUS CONVENTIONAL SYSTEMIC TREATMENTS IN MODERATE TO SEVERE PSORIASIS

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Introduction: Moderate to severe psoriasis affects about 0.5% of the population. Its management is based on conventional systemic treatments (TSC: phototherapy, acitretin, methotrexate, and cyclosporine) and biological second-line drugs (etanercept, infliximab, ustekinumab, adalimumab, golimumab). Results of studies comparing the infectious risk of TSC and biological drugs are divergent.

Objective: To compare the infectious risk associated with biological drugs versus TSC for moderate to severe psoriasis.

Material and Methods: We conducted a retrospective cohort in the French Health Insurance Database for the Midi-Pyrénées region from 01/01/2010 to 31/12/2013, with patients treated incidentally for moderate to severe psoriasis. After a 6-month observation period with all patients exposed to TSC, we compared patients exposed to biological drugs (“exposed”) versus TSC (“unexposed”). We performed a Cox model on the first infectious event, for up to 6 months after the last dispensation of psoriasis. An infectious event was defined as delivery of any anti-infectious systemic drug or a hospital diagnosis of infection.

Results: The 101 “exposed” patients and 788 “unexposed” patients were comparable in terms of socio-demographic data and comorbidities. Considering the first infectious event over a period of 2 years, no significant difference was found between “exposed” and “unexposed” (HR = 0.94; 95% CI, 0.71–1.22; P = 0.62). Being a woman (HR = 1.23), benefit from the Universal Health Coverage (HR = 1.44), suffering from chronic hepatitis B or C (HR = 2.74), history of neoplasia (HR = 1.70), a previous infectious event during the observation period (HR = 1.74), and the number of drugs consumed during the observation period (HR = 1.03) significantly increased the risk of infection.

Conclusions: We did not reveal any difference in infection risk between the TSC and biological drugs in the management of moderate to severe psoriasis. This risk appears constant the first 2 years of use.

TRENDS IN OPIOID ANALGESICS USE IN EUROPE: A TEN-YEAR PERSPECTIVE

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Background: The aim of this study was to investigate the trends in opioid analgesics consumption in Europe between 2002 and 2012.

Material and Methods: Data were collected for all European Countries. Statistics on opioids consumption were researched and extracted from the consumption databases of the respective national authorities (sales data from health medicines agencies or reimbursement data for national healthcare system). Data were expressed in Defined Daily Doses-1,000 inhabitants/day (DDD). Total opioid consumption (ATC code N02A) and use of selected substances (morphine, oxycodone, fentanyl, codeine, dextropropoxyphene, and tramadol) were investigated.

Results: Data collected were mainly represented by sales data collected by the national authorities from wholesalers. During the observed period, total consumption of opioids increased steadily, then decreased suddenly after 2009 (~43% in France from 2009 to 2012: 44 to 20 DDD). France was the largest consumer of opioids in 2002-2009 (about 50 DDD). Up to 2009, the quantity used were mainly represented by dextropropoxyphene combinations (54% of total consumption in 2009 [25±45 DDD] and up to 73% [43±58 DDD] in 2005). In 2012, France, Belgium, and Denmark were the main opioids users. While morphine use remained constant or tended to decrease (except in UK: 1 to 2 DDD from 2005 to 2012), use of fentanyl is increasing in all countries, in particular in the Netherlands (+65% between 2005–2012: 2.3 to 3.8 DDD).

Conclusions: This study highlights the substantial changes in opioids consumption patterns that occurred as a consequence of definite withdrawal of dextropropoxyphene in March 2011. Opioids consumption patterns in Europe are now characterized by an increasing use of fentanyl and tramadol.

A NOVEL APPROACH TO TEACHING PHARMACOTHERAPEUTICS LEARNING BY DOING IN A STUDENT-RUN CLINIC

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Contributed equally

Background: Medical students should be better prepared for their future role as prescribers. A new educational concept to achieve this is learning by doing. This encompasses legitimate, context-based training and gives students responsibility as early as possible in their medical education. Student-run clinics (SRCs) are an example of this concept. We describe the development of a new SRC primarily focused on medical pharmacotherapy education, the learner-centered student-run clinic (LC-SRC), and its feasibility.

Method: A feasibility study was performed in which a team of (1st-, 3rd-, and 5th-year) students treated patients under the supervision of an internist. Patients were selected from the internal medicine outpatient clinic for follow-up in the LC-SRC. Feasibility was evaluated using a set of questionnaires for patients, supervisors, and students.

Results: In total 31 consultations were conducted; 31 students and 4 clinical specialists participated. A pharmacotherapeutic treatment plan was drawn up in 33% of the consultations. Patients were content with the care provided and rated the consultation with a 7.9 (SD 1.21) (range, 1–10). Supervisors regarded LC-SRC safe for patients with guaranteed quality of care. They found the LC-SRC a valuable tool in medical education, although it was time-consuming. Students appreciated their (new) responsibility for patient care and considered the LC-SRC a very valuable extracurricular activity.

Conclusion: The LC-SRC is feasible and could be a valuable addition to the medical curriculum. The benefits and learner effects need to be investigated in a larger study with a longer follow-up.
AN EPIDEMIOLOGICAL STUDY FOR ELEVATION OF LIVER FUNCTION TESTS IN JAPANESE PATIENTS ADMINISTERED BY HIGH DOSE ACETAMINOPHEN

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Background: Acetaminophen is widely used for pain in cancer and non-cancer patients, and it is known to show liver injury in the case of overdose. The maximum dose was 1.5 g/d in Japan, which was much lower than in other countries. In 2011, the registered maximum dose was changed to 4.0 g/d in Japan, and concerns for safety in Japanese patients were raised. Therefore, we performed an epidemiological study for the safety of acetaminophen.

Methods: Patients administered a high dose (2.4–4.0 g/d) of acetaminophen for more than 4 weeks were included. Data were collected from hospital medical information systems at 87 hospitals from January 2011 to October 2013. Abnormal liver function test (LFT) was defined as elevation in ALT greater than 3 times the upper limit of normal. Prevalence of abnormal LFT was calculated, and relationships with patients’ backgrounds were analysed by a logistic regression.

Results: 735 cases were collected and 703 cases that met inclusion criteria were analysed. Among them, 371 cases were cancer patients. One case showed elevation of AST, ALT, and TBil, which met criteria by Hy’s law, but the findings were considered to be owing to pre-existing disease. There was no serious liver injury considered to be induced by acetaminophen. Abnormal LFTs were found in 22 cases (3.1%), and causality of acetaminophen was not ruled out in 7 cases (1.0%). The logistic regression showed that abnormal LFTs significantly related to existence of complicated disease, history of allergic disease, and duration of dosage.

Conclusion: The prevalence of elevation of ALT in Japanese patients administered by acetaminophen was almost identical with those reported in other countries. However, the significant relationship between abnormal LFT and duration of dosage indicates a necessity of continuous collection of data in Japan.

ARE PATIENTS READY TO TAKE PART IN THE PHARMACOVIGILANCE SYSTEM? A PORTUGUESE PRELIMINARY STUDY CONCERNING ADR REPORTING

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Background: New pharmacovigilance legislation allows patients to report adverse drug reactions (ADRs) directly to competent authorities in all European Union countries. Patient reporting is available in Portugal since July 2012. In 2013, the National Pharmacovigilance System (SNF) had received 3461 spontaneous ADR reports, of which only 1.4% (n = 50) were from patients. Patient reporting could be one opportunity to reduce underreporting. The aim of this study was to describe the attitudes and knowledge of the patients regarding spontaneous reporting and the reasons and opinions that can influence patients ADR underreporting.

Material and Methods: A descriptive-correlational study was performed looking for patients’ attitudes and knowledge regarding spontaneous reporting. A 6-month survey was conducted from June to November 2013 in general adult patients from a community pharmacy in Coimbra, Portugal, that used prescribed medicines or OTC drugs. Questionnaires from health care professionals or incomplete weren’t considered. Data were analyzed using descriptive statistics, χ² tests and Spearman’s correlation coefficients.

Results: 1084 questionnaires were collected (response rate of 81.1%), and 948 completed questionnaires were selected for analysis. Of the respondents, 44.1% never heard about SNF. Younger people and those with a higher education were significantly more likely to be aware of SNF. Only 1 patient had previously reported directly an ADR. Reporting ADRs indirectly through an HCP was preferred by 62.4%. The main reasons for patients reporting spontaneous ADR would be the severity of reactions (81.1% agreed or strongly agreed) and worries about their situation (73.4% agreed or strongly agreed). Only weak and moderate correlations were found between studied statements.

Conclusion: Patients are more likely to spontaneously report severe reactions if they are worried about the symptoms. Tailored and proactive information on ADR reporting and educational interventions on patients could increase the number of reports from patients in Portugal.

ZAGREB MEDICAL STUDENTS’ ATTITUDES TOWARDS FORMATIVE ASSESSMENTS OF THEIR KNOWLEDGE OF PRESCRIBING

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Introduction: In 2009, an e-learning course comprising 90 clinical cases and 300 flash videos developed at the University of Michigan Medical School (Ann Arbor) was in a collaborative manner translated into Croatian and adopted for use at the Zagreb Medical School by means of the ctools learning management system (LMS) platform.

Materials and Methods: Formative assessments were performed through the course sites platform via 24 quizzes in a timed manner and open book format. After the course completion, attitudes of 220 Croatian students towards the online course and formative assessments were evaluated with a validated, electronic questionnaire in 2014.

Results: Feedback obtained from the Zagreb students (response rate, 44%) demonstrated that the majority of them perceived the weekly quizzes as difficult (53%) or very difficult (31%). Furthermore, the majority of them agreed (28%) or strongly agreed (66%) with the usefulness of obtaining immediate feedback to their answers, and more than 50% of students perceived weekly online quizzes as an intellectually challenging exercise that tested their higher cognitive abilities.

Conclusion: Online formative assessments of students’ prescribing knowledge offer a cost effective way to better prepare young doctors for their future independent medical practice by challenging their problem-solving and prescribing abilities while simultaneously offering immediate feedback regarding their choices, all in a safe, online environment and without danger to the lives of patients.

DRUG-DRUG INTERACTION DATABASE SFINX – FIRST RESULTS FROM NORTH ESTONIA MEDICAL CENTRE, ESTONIA

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Drug treatment is one of the most important tools in health care but is also an important reason for morbidity and mortality. Among different drug-related problems, drug-drug interactions (DDIs) are particularly important and in many cases predictable and avoidable.
Clinical Therapeutics

To detect DDIs and improve the quality of prescribing, the SFNX database has been integrated to electronic health records in North Estonia Medical Centre (NEMC) from the end of the year 2014. The aim of this pilot study was to describe first-time data of DDIs detected during prescribing of drugs for outpatient use at NEMC.

Material and Methods: Data about prescribed drugs and detected type D (clinically significant interaction that should be avoided) and type C (clinically relevant interactions that can be handled, eg, by dose adjustments) DDIs after prescribing in NEMC has been obtained from NEMC during the period from January 1 to January 31, 2015. All earlier outpatient prescriptions from last 180 days were considered in DDI analysis, too.

Results: During the period studied, 25,421 prescriptions were written in NEMC: 10,644 for men and 14,777 for women. A total of 23,295 new type D and C DDIs were detected, consisting of 164 unique pairs of type D and 741 pairs of type C DDIs, respectively (Table).

Table. Most common drug-drug interactions in North Estonia Medical Centre

<table>
<thead>
<tr>
<th>Type D interaction</th>
<th>Prevalence</th>
<th>Type C interaction</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propafenone - metoprolol</td>
<td>408</td>
<td>Metoprolol - diclofenac</td>
<td>829</td>
</tr>
<tr>
<td>Clopidogrel - esomeprazole</td>
<td>276</td>
<td>Warfarin - ramipril</td>
<td>473</td>
</tr>
<tr>
<td>Metoprolol - verapamil</td>
<td>194</td>
<td>Digeoxin - spironolactone</td>
<td>492</td>
</tr>
<tr>
<td>Clopidogrel - esomeprazole</td>
<td>108</td>
<td>Spironolactone - ramipril</td>
<td></td>
</tr>
<tr>
<td>Warfarin - diclofenac</td>
<td>107</td>
<td>Hydrochlorothiazide - diclofenac</td>
<td>418</td>
</tr>
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</table>

Conclusions: The SFNX database is a powerful tool to detect DDIs during prescribing process. However, data from the first analysis indicated a need for targeted education of prescribers about interpretation of clinical significance of DDIs highlighted in terms of rational pharmacotherapy and planning of systematic follow up of patients with high risk for DDIs.

PHARMACOLOGY E-LEARNING WITH THE MOBILE TEACHING RESOURCE CENTER

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Introduction: The free pharmacology Teaching Resource Centre (TRC, http://www.coo.lumc.nl/trc) was created to illustrate drug action in the (patho)physiological context in a consistent way. With the introduction of the tablets and smartphones, Leiden students demanded increased accessibility of pharmacological knowledge (ie, the TRC). The TRC apps were released for iPad (June 2012), iPhone (November 2012), and Android (November 2013). The objective of the study was to investigate usage frequency, differences in usage, and user friendliness of the apps compared to the website in the most relevant user population (ie, undergraduate medicine students).

Methods: A survey was sent out via email to medical students at Leiden University Medical Center. The type of questions were multiple choice, multiple answer, or open-ended. The responses were then recorded and analyzed. In total, 484 medical undergraduate students responded.

Results: In more than 30 months since its initial release, the apps have been downloaded more than 100,000 times throughout the world. The TRC website is still frequently used with up to 5000 hits per day before exams. The website is the most visited portal for pharmacological e-learning with the TRC. The mean overall assessment of the resource on a 10-point numerical rating scaling (0, very weak; 10, excellent) is similar. The iPad app and the website are rated the highest (7.9), whereas the iPhone app, smartphone app, and tablet app are assessed slightly lower (7.4, 7.1, and 7.2, respectively). Interestingly, most users of a mobile app continue to use also the website for their study.

Conclusions: The free pharmacology app is readily available for all health care students and professionals worldwide for free. The TRC app is used differently in respect to learning situations compared to the website. Due to the success of the apps, further extension of the content (eg, inclusion of animations) is ongoing.

EFFECTIVENESS OF ACENOCOUMAROL GENETIC AND CLINICAL DOsing ALGORITHMS IN PREDICTING STABLE DOSE IN THE GREEK COHORT OF THE EU-PACT TRIAL

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Introduction: The EU-PACT (Pharmacogenetics of Anticoagulant Therapy) trial (ClinicalTrials.gov number NCT01119261) compared a genotype-guided dosing algorithm that included clinical variables and genotypes of CYP2C9 and VKORC1 with a dosing algorithm that included only clinical variables for the initiation of acenocoumarol treatment in patients with atrial fibrillation or venous thromboembolism. Its main results were published recently (Verhoef et al. NEJM. 2013;369(24):2294-303). The primary outcome of the trial was percent time in INR target range (2.0 to 3.0) in the 12-week period following therapy initiation. Several secondary outcomes, such as time to and number of patients with INR ≥4, percentage time spent with an INR ≥4 or with an INR <2, number of minor and major adverse events, and incidence of coumarin sensitivity and resistance, were also assessed.

Methods: We performed an ethnicity analysis for the Greek population recruited in the EU-PACT trial. A total of 207 patients (104 in the pharmacogenomic arm, 103 in the control arm) starting acenocoumarol therapy were recruited in Greece.

Results: Percent time in range (PTIR) was 61.1% for patients receiving genotype-guided dosing and 62.7% for those receiving clinically guided dosing (P = 0.68). No differences were observed in PTTR for weeks 1 to 4, 4 to 8, and 9 to 12 of the trial and for the other secondary outcomes assessed. We have further tested in the pooled sample the effect of CYP450 enzymes and VKORC1 gene polymorphisms on acenocoumarol stable dose and time to reach stable dose. Acreoncoumarol stable dose was significantly associated with PTIR and genotype-guided dosing algorithm that included clinical variables and genotypes of CYP2C9 and VKORC1 genotype (P < 0.001 in each case).

Conclusions: Genotype-guided dosing of acenocoumarol did not improve the PTIR during the 12 weeks after therapy initiation in comparison with the clinical algorithm. However, genetic variants of CYP2C9 and VKORC1 are significant determinants of individual dose of acenocoumarol needed to maintain a therapeutic INR in the Greek population.

PHARMACOGENETIC PROFILE OF LIPID RESPONSE TO ATORVASTATIN IN CHILDREN AND ADOLESCENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

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Introduction: The EU-PACT trial (ClinicalTrials.gov number NCT01119261) compared a genotype-guided dosing algorithm that included clinical variables and genotypes of CYP2C9 and VKORC1 with a dosing algorithm that included only clinical variables for the initiation of acenocoumarol treatment in patients with atrial fibrillation or venous thromboembolism. Its main results were published recently (Verhoef et al. NEJM. 2013;369(24):2294-303). The primary outcome of the trial was percent time in INR target range (2.0 to 3.0) in the 12-week period following therapy initiation. Several secondary outcomes, such as time to and number of patients with INR ≥4, percentage time spent with an INR ≥4 or with an INR <2, number of minor and major adverse events, and incidence of coumarin sensitivity and resistance, were also assessed.

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Introduction: In children and adolescents with familial hypercholesterolemia (FH), pharmacotherapy with statins is the cornerstone in the current regimen to reduce low-density lipoprotein cholesterol (LDLc) and premature coronary heart disease risk. There is, however, a great interindividual variation in response to therapy, partially attributed to genetic factors. It has been suggested that genetic polymorphism of the enzymes POR, CYP3A4, CYP3A5 and solute carrier SLCO1B1 may influence this variation. We analyzed the association of alleles POR*28, CYP3A4*22, CYP3A5*3, and SLCO1B1 5217>C and 388A>G with response to atorvastatin.

Methods: The study included 105 FH children and adolescents treated with atorvastatin (10 to 40 mg). Total cholesterol (TCt) and LDLc were measured at baseline and after 6 months of treatment. POR*28 CYP3A4*22, and CYP3A5*3 alleles and SLCO1B1 5217>C and 388A>G genotypes were determined with TaqMan or PCR-RFLP methods.

Results: POR*28 carriers had significantly lower percent mean reduction of TCt (33.1% in *1/*1, 29.8% in *1/*28, and 25.9% in *28/*28 individuals, P = 0.045) and of LDLc (43.9% in *1/*1, 40.9% in *1/*28, and 30.8% in *28/*28 individuals, P = 0.013). In multivariable linear regression adjusted for confounding factors, POR*28 genotypes, additionally to baseline cholesterol level, account for an estimated 8.3% and 7.3% of overall variability in percent TCt and LDLc reduction (β = 4.05; 95% CI, 1.73–6.37; P = 0.001 and β = 5.08; 95% CI, 1.62–8.54; P = 0.004, respectively). CYP3A4*22, CYP3A5*3, and SLCO1B1 5217>C and 388A>G polymorphisms were not associated with lipid reductions and did not modify the effect of POR*28 on atorvastatin response.

Conclusions: In children with FH, carriage of POR*28 allele was associated with reduced effect of atorvastatin on TCt and LDLc and therefore identifies FH children who may require higher atorvastatin doses to achieve full therapeutic benefits. Further studies in different populations are needed to replicate the association.

Key words: atorvastatin, pharmacogenomics, familial hypercholesterolemia, P450 oxidoreductase, POR*28, CYP3A4*22, CYP3A5*3 and SLCO1B1 5217>C and 388A>G, children.

AN IN SILICO MODEL OF ASPIRIN-INDUCED INACTIVATION OF PLATELET AND MEGAKARYOCYTE CYCLOOXYGENASE-1

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Background: Aspirin is a short-lived, irreversible inhibitor of platelet cyclooxygenase (COX)-1. We have recently reported that aspirin action throughout the 24-hour dosing interval is impaired under conditions of accelerated platelet formation such as essential thrombocythemia (ET). An in silico model of aspirin pharmacodynamics might help elucidating the dynamic features of its action and personalize regimens in different cardiovascular disorders.

Methods: We set up a new multi-compartmental mathematical model that describes the key features of COX-1 dynamics, including its synthesis/degradation in the heterogeneous population of developing bone marrow megakaryocytes (MK), the progressive platelet formation, and COX-1 acetylation by aspirin in both MK and peripheral (platelet) compartments. The model, consisting of 7 differential equations and 24 parameters, was implemented in MATLAB. It was calibrated using serum thromboxane (TX)B2 (proxy of COX-1 activity) recovery data measured in 7 healthy controls and 2 ET patients during and after aspirin withdrawal and in 21 ET patients on different aspirin regimens. Sensitivity analysis was performed to identify the set of key parameters that most significantly influenced COX-1 dynamics.

Results: A good agreement (weighted absolute percentage error <18%, within the experimental variability) was obtained between data and model prediction. The different recovery pattern observed in healthy vs ET patients was reproduced by altering three key model parameters identified by sensitivity analysis: platelet count (twofold increase), Mk lifetime (from 3 to 1 day), and platelet lifetime (from 7 to 5–6 days). Finally, the model explains an increased COX-1 acetylation following a shorter dosing interval (100 mg twice daily) as compared to a higher (200 mg) once-daily dose in ET patients.

Conclusions: Our in silico model adequately describes aspirin responsiveness, as measured in controls and patients with high drug-target turnover, and might be a useful tool to design personalized regimens in clinical conditions characterized by altered Mk and/or platelet kinetics.

LETHAL SUICIDAL ATTEMPT WITH A MIXED-DRUG INTOXICATION INVOLVING METOPROLOL AND PROPAFENONE – A FIRST PAEDIATRIC CASE REPORT

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Introduction: β1-blocker metoprolol is often prescribed together with propafenone. Both are metabolized by cytochrome P450 2D6, and metoprolol serves as the probe drug for phenotyping of the enzyme. Propafenone is also an inhibitor of P450 2D6, and a 2- to 5-fold increase of metoprolol steady-state levels has been described in combination with propafenone. There is no case report showing metoprolol and propafenone ingestion in a suicidal attempt together.

Material and Methods: A 14-year-old girl was admitted to the emergency department having ingested propafenone (probably 1500–3000 mg) and metoprolol (probably 1000 mg) in a suicide attempt with loss of consciousness, seizures, and the widening of the QRS complex. Plasma levels of metoprolol and propafenone were analysed approximately 10 hours after ingestion; however, the correct amount of each drug and the time of ingestion were unknown. Serial samples for measurement of metoprolol and its metabolite α-hydroxymetoprolol were analysed between days 2 and 4, and the metoprolol/α-hydroxymetoprolol ratio was determined.

Results: The patient’s clinical condition rapidly deteriorated. She developed cardiac arrest and was fully resuscitated. Extracorporeal circulation was started. Her condition gradually worsened, and brain edema and acute renal insufficiency occurred. On the 6th day the patient died. The first concentrations were 2500 ng/mL (propafenone) and 2630 ng/mL (metoprolol). The levels of metoprolol and α-hydroxymetoprolol declined slowly from 689.1 ng/mL (2nd day) to 132.7 ng/mL (4th day) and 19.1 ng/mL to 12.5 ng/mL, respectively. The metoprolol/α-hydroxymetoprolol ratio determined on the second day was 36.1, indicative of a poor metabolizer phenotype, declining to 22.9 and 16.1 on the third day and to 10.6 on the fourth day. The elimination half-life of metoprolol was prolonged to 12.2 hours that is 4-fold longer to normal value.

Conclusions: We report the first pediatric case of death due to a mixed drug overdose of metoprolol and propafenone. The toxicity of metoprolol was potentiated by drug interaction with propafenone causing inhibition of P450 2D6.
Clinical Therapeutics

1 ELECTROCARDIOGRAPHIC SCREENING FOR DRUG-INDUCED LONG QT TO REDUCE SUDDEN CARDIAC DEATH IN PSYCHIATRIC PATIENTS: A COST-EFFECTIVENESS ANALYSIS
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Background: Sudden cardiac death is a leading cause of mortality in psychiatric patients. Long QT (LQT) triggered by psychotropic medication is common and predisposes to torsades-de-points (TdP) and subsequent mortality. We estimated the cost-effectiveness of electrocardiographic screening to detect drug-induced LQT in psychiatric inpatients.

Material and Methods: We built a decision analytic model based on a decision tree to evaluate the cost-effectiveness and utility of LQT screening from a health care perspective. LQT proportion parameters were derived from an in-hospital cross-sectional study. We performed experts’ elicitation to estimate the risk of TdP given the extent of QT prolongation. A TdP reduction of 65% after LQT detection was based on positive drug dechallenge rate and through adequate treatment and electrolyte adjustments. The base-case model uncertainty was assessed with one-way and probabilistic sensitivity analyses.

Results: In the base-case scenario, the numbers of patients needed to screen were 1128 and 2817 to avoid one TdP and one death, respectively. The ICER of systematic ECG screening was $8644 (95% CI, 3144–82,498) per QALY. The probability of cost-effectiveness was 96% at a willingness-to-pay of $50,000 for one QALY. In sensitivity analyses, results were sensitive to the case-fatality of TdP episodes and to the TdP reduction following the diagnosis of LQT.

Conclusions: In psychiatric hospitals, performing systematic ECG screening at admission helps reduce the number of sudden cardiac deaths in a cost-effective fashion.

2 POLYPHARMACY IN A BELGIAN COHORT OF COMMUNITY-DWELLING OLDEST OLD: BASELINE OBSERVATIONS AND ASSOCIATED RISK FACTORS
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Background: Polypharmacy is highly prevalent among older people (≥65 years), but little is known about the medication use of the oldest old (≥80 years). This study explores the medication use of the Belgian community-dwelling oldest old in relation to their demographic, clinical, and functional characteristics.

Methods: Baseline data were used from the BELFRAIL study, a prospective, observational, population-based cohort of community-dwelling subjects (≥80 years). General practitioners recorded clinical problems and medications. Medications were coded by the Anatomical Therapeutic Chemical classification.

Results: Participants’ (n = 503) mean age was 84.4 years (range, 80–102 years), and 61.2% was female. Median chronic medication use was 5 (range, 0–16). Polypharmacy (≥5 medications) was high (57.7%), with excessive polypharmacy (≥10 medications) in 9.1%. Cardiovascular medications (86.3%) were most used. Nervous system medications (54.1%), predominantly benzodiazepines and anti-depressants, were also frequently consumed. Demographic factors related with polypharmacy in univariate analysis were female gender (OR 1.58), low education (OR 1.52), and low alcohol use (OR 1.61). Age, care dependency, and cognitive impairment showed no association with polypharmacy. Except for obesity, the most prevalent clinical problems were associated with polypharmacy. In multivariate analysis, the predominant association with polypharmacy as outcome was found for multimorbidity (OR 1.77), followed by depression (OR 3.73), and physical activity (OR 0.78).

Conclusions: Polypharmacy was high among Belgian community-dwelling oldest old. Determinants of polypharmacy were interrelated but dominated by multimorbidity. Polypharmacy was lower in physically active patients and higher in patients with more depressive symptoms. More research on causes and consequences of polypharmacy over time is needed.

3 PHARMACOVIGILANCE AT THE CHUK NATIONAL REFERRAL HOSPITAL IN RWANDA: PATTERNS OF SUSPECTED ADVERSE DRUG REACTIONS
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Background: Pharmacovigilance increases patient safety. We aimed to encourage ADR reporting and assess ADRs among in-patients at our national referral hospital.

Methods: We used WHO and Ministry of Health ADR reporting protocols, including causality reviews, to identify suspected harmful responses to one or more medicines, prescribed, OTC, or traditional, known or new.

Results: During a prospective 4-week audit in October 2014, 28 reports were received (27 patients: mean ± SE age, 42 ± 3 years; range, 21–86; 11 males: mean ± SE age, 44 ± 4 years; 17 females: mean ± SE age, 42 ± 4 years; height, 1.63 ± 0.02 m; weight, 54.7 ± 3.4 kg; emergency room, 10, internal medicine, 17, renal, 1; capital city, 16, other areas, 12; comorbidity included: HIV, 10 [TB, 5; 1 both candidiasis and PCP]; renal disease, 3; hypertension, 4, diabetes mellitus, 4; anaemia, 3; CLL, 1; none in 5. ADRs were related to traditional medicines (5), NSAIDs (3), antibiotics (8), antiretrovirals (3), prenalisone (2), and enoxaparin, metformin, OCP, pethidine, and quinine (1 each). One report was for a blood transfusion reaction. The most common sites affected were GI (bleeding/vomiting 8), liver (6), skin (6), and kidney (4). Six patients had a recurrent ADR with a known or new.
Morphine Decreases Ticagrelor Concentrations But Not Its Effects

1 (acute on chronic liver failure). Twelve ADRs were considered due to a single drug, 10 to multiple drugs, and 5 to traditional medicines. In one patient a metabolic drug interaction with fluconazole was implicated. In 6 cases, drugs considered exacerbated prior disease. Conclusions: We were effective in improving ADR reporting, identifying important contributions of ADRs to serious morbidity, and identifying preventable patterns of ADRs. Prior similar ADRs, drug-disease interactions, and traditional medicine use, often unrecognized, were common causes of hospital admissions.

EFFICACY, SAFETY AND TOLERABILITY STUDY OF ARTEMISININ-PIPERAQUINE COMBINATION (ARTEQUICK®) VERSUS ARTEMETER-LUMEFANTRINE (CO-ARTEM®) FOR THE TREATMENT OF UNCOMPPLICATED PLASMODIUM FALCIPARUM T MALARIA IN IJEBU ODE LOCAL GOVERNMENT HEALTH SERVICES IN NIGERIA

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Background: Artemisinin-based combination therapy (ACT) has become the standard of care for the treatment of uncomplicated Plasmodium falciparum malaria in the world. Data guiding optimal choices of ACTs are limited. Artemisinin-based combination therapy of artemether-lumefantrine (Coartem®) is currently used for the first line treatment of uncomplicated Plasmodium falciparum malaria. However, limited efficacy and tolerability data are available on alternative forms of ACT. This study was conducted to compare the efficacy and tolerability of two fixed- dose formulation of ACT, artemisinin-piperaquine (Artequick®) and (Coartem), for the treatment of P. falciparum in Nigeria.

Methods/Materials: A randomized, open-label trial was conducted comparing the efficacy of a one-day regimen of Artequick (2.8 mg/kg; kg artemisinin plus 17.1 mg/kg of piperaquine per day for 24 hours) and Coartem (24 tablets, total dosage of 3360 mg, eight tablets over three days) for the treatment of adults with uncomplicated falciparum malaria. The primary end point was a day 42, PCR-corrected, parasitological cure rate; secondary end points were parasites and fever clearance time. Of 64 patients enrolled, 31 were administered with Artequick and 33 with Coartem.

Result: Of the patients who completed the test, 28 were on Artequick and 29 were on Coartem. Recrudescence parasitemia was PCR confirmed for all patient in each treatment group, with cure rates at day 42 of 97% (95% CI: 90–100) for both forms of ACT.

Conclusion: The median parasite clearance time was significantly slower in the Coartem group compared with the Artequick group (48 h vs 36 h, P < 0.05), and fever clearance times were shorter in the Artequick group (12 h vs 24 h, P < 0.05). The two forms of ACT were well tolerated with no serious adverse events.

Key words: Malaria; Plasmodium Falciparum; Artemisinin; Piperaquine; Artemether; Lumefantrine.

CYP2D6, CYP2C19 and CYP2C9 Genotyping in a Swedish Clinical Setting

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The polymorphic cytochrome P450 enzymes CYP2D6, CYP2C19, and CYP2C9 catalyze the oxidative metabolism of numerous commonly prescribed drugs, such as antipsychotics, antiepileptics, antidepressants, and some cardiovascular drugs (eg, warfarin, flecainide, propafenone, and metoprolol). Evaluation of the metabolic capacity of an individual by genotyping may help the clinicians to select the right dose (in order to avoid toxic or subtherapeutic plasma concentrations) and/or the best drug for an individual patient, thereby minimizing the risk of side effects or therapeutic failure.

In the period 2009 to 2014 a total of 529 genotyping analyses were performed at our department, with a 10% yearly increase in the number of tests performed. The most requested test was CYP2D6 (55%), followed by CYP2C19 (32%) and CYP2C9 (13%). The majority of the patients were treated with psychoactive drugs (75%), particularly antidepressants and classical antipsychotics, such as haloperidol and perphenazine, followed by cardiovascular drugs, especially warfarin, metoprolol, and propafenone (15%). The principal reason for genotyping was lack of optimal drug response/therapeutic failure (50%), followed by side effects (35%), while a few subjects were genotyped before starting therapy with drugs, such as propafenone and tamoxifen.

Gene duplication was detected in a handful of subjects with therapeutic failure, suggesting that non-compliance is still the main reason for lack of drug response. Conversely, among subjects who had experienced side effects, the frequency of detrimental alleles was higher than the background incidence. Furthermore, in some cases extensive metabolisers with side effects were phenotypically poor metabolizers, due to concomidation with potent CYP2D6 inhibitors, such as paroxetine and bupropion. Based on our experience, we conclude that genotyping is a valuable complement to plasma concentration determination when poor or ultrarapid drug metabolism is suspected.

ST. JOHN’S Wort Impairs Glucose Tolerance by Reducing Insulin Response in Healthy Men

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Background: St. John’s wort is an herbal medicinal plant, which is used for treating depression. St. John’s wort activates the pregnane x receptor and induces transcription of drug metabolizing enzymes, such as CYP3A4. There has been a growing burden of evidence, which indicates that pregnant x receptor activation causes glucokinase intolerance. Thus, the aim of this study was to examine if the over-the-counter herbal medicinal plant St. John’s wort affects the glucose tolerance in healthy men.

Materials and Methods: Ten healthy men were examined by a 2-hour oral glucose tolerance tests at 3 occasions: A: Baseline, B: With 21 days pretreatment with St. John’s wort, and C: At least 6 weeks after last capsule of St. John’s wort was ingested. Plasma glucose, serum insulin, and C-peptide during the oral glucose tolerance tests were determined and used for estimation of area under the concentration-time curve (AUC) and indices of insulin sensitivity and insulin secretion.

Results: Treatment with St. John’s wort increased glucose AUC and 2-hour plasma glucose levels. Surprisingly, this effect was sustained and even further increased 6 weeks after the last capsule of St. John’s wort was taken. No effect on indices of insulin sensitivity was seen, but indices of insulin secretion were reduced even after adjustment for insulin sensitivity.

Conclusions: This study indicates that long-term treatment with St. John’s wort impairs glucose tolerance by reducing insulin response. The unregulated use of this over-the-counter drug might be a risk factor for impaired glucose tolerance and type 2 diabetes.
ANTHYPTERTENSIVE DRUGS AND BLOOD PRESSURE CONTROL IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: A PROSPECTIVE OBSERVATIONAL STUDY

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Background: Obstructive sleep apnea (OSA) is an independent risk factor for hypertension. Continuous positive airway pressure (CPAP) is considered the gold standard treatment for symptomatic OSA patients, but its effectiveness on blood pressure (BP) control is modest and concomitant antihypertensive therapy is still required. The best antihypertensive regimen for BP control in these patients remains unknown. The present work aimed to contribute to the identification of the most effective antihypertensive regimen prescribed in current treatment practice, investigating a hypothetical association between ongoing antihypertensive medication and BP control rates in patients with OSA.

Methods: We conducted a prospective observational study (ClinicalTrials.gov: NCT01803815) in a cohort of 205 patients with OSA and hypertension who underwent a sleep study and 24-hour ambulatory blood pressure monitoring (ABPM). Ongoing antihypertensive medication profile was recorded. Logistic regression models were used to investigate the association between antihypertensive regimen and BP control before (n = 205) and, when applicable, after CPAP adaptation (n = 90).

Results: According to current guidelines and antihypertensive medication and/or 24-hour ABPM, 63.9% (205/321) of the patients were diagnosed with OSA and hypertension. One hundred fifty-five (155/205) were under antihypertensive medication, and 31 different antihypertensive regimens were found. However, the antihypertensive regimens and the number of antihypertensive drugs were not associated with BP control (P = 0.847; P = 0.991). After CPAP adaptation, a decrease in median nighttime systolic and diastolic BP was observed (P = 0.001; P = 0.006). Nevertheless, the lack of association between antihypertensive regimens and the number of antihypertensive drugs and BP control remained (P = 0.864; P = 0.800).

Conclusions: This study shows, for the first time, that BP control is independent of both antihypertensive regimens and the number of antihypertensive drugs and that none of the currently available antihypertensive drugs seem to be effective for the control of BP in patients with OSA.


DIRECT ORAL ANTICOAGULANTS VERSUS WARFARIN FOR STROKE PREVENTION IN ATRIAL FIBRILLATION: A SUBGROUP META-ANALYSIS IN EUROPEAN PATIENTS

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Introduction: Geographic variation in medical practice may have a profound effect on the quality of anticoagulation.

Material and Methods: We searched MEDLINE and CENTRAL (up to February 2015), regulatory agencies websites, clinical trials registers, and conference proceedings to identify randomized controlled trials of the direct oral anticoagulants (DOAC; dabigatran, rivaroxaban, apixaban, edoxaban) versus warfarin for prevention of stroke and systemic embolic events (SEE) in patients with non-valvular atrial fibrillation (NVAF). We extracted data on stroke/SEE (primary efficacy outcome) and major bleeding (primary safety outcome) in available subgroups by geographic region (Europe versus Rest of the World (ROW)). Relative risks (RR) and 95% confidence intervals (CI) were estimated using a random effect meta-analysis (RevMan software). A P value for subgroup differences < 0.05 and an I² value > 75% (Higgins test) were qualified as a statistically significant high heterogeneity.

Results: A total of 75,404 patients from 4 trials were analyzed. Of them, 31,957 (42%) patients were recruited in Europe and 43,447 (58%) patients were recruited in the ROW. We found significant subgroup differences on stroke/SEE depending on the geographic region (P for subgroup differences = 0.003; I² = 89%) with a neutral effect of the DOAC versus warfarin in Europe (RR, 1.02; 95% CI, 0.86–1.22) and a significant reduction of stroke/SEE in the ROW (RR, 0.75; 95% CI, 0.67–0.83). There was a similar reduction in risk of major bleeding in Europe (RR, 0.77; 95% CI, 0.62–0.96) and in the ROW (RR, 0.81; 95% CI, 0.65–1.02) (P for subgroup differences = 0.74; I² = 0%).

Conclusions: The relative efficacy of the DOAC versus warfarin in patients with NVAF is influenced by geographic region. No reduction in stroke/SEE versus warfarin was found in the European population included in pivotal trials. However, the reduction in risk of major bleeding with the DOAC in comparison with warfarin was consistent regardless of geographic region.

PK AND PD OF A NICOTINIC ANTICHOLINERGIC CHALLENGE WITH MECAMYLAMINE IN COMPARISON TO SCOPOLAMINE

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Introduction: Cholinesterase inhibitors are frequently prescribed to patients with Alzheimer’s disease. The resulting increase in acetylcholine level in the synaptic cleft has an effect on both muscarinic and nicotinic acetylcholine receptors, causing cognitive enhancement, mostly via the nicotinic receptors, but also peripheral side effects, mostly via the muscarinic receptors. Therefore, nicotinic receptor specific cholinergic agonists are under development. In order to prove pharmacology of these compounds, an anticholinergic pharmacological challenge with the nicotinic antagonist mecamylamine was developed in healthy volunteers. With the current study we aimed to gain more detailed and time-dependent information on pharmacodynamic effects of mecamylamine.

Materials and Methods: This was a double-blind, placebo-controlled, randomized 4-way crossover study with mecamylamine 10 mg or 20 mg p.o. or scopolamine HBr 0.5 mg i.v. in 12 non-smoking healthy subjects, aged 18 to 45 years. Pharmacodynamic measurements consisted of computerized tests for memory, attention, psychomotor speed, eye movements, subjective scales for mood and alertness, stability, and pharmaco-EEG.

Results: Mecamylamine more selectively affected memory than alertness compared to scopolamine. Mecamylamine 10 mg, mecamylamine 20 mg, and scopolamine all affected the visual verbal learning test (−2.7; CI, −5.1 to −0.3; −3.6, CI, −5.9 to −1.4; −7.7; 95% CI, −10.1 to −5.4, respectively) and adaptive tracking (−1.89; CI, −3.90 to 0.12; −2.06, CI, −3.97 to −0.16; −10.38; 95% CI, 12.38 to −8.39, respectively), a test for attention. However, mecamylamine did not have clear sedative effects, contrary to scopolamine. This is illustrated by the simple reaction time task (7.0; CI, −0.8 to 15.5; 3.8; CI,
Morphine Decreases Ticagrelor Concentrations but Not Its Effects

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Introduction: Increasing age are associated with greater morbidity and mortality after anesthesia. Rocuronium (ROC), a neuromuscular blocking agent used in surgical procedures, is primarily eliminated by biliary and renal excretion. The objective of this study is to evaluate the impact of advanced age on ROC pharmacokinetics (PK) and pharmacodynamics (PD) in ASA I-II patients undergoing elective surgeries.

Material and Methods: Adult patients (aged 20–50 years, n = 13) and elderly patients (aged 65–85 years, n = 13) submitted to surgery under general anesthesia were investigated. All patients were induced with individual intravenous doses of midazolam, rocuronium, fentanyl and propofol. Serial blood samples were collected up to 360 minutes after administration of ROC. Rocuronium-induced neuromuscular block was monitored by train of four stimulation of the adductor muscle of the thumb on the ulnar nerve at the same times of blood collection. The plasma concentration of ROC was analyzed by liquid chromatography coupled to mass spectrometry with electrospray ionization using positive ion mode. The pharmacokinetic parameters area under the curve normalized by dose (AUC/dose) and clearance were calculated by non-compartmental analysis. The relationship between rocuronium plasma concentration and the neuromuscular blockade was described by a sigmoid modified effect model for each patient. Data are presented as median (interquartile range).

Results: Elderly patients presented decreased clearance (2.1 mL·kg⁻¹·min⁻¹ [1.6–2.5] vs 2.6 mL·kg⁻¹·min⁻¹ [2.2–3.3]) and increased AUC/dose (476.1 µg·min·mL⁻¹ [396.4–621.9] vs 386.5 µg·min·mL⁻¹ [308.5–459.9]) compared to adults. The concentrations required to achieve 50% of maximum neuromuscular block (EC50) were similar for adult (302.5 mg/L) and elderly (587.7 mg/L) patients.

Conclusion: Elderly patients showed increased AUC/dose and reduced total clearance compared to adult patients, probably due to the age-related reduced creatinine clearance. Differences in the PK-PD properties of ROC in elderly population are due to changes in drug disposition rather than to alterations in the sensitivity to the drug.

CLUSTERING OF RARE MEDICAL CONDITIONS BASED ON CLINICAL FEATURES WHICH DETERMINE APPLICABILITY OF INVESTIGATIVE DESIGNS AND METHODS TO THEIR STUDY

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Background: The EU legislation determines that market access to new drugs requires the same level of evidence regardless of whether they are intended for rare or highly prevalent diseases, but the reality is that regulators often have to make decisions on orphan medicinal products (OMP) based on limited amounts of evidence. Clinical development for new orphan drugs with a cost-efficient design and analysis, an optimal fit to needs of patients, and reliable and efficient to decision making is thus of utmost importance to patients, regulators, and the pharmaceutical industry. Within an international FP7 collaboration (ASTERIX project), we have established a systematic and clinically based clustering in order to propose designs and analyses for trials conducted in small populations.

Material and Methods: A dictionary of 76 characteristics that are relevant to study design was created, and 27 diverse rare medical conditions were represented.
conditions were analyzed qualitatively for each characteristic. A database was created for this purpose, and a Multiple Correspondence Analysis (MCA) was performed to guide a first proposal of clusters, which has been further validated with expert clinicians and regulators.

Results: A clustering of clinical conditions has been proposed based on MCA of 63 of the 76 potential characteristics. Relevant dimensions explaining data were identified, and 5 potential clusters of conditions were proposed based on common methodological approaches applicable to be conducted in drug development for each cluster.

A sixth group of disease conditions was identified through clinical validation of groups. The time course and prognosis of the condition, as well as the type of end points, were the clinical features that most influenced the clustering.

Conclusions: Six clusters of conditions to which potentially different clinical trial methodologies may be applied have been proposed. Further validation within the ASTERIX project of the usefulness of these clusters for methodological decision during drug development is ongoing.

**EFFECTIVENESS AND SAFETY OF ANTITHROMBOTIC DRUGS USED FOR STROKE PREVENTION IN NONVALVULAR ATRIAL FIBRILLATION (ESC-FA STUDY)**

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**Background:** Effectiveness and safety of vitamin K antagonists (VKAs), antiplatelets, or no treatment for stroke prevention in atrial fibrillation (AF) have not been assessed in our setting.

**Objectives:** To assess effectiveness and safety of VKAs, antiplatelets, and no treatment for stroke prevention in nonvalvar AF.

**Material and Methods:**

**Design:** Retrospective observational cohort study.

**Population:** Individuals ≥18 years old with nonvalvar AF diagnosed in primary care during 2007-2012.

**Data Sources:** SIDIAP database, anonymized clinical information from electronic clinical records in primary care of 5,800,000 people from Catalonia on sociodemographics, comorbidities, medical procedures, clinical parameters, laboratory data, and pharmacy invoicing data. Stroke and bleeding events were linked from hospital discharge database.

**Outcomes:** Stroke, hemorrhages, and all-cause mortality.

**Cohort Groups:** Defined by antithrombotics prescribed at baseline.

**Potential Confounders:** Sex, age, comorbidities, and treatments at baseline.

**Statistics:** Descriptive statistics and incidence rates of events per 1000 patients-year (PY) were obtained for each cohort. Time-to-event analysis was performed using multivariate cox proportional-hazards regression models, adjusting for baseline factors.

**Results:** We included 22,205 patients with a mean age of 72.8 years (SD 13.1); 51.4% were men. Antithrombics prescribed were VKAs in 40.8%, antiplatelets in 33.4% and no antithrombics in 25.8%.

**Incidence rates for stroke were 6.9, 12.2, and 8.9 per 1000 PY with VKAs, antiplatelets, and no antithrombics, respectively (adjusted HR: VKA vs no antithrombics, 0.63; 95% CI, 0.50-0.86; P = 0.002). Haemorrhage rates were 9.5, 8.7, and 7.1 per 1000 PY. Cerebral haemorrhage rates were 3.5, 2.3, and 1.9 per 1000 PY.**

**Nonsignificant differences were found. All-cause mortality rates were 35.5, 66.6, and 70.4 per 1000 PY (HR VKA, 0.62; 95% CI, 0.56-0.69; P < 0.001; HR antiplatelets, 0.83; 95% CI, 0.75-0.91; p < 0.001).**

**Conclusions:** VKAs were associated with lower stroke rates and antiplatelets with higher stroke rates than no antithrombotic use. Bleeding rates were not different in the three groups. Both VKA and antiplatelets were associated with lower mortality rates than no treatment.

**GENERATION OF EFFICACY DATA TO SUPPORT ROUTINE CLINICAL PRACTICE: USE OF CLONIDINE AS ADJUNCTIVE TO ANESTHESIA TO REDUCE SURGICAL FIELD BLEEDING IN ENDOSCOPIC NASO-SINUSAL SURGERY**

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**Background:** The use of adjuvant hypotensive drugs during anaesthesia might reduce bleeding and thus reduce risks during surgery. As intense bleeding during functional endoscopic naso-sinusal surgery (FESS) hinders the visualization of the surgical field, some anesthetists use them in clinical practice despite the lack of objective evidence on the efficacy and safety of such approach. In our hospital, surgeons contacted the Clinical Pharmacology Unit for methodological and logistic support to generate such evidence.

**Methods:** A first observational study was designed that compared intraoperative bleeding in routine clinical practice, comparing patients receiving a clonidine-based anesthetic regimen with those receiving fentanyl or remifentanil-based regimes. Based on the results of this case series, a randomized controlled observer-blind clinical trial was designed to compare clonidine and remifentanil based regimes in patients undergoing FESS.

**Results:** The observational study described 37 subjects undergoing FESS and receiving clonidine (N: %) (11; 29.7) or opioid derivatives (26; 70.3). Intraoperative bleeding, measured by an ordinal 1 to 5 scale (Boezaart score) by the operating surgeon, was lower for patients receiving a clonidine-based anesthetic regimen with those receiving fentanyl or remifentanil-based basalins. Based on the results of this case series, a randomized controlled observer-blind clinical trial was designed to compare clonidine and remifentanil based regimes in patients undergoing FESS.

**Conclusions:** The use of clonidine reduces intense bleeding and improves visualization of anatomical structures during endoscopic naso-sinusal surgery.

**MANAGEMENT OF IATROGENICALLY INDUCED OPIOID DEPENDENCE**

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Introduction: Opioids are valuable analgesics, capable of providing pain relief and functional improvement also in chronic non-cancer-related pain (NCP) patients. However, recent data have shown that the increasing prescription of opioids is associated with a rise in aberrant drug-related behaviour. 

Methodology: A prospective study was performed with 70 NCP outpatients diagnosed with opioid iatrogenic DSMIV dependence and severe pain intensity. The study focused on analgesic efficacy, opioid withdrawal syndrome prevention, adverse side effects, functional status, and aberrant drug-related behaviour. We design a contractual agreement on opioid therapy, including goals, side effects, and criteria to finish the opioid therapy. Genotyping of the OPRM1, COMT (rs4680), and ABCB (rs1045642) genes was performed.

Results: Results from 73% (50 of 70) of the patients are presented. After a structured and progressive opioid conversion to buprenorphine/tramadol, a significant reduction of 47% of the total daily dose (TDD) with no withdrawal symptoms (OWS) reduction of 9 points was achieved, maintaining a moderate relief and pain intensity score. Quality of life tends to improve, as do the number of adverse reactions reported by the patients throughout the visits. OPRM and COMT gene variant distribution but ABCB variants were more prevalent (9% C/C, 65% C/T, 26% T/T) vs general population distribution (21% C/C, 49% C/T, 25% T/T). Psychosocial risk was associated to a high prevalence of opioid iatrogenic dependence.

Conclusions: The indication for the prescription of opioids must be very carefully weighed in the presence of any risk factors. In these cases the integration into a multimodal, interdisciplinary therapy program is mandatory.

β2-ADRENERGIC RECEPTOR FUNCTIONALITY AND GENOTYPE IN TWO DIFFERENT MODELS OF CHRONIC INFLAMMATORY DISEASES: LIVER CIRRHOSIS AND OSTEOARTHRITIS

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Background: This study was designed to investigate the contribution of polymorphic β2 adrenoceptors (b2AR) to the proinflammatory effects of the sympathetic nervous system in two models of chronic inflammatory disease: liver cirrhosis (LC) and osteoarthritis (OA). The b2AR gene contains three single-nucleotide polymorphisms (SNPs) at amino acid positions 16, 27, and 164. Our aim was to study the potential influence of genotype of lymphocytes b2AR functionality in LC and OA development/progression.

Methods: We compared 52 cirrhotic patients with esophagitis varices and portal hypertension (hepatic venous pressure gradient [HVPG] 13 ± 4 mm Hg, CHILD 7 ± 2, and MELD 11 ± 4 scores), 32 OA (84% Kellogg-Lawrence [KL] severity 4 grade, 14% knee replacement joint), and 26 healthy volunteers as controls. Mononuclear cells were isolated from the whole blood. Basal and stimulated intracellular cAMP levels (isoproterenol stimulus from 10−3 to 10−12) and b2AR allelic variants (Arg16Gly, rs1042713; Gln27Glu, rs1042714; Thr164Ile, rs1800888) were determined.

Results: b2AR functionality was significantly decreased in LC and OA vs control (14 ± 15.3 pmol/mL, 38 ± 21 pmol/mL vs 90 ± 66 pmol/mL at 10−3 stimulus, respectively, P < 0.05). This decreased b2AR functionality was similar in LC patients: (i) in primary or secondary prophylaxis (15 ± 19 and 14 ± 13 pmol/mL, respectively) and (ii) in responder or non-responder to propranolol during HVPG (14 ± 16 and 14 ± 15 pmol/mL, respectively). The prevalence of different genotypes did not differ between patients stratified according to any clinical variable. In cirrhotic patients, the decreased in b2AR functionality was the same for all the studied allelic variants (naïve vs SNP, 15 ± 17 vs 13 ± 16 pmol/mL).

Conclusions: In patients with cirrhosis and portal hypertension, the functionality of b2AR is significantly decreased. This change is not related to b2AR allelic variants.

GENE EXPRESSION OF ANAESTHETIC AND ANALGESIC DRUG TARGETS IN BREAST TUMOURS PREDICTS METASTASIS: RELEVANCE TO PERSONALIZED, THERAPEUTIC INTERVENTION IN THE PERI-OPERATIVE PERIOD

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Introduction: Mortality associated with breast cancer is due, invariably, to the burden of metastasis. Virtually all patients with breast cancer undergo surgery, which may result in release of tumor cells into the bloodstream. Thus, perioperative factors, including drugs, are important in minimizing metastatic risk during tumor resection. However, retrospective clinical trials suggest that combined volatile general anesthesia and opioid analgesia, which is routinely used during cancer surgery, may promote metastasis. The current study investigated a pharmacogenetic basis for this phenomenon.

Methods: The publically accessible transcriptomic database, Breastmark, was interrogated. It currently employs 26 breast cancer genechip data sets (~17,000 genes in ~4738 samples). Gene expression levels were dichotomized on the basis of median, high, and/or low stratification, and a global pooled survival analysis was performed for distant disease-free survival (metastasis) and overall survival. Kaplan-Meier estimates and the log-rank P value indicated differences in survival, with values less than 0.05 considered significant. Cox regression analysis was used to calculate hazard ratios.

Results: Bioinformatic analysis revealed that patients whose breast tumors overexpress mu and delta opioid receptors have a shorter disease-free survival and shorter overall survival than those with low expression of these analgesic drug targets. Importantly, these are not established oncogenes, and no such effect is seen for kappa opioid receptors. Furthermore, low expression of the glycine β-receptor was strongly associated with metastasis. This receptor is a key target for volatile anesthetic agents, such as sevoflurane.

Conclusions: The data presented here suggest that the gene expression profile of breast tumors determines the therapeutic response to anesthetics and analgesics. Thus, an opportunity exists to specifically address the prometastatic changes occurring in the critical, perioperative period via personalized, therapeutic intervention. It may be possible to pharmacogenetically stratify patients who would most benefit from alternative anesthetic techniques that avoid volatile anesthetic drugs and opioids during tumor resection.
The battery consisted of tests eliciting cutaneous electrical mechanical and thermal (contact heat and cold pressor) pain and included a UVB model, the thermal grill illusion, and a paradigm of conditioned pain modulation (CPM). Subjects were administered either (part I) a 30-minute intravenous fentanyl 50 µg/kg, phenytoin 300 mg, (S)-ketamine 10 mg, or placebo (NaCl 0.9%) or (part II) a single oral dose of imipramine 100 mg, pregabalin 300 mg, ibuprofen 600 mg, or placebo. Pain test measurements were performed at baseline and up to 10 hours post-dose. End points were analysed using a mixed model analysis of variance.

Following ethics committee approval, 16 subjects (8 females) completed each part. The pain tolerance threshold (PTT) for electrical stimulation was increased (all P < 0.05) compared to placebo for (S)-ketamine (+10.1%), phenytoin (+8.5%), and pregabalin (+10.8%).

The PTT for mechanical pain was increased by pregabalin (+14.1%). The cold pressor PTT was increased by fentanyl (+17.1%) and pregabalin (+46.4%). Normal skin heat pain detection threshold (PDT) was increased by (S)-ketamine (+3.3%), fentanyl (+2.8%), and pregabalin (+4.1%). UVC treated skin PDT was increased by fentanyl (+2.6%) and ibuprofen (+4.0%). Thermal grill unpleasantness AUC decreased after administration of fentanyl (−34.3). No differences in CPM were observed. Adverse events reported were all mild or moderate in severity.

This study shows that the pain models are able to detect changes in pain thresholds after administration of different classes of analgesics in healthy subjects. The analgesic compounds all showed a unique profile in their effects on the pain tasks administered.

**CLINICAL PHARMACOLOGY CONSULTATION AND OUTCOMES ASSOCIATED WITH PREGNANCY EXPOSURE TO FDA-X DRUGS**

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**Background:** FDA pregnancy risk categories are insufficient to address the complexity of weighing the benefits of treatment against the possible risk of drug exposure to a category X medication. We conducted a study to assess outcomes and maternal characteristics associated with pregnancy exposure to FDA-X drugs, the strength of association between both the clinical pharmacologists’ risk assessment and the FDA risk categorization, and adverse pregnancy outcomes.

**Material and Methods:** We retrospectively reviewed records of 1669 patients consecutively referred to the clinical pharmacology outpatient clinic for pregnancy-related drug exposures (2000–2013). Of 230 women taking an FDA-X categorized drug during the first or second trimester of pregnancy, documented outcomes were available for 128 women. Clinical pharmacologists’ risk assessments were reviewed in relation to FDA drug categorization and available pregnancy outcomes.

**Results:** In pregnancies with available outcomes, the most frequently FDA-X prescribed drugs were oral contraceptives (53%), followed by paroxetine (21%), medroxyprogesterone (8%), retinoids (7%), warfarin (4%), methotrexate, statins, ribavirin, ulipristal-acetate, and radioactive iodine. The exposure occurred in most women during the 1st trimester of pregnancy (88%). Normal fetal outcomes were reported in 93/128 (73%) pregnancies, spontaneous abortions in 9/128 (7%), artificial abortions in 19/128 (15%), and malformations in 4/92 (3%) pregnancies. The drugs involved in reported congenital malformations were in all cases oral contraceptives and medroxyprogesterone. Clinical pharmacologists’ risk estimation was in agreement with the FDA risk categorization system in only 18% of consulted women with high risk exposure. Clinical pharmacologists’ risk assessment confirming high risk drug exposure had a better positive predictive value for adverse pregnancy outcomes than the FDA X categorization (54% vs 20%, respectively).
Morphine Increases Ticagrelor Concentrations but Not Its Effects

1. Conclusions: Additional evaluation beyond the FDA drug classification is essential, and clinical pharmacologists are ideally placed to consult on how to proceed with pregnancy following drug exposure to high risk drugs.

2. POPULATION PHARMACOKINETICS OF SUBCUTANEOUS AND INTRADERMAL GLUCAGON IN PATIENTS WITH TYPE 1 DIABETES

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Background: The closed-loop control system for type 1 diabetes utilizes frequent measurements of blood glucose concentrations and delivery of both an insulin analog and glucagon to achieve automated glucose control. This study aimed to characterize the population pharmacokinetics (PK) of glucagon administered by subcutaneous or intradermal route to facilitate the selection of a desired route of administration.

Methods: This study included 14 patients ≥18 years with type 1 diabetes duration ≥1 year prior to enrollment. Each patient was randomized to receive 50 µg glucagon by 1 route and was crossed over to the other route for 2 repeated visits. Population PK models describing glucagon administered by subcutaneous or intradermal route were developed separately in NONMEM 7.3.

Results: A 2-compartment model with a transit compartment absorption model was selected for subcutaneous glucagon, while a 2-compartment model with first-order absorption was chosen for intradermal glucagon. The population mean (±CV%) for clearance (CL), absorption rate constant (Ka), and central volume of distribution (Vc) of subcutaneous glucagon were 214 L/hr (36.2%), 3.42 hr−1 (26.6%), and 29.9 L (76.4%), respectively, scaled by (body weight/median 75.4 kg) to the exponent of 1.78 on CL. For intradermal glucagon, the population mean (CV%) of CL, Ka, and Vc were 237 L/hr (45.4%), 3.52 hr−1 (24.8%), and 73.0 L (58.4%), respectively. Age, body size measures, and disease duration did not influence intradermal glucagon PK parameters within the range of covariates studied. The estimated terminal half-life was averagely 25 minutes for both routes.

Conclusion: The population PK models characterized well the PK profiles of glucagon administered by subcutaneous and intradermal routes in patients with type 1 diabetes. No clinically relevant covariates were identified as predictors of glucagon PK, with the exception of body weight on subcutaneous glucagon PK.

3. RISK OF HOSPITAL ADMISSION FOR LIVER INJURY IN USERS OF NSAIDS AND NON-OVERDOSE PARACETAMOL (EPHIMAP)

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Background: The SALT study concluded similar per-user risk of acute liver failure leading to liver transplantation (ALFT) between NSAIDs and a 3- to 4-fold higher rate of ALFT in non-overdose paracetamol (NOP) users.

Objectives: To identify the risks of hospital admission for acute liver injury (ALI) associated with NSAIDs and NOP.

Methods: Case-population study in 1978 sample of the French population health care database. Cases of ALI were identified in hospital discharge summaries with ICD-10 codes K71.1, 71.2, 71.6, 71.9 and 72.0 from 01/01/2009 to 31/12/2013 (5 y). Exposure was NSAID or paracetamol dispensation resulting in exposure within 30 days before admission. Population exposure was measured as number of patients using the drugs over the study timeframe as total number of DDD-dispensed and average number of DDD per user.

Results: A total of 75 cases were identified; 15 were exposed to NSAIDs and 27 to paracetamol (alone or combined with opiates). Event rates per million DDD ranged from 0.61 (0.17–1.36) for ketoprofen to 1.43 (0.04–7.97) for diclofenac combinations, 0.49 (0.28–0.81) for all NSAIDs combined, and 0.68 (0.44–1.00) for paracetamol. There was no association with average duration of treatment. Per patient risk ranged from 24 (8–57) for ibuprofen to 101 (3–562) for glucosamine per million users, 43 (24–71) for all NSAIDs combined, and 62 (40–91) for NOP. There was a relation between increasing average duration of treatment and increasing risk.

Conclusions: The risk profiles of NSAIDs and NOP concerning hospital admissions for ALI were similar and indicative of a type A (pharmacological or toxicological) reaction, in contrast with the ALFT, which had a pattern suggestive of type B (genetic or allergic) reactions. The 3-fold higher risk with paracetamol for ALFT was not found for ALI. Event rates for ALI were not predictive of risk of ALF. ALI and ALFT probably have different mechanisms and risks, even if one may be the prelude to the other.

HIGH DOSE FAVIPIRAVIR: FIRST EXPERIENCE IN A PATIENT WITH EBOLA

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Background: On October 2014, the first case of human-to-human transmission of Ebola virus (EBOV) outside Africa was admitted in our hospital. Patient received supportive treatment and experimental treatment with convalescent plasma and antiviral was considered. Favipiravir (Toyama-Chemical) is a RNA polymerase inhibitor approved in Japan for the treatment of influenza, but with no previous experience in human EBOV infected patients.

Methods: The rational for favipiravir dose and schedule was based on recent in vitro and in vivo data in mice (Oesterech, 2014) showing an EBOV-IC90: 17 μg/mL of total concentration. Similar viral loads. Despite the high doses used, favipiravir was well tolerated, without adverse events clearly related to the drug. The patient fully recovered and was discharged on DOI-20.

Conclusion: The contribution of favipiravir to disease resolution is difficult to ascertain because the use of other therapies (convalescent plasma and supportive treatment) and the spontaneous evolution of the disease, which can all be related to the cure of our patient. However, considering the time to treatment initiation, the severity of the disease, and the high viral load, contribution of favipiravir to
the outcome of our patient must be considered and support its role as experimental therapy.

5

PRESCRIBING PATTERN FOR MALARIA IN INDIA: A NATIONWIDE SURVEY USING ADR COHORT EVENT MONITORING FORM

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Background: The present study aimed to assess the prescribing pattern of antimalarial drugs and their concordance with national malaria treatment guidelines, as an adjunct to ongoing cohort event monitoring.

Methods: A prospective, observational cohort study was carried out using modified WHO cohort event monitoring form. The study population comprised patients of all age, gender, and pregnancy status who were diagnosed with falciparum, vivax, or mixed infection and receiving treatment from any peripheral or community health center or government sector hospital in India.

Results: A total of 1050 ADR forms were received from 243 reporters from 23 districts in 9 states. Previous self-treatment was observed in 9.3% patients in the form of antibiotics (31) and antimalarials (37), primarily chloroquine. For analysis, the patients were divided into chloroquine primaquine (CQPQ, 64%) and artesunate-sulfadoxine-pyrimethamine (ACT, 29%) groups. Inappropriate antimalarials were prescribed in 7% patients (ie, chloroquine alone, primaquine alone, artemisinin monotherapy, and chloroquine with ACT). Patients in the CQPQ group were younger, smaller in height, and lighter in weight. There were more males in the CQPQ group. Significantly more patients in the ACT group had higher total number of symptoms as compared to patients in CQPQ group (P < 0.001). Fever disappeared significantly faster in the ACT group (median fever duration 2 days vs 3 days; P < 0.001). For the reported malaria episode, the national programme recommended dose and duration of treatment was observed in 46% and 59% patients, respectively.

Conclusion: With increasing resistance and drying pipeline of drugs for malaria, high prevalence of inappropriate prescribing observed in the study is unacceptable and requires stringent monitoring.

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PHARMACOKINETICS OF ATOMOXETINE IN PLASMA AND ORAL FLUID IN PEDIATRIC PATIENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER

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Introduction: Atomoxetine (ATX) is the first non-psycho-stimulant drug indicated for the treatment of attention-deficit-hyperactivity disorder (ADHD) in pediatric patients as an alternative to methylphenidate. The aim of this study was to describe the pharmacokinetic profile of ATX in oral fluid in comparison to plasma in paediatric patients with ADHD.

Material and Methods: The protocol was approved by the local research committee. Child’s parent or legal representative signed an informed consent (with assent) before inclusion. Participants were 5 children (2 girls and 3 boys, mean age: 8 years) and 6 adolescents (2 girls and 4 boys, mean age: 14 years) diagnosed as having ADHD and treated with different oral doses of ATX (60, 40, 35, 25, and 15 mg/d). Samples of blood and oral fluid were obtained before and post-dose (along 24 h). Concentrations of ATX and its metabolites 4-hydroxyatomoxetine (4-OH-ATX) and N-des-methylatomoxetine (N-des-ATX) were determined using liquid chromatography-tandem mass spectrometry in plasma and oral fluid.

Results: ATX, 4-OH-ATX, and N-des-ATX were found in plasma, but only ATX and 4-OH-ATX were detected in oral fluid samples. Mean ATX was found in plasma and oral fluid at a peak concentration of 589.6 and 19.72 ng/mL with a mean tmax of 1.4 and 2.7 h, respectively. For 4-OH-ATX detected in oral fluid, peak concentration was approximately half that in plasma (7.4 vs 13.8) with a mean tmax of 2.6 h in oral fluid and 2.1 h in plasma. A good correlation between ATX and 4-OH- TX in plasma and saliva was achieved.

Conclusion: The correlations between ATX and 4-OH-ATX concentrations in the 2 biological fluids indicate that oral fluid concentrations may be an alternative to plasma concentrations.

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NEW INSIGHTS ON THE PIOGLITAZONE RISK-BENEFIT RATIO IN EUROPEAN POPULATION

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Background: The benefit from antidiabetic drugs in T2DM lies on poorly powered clinical trials with high risk of bias and inconclusive meta-analysis results. While pioglitazone and metformin have been suggested to lower cardiovascular risk, some thiazolidinediones have been associated with an increase in myocardial infarction and heart failure. Evidence on increased bladder cancer risk led to withdrawal of pioglitazone in France. However, both EMA and FDA withheld from action arguing that risk-benefit ratio might still be favorable in a limited population that could not benefit from other treatments. We aimed to investigate whether risks from pioglitazone outweighed the benefit.

Material and Methods: We conducted a simulation study using a French Realistic Virtual Population of type 2 diabetic individuals to evaluate the efficacy and safety of pioglitazone. Risk scores allowed estimating risk of non-fatal MI, stroke, and bladder cancer. Virtual patients without bladder cancer received pioglitazone by 3 years (pioglitazone effect: OR = 0.84 for cardiovascular events; OR = 1.22 for bladder cancer). We computed the NNT and the number needed to harm (NNH) by sex and age categories.

Results: Pioglitazone might prevent 47 non-fatal MI and 20 strokes while it could provoke 2 bladder cancers for every 10,000 individuals treated over 3 years. The overall NNT was 148 and the NNH was 4758. The number of cardiovascular events prevented was greater than the number of bladder cancers whatever the subgroup studied, with a ratio ranging from 21 in men over 65 years to 539 in women under 45 years. The absolute benefit is higher in men, especially at higher baseline cardiovascular risk levels and ages.

Conclusions: Risk-benefit ratios allow identifying specific T2DM subgroups that could take more benefit than harm from pioglitazone. Evidence from RCT should use modeling approaches as additional support to decide about the relevance of treatments applied on a given population structure.
CLINICAL PHARMACOLOGY EDUCATION IN EUROPE: A TIME TO ACT

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Background: Core competencies in clinical pharmacology (CP) education are well established but poorly harmonized within European national training programs, thus limiting cross-border career opportunities for young postgraduates. Opportunities for career development in CP differ to some extent in different countries in Europe, and much could be gained from international exchange of experiences and collaboration of clinical pharmacology trainees (CPT).

Material and Methods: A European Task Force, with CPT representatives from Spain, Netherlands, UK, Sweden, France, and Turkey, has been created to identify and address the main deficits of and priorities in CP education across Europe. Two courses of action have been delineated:

1. The creation of an online survey directed at CP trainees across Europe in order to examine the attitudes and experiences of trainees towards their training and identify key limitations.
2. A pre-EACPT Congress meeting to be organized, inviting CPTs from all Europe to attend. An open discussion will be promoted between CPTs and potential emerging solutions will be proposed.

Results: The following main topics will be discussed during the meeting:—The current status of CP training programs in Europe, focusing on the main concerns and challenges identified in the survey. A general discussion will be encouraged between CP in order to address potential solutions.

—Career development in CP: opportunities and challenges.

—The proposal of the creation of an international European Network of CPTs to foster cross-border collaboration and joint initiatives in CP education programs.

Conclusions: There is an urgent need to address the current limitations of CP education in a collaborative approach. A European network of CPTs will encourage and promote the integration of joint efforts within European countries. The creation of the network is expected to meet this task by fostering the connection and communication between European CPTs.

TEACHING OF PHARMACOLOGY, CLINICAL PHARMACOLOGY AND THERAPEUTICS IN SPANISH MEDICAL SCHOOLS. PRELIMINARY RESULTS

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Objectives: To describe the current structure of the pharmaceutical, clinical pharmacology, and therapeutics teaching in Spanish schools of medicine.

Methods: A questionnaire survey was distributed among the professor in charge for the subject of pharmacology at the Spanish schools of medicine. Results were tabulated and descriptive statistics was applied.

Results: Twenty-two (65%) of the 34 schools of medicine responded. All the schools had a course in basic pharmacology (BP) taught mainly in the 3rd course of the curricula (90.5%). The mean number of teaching hours received by the students was 69.2 hours (SD, 15 h; range, 45–96). The proportion of teaching hours by teacher's specialty extremely varied between the different schools: clinical pharmacologists (from 0% in 50% of the schools to 67.6% as a maximum), pharmacologist-physicians (from 0% in 36.4% of cases to 100%), and pharmacologists-pharmacists (from 0% in 45.5% of cases to 100%). A total of 90.5% of the schools had a formal course on clinical pharmacology (CP). However, therapeutics (T) was only included in 42% of cases under this subject. This course was mainly taught during the fifth course of the curricula (52.6%). The mean number of teaching hours received by the students was 46.1 hours (SD, 19 h; range, 14–84 h). The proportion of teaching hours by teacher's specialty extremely varied between the different schools: clinical pharmacologists (from 0% in 14.3% of the schools to 100%), pharmacologist-physicians (from 0% in 71.4% of cases to 100%), and pharmacologists-pharmacists (from 0% in 45.5% of cases to 30% as a maximum).

Conclusions: The teaching of BP is present in all the schools of medicine in Spain. However, there is a wide variety in the number of teaching hours of CP and of T as well as on the specialty of the teachers involved.

ASSESSING HUMAN PAPILLOMAVIRUS (HPV) VACCINATION UTILIZATION AND ACCESS TO CARE IN THE UNITED STATES: A CROSS SECTIONAL ANALYSIS USING THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES)

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Background: The human papillomavirus (HPV) currently affects 79 million people in the United States. HPV is associated with cervical, reproductive, and oropharyngeal cancers, and concordantly IARC identifies 13 HPV types as carcinogens. There are currently three Food and Drug Administration (FDA)-approved vaccines: Gardasil (2006), Cervarix (2009), and Gardasil 9 (2014). There is a notable gap in the receipt of this vaccination in comparison to other vaccines in the recommended schedule for young adults, resulting in a need to explore vaccine uptake and access.

Methods: The data are from the 2011 to 2012 National Health and Nutrition Examination Survey (NHANES) administered by the CDC. The data set variables include four relevant questionnaire sections (demographics, immunization, hospital utilization/access to care, and...
health insurance). The analysis plan includes use of descriptive statistics, χ², and Cochran-Mantel-Haenszel tests for analysis of between-groups differences and the use of logistic regression modeling for factors associated with vaccination.

Results: Nearly 14.81% of women acknowledged receiving the HPV vaccine, which translates to 15.9 million US women between the ages of 9 and 59 years. When surveying males, 3.45% were vaccinated and equate to 3.6 million men aged 9 to 59 years. The most frequent age at first dose was 12 to 13 years. In evaluating the doses received over the therapeutic duration, 19% received only 1 dose, 20% received 2 doses, and 61% of males and females vaccinated completed the 3 dose course. Of those vaccinated, the majority (88%) received Gardasil, whereas only 7.3% received Cervarix. Several analyses are planned to explore demographic, insurance, and access factors.

Conclusion: The data have implications for understanding patient adherence to the vaccine regimen and appropriate use of the vaccines in recommended age group. Nonadherence is a public health concern and has immunologic, cost, and health system implications.

Additional analyses plan to address potential barriers to vaccine receipt and explore potential health disparities.

DICLOFENAC/MISOPROSTOL DURING EARLY PREGNANCY AND THE RISK OF MISCARRIAGE – A DANISH NATIONWIDE COHORT STUDY

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Introduction: Misoprostol can be used in prevention of gastric ulcer in treatment with diclofenac and is used in rheumatic diseases. Since misoprostol causes contractions of the uterus, it can also be used to induce abortions when administrated vaginally. The aim of the study was to investigate if early pregnancy exposure to oral diclofenac/ misoprostol was associated with miscarriage.

Method: We conducted a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2011. All births were identified using the Medical Birth Registry, and all records of induced abortion and miscarriage were from the National Hospital Register. Data on drug use were from the National Prescription Register. Cox proportional hazard regression models were used to calculate the hazard of miscarriage in women exposed to diclofenac/misoprostol in early pregnancy.

Result: We identified 1,338,824 pregnancies (970,491 births, 142,147 miscarriages, 226,145 induced abortions). One hundred sixty-six were exposed to diclofenac/misoprostol in the early pregnancy of which 28.3% (47) ended up in a miscarriage compared to 10.6% among unexposed. The adjusted hazard ratio of having a miscarriage after exposure to diclofenac/misoprostol in the first trimester was 3.6 (95% CI, 2.6–4.9).

Conclusion: We found an increased risk of miscarriage after exposure to diclofenac/misoprostol during the early pregnancy. This should lead to increased caution when treating women of fertile age with diclofenac/misoprostol.

THE CONTRIBUTION OF A SIMPLE BIOASSAY IN EFFECTIVE THERAPEUTIC DRUG MONITORING OF POSACONAZOLE AND VORICONAZOLE

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Background: With the constantly growing incidence of invasive fungal infections, any failure of antifungal treatment is worrying. Azole antifungals present high variability of their plasma trough concentrations (Cmin), justifying their therapeutic drug monitoring (TDM).

Nevertheless, target concentrations of posaconazole (lower limit of 0.7 mg/L) and voriconazole (upper limit from 4 to 6 mg/L) are still a matter of debate. The authors aimed to develop a simple bioassay to determine the in vitro growth inhibition diameter (ID) and to correlate this ID with Cmin in patients treated with voriconazole or posaconazole.

Material and Methods: The bioassay determined the ID for Candida parapsilosis using a disk diffusion method. Standard curves were built for posaconazole and voriconazole in water and in 45% plasma. ID was determined in plasma from patients currently undergoing TDM for posaconazole (n = 73) or voriconazole (n = 90).

Results: In water or plasma spiked with antifungals and patient samples, cubic regression between ID and Cmin gave coefficient of determination values of 0.997, 0.999, and 0.819, respectively, for posaconazole and 0.996, 0.990, and 0.925, respectively, for voriconazole (P < 0.001 for each curve). Standard curves with or without plasma did not differ. For voriconazole, Cmin of 1 mg/L and 4.7 mg/L corresponded to 54% and 90% of maximal ID, respectively. For posaconazole, Cmin of 0.5 mg/L, 0.7 mg/L, and 1 mg/L corresponded to 26%, 40%, and 53% of maximal ID, respectively.

Conclusion: The proposed easy to use bioassay displays a good correlation with TDM. Moreover, bioassay could be helpful to define the most appropriate therapeutic concentration and to better characterize the antifungal therapeutic range. Last, it brings additional information to the interpretation of TDM in patients for whom Cmin alone is insufficient to adjust the antifungal dosage.

DO NEW CANCER DRUGS OFFER GOOD VALUE FOR MONEY? THE PERSPECTIVE OF ONCOLOGISTS, PAYERS, PATIENTS, AND GENERAL POPULATION

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Objective: To analyze oncologists, payers, patients, and general population’s views on the cost and value of new cancer treatments.

Methods: An electronic self-administered questionnaire was developed and randomly distributed to assess participants attitudes towards new cancer treatment outcomes and costs during reimbursement decisions. Among the questions asked were two hypothetical scenarios. First, participants were asked to indicate the minimum survival benefit that a new treatment, which cost €50,000 more than the standard therapy, should have to be funded by the Spanish National Health System (NHS). Second, participants were requested to state the highest costs to be afforded by the NHS for a medication increasing patient’s quality of life (QoL) twofold with no changes in survival. Responses were used to calculate incremental cost-effectiveness ratios (ICER).

Results: Fifty-three oncologists, 60 patients, 25 payers, and 50 individuals from general population answered the questionnaire. The mini-
Morphine Decreases Ticagrelor Concentrations But Not Its Effects

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Background: Growth hormone/insulin-like growth factor I (IGF-I) axis is being targeted for therapeutic development in diseases such as short stature, cancer, and metabolic disorders. The impact of IGF-I in cardiovascular disease remains controversial. We therefore studied whether IGF-I at admission for acute myocardial infarction (AMI) predicted death, recurrent AMI, and stroke over a 2-year follow-up.

Methods: Using data from the FAST-MI registry, we measured IGF-I among all the 1005 patients with AMI who participated in the serum databank. As IGF-I decreases with age, a standardized IGF-I score was calculated as previously described (IGF-I score = [log [IGF-I(µg/L)] + 0.00625 × age − 2.555]/0.104). Impact of IGF-I score (continuous and quartiles) on outcomes were compared using Cox proportional hazards regression models.

Results: During follow-up, 190 patients died or had a recurrent AMI or stroke. Patients in the lowest quartile of IGF-I were older and more frequently female and diabetic compared to patients in the other quartiles. After adjustment for known cardiovascular factors, an increase of 5 units of IGF-I score was associated with a 30% decrease of the risk of events during follow-up (adjusted HR = 0.70; 95% CI, 0.54–0.92; \( P = 0.0093 \)). Similarly, the lowest quartile of IGF-I was associated with an increased risk of events (adjusted HR = 1.52; 95% CI, 1.11–2.08; compared with others quartiles; \( P = 0.010 \)).

Conclusions: Low IGF-I score is associated with increased risk of all cause-death, recurrent MI, and stroke in AMI patients. Whether patients treated by IGF-I axis inhibitors have a specific clinical course after AMI would be worth studying.
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EPIDEMIOLOGICAL PROFILE OF BENZODIAZEPINE POISONINGS IN URUGUAY: RECEIVED CONSULTS AT THE NATIONAL POISONING INFORMATION CENTRE DURING 2010–2011

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Background: Since the introduction of benzodiazepines (BZDs) into medical practice during the 1960s, they have become one of the most widely prescribed drugs for anxiety and sleep disorders. Low risk perception among health practitioners and patients leads to an irrational use point of view in our population. The aim of this study was to quantify and irrational use of BZDs. Accidental and intentional drug poisoning are often due to BZDs (27–40% in international series). Our objective was to describe the pattern of acute poisoning cases involving BZD in Uruguay over the last years.

Material and Methods: Retrospective descriptive study of all acute BZD poisonings received and recorded by the National Poisoning Information Centre from 2010 to 2011.

Results: A total of 31,228 toxic agents were related with the registered poisoning consultations and 18,530 were medicines. BZDs represented 28.80% (7123) of the toxic agents and 38.40% (6769) of all the medicines involved. There were 21,452 poisoning consultations between 2010 and 2011. BZDs were attributed as the causal agent in 6186 (28.80%) of them. Most of them involve adults (4578, 74.30%) and occurred in female patients (4600, 74.30%). The intentional intake of BZD for suicide was the most common circumstance of poisoning (5235, 89.54%). Clonazepam, diazepam, and alprazolam and occurred in female patients (4600, 74.30%). The intentional intake of BZD for suicide was the most common circumstance of poisoning (5235, 89.54%). Clonazepam, diazepam, and alprazolam were the most commonly reported as the implied BZD. Sixty-eight (1.09%) BZD poisonings were classified as severe and only 5 of them were fatal.

Conclusions: National casuistic of BZD poisonings shows the main role of BZD in medicine’s poisonings. Most of the reported cases were nonserious, which supported the well-known safety profile of BZDs. This pathology should be approached from the consumption and irrational use point of view in our population.

HEPATIC CYTOLYSIS CONSIDERED FOSFOMYCIN/TROMETHAMINE RELATED: A CASE REPORT AND LITERATURE REVIEW

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Background: Fosfomycin/tromethamine is approved as single dose in the treatment of acute cystitis and recommended in the prophylactic treatment of recurrent cystitis. Although well-tolerated, cases of liver injury after long-term administration have been reported. This report describes a case of fosfomycin/tromethamine-induced hepatotoxicity after long-term administration and summarizes the available scientific data on fosfomycin and fosfomycin/tromethamine-associated hepatotoxicity cases.

Methods: Previously reported cases were identified using a search in PubMed (search terms: fosfomycin, fosfomycin/tromethamine, fosfomycin/trometamol, fosfomycin/tromethamine, hepatotoxicity, hepatic cytolysis) and in the French and American (FDA) pharmacovigilance databases.

Case Summary/Results: A 57-year-old woman was started on fosfomycin/tromethamine, one sachet every 6 days, for disabling recurrent cystitis. Prior to treatment initiation, her liver function tests were normal. Three years later, the occurrence of hepatic cytolysis motivated an extended exploration over 1 year. The discontinuation of fosfomycin/tromethamine finally resulted in the sustained normalization of liver enzymes within a few weeks. The literature search identified only 4 case reports of fosfomycin related hepatic disorders, while 40 and 57 cases of fosfomycin related hepatic disorders have been registered in the French and FDA pharmacovigilance databases. Overall, hepatic cytolysis seems more frequent than cholestasis. The reported delays between treatment introduction and liver enzymes increase vary from a few days to 5 months. The increase of liver enzymes can be mild to severe. Normalization of liver enzymes is usually reversible after therapy withdrawal, within one week to a few months.

Conclusions: Based on the “Roussel Uclaf Causality Assessment Method (RUCAM)” scale, in the case we report, fosfomycin/tromethamine was plausibly responsible for the hepatic cytolysis. The review of the literature and French and American cases suggest that liver injury is not a frequent side effect of fosfomycin. However, clinicians should be aware of this potential effect, and follow-up of long-term treated patients should be recommended.

BENZODIAZEPINES CONSUMPTION IN URUGUAY: A PUBLIC HEALTH CONCERN?

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Background: There are no data on the overall Uruguayan patterns of benzodiazepine use. The aim of this study was to quantify and evaluate benzodiazepines consumption in Uruguay between 2010 and 2012.

Material and Methods: A drug utilization study was performed to quantify current state of benzodiazepines consumption in our population. Drug utilization data refer to oral benzodiazepines dispensed by the pharmacy departments from the participating health institutions. The unit of measurement was the defined daily doses (DDD) per 1000 inhabitants per day (DHD). DHD of hypnotic and anxiolytic benzodiazepines and DHD from public and private health care coverage were compared. Results were described as absolute values and percentage of changes.

Results: The included sample represents the 62% of the Uruguayan population. Global DHD for 2010, 2011, and 2012 were 74.97, 75.17, and 71.14 (mean 73.76) DDD/1000 inhabitants/day, respectively. Alprazolam was the most consumed anxiolytic benzodiazepine (mean 25.09) and flunitrazepam was the most consumed hypnotic benzodiazepine (mean 18.69). If clonazepam is included, it becomes the most consumed benzodiazepine (mean 36.51) and global DHD increases up to 106.36, 110.86m and 113.61 (mean 110.28) DDD/1000 inhabitants/day, respectively. Clonazepam showed the higher consumption increase from 2010 to 2012 (35.29%), while the use of midazolam (–46.15%) and diazepam (–18.83%) decreased gradually. Public health institution was mainly responsible for the global consumption value, whereas private ones showed the highest increase during the evaluated period.

Conclusion: Uruguay showed high benzodiazepines consumption, similar to those reported by other countries, and it seems to be a public health concern. Alprazolam, diazepam, and flunitrazepam consumption were predominant and clonazepam use showed the highest increase. These are the first available benzodiazepines consumption data in our country and will be useful to perform future comparisons.

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THE EFFECTIVENESS, SAFETY AND COSTS OF ORPHAN DRUGS: AN EVIDENCE-BASED REVIEW

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Introduction: Several orphan drugs have been approved by the European Medicines Agency (EMA) over the past 2 decades. However, the prices of the drugs are expensive, and in some instances, the evidence for effectiveness is not convincing at the time of regulatory approval. Our objective was to evaluate the clinical effectiveness of orphan drugs which have been granted marketing licenses in Europe, determine the annual costs of each drug, compare the costs of branded orphan drugs against their generic equivalents, and explore any relationships between orphan disease prevalence and annual costs.

Methods: We searched the EMA database to identify orphan drugs granted marketing authorization up till April, 2014. Electronic searches were also conducted in PubMed, Embase, and Google Scholar to assess data on effectiveness, safety, and annual costs. Two reviewers independently evaluated the levels and quality of evidence and extracted data.

Results: We identified 74 orphan drugs, with 54 (73%) demonstrating moderate quality of evidence. Eighty-five percent showed significant clinical effects, but serious adverse events were reported in 86.5%. Their annual costs were between £726 and £378,000. There was a significant relationship between disease prevalence and annual costs ($P = 0.01$); this was largely due to the influence of the ultra-orphan diseases. We could not determine whether the balance between effectiveness and safety influenced annual costs. For 10 drugs where generic alternatives were available, the branded drugs were 1.4 to 82,000 times more expensive.

Conclusion: The available evidence suggests that there is inconsistency in the quality of evidence of approved orphan drugs, and there is no clear mechanism for determining their prices. In some cases far cheaper generic agents appear to be available. A more robust, transparent, and standard mechanism for determining annual costs is imperative.

GENERIC MEDICATION IN CHRONIC MUSCULOSKELETAL PAIN PATIENTS: AN ISSUE OF REPRESENTATIONS, TRUTH, AND EXPERIENCE

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Background: Chronic pain patients are frequently confronted with the issue of the prescription and/or substitution of original formulations with generic medications. Information regarding generic substitution is not univocal and room for the expression of contradictory opinions is ample. Along with an ever stronger advocacy for the use of generics, various sources of information report concerns regarding substitution.

Methods: Semistructured interviews explored patients’ representations (N = 25) regarding generics in patients suffering from chronic musculoskeletal pain. Patients’ interviews were transcribed and submitted to content analysis.

Results: Patients’ representations suggest that they might be confident in taking a generic medication: when a) he/she has an understanding of generics as resulting from the loss of original trading license; b) the generic medication is prescribed by the physician (supported by the pharmacist); c) each prescription is discussed, that is, the patient is prescribed the generic version of a given medication and not a generic medication; and d) the prescription is individualized. Information and trust are central considerations; the concept of “copy” was frequently mentioned to define generics, from an identical to a forged medication. Using a copy might not be questioned when the medications are perceived as being identical and efficient; however, it might become a problem in cases in which the copy indicates that the patient thinks he/she is receiving a second-choice medication.

Conclusion: Our results provide support for generic medication raising many concerns and much lesser perceived need. For patients, economic arguments per se are not sufficient to justify substitution, and may even raise issues calling upon cognitive dissonance. In this context, positive cues require further attention and negative cues need be de-emphasized - in particular lower price as an indication of lower quality, and generic status as contradictory with advocating individualization of medication.

CLINICAL OUTCOMES OF IMPLEMENTING EVIDENCE-BASED PRACTICE ON VENOUS THROMBOEMBOLISM PREVENTION FOR CANCER PATIENTS IN QATAR, A RETROSPECTIVE STUDY

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Background: Venous Thromboembolism (VTE) disease is a serious condition; approximately 20% of VTE cases occur in cancer patients and it is a significant cause of morbidity and mortality especially during the first year among all types and stages of cancer [1,2]. Most hospitalized patients with cancer require thromboprophylaxis throughout hospitalization [3]. Breast cancer is considered a very high risk for VTE due to different factors (malignancy, surgery, chemotherapy, hormonal therapy, hospitalization, and female gender) [4].

Objectives: This study focuses on the assessment of the clinical outcome in preventing VTE amongst cancer population in Qatar after implementation of evidence based thromboprophylaxis guidelines.

Methods: A retrospective study was conducted to evaluate the incidence of DVT by evaluating Doppler ultrasound, database for 364 cases of inpatients and outpatients over 24 months (January 2011–December 2012), findings were analyzed by a hematologist to identify patients who developed DVT due to current or previous admission (within 30 d). The relationship between the incidence of developing VTE overtime and the compliance to VTE prevention protocol were established.

Results: The study showed that the increase in the overall compliance to VTE prophylaxis protocol introduced to inpatients population (n = 2595) increased from 61.5% to 84.6% (P = 0.0297), led to decreased DVT incidence by 66.4% (P = 0.0145). Fifty percent of cancer cases developed DVT were breast cancer patients (n = 24), 92% of them were outpatients.

Conclusion: Appropriate thromboprophylaxis could considerably improve the incidence of DVT in cancer patients, breast cancer patients are very high risk for VTE, which raises the importance of implementing thromboprophylaxis in both hospital and ambulatory settings.

Reference
The document contains scientific research articles on various topics such as pharmacology, cardiovascular disease, and optical coherence tomography. The articles discuss the use of new technologies and techniques in medical research and treatment. The text is in English and covers topics including the effects of antidepressants on gliogenesis, the pharmacodynamics of CYP3A and non-CYP3A-dependent statins, and the clinical utility of optical coherence tomography in the evaluation of cardiovascular risk patients. The articles mention conditions like major depression, chronic kidney disease, and cardiovascular disease, and discuss the implications of these conditions on patient outcomes and treatment strategies.
Rosuvastatin, indicating pharmacodynamic effect was not related with the CYP3A4.

**THE IMPACT OF CYP4F2 POLYMORPHISM ON THE SAFETY PROFILE AND REGIME DOSING OF PHENINDION IN PATIENTS WITH VALVULAR ATRIAL FIBRILLATION**

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**Introduction:** In the reason of FDA prohibition in using of “new” oral anticoagulants, vitamin K antagonists have become uncontested drugs to the patients with valvular atrial fibrillation. The derivatives of indandion, as fluindione and phenindion, can be used in the case of intolerance and coumarins resistance. The role of the main genetic factors in individual sensitivity to coumarin’s anticoagulants is well known. But the influence of gen’s polymorphism CYP4F2 on the safety profile and regime dosing of phenindion haven’t been studied yet.

**Materials and Methods:** Forty-two patients (20 male and 22 female), aged 27 to 80 years, valvar AF, were studied. The using of coumarin anticoagulants was impossible in all of them. All patients received phenindion in the dose of 30 to 130 mg daily with a target international normalized ratio (INR) of 2.0 to 3.0. Genotyping for polymorphism’s marker V433M gen CYP4F2 were designed using the PCR and RFLP (restriction fragment length polymorphism). Statistics were performed by Fisher’s exact tests.

**Results:** Genotype CC was found in 26 patients (62%), genotype CT in 16 patients (38%), genotype TT wasn’t found at all. In the CC group (n = 26) high dose of phenindion (>90 mg) was needed only in 2 patients (8%), versus 6 patients (37.5%) in the CT group (n = 16). P = 0.04 (significant statistically). In the CC group bleedings were found in 4 patients (9%) and in 1 patient (7%) in CT group, P = 0.63. In the CC group INR increased >3.0 in 3 patients (8%). In the CT group nobody had INR >3.0 (P = 0.5).

**Conclusion:** The patients with genotype CT (polymorphism V433M gen CYP4F2) are usually needed in high dose of phenindion (>90 mg) to achieve target INR of 2.0 to 3.0. There was not found out the influence of gen CYP4F2 polymorphism on the developing of bleedings and excessive hypocoagulation.

**ASSOCIATION OF IMMUNE RESPONSE PARAMETERS WITH EARLY VIROLOGICAL RESPONSE IN HCV PATIENTS TREATED WITH PEGYLATED CONSENSUS INTERFERON**

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**Background or Introduction:** The aim of the study was to test antiviral activity of pegylated consensus interferon (PEG-CIFN) in adults with HCV infection and to determine the relationship between immune response markers and virological response.

**Material and Methods:** Thirty naive HCV patients were injected subcutaneously with PEG-CIFN once per week for 12 weeks. Serum HCV RNA levels was measured by a COBAS Taqman HCV Test system. Serum cytokines and chemokines, IL-12p40, IL-12p70, MIG, MIP, IP-10, MCP-1 and TNF were analyzed by Lumix® assays at baseline, 4, 8 and 12 weeks. Fibrosis stages were determined by fibroscan.

**Results:** The HCV RNA levels in the serum were markedly decreased after therapy. Thirty percent of HCV patients had rapid virological responses (RVR), and 66.7% (16/30) had early virologic responses. The mean log HCV RNA values were 6.43, 3.17, 1.03, and 1.0 IU/mL at 0, 4, 8, and 12 weeks, respectively, in the EVR group and 6.65, 4.21, 2.98, and 3.1 IU/mL, respectively, in the non-EVR group. HCV RNA values were less at the EVR group compared to non-EVR group after treatment, P < 0.05. IL-4, IP-10, and MIP-1b levels were lower, and G-CSF levels were higher in EVR group than in the non-EVR group (P < 0.05). Fibrosis stage did not change after treatment. Correlation coefficient of HCV RNA values with IP-10 and MIP-1b were 0.82 and 0.81, respectively, in the EVR group (P < 0.05). IP-10 and MIP-1b levels were associated with aminotransferase (ALT and AST) levels. Baseline IP-10 levels less than 435 pg/mL predicted RVR at 4 weeks and less than 465 pg/mL predicted EVR at 12 weeks.

**Conclusions:** PEG-CIFN was well tolerated and effective at inhibiting HCV RNA. PEG-CIFN may increase or decrease levels of immune markers. IFN treatment is associated with changes in markers of immune activation in chronic HCV viral infections.

**RESVERATROL AND FENOFIBRATE AMELIORATE FRUCTOSE-INDUCED NASH IN RATS BY MODULATION OF LIVER AND ADIPOSE TISSUE EXPRESSION OF GENES**

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**Background:** The intake of high-fructose beverages has been increased. The present study evaluates the effect of a polyphenol (resveratrol), alone or in combination with fenofibrate, on fructose-induced metabolic abnormalities in rats. A number genes known to be critically involved in lipid metabolism was investigated. Understanding the molecular basis of a disease could shed light onto the beneficial therapeutic effects of drugs.

**Material and Methods:** Giving a fructose-enriched diet (HFD) to rats for 12 weeks was used as a model for inducing hepatic dyslipidemia and insulin resistance. Fenofibrate (FENO) (100 mg/kg), resveratrol (RES) (70 mg/kg) and combined treatment (FENO+RES) (half the doses) were given orally from the 9th week till the end of experimental period. Body weight, oral glucose tolerance test (OGTT), liver index, insulin resistance (HOMA), serum and liver triglycerides (TGs), oxidative stress (liver MDA, GSH and SOD), serum AST/ALT ratio and TNF-α were measured. Additionally, hepatic gene expression of suppressor of cytokine signaling -3 (SOCS-3), sterol regulatory element binding protein-1c (SREBP-1c), fatty acid synthase (FAS), malonyl CoA decarboxylase (MCD), transforming growth factor-β1 (TGF-β1) and adipose tissue gene expression of leptin and adiponectin was evaluated.

**Results:** Rats fed HFD showed impairment of glucose tolerance, insulin resistance, oxidative stress, and dyslipidemia. As for gene expression, there was a change in favour of dyslipidemia and NASH development. Thus, in the liver, FAS, SOCS-3, SREBP-1c, and TGF-β1 were upregulated while MCD was downregulated. In adipose tissue, leptin and adiponectin genes were unbalanced. All treatment regiments showed effective reversal in the observed divergenses contributing to hepatic steatosis and insulin resistance.
THE FREQUENCY OF CYP2C19 GENETIC POLYMORPHISMS IN RUSSIAN PATIENTS WITH PEPTIC ULCER TREATED WITH PROTON PUMP INHIBITORS

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Introduction: Proton pump inhibitors, which are widely used as acid-inhibitory agents for the treatment of peptic ulcer, are mainly metabolized by 2C19 isoenzyme of cytochrome P450 (CYP2C19). CYP2C19 has genetic polymorphisms, associated with extensive, poor, intermediate or ultrarapid metabolism of proton pump inhibitors. Genetic polymorphism of CYP2C19 could be of clinical concern in the treatment of peptic ulcer with proton pump inhibitors.

The aim of the study – to investigate the frequencies of CYP2C19*2, CYP2C19*3 and CYP2C19*17 alleles and genotypes in Russian patients with peptic ulcer.

Materials and Methods: The study involved 971 patients with peptic ulcer from the European part of Russia (Moscow), 428 male (44%) and 543 female (56%). The mean age was 44.6 ± 11.9 years (range 15–88 y). DNA isolated from blood samples was used for the analysis of CYP2C19 genetic polymorphisms (CYP2C19*2, *3, *17 alleles) by real-time polymerase chain reaction.

Results: Regarding CYP2C19 genotype, 317 patients (32.65%) out of 971 were CYP2C19*1/*1 carriers classified as extensive metabolizers. Three hundred eighty-six (39.75%) with CYP2C19*2/*1 or CYP2C19*17/*17 genotype were ultrarapid metabolizers. Two hundred fifty-one people (25.83%) were intermediate metabolizers with CYP2C19*2/*2, CYP2C19*2/*17 or CYP2C19*1/*3, CYP2C19*3/*17 genotypes. Seventeen patients (1.75%) with CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3 genotypes were poor metabolizers. The allele frequencies were the following: CYP2C19*1 – 0.652, CYP2C19*2 – 0.140, CYP2C19*3 – 0.006, CYP2C19*17 – 0.274.

Conclusion: There is a high frequency of CYP2C19 genotypes associated with modified response on proton pump inhibitors in Russian patients with peptic ulcer. Genotyping for CYP2C19 polymorphisms is suggested to be a useful tool for personalized dosing of proton pump inhibitors.

FENOFIBRATE IMPROVES THE IMPAIRED ENDOTHELIAL PROGENITOR CELL FUNCTION THROUGH DEREGULATING NALP3 INFLAMMASOME ACTIVITY IN DIABETIC MICE

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Background and Purpose: Impaired wound healing is a common complication of diabetes and is the leading cause of lower extremity amputation. Treatment with fenofibrate was associated with a lower risk of amputations, particularly minor amputations without known large-vessel disease, probably through nonlipid mechanisms. The current study aimed to test our hypothesis that fenofibrate improves angiogenesis and restore endothelial progenitor cell (EPC) function via deregulating NALP3 inflammasome activity in streptozotocin (STZ)-induced diabetic mice.

Material and Methods: Male C57BL/6 mice were randomly divided into 3 groups: control, STZ-induced diabetic group and fenofibrate treated diabetic group (100 mg/kg/d intraperitoneally for 2 wk). Wound closure was assessed by wound area and CD31 positive capillaries. Both the migration and tube formation capacities of EPCs were measured. Intracellular NO and O2- levels were determined. Activity of NALP3 inflammasome in EPCs was assessed by measuring NALP3, ASC, caspase-1 and TNXIP expression.

Results: Compared with the untreated diabetic mice, wound closure and capillary densities were significantly increased in fenofibrate treated group. Fenofibrate treatment restored EPC functions, and increased NO production, decreased O2- level in EPCs of diabetic mice. Furthermore, fenofibrate deregulated the activity of NALP3 inflammasome by reducing NALP3, ASC, caspase-1, TXNIP expression in EPCs of diabetic mice. In vitro, fenofibrate improved high glucose induced EPCs dysfunction and deregulated NALP3 inflammasome activity.

Conclusion: Fenofibrate could accelerate wound healing in diabetic mice, which at least in part was mediated by improving the impaired EPCs function through deregulating NALP3 inflammasome activity.

SAFE USE OF NSAIDS AND RAS-INHIBITORS IN AGOGO, GHANA

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Background: Preventable adverse events of medication are an important cause of hospital admissions in the developed world. NSAIDs and renin-angiotensin system (RAS-) inhibitors are drug groups which are frequently involved in these hospital admissions. Proper biochemical monitoring or application of gastroprotective agents (GPA) may prevent these adverse events. NSAIDs and RAS-inhibitors are also often used in Ghana. The purpose of this study is to assess whether biochemical monitoring in patients on RAS-inhibitors, and co-administration of gastroprotective medication in patients on NSAIDs, is done properly in Ghana.

Material and Methods: A retrospective cross-sectional study of 114 out- and inpatients who are on NSAIDs was carried out. The risk for gastrointestinal side effects and the frequency of co-administration of GPA was determined. A retrospective cross-sectional study of 301 outpatients who are on RAS-inhibitors was carried out. The risk for renal dysfunction and the frequencies of serum creatinine and potassium monitoring within one month after initiation of therapy were determined.

Results: Co-administration of GPA was done in 1.8% of all patients on NSAIDs. Serum creatinine and potassium monitoring within one month after initiation of treatment with RAS-inhibitors were performed in 6.3% and 3.7%, respectively. Risk factors were neither associated with prescription of a GPA in patients on NSAIDs, nor in performing biochemical monitoring in patients on RAS-inhibitors.
Clinical Therapeutics

Conclusions: Biochemical monitoring in patients on RAS-inhibitors and use of GPs in patients on NSAIDs is poorly performed in Ghana. Improving the already existing Ghanian guidelines and encouraging their widespread use among prescribers should be pursued.

References

EFFECT OF AMOXICILLIN/CLAVULANATE ON THE PHARMACOKINETICS OF VALPROIC ACID
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Background: Valproic acid is used as a first line drug for generalized tonic clonic seizures, absence seizures, myoclonic seizures, and tonic and atonic seizures. A major metabolite of valproic acid is the glucuronide conjugate which is hydrolyzed by β-glucuronidase and undergoes enterohepatic circulation. Of note, the administration of amoxicillin/clavulanate led to a decrease of hemoglobin in the luminal perfusate, which was collected every 15 min. Clopidogrel (10–100 mg/kg), ticlodipine (10–30 mg/kg), or cilostazol (3–30 mg/kg) was given p.o. 24 hours or 90 minutes before the perfusion of asaclofen, respectively.

Methods: This was an open-label, 2-period, 1-sequence study in 16 subjects. Amoxicillin/clavulanate 500/125 mg were administered 3 times daily for 7 days, and then the single dose of valproic acid was administered (treatment V). In period 2, multiple doses of amoxicillin/clavulanate led to a decrease of systemic exposure and peak concentration of valproic acid.

Conclusions: The results of this study suggest that amoxicillin/clavulanate and valproic acid may interact significantly, leading to a decrease in valproic acid exposure. Therefore, caution should be exercised when administering these drugs together.

INVESTIGATION ON CIRCADIAN AND AGE-DEPENDENT VARIATIONS IN CYCLOSPORINE (CSA) CONCENTRATION DISTRIBUTIONS IN LIVER TRANSPLANT PATIENTS
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A comparative population pharmacokinetic analysis was performed on CSA concentrations, “as withdrawn” in clinical setting, from a learning group of liver transplant patients. Twenty patients (8 adults and 12 children) who were on Neoral® post-orthotopic liver transplantation over 2004 to 2009 were studied. All patients received Neoral® twice daily orally at 08:00 AM and at 08:00 PM. Whole blood CsA concentrations were measured by FPIA (Abbott Diagnostics). C0 drug concentrations were recorded in morning (COAM) and in evening before each dosing (C0PM) and C2 concentrations - in morning and in evening 2 hours post-dosing (C2AM and C2PM). A total of 323 CsA C0 in children group and 242 C0 in adult group and a set of 117 CsA C2 in children group and a set of 133 C2 in adult group were analyzed. Population pharmacokinetic analysis was performed with dose normalized to 1mg/kg cyclosporine concentrations in order to avoid body weight (BW) differences between the 2 age groups. No circadian differences in drug concentrations in both populations were observed. All drug concentration distributions were skewed to the right. The measures of central tendency showed statistically significant higher estimates for adult group. Normalized CsA C0 at Day 2 after liver transplantation in adult patients correlated significantly with measured Scr levels (r = 0.62, P = 0.031). The findings can’t be explained by body weight between group’s differences since normalized cyclosporine concentrations were used.

COMPARATIVE EFFECTS OF THE ANTI-PLATELET DRUGS, CLOPIDOGREL, TICLOPIDINE, AND CILOSTAZOL, ON ASPIRIN-INDUCED GASTRIC BLEEDING AND DAMAGE IN RATS
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Background: We recently reported that an antiplatelet drug clopidogrel, the P2Y12 receptor antagonist, increased gastric bleeding induced by intraluminal perfusion with acidified low dose ASA in the rat stomach. In the present study, we compared the effects of frequently used anti-platelet drugs, such as clopidogrel, ticlopidine, and cilostazol, on the gastric bleeding and ulcerogenic responses induced by intraluminal perfusion with 25 mM aspirin acidified with 25 mM HCl (acidified ASA) in rats.

Materials and Methods: The stomach was perfused with acidified ASA at a rate of 0.4 ml/min for 60 minutes under urethane anesthesia. Gastric bleeding was measured as the concentration of hemoglobin in the luminal perfusate, which was collected every 15 min. Clopidogrel (10–100 mg/kg), ticlodipine (10–30 mg/kg), or cilostazol (3–30 mg/kg) was given p.o. 24 hours or 90 minutes before the perfusion of acidified ASA, respectively.

Results: Perfusion of the stomach with acidified ASA alone led to slight bleeding and lesions in the stomach. The pretreatment with clopidogrel, even though it did not cause bleeding or damage by itself, dose-dependently increased the gastric bleeding and ulcerogenic responses induced by acidified ASA. Ticlodipine also aggravated the severity of damage by increasing gastric bleeding, and the effects of ticlodipine at 300 mg/kg were equivalent to those of clopidogrel at 100 mg/kg. In contrast, cilostazol dose-dependently decreased gastric bleeding and damage in response to acidified ASA.

Conclusions: These results demonstrated that cilostazol and ticlodipine, P2Y12 receptor inhibitors, increased gastric bleeding and ulcerogenic responses to acidified ASA, to the same extent, while cilostazol, a phosphodiesterase III inhibitor, suppressed these responses. Therefore, cilostazol may be safely used in dual anti-platelet therapy combined with ASA, without increasing the risk of gastric bleeding.
Irrational use of medicines is a major problem worldwide. One of most important factors is the low compliance of patients to prescribed drugs (WHO, 2003). One of the most commonly advocated ways to enhance compliance is the improvement of the doctor-patient relationship. Therefore, we carried out an analysis of the research literature in this aspect.

Rational drug use process requires adequate drug information to provide high level of compliance. In this connection, drug information must be objective, accurate, complete, up-to-date, accessible and serviceable. Consequently the success of drug therapy is directly dependent on the skills and abilities of the physician in aspect of adequate informing of patient about the rational drug use. At the same time, it is of vital importance that the patient and doctor have good communications. Therefore the study of the therapeutic communication in physician-patient relationship in informing on the rational drug use is priority direction. It has been suggested that training patients, as well as doctors, in communication skills may be a cost-effective way to increase compliance and improve the overall health of patients.

Conclusions: In the world and Kyrgyz Republic the concept of therapeutic communication is not developed in framework of physician-patient relationship on rational drug use. So there is no evidence-based approach to a conceptual decision of this problem; there is no state support in terms of guaranteed getting of sufficient information and availability of informational materials; there is not defined any significant practical steps in healthcare on good informing of patients on the rational drug. In this regard, it is necessary i) to introduce the subject of therapeutic communication at undergraduate and postgraduate level of doctors training; ii) to examine the state of therapeutic communication in physician-patient relationship on rational drug use in Kyrgyz Republic, to identify priority areas for improvement of patient compliance and to develop standards of qualitative advisory support of drug therapy.

Background: Administration of oral medication to patients with enteral feeding tube (EFT) is challenging. Contrary to the hospital setting, medication administration via EFT has been poorly investigated in residential care facilities (RCFs) for individuals with intellectual disability (ID).

Objective: To collect observational data on drug administration practices, to identify barriers for following guidelines, and to map staff members’ knowledge on medication administration via EFT.

Method: The observational study was conducted in 6 Belgian RCFs for individuals with ID. Observations of medication preparation and administration through EFT were carried out in 2 randomly selected units per RCF, on two days per unit, using direct observation method. Afterwards, recorded observations were compared with international guidelines. Barriers were identified during a focus group study with staff members that administer medication via EFT, using vignettes to guide discussion. Thematic analysis was performed. Knowledge was tested using a self-administered questionnaire.

Results: In total, 862 drug preparations and 268 drug administrations in 48 residents with EFT were observed. Mixing together multiple drugs, not shaking suspensions/emulsions, and not flushing the EFT with at least 15 mL water were the most common deviations from guidelines. We also observed high variability in working methods, even between staff members of the same unit. Barriers to following guidelines emerging from the four focus group interviews were: time constraints, lack of medication-related knowledge, clear administration instructions, and necessary materials. In the knowledge questionnaire, RCF staff members obtained an average score of 44% (SD14%), with medication preparation guidelines being least known.

Conclusion: Current guidelines on medication preparation and administration through EFT are insufficiently known and implemented in RCFs for individuals with ID. A number of barriers to guideline adherence were identified. Based on these findings, an educational intervention can be set up in order to optimize care for this vulnerable patient population.

STORAGE AND DISPOSAL OF UNUSED MEDICATIONS: KNOWLEDGE, BEHAVIOR, AND ATTITUDES AMONG SERBIAN PEOPLE

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Background: Improper disposal of medications potentially poses a significant environmental risk and storage of expired and unused medications in households provides an increased risk of accidental childhood poisonings. The objective of this study was to investigate the storage and disposal habits of medications amongst the population in the South Bačka District of Serbia, and to gain insight into the attitudes and knowledge of the population about the proper disposal of medications.

Material and Methods: The study was conducted during the 6-month period from February 2010 to July 2010 and involved a random sample of households. The questionnaire-based study was performed by a trained interviewer.

Results: Of 230 families, 208 (108 urban and 100 rural) agreed to participate and complete the questionnaire (90 % response rate). Drugs were mostly kept in a specific place-home pharmacy (89.8 % [urban] and 89.0 % [rural]). Exposure of children to medications in the home environment was similar in urban and rural families (19.6 % [urban] and 23.1 % [rural]). The frequency of expired medications was not observed to be different between the urban and rural households (10.3 % [urban] and 11.8 % [rural]. The most
common method for disposal of household medications is disposal in the garbage (85.6% [urban] and 74.5% [rural]) or in the toilet (8.7% [urban] and 6.4% [rural]). However, inconsistent with disposal practices, half of the urban and rural participants thought that throwing medications in the garbage, toilet, or sink has a detrimental effect on the environment.

Conclusions: Public services in Serbia, including government and health sectors, need to be more proactive about educating people on how to store and dispose medications, as well as finding a way for implementation of the law on medications wastage destruction.

KNOWLEDGE ABOUT STROKE AND AWARENESS OF ITS SIGNALS AMONG HYPERTENSIVE PATIENTS WITHOUT PRIOR HISTORY OF STROKE

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Background: Stroke is a disabling disease. Prompt recognition of potential stroke signs and symptoms could increase a chance to receive appropriate medical management, thus reducing permanent disability and death. The study surveyed knowledge about stroke as well as awareness of its signals in hypertensive patients without history of stroke.

Material and Methods: The study is cross-sectional and conducted in hypertensive patients who received care at a local primary health care unit. The patients were chosen by convenient sampling. Only patients without prior history of stroke determined from medical records as well as direct patient questioning were included (N = 100). The structure questionaire was used for patient interview.

Knowledge about stroke covered risk factors, clinical outcomes, and self care once having stroke. Sources of the information was queried.

Awareness of signs and symptoms of stroke was also assessed.

Results: Of the patients studied, ages were 64 ± 11.4 years, with female being 65%. Almost a half had concurrently either diabetes mellitus, dyslipidemia, or coronary heart disease; 72% and 68% denied drinking alcohol and smoking, respectively. Average systolic blood pressure in the past 6 months was greater than 140 mmHg in almost half of the patients. Eleven patients never heard of stroke. Among those who knew, 44% could describe at least one signal of stroke, with limb weakness being the most recognized sign (34.8%).

Sixty percent would see doctor immediately. Forty percent identified hypertension as a risk factor. Majority were aware of end outcomes of stroke, and 13.5% received information about stroke from health care professionals.

Conclusions: Over a half of the hypertensive patients who have not yet had stroke in this study were not fully aware of potential signs and symptoms of stroke, although a significant number knew its consequences. There is a gap as an information provider of health care professionals.

DETERMINATION OF PREDICTIVE FACTORS ASSOCIATED WITH POOR SEIZURE CONTROL IN CANCER PATIENTS

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Background: Cancer is a leading cause of death worldwide and is associated with many complications that place significant burdens on patients, caregivers, and healthcare systems. Seizures, a highly debilitating neurological complication, occur in cancer patients with primary brain cancer and also brain metastases; little data exists to guide clinical decision making for seizure prophylaxis and management. The primary objective was to characterize and evaluate antiepileptic drug use for cancer patients in Qatar, secondary objective to determine predicting factors for failure of prophylactic regimens.

Methods: The study was designed as a retrospective electronic healthcare record review from June 1, 2012 through June 1, 2014 of patients receiving at least 1 anti-epileptic agent (carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, phenytoin, valproic acid) with a cancer diagnosis using hospital pharmacy records, the following data were extracted: demographics, cancer type, presence and localization of metastases, history of seizure disorders (on admission or in hospital), and anti-epileptic drug regimens. Multivariate logistic regression was used to assess these characteristics as predictive factors for failure of prophylactic regimens.

Results: A total of 58 patients met inclusion for the study. A total of 28% had glialoma with 43% of all patients having brain metastases.

Levetiracetam and phenytoin were the most commonly used anti-epileptic drugs (43% and 37%, respectively). The use of levetiracetam was significantly associated with a lower risk of seizures (odds ratio, 0.15; 95%, CI 0.03–0.76; P = 0.02). No other factor was deemed significant (including glioma and/or brain metastases).

Conclusion: This study found that seizures occur commonly in patients with cancer in Qatar, even while taking antiepileptic agents. Levetiracetam and phenytoin were the most commonly used agents, which is in-line with current practice guidelines. However, only the use of levetiracetam was associated with a lower risk of seizure development. Future prospective studies are needed to optimize care of these patients.

DRUG-INDUCED NEPHROTOXICITY: A FREQUENT CAUSE OF HOSPITALIZATION IN NEPHROLOGY

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Introduction: Drug-induced nephrotoxicity (DIN) is involved in 20% of acute renal failures, and many cases could be avoided. The purpose of this project was to study DIN in a nephrology setting.

Material and Methods: This study was based on an extraction of hospital stays in the nephrology department of Limoges University Hospital between May 1, 2013 and May 31, 2014 from the Medicalized Information System Program. Identification of DIN cases was performed using the extracted database and medical records. Demographic and clinical data were collected from the medical charts. A descriptive statistical analysis was followed by comparative statistical analyses based on Student-t test and χ² test, with a level of significance of P < 0.05.

Results: Overall, 72 cases of DIN among 790 hospital stays were identified. No significant difference was evidenced between patients with and patients without DIN on age (69 ± 14 vs. 66 ± 16 y), sex (67% vs. 57% males), and length of stay (12 ± 15 vs. 10 ± 11 days). The proportion of DIN was significantly lower in renal transplant patients (4.3% vs. 10%, RR = 0.42, P = 0.019).

Forty four DIN cases (61%) occurred in an outpatient setting. There was at least one aggravating factor in 46 cases (64%). Drugs involved were mainly: NSAIDs (54% cases), diuretics (39%), anti-hypertensive drugs (32%) in outpatients; antibiotics (45%) cases, diuretics (34%), antineoplastic drugs (23%) in inpatients. The drug was stopped in 38 cases, and dialysis was necessary in 10 cases. Basal renal function was not recovered in 17 cases.

Conclusions: DIN was observed in 9% of hospital stays in nephrology. Renal transplantation seemed to be a “protecting” factor against
Epidemiological Profile of Benzodiazepine Poisonings In Uruguay

1. Introduction: Benzodiazepines (BZDs) are widely prescribed medications for the treatment of anxiety, insomnia, and other psychiatric conditions. However, they are also known for their potential for abuse and dependence. In the context of emergency departments (EDs) in Uruguay, benzodiazepine poisonings have become a significant concern. The purpose of this study is to report the epidemiological profile of benzodiazepine poisonings in Uruguay and to characterize the patients who present to the ED with benzodiazepine overdose.

2. Materials and Methods: The study was conducted using data from the emergency department of the Hospital Nacional de Niños, Montevideo, Uruguay, from January 2013 to December 2014. The data collected included demographic information, clinical presentation, and outcome measures.

3. Results: A total of 108 patients were included in the study. The majority of patients were female (82.1%). The average age of the patients was 45 years (range: 15-77 years). The most common presenting symptoms were altered level of consciousness (92.6%) and respiratory depression (82.1%). The majority of patients (73.9%) were admitted to the hospital for further evaluation.

4. Discussion: Benzodiazepine poisonings are a significant public health problem in Uruguay, with a high proportion of cases involving female patients. The clinical presentation of benzodiazepine overdose is often characterized by altered level of consciousness and respiratory depression. The management of benzodiazepine overdose involves decontamination, monitoring of vital signs, and the use of activated charcoal, if indicated.

5. Conclusion: Benzodiazepine poisonings are a common presentation in the EDs of Uruguay, particularly in young females. The management of these patients should focus on the evaluation of respiratory function and the use of activated charcoal, if appropriate.

6. Future Studies: Further research is needed to understand the factors contributing to the high incidence of benzodiazepine poisonings in Uruguay and to develop strategies to prevent future overdoses.

7. References: [List of relevant studies]

8. Acknowledgments: [Acknowledgments if applicable]
SAFETY OF LISDXAMFETAMINE: A RETROSPECTIVE COHORT STUDY
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Background: Attention-deficit hyperactivity disorder is a common neurobehavioural disorder in children. Pharmacotherapy plays a main role in the multimodal treatment plan, albeit adverse effects are a concern. Lisdxexamfetamine (LDX) is a newer pharmacological option and post-marketing studies on adverse events are limited. We aimed to investigate the treatment-emergent adverse events (TEAEs) in a clinical setting.

Material and Methods: Retrospective cohort study at one Department of Child and Adolescent Psychiatry in Copenhagen, Denmark including all consecutive patients > 6 years old with an ICD-10 diagnosis of ADHD who were initiated on LDX between May 2013 and July 2014. TEAEs were assessed by a clinician and a subsequent chart audit.

Results: Forty-three patients (91% male) with a median age of 11 (range 8–15) were included. Patients received LDX for a median of 188 days (range 3–433). In total, 23.3% of the patients discontinued treatment due to a TEAE. Eighty-eight percent of the patients experienced at least one TEAE and the time to first TEAE was within the first 4 weeks of treatment in 83.8% of the patients. Compared to the TEAEs previously experienced by the individual patient on other ADHD medication, 39.5% of the TEAEs were new. The most common TEAEs (> 5%) were decreased appetite, difficulty falling asleep, tics, stomach ache and weight loss. A subjectively assessed good, or good but time-limited effect was observed in 62.7% of the patients.

Conclusions: Treatment with LDX in non-stimulant-naive patients was tolerable and the types of adverse events were consistent with findings in previous clinical trials. However, both the number of patients experiencing TEAEs and the rates of discontinuation due to TEAEs were substantially higher than previously reported in clinical trials. Furthermore, more than one third of the TEAEs were new for the individual patient compared to those previously experienced on other ADHD medication.

THERAPEUTIC DRUG MONITORING OF LAMOTRIGINE IN PEDIATRIC EPILEPSY PATIENTS
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Background: Lamotrigine (LTG) is a new antiepileptic drug (AED) that was approved in Japan in 2008. The purpose of this study was to evaluate clinical utility of therapeutic drug monitoring (TDM) for LTG and the influence of concomitant antiepileptic drugs on plasma LTG concentration in pediatric patients.

Material and Methods: We retrospectively reviewed routine TDM data during 2009 to 2014 and calculated the prevalence of TDM and the therapeutic range for each year. Measurement samples were grouped whether patients received valproic acid (VPA) or the hepatic enzymes inducers, such as phenytoin, carbamazepine, phenobarbital; LTG (group I), LTG+VPA (group II), LTG+ inducers (group III), or LTG+VPA+ inducers (group IV). We calculated the concentration to dose ratio (CD ratio (μg/mL/mg/kg)) of LTG and compared these groups. The study protocol was approved by the ethical committee of our hospital.

Results: During study period, a total of 4836 plasma concentrations of LTG were measured in 786 pediatric patients aged 3 months to 16 years. The prevalence of TDM markedly increased from 29.0% in 2009 to 94.6% in 2014. Also, there was significant change in the target concentration range of LTG (median concentration; 2.46 μg/mL in 2009 vs. 5.10 μg/mL in 2014). The median CD ratios of LTG in group I, II, III, and IV were 1.10, 2.62, 0.56, and 1.31. VPA markedly elevated CD ratio in a concentration-dependent manner. Among the inducers (group II), patients taking phenytoin had a significantly lower CD ratio than patients taking phenobarbital or carbamazepine (P < 0.001). The effect of VPA and inducers was unchanged regardless of the patient’s age, but infants had a higher CD ratio.

Conclusions: Our findings suggest clinical utility of TDM for LTG and can be used to estimate the inducing or inhibiting effects of concomitant AEDs.

POST-APPROVAL WITHDRAWAL OF MEDICINES BECAUSE OF ADVERSE DRUG REACTIONS: A SYSTEMATIC REVIEW
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Introduction: Medicinal products may be withdrawn after regulatory approval when the benefit-to-harm balance is negative. Withdrawal of medicinal products can be controversial, especially when the link between the drug and the associated harm is not established. We have identified medicinal products that have been withdrawn because of adverse drug reactions after regulatory approval, examined the evidence used to support such withdrawals, and explored the pattern of withdrawals across countries.

Methods: We searched PubMed, GoogleScholar, the WHO’s database of drugs, the websites of drug regulatory authorities, and textbooks. We also hand searched references in retrieved documents. We included medicinal products that were withdrawn between 1950 and 2014. We assessed the level of evidence used for making withdrawal decisions using the criteria of the Oxford Centre for Evidence Based Medicine.

Results: We identified 428 medicinal products that were withdrawn between 1953 and 2011; 42 were withdrawn worldwide and 232 were withdrawn in two or more countries. The evidence used for withdrawal in over 70% of cases consisted of anecdotal reports. In 106 cases (25%), deaths were reported as one of the reasons for withdrawal. Hepatotoxicity was the most common reason attributed. Withdrawals were significantly less likely in African countries than in Europe (P < 0.0001). The intervals between the first reports and first withdrawals were shorter when the adverse reactions involved children. The interval between the first report of the adverse reaction and the year of the first withdrawal has not consistently shortened over time.

Conclusion: There are discrepancies in the patterns of withdrawal of medicinal products from the market when adverse reactions are suspected. Withdrawals are significantly less likely in low- to middle-income countries. Greater co-ordination among drug regulatory authorities and increased transparency in the reporting of suspected adverse drug reactions would help improve the current flaws in decision making processes.

RELABILITIY OF ANIMAL MODELS IN BIOMEDICAL RESEARCH: A WORD OF CAUTION
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Epidemiological Profile of Benzodiazepine Poisonings in Uruguay

Man had purely relied on observation to study complex physiologic principles for long with hardly any intervention possible. But ever since scientists started using animal models as human replicas, it has been possible to employ a lot of intervention and experimental strategies. Spontaneously hypertensive rat (SHR) is considered as one of the best and most widely used models of human hypertension. We have shown that acidosis induces a contraction in aortas from SHR and normotensive Wistar-Kyoto (WKY) rats. Since acidosis is not an uncommon condition in the setting of diabetes mellitus and chronic renal failure, which are often co-morbid with hypertension, this change in the behavior of arterial contractility was of immense interest. These findings in rodent animal model compelled us to investigate further the underlying mechanisms and the intracellular signaling pathways involved in contraction. However, much to our surprise, when the similar experiments were repeated on human (both normotensive as well as hypertensive) internal mammary artery, acidosis caused relaxation of vessels. Although SHR is a valuable model of hypertension, its findings were not reproducible in humans. Personal experience and review of literature shows lot of discrepancies between the data generated from humans and animals. However, it is a usual practice that the results obtained from animal models are extrapolated on humans. In this presentation, this issue will be focused, that while animal models are essential for the research and development, a critical caution needs to be practiced in interpreting the results. Uncritical reliance on the results of animal experimentation can be dangerously misleading and has resulted in damages to human health in several cases. This presentation will also discuss the role of certain confounding factors in using animal models.

ASSOCIATION OF DECREASED MRNA EXPRESSION OF MULTIDRUG AND TOXIN EXTRUSION PROTEIN 1 IN PERIPHERAL BLOOD CELLS WITH THE DEVELOPMENT OF FLUTAMIDE-INDUCED LIVER INJURY

K. Nakano1; H. Ando1; S. Kurokawa1; K. Hosohata1; K. Ushijima1; M. Takada2; M. Tateishi2; A. Yonezawa2; K. Matsubara1; S. Masuda4; K. Inui5; T. Morita1; and A. Fujimura1; K. Nakano1; H. Ando1; S. Kurokawa1; K. Hosohata1; K. Ushijima1; M. Takada2; M. Tateishi2; A. Yonezawa2

Introduction:

The ant-prostate cancer drug flutamide occasionally induced liver injury (FILI) are needed to improve a safety of the drug. The ant-prostate cancer drug flutamide occasionally causes hepatotoxicity, and some predictive biomarkers of flutamide-induced liver injury (FILI) are needed to improve a safety of the drug. The aim of this prospective study was to identify such a biomarker by analyzing peripheral blood samples from patients before flutamide therapy.

Material and Methods: Blood samples were obtained from 52 patients with prostate cancer (training set, n = 15; validation set, n = 37) before flutamide therapy. FILI was defined as treatment-related elevation of serum concentration of aspartate or alanine aminotransferase to more than twice the upper limit of the reference range. The patients were monitored for at least 6 months regarding FILI. Microarray and quantitative real-time PCR analyses were conducted to compare gene expression profiles between the groups with and without FILI.

Results: Seventeen patients developed FILI (training set, n = 5; validation set, n = 12). Microarray analysis of the training set in 15 patients detected 11 annotated genes showing >2-fold expression changes between the groups (P < 0.005). Quantitative PCR analysis of both the training and validation sets confirmed that mRNA levels of multidrug and toxin extrusion protein 1 (MATE1 or SLC47A1; encoded by 1 of the 11 genes) were significantly lower in patients with FILI. A small experiment in mice (3 per group) showed that MATE1 knockout mice had the elevated serum concentration of 4-nitro-3-(trifluoromethyl) phenylamine, a major metabolite of flutamide, at 2 h after administration of the drug, suggesting that MATE1 could affect the pharmacokinetics of flutamide.

Conclusions: The MATE1 mRNA level in peripheral blood is a possible negative predictive biomarker of FILI.

GALANTAMINE: ANTI-DIABETIC EFFECT MEDIATED BY ANTI-OXIDANT/INFLAMMATORY/APOPTOTIC EFFECTS AND IMPROVEMENT OF INSULIN AND WNT/β-CATENIN SIGNALING PATHWAYS

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Background: The cholinergic anti-inflammatory pathway is one of the putative biochemical pathways that link diabetes with Alzheimer disease. Hence, here we aimed to verify the potential anti diabetic effect and to unveil the possible mechanisms of galantamine, a clinically approved acetylcholinesterase (AChE) inhibitor used in Alzheimer disease. Additionally, we evaluated its effect as an add-on therapy with vildagliptin.

Material and Methods: The neonatal streptozotocin (n5-STZ) rat model was adopted and the diabetic animals were treated with galantamine (2.5, 5, 10 mg/kg), vildagliptin (5,10, 30 mg/kg) or both (5 and 10 mg/kg, respectively) for 4 weeks.

Results: Galantamine leveled off the n5-STZ-induced elevation in body weight, food intake, and serum levels of glucose, fructosamine, ALT/AST, and the lipid profile (triglycerides, cholesterol, free fatty acids) assessed in serum, liver, and muscle. Besides, it increased the insulin level, HDL-C and % α-cell function, in a pattern similar to that of vildagliptin. Additionally, galantamine confirmed its antioxidant (nuclear factor-erythroid-2-related factor 2, total antioxidant capacity, lipid peroxide), anti-inflammatory (NF-κB, TNF-α) and anti-apoptotic (caspase-3 and cytochrome c) capabilities by altering the n5-STZ effect on all of the aforementioned parameters. Galantamine mediated its effect via improving the insulin (phosphorylated insulin receptor, p-AKT, GLUT4, GLUT2) and the Wnt/α-catenin (p-GSK-3β, α-catenin) signaling pathways. Galantamine, as expected, lowered dose dependently the n5-STZ-induced activation of AChE in brain, muscle and liver; nevertheless, the vildagliptin effect was limited to the brain enzyme. On almost all tested parameters, the galantamine effects surpassed that of vildagliptin, while combining both drugs showed the best effect.

Conclusion: The present results clearly prove that galantamine modulated glucose/lipid profile partly through its anti-cholinesterase, anti-oxidant, anti-apoptotic and anti-inflammatory properties, along with the improvement of both insulin and Wnt/α-catenin signaling pathways. Additionally, galantamine can be strongly considered as a potential anti diabetic agent and as an add-on therapy.
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**Background or Introduction:** Acute renal failure (ARF) is a rapid loss of kidney function. Causes of ARF are numerous. Among those, drugs, such as contrast agents, aminoglycosides, contribute to acute renal failure in about 20% of people. In 2012 spontaneous reporting showed a possible association between dronedarone and ARF. To further investigate such association a retrospective cohort study on

**Methods:** As previously described, we therefore derived unadjusted relative risk (RR) and number needed to treat (NNT) year values for duration of dual antiplatelet therapy (clopidogrel or prasugrel + aspirin) versus aspirin only for important reported endpoints, based on the published DAPT trial results.

**Conclusions:**: These parameters for extended duration DAPT indicate statistically significant relative and absolute benefits with respect to stent thrombosis and major cardiovascular and cerebrovascular events, though in absolute terms they were modest. Regarding harms, the risk of severe/moderate bleeds was significant (though modest in absolute terms), but there was also a small though not quite statistically significant increase in all-cause deaths.

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Reference

**Comparative Safety Profile of Biosimilars and Originator Erythropoietins: Data from the Italian Spontaneous ADR Reports Database**

**Results:**: New users without previous episodes of ARF were 56,739, dronedarone (1761) or amiodarone (54,978). The mean age of patients treated with dronedarone was significantly lower than that of amiodarone ones (70.8 vs. 74.2). The cumulative incidence rate of ARF was 1.3% (95% CI, 0.6–2.8%) among dronedarone group and 3.8% (3.3–4.4%) among amiodarone group (P from logrank test <0.001). The unadjusted HR of ARF was 0.34 (0.18–0.64) in dronedarone compared to amiodarone the adjusted HR was 0.52 (0.27–0.97), HR adjusted for high-dimensional propensity score was 0.64 (0.34–1.20).

**Conclusions:**: This large community-based study did not confirm the previous signal of an increased nephrotoxicity from dronedarone compared to amiodarone. Actually, our results revealed a lower risk for dronedarone compared to amiodarone. However, evidence of renal failure from dronedarone coming from the post marketing surveillance are growing. It is therefore advisable for clinicians and patients to be aware of the risk of kidney damage during dronedarone therapy in order to improve clinical outcomes with early intervention.

**Comparative Safety Profile of Biosimilars and Originator Erythropoietins: Data from the Italian Spontaneous ADR Reports Database**

**Methods:** Reports of suspected Adverse Drug Reactions (ADRs) due to EPO, between 1 January 1991 and 1 September 2014, were extracted. ADRs were coded using MedDRA terminology. To evaluate the correlation between drug use and occurrence of ADRs a disproportionality analysis through Reporting Odds Ratio (ROR) was performed. An analysis for drug-reaction pairs and a comparison between all originators vs biosimilars was applied.

**Results:**: Three hundred sixty-eight ADR reports associated with EPO, 68% related to originator, were retrieved. The main source of reporting for both drug categories was hospital doctors. Patients’ characteristics were comparable among originators and biosimilars groups, but some differences has been detected between the Italian regions. Most reports concerned products containing EPO-alpha (Eprex®, Binocrit® and Retacrit®). For biosimilars, significant disproportionality was observed only for headache (ROR, 4.79; 95% CI, 1.48–5.49), sickness (6.65; 1.37–32.3), drug ineffective (3.71; 1.62–8.48) and lack of therapeutic response (9.16; 2.6–32.27).

**Conclusions:**: No alarm signals have been found. The ADRs related to biosimilars “therapeutic inefficacy” probably are not due to quality concerns, but they could be interpreted as the attempt to switch from biosimilars to originators. Also literature evidence confirm the similar efficacy and safety profiles between biosimilars and
NETRIN-1 LEVELS ARE REDUCED IN HEALTHY SUBJECTS IN RESPONSE TO TREATMENT WITH ASPIRIN

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Background: Proinflammatory stimuli and prothromogenic factors are known to reduce the level of endothelial-derived netrin-1, a secreted laminin-like protein that attenuates recruitment of circulating monocytes within atherosclerotic plaques. This study investigated the effect of aspirin, routinely used for the prevention of cardiovascular disease, on serum netrin-1 levels in healthy subjects.

Materials and Methods: Serum netrin-1 was measured using an enzyme-linked immunosorbent assay (ELISA) in samples collected from 60 subjects before and after 28 days of treatment with 300 mg aspirin daily. ELISAs were performed to assess serum levels of intercellular adhesion molecule-1 (ICAM-1), E-selectin, and urinary 11-dehydro-thromboxane B2 levels (TXB2). Serum creatinine and salicylate levels were measured using the creatininas enzymeatic method on a Roche C8000 analyser and a Cobas Faro automated analyser (Roche).

Results: Serum netrin-1 levels were reduced following aspirin treatment (66.06 ± 22.98 pg/mL versus 79.79 ± 34.91 pg/mL at baseline; P = 0.0022). There was a linear association between the percentage change in netrin-1 and level of serum salicylate (r² = 0.413, P = 0.0013). TXB2 levels fell in all subjects post-treatment, confirming adherence to treatment (32.99 ± 18.35 nmol/mmol creatinine versus 143.7 ± 54.25 nmol/mmol creatinine at baseline; P < 0.0001). Serum ICAM-1 and E-selectin levels were not modified by treatment.

Conclusion: This study demonstrates that serum netrin-1 is reduced following aspirin treatment. The TXB2 measurements show effective platelet inhibition in the whole population. We observed no change in ICAM-1 or E-selectin levels suggestive of an effect on the vascular endothelial function. Netrin-1 is a known biomarker of renal impairment. We propose that the reduction in netrin-1 is secondary to drug-induced renal dysfunction, as evidenced by a decrease in creatinine clearance.

PERIOPERATIVE MANAGEMENT AND OUTCOMES OF PATIENTS TREATED WITH ANTITHROMBOTICS SUBMITTED TO ELECTIVE SURGERY

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Background: Patients treated with antithrombotics often must undergo an elective surgery. The objective of this study was to describe the impact of implementing a protocol on the perioperative management and outcomes of these patients.

Material and Methods: A protocol on perioperative management of antithrombotics was designed based on the ACCP recommendations. After protocol implementation (May 2012), information was collected on a retrospective (June–October 2011) and a prospective (October 2012–February 2013) cohort of eligible patients who were enrolled from the preoperative assessment up to 3 months after surgery.

Results: A total of 379 and 413 patients were included during retrospective and prospective period, respectively. No differences in most patients’ characteristics were observed between cohorts.

Conclusions: After protocol implementation, in patients submitted to a moderate-to-high-risk surgery and with a clinically-relevant hemorrhagic-risk-surgery, aspirin was more often kept (32.5% vs 48.8%, P = 0.01). Clopidogrel and acenocoumarol were discontinued in all patients in both cohorts, but in the prospective cohort less days before surgery: clopidogrel from 8 [7–11.5] to 7 [6–10] days (P < 0.05) and acenocoumarol from 6 [5–7.2] to 5 [4–6] days (P < 0.05). In patients submitted to a moderate-to-high or to a clinically-relevant hemorrhagic-risk surgery and with a low-thrombotic-risk, time of interruption of aspirin was shorter (from 7 [4–9] to 5 [4–7] days, P < 0.05). None of the other changes observed were statistically significant. A similar percentage of patients had hemorrhagic (34.3% and 37.8%) or thrombotic (5.8% and 4.8%) events in both cohorts.

THE INTERCHANGEABILITY OF GABAPENTIN 800 MG TABLETS: A RANDOMIZED, CONTROLLED TRIAL TO ESTABLISH INDIVIDUAL BIOEQUIVALENCE

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Background: International Nonproprietary Name (INN) prescribing, i.e. using the INN instead of the brand name for prescribing, and/or generic substitution is allowed in different European countries. For some products it is advised not to switch between medicinal products from different manufacturers once treatment started, because it is believed that they are not completely interchangeable. Therefore, we aimed to investigate (1) the interchangeability of gabapentin 800mg tablets marketed as Neurontin® and Gabasandoz® following FDA guidelines using the individual bioequivalence (IBE) approach and (2) the interchangeability in a more real-life situation by including two different batches of each product (Neurontin® & Gabasandoz®, both Batch ‘A’ and ‘B’).

Materials and Methods: Thirty healthy subjects received 6 times - in a randomized order - a single dose of 800 mg Neurontin® (Batch A or B) or 800 mg Gabasandoz® (Batch A or B). Serum concentrations of gabapentin up to 36 hours after dosing were determined. According to FDA guidelines, IBE can be established if the 95% upper-confidence bound (UCB) of η (ie, a function of different
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variance terms) is lower than the IBE limit θ, which is 2.5. For

AUC_{0-inf} and C_{max}, η and its 95% UCB were calculated.

Results: For AUC and C_{max}, η was 0.58 and 0.19, respectively, and

the 95% UCB was 1.32 and 0.63 (both P value < 0.001), respectively.

When including data on batch ‘B’ of Neurontin® and Gabasandoz®,

η was 0.46 and −0.08 for AUC_{0-inf} and C_{max}, respectively. The 95% UCB was 1.20 and 0.40, respectively (both P value < 0.001). All UCB were below the IBE limit θ, showing IBE.

Conclusion: This study indicates that Neurontin® 800 mg (Batch ‘A’)

and Gabasandoz® 800 mg (Batch ‘A’) are individually bioequiva-

lent and interchangeable in clinical practice. This interchangeability remains when resembling a more real-life situation by adding an additional batch of each product (Batch ‘B’).

PERIOPERATIVE ANTIMICROBIAL PROPHYLAXIS
OF PATIENTS UNDERGOING JOINT ENDOPROSTHESIS REPLACEMENT

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Introduction: There is no doubt that perioperative antibiotic prophylaxis is appropriate and useful. Due to the increasing antimicrobial resistance, many countries have adopted national programs for anti-bacterial prophylaxis and therapy. Kazakhstan does not have such a program on the national level. At the clinic, we developed our own optimal program based on the international recommendations according to specifics of the performed operations, predominant pathogens of nosocomial infections and their level of resistance.

Materials and Methods: We analyzed medical histories of 532 patients, which underwent operative intervention for endoprosthesis replacement of knee or hip joints. The first group (included 285 patients) received Cefazidime during 5 to 7 days for prophylaxis purposes. After approval of algorithms of antibiotic prophylaxis, the second group (247 patients) was administered only one dose of a medicine (Cefazolin, Cefuroxime or Ampicillin/subactam) 30 to 60 minutes before an operation.

Results: Development of joint replacement infection was identified in both groups. But the first group had 2 patients (5.7%) with infection, while in the second group infection had developed in one patient (2.47%). When estimating economic costs, we identified that antimicrobial drugs for first group was spent in 2.33% to 22.3% more funds than in group second patients. Based on the almost equal percentage of development of joint replacement infection in both groups, we conclude that single-stage introduction of antibacterial medicine provides adequate, efficient and comfortable medical care.

Conclusion: We developed protocols for perioperative antibiotic prophylaxis, which help to optimize usage of antimicrobial drugs, reduce its adverse effects on patients and epidemiological situation, and reduce costs of its acquisition. Cefazidime was excluded from the algorithm of perioperative antibacterial prophylaxis, because it is pseudomonas drug.

PROCESS MEASURES OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM

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Barzilai University Medical Center, Ashkelon, Israel

Introduction: Antimicrobial stewardship aims to improve patient care and reduce antibiotic overuse or misuse, antimicrobial resistance, adverse drug reactions, length of hospital stay and additional healthcare costs. Such a program was implemented at Barzilai Medical Center with goals to prevent unnecessary treatment, optimize dosing, appropriate length of therapy and lower related costs.

Methods: The program included two measures; antimicrobial restriction criteria and daily surveillance of all patients treated with any antibiotic. The program was evaluated during a 24 month antimicrobial stewardship program.

Results: Antimicrobial length of treatment for restricted drugs decreased by 10.1% and their DDD/100 hospital beds was reduced by 9.9%, both statistically significant. No improvement in hospitals’ antibiogram was observed. During the study period (years 2013–2014) 1849 interventions were carried out. Types of intervention evaluated were related to adherence to protocols of treatment (33.3%), length of treatment (38.3%), request/reminder for susceptibility testing (3.8%), change of drug selection according to cultures (9.7%) and dose optimization (14.9%).

Conclusions: Decreased antibiotic expenditures were the backbone of justification of antimicrobial stewardship programs. Although this study was evaluated for a short period, using tools as information technology and human resources through a multidisciplinary team approach, it demonstrated to be successful. Proper evaluation of this program, helped to define which method was best for our institution; process measures evaluated quality of care, but did not adequately describe clinical impact at the patient level. Adding improvements in clinical outcomes should be the next target of the antimicrobial stewardship program.

RELATIONSHIP BETWEEN AMLODIPINE PHARMACOKINETICS AND CYP3A ACTIVITY IN LACTATING WOMEN WITH PREGNANCY-INDUCED HYPERTENSION

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Background: Pregnancy induces the activity of hepatic cytochrome P450 (CYP) 3A in humans. Amlodipine, a long-acting 1,4-dihydropyridine calcium channel blocker, is mainly metabolized by CYP3A. Few clinical reports have been published on amlodipine pharmacokinetics in lactating women during the early postpartum period.

The aim of this study was to evaluate the relationship between the plasma concentrations of amlodipine and 4β-hydroxycholesterol as endogenous marker of CYP3A4/5 activity in lactating women with pregnancy-induced hypertension.

Material and Methods: Twenty-seven lactating women receiving oral amlodipine once daily for pregnancy-induced hypertension were enrolled. Predose plasma concentration of amlodipine was determined at day 6 or later after starting the medication. The CYP3A activity in lactating women was evaluated using the plasma 4β-hydroxycholesterol concentration just before the delivery and during the early postpartum period.

Results: The mean dose of amlodipine was 6.5 mg in lactating women with pregnancy-induced hypertension. The median and interquartile range (IQR) of the plasma amlodipine concentration were 15.5 and 12.1 to 21.6 ng/mL, respectively. Interindividual variation was observed in the dose-normalized plasma concentration of amlodipine (IQR, 135–206 ng/mL per mg/kg). The median and IQR of the plasma 4β-hydroxycholesterol concentration were 161 and 89–254 ng/mL, respectively. The dose-normalized plasma concentration of amlodipine was inversely correlated with plasma 4β-hydroxycholesterol concentration. Median of plasma 4β-hydroxycholesterol
concentration just before and after the delivery within 6 days were 149 and 149 ng/mL, respectively. In contract, the plasma concentration of 4β-hydroxycholesterol in non-pregnant healthy subjects was 53.5 ng/mL.

Conclusions: The lactating women with pregnancy-induced hypertension had the higher CYP3A activity based on the plasma 4β-hydroxycholesterol concentration during the early postpartum period. The lactating women with the higher CYP3A activity had the lower plasma concentration of amlopidine.

FOSFOMYCIN VERSUS MEROPENEM IN BACTEREMIC URINARY TRACT INFECTIONS CAUSED BY EXTENDED-SPECTRUM BETA-LACTAMASE PRODUCING ESCHERICHIA COLI (ESBL-EC): FOREST STUDY

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Introduction: Investigating the efficacy of old drugs in infections by multidrug-resistant Gram negatives are urgently needed. We describe the design, network established, organization of clinical teams and general management support in order to effectively carry out an investigator-driven randomized clinical trial (RCT) in a public system setting.

Material and Methods: An investigator-driven, randomized controlled trial endorsed by the Spanish Network for Research in Infectious Diseases was designed to investigate the efficacy of fosfomycin in the treatment of bacteremic urinary tract infections (B-UTI) due to ESBL-EC. The study is publicly funded (PI13/01282).

Challenges were: use of a pragmatic design reflecting real practice; decisions about comparator, dosage, inclusion/exclusion criteria and outcomes, sponsor, selection of centres, obtaining approval by committees, agreements signatures, and pharmacovigilance.

Results: The local public research Foundation is sponsor, with delegated specific responsibilities to the CTU. Twenty-two Spanish centres were selected using feasibility tests. The study was designed as a phase III, randomised, open, multicentre, non-inferiority trial. Patients hospitalized with B-UTI caused by ESBL-EC will be selected and stratified in 3:1 ratio by centre through the automatic system design for the project (e-CRF) to receive early targeted therapy with intravenous doxorubicin fosfomycin 4 giv/iv/6h in 60 minutes infusion (experimental arm) or intravenous meropenem 1 giv/iv/8h in 15 to 30 minutes infusion (control arm), stratified according to previous empirical treatment received (198 patients in total). The primary outcome is clinical and microbiological cure 5 to 7 days after the completion of treatment. Fosfomycin levels and ecological impact are being measured in a subset of patients.

Conclusion: The organization of a multidisciplinary team supporting the daily work of coordination is a key point regarding issues as design, coordination, regulatory and ethical requirements for the development of investigator-drive RCTs according to International Conference Harmonization-Good Clinical Practice and 20/CE/2001. ClinicalTrials.gov identifier: NCT02142751 (registered 16-May-2014). EudraCT no: 2013-002922-21 (registered 08-May-2014).

THE EFFECT OF FLUOXETINE ON HUMAN OVARIAN CARCINOMA CELLS

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Recent studies have shown that the antidepressant fluoxetine induces anti-tumour activity in cancer cell lines such as colon, neuroblastoma, breast and ovarian carcinoma cells (Krishnan et al., 2008; Stepulak et al., 2008; Chung et al., 2009). The aim of the present study was to investigate if treatment with fluoxetine can induce more sensitivity to chemotherapeutic drugs such as cis-platin in cis-platin resistant ovarian carcinoma cell line, A2780CP70.

A2780 and A2780CP70 cells (American Type Culture Collection) were grown and maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum at 37°C, 5% CO2. The cells were plated in 96-well culture plates at a density of 1x104 cells/well and allowed to adhere at 37°C for 24 hours. The following day, various doses of cis-platin, fluoxetine, a combination of cis-platin plus fluoxetine or vehicle were added to the cells and further incubated for 72 hours. After 72 hours the supernatant was removed and MTT (3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) assay was performed. Cytotoxicity was expressed as a relative percentage of the absorbance measured at 540 nm in the control and drug-treated cells.

Pre-treatment with both fluoxetine and cis-platin but not vehicle induced dose-dependent cytotoxic effects in A2780 cells with IC50 of 19.1 µM, 1.19 µM and A2780CP70 cells with an IC50 of 14.4 µM and 8.04 µM, respectively. A combination of fluoxetine plus cis-platin significantly (P < 0.01) reduced the IC50 to 3.26 µM when compared to the single pre-treatment with the above drugs only in A2780CP70 cells. The data showed that pre-treatment with fluoxetine can increase the sensitivity of the cells to cis-platin in resistant ovarian carcinoma cells. Chung et al. (2009). Basic & Clinical Pharmacology & Toxicology, 106:446-453.

ESTIMATION OF RENAL FUNCTION AS A PRIMARY ENDPOINT OF CLINICAL TRIALS, QUOSEQU TANDEMP

A Aldea-Peñón1; S. Lúes-Lima2; N. Negrin2; M. Cervino1; P. Delgado1; R. Miquel1; JA. Ballarín3; V. Lorenzo1; A. Jiménez1; E. Porrini1; and NEROFVID investigators team

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Introduction: Estimated GFR (eGFR) by formulas is not precise, which preclude its use in clinical practice and research. Moreover, EMA recommends (EMA/CHMP/355988/2014) the use of measured GFR (mGFR) in clinical trials. Our aim was to analyze the agreement between mGFR and eGFR in the NEROFVID clinical trial.

Materials and Method: NEROFVID is a controlled CT aimed at evaluating renal function after vitamin D supplementation in subjects with CKD stage II-IV and proteinuria (> 0.5 g/d) on top on RAAS treatment. GFR was estimated with 37 creatinine-based formulas and measured with the iohexol plasma clearance (mGFR). The agreement between eGFR and mGFR was assessed by Concordance Correlation Coefficient (CCC), Total Deviation Index (TDI) and Coverage Probability (CP). TDI is a measure that captures a large proportion of data within a boundary for allowed differences between two measurements Empirical TDI was calculated for a theoretical TDI of 10% and a coverage probability of 90%. A CCC > 0.90 reflects optimal concordance between measurements.

Funding: Fondos FEDER; Ministerio de Sanidad, Servicios Sociales e Igualdad. ISCIII EC10/248.

Results: Thirty mGFR procedures were evaluated. Patient’s characteristics included: age 60 ± 13 years, 97% male and 81% diabetic.
Clinical Therapeutics

IMMUNO MODULATOR METALLO-PEPTIDE IMPROVES INFLAMMATORY STATE IN RATS WITH METABOLIC SYNDROME

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Background: Metabolic syndrome is a prothrombotic and pro-inflammatory chronic state. In obesity, the adipose tissue secretes various adipokines that play a role in a variety of physiological and pathophysiologic processes, including immunity and inflammation. Previous studies using liver damage model treated with the immune-modulator metallo-peptide (IMMP) showed lessening in the degree of inflammation. Therefore, this study was set up to evaluate the anti-inflammatory effect of IMMP in obese Zucker fa/ra rats. We used Zucker-Lepr fa/ra and Zucker-Lean in this protocol.

Material and Methods: The groups received IMMP 50 ng/kg by i.p., 3 times per week for 8 weeks. Blood samples were collected by cardiac puncture and the serum was preserved at −80°C until analysis. The liver was excised and preserved in formaldehyde 4%. Analyses were performed to determine cytokine, insulin, glucose, triglyceride and cholesterol levels in serum, and histological analyses was also performed.

Results: IMMP treatment of obese rats resulted in decreased levels of proinflammatory cytokines (leptin, IL-6, IL-1β, IFN-γ) and a chemokine (MCP-1), and increased levels of anti-inflammatory adipokine (adiponectin). In addition, treatment decreased the damage and hepatic steatosis generated in the tissue of obese rats and avoids changes in thymus and spleen in the same animals.

Conclusions: IMMP exerted an anti-inflammatory effect in obese rats and therefore may be an effective and safe therapeutic alternative in the treatment of metabolic syndrome.

AZITHROMYCIN IS NOT ASSOCIATED WITH QT PROLONGATION IN PATIENTS HOSPITALIZED WITH COMMUNITY ACQUIRED PNEUMONIA

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Background: Large data based studies have reported excess cardiovascular mortality in high risk patients treated with azithromycin, but whether or not azithromycin causes QT prolongation remains controversial. The purpose of this study was to examine the association of azithromycin treatment on QT prolongation in a cohort of patients hospitalized with community acquired pneumonia (CAP).

Materials and Methods: One hundred twenty-two hospitalized patients with CAP were enrolled in the study. We compared the baseline QTc, with daily post antibiotic QTc. Other risk factors for QT prolongation such as medication or electrolyte abnormalities were recorded.

Results: Ninety (73.8%) patients were treated with azithromycin (usually in combination with ceftriaxone), and 32 (26.2%) patients with other antibiotics (ampicillin-clavulinate, chloramphenicol, doxycycline, or ceftriaxone); 72.1% (88) of the cohort experienced QT lengthening, and 72.7% with QT lengthening had a normal baseline QTc. QT lengthening was not associated with type of antibiotic, age, pneumonia score or any specific comorbidity. None of the patients had other risk factors for QT lengthening such as concomitant medications or electrolyte abnormalities. Azithromycin was not associated with the post antibiotic QTc. Wide (pathological) post antibiotic QTc was associated with the pneumonia score. Every 10 point increase in the pneumonia score raised the risk for a pathological post antibiotic QTc by 1.249 (95% CI, 1.050–1.486). Analysis of patients with non-pathological baseline QTc revealed that pathological post antibiotic QTc was only associated with previous stroke. Patients with a normal baseline QTc, and history of a previous stroke had an increased risk of 6.459 (95% CI, 1.910–21.838) for developing a pathological QTc after antibiotic treatment, irrespective of the type of antibiotic used.

Conclusions: Azithromycin treatment was not associated with QT prolongation in patients with severe CAP. Nonetheless, in a large majority of hospitalized CAP patients QT prolongation and pathological QTc develops regardless of the antibiotic used, especially in patients with previous stroke or a higher pneumonia score.

SURVEY OF INFORMATION SOURCES ON DRUG SAFETY IN PATIENTS TAKING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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Background: Information on drug use can be provided to patients by health professionals and educational materials. Nonsteroidal anti-inflammatory drugs (NSAIDs) potentially cause serious adverse effects in those with long-term use. This study aimed to explore sources of NSAID information and to evaluate factors related to drug information sources receiving by patients.

Methods: This study was a cross-sectional survey. Self-completed questionnaires were distributed directly to 500 outpatients prescribed any NSAIDs from Orthopedic Unit at a university hospital in Thailand, during 4-month period. Data was analyzed using descriptive statistics and logistic regression.

Results: There were 474 completed questionnaires (94.8%). The average age of patients was 56.14 ± 12.38 years, and 75.4% were female. Most of the patients received information about NSAIDs from pharmacists (94.9%) and physicians (78.5%). Sources included leaflets (7.6%), internet (5.3%) and relatives (4.2%). Information involving drug administration (96.2%) and indications (79.7%) were commonly received from healthcare professionals. However, only 39.2% of patients reported that they had ever obtained adverse drug reaction (ADR) information. Patients taking selective COX-2 NSAIDs were significantly less likely to receive information about ADRs (OR, 0.33; 95% CI, 0.21–0.57), ADR monitoring (OR, 0.20; 95% CI, 0.08–0.47) and ADR management (OR, 0.64; 95% CI, 0.26–0.10) than those taking non-selective NSAIDs. Greater proportion of patients with intermittent NSAID therapy significantly gathered ADR information (OR, 2.19; 95%
### A NOVEL GRADUAL UP-TITRATION REGIMEN MITIGATES THE FIRST-DOSE EFFECTS OF PONESIMOD, A SELECTIVE S1P1 RECEPTOR MODULATOR

M. Hoch; A. Vaclavkova; A. Krause; A. Strong; J. Bush

*Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; and Covance Clinical Research Unit Ltd, Leeds, United Kingdom*

**Introduction:** The aim of this study was to compare the effects of ponesimod on heart rate (HR) and AV-conduction using a novel gradual up-titration regimen (regimen A) suggested by PK/PD modelling with the up-titration regimen (regimen B) previously used.

**Material and Methods:** This was a single-centre, double-blind, placebo-controlled, randomized, two-way cross-over study in 32 healthy male and female subjects (n = 24 on ponesimod, n = 8 on placebo).

The 2 regimens consisted of the following once daily ponesimod/placebo treatments. Regimen A: Day 1 (D1): placebo, D2–3: 2 mg, D4–5: 3 mg, D6–7: 4 mg, D8: 5 mg, D9: 6 mg, D10: 7 mg, D11: 8 mg, D12: 9 mg, D13–14: 10 mg, D15: 20 mg. Regimen B: D1: placebo, D2–8: 10 mg, D9: 20 mg, D10–15: placebo. Subjects in the placebo group received placebo on all study days.

**Results:** The decrease in HR (Holter ECG) observed after the first dose of ponesimod was less pronounced with regimen A (mean decrease: 6 bpm [±6]) compared to regimen B (12 bpm [±7]). Occurrence of HR <45 bpm was less frequent during regimen A (12.5%) than B (16.7% of subjects). Fewer subjects experienced a decrease from baseline in HR >20 bpm following the first dose of ponesimod during regimen A (12.5%) than B (20.8%). Fewer AV-blocks (defined as PR interval >210 ms) were observed during regimen A (79 events in 25% of subjects) compared to B (143/25%). Second degree AV-block Mobitz II was observed in 0, 1, and 2 subjects during regimen A, B, and placebo, respectively. Sinus bradycardia, palpitations, and dizziness were reported more frequently during regimen B compared to regimen A.

**Conclusions:** The cardiodynamic first-dose effects of ponesimod are mitigated by the novel gradual up-titration.

### FACTORS AFFECTING THE DEVELOPMENT OF ADVERSE DRUG REACTIONS OF BETA BLOCKERS

S. Mugosa; Z. Todorovic; M. Sahman-Zaimovic; I. Radosavljevic; Z. Bukumiric; and N. Djordjevic

*Agency for Medicines and Medical Devices, Podgorica, Montenegro; Medical School, University of Belgrade, Serbia; and Faculty of Medical Sciences, University of Kragujevac, Serbia*

**Introduction:** Adverse drug reactions (ADRs) are common causes of morbidity and mortality within the hospital setting. Our main goal was to analyse risk factors, incidence and characteristics of ADRs of beta blockers in hospitalised cardiac patients and to consequently suggest measures for rationalization of pharmacotherapy practice in Montenegro which will contribute to more quality treatment of patients.

**Material and Methods:** Prospective study, which included 200 patients hospitalized at Cardiology Centre of the Clinical Centre of Montenegro, was performed. We established system of intensive monitoring of ADRs in hospital setting. Genotyping of CYP2D6 was performed in order to determine the frequency of poor and rapid metabolizers of beta blockers.

**Results:** Twenty percent of all patients experienced at least 1 ADR of beta blocker. Genotyping showed that poor metabolizers (slow, very slow and those with no CYP2D6 enzyme activity) experience ADRs of beta blockers significantly more often than rapid and intermediate CYP2D6 metabolizers ($\chi^2 = 25.325, P < 0.001$). There is a strong positive, statistically significant higher level correlation of the enzyme activity and the given dose of beta blockers. Statistically important predictors of occurrence of beta blockers’ ADRs in the multivariate logistic regression model are: duration of hospitalization ($B = 0.124, P = 0.008$), enzyme activity ($B = 3.544, P < 0.001$) and the concomitant use of other medicines metabolized by CYP2D6 ($B = 3.236, P < 0.001$).

**Conclusions:** The implementation of preventive measures for patients with detected risk factors, like pharmacotherapy rationalization and continual education for health care professionals, could reduce the occurrence of ADRs.
CHALLENGES OF GENERIC IMATINIB

1. Therapy for CroAtian patients with gastrointestinaL StromaL tumors (GISt)
2. I. Kraljicovicio1; r. likico1;2; i. cege1; m. radacic Ausmi1; k. Makar Ausmi2; v. erdelic Turk1; and i. francetic1,2
3. 1University hospital zagreb, zagreb, croatia; and 2University of zagreb, zagreb, Croatia
4. Despite proven effectiveness and safety during the last 30 years, unfolded skepticism about generic prescribing still persists.
5. Recently, 2 patients on imakrebin for metastatic GIST were admitted for ADR testing. The first reported stomach pain, cramps, skin rash, eye swelling, headache and chills while the second one complained of diarrhea, abdominal pain and hemorrhoids. They claimed symptoms were absent while on Glivec therapy.
6. During hospitalization both were single-blindedly exposed to placebo, Glivec and Imakrebin. While the second patient was asymptomatic during testing, the first developed similar symptoms regardless of the administered substance, without signs or symptoms of acute allergy. All reported symptoms were listed as ADRs to Glivec, but could also be attributed to disease progression or considered psychosomatic and in our view therapy change in both patients was not required.
7. In Croatia, all oncology treatments are financed by the National Health Insurance Fund. Due to budgetary constraints, original drugs are substituted with generics whenever possible. In case of objective intolerance original drug use is possible. Apart from Glivec, priced 1866€ for 30 pills of 400 mg, there are 4 generic parallels of imatinib available since 2013 in croatia: Neopax (1615€), Astrea (1307€), Imakrebin (1307€) and nibix (1177€), with actual prices significantly lower due to volume discounts. First generic imatinib in the USA will be launched, after substantial controversy, on February 1, 2016 by sun Pharma.
8. High prices of new tyrosine kinase inhibitors and Glivec, are significantly cost burden for insurers and patients who require therapy for prolonged periods of time.
9. Better communication among physicians themselves and with patients is crucial to avoid similar cases in the future. Generic prescribing promotion is still very much needed.
10. Improper communication among physicians themselves and with patients is crucial to avoid similar cases in the future. Generic prescribing promotion is still very much needed.

PROMOTING PUBLIC AWARENESS OF CLINICAL TRIALS IN MONTENEGRO

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Introduction: In order to successfully build a clinical research infrastructure one of the key imperatives is that the public understand and strongly support clinical research. Literature data showed that the general public is not sufficiently informed about the purpose and importance of clinical trials. The aim of this study is to investigate awareness of general public in Montenegro regarding clinical trials.

Material and Methods: The data from questionnaire completed by 400 randomly selected people aged 19 and over was collected. SPSS software was used for statistical analysis.

Results: There were statistically significant gender differences with regards to clinical trials awareness. Only 44.2% of all male subjects versus 70.8% of all female ones were informed about the definition of clinical trials (P < 0.001). Both were mostly informed through the media. While 49.8% of women thought that medicines on the market were clinically tested, 47.5% men were not sure about that (P = 0.037). The main motive for clinical trial enrolment for subjects under the age of 25 and over the age of 50 was curing the existing disease, while for subjects aged 26–50 was financial reimbursement (37.6% and 44.2% versus 34.9%; P < 0.001).

Conclusions: These results indicate that additional educational efforts are needed in order to improve the knowledge of significance of clinical trials. Therefore, the Agency for Medicines and Medical Devices of Montenegro, in accordance with its competences - education about medicines, will be providing more information relevant to clinical trials to general public in the future.

POLYPHARMACY AND ASSOCIATED FACTORS AMONG COMMUNITY-DWELLING OLDER PERSONS IN A SWISS CANTON

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Background: Polyparmacy in older persons has been scarcely studied in Switzerland. Our aim was to investigate which socio-demographic factors are associated to polyparmacy in a sample of Swiss older persons.

Material and Methods: The study population consisted of community-dwelling persons aged 69+ years living in the canton de Vaud (Switzerland). Information about current medication was self-reported by 3133 participants in a postal survey nested into a population-based cohort study (participation rate: 71% of eligible subjects). Data were weighted to reflect the age and sex distribution of the source population. Polyparmacy was defined as currently taking five or more different registered drugs on a regular basis (further referred to as “drugs”).

Results: Median age was 77 years; 57% were female. Most (84%) were taking at least one drug; the maximum reported was 17. Polyparmacy was present in 27% of our population and increased from 18% among persons aged 69–74 to 29% in those aged 75–84 and 38% in those aged 85+ (P < 0.001). Polyparmacy was observed in 38% of the subgroup reporting two or more chronic diseases versus 9% of those without comorbidity (P < 0.001). In multivariate logistic regression analysis, polyparmacy remained significantly associated with the number of chronic diseases (adjusted OR(per unit increment) 2.14; 95% CI, 1.85-2.48) and with oldest age (adjusted OR, 8.54 versus 69–74: 2.64; 95% CI, 1.61–4.34). No association was observed between either education level or gender and polyparmacy.

Conclusions: Polyparmacy was reported in 27% of community-dwelling persons aged 69+. Comorbidity and age 85+ were significantly and independently associated factors. While polyparmacy was particularly frequent in the older age group, it already concerned nearly one in five persons at the age of 69–74. These findings emphasize the need for scheduled medication reviews not only in oldest-old, but also in the polymorbied youngest-old patients.
Clinical Therapeutics

DRUGS REGULARLY TAKEN BY COMMUNITY-DWELLING OLDER PERSONS IN A SWISS CANTON

D. Renard1; S. Fustinoni2; L. Seematter-Bagnoud3; and B. Santos-Eggimann4

1Division of Clinical Pharmacology, Lausanne University Hospital, 1011 Lausanne, Switzerland; and 2Center for Aging Studies, Lausanne University Hospital, 1010 Lausanne, Switzerland

Background: Studies about polypharmacy may fail to present data in a clinically meaningful way. Our aim was to report the frequency of drugs taken by older people according to clinically relevant pharmacological classes.

Material and Methods: The study population consisted of community-dwelling persons aged 69+ years living in the canton de Vaud (Switzerland). Information about current medication was self-reported by 3133 participants in a postal survey nested into a population-based cohort study (participation rate: 71% of eligible subjects). Data were weighted to reflect the age and sex distribution of the source population.

Results: Median age was 77 years; 57% were female; a majority (84%) were currently taking at least one registered drug on a regular basis. The frequency of major pharmacological classes was as follows:

<table>
<thead>
<tr>
<th>Percentage of participants currently taking at least one such drug on a regular basis (%)</th>
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<tbody>
<tr>
<td>ALL CARDIOVASCULAR DRUGS, among which:</td>
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<tr>
<td>Statins</td>
</tr>
<tr>
<td>Renn-angiotensin system inhibitors</td>
</tr>
<tr>
<td>Beta blockers</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Duretics</td>
</tr>
<tr>
<td>Amlodipine</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
</tr>
<tr>
<td>ANTIDiABETICs</td>
</tr>
<tr>
<td>Oral antidiabetic agents</td>
</tr>
<tr>
<td>Insulins</td>
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<tr>
<td>ALL DIGESTIVE DRUGS, among which:</td>
</tr>
<tr>
<td>Antacids</td>
</tr>
<tr>
<td>Laxatives</td>
</tr>
<tr>
<td>CALCIUM AND VITAMIN D</td>
</tr>
<tr>
<td>ANALGESICS</td>
</tr>
<tr>
<td>Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)</td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Opioids</td>
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<tr>
<td>Topical NSAIDs</td>
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<td>PSYCHOTROPIC DRUGS</td>
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<tr>
<td>Antidepressants</td>
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<tr>
<td>Anxiolytics</td>
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<tr>
<td>Sedative-hypnotics</td>
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<tr>
<td>Anti-psychotics</td>
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</table>

Conclusions: The most frequent class was cardiovascular agents (almost 70% of participants report taking at least one cardiovascular drug, and 9% report taking at least one anti-diabetic) followed by psychotropic drugs (18%). By contrast, reports of calcium/vitamin D (14%) and analgesics (13%) were low, suggesting underuse. Optimizing prescribing in this population should include a) carefully weighing the risk-benefit balance of cardiovascular and psychotropic drugs, which may be double-edged swords in a potentially fragile population and b) considering the risk of under-prescribing.

MECHANISM OF THE EFFECT OF VISFATIN ON HUMAN INTERNAL THORACIC ARTERIES

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Background or Introduction: Visfatin, also known as pre-B-cell colony-enhancing factor and nicotinamide phosphoribosyltransferase (Nampt) is a novel adipocytokine. The present study aimed to investigate the functional effects and the possible underlying mechanism(s) of visfatin on human left internal thoracic artery (ITA) preparations.

Material and Methods: Samples of redundant ITA obtained from patients undergoing a coronary artery bypass surgery were cut into 3–4 mm wide rings and suspended in 20 mL organ baths. Isometric tension was continuously recorded with isometric force transducers connected to a computer-based data acquisition system.

Results: Contraction responses of human ITA rings to angiotensin II, endothelin-1, noradrenaline and phenylephrine did not change significantly before and after incubation with different visfatin concentrations. Visfatin (10−12–10−7 M) produced concentration-dependent relaxation responses in human ITA rings precontracted with phenylephrine (10−6 M) that were significantly higher in endothelium-intact than endothelium-denuded preparations. Incubation of tissues with cyclooxygenase inhibitor indomethacin (10−5 M) did not cause a significant alteration, while incubations with nitric oxide (NO) synthase inhibitor L-NAME (10−5 M) and specific guanylyl cyclase inhibitor ODQ (5×10−4 M) caused statistically significant decreases in relaxant responses to visfatin. Visfatin-induced relaxation responses were almost completely blocked in the presence of Namp enzyme inhibitor FK866 (10 µM). Incubation of the tissues with a combination of high-conductance Ca2+-activated potassium channel blocker charybdotoxin and small-conductance Ca2+-activated potassium channel blocker apamin (10−7 M, both) did not cause a statistically significant alteration in visfatin-induced relaxations. Acetycholine-induced (10−10–10−5 M) endothelium-dependent relaxations significantly increased whereas sodium nitroprusside-induced (10−10–10−5 M) endothelium-independent relaxations did not change following incubation of human ITA rings with 10−6 and 10−8 M visfatin.

Conclusions: The findings of the present study demonstrated that visfatin did not affect contraction responses to various contractile agents, but produced concentration-dependent relaxation responses in endothelium-intact human ITA rings through Nampt enzymatic activity and NO-cGMP pathway.

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INTRA-ARTERIAL MICRODOSING (IAM), A NOVEL DRUG DEVELOPMENT APPROACH, PROOF OF CONCEPT IN RATS

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Background: Intra-Arterial Microdosing (IAM) is a novel drug development approach combining intra-arterial drug delivery with microdosing. We aimed to demonstrate that IAM leads to similar target exposure as systemic full-dose administration but with minimal systemic exposure.

Methods: Insulin 0.34 IU/kg was administered intra-arterially (ipsilateral femoral artery) to 2 CD IGS rats just prior to 60-minute
18F-FDG uptake imaging of ipsilateral (leg), contralateral (leg), and systemic (spine) muscles. Area under the curve (AUC) was calculated by the linear trapezoidal method and together with maximum glucose uptake (Emax) were summarized by descriptive statistics. 

Results: Contralateral and systemic Emax (mean ± SD: 0.323 ± 0.129 and 0.297 ± 0.205, respectively) and AUC (mean ± SD: 13.08 ± 8.12 and 13.39 ± 10.78, respectively) post IAM were similar but lower than ipsilateral Emax and AUC (0.615 ± 0.367 and 22.13 ± 15.33, respectively; Figure). 

Conclusion: Target exposure post IAM was similar to systemic full dose administration but with minimal systemic effects. Our findings are being validated in larger studies in animals and humans using different targets and classes of drugs. IAM could enable safe, inexpensive and early study of novel drugs at the first-in-man stage and the study of established drugs in vulnerable populations. 

### PHARMACOKINETICS AND PHARMACODYNAMICS MODELING TO OPTIMIZE DOSAGE REGIMENS OF ORAL LEVOFLOXACIN 

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**Background:** Levoﬂoxacin, a ﬂuoroquinolone antibiotic, is S isomer of ofloxacin with a broad spectrum of activity against Gram-positive cocci and Gram-negative bacilli bacteria. In common with other ﬂuoroquinolones, the main pharmacokinetic/pharmacodynamic (PK/PD) index that correlates with its therapeutic eﬃcacy is the AUC/MIC. The aims of the study were to: (i) reveal the population pharmacokinetics, and (ii) assess the eﬃcacy of various dosage regimens in achieving the probability of target attainment (PTA) and the cumulative fraction of response (CFR) of levoﬂoxacin.

**Materials and Methods:** The study was conducted in 45 healthy volunteers. Each subject received one 500 mg tablet of levoﬂoxacin, after which PK studies were carried out, using a Monte Carlo simulation to determine the PTA. By referral to the EUCAST MIC distributions database, the dosage regimens were predicted to achieve CFR≥90%.

**Results:** The population PKs of levoﬂoxacin were: Vd = 29.60 ± 1.84 L, CL = 8.51 ± 1.43 L/h, and AUC = 66.19 ± 1.30 mg·h/L. The predicted CFRs for a target of AUC/MIC=30 for S. aureus and S. pneumoniae were 75.59% and 92.63%, respectively for 500 mg levoﬂoxacin and 84.56% and 98.16%, respectively for 750 mg levoﬂoxacin. The predicted CFRs for a target of AUC/MIC=125 for E. coli and Klebsiella spp. were 84.25% and 88.81%, respectively for 500 mg levoﬂoxacin and 86.00% and 91.34%, respectively for 750 mg levoﬂoxacin. The PTAs for selected regimens were as follows.

<table>
<thead>
<tr>
<th>Dose</th>
<th>MIC (mg/L)</th>
<th>PTA of AUC/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>125</td>
</tr>
<tr>
<td>500 mg</td>
<td>0.25</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>99.96</td>
<td>33.85</td>
</tr>
<tr>
<td>1</td>
<td>94.23</td>
<td>1.44</td>
</tr>
<tr>
<td>2</td>
<td>39.97</td>
<td>0.00</td>
</tr>
<tr>
<td>750 mg</td>
<td>0.25</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
<td>73.90</td>
</tr>
<tr>
<td>1</td>
<td>99.95</td>
<td>13.12</td>
</tr>
<tr>
<td></td>
<td>79.17</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Conclusion:** High PTAs (≥90%) achieving AUC/MIC = 30 for an MIC of 1 mg/L and AUC/MIC=125 for an MIC of 0.25 mg/L were observed when levoﬂoxacin was administered in a 500 mg or 750 mg. Both regimens had high probabilities of achieving optimal exposure against S. pneumoniae.

### SCREENING FOR PHENOTYPICAL VARIATION IN CYP ACTIVITY IN PATIENTS WITH THERAPEUTIC PROBLEM IN PSYCHIATRIC SETTINGS 

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CHALLENGES OF GENERIC IMATINIB THERAPY FOR CROATIAN PATIENTS WITH GASTROINTESTINAL STROMAL TUMORS (GIST)
Background or Introduction: The clinical relevance of seeking for variation in cytochrome P450 activity in case of non-response or adverse effects to drugs is poorly documented. This retrospective study aimed to assess how much the assessment of CYP activity recommended by clinical pharmacologist allowed to explain therapeutic problems in patients on psychotropic agents.

Material and Methods: We retrospectively collected the results of the genetic and phenotypic investigations that were performed from 2003 until November 2014 in patients receiving psychotropic drugs as well as their indication. According to a semi-quantitative scale, two clinical pharmacologists determined independently the link between CYP activities and the clinical or biological event. In case of disagreement, a third clinical pharmacologist scored the link.

Results: Among the 695 pharmacological advices involving metabolic exploration, 260 concerned psychotropic drugs. Among them, 135 cases included a complete statement of drug metabolic pathways.

Advices mostly concerned antidepressants (n = 90), including tricyclic antidepressants (n = 14), followed by antipsychotics (n = 27), benzodiazepines and hypnotics (n = 14), and psychostimulants (n = 4). The phenotype and/or genotype determination was performed for the following reasons: side effects (n = 73, 54.1) lack of efficacy (n = 44, 32.6%), low concentrations (n = 14, 10.4%), high concentrations (n = 4, 3.0%). There was a good agreement between the two clinical pharmacologists, who scored the same way in 97% of cases (131/135).

According to the statement of the three pharmacologists, in 22% (n = 30) and 12.6% (n = 17) of the cases, a modified activity of CYP450 explained the therapeutic problem with a high and intermediate probability, respectively. In patients with side effects, these probabilities were 22.3% and 17% respectively whereas for a lack of efficacy, they were 13.6% and 11.4% respectively.

Conclusions: When indicated by clinical pharmacologists, metabolic exploration explained clinical or biological events related to drug intake in approximately 35%. These findings should encourage more systematic assessment of metabolic pathways in psychiatric patients.

HIGHLIGHTS OF MONTELUKAST IN CHILDREN. UPDATED ANALYSIS OF THE RELATED SUICIDE BEHAVIOURS IN THE WHO DATABASE. JANUARY 2015.

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Introduction: At present, there are divergent opinions on the association of suicide behaviour and the use of montelukast in asthmatic or allergic patients.

Material and Methods: The BCPNN method was used to analyse the ICSR of the association montelukast-suicide behaviours, up to January 2015, in order to evaluate the safety concerns that have been raised regarding the increased risk of completed, ideation and attempt suicide with its use.

Results: The most frequent fatal cases reported with Psychiatric disorders and montelukast were (Nfatal/Ncomb): 183/183 completed suicide, 26/1083 depression, 10/832 insomnia, 10/815 anxiety. The ICSR of suicidal ideation, aggression, suicide attempt or depression have positive dechallenge in 52 %, 44%, 22% and 48%, of the cases respectively. Positive rechallenge were reported in 3 cases of suicide ideation.

In the global WHO Database there were 6,722 ICSR for the “Suicidal and self-injurious behaviours” HLG7 for all drugs in pediatric population. Out of them 10% (674) corresponds to Montelukast. These 10% reports included several PT: Suicidal ideation (447; 66%), Suicide attempt (95; 14%), Intentional self-injury (60; 9%), Completed suicide (56; 7%), Self-injurious ideation (44; 7%), Self-injurious behaviour (44; 7%) and, Suicidal behaviour (27; 4%).

Within the “Suicidal and self-injurious behaviours” HLG7, Completed suicide PT (82%) and Suicide attempt PT (78%) were more frequently reported for adolescents and suicidal ideation (66%) for children (2-11y). The IC values for completed suicide reached 3.15 in children and 3.11 in adolescents, however, the IC for the total population was 1.95.

Conclusions: The presence of fatal cases without previous anxiety/ depression reported, the positive dechallenge in ideation, attempt suicidal or self injurious behaviours and the positive rechallenge in few cases, support the urgent need to implement well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level among children using montelukast.

TRENDS IN ANTIBIOTIC CONSUMPTION UPON IMPLEMENTATION OF EDUCATIONAL MEASURES

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Introduction: Despite antibiotic’s remarkable value, their misuse leads to decreased effectiveness. Infection with resistant bacterial strains requires longer and more expensive therapy and increases morbidity and mortality. Within antimicrobial stewardship program, educational measures pinpointing appropriate antimicrobial use are important and well-established tools in fighting irresponsible antibiotic use.

Patients and methods: Population-based cross sectional survey was conducted in Primorsko-goranska County in Croatia in 2009, 2010, 2011 and 2014. Questionnaires were used to investigate general population attitudes, habits and knowledge on antibiotic use before and after educational activities delivered through public campaigns. Time series analysis of antibiotic outpatient’s consumption through the period of five years was also conducted.

Results: Improvement in cognitive (91.08 to 95.03%) affective (17.76 to 11.2%), and behavioural (17.71 to 8.14%) component is observed during the period of five years. The willingness to self-medicate was lowering over the years from 26% in 2009 to 13.6% in 2014. After the educational measures among the population and physicians were implemented, the reduction of outpatient antimicrobial drug use was noted in Primorsko-goranska County from 7.91 DDD/inhabitant in 2008 to 7.37 DDD/inhabitant in 2013.

Conclusion: Educational measures through the public campaign significantly improved knowledge of the population and have had a substantial positive impact on more appropriate antibiotic consumption in outpatient setting.

BIOLIGIC AGENTS IN RHEUMATIC DISEASES - A REAL LIFE EXPERIENCE

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Introduction: Since biologic-agents have recently become part of regular treatment protocols for rheumatic disorders the aim of this study was to evaluate their use, efficacy and safety at the University Hospital Centre Rijeka in Croatia.
Challenges of Generic Imatinib Therapy for Croatian Patients With Gastrointestinal St Romal Tumors (GIST)

Patients and Methods: A total of 108 patients diagnosed with rheumatoid arthritis (RA) (50), ankylosing spondylitis (AS 33), psoriatic arthritis (PsA 16), treated with biologicals (TNFα inhibitors – adalimumab, infliximab, golimumab, etanercept, tocilizumab, rituximab) were evaluated in a retrospective study conducted in eight-year period.

Results: Average treatment period for the first-line biological was 56, 41, 36, 36, 28, 20 months for etanercept, adalimumab, infliximab, rituximab, tocilizumab and golimumab respectively. In patients with RA, first-line TNFα inhibitors were prescribed in 53% cases, followed by etanercept and tocilizumab in 18% and rituximab in 10%. For AS and PsA, TNFα inhibitors were more frequently first choice biological when compared to etanercept (AS 79% and 21% vs. PsA 63% and 37%). The longest duration of biologic therapy was in AS patients (47 months). Regardless of diagnosis, 31% patients required switching to another biological due to non efficacy (94, 1%). TNFα inhibitors were switched in 73% cases and etanercept in 27% patients. Seven patients discontinued treatment due to complete remission, serious infection, chemotherapy, cerebrovascular insult, newly diagnosed psychiatric disorder, moving to another city and private reason. There were 21 adverse drug reactions: infections (16), leucopenia and anemia (4) and pharyngeal carcinoma (1).

Conclusion: Six biologic agents with different mechanism of action (TNFα inhibitors (4), anti-CD20 (1) and IL6 inhibitor (1)) are used in treatment of RA. For AS and PsA, four TNFα inhibitors were used what is in accordance with Croatian clinical practice guidelines. More frequent switching between different TNFα inhibitors is consistent with similar reports.

INTERACTION BETWEEN TRAMADOL AND SSRIS: DO WE CARE?

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Introduction: The combination of a selective serotonin reuptake inhibitor (SSRI) with tramadol can result in serotonin syndrome, characterized by neuromuscular excitation, autonomic nervous system excitation, and altered mental state. The serotonin syndrome can be mild but also life-threatening and is more easily prevented than treated. Most overview articles consider awareness of the serotonin syndrome the most important step to prevent it, yet research among GP’s showed that a mere 15% was aware of this potentially dangerous syndrome. We aimed to investigate whether prescribers in a general hospital were aware of this risk and if it influenced their prescriptions.

Material and Methods: A questionnaire was sent to 858 physicians and 9 physician assistants in a general teaching hospital with over 650 beds in the Netherlands. The questionnaire presented four cases, two of whom used an SSRI among other medications, and asked the respondent to prescribe an opioid in each case. The respondent was not made aware of the focus of the research. In addition, we explored actual prescription rates of tramadol in admitted patients who used or did not use an SSRI by using the database of the hospital pharmacy.

Results: Eighty-four questionnaires were available for analysis (response rate 46%). About one-third of respondents prescribed tramadol and indicated they were aware of the interaction with SSRIs. About one-fifth deliberately avoided tramadol because an interaction with SSRIs was identified. However, there was no difference in actual tramadol prescriptions: 23.8% of SSRI-users received tramadol, versus 24.6% of non-SSRI-users.

Conclusions: A small part of prescribers in a general hospital is aware of the interaction between tramadol and SSRIs, yet this does not translate to a difference in tramadol prescriptions in clinical practice. Hospital pharmacies may play an important role in signaling the interaction and advising prescribers.

INTRAgaSTRIC PH TRANSITION INDUCED BY RABEPRAZOLE: INVESTIGATION OF CLINICAL STUDY DESIGN

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Background: Gastric pH is known to vary depending upon diverse populations and may affect the solubility, dissolution or absorption of a drug. In drug development, if the investigational drug increases gastric pH, the effects on other drugs sensitive to this should be predicted and considered in vivo studies for further evaluation. However, since it is difficult to conduct a study with healthy volunteers who have suppressed gastric acid secretion, we evaluated the study design using Proton Pump Inhibitor (PPIs).

Materials and Methods: Eighteen healthy male volunteers who provided written informed consent participated. This study was an open-label, 3-period, 2-part, crossover study. Part 1 was the control period, and Part 2 was for effects of food and Rabeprazole determination. The 24 hour intragastric pH was monitored starting at 17:00 for each period. Rabeprazole (20 mg) was administered orally as PPI at 19:30 after dinner and at 06:00 the next morning. Moreover, we evaluated the difference in intragastric pH transitions among the three different genotypes of CYP2C19: homoEM (EM: Extensive Metabolizer), heteroEM, and PM (Poor Metabolizer).

Results: Rabeprazole increased the intragastric pH (pH > 5.5) and maintained this condition at the target time between 09:00 and 13:00 the next day. Food did not affect the results considerably, but the intragastric pH increased slightly in the group without food after Rabeprazole. Furthermore, Rabeprazole had a tendency to increase the intragastric pH in CYP2C19 PM compared to CYP2C19 homoEM.

NONINVASIVE RETINAL AND CUTANEOUS MICROCIRCULATION IMAGING IN SICKLE CELL DISEASE PATIENTS AND HEALTHY VOLUNTEERS

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Validated methodology to assess microvascular function in sickle cell disease (SCD) patients is not readily available, but could be of great benefit in clinical research. We explored the feasibility and robustness of two quantitative methods for microvascular function: laser-speckle contrast imaging (LSCI) and non-invasive retinal function imaging (RFI).
Clinical Therapeutics

1 Microvascular function was assessed in moderate to severe SCD patients, male/female, aged 18-65 (n = 6), healthy volunteers matched for age, BMI, smoking behavior and skin color (n = 6) and unmatched healthy volunteers (HV; n = 12). Measurements were conducted twice on two study days separated by one week. LCSI was performed before, during and after 5 minutes brachial artery occlusion and after inspiratory breath holding (IBH) of 20 seconds, endpoints included basal flow, flow upon occlusion-reperfusion and flow during an IBH (measured in arbitrary units (AU)). RFI was performed after LCSI for assessment of arterial and venous retinal blood flow (measured in mm/sec). Variability of these measurements was calculated between and within subjects, and contrast between groups was assessed with a mixed model analysis of variance: LCSI basal flow, LCSI maximal flow, RFI arterial flow and RFI venous flow showed excellent intra subject repeatability between days (CVC of 7.6%, 7.6%, 7.9% and 9.8% respectively) and between measurements (CVC of 7.6%, 4.9%, 7.0% and 7.3% respectively).

There were significant differences between SCD patients and matched HV in LCSI basal flow AU (35.31 vs. 25.25; P < 0.0001), LSCI maximal flow AU (96.16 vs. 75.16; P < 0.0001), LSCI Delta flow during an IBH (10 vs. 5; P ≤ 0.0001), RFI arterial flow mm/sec (4.013 vs. 3.532; P < 0.007) and RFI venous flow mm/sec (3.054 vs 2.737; P = 0.0310).

The relatively low variability for most LCSI and RFI readout measures and the discriminating power between SCD patients and matched healthy volunteers demonstrate the feasibility of both techniques to assess the microcirculation in clinical research.

ASSOCIATION ANALYSIS OF CYP3A4 RS4646437(G>A) WITH SUNITINIB RESPONSE IN RENAL CANCER

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Introduction: Sunitinib is a widely prescribed drug in metastatic renal cell carcinoma (mRCC) with a large inter-individual variability in response. Identification of genetic biomarkers to predict sunitinib treatment outcome could improve clinical practice. Recently, rs4646437(G>A) in CYP3A4 was suggested to be related to sunitinib induced toxicity. Therefore, we aimed to investigate whether there was a relationship between this single nucleotide polymorphism (SNP) and sunitinib treatment response in a cohort of mRCC patients.

Material and Methods: An observational retrospective multicentre study was performed. Germ line DNA and clinical information from medical records of clear cell mRCC patients, treated with sunitinib was obtained. Genotyping analysis was performed by real-time PCR with Taqman® probes on LightCycler480® platform. Toxicity was evaluated during the first 4 cycles of treatment according to CTCAE version 4.0. The association of the SNP with leukopenia, thrombocytopenia, hand-foot syndrome (HFS), mucositis, hypertension and any other toxicity above grade 2 was tested with logistic regression. Progression free survival (PFS) and overall survival (OS) were evaluated during the first 4 cycles of treatment according to CTCAE.

Results: SNP CYP3A4 rs4646437(G>A) was not associated with sunitinib treatment outcome in our cohort of clear cell mRCC patients.

PHARMACOKINETICS AND CIRCULATING MICRORNA PROFILES OF EXTENDED RELEASE HYDROMORPHONE IN HEALTHY SUBJECTS

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Background: Hydromorphone is a semisynthetic opioid analgesic which has been used extensively as an effective alternative to morphine for the relief of acute and chronic pain. However, currently, no hydromorphone formulation has been approved in Japan. A new hydrophilic matrix extended-release (ER) tablet has been developed to deliver hydromorphone over an extended period resulting in sustained plasma concentrations. The objective of this study was to assess the pharmacokinetics and safety of hydromorphone to healthy Japanese subjects. In addition, circulating microRNAs (miRNAs) were evaluated to explore candidate biomarkers for pharmacodynamics and safety of hydromorphone.

Material and Methods: Healthy male subjects participated in an open-label study to receive a single oral dose of the ER hydromorphone tablet. The plasma and urinary concentrations were measured by LC-MS/MS. Plasma miRNA profiling was performed with an Exiqon Serum/Plasma focus PCR panel (179 miRNAs). Safety was assessed by clinical evaluation and laboratory measurements.

Results: The median plasma hydromorphone concentration peaked rather late. AUC and C max increased almost dose-proportionally. The degree of fluctuation in the plasma concentration for the ER tablet was low and certain levels of plasma concentrations were maintained after 24 h of ER dosing. The cumulative urinary excretion amounts of hydromorphone and hydromorphone-3-glucuronide were 3% and 30% of the dose, respectively. A number of miRNAs were measured and the discriminating power between SCD patients and matched healthy volunteers demonstrate the feasibility of both techniques to assess the microcirculation in clinical research.

PARTICULARITIES OF THE PHARMACOLOGICAL MANAGEMENT OF DILATED CARDIOMYOPATHY IN CLUJ-NAPOCA COUNTY HOSPITAL

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Volume XX Number XX
Challenges of Generic Imatinib Therapy for Croatian Patients With Gastrointestinal Stomal Tumors (GIST)

Background: Imatinib mesylate (STI571), a tyrosine kinase inhibitor of the platelet-derived growth factor receptor and the c-KIT, is a first-line treatment for patients with metastatic gastrointestinal stromal tumors (GIST). Generic imatinib is under evaluation in the USA for its clinical and economic utility.

Objectives: To compare the clinical and pharmacokinetic characteristics of generic imatinib with that of the reference product (R-P). The study also aimed to identify and model the factors influencing variability in metabolite serum concentration.

Methods: Two compounds (mofetil and sodium) and displays large between-subject pharmacokinetic (PK) variability. The aim of this study was to identify and model the different factors influencing MPA variability.

Methods: A cross sectional observational study of total 75 subjects had been performed. Data was collected from the prescriptions, medical history and self designed questionnaire. The subjects were enrolled according to the inclusion and exclusion criteria.

Results: In the study it was found that people consuming Guraku had a high level of Hba1c thus are more prone to the development of diabetic cataract. Male subjects (57%) are the more than female subjects (43%). Most of the subjects belong to the lower socioeconomic class and not very educated. Average blood glucose (29%), Subjects with high level of HbA1c (40%) and subjects with high level of Glucose tolerance value (30%) in diabetic cataract were observed.

Conclusion: It could be concluded that this type of study could be useful in identifying number of subjects suffering from diabetic cataract whose condition get worse by use of nicotine product like Guraku. and preventive measure to be taken in prevention of this type of diabetic complication.

Key words: Diabetic cataract, Hba1c, Guraku, Diabetogenic potential.

Pharmacokinetic issues in Obese Patients

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Introduction: Obesity is associated with several pathophysiological changes that may interfere with pharmacokinetic properties of drugs including increased plasma volume, fatty liver disease, and changes in glomerular filtration rate (GFR). Drastic weight changes with bariatric surgery further complicate the issue. Correct drug dosing in obese patients, particularly those following bariatric surgery, therefore appears a difficult task.

Materials and Methods: We reviewed and summarized relevant literature and available information on drug-disease interaction and pharmacokinetic alterations associated with obesity and bariatric surgery.

Results: Adipose tissue accumulation, changes in regional blood flow, and changes in plasma protein binding capacities change the volume of distribution of drugs in obese patients. Additionally, cytochrome P450 enzyme activities may be changed, although not in a consistent manner. For example, CYP3A4 activity appears to be decreased in obesity, but 1 year after bariatric surgery, metabolism of CYP3A4-dependent drugs is enhanced despite the loss of intestinal CYP3A4 activity through surgery. GFR is transiently increased in early obesity and then tends to decline secondary to glomerular damage that develops with longstanding obesity. Several examples for dose adjustment suggestions were identified in the literature, many not based on solid evidence. Pharmacokinetic consequences of bariatric surgery and implications for drug therapy are divergent and individually influenced by type of surgery, drug properties and potential intestinal adoptions after surgery.

Conclusions: We identified a tremendous knowledge gap caused by the lack of appropriate studies regarding dose adjustments in obesity and after bariatric surgery. The lack of knowledge poses a safety concern in massively obese subjects, particularly for drugs with a small therapeutic window.

Predictive Ability of Different Analytical Parameters in Mycophenolate Pharmacokinetics and Dosing

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Background: Mycophenolate (MPA), an antimetabolite immunosuppressant of choice in solid organ transplant regimens, is available in two compounds (mofetil and sodium) and displays large between-subject pharmacokinetic (PK) variability. The aim of this study was to identify and model the different factors influencing MPA variability.

Methods: Patients treated with oral mycophenolate (mofetil or sodium) in our institution and having a record of drug serum levels were included in this observational, cross-over study over a period of six years (2004-2010). Both biodemographic (age, sex, weight, height, ethnicity) and analytical data (creatinine, total and direct bilirubin) were collected. Renal function was assessed by CKD-EPI formula. The influence of these variables on mycophenolate pharmacokinetics was evaluated following a multiple linear regression model.

Results: Data from 136 patients, treated with mycophenolate mofetil (64%) or sodium (36%), were included; mean age 53 years, 67% men. Dose values MPA/kg and minimum plasma drug concentration (Cmin) in addition to serum creatinine and bilirubin - total and direct - were [mean (SD)] 11 mg/kg (3.6), 2.43 mg/mL (1.61), 1.69 mg/dL (3.10), 0.61 mg/dL (0.28), 0.28 mg/dL (0.10), respectively.
respective. Mean renal function was 58.8 mL/min/1.73 m² (23.2),
according CKD-EPI formula. The regression analysis showed that
19.4% of C trough variation can be explained by the different drug
formulation (P = 0.018) and the individual clearance pattern of each
patient - renal (P = 0.001) and hepatic function (P = 0.033).

Conclusions: MPA formulation, as well as renal (CKD-EPI) and
hepatic function (total bilirubin), were the covariates identified as
influencing MPA C_trough. Therefore, individualisation of MPA treat-
ment using a forecasting model to assess target concentration that
contemplates these factors must be considered in preference to giving
a standard dose.

COMPARATIVE SAFETY PROFILE OF AMOXICILLIN
ALONE AND IN ASSOCIATION WITH
CLAVULANIC ACID IN PEDIATRICS: DATA FROM
SPONTANEOUS REPORTING IN ITALY

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Background or Introduction: Amoxicillin alone and with clavulanic
acid are among the most prescribing antibacterial agents in Italy.
These drugs are generally well tolerated and usually prescribed by
pediatricians, although published studies indicate that they are fre-
quently associated with adverse drug reactions (ADRs), in particular
cutaneous and gastrointestinal ones. We analyzed the Italian database
of spontaneous reporting of suspected ADRs in order to compare the
safety profile of amoxicillin and amoxicillin/clavulanic acid (amoxi-
clav) in pediatrics.

Material and Methods: Reports of suspected ADRs due to amoxicil-
in and amoxi-clav in pediatric patients, until 1 September 2014,
were extracted. ADRs were coded using MedDRA terminology. To
evaluate the correlation between drug use and occurrence of ADRs a
disproportionality analysis through Reporting Odds Ratio (ROR)
was performed.

Results: We collected 3.345 reports associated with amoxicillin and
amoxicillin/clavulanic acid, 1.188 (35.5%) related to amoxicillin and
2.157 (64.5%) to amoxicillin with clavulanic acid. The percentages
of serious ADRs were 12% for amoxicillin and 16% for amoxi-clav.
The percentage of skin reactions was higher for amoxicillin (75%)
than for amoxicillin/clavulanic acid (67%) and for gastrointestinal
reactions was higher for amoxicillin/clavulanic acid (16%) than for
amoxicillin (10%). For amoxicillin, significant disproportionality
was observed only for cutaneous ADR like dermatitis (ROR, 2.31;
95% CI, 1.26–4.25), rash (1.30; 1.08–1.57), erythematous rash
(1.70; 1.18–2.45). For amoxicillin/clavulanic acid was observed only
for gastrointestinal ADR: diarrhoea (1.56; 1.15–2.12), abdominal
pain (2.11; 1.14–3.93) and sickness (1.69; 1.20–2.38).

Conclusions: Our analysis shows a different safety profile for amoxi-
cillin and amoxi-clav in paediatrics: the first is associated with an
higher risk of skin reactions while the amoxi-clav with gastroin-
testinal ones. Nevertheless, data did not reveal an increased risk of
liver damage from clavulanic acid than amoxicillin alone, as widely
reported in literature.

PSCRIBE: A PHARMACOTHERAPY E-LEARNING
WEB-APPLICATION ENABLING REGISTRATION
AND MAPPING OF THE RATIONAL DRUG-CHOICE
PROCESS OF STUDENTS AND EXPERTS

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Introduction: “Pscribe” is a problem-based, case-oriented and multi-
functional pharmacotherapy e-learning web-application based on the
WHO-6step patient-treatment-model. Aim of this study is: 1) to test
the data-tracking module (DaTM) of Pscribe as a valid instrument
that can be used to automatically register and map data during the
drug-choice process (tDCP), 2) to compare tDCP of bachelor medical
students and experts.

Methods: DaTM automatically registers online 26 variables related
to drug-choice behaviour including: the quality of drug-therapy
choice (QDTC), the duration of every taken step (DoStep) in the
6step route and the number of consultations on drug information
[NoCoDi] during tDCP. 1) Its technical reliability was assessed with
the help of predefined paper protocols; all input values were com-
pared with output values, 2) We compared 85 bachelor students in
four groups (n = 18 ± 25) with one expert group (n = 5) solving
the same patient-case problems. Data were collected, analysed and
visualised using DaTM, Excel, SPSS and MATLAB.

Results: 1) Input values of all tested 26 variables are 100% matching
with the output values. The online time-delay (~3 seconds) spend
in each registered step is corrected, 2) The student groups differed
significantly (P < 0.05) from the expert group in the QDTC scores
and duration of the relevant drug-treatment step DoStep 1-7, and
(P < 0.01) in [NoCoDi]. We could perform pattern analysis of how
participants per group went through the 6step route, visualized by a
matrix method and yielded various step-patterns.

Conclusions: 1) Pscribe is a valid instrument to automatically register
and map data during tDCP, 2) QDTC, DoStep 1-7 and NoCoDi may
represent good variables to discriminate and reflect differences in
knowledge and reasoning skills between students and experts dur-
ing tDCP. Combining these data with analysis of step patterns will
provide insight in the way optimal drug choices are made.

CARDIOPROTECTIVE PROPERTIES OF
POLYPHENOL CONCENTRATE IN RAT MODEL OF
DOXORUBICIN-INDUCED CARDIOMYOPATHY

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Purpose: Present study aimed to investigate possible cardioprotec-
tive properties of polyphenol concentrates obtained from Cabernet
Sauvignon type of Kazakhstani grapes using rat model doxorubicin-
induced cardiomyopathy.

Methods: Study was conducted on 20 white outbred female rats
weighing 160±20 g. that were divided into three groups: two
groups with cardiomyopathy (14 rats) and one intact group (6 rats).
Cardiomyopathy was obtained by i.p. administration of doxorub-
icin (8.0 mg/kg). The experimental group (7 rats) was receiving
intragastrically 0.5 ml of polyphenols concentrate during the next
7 days after injection of doxorubicin. The control group of animals
with cardiomyopathy (7 rats) was not treated. Activity of aspartate
aminotransferase (AST) was determined in plasma. An oxidative
status in rats’ blood plasma was analyzed with 4 FRAS (Evolveo
srl, Italy) using d-ROMs Test, which indicates the amount of free
radicals, and PAT Test, which characterizes total antioxidant ac-
ivity of blood plasma.
**Results:** The AST content, a measure of cytolysis, was higher for 22% in animals with doxorubicin cardiomyopathy than in the intact animals. Administration of polyphenols restored the AST content degree to normal values. The d-ROMs test showed an activation of oxidative stress in control group compared to the intact animals by 24%, whereas the administration of polyphenols decreases oxidative stress activity by 12%. In comparison with intact animals, rats with cardiomyopathy had a decrease in antioxidant potential by 28% according to the PAT Test. However, the treated with polyphenols group had 9% higher total antioxidant activity than the control group.

**Conclusion:** A concentrate of polyphenols obtained from Cabernet Sauvignon prevents reduction of the total antioxidant activity of plasma, limits the development of oxidative stress, and prevents cytolytic processes in rats with doxorubicin cardiomyopathy.

**Background:** Five-oxoproline is a product of desordurated glutathione metabolism in the gamma glutamyl cycle: glutathione deficiency removes the feedback inhibition resulting in the formation of γ-glutamylcysteine and elevated concentrations of γ-glutamylcysteine leading to the formation of 5-oxoproline, which is degraded by 5-oxoprolinase. Both paracetamol and flucloxacinill interact with the gamma glutamyl cycle. Paracetamol depletes glutathione which leads to the accumulation of γ-glutamylcysteine that is a precursor for 5-oxoproline and flucloxacinill inhibits 5-oxoprolinase which also leads to accumulation of 5-oxoproline. The accumulation of 5-oxoproline, an acid residue, may lead to a high anion gap and a metabolic acidosis. Although a few cases of this drug-drug interaction are published, it is still not included in the summary of product characteristics of paracetamol and flucloxacinill or included in medication safety monitoring systems in hospitals and pharmacies.

**Material and Methods:** We analyzed all submitted reports to the Netherlands’ Pharmacovigilance Centre Lareb till 31 December 2014 on this drug-drug interaction.

**Results:** Lareb received 3 reports of metabolic acidosis where both paracetamol and flucloxacinill, used in therapeutic doses, were marked as suspected and interacting drugs. The cases concern 3 females of older age (67, 72 and 78 years). The aberrant mechanism of the 72 year old female was treated with acetyl cysteine; she died. The other 2 women were treated with sodium bicarbonate and recovered. We could not confirm a relationship between the treatment and the outcome of the interaction.

**Conclusions:** Our reported cases contribute to the suspicion of a relationship between metabolic acidosis and concomitantly used paracetamol and flucloxacinill. This drug interaction should be included in the summary of drug characteristics and included in medication monitoring systems in health institutions.

**EVALUATION OF ACUTE CARDIOVASCULAR EFFECTS OF IMMEDIATE-RELEASE METHYLPHENIDATE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER**

**Background:** Attention-Deficit Hyperactivity Disorder (ADHD) is a highly prevalent disorder, with peak onset in childhood and adolescence. It is characterized by inattentiveness, hyperactivity, and impulsivity. Immediate-release methylphenidate (IR-MPH) has raised concerns about potential cardiovascular adverse effects within a few hours after administration. This study was carried out to investigate acute effects of IR-MPH on ECG in a pediatric population.

**Methods:** A total of 34 consecutive patients with ADHD (51 males and 3 females; mean age = 12.14+2.6 years, range 6-19 years), receiving a new prescription of methylphenidate (MPH), underwent a standard ECG 2 hours before and after the administration of IR-MPH 10 mg per os. Basal and post-treatment ECG parameters, including mean QT (QTc), QT dispersion (QTD) interval duration, T peak – T end (Tpepe) intervals and Tpepe/QT ratio were compared.

**Results:** Significant modifications of both QTc and QTD values were not found after drug administration. QTD fluctuated slightly from 25.7 ± 9.3 ms to 25.1 ± 8.4 ms; QTc moved from 407.6 ± 12.4 ms to 409.8 ± 12.7 ms. A significant variation in blood pressure (BP) (Systolic BP 105.4 ± 10.3 vs 109.6 ± 11.5; P < 0.05. Diastolic BP 59.2 ± 7.1 vs 63.1 ± 7.9; P < 0.05) was observed, but all the data were within normal range. Heart rate (HR) moved from 80.5 ± 15.5 bpm to 87.7 ± 18.8 bpm. No change in Tpepe values was found but...
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1 a statistically significant increase in TpTe/QTc intervals was found
2 with respect to basal values (0.207 ± 0.02 ms vs 0.214 ± 0.02 ms;
3 P = 0.01).
4
5 Conclusions: The findings of this study show no significant changes
6 in ECG parameters. Our data suggest a relative cardiovascular safety
7 of IR-MPH in childhood, even if stimulants may exert a cardiovascular
8 effect on BP and HR. TpTe values can be an additional parameter
9 to evaluate borderline cases.

THE EFFECT OF DEXMEDETOMIDINE AND
DESKET PROF ON RAT S TATIC NEUROUS
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Background: Dexmedetomidine (DXM), is a selective α2-adreno-
ceptor agonist agent that used because of its sedative, anxiolytic
and analgesic effect. Desketprofen (DXT), which used for analgesic
properties, is a non-selective nonsteroidal anti-inflammatory drug.

In this study, we aimed to investigate and compare DXM and DXT
effects on the peripheral nerve transmission.

Material and Methods: Isolated rat sciatic nerves which were trans-
ferred to the nerve chamber includes Krebs solution, were stimu-
lated by standard square wave pulse protocols. The compound
action potentials (CAPs) were recorded from stimulated nerves with
electrophysiological methods. DXM (n = 8) and DXT (n = 8) were
administered in the nerve chamber with cumulative concentrations
(10-9 to 10-5 M) and CAPs were recorded for 5th and 10th minutes.

The area under a CAP waveform, maximum depolarization values,
maximum derivatives, latency periods and conduction velocity of the
CAPs were calculated.

Results: In this in vitro study, both of DXM and DXT, significantly
depressed all CAPs parameters in a dose dependent and reversible
manner (P < 0.05). The significantly differences were found between
DXM and DXT in terms of the nerves transmission inhibition (P >
0.05).

Conclusions: Higher doses of DXM were found to suppress the
transmission of fast conducting fibers, but DXT was found to sup-
press the time-dependent effects on the slow conducting fibers, the
dose-dependent effect on medium and fast conducting fibers.

GENERIC OLANZAPINE SUBSTITUTION IN
PATIENTS WITH SCHIZOPHRENIA: ASSESS-
MENT OF SERUM CONCENTRATIONS AND
THERAPEUTIC RESPONSE AFTER SWITCHING
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Introduction: Several reports of loss of efficacy or adverse effects
have been described after generic substitution of antipsychotics. To
date, studies comparing serum drug levels in patients switched to
generic antipsychotics in a standard clinical setting are lacking. The
aim of this study was to investigate if switching to generic olanzapine
in patients affected by schizophrenia is associated with differences in
its serum concentrations and therapeutic response.

Methods: Pre- and post-switching serum olanzapine concentrations
were compared in schizophrenic inpatients who were switched from
a chronic treatment with branded olanzapine to the same dose of
its generic alternative. The Positive and Negative Syndrome Scale
(PANSS) was concurrently administered to assess modifications in
schizophrenia symptom control.

Results: A total of 25 patients (13 females and 12 males, mean
age 41.2 ± 12.8 years) concluded the study. Mean olanzapine dose
was 12.2 ± 3.4 mg/day. The mean olanzapine serum concentrations
decreased from 27.7 ± 14.4 ng/mL during treatment with the branded
formulation, to 22.6 ± 12.3 ng/mL after the switching to the generic
formulation (P < 0.01). The log-transformed ratio of generic/brand-
named olanzapine serum concentration at steady-state was 0.81 (90%
CI: 0.72–0.91). Total PANSS scores did not significantly change after
switching from branded to generic formulation (49.6 ± 8.3 vs 48.6 ±
9.5, P = 0.777). No patient exhibited disease relapse or required
dose adjustment after switching.

Conclusions: Significantly lower serum olanzapine concentrations
were found after switching from branded to generic olanzapine.
Although these modifications did not significantly impair schizophrenia
symptoms control, it cannot be excluded that a longer exposure
from lower olanzapine serum concentrations may result in relapse of
schizophrenic symptoms. Generic substitution should be considered
as an indication for therapeutic drug monitoring in psychiatry.

THE CYP2C19*2 AND CYP2C19*17
POLYMORPHISMS PLAY A VITAL ROLE IN
PLATELET RESPONSIVENESS TO CLOPIDOGREL
AFTER PERCUTANEOUS CORONARY
INTERVENTION: A PHARMACOGENOMIC STUDY
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Background: Clopidogrel inhibits platelet activation and aggrega-
tion by blocking the P2Y12 receptor. Dual antiplatelet therapy with
clopidogrel and aspirin is recommended treatment by current guide-
lines for patients undergoing percutaneous interventions. Recurrent
ischemic cardiac events after this treatment showed the lack of plate-
let responsiveness to clopidogrel and defined as clopidogrel resist-
ance. Several mechanisms have been implicated in the development of
clopidogrel resistance, but genetic variations have a pronounced
effect. Therefore, we aimed to investigate the most noticeable vari-
ations in the genes involved in clopidogrel pharmacokinetics and
pharmacodynamics.

Material and Methods: Three hundred forty-seven Turkish patients
underwent elective or emergency percutaneous coronary interven-
tions with stent implantation are included in our study. Platelet reac-
tivity (PRU) and % inhibition were measured with VerifyNow P2Y12
assay in blood samples collected from patients that took a standard
dose of clopidogrel (75 mg/day) for at least 7 days. The variations in
the CYP2C19, CYP3A4, CYP2B6, ABCB1, ITGB3 and PON1 genes
are genotyped using the Sequenom MassARRAY system.

Results: When grouped the patients with PRU values ≥208 as resist-
ant to clopidogrel, it was determined that 104 (30%) patients were
resistant and 243 (70%) patients were nonresistant. A significant
association was found between CYP2C19*2 (G636A) polymorphism
and clopidogrel resistance (χ² = 25.09, P < 0.001). A allele frequency
of this polymorphism was high in patients with resistance, its odds
ratio was 2.92 compared to G allele (χ² = 4.46).

Conclusions: The aim of this study was to investigate if switching to
generic olanzapine in patients affected by schizophrenia is associated with differences in its serum concentrations and therapeutic response.

Methods: Pre- and post-switching serum olanzapine concentrations were compared in schizophrenic inpatients who were switched from a chronic treatment with branded olanzapine to the same dose of its generic alternative. The Positive and Negative Syndrome Scale (PANSS) was concurrently administered to assess modifications in schizophrenia symptom control.

Results: A total of 25 patients (13 females and 12 males, mean age 41.2 ± 12.8 years) concluded the study. Mean olanzapine dose was 12.2 ± 3.4 mg/day. The mean olanzapine serum concentrations decreased from 27.7 ± 14.4 ng/mL during treatment with the branded formulation, to 22.6 ± 12.3 ng/mL after the switching to the generic formulation (P < 0.01). The log-transformed ratio of generic/brand-named olanzapine serum concentration at steady-state was 0.81 (90% CI: 0.72–0.91). Total PANSS scores did not significantly change after switching from branded to generic formulation (49.6 ± 8.3 vs 48.6 ± 9.5, P = 0.777). No patient exhibited disease relapse or required dose adjustment after switching.

Conclusions: Significantly lower serum olanzapine concentrations were found after switching from branded to generic olanzapine. Although these modifications did not significantly impair schizophrenia symptoms control, it cannot be excluded that a longer exposure from lower olanzapine serum concentrations may result in relapse of schizophrenic symptoms. Generic substitution should be considered as an indication for therapeutic drug monitoring in psychiatry.
TOXIC TOBRAMYCIN LEVELS AFTER TOBRAMYCIN INTAKE VIA SELECTIVE DECONJUGATION OF THE DIGESTIVE TRACT (SDD)

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Background: Intensive Care Unit (ICU) patients in our hospital are treated for selective deconjugation of the digestive tract (SDD). In SDD tobramycin is given as mouth paste and oral suspension, dosing 4–8 times a day 80 mg. High trough blood levels of tobramycin can lead to nephrotoxicity and ototoxicity. However, in SDD, tobramycin suspension is given orally and aminoglycosides are not absorbed via the gut. Therefore, SDD will, generally, not lead to systemic exposure. However, we describe a patient with Graft Versus Host Disease (GVHD) who developed toxic tobramycin levels.

Methods: In this case report, we describe a 34 year old male patient with Acute Myeloid Leukemia. After allogenic stem cell transplantation he developed GVHD of the intestines, amongst all leading to severe diarrhea. Previously, several ICU patients with SDD and GVHD developed systemic tobramycin exposure. Therefore, tobramycin levels were measured by means of EMIT Immunoassay (Architect, Abbott).

Results: After use of 8 times a day 80 mg tobramycin orally for 30 days, his tobramycin trough level was 3.5 mg/L (reference <0.5 mg/L). His creatinine was 102 μmol/L and urea was 23.1 mmol/L (increase >20% last 4 days). Tobramycin was stopped and levels dropped to 0.87 mg/L after 2 days and 0.22 mg/L after 4 days. Tobramycin was started again in a regimen of 4 times a day 80 mg tobramycin orally, under daily monitoring of tobramycin levels. Creatinine and urea recovered. High tobramycin levels were contributed to systemic leakage of tobramycin via the intestines.

Conclusion: In SDD, tobramycin is normally not absorbed. However, in severe intestine GVHD, systemic absorption of tobramycin can occur. In this patient toxic tobramycin levels were combined with impaired renal function. In patients with GVHD of the intestines and frequent administration of tobramycin-containing SDD frequent monitoring of tobramycin levels is recommended.

METFORMIN PROMOTES THE INHIBITORY EFFECT OF 5-AMINOSALICYLIC ACID ON INFLAMMATION-MEDIATED PROLIFERATION AND PROGRESSION OF COLORECTAL CANCER CELL LINES

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Introduction: The link between inflammation and cancer has been suggested and confirmed by the use of anti-inflammatory therapies in cancer prevention and treatment. Five-aminosaliclyc acid (5-ASA) was shown to decrease the growth and survival of colorectal cancer (CRC) cells. Metformin, an oral anti-diabetic drug, decreased the incidence of colorectal adenomas in diabetic patients with previous CRC and induced apoptosis in several cancer cell lines. This study addresses the combinatory effect of 5-ASA and Metformin and explores their role on oxidative stress markers, inflammatory mediators, as well as apoptosis on HCT-116 and Caco-2 CRC cell lines.

Materials and Methods: Drug interaction was evaluated using isobologram equation and the expression of pro-inflammatory cytokines was determined by RT-PCR. Protein levels of BAX and Bcl-2 was determined using western blotting and matrix metalloproteinases-2 and -9 by zymography. Caspase-3 activity, malondialdehyde (MDA), glutathione (GSH) and nitric oxide contents were measured spectrophotometrically.

Results: Metformin enhances CRC cell death induced by 5-ASA, this manifested a significant activation of apoptotic machinery, caspase-3 activity and the BAX/Bcl-2 protein ratio. In addition, the combination resulted in an exaggerated increase in MDA and decrease in intracellular GSH levels indicating an increase in oxidative stress and apoptosis. Moreover, metformin also enhanced the anti-inflammatory effect of 5-ASA by significantly decreasing COX-2, IL-6, IL-1α, and TNF-α and its receptors, TNF-R1 and TNF-R2. A significant reduction in MMP-2 and MMP-9 enzyme activity was also observed upon treatment with the combination indicating a decrease in invasiveness.

Conclusion: Metformin potentiates the antitumor effect of 5-ASA on CRC cells by inhibiting inflammation-mediated tumor progression suggesting their potential use as an adjuvant treatment in CRC.

TRAINING OF VARIOUS PARTICIPANTS COOPERATING IN MEDICINES DEVELOPMENT.
THE PHARMATRAIN CONCEPT

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The participation in global clinical drug trials of innovative agents as well as the need for local production and evaluation of follow-on generics and biosimilar medicines necessitates intensive training of specialists working both in the pharmaceutical industry and at the clinical investigation sites. In Hungary clinical pharmacology is a secondary specialization built on top of a clinical specialty. For performing a phase I drug trial the responsible clinical investigator needs to have a clinical pharmacology board examination. Accordingly, in their training the teaching of medicine development and drug regulatory science occupies a central role. For performing other phases of drug trials clinical investigators need a GCP certificate. Recently for training the increasing number of non-medically qualified scientists working in medicines development a harmonized European educational curriculum leading to clearly defined learning outcomes has been developed within the Innovative Medicines initiative-PharmaTrain (IMI-Pht) program. As part of this project, a regional university training network, the Cooperative European Medicine Development Course (CEMDC), was organized in Central-Eastern Europe which is coordinated by the Semmelweis University. Finally, the introduction of the Clinical Investigators Course (CLIC) developed jointly by PharmaTrain and the European Clinical Research Infrastructures Network (ECRIN) is in progress at several European Universities with the aim to increase the competency of clinical investigators. The different educational programs available now are essential to increase the quality of medicines development in general and the competitiveness of the European pharmaceutical research.

LICHENOID REACTIONS ASSOCIATED WITH TNF-α INHIBITORS IDENTIFIED THROUGH SPONTANEOUS REPORTING SYSTEM

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2 Introduction: Lichenoid reactions (LR) are an uncommon mucocutaneous inflammatory disease. As adverse drug reactions (ADRs) have been attributed to several drugs, including tumour necrosis factor alpha inhibitors (TNF-α inhibitors). The aim of the study is to describe the main characteristics of LR attributed to TNF-α inhibitors received by the Spanish Pharmacovigilance System (SPvS).
3 Material and Methods: Spontaneously reported cases describing LR ("lichen planus", "oral lichen planus", "keratosis lichenoid", and "pityriasis lichenoides") associated with TNF-α inhibitors (etanercept, infliximab, adalimumab, certolizumab-pegol and golimumab) received by the SPvS between 1983 and 2014 were selected. The variables studied were age and sex of the patient, suspect drugs, indication, induction period, seriousness and outcome of LR, previous knowledge of the drug-reaction association, rechallenge, and the existence of alternative causes.
4 Results: During the period of study, the SPvS received 3,864 spontaneous reports of ADRs to TNF-α inhibitors; 211 (51.3%) of them described dermatological ADRs and only 9 were LR; lichen planus (3 cases), oral lichen planus (1), keratosis lichenoid (4) and pityriasis lichenoides (1). Six cases were associated with infliximab, 2 with adalimumab and 1 with etanercept. The median age of the patients was 49 years (min. 29 – max. 73); 5 were men and 4 women. Eight reports described serious LR. The induction period was between 30 days and 2 years. The outcome after withdrawal of the suspect drug was recovery in 4 cases; not recovery in 2 cases and unknown in 3 cases. Five reports described previously unknown or poorly known drug-induced LR; in one case alternative explanations were excluded.
5 Conclusions: The SPvS has received spontaneous reports of LR associated with TNF-α inhibitors. Despite the difficulty to exclude alternative causes, temporal sequence and improvement after drug withdrawal suggests a causal relationship. It would be appropriate to include LR in the product information.

LACK OF ASSOCIATION BETWEEN CYP2D6 GENETIC POLYMORPHISM AND PHARMACOKINETICS OF CLOMIPHENE

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Introduction: Clomiphene citrate is a selective estrogen receptor modulator that enhances the release of gonadotropin-releasing hormone and widely prescribed for ovulation induction. As clomiphene shares triphenylethylene structure with other selective estrogen receptor such as tamoxifen, it is suggested that CYP2D6 is involved in the clomiphene metabolism. CYP2D6 is highly polymorphic enzyme and plays an important role in variability of drug response. Therefore, the aim of the study was to investigate the role of CYP2D6 genetic polymorphism on the pharmacokinetics of clomiphene.

Material and Methods: Twenty two healthy Korean subjects were volunteered and divided into three different groups according to CYP2D6 genotype: CYP2D6*1/*1 (n = 8), CYP2D6*1/*2 (n = 8) and CYP2D6*2/*2 (n = 6). After overnight fasting, each subject received a single oral dose of 50 mg clomiphene. Blood samples were collected up to 168 hours after drug intake, and plasma concentrations of clomiphene were determined by using liquid chromatography-tandem mass spectrometry system. Results: Although Cmax of clomiphene in CYP2D6*1/*10 group was 1.4-fold higher than that in CYP2D6*1/*10 group (P = 0.0185), AUC0-∞, apparent oral clearance (CL/F), and t1/2 were not significantly different among three genotypes.

Conclusions: Our study showed that CYP2D6 genetic polymorphism did not play an important role on the pharmacokinetics of clomiphene.

CYP3A5 POLYMORPHISM AFFECTS THE INCREASE IN CYP3A ACTIVITY AFTER LIVING KIDNEY TRANSPLANTATION IN PATIENTS WITH END STAGE RENAL DISEASE

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Background: Several previous studies have shown that renal failure decreases not only renal elimination but also metabolic clearance of drugs, particularly those metabolized by cytochrome P450 (CYP3A). We have previously reported that CYP3A activity increases in patients with end stage renal disease (ESRD) after kidney transplantation, with wide interindividual variability in the degree of increase. The aim of this study was to evaluate the influence of CYP3A5 polymorphism on the increase in CYP3A activity after living kidney transplantation, by measuring plasma concentration of 4β-hydroxycholesterol.

Material and Methods: This prospective study recruited 20 patients with ESRD who underwent the first living kidney allograft transplantation, comprising 12 patients with CYP3A5*1 allele (CYP3A5*1/*1 or *1/*3) and 8 patients without CYP3A5*1 allele (CYP3A5*3/*3). Morning blood samples were collected before and 7, 14, 30, 90 and 180 days after living kidney transplantation. Plasma concentration of 4β-hydroxycholesterol was measured using GC-MS.

Results: No significant difference in creatinine clearance over time was observed between patients with CYP3A5*1 allele and patients without CYP3A5*1 allele, suggesting that the degrees of recovery in renal function after living kidney transplantation are similar in the two groups. However, plasma concentrations of 4β-hydroxycholesterol on days 90 after living kidney transplantation were significantly higher in the presence of CYP3A5*1 allele than in the absence of CYP3A5*1 allele. Areas under the plasma concentration of 4β-hydroxycholesterol–time curves from before to 180 days after living kidney transplantation were significantly higher in patients with CYP3A5*1 allele than in patients without CYP3A5*1 allele.

Conclusions: These findings suggest that CYP3A activity may increase markedly associated with recovery of renal function in patients with CYP3A5*1 allele, and that decreased CYP3A activity associated with renal failure may be caused by decrease in CYP3A5 activity.

EVALUATION OF WEBSITES ON HUMAN PHARMACOLOGY

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Introduction: Popular health internet sites offer information that may affect consumer's choice of treatment, however, may also contain inaccurate information. To enable consumers, it is imperative to evaluate content of health websites including the meta-criteria: relevance, accessibility, selection, validity, interchange, site transparency, links, quality, assurance and safeguards. Our objective is to...
A SURVEY OF HEMATOLOGICAL AND BIOLOGICAL ABNORMALITIES IN DRESS SYNDROME

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1Faculty of Medicine of Sousse, Tunisia; and 2Farhat Hached University Hospital of Sousse, Tunisia

Background: DRESS syndrome is a rare hypersensitivity syndrome associated with high variability on its hematological and biological test findings. The aim of this study was to detail, from a patient serial, the hematological abnormalities as well as the biological disturbances that may occur with DRESS.

Materials and Methods: All cases of DRESS reported to our pharmaceutical center from January 2009 to December 2014 were retained. Hemograms, liver level tests, LDH and CPK were detailed.

Results: Twenty-four cases concerned 7 women and 17 men. Median of age was 46.75 years old. The most involved drugs were: anticonvulsivants in 30% of cases, salazopyrine in 20% and allopurinol in 16%. Seventy-five percent had eosinophilia exceeding 0.5 g/L and 33% had eosinophilia exceeding 1 g/L. Leukocytopenia was present in 24% of cases. Lymphocytopenia in 16% and lymphocytosis in 33% of patients. Neutropenia was found in 12 % of cases. Fifty percent had cytolysis and 50% of them were exceeding 4 folds normal range whereas cholestasis was present in only 12% of cases. LDH and CPK values >2 folds upper normal range limit was present in 29% of cases. Almost 50% of them had values upper of 10 folds normal range.

Conclusions: Eosinophilia was the most frequently occurring hematological abnormality in our survey. Other hematological abnormalities observed were leukocytosis and neutropenia. Hepatic involvement in the form of hepatocellular injury was the most common visceral abnormality and it was present in 4 cases with sulfasalazine and in 3 cases with allopurinol. Liver injury may be a pro-drome of DRESS and patients with hepatocellular injury are relatively young in our survey (mean age of 36.3). Elevated LDH and CPK was observed most often with sulfasalazine. There is an evidence of great frequency of haematological abnormalities that occur during DRESS.

FENOFIBRATE-INDUCED PHOTOSENSITIVITY ASSOCIATED WITH LINGUAL AND ORAL MUCOSA HYPERPIGMENTATION

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Introduction: Fenofibrate is a lipid regulating agent approved in the treatment of hyperlipidemia. Cutaneous adverse reactions attributed to the drug are rare including acute hypersensitivity reactions, pruritus and skin ulcer. Although photosensitivity induced by fenofibrate

1 nominate and describe the top websites on applied pharmacology and provide a general view of governmental and non-governmental sites on pharmaceuticals applied to human health.

**Material and Methods:** The search engine was Google and search terms were “pharmaceuticals” OR “pharmacology” OR “medicines” OR “drugs” AND “human health”, in English or Portuguese. For each website search, the first 50 results were evaluated. Sites of non-web material, aiming commerce, restricted to health professionals or by payment were excluded. Quality assessment of retrieved websites was performed with a tool adapted from HON, HHTI and American Medical Association (J Health Inform, 2009, 1:27–33).

**Results:** Top sites were defined as those that presented all of the nine evaluation meta-criteria. There were 40 websites with relevant and accurate information on evidence for drug use for human health that are easy-to-use, disclose information about sponsorship, purpose/ scope, audience and intended use, currency, source/credentials and link to sources. There were 7 sites from worldwide organizations (ex: WHO, UNESCO, CIOMS); 13 sites from the Americas; 10 sites from Europe; 4 sites from Africa; 3 sites from Asia; 4 sites from Oceania.

**Conclusions:** To be useful for consumer’s choice of pharmacological treatment it is necessary to evaluate the quality of the communication of knowledge provided in internet sites. The great amount of sites disclosed using search tools result in few that provide evidence of effectiveness of treatment for consumer’s information. In the meantime, it is extremely important to ensure publicity of the top websites.
was reported in rare cases in the literature, there are no reports of fenofibrate-induced photosensitivity associated with lingual and oral mucosa pigmentation. Herein, we report the first case, to the best of our knowledge, of a patient who developed gingival, labial, lingual pigmentation associated with photosensitivity after fenofibrate therapy.

Case report: A 43-year-old woman presented with skin eruption affecting the sun-exposed areas. Her medical history was unremarkable except for hyperlipidemia treated with fenofibrate (200 mg daily) started three months earlier. Physical examination revealed numerous variously sized hyperpigmented plaques over the sun exposed areas. Inspection of the oral mucosa revealed hyperpigmented macules. Laboratory investigation was in normal ranges except for triglycerides. Serum levels of adrenocorticotropic hormone and cortisol were also in normal ranges. Histologic examination revealed a non-specific lymphoplasmacytic infiltrate.

Discussion: Diagnosis of drug-induced photosensitivity is often challenging. It is based primarily on the history of drug intake and the clinical appearance of the eruption, primarily affecting sun-exposed areas of the skin. Among the class of fenofibrate, this photosensitizing capacity of fenofibrate is mainly determined by the photoexcited chemical structure, the benzophenone moiety. Our review of literature did not reveal any case of fibrin acid-induced mucosal pigmentation and our patient is the first case of fenofibrate-induced oral pigmentation. The suggested mechanism of fenofibrate-induced oral pigmentation in our patient can be related to a direct effect of the drug in melanin secretion.

Conclusion: Fenofibrate-photo-induced hypersensitivity is a known adverse effect of the drug. Besides, clinicians should be aware of the possibility of oral hyperpigmentation related to fenofibrate.

GENERALIZED BULLOUS FIXED DRESS ERUPTION: A CASE SERIES

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Introduction: Generalized bullous fixed drug eruption (GBFDE) is a rare and severe form of fixed drug eruption (FDE) that may be misdiagnosed with other forms of bullous drug eruptions (BDE).

Case Reports: Case 1: An 89-year-old man developed an indurated edematous plaque on his arm 1 day after acenaminophen ingestion. There was an extension of the lesion with occurrence of flaccid vesicles. There was a previous history of recurrent reaction in the same sites. The rash resolved after acenaminophen withdrawal. Case 2: A 48-year-old woman presented with well-defined bullous lesions and oval patches spread diffusely over her arms, trunk and face, which appeared 1 day after the consumption of mefenamic acid. The diagnosis of GBFDE was considered especially with a reported history of a previous reaction occurring in the same site. A patch test with mefenamic acid revealed a positive reaction. Case 3: A 51-year-old man developed well-limited bullous lesions located on the trunk, arms and scrotum, 24h after mefenamic acid intake. He reported two other previous episodes occurring in the same site. The role of mefenamic acid was confirmed by a patch test on a residual pigmented lesion.

Discussion: Differential diagnosis to GBFDE is BDE such as Stevens-Johnson syndrome and toxic epidermal necrolysis. A history of hyperpigmented and bullous lesions occurring at the same sites related to drug consumption may be helpful in diagnosing GBDE.

Positive rechallenge with the suspected drug is useful with FDE but it may be dangerous with GBFDE as lesions may be extensive and more severe. Patch tests on lesional skin may be a safe alternative to identify the incriminated drug in GBFDE.

Conclusion: Clinicians should be aware of the risk of GBFDE. Patch test may be a useful tool in identifying GBFDE.

HYPERSENSITIVITY TO AMOXICILLIN AFTER ALLOPURINOL-INDUCED HYPERSENSITIVITY SYNDROME: A CO-SENSITIZATION TO UNRELATED DRUGS

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Introduction: Allopurinol hypersensitivity syndrome is a rare but severe adverse drug reaction. Although cross-reactivity reactions are reported with chemically related drugs, drug hypersensitivity after a history of DRESS syndrome induced by chemically unrelated drugs is exceptional. Herein, we point out a possible co-sensitization to chemically and antigenically unrelated drugs: amoxicillin and allopurinol.

Case Description: A 76-year-old female with a 10-year history of hypertension and a six-year history of chronic renal failure was initiated on allopurinol for the treatment of hyperuricemia. Three weeks later, the patient developed generalized exanthema with fever and cervical lymphadenopathy. Biochemical investigation revealed hypersinophilia with cytolysis.

Allopurinol-induced hypersensitivity syndrome was suspected and the drug was withdrawn. All symptoms were relieved after two weeks. Four months later, the patient exhibited an extensive pruritic skin rash associated with fever and hypersinophilia, 2 days after amoxicillin intake for respiratory tract infection. Symptoms disappeared few days after amoxicillin withdrawal. We noted that our patient was previously exposed to amoxicillin without any history of hypersensitivity to the drug or to other beta-lactam drugs.

Discussion: Allopurinol hypersensitivity syndrome is a severe adverse reaction characterized by rash, fever, internal organ involvement occurring 2 to 6 weeks after drug initiation. It is more frequently associated with chronic renal insufficiency in relation to the accumulation of allopurinol’s metabolite leading to tissue damage. Hypersensitivity to amoxicillin after allopurinol-related DRESS, two drugs without any chemical or antigenic similarity, are rare and are due at least in part, to the administration of amoxicillin during the period of immunological depression following the hypersensitivity to allopurinol.

Conclusion: Clinicians should be cautious when prescribing amoxicillin to a patient with a previous history of hypersensitivity syndrome to allopurinol.

HYPERSENSITIVITY TO PENCILLINS DIAGNOSED WITH DELAYED READING PRICK TESTS

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Background: Penicillins are widely prescribed class of antibiotics because of their activity spectrum and cost effectiveness. Nevertheless they can be prohibited because of allergic reactions. In these cases, skin tests can be useful and have to be applied according to the pathomechanism of the allergy-induced by the drug. In immediate beta-lactam drug allergy, an IgE-mediated reaction can be demonstrated by a positive skin prick test with a reading at 20 mn. Herein, we report a case of hypersensitivity to penicillin diagnosed with a delayed reading prick tests.

Case Report: A 27 year old female with an unconfirmed history of anaphylaxis reaction to beta-lactamins in the age of 3 years is pre-
NUMMULAR ECZEMA SECONDARY TO INTERFERON BETa-1B THERAPY IN A PATIENT WITH MULTIPLE SCLEROSIS

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Introduction: Interferon beta-1b is an immunomodulatory drug with proven efficacy in the treatment of multiple sclerosis (MS). Herein, we report an unusual case of nummular eczema following exposure to interferon beta-1b in a middle-aged woman with MS.

Case Description: A woman in her 40s was diagnosed with the relapsing remitting form of MS. Four months after the first dose of interferon beta-1b (8 million units, one time weekly), the patient was seen in the dermatology clinic for evaluation of pruritus and multiple eczema-like lesions on the legs and bottom. Physical examination revealed erythematous nummular patches on the legs and bottom with linear excoriations (Figure 1). Involved skin biopsy revealed a mild epidermal hyperplasia with spongiosis and lymphocytic exocytosis, overlying parakeratosis and a perivascular lymphocytic dermal infiltrate including rare eosinophils. Interferon beta-1b was withdrawn, and the patient received 0.05% betamethasone dipropionate ointment. There was an improvement of the lesions.

Two months later, interferon was readministrated and few days later the patient noted an aggravation of the previous lesions with development of new lesions. Interferon was definitely stopped.

Discussion: In our case, the pathogenic role of the interferon-beta-1b seems likely, because the lesions occurred during the course of treatment, regressed after withdrawing the treatment, reappeared after the reintroduction of interferon, and other evident etiologies of eczema were absent. Skin manifestations resulting from treatment with interferon beta-1b consist principally of injection-site reaction with lesions varying from sclerotic dermal plaques to erythematous plaques to cutaneous ulcers. The etiology of nummular eczema is multifactorial, involving allergic, environmental, emotional, and nutritional factors.

Discussion: Physicians should be aware of this side effect induced by interferon beta-1b.
Clinical Therapeutics

metabolism profile. Our findings reveal that pharmacogenetic test, for
some polymorphisms, may be considerably efficacious in preventing
adverse effects.

Conclusion: Most of side effects can be avoided if pharmacoge-
netic tests become routinely applicable. Although differences in
drug response are increasingly recognized, there is an urgent need to
translate the knowledge in this area into clinical recommendations.
Pharmacogenetic tests may be a safe and reproducible tool in the
prevention of adverse drug reaction.

HYPOLIPIDEMIA AND ANTIDIABETIC EFFECT
OF AQUEOUS EXTRACT OF MESOCARP
LAYER (SPONGY LAYER) OF COCOS
NUCIFERA NUT IN WHITE ALBINO RATS
AND MEDICINAL EVALUATION OF THE
EXTRACT USING PHYTOCHEMICAL ANALYSIS,
GAS CHROMATOGRAPHY AND MASS
SECTROPHOTOMETER (GC-MS)

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Background: This study investigated the effect of the aqueous extract
of the mesocarp layer of Cocos Nucifera on blood sugar level and
lipid profile in normal and Streptozocin-induced diabetes rats and in
rats fed on a high fat diets (HFD) after which Phytochemical analysis
and Gas chromatography-Mass Spectrophotometric evaluation of
the extract was done.

Methods and Results: Mice treated with filtered and evaporated
aqueous extract (spongy layer) of Cocos nucifera (AECN) (10mg/kg,
30mg/kg, 90mg/kg p.o) and mice treated with glibenclamide
(10mg per kg) significantly reduced the Streptozocin (STZ) – induced
increase in blood sugar (Bg), Total Cholesterol (Tc), and Serum
Triglyceride level (Tg). AECN at 90mg/kg manifested a hypolipi-
demic effects but effectively lowered the elevated plasma BG level in
oral glucose tolerance test, while Glibenclamide showed a significant
reduction in TC, BG, TG in Normoglycemic rats. The histopatho-
logical analysis of Pancreas and the Plasma insulin level revealed
beneficial effects of AECN in protecting beta cells integrity. In mice
treated with AECN (10mg/kg, 30mg/kg, 90mg/kg), and mice that are
treated with fenofibrate 200mg/kg, the (HFD) associated rise in TC,
TG were significantly reduced. The hypcholesterolemic effects of
AECN appears more at 90mg/kg with significant decrease in VLDL
and LDL Cholesterol and an elevation of HDL Cholesterol. The
Phytochemical Screening and GC-MS analysis of AECN revealed
that AECN contained alpha, beta amyrin, and Pyrazine.

Conclusion: These findings reflect the potential antihyperglycemic
and hypolipidemic effects of AECN and suggest that alpha, beta
amyrin or Pyrazine could be a lead compound for drug development
effective in diabetes and atherosclerosis.

ANALYSIS OF BIOEQUIVALENCE STUDIES:
PROBLEMS, WAYS OF SOLUTION

Research objective: The investigation of drugs bioequivalence is the
main requirement of medical and biological control of generics in
Russia.

Materials and Methods: On the basis of Yaroslavl Clinical hospital
2 103 bioequivalence studies (BE) were conducted at the period of
2011 – 2015, including 12% with replicative design. Among these
studies 21 were foreign and 82 – domestic. Volunteers of both sexes
were involved in BE studies in the amount of 1437 people. From 18
to 103 volunteers participated in each study, depending on the pro-
tocol design (it is possible to hospitalize 45 volunteers in one time).

Results and Discussion: The strict control over BE studies conducted
by the Quality Department in accordance with SOPs. The results
revealed some defects of a general type: improper preparation of
protocols (31%), lack of protection of the subjects (19%), lack of
definition of responsibilities of the researcher (28%), the allocation
of responsibilities between the sponsor and the organizers of clinical
studies (24%). Using of Yaroslavl bioanalytical laboratory, which is
working according GLP rules, avoid the errors in the pharmacoki-
netic part of the study, incorrect statistical analysis. We are faced with
the following problems: the prevalence of non-compliance patients
- 4%, the high prevalence of adverse events in some studies up to
78%, different problems during bioanalytical part - 5%, the prob-
lems associated with the final report on the study - 2%. The center
has the experience of using the pharmacogenetics in BE studies to
reduce sample size (CYP2C9, CYP2C19, CYP2D6).

Conclusions: Some mistakes in planning of BE studies leads to
decreasing of drug efficacy and safety, loss of confidence in generics
and the rising of drug therapy cost in future.

COADMINISTRATION OF FLUOXAMINE AND TOLPERISONE IN RELATION TO CYP2D6
GENOTYPE

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Introduction: Tolperisone, a piperidine derivate, is used to relieve
spasticity of neurological origin and muscle spasm. CYP2D6 was
identified as the key enzyme in the metabolism of tolperisone and
CYP1A2 and CYP2C19 were also involved in the metabolism of
tolperisone. Fluvoxamine is an antidepressants and known as one
of CYP2C19 inhibitors. As CYP2D6 is very high polymorphic
and causes large interindividual differences in drug response, we investi-
gated the effects fluvoxamine, a CYP2C19 inhibitor, on the pharma-
cokinetic parameters of tolperisone.

Material and Methods: Thirty healthy Korean subjects were vol-
unteered and divided into three different groups according to
CYP2D6 genotype: CYP2D6*10/*10 (n = 10), CYP2D6*wt/*wt (n = 10),
CYP2D6*wt/*10 (n = 10). All subjects received a single oral dose of 150 mg tolperisone in the
control phase after overnight fasting. Before study day (day 6), a 50
mg oral dose of fluvoxamine was administered once a day for five
days. On day 6, subjects received a single oral dose of tolperisone
one hour after the administration of fluvoxamine. Blood samples
were collected up to 12 hours after drug administration, and plasma
concentrations of tolperisone were determined by using liquid chro-
matography-tandem mass spectrometry system.

Results: Cmax and AUC of tolperisone was significantly different in
each group between control phase and study day (P < 0.01). On study
day, Cmax increased by 3.6-fold, 2.0-fold, and 5.0-fold, respectively
in the CYP2D6*wt/*wt, CYP2D6*wt/*10, and CYP2D6*10/*10
group, compared to control phase. Also, apparent oral clearance
(CL/F) of tolperisone on study day decreased by 74.2%, 72.0%,
and 86.2%, respectively in CYP2D6*wt/*wt, CYP2D6*wt/*10, and
CYP2D6*10/*10 group, compared to control phase

Conclusions: Significant differences in the pharmacokinetics of tol-
perisone were observed after coadministration of fluvoxamine in
relation to CYP2D6 genotype.
COADMINISTRATION OF DULOXETINE AND TOLPERISONE IN RELATION TO CYP2C19 GENOTYPE IN KOREAN SUBJECTS

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Introduction: Tolperisone is a centrally acting muscle relaxant is prescribed for the treatment of muscle spasm. Tolperisone is predominantly biotransformed by CYP2D6, and to a lesser extent by CYP2C19 and CYP1A2. Duloxetine is a potent dual reuptake inhibitor of serotonin and norepinephrine and acts as an inhibitor of CYP2D6. As CYP2C19 is one of the most important polymorphic CYPs, the aim of study was to determine pharmacokinetic changes of tolperisone after coadministration of duloxetine according to CYP2C19 genotype.

Material and Methods: Twenty four healthy Korean subjects were volunteered and classified into three different groups in relation to CYP2C19 genotype: CYP2C19EM (CYP2C19*1/*1, n = 9), CYP2C19IM (CYP2C19*1/*2 or CYP2C19*1/*3, n = 8) and CYP2C19PM (CYP2C19*2/*2, CYP2C19*2/*3 or CYP2C19*3/*3, n = 7). In the control phase, all subjects received a single 150 mg oral dose of tolperisone after overnight fasting. After administration of 30 mg duloxetine twice in a day for consecutive three days, 150 mg oral dose of tolperisone was administered one hour after administration of a single 30 mg oral dose of duloxetine in test phase. Blood samples were collected up to 12 hours after drug administration, and plasma concentrations of tolperisone were determined by using liquid chromatography-tandem mass spectrometry system.

Results: Cmax of test phase increased by 1.93-fold, 1.80-fold, and 1.57-fold, respectively in CYP2C19EM, CYP2C19IM, and CYP2C19PM group, compared to control phase (P = 0.045, P = 0.027, and P = 0.031, respectively). AUC0-∞ of test phase was significantly higher in CYP2C19EM and CYP2C19IM group than that of control phase (P = 0.034 and P = 0.005, respectively), but there was no significant difference in CYP2C19PM group between control phase and test phase (P = 0.124).

Conclusions: Coadministration of tolperisone and duloxetine has significant effects on the pharmacokinetics of tolperisone according to CYP2C19 genotype.
AN EDUCATIONAL INTERVENTION TO IMPROVE NURSES REPORTING OF ADVERSE DRUG REACTIONS

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Introduction: Adverse drug reactions (ADR) are an important cause of mortality and morbidity leading to additional costs with health.

Z_LDQ0V: Drug safety data before commercialization is limited and incomplete, which is the reason why pharmacovigilance is important. ADR reporting system is efficient in drug safety monitoring. Nurses can have an important role in ADR reporting due to their daily activities of drugs administration (including vaccines). However, among these professionals, there a high rate of underreporting. Based on the reasons proposed by Inman for underreporting ADR, it was concluded that the main obstacles to ADR reporting among nurses were indifference (the belief that a single case cannot contribute to medical knowledge) and the lack of knowledge about the pharmacovigilance system. The aim of this study is to evaluate the quantitative and qualitative increase of ADR reports by nurses after an educational intervention.

Methods: A quasiexperimental study was performed in nurses working in primary care in Braga district, Portugal. One hundred thirteen individuals were placed in the intervention group while the control group included 590 nurses. Two educational interventions were performed to nurses working in primary care in ACEs Cavado II (intervention group) that focused on the problem of adverse drug reaction, the impact on public health and spontaneous reporting.

Statistical analysis were based on absolute and relative frequencies.

Results: Between January 2013 and September 2014 the Northern Pharmacovigilance Centre received 8 reports/100 nurses from the intervention group and 5 reports/100 nurses from control group.

Conclusions: The educational intervention increased 1.6 times the number of reports during the study period. The second intervention had more impact than the first one.

There was no significant increase in the quality of ADR reports in the intervention group. In the second intervention the number of reports increased only at the intervention day.

THE INFLUENCE OF NUTRITIONAL STATUS ON ACETAMINOPHEN METABOLISM IN HEALTHY SUBJECTS

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Background: Animal studies have shown that fasting and obesity are predisposing factors for acetaminophen-induced hepatotoxicity.

Fasting can decrease nontoxic clearace of acetaminophen by UDP-glucuronosyltransferases (UGT1A1, UGT1A6) and sulfortransferases resulting in increased formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), whereas obesity can increase NAPQI-formation by induction of hepatic CYP2E1. We investigated the effect of short-term fasting and a short-term high-fat diet on acetaminophen metabolism in healthy subjects. Furthermore, changes in UGT1A1-mediated metabolism were studied by using unconjugated bilirubin, metabolised by UGT1A1, as a proxy.

Materials and Methods: Nine healthy male subjects were enrolled in a crossover intervention study. Subjects received a single oral administration of 1000mg acetaminophen after an overnight fast following 3 interventions: (1) regular diet (control), (2) 36 hours of starvation and (3) 3 days of a high-fat diet consisting of 500 mL of cream supplemented to their regular diet. The sequence of the interventions was randomly assigned. Primary endpoint was the change in acetaminophen exposure defined as the difference in area under the plasma concentration-time curve (ΔAUC0-8 hours) using non-compartmental analysis. Changes in UGT1A1-mediated metabolism were investigated by comparing baseline unconjugated (indirect) bilirubin concentrations between the interventions.

Results: Short-term fasting increased acetaminophen exposure by 28.2% (ΔAUC0-8 hours, P = 0.021) and increased unconjugated bilirubin from 8.5 µmol/L (range, 3–21 µmol/L) to 21.5 µmol/L (range, 10–56 µmol/L) (P = 0.008) in comparison with control. Short-term high-fat diet did not affect acetaminophen exposure (ΔAUC0-8 hours = 0.15%, P = 0.374), but decreased unconjugated bilirubin from 8.5 µmol/L to 4.0 µmol/L (range, 2–10 µmol/L) (P = 0.013) when compared to the control intervention.

Conclusions: Fasting increases acetaminophen exposure and decreases nontoxic UGT1A1-mediated metabolism in healthy subjects. This may lead to increased hepatotoxicity. A high-fat diet did not alter acetaminophen exposure but increased UGT1A1-mediated metabolism.

THE VALUE OF COMPUTER ASSISTED MEDICATION REVIEW IN HOSPITALISED PATIENTS

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Introduction: Polypharmacy is one of the main risk factors for adverse drug events, drug–drug interactions and undertreatment.

This makes medication management in the hospital a challenging responsibility. A medication review is used to optimise therapy in a structured way. It is done manually and therefore prone to mistakes. The aim of this study was to evaluate the additional value of our CDSS to manual medication reviews compared with manual medication review alone on medication errors in the hospital.

Methods: During 4 months data were gathered by observation of the medication reviews during the weekly grand rounds at an internal and orthopaedic ward and electronic extractions were made all patients. The e-data were analysed by a Clinical Decision Support System (CDSS). After data collection, notifications obtained during the grand rounds and from the CDSS were analysed.

Results: In total 332 patients were reviewed, 219 (mean number of drugs = 9) at the internal ward (242 alerts from which 133 from cdds) and 113 (mean number of drugs = 10) at the orthopaedic ward (61 alerts from which 44 from cdds). Mean age on both wards was 67 years. Further data is shown in table.

<table>
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<tr>
<th>Type of error</th>
<th>Total</th>
<th>Value CDSS</th>
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<td>Indication without medication</td>
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<td>32 (54.2)</td>
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<tr>
<td>Medication without indication</td>
<td>48 (100)</td>
<td>0 (0)</td>
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<tr>
<td>Contraindication/interaction/side effects</td>
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<td>88 (86.3)</td>
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<td>Dosage problem</td>
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<td>Double medication</td>
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<td>24 (70.6)</td>
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</tbody>
</table>

Conclusions: The CDSS is a relevant addition to the manual performed medication reviews in the hospital. An accurate CDSS is imperative to assist the physician in performing medication reviews. Future developments include adding medical history to the clinical rules, fine-tuning the CDSS and determine relevance on patient outcome.
CHARACTERIZATION OF THE STRUCTURE OF HUMAN SERUM ALBUMIN IN PATIENTS WITH END STAGE RENAL DISEASE AFTER KIDNEY TRANSPLANTATION

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Introduction: The degree of oxidized cystein (Cys) 34 in human serum albumin (HSA) is a sensitive biomarker for diagnosis of the oxidative stress in various diseases. Although previous report suggested that the oxidation of Cys 34 in HSA was significantly increased with the progression of end stage renal disease (ESRD), a representative oxidative stress-associated disease, little is known regarding its variation in ESRD patients after kidney transplantation. The purpose of this study was to assess whether improvement of renal function after kidney transplantation had an impact on the redox state of Cys 34 in HSA.

Material and Methods: Eighteen patients with ESRD who were scheduled to undergo the first kidney allograft transplantation were enrolled. Plasma sample was collected from the ESRD patients before and 7, 14, 30, 60, 90, 180 and 360 days after kidney transplantation. Structural heterogeneity of HSA was analysed using electrospray ionization time-of-flight mass spectrometer (ESI-TOFMS).

Results and Discussion: Since creatinine clearance increased significantly from day 7 after kidney transplantation compared to before kidney transplantation and remained almost stable thereafter, it was suggested that these allograft transplantations were successful. Two major peaks, corresponding to the cysteinylation of Cys 34 (Cys-Cys 34-HSA) and reduced Cys 34-HSA in plasma samples obtained from these patients before kidney transplantation, were identified by ESI-TOFMS. A significant decrease in the ratio of Cys-Cys 34-HSA and reduced Cys 34-HSA was observed from day 7 after kidney transplantation compared to before. In addition, the gradual decrease of its ratio was confirmed until 360 day after kidney transplantation.

Conclusion: These results suggested that the redox state of Cys 34 in HSA was improved by the restoration of renal function after kidney transplantation.

RELATIONSHIPS BETWEEN PLASMA CONCENTRATIONS OF FENTANYL AND 4BETA-HYDROXYCHOLESTEROL IN CANCER PATIENTS

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Background and Introduction: Transdermal fentanyl possesses a large pharmacokinetic variation in cancer patients. Genetic polymorphism of cytochrome P450 (CYP) 3A5 influences the plasma exposure of fentanyl. Recently, the serum concentration of 4β-hydroxycholesterol has been reported as an endogenous marker of CYP3A4/5 in humans. The aim of this study was to evaluate the concentrations of plasma fentanyl and serum 4β-hydroxycholesterol based on CYP3A5 genetic polymorphisms in cancer patients.

Material and Methods: Forty Japanese cancer patients treated with transdermal fentanyl were enrolled in this study. Blood samples were obtained at day 8 or later after starting the medication. The concentrations of plasma fentanyl and serum 4β-hydroxycholesterol were measured using LC-MS/MS. The relationships between the concentrations of plasma fentanyl and serum 4β-hydroxycholesterol, and CYP3A5 genotype were evaluated.

Results: The medians of theoretical absorption rate and plasma concentration of fentanyl were 0.64 μg/h/kg and 1.74 ng/mL, respectively, in Japanese cancer patients. The plasma concentration of fentanyl normalized with theoretical absorption rate was significantly higher in the CYP3A5*3/3 group than in the *1 allele carrier group. The median and the interquartile range of serum 4β-hydroxycholesterol concentration were 41.1 and 27.6 to 61.4 ng/mL, respectively. The serum concentration of 4β-hydroxycholesterol was significantly lower in the CYP3A5*3/3 group than in the *1 allele carrier group. The concentration of plasma fentanyl normalized with the theoretical absorption rate was not correlated with that of serum 4β-hydroxycholesterol.

Conclusion: CYP3A5*3 affected the blood exposures of fentanyl and serum concentration of 4β-hydroxycholesterol in cancer patients. However, the blood exposure of fentanyl was not able to explain the serum concentration of 4β-hydroxycholesterol. Nonmetabolic factors may affect the plasma exposure of fentanyl in cancer patients.

EFFECT OF CYP2D6 GENETIC POLYMORPHISM ON THE PHARMACOKINETICS OF MULTIPLE-DOSE METOCLOPRAMIDE

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Introduction: Metoclopramide is indicated for the treatment of heartburn caused by gastroesophageal reflux and is commonly used to treat nausea and vomiting. Metoclopramide is mainly metabolized by CYP2D6, and to some extent by CYP3A. Metoclopramide is also known for potent inhibitor of CYP2D6. CYP2D6 is highly polymorphic and the polymorphism of CYP2D6 significantly affects the pharmacokinetics of drugs in clinical use, such as codeine, risperidone, and fluoxetine. Therefore, we investigated the effect of CYP2D6 genetic polymorphism on the pharmacokinetics of metoclopramide after multiple-dose.

Material and Methods: Forty one healthy Korean subjects were recruited and classified into three different groups according to CYP2D6 genotype: CYP2D6*wt/*wt (n = 11), CYP2D6*wt/*10 (n = 15), and CYP2D6*10/*10 (n = 15). After overnight fasting, each subject received a single oral dose of 10 mg metoclopramide. Blood samples were collected up to 24 hours after drug ingestion, and plasma concentrations of metoclopramide were determined by using validated liquid chromatography-tandem mass spectrometry system.

Results: After multiple-dose metoclopramide, Cmax and AUC0-24 of metoclopramide in CYP2D6*10/*10 group were significantly higher than those in CYP2D6*wt/*wt group (P = 0.014 and P = 0.007, respectively). Also, apparent oral clearance (CL/F) in CYP2D6*10/*10 group was 24.6% lower than that in CYP2D6*wt/*wt group (P = 0.018). There were no significant differences in t1/2 and tmax among 3 different groups.

Conclusions: The present study showed that CYP2D6 genetic polymorphism had significant effects on the pharmacokinetics of multiple-dose metoclopramide.

INFLUENCE OF CYP2D6 GENETIC POLYMORPHISM ON THE PHARMACOKINETIC PARAMETERS OF RISPERIDONE AND ITS ACTIVE METABOLITES

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Introduction: Risperidone is an antipsychotic drug that is used to treat schizophrenia and symptoms of bipolar disorder. Risperidone...
CYP2D6*10 ALLELE HAS SIGNIFICANT EFFECTS ON THE PHARMACOKINETICS OF TRAMADOL AND ITS METABOLITE

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Introduction: Tramadol is a centrally acting analgesic used to treat moderate to severe pain. Tramadol exerts its activity by binding to the \( \mu \)-opioid receptor and inhibiting the reuptake of serotonin and norepinephrine. Tramadol is metabolized to its active metabolite, \( \text{-desmethyltramadol} \), by CYP2D6. About 20 to 30% of drugs in clinical use are metabolized by CYP2D6 and CYP2D6 genetic polymorphism have been associated with altered enzyme activity. As CYP2D6*10 allele is the most common allele in the Asian population, we investigated the effect of CYP2D6*10 allele on the pharmacokinetics of tramadol and its active metabolite.

Material and Methods: Forty-four healthy Korean subjects were recruited and divided into 3 different groups according to CYP2D6 genotype: CYP2D6*wt/*wt \((n = 15)\), CYP2D6*wt/*10 \((n = 14)\) and CYP2D6*10/*10 \((n = 15)\). After overnight fasting, each subject received a single oral dose of 100 mg tramadol. Blood samples were collected up to 30 hours after drug intake, and plasma concentrations of tramadol and its metabolite were determined by using validated liquid chromatography-tandem mass spectrometry system.

Results: Although \( C_{\text{max}} \) of tramadol was not significantly different among 3 different groups, \( AUC_{\text{0-\infty}} \) of tramadol in CYP2D6*10/*10 group was 1.56-fold higher than that in CYP2D6*wt/*wt group \((P < 0.001)\) and apparent oral clearance \((\text{CL/F})\) of tramadol in CYP2D6*10/*10 group was 32.9% lower, compared to CYP2D6*wt/*wt group. In terms of its active metabolite, \( C_{\text{max}} \) and \( AUC_{\text{0-\infty}} \) in CYP2D6*10/*10 group were significantly higher than those in CYP2D6*wt/*wt group \((P < 0.001)\).

Conclusions: CYP2D6*10 allele has significant effects on the plasma exposure of tramadol and its active metabolite.

CYP2D6*10 allele has significant effects on the pharmacokinetics of tramadol and its active metabolite.
INTRODUCTION: Tolperisone is used to treat the painful reflex muscle spasm or spasticity. CYP2D6 plays an important role in the metabolism of tolperisone and CYP2C19 also contributes to the metabolism of tolperisone. Fluoxetine is one of the widely prescribed antidepressant and is known for CYP2D6 inhibitor. CYP2C3 is highly polymorphic and involved in the metabolism of a lot of drugs, such as proton pump inhibitors and clopidogrel. In this study, we investigated the effect of fluoxetine on the pharmacokinetic parameters of tolperisone in relation to CYP2C19 genetic polymorphism.

MATERIAL AND METHODS: Twenty-five healthy Korean subjects were volunteered and classified into 4 different groups according to CYP2C19 genotype: CYP2C19EM (CYP2C19*1/*1, n = 10), CYP2C19IM (CYP2C19*1/*2 or CYP2C19*1/*3, n = 11) and CYP2C19PM (CYP2C19*2/*2, CYP2C19*2/*3 or CYP2C19*3/*3, n = 4). In the control phase, a single 150 mg oral dose of tolperisone was administered to each subject. During the test phase, each subject received a single 20 mg oral dose of fluoxetine in the morning for 5 consecutive days. On day 6, a single 150 mg oral dose of tolperisone and a single 20 mg oral dose of fluoxetine were coadministered. Blood samples were obtained up to 12 hours after drug intake, and plasma concentrations of tolperisone were determined by using liquid chromatography-tandem mass spectrometry system.

RESULTS: Cmax of tolperisone in each group were significantly lower than that in control phase (6.3 ± 1.6 ng/mL versus 3.5 ± 0.8 ng/mL, P < 0.0001). Also, AUC0-12 h of tolperisone in each group were significantly higher than that in control phase (0.35 ± 0.12 ng·h/mL versus 0.75 ± 0.35 ng·h/mL, P < 0.001). Although tmax and t1/2 were not significant different between control phase and test phase in each group, apparent oral clearance (CL/F) of tolperisone was significantly different between control phase and test phase: 85.5%, 60.9%, 35.3% was decreased in CYP2C19EM, CYP2C19IM, and CYP2C19PM group, respectively.

CONCLUSIONS: Coadministration of fluoxetine had significant effects on the pharmacokinetics of tolperisone according to CYP2C19 genotype.

DRUG-DRUG INTERACTION BETWEEN MELOXICAM AND AMIODARONE

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INTRODUCTION: Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) and is used to relieve pain and tenderness caused by osteoarthritis. CYP2C9 and CYP3A4 are predominantly involved in the metabolism of meloxicam and 5’-carboxymeloxicam is a major metabolite. Amiodarone is an antiarrhythmic agent and is prescribed for treatment and prevention of ventricular arrhythmias. Amiodarone is known for a moderate CYP2C9 inhibitor. Therefore, we determined the effect of amiodarone on the pharmacokinetics of meloxicam in CYP2C9*1/*1 subject, in order to minimize the effects of CYP2C9 genetic polymorphism.

MATERIAL AND METHODS: Fourteen healthy Korean subjects genotype as CYP2C9*1/*1 were recruited. In control phase, each subject ingested oral dose of 15 mg meloxicam after overnight fasting. An oral dose of 600 mg oral dose of amiodarone was administered once a day for 5 consecutive days and on study day meloxicam was administered 1 hour after sixth administration of amiodarone. Blood samples were collected up to 72 and 144 hours, respectively in control phase and amiodarone phase, and plasma concentrations of meloxicam and its major metabolite were simultaneously determined by using liquid chromatography-tandem mass spectrometry system.

RESULTS: Cmax of 5’-carboxymeloxicam in amiodarone phase was significantly lower than that in control phase (6.3 ± 1.6 ng/mL versus 3.5 ± 1.0 ng/mL, P < 0.0001). Also, AUC0-12 h of meloxicam in amiodarone phase was 1.43-fold higher (P < 0.0001) than that in control phase and apparent oral clearance (CL/F) of meloxicam in amiodarone phase decreased by 30.6%, compared to control phase (P < 0.0001).
Conclusions: There were significant drug–drug interaction between meloxicam and amiodarone, a moderate CYP3A4 inhibitor.

SMOKING HAS SIGNIFICANT EFFECTS ON THE PHARMACOKINETIC PARAMETERS OF TOLPERISONE
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Introduction: Tolperisone is a muscle relaxant and has been authorised in several countries for the treatment of muscle spasm and spasticity. In the metabolism of tolperisone, CYP2D6, CYP2C19, and CYP1A2 are involved. CYP1A2 activity is largely determined by smoking behaviour as smoking is a potent inducer of CYP1A2. Therefore, we investigated the effects of smoking on the pharmacokinetics of tolperisone in healthy Korean subjects.

Material and Methods: One hundred healthy Korean subjects were volunteered and divided into 2 groups: Smokers (n = 50) and Non-smokers (n = 50). After overnight fasting, a single 150-mg oral dose of tolperisone was administered to every subject. Blood samples were collected up to 12 hours after drug ingestion, and plasma concentrations of tolperisone were determined by using validated liquid chromatography-tandem mass spectrometry system.

Results: As expected, Cmax in non-smoking group was 1.58-fold higher than that in smoking group (P = 0.019). AUC∞ in non-smoking group was significantly higher than that in smokers (188.5 ± 198.2 versus 122.9 ± 140.2, P = 0.0323). Also, apparent oral clearance (CL/F) of tolperisone decreased by 33% in non-smoking group, compared to smoking group (P = 0.021).

Conclusions: Smoking, which is a potent inducer of CYP1A2, has significant impacts on the pharmacokinetic parameters of tolperisone.

INFLUENCE OF MRP2 C24T GENETIC VARIANT ON THE PHARMACOKINETICS OF VALSARTAN
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Introduction: Valsartan is a high-performance liquid chromatography-tandem mass spectrometry system.

Results: Cmax and AUC values of lamivudine were not significantly different between CC type and CT type. Cmax of lamivudine in CC type and CT type was 1150.0 ± 191.4 ng/mL and 1255.6 ± 249.8 ng/mL, respectively. AUC∞ of lamivudine in each genotype group was 4429.4 ± 427.5 ng/hr/mL and 4297.4 ± 1047.9 ng/hr/mL, respectively. Also, apparent oral clearance (CL/F) and elimination half-life (t1/2) of lamivudine were not significantly different between 2 genotype groups.

Conclusions: In conclusion, there were no significant changes in the pharmacokinetics of lamivudine in relation to OCT2 C602T genetic variant.

LACK OF ASSOCIATION BETWEEN OCT2 C602T GENETIC VARIANT AND THE PHARMACOKINETICS OF LAMIVUDINE IN HEALTHY KOREAN SUBJECTS
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Introduction: Lamivudine is an analogue of cytidine and prescribed for the treatment of chronic hepatitis B. Lamivudine is in a class of medications called nucleoside reverse transcriptase inhibitors (NRTIs). The renal excretion of lamivudine is mostly mediated by OCT2, an influx transporter encoded by SLCC2A2 gene. The aim of the present study was to investigate the effects of OCT2 C602T variant on the pharmacokinetics of lamivudine.

Material and Methods: Nineteen Korean subjects were volunteered and divided into 2 different groups according to OCT2 C602T: c.602CC (CC type, n = 12) and c.602CT (CT type, n = 7). After overnight fasting, a single 100-mg oral dose of lamivudine was administered to every subject. Blood samples were collected up to 24 hours after drug administration, and plasma concentrations of lamivudine were determined by using validated liquid chromatography-tandem mass spectrometry system.

Results: Cmax and AUC values of lamivudine were not significantly different between CC type and CT type. Cmax of lamivudine in CC type and CT type was 1150.0 ± 191.4 ng/mL and 1255.6 ± 249.8 ng/mL, respectively. AUC∞ of lamivudine in each genotype group was 4429.4 ± 427.5 ng/hr/mL and 4297.4 ± 1047.9 ng/hr/mL, respectively. Also, apparent oral clearance (CL/F) and elimination half-life (t1/2) of lamivudine were not also significantly different between 2 genotype groups.

Conclusions: In conclusion, there were no significant changes in the pharmacokinetics of lamivudine in relation to OCT2 C602T genetic variant.

EFFECT OF DILTIAZEM, A MODERATE CYP3A4 INHIBITOR, ON THE PHARMACOKINETIC PARAMETERS OF TAMOSULIN
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Introduction: Tamsulosin is selective α1-adrenoceptor antagonist that is used to treat symptoms of benign prostatic hyperplasia (BPH). CYP2D6 and CYP3A4 are involved in the metabolism of tamsulosin. Diltiazem is one of calcium channel blockers used to treat high blood pressure and to control angina and it is known for a moderate CYP3A4 inhibitor. We investigated the effects of coadministration of diltiazem on the pharmacokinetics of tamsulosin.

Material and Methods: Ten healthy Korean subjects genotyped as CYP2D6 *1/*1 (*1 or ‘2) were volunteered. After overnight fasting, each subject received a single 0.2-mg oral dose of tamsulosin in control phase. In the diltiazem phase, all subjects received 60 mg diltiazem 3 times a day for 4 days. On study day, 0.2 mg oral dose of tamsulosin was administered to each subject 1 hour after the administration of diltiazem. Blood samples were collected up to 48 hours after drug intake, and plasma concentrations of tamsulosin were determined by using liquid chromatography–tandem mass spectrometry system.

Results: Cmax and AUC∞ of tamsulosin in diltiazem phase were both 1.71-fold increased than those in the control phase (both, 1.71-fold increased than those in the control phase (both,
Clinical Therapeutics

1. Introduction: CYP2D6 is a cytochrome P450 enzyme that plays a crucial role in the metabolism of many drugs, including antidepressants, antipsychotics, and antiarrhythmics. Genetic variations in the CYP2D6 gene can lead to differences in drug metabolism and efficacy. This study aimed to investigate the impact of CYP2D6 genetic variants on the pharmacokinetics of metoclopramide.

2. Material and Methods: Twenty-eight Korean subjects were selected, and their CYP2D6 genotype was determined using a validated method. CYP2D6*1/*1, CYP2D6*10/*10, and CYP2D6*1/*10 individuals were included in the study. The subjects ingested a single 1-mg oral dose of metoclopramide, and blood samples were collected for 24 hours after drug ingestion.

3. Results: The pharmacokinetic parameters of metoclopramide were compared between the three CYP2D6 genotype groups. The results showed significant differences in the area under the curve (AUC), half-life, and clearance between the groups.

4. Conclusions: The CYP2D6 genetic variant has a significant impact on the pharmacokinetics of metoclopramide.

HEMODYNAMIC ADRENERGIC STIMULATION CAN BE ATTENUATED BY (-)-EPIGALLOCATECHIN-3-O-GALLATE (EGGC)

5. Background: Caffeine is a popular stimulant that can increase blood pressure and heart rate. However, its effects can be attenuated by (-)-epigallocatechin-3-O-gallate (EGGC), a flavonoid found in green tea.

6. Methods: Volunteers were divided into three groups: a control group and two groups that ingested different doses of EGGC. The pharmacokinetic parameters of metoclopramide were measured before and after ingestion of the EGGC.

7. Results: The AUC and half-life of metoclopramide were significantly lower in the EGGC groups compared to the control group.

8. Conclusions: EGGC can attenuate the hemodynamic adrenergic stimulation induced by caffeine.

PHARMACOKINETICS OF CETRAXONE INCLUDED IN CELLULAR TRANSPORT SYSTEM

9. Background: Cetrixone is an antibiotic that is extensively used in clinical practice. However, its pharmacokinetics in human plasma remain poorly understood.

10. Methods: Cetrixone was administered intravenously to patients, and plasma samples were collected for analysis. The pharmacokinetic parameters were determined using a validated LC-MS/MS method.

11. Results: The pharmacokinetics of cetrixone were significantly different in the three groups: Group 1 (intravenous administration in free form), Group 2 (intravenous administration in leukocyte cell systems), and Group 3 (intravenous administration in leukocyte cell systems after diltiazem administration).

12. Conclusions: There was no significant difference between the pharmacokinetic parameters of cetrixone in the composition of erythrocyte compared to leukocyte cell systems. However, the main difference of pharmacokinetics parameters between antibiotic in free form and cetrixone included in transport system were: increased half-elimination period, distribution volume and increased area under the curve whereas elimination constant and clearance were decreased.

DETERMINATION OF METHYLPHENIDATE IN HUMAN PLASMA BY A VALIDATED LC-MS/MS METHOD

13. Background: Methylenidate is a stimulant medication used to treat attention-deficit/hyperactivity disorder (ADHD). Its pharmacokinetics in human plasma are crucial for optimizing its therapeutic effects.

14. Methods: Methylenidate was administered to patients, and plasma samples were collected at different time points. The concentration of methylenidate was determined using a validated LC-MS/MS method.

15. Results: The pharmacokinetic parameters of methylenidate were determined, and the accuracy of the method was validated.

16. Conclusions: The validated LC-MS/MS method is suitable for the determination of methylenidate in human plasma.
An Educational Intervention To Improve Nurses Reporting of Adverse Drug Reactions

Introduction: We studied the incidence of fatal adverse drug reactions (ADR) in a tertiary hospital in order to find out which drugs are involved and whether there are changes compared to 12 years earlier published data from the same hospital.

Methods: All 1708 death cases in the Helsinki University Central Hospital during the year 2012 were retrospectively evaluated. All suspected drug-related deaths, excluding suicides, were scrutinized by an expert panel using the WHO ADR probability classification.

Results: Of all death cases, 52 (3.0%) were classified as certainly or probably drug-related and 24 (1.4%) as possibly drug-related. Together, these correspond to 0.02% of all hospital admissions (394 338 admissions). The most commonly involved drugs in certain or probable cases were cytostatics (18 cases, 1.1% of all cases) and anthracyclines (17, 1.0%). Twelve years earlier, these caused 27 (1.8%) and 22 (1.5%) cases, respectively. Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids caused less (2 and 0 cases) fatal ADRs than earlier (12 and 4 cases, P = 0.048 and P = 0.005, respectively). Most of the ADRs leading to death were present already in admission and affected seriously ill or elderly patients. Hospital-born fatal ADRs occurred in 0.003% of patients.

Conclusions: The current incidence of fatal ADRs (3.0% of all death cases) seems to be less than that (5.0%) observed 12 years earlier in the same hospital. Despite declining trends, cytostatics and anthracyclines are still the leading causes. NSAIDs and glucocorticoids seem to cause fatal ADRs less often than previously. Improved awareness, prevention and treatment of ADRs as well as safer medicines may explain these declining trends.

AGGREGATED DATA OF CLINICAL TRAILS: BEMIPARIN BLEEDING RISK IN ELDERLY AND PATIENTS WITH RENAL IMPAIRMENT

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Introduction: Bleeding in elderly and patients with renal impairment (RI) are a safety concern with LMWH. The antiXa activity of bemiparin was assessed in elderly and patient with RI, only severe RI could produce accumulation of bemiparin. Aggregation of data of clinical trials (CT) is useful for identifying subgroups at higher risk of adverse reactions.

Material and Methods: CT were aggregated if bemiparin was used for more than 3 weeks. RI was defined according to creatinine clearance and Cockcroft-Gault equation: mild (≥50 y ≤80 mL/min); moderate (≥30 y <50 mL/min) and severe (<30 mL/min). Elderly were >65 years. Bleeding Rate (BR) and relative risk reduction (RRR) with confidence interval (CI) at 95% was calculated for bemiparin and placebo.

Results: Six CT fulfilled selection criteria; 782 patients were treated with bemiparin and 649 with placebo; 277 (17.8%) and 242 (15.6%) were elderly in bemiparin and placebo, respectively; median treatment with bemiparin was 56.69 (SD 34.02) days, and placebo 36.05 (SD 36.81). Regarding RI classification, 264 (23.6%)/235 (39.2%) had mild, 51 (7.1%)/59 (9.8%) moderate and 7 (1%)/1 (0.2%) had severe RI in bemiparin and placebo. BR in RI was in mild 3.4% and 3.4% in bemiparin and placebo (RRR = 0; 95% CI, −1.55 to 0.61; P = 0.598); in moderate was 3.9% in bemiparin, no bleeding events occur in placebo; no bleeding events occurred in severe RI. BR in subjects with normal renal function was 2.3% and 4.3% in bemiparin and placebo (P = 0.097; RRR = 0.47; 95% CI, −0.22 to 0.77). BR in elderly was 3.4% and 1.9% (P < 0.216 in bemiparin and placebo; RRR = −0.75; 95% CI, −4.06 to 0.39); in adult were 2.1% and 4.4% (RRR = 0.53; 95% CI, −0.02 to 0.78; P < 0.039 in bemiparin and placebo).

Conclusion: Aggregated data of CT did not showed an increase of bleeding in mild and moderate RI and in elderly, after receiving bemiparin in comparison with placebo.
immediate cessation of the suspected drug is primordial to prevent potentially fatal outcomes.

ETNIC NORWEGIAN DOCTORS AND DIABETIC PAKISTANI WOMEN IN OSLO - WHAT IS THE PATIENTS’ NEED FOR INFORMATION?

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Background: The Pakistanis constitute a big immigrant population in Oslo with a high prevalence of diabetes. The aim of the project was to study challenges Norwegian GPs experience with non-western immigrants, and what knowledge diabetic Pakistani women have about their disease, and their need for information.

Material and Methods: The material was 22 ethnic Norwegian GPs with many immigrant patients, and 125 diabetic Pakistani women (29–80 y old), recruited through mosques and female networks. All participants were interviewed personally with structured questionnaires; the women in their homes. Approval was obtained from the Norwegian Social science data services.

Results: The main obstacle for the GPs was language. Consequently it was difficult to diagnose and to explain drug treatment. The main chronic disease was diabetes. The doctors could see from blood levels how drug adherence decreased during Ramadan. The language was the main challenge also for the patients, even with an average stay of 30 years in Norway. Seventy percent had to be interviewed in Urdu; 27% were illiterates. Almost 40% reported poor/very poor health status. Above half did not know their type of diabetes. The treatment was tablets for 70%, insulin for 4% and both medication forms for 24%. Twenty-five percent altered their medication intake during Ramadan. Macrovascular diseases were widely spread among all ages. Number of meals per day was too low according to guidelines. Two third admitted high calorie intakes between meals. Physical activity was reported by 46%. The majority could only benefit from oral information, and in Urdu. Most participants primarily missed information about the drugs they were using.

Conclusion: The study shows how cultural and religious barriers prevent Norwegian doctors to have a good communication with non-Western patients and also how difficult it is for diabetic Pakistani women to get the right information about their disease.

EFFECT OF MEDICATION REVIEW AND PHYSICIAN TRAINING PROGRAMME ON DRUG RELATED EVENTS IN HIGH RISK SURGICAL PATIENTS (P-REVIEW STUDY)

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Background: Prescription errors in the hospital can lead to preventable harm to patients. These events are often caused by NSAIDs, anti-coagulants, diuretics, antibiotics and opioids. Especially patients on surgical departments are at risk, since patients with complex co-morbidities in complex situations are treated by physicians who have had no specific additional training on prescribing. The hospital pharmacist has an important role to safeguard patients for medication errors.

Material and Methods: The P-REVIEW study is an open intervention study with a before after design that introduces a structured education program on pain management, anticoagulants, fluid and electrolyte management and antibiotics for prescribing physicians on surgical departments of large community hospitals. In addition a weekly structured medication review is performed by hospital pharmacists on high risk surgical patients and discussed with the physician (assistant) on the ward. Risk assessment is based on pain medication, anticoagulant therapy and comorbidities (for example, heart and renal failure). The aim of this intervention is to educate and support the prescribing physician on high risk patients, aimed at qualitatively improved prescribing. Also an economic evaluation was performed.

Results: A total of 13,264 admissions of surgical patients were included (6780 admissions in the usual care group vs 6484 admissions in the intervention group). Results of the study show that this intervention leads to a significant reduction of preventable serious adverse events (disability, death, increases hospital stay and readmission) due to prescription errors (106 events versus 73 events, P = 0.029). The pharmaco economic analysis shows that the intervention does not incur higher costs due to time spent by involved health-care providers ($6.04 vs $6.18 per admission, P = 0.272).

Conclusion: This large study shows that education and support of the prescribing physician on high risk patients on surgical departments by the hospital pharmacist leads to a significant clinical relevant benefit for patients.

ANALGESIC DRUG CONSUMPTION INCREASES AFTER CARPAL TUNNEL SURGERY: A PHARMACOEPIDEMIOLOGICAL STUDY INVESTIGATING POSTOPERATIVE PAIN

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Background or Introduction: The aim of this pharmacoepidemiological study was to investigate analgesic drug consumption before and after surgery as a surrogate of chronic postoperative pain.

Material and Methods: A retrospective cohort study of French beneficiaries from the main health insurance scheme in Midi-Pyrenees area was designed using data from the SNIIRAM (Système National d’Information Inter-Régime de l’Assurance Maladie). All patients undergoing carpal tunnel surgery between 1 January 2010 and 30 June 2010 were identified. Definition of increase in antinflammatory drugs (carnbamezpine, gabapentine, prégabiline, clomipramine, amitriptyline, duloxetine, clonazepam) or opioids (ATC code N02A) was based on the comparison of the accumulated Defined Daily Doses (DDDs) received by months between pre (2 mo before) and late postoperative period (2–12 mo after surgery). A multivariate logistic regression model was used to identify factors associated with increase in either antinflammatory or opioid analgesic drug consumption.

Results: Among the 3495 patients included, 3082 received at least one analgesic during the late postoperative period (29%, n = 359) for antineuropathics (359) for antineuropathics). History of diabetes, rheumatoid arthritis and psychiatric disorders were associated with an increase in opioid use, whereas hospitalisation (versus ambulatory surgery), high level of preoperative pain and psychiatric disorders were found to be associated with an increase in antinflammatory drug use.

Conclusions: This study revealed that around 1 out of 3 patients undergoing carpal tunnel surgery had persistent and even increased...
use of opioids and antineuropathic drugs more than two months after surgery, in relation with possible chronic postoperative pain.

Considering the incidence of carpal tunnel syndrome, the risks associated with persistent opioid use in this population should be further monitored.

THROMBOPROPHYLAXIS IN MULTIPLE MYELOMA PATIENTS TREATED WITH LENALIDOMIDE OR THALIDOMIDE

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Background: Immunomodulatory drugs IMiDs (lenalidomide and thalidomide) have contributed to improve patients' survival in multiple myeloma. However, they increase the risk of thromboembolic events and often require a concomitant thromboprophylaxis based on treatment received and level of risk. Strategy of prophylaxis is still debated, while international guidelines tend to recommend either aspirin or low weight molecular heparin (LWMH). The aim of this study was to describe strategy of thromboprophylaxis in a cohort of multiple myeloma patients during their first imid-based regimen.

Material and Methods: A retrospective cohort study of French beneficiaries from the main health insurance scheme database -SNIIRAM (Système National d’Information Inter-Régime de l’Assurance Maladie) was designed in the Midi-Pyrénées area (South West France, 2.8 million inhabitants). Multiple myeloma patients were identified through hospital diagnosis or long-term conditions. Beneficiaries with at least 1 dispensing record for lenalidomide or thalidomide in hospital pharmacy from January 2010 to March 2014 were included.

Results: Among the 271 multiple myeloma patients (62% male, 60% > 65 y) starting an imid-based regimen: 21% (n = 58) received thalidomide alone or thalidomide-dexamethasone (T-D); 14% (n = 38) bortezomib-thalidomide-dexamethasone (VT-D); 25% (n = 68) melphalan-prednisone-thalidomide (MPT) and 40% (n = 107) had lenalidomide-dexamethasone (RD) therapy; Forty-eight percent were at first-line therapy, 42% in second-line therapy and 10% in third-line therapy. Around 85% (n = 230) of the patients received > 1 drug for thromboprophylaxis after starting their imid regimen: 63% aspirin (n = 198), 36% unfractionated heparin or LMWH (n = 98); 15% vitamin K antagonists (n = 42). No prophylaxis was retrieved for 15% of the patients (n = 41). Further analyses are currently implemented to describe thromboprophylaxis in high risk cases: radiotherapy, previous thromboembolism, current use of bisphosphonates, or hormonal treatments.

Conclusions: These preliminary results revealed a great variability in the implementation of thromboprophylaxis strategy in real-life, even in high risk treatment lines with chemotherapy or dexamethasone in which thromboprophylaxis should be systematically applied.

PROSPECTIVE CLINICAL STUDY OF FOSFOMYCIN EFFICACY IN THE TREATMENT OF COMPLICATED URINARY TRACT INFECTIONS CAUSED BY E. COLI AND K. PNEUMONIAE PRODUCING EXTENDED SPECTRUM BETA LACTAMASES

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2University Clinical Hospital Center Zagreb, Croatia

Introduction: In the era of rising antibiotic resistance rates, treatment of complicated urinary tract infections (cUTIs) caused by bacterial strains producing extended spectrum beta lactamases (ESBL) represents a major therapeutic problem. Hence, there is a growing interest in the investigation of other antibiotics like fosfomycin, especially due to its rapid bactericidal activity, oral route of administration, low resistance rates and low cost.

Material and Methods: One hundred forty-five urinary isolates of ESBL producing E. coli and K. pneumoniae from ambulatory patients were prospectively in vitro tested to fosfomycin and other routinely used antibiotics. Those patients with isolates sensitive to fosfomycin and fulfilling inclusion and exclusion criteria then received on average 3.7 doses of fosfomycin. Fosfomycin was administered orally, every 2 days. Patients on average had 2.3 complicating factors (most common recurrent UTIs, diabetes mellitus and chronic kidney disease).

Microbiological cure was evaluated 7 to 9 days after completion of treatment by means of urinary culture.

Results: All E. coli ESBL isolates (n = 81) were in vitro sensitive to fosfomycin, which was statistically different from all other tested orally administered antibiotics, P < 0.001 (nitrofurantoin 73%, ceftriaxone 66%, amoxicillin-clavulanate 51%, trimethoprim sulfamethoxazole 20%, ciprofloxacin 11%). Thirty-three of 64 K. pneumoniae ESBL isolates were in vitro sensitive to fosfomycin (52%), which was statistically different from trimethoprim sulfamethoxazole (32%) and ciprofloxacin (11%), P < 0.05, and similar to ceftriaxone (55%) and amoxicillin-clavulanate (39%). Eradication of ESBL strain was achieved in 29 of the 44 patients with cUTIs (66%), while clinical improvement was achieved in all patients, at least temporarily.

Conclusions: In vitro sensitivity of E. coli ESBL to fosfomycin is excellent while that of K. pneumoniae ESBL is much lower. Fosfomycin administered orally in several doses represents a potentially attractive oral therapeutic option for cUTIs caused by ESBL producing strains.

RANDOMIZED PRAGMATIC CLINICAL TRIAL ON THE DURATION OF ANTIMICROBIAL TREATMENT FOR ENTEROBACTERIAEACEAE BACTEREMIA IN ADULT PATIENTS (SHORTEN STUDY)

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Background: The optimal duration of antibiotic treatment in this clinical setting has not been established.

Material and Methods: SHORTEN study is a randomized, multi-center, open-label and phase IV trial designed to prove that a 7-day course with any authorized antibiotic for uncomplicated EB treatment according to clinical practice guidelines, is more efficient and equally safe than a 14-day scheme. Two hundred thirty-eight patients will be randomized in 1:1 ratio to experimental/control arm and followed up to 28 days to evaluate clinical and microbiological cure and safety of both arms. The optimal cut-off of PCT level for safely interrupting antibiotic treatment was included as secondary objective.
Results: The study is publicly funded (PI-0161-2013) and is being conducted in 3 public hospitals. It has been approved by Spanish Medicines Agency and central Ethical Review Board and for the 3 local Ethic Committees on which is developed. Severity and frequent complications of this infection are cause of a specific surveillance regarding pharmacovigilance applicable in CT as there are several drugs included as IMP. The study organization and coordination requires a multidisciplinary group in order to cover with all the requirements and to obtain real data.

Conclusion: The use of drugs from the own hospital provision and the similarities of procedures to daily practice makes this study an example of real pragmatic trial supported for noncommercial clinical research unit in order to accomplish with ethic and legal requirements.

ANTI-TNF BUT NOT USTEKINUMAB INDUCED PARADOXICAL PSoriasiform LESIONS IN PATIENTS WITH PSORIASIS: ASSOCIATION WITH GENETIC POLYMORPHISMS

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Background: Biological drugs are effective in several chronic inflammatory diseases such as psoriasis. Paradoxically, psoriasisform lesions have been described following anti-TNFα therapy. We aimed to study the association between the development of these lesions and genetic polymorphisms.

Material and Methods: One hundred eighty psoriasis patients (107 men and 73 women) treated with anti-TNFα drugs and ustekinumab were genotyped through the Illumina Veracode genotyping platform for different genes previously associated with psoriasis or other autoimmune diseases or to response to biological drugs.

Results: Among 180 patients, 25 (11 men and 14 women) developed a psoriasisform lesion, mostly a psoriasis guttata (88%). These lesions were developed 9.20 ± 13.52 months after initiating treatment in 9.8% patients treated with adalimumab, 21.4% with etanercept, 7.7% with infliximab, and 0% with ustekinumab. Gender, psoriasis type and PASI75 were not associated with the development of psoriasiform lesions. After a multivariate logistic regression, 5 SNPs were associated to the development of a psoriasiform lesion: rs11209026 in TNFAIP3, rs3087243 in SLC12A8, rs1800453 in TAP1, and rs96844 in MAP3K1.

Conclusions: Genetic polymorphisms are associated with the development of psoriasiform lesions in patients with psoriasis after anti-TNFα drugs. This adverse reaction was not induced by ustekinumab.

CYSITIN AMIDOPHOSPHATE – PROMISING ROLE FOR THE LIVER TREATMENT

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PI “Center for Life Sciences”, Nazarbayev University, Astana, Kazakhstan

This study was carried out to investigate hepatoprotective effect of “Cytaphat” drug, which is a semisynthetic derivative of the alkaloid cystine – 0,0-dimethyl-N-(methylcysitine)-phosphate. During the preclinical studies were found that Cytaphat has hepatoprotective, antioxidiant, membrane stabilizing and choleretic activity. Cytaphat accelerates regeneration of liver tissue after resection. Phase 1 clinical trial on healthy volunteers allowed to determine that the optimal tolerated dose of Cytaphat was 200 mg/kg. Side effects with high doses (100–200 mg/kg) are tachycardia and increased blood pressure. Currently Cytaphat passes Phase 2 clinical trials in Kazakhstan as hepatoprotector for the treatment of acute toxic hepatitis.

There are 142 patients with an acute toxic hepatitis which were participating in phase 2 clinical trial. Patients were divided into 3 groups: I – patients were taking Essentiale (200 ml of 5% glucose + 10 ml of Essentiale) i/v once per day for 3 days; II – patients were taking Cytaphat (10 mg/kg + 200 ml of 5% glucose) i/v once per day for 3 days; III – patients were taking placebo. The method of clinical trials was double-blind.

The table shows that Cytaphat has significantly better positive effect compare to placebo.

The average time of the elimination of toxic hepatitis using Cytaphat was 2.8 days, using Essentiale – 7.2 days and placebo – 10.6 days. Cytaphat has showed high efficiency compare to placebo and comparative drug Essentiale. Results indicate the presence of hepatoprotective activity of Cytaphat for the treatment of acute toxic hepatitis.

INHIBITION OF ACUTE VASCULAR INFLAMMATION BY NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD)-CONTAINING DRUG IN EARLY FORM OF ATHEROSCLEROSIS IN EXPERIMENTS

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Introduction: The aim of the present study was to evaluate the effect of reduced form of NAD-containing drug, Nicadın®, on cardiovascular benefit by inhibiting vascular inflammation and decreases of redox-potential level in early form of experimental atherosclerosis.

Materials and Methods: Forty-one male rabbits were included in this study. The animals were randomized into 3 groups: I (control) - rabbits were fed normal diet for 12 weeks; II - rabbits fed 1% cholesterol enriched diet (CED) for 12 weeks; III - rabbits fed with CED for 6 weeks, and then continued on CED and treated with 10 mg/kg/day orally Nicadın® for the next 6 weeks. Blood and aortic tissue samples were collected at the start of the study, at 6 weeks, and at the end of treatment course to measure serum lipid profile, C-reactive protein (CRP), tumor necrosis factor (TNFα), intercellular adhesion vascular molecule (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) with ELISA-tests.

Results: In group II significant progression of atherosclerosis was developed. Compared with the control, levels of blood lipids, TNF-α, CRP,
IN VITRO EVALUATION OF PHARMACOLOGICAL PROPERTIES OF A NEW-DEVELOPED SHORT ACTING INSULIN ANALOGUE

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Introduction: Short acting insulin analogues are the essential drugs of an intensive antidiabetic therapy. The analogues administered before meals together with the basal long acting insulins allow to achieve pharmacokinetic profile that most closely mimics physiological secretion of endogenous insulin.

The objective of the study was to assess pharmacodynamic activity in vitro and describe molecular mechanism of action of the B28Lys-B29Pro human insulin (KP) in comparison to EU Pharmacopeia human insulin standard (HIS) and insulin growth factor-1 (IGF-1).

Material and Methods: ELISA tests were adapted to analyze the (auto)phosphorylation/dephosphorylation of insulin receptor (IR), IGF-1 receptor, insulin receptor substrate-1 protein (IRS-1) and activation of kinases (Akt1, p44MAPK). Tests were performed on human breast adenocarcinoma cell line (MCF7). Radioligand binding assay was used to assess the affinity of the tested compounds for the agonist site of IR on membrane homogenates of the rat liver cells. Kd (equilibrium dissociation constant) in phosphorylation assays, t1/2 (half-life of reaction) in dephosphorylation assays and IC50 (half-maximal inhibitory concentration) for binding assay were statistically analyzed for each tested pair using sum-of-squares F test.

Results:

<table>
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<th>Metabolic activity</th>
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<th>Tested compound</th>
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<tr>
<td></td>
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<td>Tested compound</td>
<td>KP</td>
<td>HIS</td>
<td>IGF-1</td>
</tr>
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<td>IR</td>
<td>Kd [nM]</td>
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<td>2.11</td>
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<td>IGF-1</td>
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<td>82.92</td>
<td>3.91*</td>
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<tr>
<td></td>
<td>Akt1</td>
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<td>8.87</td>
<td>1.65*</td>
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<tr>
<td></td>
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<td>4.02*</td>
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</tr>
<tr>
<td>dephosphorylation</td>
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<td>t1/2 [min]</td>
<td>5.61</td>
<td>3.20*</td>
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<tr>
<td></td>
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<td>1.26</td>
<td>1.16</td>
<td>11.79*</td>
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<td>11.49</td>
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</tr>
<tr>
<td>binding</td>
<td>IR</td>
<td>IC50 [μM]</td>
<td>0.055</td>
<td>0.052</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

n.a. – not applicable
* – statistically significant differences (P < 0.05) detected between KP and tested compound

Conclusions: New-developed KP insulin has the same ability to inhibit binding of [125I] insulin to IR and induces at the similar level as human insulin standard the intracellular signalling. The structural differences between KP and IRS-1 are so essential to generate the differences at the molecular activity.

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DRUG INTERACTION WITH MILK AND THE RELEVANCE OF ACIDIFYING/ALKALIZING NATURE OF FOOD

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Background: An interaction is a clinical event in which the effects of a drug are affected by presence of another drug, herbal, food, drink or some chemical agent. The drug–food interactions can cause changes in bioavailability and excretion of the drug may lead to treatment failure or may have beneficial effects. The aim of this study is to explore the milk interactions with certain medicines to inform healthcare professionals and patients.

Material and Methods: This study is classified as a secondary study, a systematic review of the literature without meta-analysis. The information was collected from electronic databases such as PubMed, Google academic and b-on, with the aid of computer software. The research was carried out with keywords like “drug Interactions”, “milk and drugs”, “interaction between the drug and milk”, among others. We selected studies published in the last 25 years and at the end were obtained 20 references relevant to the development of this article.

Results: The milk interferes with the absorption of various antibiotics such as tetracycline’s (decreasing absorption) and few quinolones, propranolol, mercaptopurine (reduce bioavailability), nonsteroidal anti-inflammatory drugs, digitalis, amiloride, omeprazole, spironolactone and ranitidine. The main effects of these interactions are decreased bioavailability of drugs, increase/decrease the excretion of drugs, depletion of absorption of nutrients, among others.

Conclusion: As already known drug–food interactions can influence the safety and efficiency of drug therapy. The interactions between milk and drugs are mostly pharmacokinetic interactions, since the milk affects the absorption and excretion of drugs and are classified as moderate in severity because can occur a failure in the treatment and need for additional treatment. To avoid them just that medicines and milk are taken at different times. Also, having knowledge about medicines and which foods affect its therapeutic action is of utmost importance.

CHARACTERIZATION OF TARGET TOPICAL OCULAR DELIVERY FORM OF LEVOFLOXACIN

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Introduction: In the present work we developed and optimized levofoxacin loaded PLGA nanodispersions for enhanced ocular delivery of levofoxacin.
**CITIZEN PERCEPTION REGARDING DRUG INFORMATION AND SAFETY**

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**University of Oviedo**

**Introduction**: To ascertain public opinion on drug information aimed at citizens enclosed in the package leaflet information and public perception of some safety aspects of medicines.

**Methods**: Descriptive, cross-sectional study by means of a voluntary, anonymous survey aimed at citizens from May to December 2014 in Asturias, Northern Spain. An initial pilot study was performed to analyse the validity and feasibility of the survey. Surveys were filled out by the researcher according to the answers provided or self-completed. Considering the characteristics of the surveyed population, we analysed the reading comprehension difficulty of the package leaflet information as well as the public perception of drug safety.

**Results**: A total of 223 (84.5%) of those surveyed claimed to read the medicine information leaflet; always read 166 (62.9%) (women 105 [39.8%], men 61 [23.1%]) and sometimes 57 (21.6%) (women 38 [14.4%], men 19 [7.2%]). Regarding educational level, 109 (41.3%) of those surveyed with higher or secondary education and 46 (17.4%) with primary studies, always read the information. Of those interviewed, 196 (74.2%) perceived prescribed medicines to be safer. Only 37 (14.0%) consider that both prescription and over-the-counter medicines are safe. In total 110 (41.7%) claimed to have had some adverse drug reaction (78.2% of them reported it to their doctor, 9.9% to the pharmacist, and 1.8% to both). Other medicine-related problems were experienced by 36 (13.6%) of those surveyed.

**Conclusions**: Women claimed to read the package leaflet information more than men and also recognized a greater difficult in understanding. Although understanding the information leaflet is directly related with educational level, a high percentage of interviewees with higher or secondary education claimed to occasionally have comprehension difficulty. Prescription medicines are perceived as safer. Most of the citizens that suffered an adverse drug reaction claimed to report it to their doctor.

**THE PREVALENCE OF ENOS AND AGTR2 GENE POLYMORPHISM IN PATIENT WITH CORONARY ARTERY DISEASE**

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**Background**: The aim is to study the prevalence of polymorphisms 894G>T EnOS gene and 1675G>A AGTR2 gene in patients with coronary artery disease in the form of stable angina (SA), unstable angina (UA) and acute myocardial infarction (AMI).
Material and Methods: The study involved 100 patients, of both sexes, aged 36 to 86 years (63.7 ± 11.4). Determination of gene polymorphisms was performed by polymerase chain reaction. Statistical processing was performed by using the Statistica 10.0

Results: In the AMI group distribution of alleles of eNOS gene was

GG-81.25% (P < 0.05), GT-18.75%, TT-0% (P < 0.05). AGTR2 alleles were GG-50%, GA-18.75%, AA-31.25%. In the SA group distribution of alleles of eNOS gene was GG-46.8%, GT-48.9%, TT-4.3% (P < 0.05); AGTR2 alleles were GG-34%, GA-39.8%, AA-26.2%. In the UA group distribution of alleles of eNOS gene was GG-56.8%, GT-37.8%, TT-5.4% (P < 0.05); AGTR2 alleles were GG-40.5%, GA-19%, AA-40.5%. In postinfarction cardioclesion group distribution of alleles of eNOS gene was GG-60% (P < 0.05), GT-31.4%, TT-8.6% (P < 0.05); AGTR2 alleles were GG-42.9%, GA-17.1%, AA-40%. Furthermore it is elicited that the genotype AA and GA AGTR2 gene influences on debut of angina. In the case of AA genotype the age of the debut of angina was 53 (P < 0.05), GA-60.5 (P < 0.05) and GG-54.

Conclusions

1. The high prevalence is elicited in mutant alleles of eNOS and AGTR2.
2. The high prevalence is elicited in homozygous mutation of the allele A of AGTR2 gene in the structure of patients with coronary artery disease, particularly in post infarction cardio sclerosis patients.
3. The influence of the mutant allele A AGTR2 is detected on debut of angina.

POTENTIAL DRUG-DRUG INTERACTIONS FROM ANALGESIC PRESCRIPTIONS IN ROMANIA

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Introduction: Analgesics are among the most frequently used drugs worldwide, being dispensed both with and without prescription. The present study aims to detect potential drug–drug interactions (DDIs) of analgesics by analyzing prescriptions covered by the healthcare system and dispensed in a Romanian community pharmacy.

Methods: We included in the analysis analgesic medical prescriptions issued during one month. We recorded patients' demographics and medications and we used Thomson Micromedex® 2.0 database to detect DDIs.

Results: We selected 238 prescriptions corresponding to a number of 236 patients (female/male ratio = 1:1), aged 36 to 86 years (63.7 ± 11.4). Nonsteroidal anti-inflammatory drugs (NSAIDs), 67%, opioid analgesics (17.5%), and anticonvulsants (15.5%). Diclofenac (15.5%) and gabapentin (15.1%) were the most widely prescribed for analgesic action, followed by ketoprofen (13.4%), etoricoxib (12.7%) and tramadol alone or in combination with paracetamol (7.6%).

We detected 104 potential DDIs in which NSAIDs associated with cardiovascular medications (diuretics 25%, angiotensin-converting enzyme inhibitors 22%, beta-blockers 19%) or methotrexate (14%) were most commonly involved. Eighteen major potential DDIs (17.3%) were found and 7 prescriptions (3%) contained 2 NSAIDs used concurrently.

Discussion and Conclusions: Our study showed that on reimbursed prescriptions NSAIDs were the leading analgesics involved in potential DDIs. The main potential risk when combining NSAIDs with other drug classes were decreased efficacy of antihypertensive drugs and increased methotrexate toxicity. Diclofenac, recently associated with safety issues concerning the cardiovascular risk similar to coxibs, was the most prescribed NSAID. Acknowledging and preventing the potential risks of analgesics represents an important step in minimizing their negative effects on patients.

DRUGS OF ABUSE, PHARMACOLOGY CURRICULUM AND LEARNING STYLES OF MEDICAL STUDENTS

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Introduction: Drug abuse (tobacco, alcohol and illicit drugs) can worsen several health disorders; are among the twenty most common burden to health problems worldwide. Medical student education should provide detailed knowledge of these issues together with skills needed to detect/counsel patients with unhealthy drug use patterns. Time to include subjects in the clinical pharmacology curriculum to medical students is limited. Online educational strategies are often sought. It is necessary to evaluate the educational outcomes. This study was designed to develop and evaluate an online module on drug abuse to teach medical students about pharmacology of drugs and brief intervention of drug use problems.

Material and Methods: Eighty-nine medical students of UFCSPA were taking the Pharmacology Course in 2014. Drug abuse is not part of their currucul medical program and an online training was offered as additional set of studies for volunteer enrolment. Information (written and videos, exercises, reading recommendations) on drugs of abuse and health, mechanisms of action, biological effects of drugs, methods of drug screening, brief interventions and treatment protocols for drug abuse and dependence were presented online. After the course, all students, volunteering or not, completed an evaluation and the Kolb Learning Style Inventory (KLSI).

Results: Seventy students enrolled and completed the online training with success. The range time for completion was 5 to 20 hours. The mean knowledge score after completing the online training was 90/100. All medical students who completed the online Training described satisfaction. A difference in KLSI was detected between students who had/had not volunteered to the online training.

Conclusions: The online training on drugs of abuse resulted in significant changes in knowledge. This online format could be incorporated into the medical school curriculum, with students learning the material at their own pace and in their available time.

BIOCOMPARISON OF THREE FORMULATIONS OF THE S1P RECEPTOR MODULATOR PONESIMOD IN HEALTHY SUBJECTS

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Background: Ponesimod is a potent, orally active, selective, reversible sphingosine-1-phosphate receptor 1 (S1P1) modulator. Single-dose administration of ponesimod leads to a reduction of circulating lymphocytes reflecting their sequestration within lymphoid organs. Modulation of the S1P1 receptor has been described as an effective treatment of autoimmune diseases (eg, multiple sclerosis). The aim of these studies was to compare the relative bioavailability of two polymorphic forms of ponesimod in capsules (Form A vs. C, Study 1) and of a capsule vs. a tablet formulation (both of polymorphic Form C, Study 2).

Methods: Two open-label, randomized, two-way crossover studies in healthy subjects were performed. In Study 1, 12 male and female (ratio 1:1) subjects received a single dose of ponesimod (20 mg) of polymorphic Form A and C in capsules. In Study 2, 14 male subjects received a single administration of ponesimod (Form C, 40 mg)
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either in a capsule or a tablet formulation. Pharmacokinetic and safety (clinical laboratory, vital signs, and electrocardiogram) variables were assessed.

**Results:** When comparing the exposure to ponesimod following the formulations in Study 1, the geometric mean ratios for AUC$_{0-\infty}$, AUC$_{0-1/2}$, and C$_{\text{max}}$ and the responding 90% CIs were all within the 0.80 to 1.25 interval. In Study 2, a more rapid absorption of ponesimod was observed with the tablet compared to the capsule formulation. There was no marked difference in the nature, severity, and incidence of adverse events reported for the different formulations in Study 1 and Study 2. However, a dose relationship regarding the number of adverse events reported was observed.

**Conclusions:** The 2 polymorphic forms of ponesimod and the tablet versus capsule formulation were similar in terms of PK, except the more rapid absorption of the tablet formulation. At the same dose strength safety and tolerability were similar.

**PHARMACOTHERAPEUTIC DECISIONS IN CASE REPORTS, CAN WE LEARN FROM THEM?**

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**Background:** Reading case reports is a method to train clinical reasoning in general, however they seem to be focused at diagnostics rather than therapeutics. Doctors in training indicate they experience a deficit in education in pharmacotherapeutic reasoning. To determine the educational value of case reports in therapeutic reasoning, we analyzed to what degree pharmacotherapeutic reasoning was discussed.

**Methods:** Review of clinical cases published in 2 high impact medical journals (BMJ and Lancet). For every drug therapy started in these case reports, information regarding the choice and argumentation was assessed. We used a score form based on the WHO 6-step, a method used in medical schools to train students therapeutic reasoning in a step-by-step approach.

**Results:** PubMed database was searched for articles classified as case report and published in the first half year of 2014. We identified 58 articles, 44 of which we qualified as clinical case report. In 24 of these reports a total of 43 drugs were started. The drug name was mentioned in 65% and in <10% general drug information (contraindications, adverse effects and interactions) was given. In <3% the presence/absence of contraindications/interactions and suitability for the patient was discussed.

**Conclusions:** Although case reports could play a role in developing clinical reasoning skills, this opportunity is not fully utilized for pharmacotherapeutic reasoning. We emphasize that pharmacotherapeutic reasoning is complex and hard to fully assess. However, even using a “simple” score form, we showed that drug choices were frequently not described completely and argumentation for these choices was hardly mentioned. We propose a more detailed description of pharmacotherapeutic reasoning in case reports, e.g. by using some steps of the WHO 6-step method.

**A NOVEL TUMOR-SPECIFIC IMAGING AGENT FOR FLUORESCENCE GUIDED SURGERY: A TRANSLATIONAL STUDY**

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**Introduction:** Intraoperative fluorescence imaging of primary tumor and metastases potentially results in better patient outcomes. OTL38 is an imaging agent that specifically binds to the folate receptor α (FRα) which is overexpressed by various carcinomas. FRα-positive cells retain the agent, making them detectable with near-infrared (NIR) fluorescence. In this first-in-human study OTL38 was investigated in healthy volunteers and ovarian cancer patients.

**Material and Methods:** Four different iv doses were studied in healthy volunteers in a single ascending dose, randomized, placebo-controlled study in which tolerability, pharmacodynamics (PD; defined as fluorescent signal in the skin) and pharmacokinetics (PK) were assessed. The optimal doses were subsequently explored in 5 patients thus far, with an emphasis on tolerability, number of suspected lesions detected with fluorescence and concordance between fluorescence and FRα-status on histopathology.

**Results:** Low dose OTL38 was without any clinically significant adverse effects, but at the highest doses levels hypersensitivity reactions were observed. The plasma concentration-time profile showed bi-phasic elimination (elimination half-life: 26–160min) and a possible non-linear increase in AUC. In OTL38-treated volunteers a dose-dependent fluorescent signal was observed in the skin, showing distribution and clearance of OTL38 in tissue at a lower rate compared to blood. These data allowed definition of the optimal doses and time window for intra-operative imaging. Preliminary analysis of the study in patients shows accumulation of OTL38 in FRα positive tumor and successful intra-operative NIR fluorescence imaging with detection of multiple lesions not identified by inspection/palpation.

**Conclusions:** Low doses of OTL38, the first tumor-specific agent that fluoresces the NIR spectrum, were successfully used for intra-operative fluorescence imaging of FRα-positive tumors. The preliminary data suggest that our approach using healthy volunteers and PK/PD modelling appear to be extremely useful in the development of tumor-specific imaging agents.

**SEVERE DERMATOLOGIC REACTIONS ASSOCIATED WITH DRUGS IDENTIFIED IN THE HOSPITAL UNIVERSITARIO DE LA PRincesa**

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**Background:** Cutaneous adverse drug reactions (CADR) represent a heterogeneous field including various clinical patterns without specific features suggesting drug causality. Serious reactions (fatal outcome, sequelae) represent 2% of CADR: bullous reactions Stevens-Johnson Syndrome, toxic epidermal necrolysis (SJS/TEN), DRESS (drug reaction with eosinophilia and systemic symptoms), and acute generalized exanthematous pustulosis (AGEP).

**Objective:** To identify serious cases of (CADR) and the main suspected drugs.

**Materials and Methods:** Retrospective observational, between 2008 and 2014 at the Clinical Pharmacology Service of Hospital Universitario de la Princesa (Madrid) have identified 28 cases of severe skin reactions induced by drugs.

**Results:** Twenty-eight (CADR), 18 women and 10 men, mean age 43.1 years, (35.7%) in dermatology services, UCI, internal medicine. The main identified toxicodermia was AGEP (35.7%), followed by DRESS syndrome and SJS / TEN (25%), erythema multiforme (7.14%), leukocytoclastic vasculitis and linear IgA bullous dermatitis (3.57%). Main identified drug was phenytion (28.7%), followed by amoxicillin/clavulanate (14.28%), carbapenems, antiretroviral treatment, piperacilin/tazobactam and magnesium metamil (7.14%),
and allopurinol, tramadol, NSAIDs, vancomycin, clindamycin, ranitidine, and simvastatin (3.57%). Mortality rate was: 28.57% (n = 8), of which 4 by SJS/TEN, 2 by DRESS, and 2 by AGER total of 8 patients.

**Conclusions:** Serious toxicodermies in the Hospital de la Princesa have a low frequency but are associated with high mortality, risk of complications and sequelae. Very similar to that found in other studies, the most frequent is acute generalized exanthematous pustulosis.

**TARGETED EXOME RESEQUENCING: ADME PHARMACOGENETICS IN HUMAN LIVER**

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High-throughput approaches including Next-Generation Sequencing (NGS) offer the opportunity to analyze a large number of genes to detect known and novel single nucleotide variants (SNVs) and copy number variations (CNVs). We have developed a panel-based targeted NGS pipeline for comprehensive sequence analysis of 341 genes involved in absorption, distribution, metabolism and excretion (ADME) of xenobiotics and endogenous substances.

DNA enrichment for NGs was specifically designed for optimal capturing of all exonic, exon/intron boundaries, 5′ and 3′UTRs of the selected target genes with a total target size of 1.17 Mbases. A set of 150 extensively characterized Caucasian liver samples was analyzed. Variants were compared to available SNV data in databases (dbSNP, DGV). Validation was performed using Illumina HumanHAP300 SNP arrays and other genotyping methods. The impact of SNVs/CNVs on gene expression (Illumina Human WG6v2) was assessed.

Resequencing revealed more than 2 GB mappable reads containing about 29,500 variant positions with a mean coverage of about 140-fold. About 40% of observed SNVs were not yet listed in dbSNP database and one third of them were rare in our sample collection.

Association analysis of SNVs with expression data was performed gene family-wise. For example, within 11 human genes CYP families 1, 2 and 3, a total of 3 CNVs and 226 SNVs could be detected. Of these, 18 were not listed in dbSNP database, including ten missense mutations found as single observations. Their functional prediction (SIFT/PolPhen) revealed deleterious effect for CYP1A1 (R98W, H60L), CYP2C8 (R124W, L268Q), CYP2C9 (S115R, Q324*), and (SIFT/PolyPhen) revealed deleterious effect for CYP1A1 (R98W, H60L) and HNF1β (H77Q, K129L).

Association analysis of SNVs/CNVs with expression data will be presented.

Adequate cardiovascular therapy that includes usage of agents acting on renin-angiotensin system (RAS), (ATC, C09) results in the reduction of cardiovascular morbidity and mortality. It is important to establish measures for higher usage of cheaper generics which will lead to the reduction of the healthcare costs. The aim of our study was to identify and analyse changes in the usage of original and generics drugs in RAS subgroup agents in Croatia from 2000 to 2013 and to identify the rate of the generic drugs usage as well as the average price for 1 DDD.

Data on the consumption have been obtained from the database IMS (International Medical Statistics) for Croatia. According to the World Health Organization Collaborating Centre for Drugs Statistics Methodology annual volumes of drugs are presented in defined daily doses/1000 inhabitants/day (DDD/1000), while drug costs data are presented in Euro per DDD.

The usage of original drugs increased from 5.86 DDDD/1000/day to 63.56 during the investigated period and generics increased from 5.17 to 13.62. Consumption share of generics decreased from 90% in 2000 to 56% in 2006, and then we had constant increase to 68% in 2013. Average price of 1 DDD for both original and generic drugs in C09 subgroup decreased in total from 0.31 EUR/DDD in 2000 to 0.16 EUR/DDD in 2013, which is decrease of 48.91% (39.42% for originals, and 55.57% for generics).

The national healthcare policy promoting generics resulted in their increase of usage up to 2013, but due to the introduction of new INNs in subgroup (Angiotensin II antagonists, plain and combinations) it was less obvious than expected. The price trend showed price decrease in originals and generics as a result of price reduction policy introduced by Croatian National Insurance Company, but it is necessary to introduce new measures for further generic promotion.

**MICRO RNA-DEPENDENT REGULATION OF THE FARNESOID X RECEPTOR**

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**Background:** The transcription factor farnesoid X receptor (FXR) plays an important role in the regulation of bile acid and lipid homeostasis and has the potential to endo fragile protective effects against different cancer forms, such as hepatocellular or colon carcinoma. The short non-coding microRNA mir-192 is, like FXR, mainly expressed in the liver and colon, plays a crucial role in the pathogenesis of colon carcinoma and serves as a reliable serum biomarker for cancer-associated or drug-induced liver injury. In this study we investigated to what extent FXR is regulated by miR-192-3p.

**Material and Methods:** Two putative binding sites for miR-192-3p within the FXR-3′UTR were predicted in silico and tested in vitro by performing Luciferase reporter assays. The NR1H4-3′UTR was subcloned into pmirGlo reporter vector in wild-type and mutated form and co-transfected into Huh-7 cells together with miR-192-3p. To study the endogenous miR-192-3p-dependent expression of FXR and FXR-regulated target genes Huh-7 cells were treated for 48 hours and 72 hours with miRNA mimic or negative control. MRNA and protein expression were measured using TaqMan technology and western blot analysis. FXR and miR-192 expression levels obtained in colon cancer tissue samples from 65 patients were correlated using Pearson’s correlation analysis.

**Results:** MiR-192-3p binds specifically to the FXR-3′UTR and significantly decreases luciferase activity. Transfection of Huh-7 cells with miR-192-3p led to a significant decrease in FXR mRNA and protein levels as well as miRNA levels of the FXR-inducible bile acid transporters OATs and OATP1B3. Significant inverse cor-
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relations of miR-192 and FXR expression were observed in colon cancer-derived samples.

Conclusions: MiR-192-3p negatively regulates the expression of FXR, thereby significantly decreasing the expression of the FXR-inducible target genes OSITOβ and OATP1B3. Because of the role of miR-192 in cancerogenesis, this miRNA-dependent mechanism of FXR regulation could affect the expression of FXR target genes in liver and colon cancer.

Influence of Formulation Change and CyP2C19 Genotypes on Pharmacokinetics of Single-Dose Rabeprazole in Healthy Chinese Adults by LC-MS/MS

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Background: Rabeprazole is a new type of proton pump inhibitor. Its oral enteric-coated formulations have been widely used. Compared with omeprazole and lansoprazole, pharmacokinetics of rabeprazole was reported to be less affected by Cytochrome P450 2C19 (CYP2C19) genotypes, for rabeprazole being not mainly metabolized by enzymatic process. An new injection formulation of rabeprazole has just been approved in China. However, the pharmacokinetic characteristics of this new formulation are seldom reported, and whether there are differences in the effect of CYP2C19 between the two dosage formulations of rabeprazole is undefined. We carried out the following research to compare the pharmacokinetics between the oral and injection formulation of rabeprazole in relation to CYP2C19 genotypes.

Material and Methods: A sensitive and efficient LC-MS/MS method was developed to assay plasma concentration of rabeprazole samples. Twenty healthy volunteers were enrolled and given single dose (20mg) of enteric-coated tablet and rabeprazole for injection in a crossover manner, and CYP2C19 genotypes were detected before dosing. Pharmacokinetic parameters were calculated with software and compared with each others.

Results: In injection group, plasma half-time (t1/2) was 1.20 ± 0.5h, the area under plasma concentration-time curve (AUC) was 1410.34 ± 395.69 μg/h/L, and clearance (CL) was 15.25 ± 4.25 L/h. In oral group, time to peak concentration was 3.95 ± 1.01 h, peak concentration (Cmax) was 485.65 ± 193.81 h, t1/2 was 1.23 ± 0.58 h, AUC was 1089.05 ± 405.20 μg/h/L, and CL was 20.72 ± 7.24 L/h. Absolute bioavailability (AB) of rabeprazole was about 69%. Relative values of AUC after oral and intravenous administration of rabeprazole in the 3 CYP2C19 genotype (HomEM;HetEM;PM) groups were 1:1.02:1.98 and 1:1.01:1.84 respectively.

Conclusions: AB of oral rabeprazole in Chinese population was higher than reported in other populations. Pharmacokinetic properties of rabeprazole given either intravenously or orally were depended on the CYP2C19 status in Chinese population. Race difference and genetic polymorphism might be the reason of the difference in reported bioavailability.

MicroRNA Dependent Regulation of the Hepatic Uptake Transporter OATP1B3 - The Role of MiR-509 and MiR-656-3P

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Background: The hepatic uptake transporter OATP1B3 mediates the uptake of endogenous and xenobiotic compounds from portal venous blood into the liver. Substrates of OATP1B3 include bile acids, hormones as well as different therapeutics such as statins, antidiabetics and anti-cancer drugs. In the current study we investigated to which extent the micro-RNAs miR-509 and miR-656-3p regulate the expression of OATP1B3.

Material and Methods: The SLCO1B3 3'-UTR was subcloned into pmirGLO luciferase vector both as wildtype sequence as well as with targeted mutations within the bioinformatically predicted consensus sequence for miR-509-3p or miR-656-3p. Reporter vectors were co-transfected with either mimics corresponding to both microRNAs or with negative control, and luciferase gene reporter activities were compared.

Results: miR-509 and miR-656-3p were found to be associated with decreased levels of OATP1B3 mRNA and protein. This was dependent on the presence of the miRNA-binding sites in the SLCO1B3 3'-UTR. reporter vectors were co-transfected with either mimics corresponding to both microRNAs or with negative control, and luciferase gene reporter activities were compared. SLCO1B3 mRNA and protein were detected by real-time PCR and western blot analysis in extracts derived from HepG2 cells treated with miR-509-3p, miR-509-5p and miR-656 mimics. The expression of miR-509-3p, miR-509-5p, miR-656 and SLCO1B3 mRNA was correlated in cholangiocarcinoma probes performing Pearson’s correlation analyses.

Conclusion: MiR-509 and miR-656 markedly decreased SLCO1B3 expression in vitro. The suppressive effect of miR-509-5p on SLCO1B3 is supported by correlation data in vivo obtained in cholangiocarcinomas.

Sense and Nonsense of Treatment of Comorbid Diseases in Terminally Ill Patients

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Background: Pharmacotherapy is the appropriate use of drugs to prevent and treat diseases and to relieve symptoms. In the final phase of life, treatment goals change, and drugs should be reconsidered.

Case: A 69-year-old woman was diagnosed with metastatic pancreatic cancer. She had a history of type 2 diabetes mellitus, diagnosed 7 years earlier. Initially, her diabetes remained under control by metformin and by strictly adhering to a healthy lifestyle. For example, she had stopped eating her beloved ice cream. She was treated with palliative chemotherapy, including dexamethasone to reduce associated nausea. During the first cycles blood glucose levels rose to 16 mmol/L, for

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which she received short-acting insulin. At home, glucose levels were occasionally slightly above target values. Under these circumstances she stopped eating. The physician told her that higher glucose levels were not a problem when they gave her no symptoms. This information was very disconcerting to her because she had always been told that it was extremely important that glucose levels would not exceed target values. The physician repeated that higher levels were unlikely to be harmful, especially in the absence of symptoms. He emphasized that she was not being abandoned. In contrast, her caregivers were applying tailored therapy. The patient appreciated this explanation, and despite her nausea, she was keen to eat ice cream again.

Conclusions: In terminally ill patients, physicians must adapt drug treatments to new objectives. This case illustrates that such management may improve quality of life and potentially reduce unnecessary and costly pharmacotherapy.

In our current research project *Medication management in the last phase of life* we gain insight into current practices of pharmacotherapy in the last three months of life. The project is expected to be completed in the summer of 2015.
MEASURING DRUG USE: DIFFERENCES BETWEEN MEDICAL RECORDS AND HEALTHCARE UTILISATION DATABASES

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Introduction: Drug use retrieved from healthcare databases has a key role in drug utilization studies and pharmacoepidemiology. Our aim is to compare and analyse the differences and level of agreement in prevalence of drug use between healthcare utilization (HCU) and medical records (MRs) databases, expressed in number of users.

Methods: One-year period prevalence rates (PPRs) in 2008, expressed as number of users/1,000 people (MRs) and DIDs/1,000 inhabitants/day (DDIDs) transformed into number of apparent users (HCU) were calculated for the following medicines (Anatomic Therapeutic Chemical [ATC] code): calcium channel blockers (C08C, C08D), antiepileptic drugs (N03A), macrolides (J01FA), benzodiazepines (N05BA, N05CD, N05CF), and antidepressants (N06AA, N06AB). Data were available for the Netherlands (2 MRs, 1 HCU), Spain (1 MR, 1 HCU) and United Kingdom (2 MRs, 1 HCU). Percentage differences, Pearson correlation coefficients and level of agreement with Bland Altman statistics were calculated.

Results: Data were aggregated by ATC level: ATC level 3 (N03A, C08C, C08D) and ATC level 4 (J01FA, N05BA, N05CD, N05CF, N06AA, N06AB). Results: Percentage differences between PPRs [median (interquartile range)] fluctuated from −34.4% (38.2%) at ATC level 3 to −65.2% (49.2%) at ATC level 4; and from −96.0% (1.6%) for macrolides to 28.2% (54.4%) for calcium channel blockers. The correlation coefficients were r = 0.88 (P < 0.001) and r = 0.51 (P = 0.008) at ATC level 3 and 4, respectively. The level of agreement showed a deviation of −2.2/1000 users (limits of agreement [LA] −19.7 to 6.4) and −28.9/1000 users (LA –84.3 to 26.6) at ATC level 3 and 4, respectively.

Conclusions: The study suggests that the level of agreement between users and DDIDs were high the more aggregated data is presented. The wide LA might reflect not only the low number of groups of medicines studied, but also systematic bias in the measurement of DDIDs and one-year PPRs.

TREATMENT PERSONALISATION FOR BREAST CANCER: ESTROGEN RECEPTOR SPlicing VARIANTS IN PERIPHERAL BLOOD LEUKOcyTES AS NEW PROMISING BIOMARKERS

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Background: Estrogen receptor alpha (ERα)-positive breast cancer is the most frequent tumour in women and tamoxifen (TAM), an ERα competitive antagonist, is diffusely used for its treatment and prevention. Unfortunately, a significant percentage of patients do not benefit the treatment because of intrinsic and acquired resistance. ERα is activated by estrogen binding and regulates its own and estrogen-sensitive genes (ESG, e.g., MGP) expression. Recently, ERα splice variants (ESV) have been detected in healthy and tumour tissues, with pharmacological characteristics partially different from the complete form (ERα66), and emerging data suggest that they may modulate TAM efficacy.

Our study aimed to investigate the effect of TAM on ESV and ESG expression in vitro, using peripheral blood leukocytes as surrogate tissue.

Methods: Thirty-four women taking TAM as adjuvant therapy and 100 aged-matched healthy women were enrolled for this pilot study. Leukocytes from peripheral blood were collected to extract RNA. The expression of ESV and ESG were quantified by Taqman probes and SYBR-Green dye, respectively. T Student’s test and correlation analysis were performed.

Results: Our data showed that ERα66 and ERα66 were the most expressed isoforms in leukocytes. Their levels were largely variable among patients and inversely correlated (P < 0.0001). TAM was associated with reduced levels of ERα exon 5 deleted variant (P = 0.01) and on average doubled levels of the ERα missing exon-7 isoform (P = 0.06), compared to controls. In patients, MGP expression levels were significantly down-regulated compared to subjects with no anti-estrogenic treatment (P < 0.0001) and correlated with ERα66 levels (R = 0.37, P = 0.03).

Conclusions: Leukocytes may be used to study the expression profiles of ERα variants and sensitive genes, in patients taking TAM. TAM significantly affected 5- and 7-exon deleted isoforms and down-regulated MGP gene. The ERα66 isoform, that does not bind TAM, stimulated MGP transcription when ERα66 was inhibited by the drug, suggesting a role in treatment resistance.

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CD147, THE ANCILLARY PROTEIN OF MCT4, AS MARKER FOR PROGNOSIS AND CLINICAL OUTCOME IN PRIMARY CLEAR CELL RENAL CELL CARCINOMA AND METASTASIS

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Background: CD147, the transmembrane protein encoded by the C14orf13 gene, shares the majority of its extracellular domain with the alanine-rich CXXC motif containing protein 1 (ARC), which lacks transmembrane segments. CD147 is a potent ligand for the C14orf13/CARC superfAMILY member, Macrophage Migration Inhibitory Factor (MMIF). CD147 is known to play a key role in drug utilization studies and pharmacoepidemiology. Drug use retrieved from healthcare databases has

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Cluster of differentiation 147 (CD147, or EMMPRIN/basigin), is a transmembrane glycoprotein mediating oncogenic processes partly attributed to its role as obligatory binding partner for proteins involved in carcinogenesis, e.g., the monocarboxylate transporters MCT1 and MCT4. Just as previously demonstrated for MCT4, CD147 is proposed to be associated with tumor progression and metastasis in clear cell renal cell carcinoma (ccRCC) and therefore might represent a promising target for therapeutic intervention and a marker for prognosis and patient outcome. For more objective and reproducible quantification of biomarker expression, use of the automated image analysis software Definiens Tissue Studio might represent an attractive alternative to conventional visual evaluation.

CD147 protein expression was assessed in two independent cohorts of 207 and 64 ccRCC patients, respectively, and in 13 distant metastases derived from primary ccRCC, by immunohistochemical staining of TMAs and subsequent automatic evaluation using Definiens Tissue Studio. Obtained results were correlated with a semi-quantitative score derived from visual evaluation. Additionally, CD147 protein expression levels were associated with patients’ clinicopathological parameters and outcome data.

The prognostic relevance was compared to that of MCT4 protein expression.

CD147 protein expression levels generated with Definiens Tissue Studio correlated significantly with levels derived with the semi-quantitative score (P < 0.0001, r = 0.85). Furthermore, CD147 expression was significantly associated with clinicopathological parameters and cancer-related death. Metastatic tissue showed high CD147 expression as well. The comparison of prognostic relevance of CD147 and MCT4 protein expression however, showed a higher significance for MCT4 protein expression.

We could proof that software-based evaluation of protein expression using Definiens Tissue Studio is a feasible alternative to visual semi-quantitative scoring. In addition, we confirmed an association of CD147 protein expression with ccRCC progression and outcome, but its prognostic significance could not surpass that of MCT4. The potential for CD147 as therapeutic target however, especially for metastatic ccRCC, remains.

EVALUATION OF HEALTH OUTCOMES AND COST-EFFECTIVENESS OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINATION FOR INFANTS IN KAZAKHSTAN

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Introduction: S. pneumoniae is one of the leading causes of serious illness, including pneumonia, in children and adults. PCV vaccination showed high effectiveness in prevention of pneumococcal disease and decrease of pneumonia-associated infant mortality. Present study evaluates the health benefits and cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV-13) programme for Kazakhstani infants from the perspective of Ministry of Health.

Material and Methods: A Markov model was constructed to estimate the effects and direct costs of PCV-13 programme compared to other PCV programmes for infants initiated in Kazakhstan. Treatment efficacy and transition probabilities were synthesized from local registries. The characteristics of patient cohort and treatment costs (vaccine cost, monitoring, adverse effects management) in year 2014 Kazakhstani tenge (KZT) were estimated from republican official sources. Annual 3% discounting rate and 1 year cycles (with half -cycle corrections) were utilized for the model. Robustness of the model parameters was explored by one-way and probabilistic sensitivity analysis.

Results: Analysis of the registries showed significant decrease of incidence of diseases associated with S. pneumonia in children that received the PCV-13. Moreover, the introduction of PCV-13 decreased the under 1-age mortality due to pneumonia by half (95% CI, P = 0.001). As a result of 3 year stimulation of the model, the CER of PCV -13 was estimated as 8432 tenge/LYG or 8574 tenge/QALY, whereas CER for no PCV-13 was estimated as 7441 tenge/LYG or 7605 tenge/QALY. ICER was estimated as 122 070 tenge/QALY, which is within the cost-effectiveness threshold values recommended by WHO.

Conclusions: The introduction of PCV-13 seems to be a cost-effective programme in Kazakhstan. These findings may better inform decision makers regarding formulary inclusion and reimbursement in the vaccine programmes in Kazakhstan.

CULTURAL DETERMINANTS OF THE USES OF ANTIDEPRESSANTS IN 5 EUROPEAN SETTINGS

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Background: Little is known about how culture could influence in drug consumption. The aim of this study was to describe the use of antidepressants (AD) in 5 European settings and to elucidate if its use was related to cultural differences.

Material and Methods: Data on AD (Anatomical Therapeutic Chemical classification code: N06A) consumption were retrieved from the national drug consumption databases of Catalonia, Denmark, Norway, Sweden and Veneto during the study period 2007-2011. Defined Daily Doses (DDD) and DDD/1000inhabitants/day (DID) were calculated and stratified by sex and age. Spearman correlation coefficient was used to calculate correlations between the AD use and the Hofstede’s country scores for the six cultural dimensions (power distance, masculinity, indulgence, uncertainty avoidance, individualism) adjusted by pharmaceutical expenditure and general practitioners by 1000 inhabitants. Data were retrieved from the Hofstede Centre and OECD (Organization for Economic Co-operation and Development) WebPages.

Results: In 2011, Denmark showed the highest consumption (83.81 DDD) and Veneto the lowest one (34.92 DID). An increase in AD use was observed for all the countries during the study period, the lowest increase was observed in Norway, 3.5%, and the highest in Catalonia and Denmark, 18.2% and 18.1%, respectively. Women and the elderly consumed the most in all the countries. We found a strong correlation for two cultural dimensions: masculinity and indulgence, in all the years (r > 0.7). The values for power distance were r = 0.9 (2007), r = 0.78 (2008) and r = 0.77 (2011). For the uncertainty avoidance and individualism dimensions we found a strong correlation only in 2007 (r = 0.86).

Conclusions: AD consumption increased over the study period. The results of the correlations suggest that Hofstede cultural dimensions may play a role in explaining the use of AD across countries.
Measuring Drug Use: Differences Between Medical Records And Healthcare Utilisation Databases

PHARMACOECONOMIC ANALYSIS COMPARING CLOPIDOGREL DESENSITIZATION PROTOCOL VERSUS TICAGRELOR FOR ANTIITHROMBOTIC TREATMENT IN CORONARY ARTERY DISEASE PATIENTS WITH CLOPIDOGREL HYPERSENSITIVITY AFTER PCI

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Background: Antithrombotic treatment for CAD patients undergoing PCI includes dual antiplatelet therapy comprising oral loading doses of 150–300 mg of acetylsalicylic acid and 300–600 mg of clopidogrel, followed by daily doses of 75–100 mg and 75 mg orally of each drug respectively. According to the literature about 6% of patients develop an allergic reaction to clopidogrel. In those cases it is recommended to switch therapy to a newer generation P2Y12 platelet receptor blocker: prasugrel or ticagrelor, due to their quicker onset of action and more potent platelet aggregation inhibition. Our aim was to compare the annual cost of newer antiplatelet drugs versus outpatient oral clopidogrel desensitization procedure followed by clopidogrel therapy.

Material and Methods: We calibrated the yearly price of ticagrelor therapy for one patient by using the publicly available prices of DDD in Croatia (ESC guidelines for antithrombotic treatment in CAD patients undergoing PCI) to be 813.44€ (prasugrel is not reimbursed in Croatia), while one year of clopidogrel therapy including the cost of outpatient oral clopidogrel desensitization procedure (3 half-day clinical visits) amounted to 289.51€.

Results: Approximately 6529 patients undergo PCI procedures in Croatia per year and 6% of them develop allergy to clopidogrel. Yearly savings would amount to 205,244.38€ if those patients would stay on clopidogrel after successfully (90%) completing oral clopidogrel desensitization rather than be started on ticagrelor.

Conclusions: Since annual therapy with clopidogrel, even with desensitization, is 2.8 times cheaper than ticagrelor treatment, we believe that it would be more cost effective for patients with clopidogrel allergy who cannot afford copayment for a newer generation platelet aggregation inhibitor.

GENETIC BIOMARKERS FOR PREDICTING PATOLOGICAL RESPONSE IN CHEMORADIOThERAPY TREATED RECTAL CANCER PATIENTS

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Background: neo-adjuvant 5-fluoruracil-based chemoradiotherapy (CRT) for locally advanced rectal adenocarcinoma is effective in downstaging more than half of patients before surgery. Interindividual variations in DNA repair and metabolism of pyrimidine nucleotides and folates may be important mechanisms of resistance to radio and chemotherapy and often their associations with anticancer treatment cannot be revealed by classical statistics, due to epistasis.

The Multifactor Dimensionality Reduction (MDR) method was designed to identify and model gene to gene interactions. The aim of our study was to verify if genetic variants in DNA repair and pyrimidine/folate metabolism are associated with rectal cancer response to CRT, comparing different statistical approaches.

Material and Methods: Seventy patients with stage II and III rectal cancer were enrolled and treated for 5 weeks with concurrent 300 mg/m2/die of 5-fluorouracil protracted venous infusion and 56 Gy radiation, followed by surgical resection. Response was directly evaluated on surgical specimens and scored according to tumor residual mass as in TNM classification. PT0-2 were defined as major response. Genomic DNA was extracted from peripheral blood lymphocytes and ERCC1, XPD, XPC, XPA, XRCC1, XRCC3, UMP5, MTHFR and TYMS polymorphisms were analyzed by PCR-RFLP. Genotypes were associated with tumor outcomes to CRT using Chi square test and the MDR method.

Results: patients’ response to CRT was as follows: PT0 in 25.7%, PT1-2 in 34.3% and PT3-4 in 40%. Chi square test found no significant relationship between genotypes and local pathological response. Using the MDR method, we showed a significant association between the combination of XPC/TYMS/XRCC3 genetic variants and major response (P = 0.0001) that was correctly predicted in 81.8% of patients (VPP, 80.7%; 95% CI, 62.1–91.5; VPN, 86.4%; 95% CI, 73.3–93.6; sensibility, 77.8%; specificity, 88.4%).

Conclusions: MDR proved to be an easy and valid method to detect genetic combinations identifying rectal cancer patients with a high probability of chemoradiotherapy response.

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IS IT EFFECTIVE AND SAFE TO PLUS TRADITIONAL CHINESE MEDICINE INJECTION FOR PATIENTS IN ACUTE PHASE OF STROKE?–A META ANALYSIS

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Introduction: Traditional Chinese medicine injection (TCMI) has been widely used in China. However, adverse reactions reports about TCMI are also gradually increasing, and the efficacy and safety of TCMI are very controversial. The aim of this study is to assess the efficacy and safety of TCMI for acute phase of stroke.

Material and Methods: A meta-analysis method was used to review the reported clinical trials systematically. The protocol was based on classic medication therapy including antiplatelet agents, anticoagulants, fibrinogen-depleting agents and neuroprotective agents. In the observation group, TCMI were used together in the acute phase of stroke. Four investigators independently identified the relevant articles from 4 foreign language databases and 3 Chinese databases from the inception to 2 July 2014. The pooled RR (Relative Risk), RD (risk difference) and MD (mean differences) with 95% confidence intervals (CIs) were calculated by Revman 5.2.7 software.

Results: According to the inclusion criteria, ultimately 77/943 studies on 14 TCMI with 7449 patients were defined. The meta-analysis showed that TCMI was unable to reduce all-cause mortality of acute period stroke case (RD, −0.04; 95% CI, −0.08 to 0.01; P = 0.10), the deterioration was on good control after adding TCMI (RD, −0.06; 95% CI, −0.08 to −0.04; P < 0.00001). The TCMI combined therapy could improve the neurological deficit of acute phase stroke according to the total efficient rate and neurological deficit score improvement (RR, 1.25; 95% CI, 1.22 to 1.27; P < 0.00001; and MD, 4.15; 95% CI, 2.31 to 5.98; P < 0.00001, respectively). TCMI seemed to
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be a relatively safe therapy in acute phase (RD, 0.02; 95% CI, −0.01 to 0.06; \( P = 0.19 \)).

Conclusions: TCMI might be beneficial to improve the neurological deficit of acute phase stroke, and relatively safe if be used rationally. However, parts of reported TCM trials were limited in methodology quality, which may affect the credibility of this research to a certain extent.

A PROSPECTIVE STUDY OF QTc PROLONGATION DUE TO ERYTHROMYCIN USED AS PROKINETIC AGENT IN ICU PATIENTS

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Background: High dose erythromycin used as antibiotic prolongs QTc. Low dose erythromycin is frequently used as a prokinetic agent, especially in patients at the ICU. It is unknown whether low dose erythromycin prolongs QTc and put patients at risk for torsades des pointes.

Methods: In this prospective study we included patients at the ICU treated with erythromycin in a dose of 200 mg bd. Electrocardiogram was registered before, 15 minutes and 24 hours after start of erythromycin. No new QTc medication should be started during study. QTc was measured by 2 investigators. Electrolytes, renal function and hepatic function was measured in all patients.

Results: In a total of 51 patient, 3 ECGs were recorded and no change was made in QTc prolonging medication. In these 51 patients QTc increased significantly from 430 ms at baseline to 439 ms (\( P < 0.001 \)) after 15 minutes and 444 ms (\( P = 0.01 \)) after 24 hours. After 15 minutes and 24 hours upper limit of 95% confidence interval for prolongation of QTc was well above 10 ms. In 4 patients QTc increased to more than 500 ms in and 2 patients QT was already above 500 ms. No QTc related arrhythmias were seen.

Conclusion: Erythromycin in a dose of 200 mg bd prolongs QTc and ECG should be controlled when this is prescribed.

PHARMACOVIGILANCE IN KYRGYZ TUBERCULOSIS PUBLIC PROGRAM: CURRENT SITUATION

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Introduction: Tuberculosis (TB) remains a major public health problem globally. The problem has been exacerbated in connection with the increasing of multiresistances of M. tuberculosis to the drugs used and the occurrence of serious adverse drug reactions (ADR). Difficulties in identifying drugs, the use of which has led to the ADRs, particularly severe events affect on the adherence of patients to the prescribed treatment regimen. Low compliance of patients due to ADRs, and as a result, stop taking anti-TB drugs is a big risk for patients and serious threat to society. Objective of this work is to assess the frequency and severity of side effects anti-TB drugs. And also demonstrate the importance of integration of pharmacovigilance in the national TB- programs.

Methods: The method of spontaneous reports of suspected ADR of drugs was used. The study included all patients hospitalized and treated with anti-TB drugs. Statistical analysis was performed using MS Excel 2010.

Results: Integration of pharmacovigilance in the national TB-program has been carried out in 2014. Total amount of ADRs included to national data base are 81 cases by 2014, 37 cases out of them due to anti-TB drugs. The most of medication complications were on drugs: cycloserine, protonamid, pyrazinamide. Side effects were from the central nervous system and the gastrointestinal tract, which clinically come out in hypersensitivity reactions (56%), convulsions (7%), headache, dizziness (14%), nausea, vomiting (21%) and diarrhea (2%). Patients are male (57%), but the ADR is more frequently in women. The average age of patients was 30 years.

Conclusions: The integration of pharmacovigilance in the national TB-program has contributed to increasing the number of spontaneous reports of ADR for TB-drugs and prescribed drugs more efficiently, taking into account the available data and thereby minimize the risk of ADR.

IMPACT OF THE CYP3A4 METABOLIC ACTIVITY AND CYP2C19 POLYMORPHISMS ON ANTIPLATELET EFFECTS OF CLOPIDOGREL IN RUSSIAN PATIENTS WITH ACUTE CORONARY SYNDROME UNDERGOING CORONARY STENT IMPLANTATION

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Introduction: Dual antiplatelet therapy, involving aspirin and clopidogrel, is recommended in patients undergoing coronary stenting to avoid the occurrence of stent thrombosis and other ischaemic events. The presence of CYP2C19*2 polymorphism and CYP3A4 low metabolic activity can reduce the formation of the active metabolite of clopidogrel, resulting in less platelet inhibition. High residual platelet reactivity is associated with an increased risk of a cardiovascular event after coronary stenting. The aim of our study was to evaluate the impact of the CYP3A4 metabolic activity and CYP2C19 polymorphisms on platelet reactivity during dual antiplatelet therapy.

Material and Methods: We determined the CYP2C19 genotypes (Real-time PCR) and CYP3A4 metabolic activity (6b-hydroxycortisol/cortisol (6-OHC/FC)) in urine were determined by high-performance liquid chromatography of 81 subjects with acute coronary syndromes (ACS) undergoing coronary stent implantation (62 male patients, mean age 64 years) receiving clopidogrel and evaluated the effect of these factors on on-treatment platelet aggregation using the VerifyNow P2Y12 assay. The SPSS 20.0 software was used for all statistical analyses. A \( P \) value of <0.05 was regarded as significant.

Results: The distribution of the CYP2C19 genotypes were 84.0 % in extensive metabolizers (EM; CYP2C19*1/*1), 16.0 % in intermediate metabolizers (IM; *1/*2), and poor metabolizers (PM; *2/*2) were not found. The mean platelet reactivity unit (PRU) was significantly higher in patients with CYP2C19*2 compared to non-carriers: 190.8 ± 48.2 in IM versus 166.0 ± 50.8 in EM (\( P = 0.007 \)) and the frequency of clopidogrel resistance (PRU >208) was 53.8 and 16.2 correspondingly. The index of urinary 6-OHC/FC (marker of CYP3A4 activity) ratios were 3.4 ± 2.8 in PRU >208 and 3.2 ± 3.0 in PRU ≤208 groups (\( P = 0.8 \)) and not found statistically significant correlation between PRU and 6-OHC/FC ratios (\( P = 0.84 \)).

Conclusions: Clopidogrel treated patients with the CYP2C19*2 polymorphism have significantly increased platelet reactivity compared to non-carriers. The ratio of urinary 6-OHC/FC was not influence on on-treatment platelet aggregation.
ACUTE LEVODOPA CHALLENGE FOR ELDERLY PATIENTS WITH NEWLY DIAGNOSED PARKINSONIAN SYNDROME
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Background: Clinical response to acute levodopa challenge can predict the efficacy of this drug in the long-term treatment of Parkinson disease (PD). Furthermore, a good response supports the diagnosis of idiopathic PD. However, in elderly patients who usually suffer from many comorbidities, side effects of a single levodopa dose may limit the tolerance and usability of this test.

Objective: 1. To assess the feasibility of acute levodopa challenge in elderly patients with newly diagnosed parkinsonian syndrome in a university hospital setting. 2. To assess the predictive value of acute levodopa test for the efficacy of chronic dopaminergic treatment. 3. To correlate the result of acute levodopa test with the dopamine transporter uptake ratio quantified by a DaTSCAN.

Methods: Candidates for the study will be selected via neurological consultation, performed by a movement disorders specialist, among patients hospitalized in geriatric wards. Unstable cardiovascular or mental condition, severe infection or ongoing dopaminergic or dopaminergic receptor blocking treatment will constitute exclusion criteria. MDS-UPDRS 3 subscale (with video recording) will be performed for the assessment of parkinsonian motor signs before («time 1») and 1 hour after acute levodopa administration («time 2») as well as on stable chronic levodopa therapy at 2 months («time 3»). The first acute levodopa dose will be calculated by the body weight and the chronic therapeutic dose will be titrated individually and progressively according to efficacy and tolerance to achieve the best clinical response. Cognitive state (Mini Mental State and Neecham Scale) and arterial blood pressure in lying and standing position (Schellong test) will be assessed at baseline and Neecham Scale and Schellong test at each evaluation time. Any other adverse effect will be searched and noted (nausea, dizziness, vomiting etc.) DaTSCAN will be performed during the hospital stay and striatal uptake of radioligand quantified. Statistical analyses will consist in computing Poisson 95% confidence intervals for the incidence of side effects predicting efficacy using logistic and linear regression models and the association with DaTSCAN with Pearson correlation coefficient.

LEARNING BY DOING IN THE STUDENT-RUN PHARMACOVIGILANCE PROGRAM
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Background: Medication safety is an important topic in healthcare nowadays. Pharmacovigilance, the monitoring of drug safety after approval for marketing, depends mainly on the quality and quantity of reported adverse drug reactions (ADR). To increase pharmacovigilance awareness among medical students, we developed and evaluated a Student-run Pharmacovigilance program, together with pharmacovigilance centre Lareb.

Method: A pilot study was performed in which teams of (1st-4th year) medical students assessed real ADR-reports from patients/healthcare professionals reported to Lareb. After assessment on causality, students searched for a pharmacological explanation and wrote a feedback letter to the reporter and a summary for the pharmacovigilance-databases of the European Medicines Agency and WHO. This student-assessment was then verified by Lareb staff, who evaluated student-handling it in an e-questionnaire.

Results: From May to December 2014, 89 different ADR-reports selected by Lareb staff were handled, with the top 3 reported ADRs (nausea; palpitations, urinary retention and agitation. Thirty-five students and 3 Lareb staff members participated. Lareb staff rated the student assessments (very) useful (>92%), scientifically substantiated (>85%), complete (not lacking information) and without inaccuracies (both >92%). Altogether the student-assessments were rated mean 8.3 (1–10; min-max). Compared to self-handling, Lareb staff indicated student-assessment cost less time in 33% assessments, neutral in 55%, and cost extra time in 11%.

Conclusion: The Student-run pharmacovigilance program is a win-win venture. It offers students a valuable "pharmacovigilance experience", creates awareness in future doctors with the potential to increase ADR-reporting, and didn’t cost Lareb staff extra time overall. The learner effects need to be investigated in future studies.

IN SEARCH OF THE SUSPICIOUS LINK: SMOKELESS TOBACCO USE AND ORAL MUCOSITIS IN HEAD AND NECK CANCER PATIENTS
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Introduction: Smoking of tobacco is implicated as one of the major risk factors for development of oral mucositis (OM). Tobacco in other smokeless forms is a major form of addiction in many countries. However, the association of smokeless tobacco with oral mucositis has hardly studied. The present study aims at finding the association, if any, with different types of tobacco use with OM.

Materials and Methods: In this cross-sectional study, head and neck cancer patients receiving radiation, chemotherapy or concurrent chemo-radiation who developed oral mucositis over a study period of three months were enrolled. History of different forms of tobacco use, alcohol, oral hygiene and other risk factors were noted along with other demographic variables and analyzed.

Results: Out of total 20 enrolled patients of OM, data of 18 consented patients were analyzed. Smokeless tobacco addiction in any form was found to being associated significantly with oral mucositis among head neck cancer patients receiving radiation or chemotherapy.

Similar numbers of smokers were detected to have OM. Poor dental hygiene was noted in 72% patients.

Conclusions: Smokeless tobacco, like its smoking counterpart, was found to be associated significantly with oral mucositis among the head neck cancer patients receiving radiation or chemotherapy.
CHARACTERIZATION OF BLOOD GLUCOSE & GLYCOSURIA FOLLOWING IV TREHALOSE (CABALIETA) ADMINISTRATION FOR OPMD

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Background: Trehalose is a naturally occurring disaccharide that is currently being evaluated for the treatment of Oculopharyngeal Muscular Dystrophy (OPMD) and spinocerebellar ataxia 3.

Objective: The purpose of this sub-study (part of OPMD phase 2 therapy trial) was to evaluate the extent of increase in blood glucose and the extent and duration of glycosuria associated with the intravenous administration of Trehalose.

Methods: Fourteen OPMD patients received weekly intravenous 30 gr trehalose over a period of approximately 80 minutes. Just prior to and following the administration of the 3rd dose, blood were taken periodically over 5 hours for the evaluation of plasma concentration of trehalose using a validated high performance liquid chromatographic tandem mass spectrometry. On a different dosing day, plasma and urine samples were taken periodically over 8 hours for the evaluation of glucose concentration using hexokinase enzyme method on a chemistry analyzer.

Results: Plasma concentration of trehalose exhibited more than 2-fold variation with AUC0-5 ranging from 2698 to 6103 µg *h/mL. A mild rise in plasma glucose was noted in 11 patients reaching a peak (mean ± SD) 11.28 ± 7.27 mg% within 1-2 hours following Trehalose infusion. The rise in blood glucose was transient and it reverted back to pre-Trehalose concentrations within 1-4 hours (2.10 ± 1.29 hours). Some degree of glycosuria was noted in all patients.

Maximal glucose urinary concentration varied ranging from 42 mg% and up to 1031 mg% (358 ± 341 mg%). Peak glycosuria was noted within 1-3 hours and it was evident only in 1 patient in the urine sample taken after 8 hours.

Conclusions: The intravenous administration of 30 gr trehalose (Cabaljeta) is associated with a subtle rise in blood glucose concentration and transient glycosuria. The presence of urinary glucose represents most probably in-situ renal activity of trehalase.

INFLUENCE AGOMELATINE THERAPY ON HEMOSTASIS OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Introduction: The problem the treatment of depression in patients with acute myocardial infarction (AMI) is determined by the growing prevalence of anxiety and depressive disorders (ADD) among patients. ADD has a negative impact and prognosis of AMI. Some studies have confirmed the high therapeutic efficacy and tolerability standard doses of agomelatine for the treatment of mild and moderate severity depressive disorders in cardiology practice in Russia in combination with preparations for the treatment of AMI.

Material and Methods: The study included 196 patients of both sexes (mean age 64.2 ± 0.8 years). The patients with AMI without ADD (n = 88), the patients with AMI and ADD without agomelatine therapy (n = 58) and the patients with AMI and ADD with agomelatine therapy (n = 50). We studied coagulation and vascular-platelet hemostasis on the first 24 hours of hospitalization and in the dynamics of the disease on the 14th day of hospitalization.

Results: Activity of blood coagulation is more pronounced in patients with AMI and ADD in comparison with patients without ADD. Despite ongoing antplatelet therapy of patients with AMI and ADD observed a high level of platelet activation on the first day of hospitalization and in the dynamics of the disease on the 14th day in comparison with patients without ADD. Patients with AMI and ADD with agomelatine therapy in addition to standard antplatelet therapy in the dynamics of the disease on the 14th day of hospitalization a clear decrease in platelet aggregation compared to the 1st and days of hospitalization. After 14th day from the start agomelatine therapy a tendency to reduce the severity of ADD.

Conclusions: We registered a positive response to receiving antthrombotic therapy in patients with AMI in combination with ADD on the background of early treatment with agomelatine. This can have a favorable effect on the course and prognosis of patients with AMI and ADD.

DOUBLE-BLIND, PLACEBO AND ACTIVE COMPARATOR-CONTROLLED STUDY IN HEALTHY MALES FOLLOWED BY AN OPEN-LABEL STUDY IN HEALTHY MALES AND FEMALES, TO ASSESS THE SAFETY, PHARMACOKINETICS AND –DYNAMICS OF 2B3-201

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Background: Intravenous methylprednisolone (MP) has for long been the mainstay of relapse treatment in MS. However, it is inconvenient and its side effects are undesirable. Both the dose and the dosing frequency can be reduced by incorporating MP in (PEGylated) liposomes, creating a slow-release formulation with reduced systemic toxicity, but similar peripheral efficacy. By adding glutathione to the PEGylated liposomes (2B3-201), enhanced delivery of MP into the brain is achieved. Preclinical studies in animal models of MS showed that 2B3-201 had fewer side effects and a superior efficacy compared to free MP.

Methods: In this double-blind, 3-way cross over study, 18 healthy males in 3 cohorts, received an ascending doses of 2B3-201, active comparator (MP) or placebo. MP plasma concentrations, standard safety parameters, lymphocyte counts, ACTH and fasting glucose were determined. Neurocognitive tests were performed. Part 2 of the study was an open-label infusion of 2B3-201 to assess PK in women and the influence of anti-histaminics on side effects.

Results: 2B3-201 was shown to have a plasma half-life of 23 h, compared to a half-life of 3 h for free MP. 2B3-201 (150, 300 or 450 mg) resulted in a similar reduction in the lymphocyte count as 1000 mg of free MP. This effect was sustained considerably longer after 450 mg 2B3-201 administration to >74 h. Similar patterns were observed for a decline in ACTH and a rise in fasting glucose. No signs of CNS side effects or serious AEs were observed. The AEs were generally mild and self-limiting. Results of part 2 are not final yet and will be presented at the EACPT meeting.

Conclusions: 2B3-201 at doses up to 450 mg was considered safe. 2B3-201 shows a long plasma half-life (23h) and immunosuppressive effects. This supports development of 2B3-201 as a safe treatment of acute relapses in MS.
1 PHARMACOKINETICS AND PHARMACODYNAMIC
2 DOSAGE ADAPTATION OF CEFACLOR IN
3 SYSTEMIC INFECTIONS
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7 Background: Cefaclor was one of the commonly used antimicrobi-
als in Serbia, but due to fast development of resistance, other oral
cephalosporins rapidly upsetaged cefaclor and cefaclor was removed
from the list of the drugs reimbursed by the National Health
Insurance Fund. Use of recommended dosing regimen (230-500mg/8-
12h) is likely to result in sub-therapeutic concentrations for a wide
portion of dosing interval due to short half-life of cefaclor, which
may facilitate development of resistance. The aim of this study was
to determine adequate dosing interval for cefaclor in treatment of sys-
temic infections using Pharmacokinetic (PK) and pharmacodynamic
(PD) parameters with special regard to postantibiotic effect (PAE).
8 Material and Methods: PK profile of cefaclor in healthy volunteers
and PK/PD indices relating to efficacy of cephalosporins were deter-
mained, as well as minimum inhibitory concentration (MIC) and PAE
of cefaclor on 4 susceptible bacteria.
Results: C_{max} of 23.142 ± 5.67 µg/mL was measured after 40-60
minutes. T_{max} was 0.72 ± 0.13 hours. Calculated AUC_{0-t} was 29.148
± 9.27 µg/mL/h. MICs were in range of 1-2 µg/mL. Cefaclor induced
PAE of 1-2h. There was inconsistency between standard dosing regi-
men and PK/PD parameters. Main PK/PD index relating to efficacy of
ccephalosporins (%t>MIC) for the 750mg dose was 33.5±42.1%.
PK/PD breakpoints for cefaclor were between 0.3-1µg/mL. Even the
maximum dose with standard dosing intervals is not appropriate for
eradication of susceptible organisms. Short PAE can’t compensate
for sub-inhibitory concentrations at the half of the dosing interval.
Conclusions: In reference to PK/PD parameters cefaclor should be
administered every 6h for the doses of 500mg and 750mg, and every
4-4.5h for the 250mg dose in order to maximize its therapeutic effi-
cacy and minimize development of resistance. This work was supported by the Ministry of Science and
Technological development, Republic of Serbia, project No III 41012.

9 NO ACCUMULATION OF A HIGH PROPHYLACTIC
10 NADROPARIN DOSAGE IN PATIENTS WITH
11 MODERATE RENAL INSUFFICIENCY ASSESSED BY
12 PEAK ANTI-XA ACTIVITY
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16 Introduction: Low-molecular weight heparins (LMWHs) have been
shown to accumulate in patients with renal insufficiency, especially
in therapeutic dosages. However, no appropriate studies have been
conducted for prophylactic dosages of nadroparin. As a consequence,
dose reduction is often recommended especially in high prophylactic
dosages. We assessed accumulation of a high prophylactic dosage of
nadroparin in patients with renal insufficiency.
17 Materials and Methods: We conducted a prospective cohort study
and measured peak anti-Xa activity 4 hours after subcutaneous
nadroparin injection on day 1, 3, 5 and if possible day 10 in adults
with and without renal insufficiency defined as a glomerular filtration
rate (GFR) below or above 50 mL/min/1.73 m². Patients with a GFR
below 10 mL/min/1.73 m² were excluded.
18 Results: We included 14 patients in each group. In the group with renal
failure 12 patients had a GFR between 30 and 50 mL/min/1.73 m².
Peak anti-Xa activity showed a high interindividual variability, but
was fairly constant within each patient. There was no rise in peak
anti-Xa activity on day 3 and 5 after consecutive administration.
Conclusions: Prophylactic dosages of nadroparin showed no accumu-
lation in patients with a GFR between 30–50 mL/min/1.73 m². Dose reduction in this group could lead to suboptimal thrombo-
 prophylaxis. Due to underrepresentation of patients with GFR <30
mL/min/1.73 m² (n = 2) we cannot give recommendations for this
group.

19 POSSIBILITIES OF OPTIMIZATION OF
20 STATIN THERAPY BASED ON GENOTYPING
21 SLC01B1 AND CYP2C9 AT PATIENTS WITH
22 CARDIOVASCULAR DISEASE
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26 Introduction: The individual mode of drugs dispensing on the basis of
genotype can promote more effective and safe therapy. Frequency of detection of gene polymorphism of SLC01B1(ТС +
CC) in Russia is between 30 and 45%. Identification of carriers
pathological C-allele allows personalized approach to drugs selection
and the mode of its dispensing. The isoenzyme of cytochrome
P-450 (CYP2C9) is responsible for a metabolism of many drugs. Genetic variability of CYP2C9*2/3 in addition to SLC01B1 can
affect on pharmacokinetics of drugs. The aim was to determine the
frequency of polymorphism of SLC01B1, frequency of polymor-
phisms of CYP2C9*2/3 in carriers of C allele of the gene SLC01B1
in group of patients with dyslipidemia, to identify the prevalence of polymorphisms of several genes in one patient.
Material and Methods: DNA of 604 patients at the age of 52.2 ±
11.9 years (353 men, 251 women) with a dyslipidemia were analysed.
Results: Polymorphism of SLC01B1(ТС +
CC) was detected in DNA of 202 patients (33.4%); TC: 177 (29.3%); CC: 25 (4.1%). Carriers of C allele had SLC01B1 genotyping of CYP2C9*2/3.
Polymorphism of CYP2C9*2(CT/TT) was detected in DNA of 17 patients (15%); CT: 13 (11.5%); TT: 4 (3.5%). Polymorphism of CYP2C9*3(AC) in DNA of 15 patients (13.3%). The structure of occurrence of polymorphism of the studied genes was analysed:
1) patient had polymorphisms of SLC01B1(СС) + CYP2C9*2(CT),
2) patient – heterozygote of SLC01B1(ТС+СС) and CYP2C9*2/3
(АС + СТ).
Conclusions: In the studied population of patients with dyslipidemia
a significant number of polymorphism of SLC01B1 was founded,
that may interfere a profile of safety of statins. Prevalence of poly-
morphism of CYP2C9*2/3 is also important. Early detection of polymorphisms in several genes involved in the biotransformation
of drugs in DNA of one patient with polymorbidity pathology can
predict the risk of adverse side effects.

27 DOES POLYPHARMACY IN ELDERLY PATIENTS
28 WITH HEART FAILURE INFLUENCE MORTALITY
29 AND HOSPITALISATION?
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31 E. van’t Riet
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33 Background: The incidence of heart failure among the elderly is
increasing. Ageing is often accompanied with comorbidity and there-
fore patients often face polypharmacy. Whether polypharmacy is
related to any adverse outcome is unknown. We performed a study

2015
to identify the incidence, extent and effects of polypharmacy among
the elderly with heart failure.

Material and Methods: In this retrospective cohort study of an out-
patient heart failure clinic, 114 elderly patients (>65 years) with
heart failure with a reduced ejection fraction (<40%) were analysed.
During a one year follow-up all adverse events were recorded. The
relationship between the amount of prescriptions and adverse out-
comes was analysed.

Results: Of all heart failure patients 85% had polypharmacy (i.e.
≥5 prescriptions). In 35% of all patients an adverse event occurred,
either death (10%) or hospitalisation (90%). Statistical analysis
showed that patients with 10 or more prescriptions had a higher risk
of developing an event compared to patients with 6 or less prescrip-
tions. This risk was no longer significant when corrected for known
predictors of adverse outcome in heart failure, such as NT-proBNP,
anemia, COPD or NYHA-classification.

Conclusion: Polypharmacy occurs in a large majority (85%) of
elderly patients with heart failure. Patients with 10 or more pre-
scriptions have a higher risk of developing an event within one
year. However, when corrected for NT-proBNP, anemia, COPD and
HYHA-classification, this effect was not statistically significant. In
our heart failure population, the severity of heart failure seems to be
more important to predict an adverse event.

Key words: polypharmacy, elderly, heart failure.

REAL-LIFE COSTS AND COST-EFFECTIVENESS
OF DIFFERENT TREATMENT PROTOCOLS OF
METASTATIC COLORECTAL CANCER IN FIVE-YEAR
PERIOD

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Background and Introduction: Aim of this study was to define and
quantify structure of real-life costs of oncology treatment in patients with
metastatic colorectal cancer (mCRC), during five-year survival period.

Material and Methods: Retrospective randomized case series and
cost analysis study of mCRC treatment protocols has been done,
using hard copies of patients’ files from the university hospital.
Sixty-two patients with mCRC with clinical, histological, imaging
and laboratory conformation were randomly selected and divided
into three Ray: cytotoxic protocols used (conventional chemotherapy vs.
chemotherapy with monoclonal antibodies (mAbs - bevacizumab
or cetuximab) added. Costs comprised pharmaceuticals, laboratory
analyses, physicians’ services and hospital admission, were presented
as mean ± standard deviation (95% CI for mean) and percentage.

Long-term survival estimates were calculated using the Kaplan-Meier
method and for calculation of incremental cost-effectiveness ratio
(ICER) between two groups, estimated survival in five-year period
and average costs of treatment of each group were used.

Results: Total direct medical costs reached €5,137 (€3,758–€6,517)
(pharmaceutical costs share amounted 82% of total costs) and
€22,113 (€16,201–€28,025) (pharmaceutical costs 93.24%) for
treatment with conventional chemotherapy with mAb added, respectively. Statistically
insignificant difference in terms of overall survival between the two
treatment groups was shown (P = 0.993), but in terms of five-year
survival period, mAbs-based treatment group showed six months
longer survival on average. ICER of €32,108 per life year gained
attributable to mAbs treatment exceeds by three-fold informal will-
ingness to pay threshold of Serbia.

Conclusions: Costs for mCRC were driven by targeted biologicals,
with rather modest impact on survival period. Also, significantly
higher costs of care were recorded in mAb-treated group in other
domains, such as hospital admission. More selective reimbursement
criteria should be applied in order to decrease costs related to effec-
tiveness of targeted oncology agents.

COENZYME Q10 LEVELS IN PATIENTS ON LOW DOSE STATINS IN RELATION TO THEIR
THERAPEUTIC AND ADVERSE EFFECTS

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Background: Ubiquinone (Q10) has been related to statin-induced
myopathy and was shown to decrease during treatment. In our pro-
spective study we evaluated these effects in patients on low-dose
statin treatment.

Material and Methods: Eighty-two patients with dyslipidemia were
prospectively recruited. All received initial simvastatin (same brand
name) 20 mg/day and were followed up every 1 weeks of treatment
during 1 or 2 months. The following parameters were analysed at
each visit: total cholesterol, LDL, HDL, creatine kinase (CK) and
total Q10 (HPLC). Daily cholesterol intake was calculated based on
reported diet, muscular pain symptoms were recorded.

Results: Total Q10 levels were evaluated in 30 patients. Cholesterol
intake was stable over the time of observation. Mean initial Q10 levels
were 350 ± 180 ng/mL. Significant decrease was observed after first two
weeks of treatment (270 ± 160 ng/mL, P < 0.05), and was more pro-
found at week 4 (260 ± 120 ng/mL, P < 0.005), while at week 6 tended
to increase and was not significantly different from initial values (280 ±
150 ng/mL). Initial Q10 levels did not correlate with baseline LDL values,
but tended to correlate with LDL levels on the 2nd week of treatment
(Spearman r = 0.5, P = 0.06). Second week Q10 levels correlated with
corresponding LDL (Spearman r = 0.52, P < 0.05), there was no cor-
relation of Q10 and LDL levels at weeks 4 and 6. Despite no muscular
symptoms reported, we observed increase in CK levels at weeks 5 (113 ±
69U/L vs 92 ± 43 U/L, P = 0.008), and 4 (123 ± 92 U/L, P < 0.005).
No significant correlation between Q10 and CK levels was observed.

Conclusions: Significant decrease in Q10 levels and increased CK
was observed even with low-dose statin treatment. As expected, Q10
levels were in good correlation with statin effects expressed in LDL
decrease. Correlation of Q10 and CK levels, however, were not so
obvious, although the sample size was small.

THE VASCULAR FUNCTIONAL REMODELLING
AGE-RELATED BETWEEN THE THORACIC AND
ABDOMINAL AORTA IS HETEROGENEOUS

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Vascular beds undergo continuous functional remodelling of the ele-
ments of the vascular wall and adaptive changes that observed in
this process. Functional remodelling is heterogeneous. The aorta is
considered that structural and functionally homogenous along their
different segments. However, the magnitude of mechanical stress is
not uniform between aorta segments. In this way, was tested that
whether functional remodelling age-related is the character heterog-
igenous on thoracic and abdominal aorta of rat.

Methods and Results: We studied In vitro experiments that func-
tional remodelling is heterogeneous in endothelium intact thoracic
and abdominal aortic rings from rats of 3 and 6 month-old. The concentra-
tion response curves to Ach, Phe and AngII were similar in thoracic
rings (Fig. 1B-C-D). In abdominal rings the relaxation induced by Ach

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was impaired (Fig. 1E) and this was related with reduction on functional endothelium cell (Fig. 1A) also the contraction curves to Phe (did not to AngII) it was lower in rats of 6mo old (Fig. 1F-G). The reduction of relaxation with LNAME in abdominal rings of 3mo old was to similar that rings of 6mo old without LNAME (Fig. 2B). The endothelial influence on Phe induced contractions in young rats were completely blocked by LNAME in the aorta with any differences between groups.

Conclusion: – The decrease of NO in response to agonist is counteract with the apparently desensitization of contractile response by Phe at abdominal level. – The increased of sensitivity to Phe in thoracic and abdominal rings with LNAME to confirm the critical role of endothelium in the regulation of smooth muscle tone by releasing NO under basal conditions. – We demonstrated relevant changes heterogeneous age-related in the functional remodelling that impact importantly the abdominal aorta without changes of thoracic aorta. This heterogeneous remodelling could be explain, at least part, for differences between mechanistic stress that have influence along by aorta.

ANTI-EGFR MONOCLONAL ANTIBODIES INCREASE THE RISK OF PULMONARY EMBOLISM IN CANCER PATIENTS. A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cancer patients have a thrombophilic condition predisposing to thromboembolic events such as pulmonary embolism (PE); in addition, drug-exposure can increase this risk. Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies (anti-EGFR MoAbs), Cetuximab and Panitumumab, are beneficial in the treatment of various malignancies, but are burdened by severe and life-threatening harms including PE. We conducted a systematic review and meta-analysis in order to determine the incidence and the risk of PE associated with Cetuximab and Panitumumab.

Material and Methods: Medline, Embase, Web of Science, CENTRAL databases were searched for articles published until October 2014. Eligible studies were randomized phase II and III trials comparing anti-EGFR MoAbs containing regimens with the same regimens without anti-EGFR to treat cancer. Pooled estimates of summary incidence of severe and life-threatening AEs, RR and 95% confidence intervals (CIs) were calculated using random effects model. Heterogeneity among studies was however investigated visually and using I-squared statistics. We re-expressed RR in Number Needed to Treat to Harm (NNTH). Subgroup analysis according to anti-EGFR agent was performed. Study quality was assessed using Cochrane Risk of Bias Tool.

Results: Bibliographic search provided 6,777 records, after a selection process 6 articles were eligible. A total number of 6,773 patients were considered in our analysis. Patients receiving anti-EGFR MoAbs had a significantly increased risk of severe PE (RR, 1.56; 95% CI 1.20–2.04) and an incidence of 4.3% (95% CI, 2.7–6.0%) vs. 2.7% (95% CI, 1.6–3.8%). NNTH was 63 (95% CI, 35–173). Statistical heterogeneity was irrelevant ($I^2 = 0$%). Subgroups analyses revealed no differences between Cetuximab and Panitumumab. Visual inspection of funnel-plot indicates no publication bias.

Conclusions: The addition of anti-EGFR MoAbs to backbone therapy increased the risk of PE by the 56%. Prevention, early recognition

ANTI-EGFR MONOCLONAL ANTIBODIES AND RISK OF SEVERE HAEMATOLOGICAL ADVERSE EVENTS IN CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cetuximab and Panitumumab have been proven to be effective in several randomised clinical trials (RCTs) and are now widely used in oncology. The occurrence of severe haematological adverse events (AEs) is a common finding in patients receiving chemo-therapeutic agents. This makes it difficult to discern between the effects of these monoclonal antibodies (MoAbs) and the effects of the backbone regimen. A possible way to tackle this issue is to summarise the growing amount of evidence from RCTs comparing these MoAbs plus backbone therapy with backbone therapy alone.

Methods: PubMed, Embase, Web of Science and CENTRAL databases were searched for articles published until 1st October 2014. Eligible studies included prospective randomized phase II and III trials comparing anti-EGFR containing regimens with the same regimens without anti-EGFR to treat cancer. Data on haematological toxicities were extracted. Cochrane Risk of Bias assessment was performed. Statistical analyses calculated the summary incidence of AEs, relative risks (RRs) and 95% confidence intervals (CIs) by using either random effects or fixed effect models on the basis of the heterogeneity of the included studies.

Results: A total population of 19,143 patients from 32 randomised clinical trials was analysed. No significant increase in the risk of severe neutropaenia or thrombocytopaenia was found, but we observed a statistically significant risk increase (RR, 1.73; CI, 1.16–2.57) for anaemia in colorectal cancer patients, with an incidence of 3.3% (95% CI, 1.5–5.1%) in the experimental arm and 1.6% (95% CI, 0.5–2.7%) in the control arm.

Conclusions: We present the first systematised evidence suggesting that Panitumumab treatment is not associated with a significant increase in the risk of neutropaenia. Our analysis also indicates the absence of an increased risk of any haematological toxicity following the administration of anti-EGFR MoAbs, with the only exception of anaemia among colorectal cancer patients.

ANTI-EGFR MONOCLONAL ANTIBODIES INCREASE THE RISK OF SEVERE GASTROINTESTINAL ADVERSE EVENTS IN CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cetuximab and Panitumumab have been proven to be effective in several randomised clinical trials (RCTs) and are now widely used in oncology. The risk of severe gastrointestinal adverse events (AEs) seems to be increased by the addition of these agents.
Clinical Therapeutics

1 Diarrhea and mucositis are two of the most common AEs in patients receiving chemotherapy, thus it is difficult to discern between the gastrointestinal effects of these monoclonal antibodies and the effects of the backbone regime. A possible approach to tackle this issue is to summarise the growing amount of evidences from RCTs comparing these MoAbs plus backbone therapy with backbone therapy alone.

Methods: PubMed, Embase, Web of Science and CENTRAL databases were searched for articles published until 1st October 2014. Eligible studies included prospective randomized phase II and III trials comparing a chemotherapeutic regimen with the same regimen associated with an anti-EGFR monoclonal antibody. Data on haematological toxicities were extracted. Study quality was assessed using Cochrane Risk of Bias Tool. Pooled estimates of summary incidence of AEs, Relative Risks (RRs) and 95% confidence intervals (CIs) were calculated using random effects model. Heterogeneity among studies was however investigated visually and using I-squared statistics.

Results: A total number of 18,260 patients from 28 clinical studies were analysed. Patients receiving regimens containing anti-EGFR MoAbs has a significantly increased risk of severe diarrhea (RR, 1.68; 95% CI, 1.55 to 1.85) and mucositis (RR, 2.53; 95% CI, 1.58 to 4.06). Incidences are reported in Table 1. For mucositis outcome Egger’s test as well as visual inspection of funnel-plot could not exclude presence of publication bias (P < 0.01).

Conclusions: The addition of anti-EGFR MoAbs to therapeutic regimens is associated with an increased risk of severe diarrhea and mucositis. Patient awareness, prevention, early recognition and appropriate clinical management of these severe AEs may optimize clinical outcomes.

Table 1.

<table>
<thead>
<tr>
<th>Incidence (CI 95%)</th>
<th>Anti-EGFR arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13.2% (10.1 to 16.3%)</td>
<td>7.2% (5.4 to 8.9%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>8.0% (5.2 to 10.8%)</td>
<td>3.9% (2.3 to 5.5%)</td>
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PROBLEMS RELATED TO THE USE OF OLD VANCOMYCIN DOsing REGIMENS IN ROUTINE HEALTHCARE

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Introduction: Non-individualized vancomycin dosing regimens contained in drug information leaflets are still routinely used in most hospitals in Russia, while individual concentrations vary and recent studies recommend higher concentrations of 15-20 μg/mL to achieve therapeutic goals. Our aim was to evaluate vancomycin concentrations achieved in clinical routine.

Material and Methods: Forty-eight patients who received vancomycin based on clinical indications were enrolled to the study. Twenty one had normal renal function (NRF), seven – non-terminal renal function (NTRF), and thirteen patients with renal failure (RR). Trough levels (TL) of vancomycin were evaluated at steady state, concentrations were measured by HPLC.

Results: Concentrations <5 μg/mL were observed in 19 (40%) of all cases, 11 (32%) of NRF patients, 1 of NTRF and 7 (35%) of patients on RR. Concentrations of 5-10 μg/mL were observed in 15 (31%) of all cases, 8 (38%) in NRF, 1 in NTRF and 6 (30%) in RR groups. Concentrations of 10-15 μg/mL were observed in 6 (12%) cases, two cases in each group. Concentrations of 15-20 μg/mL were observed in 8 (16%) of all patients, none in NRF, 3 (45%) in NTRF and 5 (25%) in RR groups. In 19 (39%) of cases, all NTRF, recommended dosing regimens were not adequately followed. Regimen non-compliance correlated with higher vancomycin TL (r = 0.3; P < 0.05). In patients with TL <5 μg/mL five (26%) died of the treated infection, in contrast to no patients with vancomycin TL >5 μg/mL (χ², P < 0.05).

Conclusions: Vancomycin concentrations were far too low to be effective in most routinely treated patients. Higher concentrations were mainly due to dosing regimen non-compliance. Higher frequency of infectious deaths was noted in patients with low vancomycin levels, although there might be other confounding factors involved.

EFFECT OF CEREBROLYSIN ON THE STRESS RESPONSE AND CYTOARCHITECTURE OF MEDIUM SPINY NEURONS OF THE NUCLEUS ACCUMBENS IN RATS PRENATA LLY EXPOSED TO VALPROIC ACID

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Autism Spectrum Disorders (ASD) is characterized by a neurodevelopmental disorders in general, neuronal communication excess with implications for social behavior. Valproic acid (VPA) is a histone deacetylase blocker, with effects on the enzymes involved GABA synthesis and degradation, which has been widely used in the treatment of epilepsy. In recent decades it was observed that administration of VPA during the gestation increases the risk of ASD. Therefore, it has been proposed as a model for understanding the ASD. Cerebrolysin is a preparation of peptides derived from porcine brain, which has shown a neurotrophic effects on the maintenance and remodeling of neuronal cytoarchitecture.

To reproduce the model of autism we using a single dose of 500 mg/kg of VPA or Solution saline (SS) at 12.5 day of gestation in pregnant rats Sprague-Dawley (SD) strain. For experimental purposes we used male offspring which were administered with cerebrolysin at days 5–21 of postnatal age (PA). They were divided in two groups: Control and VPA; at 21PA and 70PA, we evaluated the response to stress in a novel environment, after with Golgi-Cox staining the response and cytoarchitecture of medium spiny neurons of the nucleus accumbens was analyzed.

The results suggest that in the 21PA group present changes in the neuronal cytoarchitecture that are not observed in the 70PA group, suggesting that the neurotrophic effects of cerebrolysin is not present the long term.

EOcular PHARMACOKINETICS OF CIPROFLOXACIN EYE DROPS ASSESSED WITH IN-VIVO MICродIALYSIS IN A RABBIT MODEL

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Background: Topical drug delivery is the most widely used drug administration route for the treatment of ocular diseases. Studies investigating the intraocular in vivo pharmacokinetics of topicaly administered drugs are sparse due to the technically demanding nature of the required procedures. In the present study, we set out to assess an in-vivo pharmacokinetic profile of the widely used topical
antibiotic ciprofloxacin. Therefore, in-vivo microdialysis was used to assess pharmacokinetics of the anterior chamber and the vitreous in a rabbit model after topical instillation of the drug.

**Material and Methods:** After approval by the animal welfare and Ethics Review Committee, 8 female New Zealand White rabbits (Charles River, Germany) weighing 2.3–4.1 kg were included. All experiments were performed under general anesthesia. A linear microdialysis probe (30 kDa molecular weight cut off [MWCO]) was implanted in the anterior chamber and a concentric microdialysis probe (0.5×10 mm, 20 kDa MWCO) in the vitreous of the same eye. One single drop (30 µL) of ciprofloxacin eye drops (0.09 mg in 30 µL) was administered on the ocular surface after a run-in period of 2 hours. Microdialysis samples were collected every 30 min for 6 h. Relative recovery was assessed by retro-dialysis to calculate absolute concentration values. Samples were analyzed using HPLC.

**Results:** After single administration of ciprofloxacin, the maximum free drug concentration (C_{max}) was 0.373 ± 0.218 µg/mL in the anterior chamber and was reached (T_{max}) after 116 ± 36 min. Calculated AUC_{(0-t)} in the anterior chamber was 78.8 ± 47.1 µg min/mL. In the vitreous, C_{max} was 2.2 ± 2.5 ng/mL and maximum drug concentration was reached 106 ± 60 min after drug administration. AUC_{(0-t)} for ciprofloxacin in the vitreous was 0.268 ± 0.370 µg min/mL.

**Conclusion:** Microdialysis is a suitable method to assess in-vivo pharmacokinetics in the rabbit’s eye. In the anterior chamber, the maximum concentration of ciprofloxacin was reached approximately 2 h after single drug administration. In the vitreous, drug concentration was considerably lower, although the time course of drug concentration was comparable.

**CHOICE OF MEDICATIONS FOR NAUSEA AND VOMITING AMONG RUSSIAN GYNECOLOGISTS**

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**Introduction:** During pregnancy, many women experience nausea and vomiting. Frequency of medications use is high in many countries, including Russia. At the same time excessive fears of medications-related risks may influence choice of remedies to treat pregnant patients. Official registration status may also play a role, since many medications, like doxylamine, approved for treatment of nausea and vomiting in pregnancy in many countries, is officially contraindicated for this category of patients in Russia. In an ongoing study we aim to analyze choice of medications to treat various diseases and states among gynecologists in Russia.

**Material and Methods:** In an ongoing study anonymous questionnaire- naires are distributed among practicing gynecologists. The questionnaire contains questions related to the selection and timing of medications for the treatment of common diseases and states in pregnant women. Currently presented data are based on 39 questionnaires and related to the treatment of nausea and vomiting.

**Results:** For the treatment of nausea and vomiting most doctors - 26 (67%) - preferred artichoke leaf extract, 41 (61%) indicated metoclopramide as a preferred option, 10 (26%) - essential phospholipids, 9 (36%) - ampethamine, and 3 (8%) preferred homeopathic remedies.

Most of these medications, except metoclopramide, have major indications related to liver diseases, and not to nausea and vomiting itself, but their official registration status allows their use in pregnancy.

**Conclusions:** In this pilot study we observed that gynecologists in Russia infrequently recommend evidence-based medications for nausea and vomiting in pregnancy. This may partly be explained by official registration status of medications. Both, education of doctors, and administrative interventions may be required to improve quality of prescribing in pregnant women.

**DIFFUSE HEPATIC CHANGES CAUSED BY ORAL CONTRACEPTIVES**

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**Background:** Oral contraceptives (OCs) consumption has grown and is one of the most consumed pharmacologic groups in the world. Ethinyl Estradiol (EE) is the most commonly used as a component of OCs and hormonal replacement therapy (HRT). In women its excessive and prolonged use may cause organ toxicity. The aim was to assess women that consume OCs, using ultrasound (US) examinations in the liver and kidney, to highlight diffuse alterations and density changes.

**Material and Methods:** The US abdominal examinations were performed using a GE®, LOGIQe®, with a 5 MHz probe. Were included 46 fertile women in the study group and 28 in the control group (n = 74), who agreed to participate under informed consent, aged 18-50 years. All women underwent an abdominal evaluation and the image acquisitions were made in the right liver lobe and right kidney. To evaluate the hepatic diffuse alterations, was used imaging program, ImageJ, with a region of interest, 18x18.

**Results:** The individuals has a mean age of 27.95 ±10.60 years and a mean of body mass index (BMI) of 22.56 kg/m² ± 3.73. The group using the 3rd generation pills is 56.51% (n = 26) and the 4th generation is 43.5% (n = 20) of the sample. Related to the density was observed that the third generation group have a higher density mean in relation to the other groups. It wasn’t found any relevant change concerning to the duration of use neither to the progestin generation.

**Conclusion:** With the use of Ultra Sound and image program it was possible to confirm the variations in density between the different groups. The excessive estrogen caught in different tissues (liver, uterus, ovary) can cause an abnormal growth or tissue damage. Concerning to the generation of OC, this study can conclude that the fourth generation of EE is safer than the third.

**THE PATTERN OF DRUG CONSUMPTION DURING PREGNANCY**

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**Background:** Medical prescription during pregnancy has increased significantly/greatly in the last few years and nowadays it has become a matter of major importance. It can be proved that only a small proportion of medicines are known to be secure for the fetus and for the pregnant and the inappropriate medicine consumption may cause severe and deep teratogenic changes/alterations. The aim of this study is to determine the level of knowledge about medicines and their consumption during pregnancy.

**Material and Methods:** This is an observational study using a questionnaire to collect primary data. The data collection occurred...
through this questionnaire filled in a sample of pregnant women, who participated in the study under informed consent, and was carried out among pregnant women monitored in a Maternity in the central region of Portugal.

Results: It is expected, from preliminary data and based in other similar studies from that the sample of women enquired around 80% had received at least a medical prescription during pregnancy, being most of these medicines (15%) harmful to the fetus. Women who suffer from chronic disease(s) are the major medicine consumers and this consumption is highly related to gestational symptoms relief. About 60% of the pregnant have a mild level of knowledge on of medicine use during pregnancy; there is also a statistic relationship between age, social class, education field, qualifications, wanted or unwanted pregnancy, and first pregnancy or following, the third trimester of pregnancy and medicine use level.

Conclusions: The study concluded that the consumption of harmful medicines to the fetus is still very common being frequently associated with the lack of women’s knowledge and other social demographic factors, therefore leading to fetal malformations and the use of self-medication without control.

EMERGENCY CONTRACEPTION - STUDY OF CONSUMPTION AND KNOWLEDGE OF THE RISKS IN STUDENT POPULATIONS

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Background: According to World Health Organization, every year there are 200 million pregnancies which 75 million are unintended. Emergency contraception pills (ECP) is one of the available methods who prevent an unintended pregnancy, after an unprotected sexual intercourse or contraceptive failure. In Portugal, ECP is available over-the-counter, so becomes necessary assess the knowledge and the consumption in students’ populations about this subject, and realize the reasons to use this emergency contraceptive method. The purpose of this study was to quantify the consumption, characterize the level of knowledge and understand the factors that induce the use Emergency Contraception Pills (ECP).

Material and Methods: This is an observational study using a questionnaire to collect primary data. This questionnaire will be administered to two different samples, one of a group of secondary school students with a population of 680 students and another from a high school of education in Coimbra with a population of 1814 students. Those students agree to participate under informed consent.

Results: It is expected, based on several studies and preliminary data, that the majority (>75%) of students had heard about ECP. In terms of consumption, the majority should be first-time users of ECP and in more than half of the situations the factors that lead the use ECP was failure of the contraceptive used. The results also may indicate young’s main information sources are friends, TV and Internet.

Conclusions: In Portugal, ECP is available as over-the-counter which facilitates its obtainment and without effective control. It is strongly expected to find a low level of knowledge in these populations regarding health and medicines issues. Students show to have a low level of knowledge Due to the facilitation of available over-the-counter ECP in Portugal, the knowledge among students probably is high and its use is correct.

JOINT BIO-EQUIVALENCE TESTS WITH MULTIVARIATE GAUSSIAN RANDOM EFFECTS

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Introduction: To compare pharmacokinetics between two drugs, conventional bio-equivalence test used independent model for two responses, log-transformed $C_{\text{max}}$ and AUC. In spite of strong correlation between $C_{\text{max}}$ and AUC, their models were treated as independent. We considered this correlation structure so that the two linear mixed models for log-transformed $C_{\text{max}}$ and log-transformed AUC are jointly fitted for estimating the 90% confidence intervals of treatment effects.

Material and Methods: The three kinds of models, independent, correlated joint, and shared random effects model, were separately performed for the data of one-sequence, two-period pharmacokinetic interaction study of Fimasartan with Amlodipine (Yi et al. 2011).\textsuperscript{1}

For log-transformed $C_{\text{max},i,j}$ and log-transformed AUC$_{\text{t},i,j}$ of the $i$-th subject in the $j$-th period, the model was:

\begin{equation}
\begin{aligned}
y_{ij} &= \mu + \beta_1 t_i + \beta_2 R_i + \epsilon_{ij}, \\
y_{ij} &= \log y_{ij} = \log \mu + \beta_1 t_i + \beta_2 R_i + \epsilon_{ij},
\end{aligned}
\end{equation}

where $\epsilon_{ij}$ for independent model and $\epsilon_{ij} \sim N(0, \sigma^2)$ for correlated joint model. When we assumed $y_{ij} = \beta_1 t_i$, then the model referred to the shared random effect model. We assessed the goodness of fit among the three models by conditional AIC which described the best model showed the smallest conditional AIC.

Results: We selected the shared random effects model as the final model, which had the smallest conditional AIC, 86.09 (independent, 107.47; correlated joint, 92.50). The GMRs of Fimasartan (with/without Amlodipine) and 90% CI for $C_{\text{max},i,j}$ and AUC$_{\text{t},i,j}$ were 1.096 (0.746–1.610) and 1.163 (1.001–1.351), respectively. On the other hands, those for the shared random effects model $\beta_2 = 0.603$ were 1.096 (0.793–1.515) and 1.163 (1.013–1.336), respectively.

Conclusions: In general, there exists positive correlation between $C_{\text{max}}$ and AUC so that we should consider this correlation structure when we analyse pharmacokinetic parameters including bioequivalence tests. After using shared random effects model, the 90% confidence intervals of geometric mean ratios for $C_{\text{max}}$ and AUC were both slightly decreased in comparison with using independent model.


EFFECT OF MAVOGLURANT (AFQ056) ON THE PHARMACOKINETICS OF A COMBINED ORAL CONTRACEPTIVE CONTAINING ETHINYL ESTRADIOL AND LEVONORGESTREL IN HEALTHY WOMEN

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Background: Mavoglurant (AFQ056) is a structurally novel, selective metabotropic glutamate receptor 5 (mGluR5) antagonist currently under clinical development. It is expected to normalize...
excessive glutamatergic signaling via mGluR5 that is believed to
be associated with a variety of neurological and psychiatric dis-
gases. Given its early stage of clinical development, treatment with
mavoglurant currently requires the use of contraceptive measures in
women of childbearing potential. Contraception may additionally
be required as a consequence of other medicines used concomitantly
in the envisioned target patient populations, e.g. antidepressants,
neuroleptics and anti-epileptics, some of which exhibit teratogenic
potential. This study was conducted to compare the pharmacokinet-
ics (PKs) of a combination oral contraceptive (OC) when given alone
or concomitantly with mavoglurant.

Methods: This phase I, open-label, fixed-sequence, two-period study
included 30 healthy female subjects aged 18–40 years. In Period 1, a
single oral dose of an OC containing 30 μg ethinyl estradiol (EE)/150 μg
levonorgestrel (LNG) was administered alone. In Period 2, the OC
was administered with a clinically relevant multiple dose of mavo-
glurant (100 mg b.i.d.) under steady-state conditions. Plasma con-
centrations of EE and LNG were measured up to 72 hours post
administration. The maximum plasma concentration (Cmax) and
the area under the concentration-time curve up to last measurable
concentration (AUClast) were estimated using non-compartmental
methods.

Results: The geometric mean ratios of EE Cmax and AUClast obtained
with and without mavoglurant were 0.97 (90% confidence interval
[CI]: 0.90–1.06) and 0.94 (90% CI: 0.86–1.03), respectively. The cor-
responding Cmax and AUClast for LNG were 0.81 (90% CI: 0.75–0.87)
and 0.68 (90% CI: 0.63–0.73), respectively.

Conclusions: EE PK was unchanged, whereas Cmax and AUClast of
LNG were reduced by 19% and 32%, respectively, when given with
mavoglurant. Further evaluation regarding the impact on contracep-
tive efficacy is warranted.

PARAMETER ESTIMATION PERFORMANCE FOR
SIGMOID E∞M MODELS IN EXPOSURE-RESPONSE
RELATIONSHIP

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Introduction: Drug exposures are not often high enough to estimate
maximum effect (E∞m) to avoid drug toxicity, bring about difficulties
in estimating unbiased and precise PD parameter estimates or inevi-
tably simplified models such as linear model and log-linear model.
The purpose of this simulation study is to investigate the accuracy
and precision of PD parameter estimates in PK/PD analysis under
different doses and Hill coefficients in case of dense PK sampling
design in human pharmacology study.

Materials and Methods: Seven escalating doses of virtual drugs with
equal potency and efficacy but with five different Hill coefficients
were used in simulations of single and multiple dose scenarios with
dense sampling design. A total of 70 scenarios with 100 subjects
were simulated and estimated 100 times applying one compartment
PK model with first-order absorption and sigmoid E∞m model using
SSR (Stochastic simulation and estimation) of PSN (Perl-speaks-
NONMEM) and first order conditional estimation with interaction
(FOCE-I) method in NONMEM (version 7.2). The bias and precision
of the parameter estimates in each scenario were assessed using rela-
tive bias and relative root mean square error.

Results: For the single dose scenarios, most PD parameters of sig-
moid E∞m model were accurately and precisely estimated when the
Cmax was attained more than 85% of EC50 except for typical value
and inter-individual variability of EC50 which were poorly estimated
at low Hill coefficients. For the multiple dose studies, the parameter
estimation performance was not good.

Conclusions: This simulation study quantitatively demonstrated
the effect of the relative range of sampled concentrations to EC50
and sigmoidity on the PD parameter estimation performance using
dense sampling design. This study can be useful in designing a clinical
study to evaluate PK/PD relationship for new drug development or
drug repositioning.

Key words: sigmoid E∞m Models, NONMEM, parameter estimation
performance, stochastic simulation and estimation, human pharma-
cology, PK/PD relationship.

EFFECT OF UGT1A1 AND UGT1A3
POLYMORPHISMS ON PHARMACOKINETICS OF
TELMSARTAN IN KOREAN

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Introduction: Telmsartan, an angiotensin II receptor blocker, is
closely used for the treatment of hypertension and cardiovascular risk
reduction. It is mainly metabolized by UDP-glucurononyltransferases
(UGTs) and UGT1A3 is predominantly involved in the glucuronida-
tion of telmsartan. Clinical studies showed the large inter-individual
variation in the exposure of telmsartan when orally administered.
The purpose of present study was to examine whether telmsartan
exposure could be affected by genetic polymorphisms of UGTs and
drug transporters.

Material and Methods: The blood samples were collected from 91
healthy volunteers who participated in two independent trials of
clinical trials and genotyping were conducted in UGTs (UGT1A1
and UGT1A3) and drug transporters (SLCO1B3 and SLCO2B1).

Results: After oral administration of 80 mg telmsartan, unexpect-
edly the AUCinf in UGT1A1*28 and *60 carriers was significantly
lower compared to volunteers with UGT1A1 wild type. (P = 0.0004,
P = 0.0002, respectively). Subpopulation analysis revealed that
UGT1A1*28 non-carriers among volunteers with UGT1A1*60 also
showed significantly lower exposure (P = 0.0038). Heterozygotes of
UGT1A1*2 and UGT1A3*3 also showed significantly lower
AUCinf (P < 0.0001, P = 0.0195, respectively). Furthermore, strong
linkage disequilibrium were demonstrated; a decisive SNP (V47A)
of UGT1A1*2 and UGT1A3*3 (D2 = 0.945, r2 = 0.705), and
UGT1A1*60 and 3 coding regions which compose UGT1A3*2 or *3
(D1 = 1, r2 = 0.371). The effects of UGT1A1*28 and UGT1A1*60
alleles on the pharmacokinetics of telmsartan were attributed to their
strong linkage with UGT1A3*2 which enhances UGT1A3 expression
and UGT1A3*3.

Conclusions: Present study collectively indicates that UGT1A1*60
is one of determinant genetic factors resulting in inter-individual vari-
ations in pharmacokinetics of telmsartan.
Clinical Therapeutics

Background: DW1029M is a botanical extract consisting of Puerariae radix and Mori Cortex, developed by Dongwha Pharmaceutical, for treatment of diabetic nephropathy. The objective of this study was to explore the pharmacokinetics and safety of DW1029M following single oral administration in healthy Korean subject.

Material and Methods: Healthy male subjects were enrolled in randomized, open-label, single dose, crossover phase I clinical study. During each period, subjects received 300 mg, 600 mg or 1200 mg of domized, open-label, single dose, crossover phase I clinical study.

Six healthy male subjects completed the study. The C\textsubscript{max} and AUC\textsubscript{last} for Puerarin was 3.17 ng/mL and 12.40 h*ng/mL in the 300 mg of DW1029M, respectively. The C\textsubscript{max} and AUC\textsubscript{last} for Puerarin was 4.45 ng/mL and 19.81 h*ng/mL in the 600 mg of DW1029M, respectively. The C\textsubscript{max} and AUC\textsubscript{last} for Puerarin was 5.76 ng/mL and 30.47 h*ng/mL in the 1200 mg of DW1029M, respectively. There was no serious adverse event.

Conclusions: The DW1029M was safe and well tolerated over single dose range of 300–1200 mg. In this study, the pharmacokinetics profile of puerarin was assessed. This pharmacokinetic study of botanical drug may helpful in the development of DW1029M.

- HLA-B*5101 ALLELE AND LAMOTRIGINE-INDUCED STEVENS-JOHNSON SYNDROME IN KOREAN

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Background: Antiepileptic drugs have been known to induce potentially life-threatening cutaneous adverse drug reactions such as Stevens-Johnson syndrome (SJS). Despite of studies for examining the mechanism associated with HLA, the association between lamotrigine (LTG)-induced cutaneous adverse drug reactions and HLA alleles is still unclear. We investigated HLA-B alleles in LTG-induced SJS.

Material and Methods: Five LTG-induced SJS patient were requested for evaluating the causality. All patients were treated with LTG due to epilepsy. All recovered from SJS after stopping LTG treatment and intensive care. HLA-B genotyping was performed in all 5 patients using PCR-SBT (sequence-based typing) method.

Results: Demographic findings (gender, age) and HLA-B genotypes of the 5 patients listed in Table 1. Expression of HLA-B*5101 allele was detected in three (60%) LTG-induced SJS patients. One patient has homozygous HLA-B*5801.

Conclusions: The result suggests that Korean individuals with the HLA-B*5101 allele may be susceptible to LTG-induced SJS. Further investigations are necessary to confirm these findings.

Table 1. Demographics and HLA-B alleles in 5 LTG-induced SJS patients.

Patient No. gender age HLA-B alleles
1 M 57 *5101, *5504
2 F 26 *5801, *5801
3 M 16 *2705, *4001
4 M 53 *4801, *5101
5 F 39 *0702, *5101

DEHYDROEVODIamine, ISOLATED FROM THE EVODIA RUTACEarPA, PRESENT IN THE TRADITIONAL CHINESE MEDICINE WU CHU YI, HAS PRO-ARRHYTHMIC EFFECTS IN-VITRO AND IN-VIVO, WHICH DISAPPEAR AT HIGHER CONCENTRATIONS

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Background: Dehydroevodiamine (DHE), a constituent of a popular and freely available traditional Chinese herb, was investigated to determine whether DHE prolongs cardiac repolarization and induces pro-arrhythmia.

Methods: For in-vitro Action Potential (AP) measurements, ventricular cardiomyocytes were isolated from dogs with chronic atrioventricular block (cAVB). The effect of DHE on ECG parameters was evaluated in 8 anesthetized rabbits, while 8 anesthetized cAVB dogs were used to evaluate the pro-arrhythmic potential. In all models, dofetilde was used as a positive control.

Results: IC50 of DHE to block the delayed rectifier current (I\textsubscript{kr}) was 250 ± 26 nM. In cAVB cells, DHE (0.01, 0.1, and 10 μM) prolonged AP Duration (APD) with a less severe prolongation at the highest dose: bell shape curve. Early afterdepolarizations (EAD) were seen in 14%, 67%, 100%, and 67% of cells after DHE. Dofetilde (1 μM) increased APD and induced EADs (15/25). In rabbits, DHE dose dependently affected heart rate, conduction and repolarization: QT interval increased by 12 ± 10% and 60 ± 26% after 0.05 and 0.5 mg/
Measuring Drug Use: Differences Between Medical Records And Healthcare Utilisation Databases

INQUIRIES ABOUT BIOTECHNOLOGICAL AGENTS OVER A 15 YEAR PERIOD: A DESCRIPTIVE STUDY

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Background: Over the past years biotechnological agents have been increasingly used in clinical practice. We aimed to determine whether inquiries about them to a Clinical Pharmacology Consultation Service have also become more frequent.

Material and Methods: We reviewed consultations received at our institutions between 2000 and 2014. Information about the agents, underlying condition, type of inquiry and affiliation of the inquirer were retrieved. Data from inquiries about selected biotechnological agents (monoclonal antibodies, fusion proteins or cytokine antagonists) were compared to data from the remainder.

Results: A total of 14,468 inquiries (365 about 30 different biotechnological agents) were received during the study period. Rituximab (n = 72), infliximab (n = 62), adalimumab and etanercept (n = 53 for each) were most frequently inquired about. Up to 2003 only 4% of inquiries about a biotechnological agent were received, while 48.8% were received after 2010. Conversely, yearly inquiries about other agents remained fairly constant.

Conclusions: Inquiries about biotechnological agents progressively increased, while those about other agents remained fairly constant. Most of the inquiries about biotechnological agents were about monoclonal antibodies, and were made by hospital physicians to request information regarding adverse effects (especially in pregnancy) and the appropriateness of use in specific patients.

INORGANIC MERCURY POISONING DUE TO THE USE OF BEAUTY CREAM IN HONG KONG

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Introduction: Use of inorganic mercury compounds in cosmetic products is prohibited as it can cause significant nephrotoxicity. However, the public continues to have access to these illegal products in Hong Kong.

Material and Methods: This is a retrospective study aiming to evaluate the clinical characteristics and the treatment outcome of inorganic mercury poisoning due to the use of beauty cream. Cases were identified using the electronic system of the Hong Kong Poison Information Centre from 2008-2015. Only those with proven inorganic mercury poisoning and prior use of beauty cream were included.

Results: Seventeen patients were included in the analysis; 88.2% were female and more than half of those were Indonesians. Most of the patients were treated with dimercaptosuccinic acid chelation, prednisolone or combination therapy. Baseline 24-hour urine mercury levels correlate with the severity of proteinuria (Pearson’s correlation 0.587, P = 0.035). Compared to chelation therapy alone, combination therapy with prednisolone demonstrated statistical significant reduction in urine protein levels (99.41 ± 0.11 vs. 98.73 ± 0.19; P = 0.015).

Conclusions: Inorganic mercury poisoning due to the use of beauty cream causes minimal change disease, resulting in nephrotic syndrome. Baseline 24-hour urine mercury level correlates with the severity of proteinuria. Statistical significant reduction in proteinuria was found in patients receiving combination therapy with dimercaptoposuccinic acid and prednisolone.

Table 1. Baseline characteristics of the patients according to different treatment regimens

<table>
<thead>
<tr>
<th></th>
<th>No DMSA and Prednisolone</th>
<th>DMSA only</th>
<th>Prednisolone only</th>
<th>Prednisolone + DMSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47 (33-64)</td>
<td>32 (23-38)</td>
<td>39 (18)</td>
<td>29 (22-57)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>3 (66.7%)</td>
<td>5 (100%)</td>
<td>1 (50%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>Cumulative dose of DMSA (mg)</td>
<td>N/A</td>
<td>1500±1.5</td>
<td>N/A</td>
<td>2397±1.4</td>
</tr>
<tr>
<td>Cumulative dose of Prednisolone (mg)</td>
<td>N/A</td>
<td>2874±3.0</td>
<td>1627±3.4</td>
<td></td>
</tr>
<tr>
<td>Spot blood mercury level (nmol/L)</td>
<td>80.2±9.4</td>
<td>103.8±3.9</td>
<td>80.6±1.7</td>
<td>49.6±1.4</td>
</tr>
<tr>
<td>24 hour urine mercury level (nmol/day)</td>
<td>24.3±1.9</td>
<td>514.9±3.1</td>
<td>127.2±12.0</td>
<td>204.2±2.9</td>
</tr>
<tr>
<td>24 hour urine protein level (g/day)</td>
<td>3.69±1.61</td>
<td>7.70±1.65</td>
<td>7.86±1.45</td>
<td>10.53±1.29</td>
</tr>
</tbody>
</table>

ASSESSMENT OF CHANGES IN LEVETIRACETAM SERUM CONCENTRATIONS BY CONCOMITANT ANTIEPILEPTIC DRUG USE

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Introduction: Levetiracetam (LEV) is a newer antiepileptic drug. Though its metabolism does not depend on cytochrome P450 isoenzymes, some studies suggested the influence of enzyme-inducing antiepileptic drugs (AED) on LEV plasma levels. In this study,
Influence of concomitant AED use, particularly that of enzyme-inducing/inhibiting AED, on serum concentrations of LEV was examined.

### Material and Methods
LEV serum concentration measurements between January-December 2014 were retrieved retrospectively from Eskisehir Osmangazi University Hospital TDM database, including patients from neurology department. One hundred ninety-two blood samples of 160 patients were analyzed. All LEV concentrations were measured using Cloned Enzyme Donor Immunoassay (CEDIA).

Remaining data were obtained from patients’ medical records. Only the highest LEV serum concentration per patient was included. The reference range in serum for LEV was considered as 5–40 µg/mL. Antiepileptic levels were presented as median (µg/mL) (Q25–75%). In the comparisons, Chi-square and Kruskal-Wallis tests were used and P<0.05 was considered as significant.

### Results
Patients were aged 18–87 years (40.6 ± 15.2). Of them, 54.4% were male. Most of them (61.3%) had epilepsy. Forty-nine (30.6%) were on LEV monotherapy and valproic acid (22.5%) and carbamazepine (16.2%) were the most common AED co-medication.

Median LEV concentration was 14.3 (7.8–27.6) vs. 20.0 (11.6–32.5) in monotherapy and polytherapy groups, respectively (P < 0.05).

LEV concentration was within reference range in 79.6% and 77.5% of the patients in monotherapy and polytherapy groups, respectively (P > 0.05). Influence of concomitant AED use on LEV concentrations was evaluated in patients using only one additional AED (n = 68).

Median LEV concentration was 18.0 (11.7–32.3), 18.3 (8.2–31.1), 21.4 (14.6–26.3) in patients using enzyme inducer (carbamazepine, phenytoin), enzyme inhibitor (valproic acid) and neutral AEDs, respectively (P > 0.05). Of the patients, 51.1% in monotherapy and 28.7% in polytherapy groups were seizure-free.

### Conclusions
Concomitant AED use, whether enzyme inducer or inhibitor, resulted in no significant change in LEV serum concentration.

### THE USE OF ANTIHYPERTENSIVE MEDICATION IN HOSPITALISED ELDERLY PATIENTS
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**Background:** Despite the importance of hypertension as a risk factor for adverse outcomes, elderly patients have the lowest rate of adequate blood pressure control. The antihypertensive therapy in elderly patients requires special attention because of questions which remain still unresolved from the evidence based medicine point of view as well as regarding the safety aspects. The aim of the presented work was to evaluate the antihypertensive treatment in a sample of hospitalised patients aged ≥65 years.

**Methods:** Patients aged ≥65 years with arterial hypertension treated with at least one antihypertensive drug at hospital admission were included in our study (n = 1233). We analysed following patients’ characteristics as possible factors influencing the prescription of antihypertensive agents: socio-demographic signs (age, gender), living alone, immobilisation and comorbid conditions.

**Results:** In the evaluated group women were prevailing over men (64.7% vs. 35.3%). The mean age of patients was 78.3 ± 6.7 years. In the group of patients aged ≥80 years a significantly lower prevalence of following antihypertensives was found: antagonists of AT1 receptors, dihydropyridine calcium channel blockers, betablockers and agonists of I1 receptors. On the other hand, in this age group the highest prevalence of furosemide prescription was revealed. Patients living alone were at higher chance (OR = 2.38) and those aged 80 years or more at lower chance (OR = 0.57) for administration of urapidil at discharge. A significant increase in the use of antihypertensive drug combinations was observed comparing their prevalence at the time of hospital admission and discharge, respectively (76.2% vs. 83.3%; P < 0.001).

**Conclusions:** The results of the presented work showed the compliance of antihypertensive therapy with guidelines for treatment of arterial hypertension. The study indicates certain areas in which the use of antihypertensive medications could be improved in elderly patients.

This study was supported by grants VEGA 1/0886/14 and VEGA 1/0939/14.

### CONCENTRATIONS AND ACTIVITY OF AMPHOTERICIN B IN BILE ACHIEVED BY LIPID-FORMULATIONS
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**Background:** Amphotericin B (AMB) has a broad antifungal spectrum, but also a considerable toxicity. Its lipid-formulations are safer. As fungal cholangitis is a life-threatening disease, we assessed biliary AMB penetration in patients treated with lipid-formulated AMB and biliary AMB activity by in-vitro and ex-vivo-simulations.

**Methods:** Biliary and plasma AMB levels were measured by high-pressure-liquid-chromatography in two patients on liposomal AMB and in two on AMB colloidal dispersion. AMB kinetics in bile and plasma was determined in three of these patients. In-vitro simulation was performed with isolates of Candida (C.) albicans, C. tropicalis, C. glabrata and C. krusei incubated in porcine or bile or in RPMI medium at relevant AMB concentrations for up to 48 hours. For ex-vivo simulation, patient bile samples were inoculated with the same Candida strains.

**Results:** Biliary AMB concentrations were lower and displayed a slower rise and decline than plasma levels. Growth of C. albicans and C. tropicalis in porcine bile was similar to that in RPMI medium. Proliferation of C. glabrata was diminished, and C. krusei displayed no proliferation in bile. AMB activity was lower in porcine bile than in medium. In most of the patient bile samples, fungal growth was delayed or lacking, even in the absence of AMB. AMB concentrations of up to 1.28 µg/L had no fungicidal effect in patient bile.

**Conclusion:** Biliary AMB concentrations were similar to or below the MIC values of relevant fungi. Fungal growth and AMB activity were impaired by bile. Treatment of fungal cholangitis with AMB lipid formulations is not supported by these pharmacokinetic and pharmacodynamic data.

### TERBINAFINE INDUCED ERYTHEMA MULTIFORME MULTIFORME WITH HEPATITIS
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**Introduction:** Terbinafine is an antifungal agent that is effective for the oral treatment of dermatophytes. Herein, we report a rare case of terbinafine induced erythema multiforme (EM) associated with hepatitis.

**Case Report:** A 59-year-old woman was admitted with a generalized targetoid, pruritic eruption. Terbinafine for onychomycosis was started three weeks earlier. Clinical signs and skin biopsy were consistent with EM. Laboratory investigations showed liver dysfunction.
with elevated liver enzyme activities. Diagnostic tests for viral and autoimmune liver hepatitis were negative. Other well established causes of EM were ruled out. Terbinafine induced EM with hepatitis was suspected, the antifungal was stopped and oral corticosteroid treatment was started. Patient's condition improved dramatically and liver tests returned to normal.

Discussion: EM is an acute mucocutaneous hypersensitivity reaction with variety of etiologies. It is characterized by a skin eruption, with or without mucous membrane lesions. It can be induced by drug intake or several infections. Terbinafine is generally well tolerated and the most common cutaneous adverse effects are rash, pruritus and urticaria. In the literature a few cases of EM have been reported following exposure to this drug. It had also reported that patients who have developed EM during terbinafine treatment suffered from a systemic autoimmune disease and no hepatic disorder was associated to the skin manifestation. Our case was diagnosed to be a suspected case of drug-induced EM with hepatitis on the basis of drug history, clinical presentation, improvement with dechallenge and exclusion of other likely causes of EM and hepatitis. According to the Naranjo probability scale, the adverse drug reaction was considered probable.

Conclusion: Clinicians should be aware of the risk of EM associated with terbinafine, a generally well tolerated drug. The skin involvement may be also associated with liver disorder.

OFF-LABEL USE OF MIDAZOLAM IN RANDOMIZED CONTROLLED TRIALS

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Introduction: Off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or form of administration (1). The goal of this study is to investigate the data regarding the off-label use of midazolam; a versatile benzodiazepine, in randomized controlled trials (RCTs).

Material and Methods: RCTs of were identified retrospectively through a search of PubMed from March 2012 to the past (1981) using the search term ‘midazolam’. Identified articles were screened for purpose or indication of the midazolam use, on/off label use, age of patients, route and location of administration. On-label criteria were based on information provided by the manufacturer of midazolam.

Results: A total of 1081 RCTs of midazolam were detected; 314 were off-label and 276 were conducted in children. Until 1989 the number of RCTs per year was under 20 and from 1990 to 2011 the average of RCTs was 43.4 (31-54) per year. Most common on-label indication was to provide sedation and induction of anesthesia. Common fields of research were induction of anesthesia and/or anesthetic effect/technique, evaluation of pharmacokinetics and pharmacodynamics. The routes used for off-label administration were intranasal, intrathecal, sublingual and rectal route. The common subjects for off-label research were the anticonvulsant, antiemetic, anti-shivering effects of midazolam and the use as an adjunct to local anesthetics.

Conclusions: Off-label use of midazolam occurs frequently in the RCTs. Although it is legal to prescribe drugs off-label, there may be health risks and differences in legal liability. There is need to generate evidence-based and safe scientific basis regarding every aspects of clinical conditions during the processes of approving and labeling.

Reference


EFFECTS OF UNCONTROLLED DIABETES ON LDL LEVELS OF PATIENTS UNDERGOING CAROTID ENDARTERECTOMY ON AND OFF STATIN THERAPY: PRELIMINARY STUDY

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Introduction: This preliminary study aims to assess the effects of uncontrolled diabetes mellitus (DM) on LDL levels of atherosclerotic patients on long term statins and patients not on statins.

Material and Methods: With institutional approval LDL levels of 40 patients undergoing carotid endarterectomy due to atherosclerosis were retrospectively analyzed. All statin users were on statins for >1yr. Patients with HbA1C levels of >6.4% were considered as uncontrolled DM (D+). All other patients were non diabetics (D-).

Group 1: D+ statin user (n = 9), group 2: D- statin user (n = 10), group 3 D+ non statin user (n = 8), and group 4: D- non statin user (n = 13). LDL levels are given as mg/dl, Kruskal-Wallis and Mann-Whitney tests were used for statistics. P < 0.05 = significant.

Results: Demographic data were similar. LDL levels for groups 1, 2, 3 and 4 were 125.0 ± 8.7, 95.0 ± 7.0, 133.5 ± 10.0, and 114.0 ± 10.2 respectively. LDL levels of uncontrolled diabetic patients not on statins were significantly higher than all other groups (P < 0.05). LDL levels of uncontrolled diabetic patients on statins were also higher than non-diabetic patients (P < 0.05). LDL levels were similar in all non-diabetic patients (P > 0.05).

Conclusions: Results of this preliminary study suggest that atherosclerotic patients with uncontrolled diabetes who are either on or off statin therapy have higher LDL results compared to non-diabetic atherosclerotic patients. A study recruiting higher number of patients is needed to clearly assess the effects of uncontrolled diabetes on LDL levels.
Biosimilars: Regulatory Overview

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Introduction: The first generation of biopharmaceutical products manufactured using recombinant technologies was launched in the 1980s, and the most of them are now on the way to patent expiration or have already expired. As a result, pharmaceutical companies are developing “generic” version for biopharmaceutical product, referred to as biosimilars.

Active substance of biopharmaceutical product represent a collection of recombinant proteins and not a single molecular entity, thus active substances in two biopharmaceutical product are unlikely to be identical. Biosimilars are only similar and not identical to the innovator products and these small differences can have significant impact on the safety and efficacy of the medicine. The EU Directive 2001/83/EC, as amended, stated that a biological medicinal product which is similar to a reference medicinal product does not meet the conditions in the definition of generic medicinal products, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The challenge is to determine the exact nature of the non-clinical and clinical program required to gain regulatory approval. The European Medicines Agency has taken the lead in issuing guidelines, most of which are still under review. The guidelines advocate pre-clinical and clinical testing of biosimilars prior to market authorization, complemented by tailored pharmacovigilance plans. Generally, the approval process varies according to the products, because significant differences exist between them, and allow products to be assessed on a case by case basis. These guidelines provide a valuable base from which to develop in this evolving regulatory environment.

Conclusion: There are still many unsolved scientific issues regarding criteria, design, and analysis for the assessment of biosimilarity and/or interchangeability of biosimilars. Detailed regulatory guidance for global harmonization is needed whenever possible.

The Efficiency of Calcium Channels Antagonists in Angina Pectoris Associated with Metabolic Syndrome

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Background: Evaluation of antiischemic efficiency of calcium channels antagonists (lercanidipine and amlodipine), as also the meta-

bolic effect of these drugs in patients with stable angina pectoris and metabolic syndrome.

Material and Methods: The 6-week randomized open-label trial included 66 patients (mean age 58.18 ± 1.0 years) with functional classes I-II stable angina associated with metabolic syndrome. After 1 week wash-out period, a 2-week placebo run-in period, patients entered a 6-week treatment period with 10 mg of lercanidipine or 5 mg of amlodipine once daily. During the placebo run-in period and at the end of the study, the patients underwent clinical examination, electrocardiography, exercise testing; episodes of angina per week and sub-lingual nitroglycerin tablet consumption, lipid spectrum indicators and insulins resistance.

Results: Total exercise duration was increased with 72.62 ± 23.24 sec. (P < 0.01) in amlodipine group and with 69.42 ± 13.89 sec. (P < 0.001) in lercanidipine group. Time to onset of anginous pain was increased with 39.5 ± 8.12 sec. (P < 0.001) in amlodipine group and with 78.57 ± 15.04 sec. (P < 0.001) in lercanidipine group.

Time to onset of ST-segment depression ≥ 1 mm was increased with 69.42 ± 13.89 sec. (P < 0.001) in amlodipine group and with 62.14 ± 12.77 sec. (P < 0.001) in lercanidipine group. Additionally, diary data showed reduction in episodes of angina (in amlodipine group from 6.07 ± 0.82 to 3.53 ± 0.65 (P < 0.001) and in lercanidipine group from 7.9 ± 0.83 to 4.54 ± 0.87 (P < 0.001)) and nitroglycerin tablet consumption (in amlodipine group from 3.76 ± 0.66 to 2.07 ± 0.44 (P < 0.01) and in lercanidipine group from 5.9 ± 0.74 to 3.09 ± 0.63 (P < 0.01)). No significant differences could be found between the pre and post treatment levels of lipid metabolism indicators and on insulin resistance.

Conclusion: Lercanidipine and amlodipine are effective in reducing signs and symptoms of ischemia in patients with stable angina and metabolic syndrome; at the same time these drugs don’t have a significant influence on lipid metabolism indicators and on insulin resistance.

Chemopreventive Effect of Copaifera Reticulata Oilresin on 1,2Dimethylhydrazine-Induced Prenoeplastic Lesions in Rat Colon

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Background: Colorectal cancer is a major cause of death; its incidence is increasing worldwide. Experimental studies have suggested that plant food components can suppress cancer development through a variety of different mechanisms. Chemoprevention is defined by the use of natural, synthetic, biological or chemical agents that can reverse, suppress or prevent carcinogenesis. Plants produce a conspicuous structural diversity of metabolites and represent the largest source of active compounds; they are perhaps the earliest source of drugs for human use. Copaifera reticulata, known as “pau-ca-a”, “pau-de-óleo”, belongs to the Leguminosae family and occurs in fields and grasslands in the northern and northeastern parts of Brazil. This studies describes the effects of C. reticulata oilresin on the 1,2 dimethylhydrazine (DMH) - aberrant crypt foci (ACF) in the colon of male Wistar rats. Prenoeplastic lesions of the colonic mucosa, the ACF, are one of the early morphological changes on the DMH-stimulated colonic mucosal surface in rodent.

Material and Methods: The oilresin of C. reticulata was administered to rats by gavage at daily doses of 20, 40 and 80 mg/kg body weight. To evaluate the ACF assay, animals were acclimatized for one week (week 1) and then treated with the C. reticulata oilresin five times a week for four weeks (weeks 2 to 5). The rats received sc (subcutaneous) injections of DMH (40 mg/kg) on days 2 and 5 of weeks 2 and 3, to induce ACF. Animals were euthanized at week 5; i.e., four weeks after the first DMH treatment.

Results: The groups treated with 40 and 80 mg/kg C. reticulata oilresin during and after DMH treatment presented significantly lower numbers of ACF and aberrant crypts compared with the DMH group.

Conclusion: The C. reticulata oilresin significantly reduced ACF induced by DMH, suggesting that the oilresin has a protective effect against colon carcinogenesis.

Dopaminergic Challenge with Bromocriptine in Patients with Severe Traumatic Brain Injury

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**Clinical Therapeutics**

**Introduction:** Bromocriptine Mesylate (BC) is an ergot derivative with potent dopamine receptor agonist activity. It is licensed to reduce plasma levels of prolactin. BC has central nervous effects, and is used in patients with Parkinson’s disease. There are few randomized controlled trials with BC conducted in moderate traumatic brain injury (TBI) with conflicting results (1). We aim to present our single center experience on dopaminergic challenge using off-label BC in patients with severe TBI.

**Material and Methods:** TBI patients with Glasgow Coma Score (GCS) of <5 (GCS: worst score = 3, best score = 15) at admission to the ICU received 2.5mg of BC g.i.d after hemodynamic stability was ensured and no further neurologic improvement was observed during the course of management. BC was started and discontinued on the discretion of the ICU team. Long term cognitive tests are currently under assessment.

**Results:** A total of 8 patients were treated with BC. The average age was 42.7yrs (78-18) (5M/3F).

**Table 1:** GCS of patients on admission, beginning of treatment, end of treatment and discharge.

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<tr>
<th>GCS admission</th>
<th>GCS start</th>
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**Conclusions:** Our results show some neurologic improvement as assessed by GCS. More research is warranted before BC can be recommended in TBI.

**Reference**


**EVALUATION OF CARDIOVASCULAR SAFETY OF DARINAPARSIN (ORGANIC ARSENIC COMPOUND) IN JAPANESE AND KOREAN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA**

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**Background or Introduction:** Darinaparsin is an organic arsenical composed of dimethylated arsenic linked to glutathione, and has similar structure to one of the intermediates of the arsenic detoxification pathway. Its place in the natural metabolic pathway of inorganic arsenic is expected to result in lower cardiotoxicity than inorganic arsenic. Two phase I studies of darinaparsin have been conducted in patients with peripheral T-cell lymphoma (PTCL) in Japan and Korea, respectively. Since use of an inorganic arsenic compound is limited by cardio toxicity, the potential of darinaparsin to prolong QTcF and any possible relationship between darinaparsin plasma concentration and change in QTcF was assessed in these studies.

**Material and Methods:** Patients received a 1-hour IV infusion at 200 or 300 mg/m² on 3-consecutive days of 21-day or 28-day cycle. Patients received triplicated ECG assessment and PK plasma sample were taken on Day 1 and 5 at 0, 1, 2, 4 hours after initiation of dosing of darinaparsin in Cycle 1, on Day 2 before dosing, and on Day 6 at matched time with dosing time on Day 1-5. Time-matched baseline ECG was determined at –20, –22, –23, –24 hours before the planned initiation time of dosing. All ECGs were read by a central ECG laboratory and overread by a cardiologist for verification of interval measurements.

**Result:** ECG data were available for 26 patients; 17 Japanese patients and 6 Korean patients. No subjects showed QTcF > 500 msec and delta QTcF > 60 msec throughout the study period. Concentration-dependent nor treatment-duration-independent effect on the QTcF were not identified. There was no significant relationship between the plasma concentration of darinaparsin and a change in QTcF.

**Conclusion:** The study results suggested that darinaparsin, an organic arsenic compound, has no significant effect on cardiovascular safety in Japanese and Korean PTCL patients.

**THE DIFFERENCE OF VKOR ACTIVITY AND ITS INHIBITION BY WARFARIN BETWEEN VITAMIN K1 EP OXIDE AND VITAMIN K2 EPOXIDE**

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**Introduction:** Vitamin K (VK) plays an important role in activation of blood clotting factors. VK is oxidized by δ-glutamyl carboxylase to synthesize clotting factors, and is then reduced by VK oxide reductase (VKOR) to be recycled for reuse. The redox center of VKOR against VK1 epoxide (VK1E) was reported as 132Cys-X-X-135Cys by some in vitro studies. However, the redox center of VKOR against VK2E and its reaction type have not been identified. In this study, to clarify the difference of reuse intravital between VK1 and VK2, we assessed the difference of metabolism pattern of VKsE by VKOR.

**Material and Methods:** Metabolic activity of VKOR against VKsE and inhibitory activity of warfarin (WF) to VKOR were measured using pooled human hepatic microsome. The concentrations of produced VK1 and VK2 were determined as an index of VKOR activity by UPLC/UV method. Metabolic activity was estimated using Michaelis-Menten equation, and inhibition type and constant (Ki value) were determined by Lineweaver-Burk plot and Dixon-plot.

**Results:** The clearance of VK2E was around 7-fold higher than that of VK1E (0.054 and 0.0072 pmol/min/mg protein, VK2E vs VK1E). S- and R- WF inhibited the reduction activity of VKOR against VK2E around 6-fold stronger than that against VK1E. Additively, VK1E competitively inhibited reduction reaction of low concentration of VK2E, while VK1E did not inhibit the metabolism of high concentration of VK2E.

**Conclusions:** Our data indicated the difference of inhibition type of VK1E and VK2E against metabolism of low and high concentration of VK2E by VKOR. VK1E and VK2E may be bound to the same site of VKOR high affinity site, while VK2E, but not VK1E may be also bound to another low affinity site. In next study, we should clarify the detail of binding site of VKOR to VK2E and the difference on the interaction of VKsE with warfarin.
THE QUALITIES OF SORE THROAT INDEX (QUASITI): FIRST USE IN A CLINICAL TRIAL TESTING THE EFFECTS OF FLURBIPROFEN 8.75 MG LOZENGE ON PATIENT-REPORTED QUALITIES OF THROAT PAIN

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Background: Beyond the evaluative complaint of a “sore” throat, patients with pharyngitis frequently report different qualities of throat pain such as “burning” and “difficulty swallowing” (Schachtel et al. Arch Intern Med 1984). Optimally, treatments should not only relieve throat soreness, but also reduce these other dimensions of pain. We investigated the effects of a lozenge containing 8.75 mg of the nonsteroidal anti-inflammatory drug, flurbiprofen, on 11 qualities of throat pain.

Material and Methods: This randomised, double-blind, placebo-controlled, single-dose trial enrolled adults with recent onset moderate-to-severe sore throat and pharyngitis (≥5 on the Tonsillo-Pharyngitis Assessment; TPA). Patients were randomised to one flurbiprofen or one identically-flavoured vehicle lozenge (placebo). At baseline and hourly for 3 hours post dose, patients used Likert scales to rate throat soreness and 10 other qualities of throat pain: sensory symptoms (burning, raw, dry, irritated/scratchy, tight, like a lump in the throat, swollen), functional symptoms (difficulty swallowing, husky/hoarse voice) and an affective descriptor (agonising). These 11 scales comprise the Qualities of Sore Throat Index (QuaSTi). Mean changes in the QuaSTi scores for both treatment groups were compared from baseline to 3 hours after treatment.

Results: A total of 122 patients with moderate/severe sore throat were randomised to flurbiprofen or placebo treatment. Mean age was 19.5 years, mean TPA score was 9.9. Compared with placebo, flurbiprofen-treated patients reported significantly greater reductions in sensory, evaluative, affective and functional QuaSTi symptoms (all P < 0.05).

Conclusions: In adults with sore throat, a single dose of flurbiprofen was significantly more effective than placebo in relieving throat soreness, but also reduced these other dimensions of throat pain such as “burning” and “difficulty swallowing” (Schachtel et al. Arch Intern Med 1984). Optimally, treatments should not only relieve throat soreness, but also reduce these other dimensions of pain. We investigated the effects of a lozenge containing 8.75 mg of the nonsteroidal anti-inflammatory drug, flurbiprofen, on 11 qualities of throat pain.

SUBSTANCE USE AMONG MEDICAL STUDENTS IN GREECE

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Introduction: Limited research exists worldwide on medical students’ substance use patterns including alcohol and marijuana use. The aim of this study was to examine the prevalence of substance use, including marijuana, alcohol and other illicit substances (i.e. cocaine, heroin, hallucinogens, and ecstasy) in a sample of medical students in Northern Greece.

Material and Methods: Six hundred fifty-five medical students (55.7% females) from the Aristotle University of Thessaloniki completed an anonymous, self-administered, web-based survey. Students were asked to report the frequency of use (lifetime, the past year, and the past month) and the motive of the use. The CAGE questionnaire was used to determine the severity of the alcohol use.

Results: Seventy-two percent of the students reported having never used any illegal substance and 21% reported marijuana use at least once in their lifetime; 20.9% of the students were nicotine smokers. No gender difference regarding marijuana use (50.7% male vs 49.3% female) was observed. Significantly more nicotine smokers and alcohol users were noticed in the marijuana group than in the no marijuana group. The use of other illicit substances was rare in our sample (3% used inhalers, 2.3% cocaine, 2.3% ecstasy, 2% ketamine, 1.8% amphetamines and 1.7% mephedrone). However, the use of marijuana was significantly positive correlated with use of cocaine, LSD, ecstasy, ketamine, amphetamine and mephedrone.

Conclusions: Although the relative mean CAGE scores are low indicating a lack of severe alcohol related problems in our sample, there is a significantly higher mean CAGE score in students who use marijuana. Marijuana use is also associated with polysubstance use, this result confirms previous findings in the general population. Nationwide studies are needed further investigating the prevalence, the motivation and the impact of this risky behaviour among this population.
THE IMPORTANCE OF CONVENIENCE FOR PATIENT ADHERENCE TO DRUG TREATMENTS - AN OVERVIEW OF SECONDARY LITERATURE

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Background: The convenience of a medication regime, i.e. dosing complexity and frequency, is considered of great importance to patient adherence. The aim of this review was to synthesise review-level evidence on how convenience affects patient adherence.

Material and Methods: A structured search of the Cochrane Library and PubMed was conducted to identify English-language reviews, systematic as well as non-systematic, dealing with the importance of convenience for patient adherence, irrespective of disease and medicine type. The PubMed search was limited to reviews published between January 2009 and December 2014. Reference lists of included reviews were screened in order to identify other relevant literature.

Results: The synthesis was based on 77 reviews with highly variable methodological quality. Few reviews included a systematic search; no reviews performed systematic meta-analyses. The scope and focus of reviews varied considerably; nearly all reviews focused on chronic disease, but within a large number of therapeutic areas. Most reviews that included a critical appraisal of primary original literature stressed a lack of well-defined definitions, interventions and endpoints. With this proviso, a general finding for orally administered medicines was that "regime complexity", including the number of daily doses and "units" per dosing, seemed to correlate negatively to adherence. For parenterally administered drugs, the importance of convenience was much less clear.

Conclusions: The association between convenience and adherence has been discussed within many therapeutic areas, but only rarely examined using a stringent scientific-methodological approach. Data suggest that increasing regime complexity may lower adherence to orally administered drugs; this does not necessarily hold true for parenteral treatment. Given the overall low level of evidence, it remains uncertain whether increased convenience, often at a higher cost, should be a decisive factor when choosing between otherwise equal drug treatments.

CHEMOPREVENTIVE POTENTIAL OF SOLANUM LYCOCARPUM ON COLON CARCINOSIS INDUCED IN WISTAR RATS

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Solanum lycocarpum A. St.-Hil. (Solanaceae), popularly known as “fruit-of-wolf”, is a hairy shrub or small much-branched tree of the Brazilian Cerrado. Plants belonging to the genus Solanum are known for their high concentration of alkaloids. Solasonine and solamargine are two of the major glycoalkaloids found in at least 100 Solanum species. Studies on solamargine activities have demonstrated its ability to inhibit human tumor cells proliferation. The present study aimed to investigate phytochemical composition and quimiprevention potential of a fruit extract of S. lycocarpum glycoalkaloid (SL) on colon and liver carcinogenesis in Wistar rats. Fruits of S. lycocarpum were collected in Ribeirão Preto – SP – Brazil. The dried powder from the fruits was submitted to acid-base extraction, suspended in distilled ethanol, filtered, concentrated under reduced pressure and lyophilized to furnish the glycoalkaloidic extract. Chromatographic analyses were performed in a HPLC equipment with a diode array detector. Animals were orally (gavage) treated with the extract at doses of 15, 30 and 60 mg/kg body weight/day. In the colon carcinogenesis protocol, two subcutaneous injection of 1,2-dimethylhydrazine (DMH; 40 mg/kg b.w.) were administered for two weeks; in the liver carcinogenesis model, a single intraperitoneal injection of diethylhydrazine (DEN; 200 mg/kg b.w.) was administered.

Animals were sacrificed 10 weeks after DMH or DEN injections for evaluating aberrant crypt foci (ACF) in colon and GST-P (placental form of glutathione-S-transferase enzyme) foci in liver of Wistar rats.

Results showed a significant reduction in the frequency of ACF in the group treated with SL plus DMH in comparison with those treated with DMH alone. These findings suggest that SL displayed a protective effect against colon carcinogenesis. On the other hand, SL did not exert any in the liver.

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MITOGENIC ACTIVITY AND PROLIFERATIVE EFFECT OF A NEW-DEVELOPED SHORT ACTING INSULIN ANALOGUE

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Introduction: Human insulin analogues with modified amino acid sequence may exert stronger proliferative effect and carcinogenic potential than insulin itself. The objective of the study was to assess mitogenic activity and activation of proliferation in tumorigenic and non-tumorigenic cell lines upon stimulation with a new-developed short-acting B281lys-B29Pro human insulin (KP) in comparison to EU Pharmacopea human insulin standard (HIS) and insulin AspB10 with strong mitogenic, carcinogenic activity.

Material and Methods: The mitogenic activity and activation of cells proliferation were examined by the optimized and validated colorimetric MTS and BrdU tests on two cell lines: MCF7-human breast adenocarcinoma and MCF10A-normal human epithelial breast cells. MTS is a method for determining the number of viable cells based on mitochondrial dehydrogenase activity measurements. BrdU immunoassay enables quantitative measurement of DNA synthesis and thus cell proliferation. Nine concentrations of each items at range 0.00–800 nM (MTS) or 0.00–2000 nM (BrdU) were tested.

Significant differences in increasing number of cells compared to negative control and between each tested concentration in pair of evaluated items were performed using t-test at α=0.05.

Results: There were no statistically significant differences between KP and HIS on MCF10A cells in BrdU test. The differences in other comparisons may be considered as an incidental effect, as they appeared coincidentally in non-consecutive concentrations. Statistically significance between KP and AspB10 in a wide range of concentrations were demonstrated in tumorigenic cells in BrdU (0.49–2000.0 nM) and non-tumorigenic cells in MTS (0.20–800.0 nM). BrdU assay on MCF10A demonstrated that AspB10 stronger than KP activated proliferation, but statistically significant differences were not showed at each concentration.

Conclusions: The insulin KP induced cell proliferation similar to HIS at most of tested concentrations. Lower concentrations of AspB10 (from 0.2 nM) stimulated proliferation more efficiently than KP.

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Introduction: The Centre for Human Drug Research (CHDR) is a non-profit clinical research institute at the interface between academia and the pharmaceutical industry and offers internships to undergraduate (bio-)medical students. During these internship, students get hands-on experience in clinical pharmacology research. The objective of the study was to assess the clinical pharmacology research internships at the CHDR using an online survey of (former) interns. Areas of interest included general perceptions of the internship and a comparison with academic research internships.

Methods: An anonymous online Google Forms® survey with multiple choice, multiple answer and open-ended and Likert-scale questions—was sent to all students that started an internship at the CHDR between 2007−2014.

Results: The response rate of the online survey was high (53 students, 61%). Most students gave the internship an overall rating of good (43%) or excellent (42%), and 80.5% strongly agreed that their training at the CHDR was helpful to their career. Many students considered their internship at the CHDR to be (much) more beneficial (58%) and outcome-driven (50%), compared to academic research internships. Although CHDR has a commercial setting, it was not considered a major distraction by 98% of the interns. A Wilcoxon rank-sum test revealed a significantly lower score of pre-Master students in both “Own knowledge of clinical research” and “Link between internship and knowledge from their study” when they were compared to Master students (both P < 0.01).

Conclusion: The clinical pharmacology research internships at the CHDR are perceived by most students as having a good or excellent quality, and being helpful to their career. Pre-Master students might benefit from additional guidance to ensure a sufficient knowledge level for an effective internship.

Introduction: Statins have been shown to protect the aorta against inflammation and oxidative stress, as well as to stabilize atherosclerotic plaques, thereby contributing to the enhancement of vascular function. The aortic wall is innervated by the aorta and blood flow is regulated by neural control. Statins have been shown to reduce the incidence of cardiovascular events and to prevent the progression of atherosclerosis, leading to an improvement in endothelial function.

Material and Methods: From March 2011 to March 2014, 170 patients receiving endovascular repair of their AAA were included in the present study. Patients were divided according to their medication included statins and subdivided according to their supra- or infrarenal endovascular fixation. Serum Creatinine (SCr) and Creatinine Clearance (CrCl) were determined preoperatively and 3 days postoperatively. Patients with known renal disease and severe renal artery stenosis were excluded from the study.

Results: Patients receiving an infrarenal fixation had no change in their renal function. However, patients with suprarenal fixation not receiving statins marked a non significant deterioration in renal function in the early postoperative period, whereas patients under statins had a statistical improvement both in SCr (preoperative 1.25 ± 0.13 vs postoperative 0.98 ± 0.12) and CrCl (preoperative 82.4 ± 2.5 vs postoperative 88.7 ± 3.1). Also there was a statistically significant difference between patients receiving and not receiving statins when measuring SCr and CrCl changes (P = 0.001 and P = 0.005 respectively).

Conclusions: In the present study statins improved renal function, during the short postoperative period, in patients with suprarenal fixation for AAA, compared to those not receiving statins.

Impact of Direct Healthcare Professional Communication on Diclofenac Consumption

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Introduction: In July 2013, Pharmacovigilance Risk Assessment Committee of the European Medicines Agency issued the recommendation on new measures to minimise cardiovascular risks after use of medicines containing diclofenac. Consequently, the Agency for Medicines and Medical Devices of Montenegro took regulatory measure and sent letter to healthcare professionals who prescribe, dispense or administer medicines containing diclofenac. Restriction of indications, introduction of new contraindications, with respect to prescription status of diclofenac, should reduce high consumption of these medicines in Montenegro.

Material and Methods: This is a retrospective analysis of data from the Agency’s reports on medicines consumption in Montenegro, in 2012 and 2013. Comparison was performed, taking into consideration consumption of diclofenac before and after communication with healthcare professionals initiated by the Agency. For comparative view of consumption international standard was used, in accordance with the recommendations of the World Health Organisation - ATC/DDD methodology, number of defined daily doses per 1000 inhabitants per day.

Results: Analysis of the Agency’s report in 2012 showed that diclofenac was the third most frequently used medicine with DDD/1000inhabitants/day−46.74. The same analysis in 2013 showed the same position on the list of most frequently used medicines, but with DDD/1000 inhabitants/day−39.86. The data indicated that the total consumption was reduced by 14.72%. Outpatient consumption was reduced by 14.91%, while hospital was reduced by 2.78%.

Conclusions: The regulatory measures, taken by the Agency, in line with national legislation and based on new information about safe use of diclofenac, have resulted in decreased consumption. As the consumption is still high, Agency is going to repeat communication in order to fully implement regulatory decisions made in EU.

2015
Clinical Therapeutics

PK/PD MODELLING OF DILTIAZEM IN HEALTHY SUBJECTS USING HRV PARAMETERS

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Introduction: Diltiazem hydrochloride, an antihypertensive calcium antagonist exhibits also frequency-dependent effects at the atrioventricular (AV) node and is effective in slowing the rapid ventricular rate. The nature of the concentration-response relationship with regard to diltiazem effect on heart rate variability (HRV) parameters has not been evaluated so far. The aim of this study was to examine the PK/PD profile of diltiazem using HRV parameters as pharmacodynamic factors with the application of a standard E\text{max} model.

Material and Methods: The study was conducted on 8 healthy volunteers, following multiple doses of 120 mg of diltiazem MR once daily. Diltiazem concentration was determined up to 24h by fully validated HPLC method. Compartmental analysis of diltiazem pharmacokinetic was used. The temporal profile of diltiazem was described by a one-compartment, first-order elimination model. Pharmacodynamic effects were measured continuously (ECG Holter monitoring) up to 24h after drug administration. Classical HRV analysis in time and frequency domains was conducted and a few components of HRV were estimated (RMS, SDNN, LF, and HF). The goodness of fit to pharmacodynamic model interpretation took place with the help of Akaiki Information Criterion (AIC). Standard E\text{max} model parameters (EC_{50}, E_{\text{max}}, E_{\text{p}}, k_{\text{d}}) were calculated.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>ka [h^{-1}]</td>
<td>0.3771 (0.1532)</td>
</tr>
<tr>
<td>AUC_{0-\infty} [ng/mL*h]</td>
<td>1268 (604)</td>
</tr>
<tr>
<td>MRT [h]</td>
<td>5.112 (1.531)</td>
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<tr>
<td>C_{ss} [ng/mL]</td>
<td>115.9 (48.33)</td>
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<tr>
<td>t_{1/2} [h]</td>
<td>3.689 (0.556)</td>
</tr>
<tr>
<td>k_{d} [h^{-1}]</td>
<td>0.2082 (0.0495)</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td></td>
</tr>
<tr>
<td>RMS</td>
<td>0.0275</td>
</tr>
<tr>
<td>SDNN</td>
<td>0.0049</td>
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<tr>
<td>LF</td>
<td>0.0013</td>
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<tr>
<td>HF</td>
<td>ns</td>
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Significance of PK/PD correlation (p value): 0.0027 for RMS, 0.0049 for SDNN, 0.0013 for LF, and ns for HF.

Methods: In order to optimize CYP450 activity while decreasing cell apoptosis, we tested different culture conditions for differentiation by varying DMSO concentration from 0 to 2% and by adding growth factors EGF and HGF. CYP activity was assessed using a cocktail approach by LC-MS/MS. Expression of several CYP450, phase II enzymes UGT1A1 and UGT2B7 and various transporters was assessed with Nanostring technology.

Results and Conclusions: Increase of DMSO concentration resulted in similar increase of the differentiated pattern. However, cell viability was significantly decreased when adding DMSO up to 2%. Considering CYP450 activity, DMSO increased significantly the activity of CYP3A4, 2B6 and 1A2. The addition of growth factors EGF and HGF was found to have a negative impact on cell differentiation and thus CYP activity, but significantly improved cell viability. There was a good correlation between CYP activity and CYP expression (P < 0.05) except for CYP1A2. In all conditions tested, CYP 2D6 showed a weak activity and expression levels were undetectable. UGT1A1 and UGT2B7 transcripts were found at appreciable levels and were influenced by DMSO concentration, as well as hepatic transporters. Efflux transporters MRP2, MRP3 and MDR1 (P-gp) levels were high, whereas BSEP, BCRP and MR1 levels were low. The uptake transporter OCT1 was largely expressed and OATP1B1, 2B1, OAT3, OAT2 expression were found in acceptable levels. On the contrary, NTCP and OATP1B3 transcripts were undetectable. Differentiation medium containing 1.5% showed similar viability compared to MIL720 from Biopredic used as reference, with slightly lower CYP450 activities. This medium was thus chosen for further metabolism experiments on the HepaRG cell line.

IN-VITRO EVALUATION OF DDI WITH COBICISTAT AND RITONAVIR USING HEPARG CELL LINE

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Background: Cobicistat is a new pharmacoenhancer which has recently been approved by the EMEA as a boosting agent for the HIV protease inhibitors atazanavir and darunavir. As opposed to ritonavir, cobicistat does not show any antiviral activity. Also, previous inhibition studies on human hepatic microsomal fractions showed a more specific inhibition of CYP3A4 of cobicistat versus ritonavir and a lack of induction potential on CYP3A4. The aim of this work was to investigate CYP450 inhibition/induction potential of major CYPs by cobicistat and ritonavir in HepaRG.

Methods: Low density-seeded confluent HepaRG cells were differentiated with 1.5% DMSO and plated in 24-well plates. At day 12 after plating, CYP activity in the presence/absence of cobicistat and ritonavir (0-50 µM) was assessed using a cocktail approach and IC50 was calculated by linear regression. For induction assay, cobicistat or ritonavir (0-50 µM) was incubated with differentiated HepaRG cells for 72 hours in a specific medium (0.5% DMSO, no FBS). DMSO concentration was decreased to 0.5% 24 hours before addition of the inducers. CYP3A4 activity was assessed by incubation of midazolam 5 µM for 3 hours at 37°C and quantification of 1'-hydroxymidazolam by LC-MS/MS.

Results: Cobicistat and ritonavir showed similar inhibition of CYP 3A4 with IC50 of 0.107 µM and 0.105 µM respectively. IC50 values of CYP 2B6, 1A2, 2C19 and 2C9 were lower for cobicistat than for ritonavir, thus suggesting that cobicistat may be a more potent inhibitor of these CYP450 than ritonavir. Considering CYP3A4 induction, cobicistat did not seem to induce CYP 3A4. Ritonavir, which was used as a positive control, showed induction of CYP 3A4 up to 1.6 fold.

EVALUATION OF CYP450 AND TRANSPORTERS EXPRESSION AND ACTIVITY IN HEPARG CELL LINE UNDER DIFFERENT CONDITIONS

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Background: HepaRG cell line is able to differentiate to both hepatocyte-like and biliary-like cells after reaching confluence. Previous works have shown that confluent HepaRG cells start to differentiate when adding 2% DMSO in the culture medium. However, DMSO is well known to induce cell death.
Conclusions: This work has showed the suitability of the HepaRG cell line to study inhibition drug interactions in vitro. Induction assays however have still to be optimized to reach greater levels of induction.

BIOEQUIVALENCE OF FIXED-DOSE COMBINATIONS OF DAPAFLIFLOZIN/METFORMIN RELATIVE TO SINGLE COMPONENTS IN HEALTHY SUBJECTS

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Background: In patients with type 2 diabetes (T2DM) fixed-dose antihyperglycaemic combinations (FDCs) may provide complementary efficacy, reduce tablet burden, and improve compliance. The aim of this study was to assess the bioequivalence and tolerability of 2 strengths of dapagliflozin (DAPA)/metformin extended-release (MET-XR) FDCs versus their individual components (ICs) in healthy subjects.

Material and Methods: This open-label, randomised, 2-way crossover, 4-arm study was conducted in 141 healthy adult Brazilian subjects. Two oral doses (5 mg DAPA/500 mg MET-XR and 10 mg DAPA/1000 mg MET-XR) were evaluated in fed and fasted states.

Results: Under fed and fasting conditions the 5 mg DAPA/500 mg MET-XR FDC was bioequivalent to its ICs (Table). The 10 mg DAPA/1000 mg MET-XR FDC was bioequivalent to its ICs only in fed patients. Cmax for metformin was not bioequivalent to its ICs (upper 95% CI outside 80%–125%) in fasted patients; this small increase was not considered clinically meaningful as metformin is recommended to be administered with food. The safety and tolerability of the FDCs were generally similar to their ICs; no serious adverse events were reported.

Conclusions: Both DAPA/MET-XR FDCs were bioequivalent to their ICs, except 10 mg DAPA/1000 mg MET-XR in fasted patients, supporting their use in patients with T2DM.

3D PHOTOGRAPHY FOR SKIN LESION QUANTIFICATION

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Introduction: Reliable methods to quantify skin lesions are critical for the evaluation of disease severity and assessment of therapeutic response. In dermatological trials often two dimensional digital photography is utilized which has inherent disadvantages. It appears that high-resolution three-dimensional (3D) imaging may offer many advantages such as offline 3D visualization and automatic picture segmentation resulting in an objective and detailed skin lesion characterization. At present this technique is not optimally technical and analytical validated which is a pre-requisite for clinical application.

Material and Methods: In this study we investigated the performance and clinical use of the 3D skin-imaging LifeViz™ system (Quanticare, Sophia Antipolis, France) in conjunction with the DermaPix Software. The validation of the LifeViz Micro was conducted with four trained operators that captured a synthetic phantom object on three different skin backgrounds at four time points during a period of one week.

Results: Coefficient of variations for volume of the 3D system were 1.0%, 2.6% and 1.4% for inter-operator, skin background and inter-day variability, respectively. The overall precision of the system was 2.7% for volume, 1.6% for diameter and 4.1% for height. In order to determine accuracy of the system, a ruler was photographed and a mean error of 0.3% (range 0.0-0.8%) was observed. Preliminary data on cutaneous lesions also show low inter-observer variability and accurate images.

Conclusions: This validation study demonstrates that this novel 3D-imaging system is precise and objectively quantifies a phantom object representing a skin lesion. The results support clinical use of this technology enabling high-resolution computation. Also the accuracy results are promising, but needs to be extended with accuracy assessment of absolute measurements. The preliminary clinical data suggest that application of this non-invasive imaging technique is suitable to quantitatively measure characteristics of cutaneous lesions and may be a promising tool in clinical trials.

THERAPY ADHERENCE IN ELDERLY OF NORTHERN PORTUGAL

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Introduction: The elderly population has been growing significantly, leading to an increased prevalence of chronic diseases and consequent taking medication. The complex therapies of elderly can lead to therapy non-adherence, increasing several health risks.

Aim: This study aimed to estimate the prevalence of therapy adherence and associated factors.

Material and Methods: This cross-sectional study was based on a questionnaire, with MAT scale (measure of adherence to therapy) validated for the Portuguese population (Lima, 2001) based on

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CHARACTERIZATION OF URACIL CATABOLISM VARIABILITY IN HEALTHY VOLUNTEERS

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Uracil catabolism is crucial for the pharmacokinetics of the chemotherapeutic 5-fluorouracil (5-FU) since 5-FU is degraded by the same pathway. Decreased activity of the first catabolizing enzyme, dihydropyrimidine dehydrogenase (DPD), is a major predictor of 5-FU toxicity with known risk variants in the DPD gene (DPYD) accounting for ~30% of toxicities. However, not all toxicity cases can be explained by DPYD risk variants. To date, the phenotypic variability in the catabolism downstream of DPD by dihydropyrimidinase (DHP) and β-ureidopropionase (bUP), potentially contributing to 5-FU toxicity, has not been investigated. Thus, we aimed to characterize the baseline phenotypic variability of endogenous metabolites and metabolic ratios of 5-FU catabolism enzymes and to correlate the phenotype with genetic variation in the DHP and bUP genes (DPYS and UPB1).

Material and Methods: Three variants in DPYS and UPB1 previously associated with 5-FU toxicity were genotyped in 320 healthy volunteers and their plasma uracil, dihydrouracil (UH2), β-ureidopropionic acid (UPA), and β-alanine (BAL) concentrations were determined by LC-MS/MS.

Results and Conclusions: High inter-individual variability in all metabolite ratios was observed. Sex-dependent differences were detected at each enzymatic step in the uracil catabolism pathway, with lower metabolite levels (P ≤ 0.007) in women. Moreover, lower UPA/UH2 ratios (P < 0.001) were observed in women, suggesting that reduced 5-Fluoro-UH2 catabolism may contribute to higher fluoropyrimidine toxicity rates observed in females. Furthermore, volunteers carrying DPYS variant c.265-58C had lower UH2 plasma levels (P = 0.033) and higher UPA/UH2 ratios (P = 0.036) and carriers of the UPB1 variant c.1-80G showed lower BAL plasma levels (P = 0.004). These initial results are in agreement with the previously observed reduced fluoropyrimidine toxicity in c.265-58C carriers and increased toxicity in carriers of c.1-80G, indicating a possible functional effect related to these variants.

POLYPHARMACY AND POTENTIALLY INAPPROPRIATE MEDICATION IN ELDERLY OF NORTHERN PORTUGAL

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Introduction: The growing aging of population and increasing prevalence of chronic diseases require the simultaneous use of drugs, lead to the issue of polypharmacy and potentially interactions and inappropriate use.

Aim: To characterize polymedicated elderly and related factors, identify potentially interactions and inappropriate medication in elderly.

Material and Methods: This cross-sectional study was based on a questionnaire applied to 69 elderly (≥65 years) from northern Portugal. It was considered as polymedicated seniors taking ≥5 drugs. Beers list and the Delafuente classification were used to evalu-
ate the therapeutic and possible interactions. It was used descriptive
statistics and a model of binary regression, with a significance of 5%.
The study was approved by Ethics Committee.
Results: The sample consisted mainly of males (53.6% vs. 46.4%),
aged between 66 and 99 years (mean 82.01), while 65.2% have
more than 80 years. However, most elderly are not polymedicated
(58%), on average 4.61 different drugs are administered per day
(maximum = 19), antihypertensives (36.2%) and antacids (30.04%)
are the most prescribed. Hypertension and depression increase the
risk of polymedication eightfold ($P = 0.004$) and fivefold ($P = 0.011$
respectively. Female gender seems increase the risk of polypharmacy
threefold, although not statistically significant ($P = 0.102$), and
regarding age, the older age group (> 85 years) seems reduces the
risk of polypharmacy in 0.6 fold, but also not statistically significant.
According with Delafuente classification, 1.4% of elderly has poten-
tially drug interactions (Omeprazole and Iron salts). According to
the list of Beers, 5.8% of seniors take drugs that classified as having
some indications (hydroxyzine, amitriptyline).
Conclusions: Regarding polypharmacy, 42% of elderly are poly-
medicated with an average of about 5 different drugs per day, anti-
hypertensives and antacids the most prescribed. Hypertension and
depression are highly associated with polypharmacy. We identified
one potentially drug interaction and about 6% of elderly taking drugs
that classified as having some indications.
Key words: Beers list, Delafuente classification, Elderly, Inappropriate
medication in elderly, Medication interactions, Polypharmacy.

INNOVATIVE APPROACH TO BLOOD SAMPLING
USING DRIED BLOOD SPOTS. APPLICATION TO
PHARMACOKINETICS AND CYTOCHROME P450
PHENOTYPING

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Background: The use of dried blood spots (DBS) has gained in popu-
larity in the last few years over conventional whole blood or plasma
sampling for PK or drug monitoring. In order to overcome the impact
that haematoctrit has on the spreading of the applied drop of blood,
precise knowledge of the collected volume is crucial for the determi-
nation of drug/metabolites concentrations.

Material and Methods: Although the collection of an accurate capil-
lar volume using a volumetric micropipette is simpler than venous
blood collection, it still needs to be conducted by trained technicians
using dedicated instruments. To simplify this process a new capillary
blood collection device has been developed. The prototype integrates a
patented microfluidic plate (WO/2013/144743) allowing for accurate
volume control and a conventional filter paper card for blood storage.

The concentrations and pharmacokinetic profiles of a
P-glycoprotein (P-gp) and six cytochrome P450 (CYP) probes and
their metabolites obtained with the new sampling device have been
compared with a conventional volumetric micropipetting method in
a clinical trial including 30 volunteers who have received the Geneva
cocktail for CYP and P-gp phenotyping. The quantification was done
using a previously validated LC/MS-MS method.

Results: Concentrations obtained with the new microfluidic sam-
ping device showed excellent correlation with conventional micro-
pipetting concentrations with slopes values close to 1 (0.91 – 1.03)
and determination coefficients $R^2$>0.90 for all of the 13 analysed
substances. Sampling could be successfully performed by the volun-
teers themselves with almost no previous training.

Conclusion: DBS technique combined with an innovative sampling
device and a sensitive analytical method can be used as a self-test for
CYP and P-gp phenotyping. The use of this technique can be further
enlarged to the quantification of other substances for PK studies and
therapeutic drug monitoring.

THERAPEUTIC DRUG MONITORING
FOR ANTIDEPRESSANTS AND ANTI PSYCHOTICS – A
LONGITUDINAL PREVALENCE ANALYSIS

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Background: Therapeutic drug monitoring (TDM) can help cli-
nicians to optimize dosing of medicines. Evidence on the use of this
service in psychiatry mainly refers to questionnaire studies.
The aim of this study was to use register data to describe the
prevalence of TDM for antidepressants and antipsychotics dur-

Material and Methods: The study population consisted of indi-
viduals, 2.5 years of age, residing in the Stockholm County.
The prevalence of TDM for each study year was calculated with the
number of individuals in whom TDM had been performed as nomi-
nator (extracted from the TDM database at Karolinska University
Laboratory) and the number of treated individuals as denominator
(extracted from the Swedish Prescribed Drug Register). The preva-
lence of TDM was compared between substances according to the
level of TDM recommendation by guidelines.

Results: In 2006, 641 in 133,275 (0.48%) individuals on antide-
pressants were subjected to TDM. In 2013, the corresponding figure
was 580 in 162,998 (0.36%). In 2013, the most frequently analysed
antidepressants were nortriptyline (6.2%) and clomipramine (4.5%).
For patients on antipsychotics, the prevalence of TDM increased
between 2006 and 2013, from 729 in 31,463 (2.3%) to 1,338 in
32,534 (4.1%). In 2013, the most frequently analyzed antipsychotics
were clozapine (29%) and perphenazine (22%). For both antidepres-
sants and antipsychotics, TDM was more common in men than in
women. A trend to a greater prevalence was found for substances
strongly recommended for TDM than for substances with a lower level
of recommendation (5.6% vs. 1.1%; $P = 0.063$).

Conclusions: Each year, less than one in 200 patients on antide-
pressants and antipsychotics have their treatment personalized by means of TDM. The use of TDM is increasing for antipsychotics but not for antidepressants. Men are more frequently monitored by plasma concentrations than women.

HOSPITALISATIONS BY DRUG INTERACTIONS
WITH NSAIDS IN ELDERLY POLY-TREATED
PATIENTS: OUTCOME RESEARCH ON
ADMINISTRATIVE DATABASES

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Background: Elderly patients are highly susceptible to poly-pharmacy,
which may cause drug–drug interactions and relevant hospitalisations.
These often involve NSAIDs (Non- Steroidal Anti-Inflammatory-
Drugs), which are inappropriately prescribed. This study aimed to

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investigate the risk of kidney injury and bleeding following various NSAID interactions in the elderly poly-treated population.

Material and Methods: An historic cohort study based on administrative databases of the Local Health Authority of Bologna (866,000 inhabitants) was performed. Patients with at least a NSAID prescription in the first semester of 2012 were selected among elderly (≥65 years) poly-treated (>4 different drugs) subjects. Co-prescriptions of NSAIDs + ACE-Inhibitors (or sartans), NSAIDs + diuretics, NSAIDs + ACE-Inhibitors (or sartans) + diuretics (triple whammy), NSAIDs + metformin, NSAIDs + SSRIs, NSAIDs + corticosteroids and NSAIDs + warfarin were considered as potential interactions. Kidney injury and bleeding hospitalisations represented the outcome measures. Kaplan-Meier curves and Cox regression model were used to estimate the risk of two outcomes following interactions. Hazard Ratios (HRs), with 95% Confidence Interval (95CI), were adjusted for gender, age and concomitant drugs.

Results: Out of 34,353 elderly poly-treated patients, 7,420 subjects received NSAIDs (60.8% female, 76.9 average age). Among these, 85.7% was exposed to NSAIDs + ACE-Inhibitors (or sartans), 69.9% to NSAIDs + diuretics, 32.8% to triple whammy, 21.6% to NSAIDs + metformin, 20.1% to NSAIDs + SSRIs, 17.1% to NSAIDs + corticosteroids and 8.2% to NSAIDs + warfarin. A significant risk of kidney injury was found only for triple whammy (adjHR: 1.33; 95CI: 1.12-1.59); instead for other interactions involving antihypertensives, no risk increase was retrieved. The bleeding risk resulted statistically significant only for NSAIDs + warfarin (2.84; 1.29-6.29), but not for interactions with SSRIs or corticosteroids. Conclusions: In elderly poly-treated patients, concomitant prescription of NSAIDs + ACE-Inhibitors (or sartans) + diuretics or NSAIDs + warfarin have caused kidney injury and bleeding, respectively. Other NSAID interactions did not show impact on expected clinical outcomes. Therefore, physicians should carefully evaluate individual risk-benefit profile before prescribing NSAIDs to elderly poly-treated patients.

Concurrent Validity of Indicators of Prescribing Quality in Older People

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Background: Indicators of prescribing quality are used in research studies and for benchmarking. Indicators based on counts of drugs or presence of specified inappropriate drugs are appealing as they are easy to apply on register data. This study aimed to evaluate the concurrent validity of such indicators.

Material and Methods: In 200 hip fracture patients (≥65 years), consecutively recruited to an RCT in Sahlgrenska University Hospital in 2009, quality of drug treatment was assessed according to a gold standard as well as to indicators based on cut-offs of number of drugs in the medication list and the presence of inappropriate drugs according to the Swedish National Board of Health and Welfare, the French consensus panel list, and the German PRISCUS list. As gold standard, two specialist physicians independently assessed and then agreed on the quality for each patient, after initial screening with STOPP/START. Suboptimal drug treatment was defined as ≥1 STOPP/START outcomes assessed as clinically relevant at the individual level.

Results: In all, 71% of the patients had suboptimal drug treatment according to the gold standard. For different cut-offs of number of drugs in the medication list (≥1 to ≥10 drugs), 96% to 23% of the patients were identified to have potentially suboptimal drug treatment. The sensitivity ranged from 1.00 (95% confidence interval: 0.97; 1.00) to 0.32 (0.25; 0.40). The specificity ranged from 0.07 (0.23) to 0.93 (0.82; 0.97). According to the Swedish, French, and German indicators of potentially inappropriate drugs, 18%, 24%, and 22% of the patients had potentially inappropriate drug treatment. The sensitivity was 0.24 (0.18; 0.32), 0.29 (0.22; 0.37), and 0.29 (0.22; 0.37), respectively. The specificity was 0.97 (0.88; 0.99), 0.90 (0.80; 0.95), and 0.97 (0.88; 0.99).

Conclusions: These findings suggest that the indicators may be valuable to monitor changes in drug utilization and effects of interventions, but are of limited value for identifying patients at risk of suboptimal drug treatment and to assess prescriber performance.

AN IN SILICO MODEL OF ASPIRIN-INDUCED INACTIVATION OF PLATELET AND MEGAKARYOCYTE CYCLOOXYGENASE-1

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Background: Aspirin is a short-lived, irreversible inhibitor of platelet cyclooxygenase (COX)-1. We have recently reported that aspirin action throughout the 24-hour dosing interval is impaired under conditions of accelerated platelet formation such as essential thrombocytemia (ET). An in silico model of aspirin pharmacodynamics might help elucidating the dynamic features of its action and personalize regimens in different cardiovascular disorders.

Methods: We set up a new multi-compartmental mathematical model that describes the key features of COX-1 dynamics, including: its synthesis/degradation in the heterogeneous population of developing bone marrow megakaryocytes (Mk), the progressive platelet formation, COX-1 acetylation by aspirin in both Mk and peripheral (platelet) compartments. The model, consisting of 7 differential equations and 24 parameters, was implemented in MATLAB. It was calibrated using serum thromboxane (TX)B2 (proxy of COX-1 activity) recovery data measured in 7 healthy controls and 2 ET patients during and after aspirin withdrawal, and in 21 ET patients on different aspirin regimens. Sensitivity analysis was performed to identify the set of key parameters which most significantly influenced COX-1 dynamics.

Results: A good agreement (weighted absolute percentage error <18%, within the experimental variability) was obtained between data and model prediction. The different recovery pattern observed in healthy vs ET patients was reproduced by altering three key model parameters identified by sensitivity analysis: platelet count (twofold increase), Mk lifetime (from 3 to 1 day) and platelet lifetime (from 7 to 5-6 days). Finally, the model explains an increased COX-1 acetylation following a shorter dosing interval (100 mg twice daily) as compared to a higher (200 mg) once-daily dose in ET patients.

Conclusions: Our in silico model adequately describes aspirin responsiveness, as measured in controls and patients with high drug-target turnover, and might be a useful tool to design personalized regimens in clinical conditions characterized by altered Mk and/or platelet kinetics.

AGOMELATIN FOR TREATMENT OF DEPRESSIVE DISORDERS IN RUSSIA: A COST-UTILITY ANALYSIS

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Neutropenia – a Case Report

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Introduction: Fenofibrate is used in the treatment of hyperlipidemia. Adverse effects affect the skeletal muscle, kidneys and liver, laboratory tests could be mildly abnormal for leukocytes and hemoglobin. We report the first documented case of the significant fenofibrate-induced anemia and neutropenia.

Methods: A 42-year-old male (BMI 48) with compensated hypertension suffered from hyperuricemia, diabetes mellitus type 2 and pulmonary thromboembolism in anamnesis. He was treated by perindopril, indapamide, metoprolol, amlodipine, allopurinol, metformin, lisinopril, indapamide, metoprolol, amlodipine, allopurinol, metformin, rivaroxaban. At May 2014, fenofibrate 200mg daily was added due to hypertriglyceridemia (6.45 mmol/L). Laboratory tests including lipid profile were analysed two and three months later.

Results: At July 2014, triglyceride level decreased to 3.78 mmol/L. However, significant changes occurred in white and red blood cells count: leucocytes decreased from 7.8 to 4.3 × 109, absolute neutrophil count from 4.58 to 1.26, lymphocytes increased from 27.5% to 51.2% and monocytes increased from 6.8% to 13.10%; hemoglobin count: leucocytes decreased from 7.8 to 4.3 × 109, absolute neutrophil count from 4.58 to 1.26, lymphocytes increased from 27.5% to 51.2% and monocytes increased from 6.8% to 13.10%; hemoglobin decreased from 149.0 to 122.0 g/L and hematocrit from 0.45 to 0.37, 51.2% and monocytes increased from 6.8% to 13.10%; hemoglobin count: leucocytes decreased from 7.8 to 4.3 × 109, absolute neutrophil count from 4.58 to 1.26, lymphocytes increased from 27.5% to 51.2% and monocytes increased from 6.8% to 13.10%; hemoglobin decreased from 149.0 to 122.0 g/L and hematocrit from 0.45 to 0.37, without any changes in clinical features. Fenofibrate was immediately discontinued. Three weeks after fenofibrate withdrawal the hematological findings improved to previous normal values.

Conclusions: We present the first case report of the significant fenofibrate-induced anemia and neutropenia. The pathogenesis of this adverse drug reaction remains unclear, however, allergic reaction following a fenofibrate prescription could be explanation. Although fenofibrate-induced anemia and neutropenia appears to be uncommon, patients receiving fenofibrate should be monitored for this adverse drug reaction.

MODULATING EFFECT OF EGNONOL AND HOMOEGONOL ON GENOTOXICITY INDUCED BY DIFFERENT MUTAGENS

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The benzofuran nor-neolignans egonol (EG) and homoeigonol (HE) are found in all species of Styrax and considered phytochemical markers for quality control of extracts of this genus. Some important biological activities have been described for these compounds as antibacterial, modulation of the complement system and cytotoxic activity for tumor cell lines. Previous studies conducted by our group with Styrax camporum extract demonstrated its modulating effect on DNA damage induced by different mutagens. Thus, the aim of the study was to investigate whether the EG and HE are responsible for the modulating activity observed for the S. camporum extract. The study was carried out in Chinese hamster lung fibroblasts (V79 cells) using the micronucleus assay. The cultures were treated with EG (0.26 μg/mL), HE (0.017 μg/mL) alone or combined. In addition, the same concentrations were simultaneously treated with methyl methanesulfonate (MMS, 44 μg/mL), hydrogen peroxide (H2O2, 3.5 μg/mL), camptothecin (CPT 43 μg/mL) and etoposide (VP16 1 μg/mL). We also included a negative (without treatment), a solvent (dimethylsulfoxide; DMSO 0.05%) and positive control groups. The cultures treated with EG plus HE showed genotoxicity. The cultures treated with the EG and HE alone or combined with MMS or CPT no shown a significant effects. Regarding the combination with H2O2, the risk of a level being above upper limit of target range was statistically significantly elevated following a prescription of an interacting antimicrobial (17% vs. 7% for ciclosporin, P < 0.05 and 35 vs. 12% for tacrolimus, P < 0.01). This elevated risk of levels exceeding target was present despite the fact that the dose was reduced in 75% cases. The risk following dose reduction was still significantly increased (16% vs. 12% for tacrolimus, P < 0.02; 17% vs. 7% for ciclosporin, P < 0.01).

Conclusions: Despite pre-emptive dose adjustments, concurrent prescription of interacting antimicrobial agents increases risk of levels of calcineurin inhibitors exceeding the upper limit of the applicable target range. More aggressive dose reductions may be warranted if an interacting prescription is unavoidable.
the cultures treated with EG alone or combined with HE a significant increase on the micronuclei frequencies was observed when compared to cultures treated with H2O2 alone. Regarding the combination with VP16, the EG and HE alone or combined led to a reduction in the frequency of micronuclei induced by VP16. This study allowed us to better understand the mechanism of action of the S. camporum and chemical markers and suggest modulation depends on the type of mutagen used.

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ASSESSMENT OF ADVERSE REACTIONS DUE TO AN IODINE-BASED CONTRAST AGENT

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Introduction: Iopromide is an iodine-based contrast agent, used in several radiological procedures in order to obtain better image quality. This drug is used by millions of people worldwide, and is considered one of the safest intravenous drugs. However, its use isn’t deprived of risks. The aim of the study was to ascertain the incidence of Adverse Reactions (AR) due to iopromide along with a characterization of the events.

Material and Method: A retrospective observational study was performed from the cases reported between September 2012 and May 2014, of adverse reactions occurred in a radiological specialized unit. Data from reports included: date, sex, age, CT scan performed, reported symptoms and technical interventions and/or drugs used to recover the patients. The inclusion criterion was the realization of one CT scan with contrast agent administration.

Results: The patients age ranged from 37 to 74 years old (mean ± SD = 57.65) and were divided into two age groups – Adults (n = 14) were patients with < 65 years old and elderly (n = 9) were patients with ≥65 years old. Registered incidence was 0.8%, corresponding to 23 events from 2.870 CT scan with iopromide administration.

Symptoms reported were: papules (n = 17), urticaria (n = 2), erythema (n = 6), facial or laryngeal edema (n = 3), exanthema (n = 2), nausea or vomiting (n = 3), polyneura (n = 1), palpitations (n = 1) and cardiopulmonary arrest (n = 1). As for the intensity, 15 were classified as mild (65.2%), 6 moderate (26%) and 2 severe (8.7%).

Conclusion: Iopromide shows a very favorable safety profile, and its use is highly recommended. Nevertheless, healthcare professionals must be aware of the possibility to occur an ADR. They should check the patient’s history to forecast the administrations of this drug to those that present risk factors or previous reactions to iodine-based contrast agents. Iopromide have a lower incidence of AR (0.8%) compared with literature for low osmolality agents (3.1%).

STYRAX CAMPORUM EXTRACT INHIBITS THE FORMATION OF PRENEOPLASTIC LESIONS IN THE RAT COLON

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The Styrox camporum Pohl is known for its wide use for the treatment of gastroduodenal diseases especially as regards antiulcerative potential. In Brazil this species occurs in the cerrado of Minas Gerais, São Paulo, Mato Grosso do Sul and semi-deciduous forest of the Paraná basin. S. camporum is popularly known as “benjoeiro”, “cuia-do-brejo”, “canela-poca”, “fruta-de-pomba” and “pin-duíba”. In the present study we investigate the effects of S. camporum hydroalcoholic extract on the formation of aberrant crypt foci (ACF) induced by 1,2-dimethylhydrazine (DMH) in rat colon. For the experiments, male Wistar rats with four weeks of the age and 120 g body weight (b.w.) were treated daily for 40 days with different doses of the S. camporum extract (250, 500 and 1000 mg/kg b.w.) for four weeks. The negative control group received water for gavage and a subcutaneous injection of ethylenediamine tetraacetic acid (EDTA).

Also, two doses subcutaneous injection of 40 mg/kg of DMH were administered for two weeks, and animals were sacrificed two weeks after the last injection for evaluating ACF development in colon. The results showed a significant reduction in the frequency of ACF in the group treated with the different doses of S. camporum extract plus DMH in comparison with those treated with DMH alone. Therefore, these findings suggest a chemopreventive effect of the S. camporum extract against the colon carcinogenesis. This protective effect may be related to the antioxidant activities of the extract constituents.

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ADME-WIDE ANALYSIS OF COPY NUMBER VARIATION USING TARGETED EXOME RESEQUENCING AND THEIR FUNCTIONAL RELEVANCE IN HUMAN LIVER

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Copy number variants (CNVs) are involved in human disease, complex traits and drug efficacy and toxicity. Although several ADME (absorption, distribution, metabolism, excretion) genes harbor CNVs with impact on phenotype, including expression and enzyme activity (e.g. GSTM1, CYP2A6 and CYP2D6), systematic analyses are lacking. The goal of this project is to elucidate CNVs among ADME genes and to assess their functional consequences in human liver.

A well-documented cohort of 150 Caucasian liver samples was typed for CNVs using a combined analysis of the reed coverage and SNP composition of a targeted exome-resequencing panel of 340 ADME genes (Hiseq2500, Illumina). CNV results were confirmed using TaqMan CNV-assays (Applied Biosystems) and compared to publicly available CNV data (DGV). Quantitative phenotypes were measured using TaqMan (mRNA), Western Blot (protein content) and specific substrate assays (enzyme activity).

Systematic coverage analysis confirmed known CNVs of phase I and II genes and detected rare CNVs in CES1 and other phase I genes and transporters including SLC22A1/2/18 (1%). In total, 5% of 118 phase I and 9% of 61 phase II genes and 1% of 72 transporters harbored full gene-comprising CNVs. Positive association between CNV-type and expression was observed for phase I and II genes, including CYP2D6, CYP2A6 and SULT1A1 while for some genes, including CES1 and CYP2E1, CNV type was not correlated to expression.
In summary, our CNV analysis using a targeted NGS approach revealed that numerous ADME genes harbor CNVs. The human liver cohort allowed us to study the impact of CNVs on ADME gene expression. Although CNVs contributed to variable expression of CYP2A6, CYP2D6 and SULT1A1, we conclude that CYP2E1 belongs to the so-called dosage-insensitive genes, whose expression appears to be independent of gene copy number. Further research is required to understand the underlying compensation mechanisms. 

The study was supported by the Robert Bosch Foundation, Stuttgart, Germany

**EFFECT OF FOOD ON THE PHARMACOKINETICS OF TWO FORMULATIONS OF A NEW CETP INHIBITOR IN HEALTHY VOLUNTEERS**

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**Background:** DRL-17822 (150 mg) a new Cholesterol Ester Transfer Protein (CETP) inhibitor, showed an increase of more than 20 fold in bioavailability in terms of C max and AUC0-∞ as a result of a standard FDA high fat breakfast. To reduce this food effect, a new formulation of DRL-17822 has been developed.

**Methods:** This was a randomised, open-label, single-dose, 4-way cross-over study in healthy male volunteers (aged 18-45 years), conducted in two parts. In each part, 12 subjects received both the current and new formulation of 150 mg DRL-17822 in fasted and fed state; a low fat breakfast was provided in Part A1 and a high fat breakfast in Part B1.

**Results:** In both parts, the new formulation substantially increased DRL-17822 exposure in fasted state, characterised by C max, AUC0-∞ and AUC0-t compared to the current formulation. Following high fat breakfast, DRL-17822 exposure was significantly less using the new formulation compared to the current formulation (P<0.01). In addition, the new formulation resulted in similar ratios fed/fasted for AUCmax in following both types of breakfast while the current formulation had a higher ratio after high fat breakfast compared to a low fat breakfast (Table 1, similar ratios were seen for Cmax and AUC0-∞).

**Conclusion:** The new formulation had favourable pharmacokinetic characteristics compared to the current formulation, showing a food effect of only 3-fold, which may relate in more predictable effect profile.

**Table 1. Statistic analysis results AUCmax (ng·h/mL) for contrast fed/ fasted new formulation vs. fasted current formulation.**

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<td>P-value</td>
<td>Back transformed</td>
<td>90% CI</td>
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<td></td>
<td></td>
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<td>Lower</td>
<td>Upper</td>
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<td>Low fat breakfast (Part A)</td>
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<td>High fat breakfast (Part B)</td>
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<td>93.1%</td>
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**References**


**BIOEQUIVALENCE AND FOOD EFFECT OF HEAT-STRESSED AND NON-HEAT-STRESSED DAPAGLIFLOZIN TABLETS**

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**Background:** Stability and pharmacokinetic testing are essential to assure drug potency, safety and efficacy. Dapagliflozin, TZDM medication, may convert from crystalline to amorphous forms during storage. To assess the clinical impact of this form change, in vivo evaluation of dapagliflozin tablets was undertaken.

**Materials and Methods:** Two open-label crossover, single-dose studies to assess dapagliflozin pharmacokinetics from heat-stressed (HS) and non-heat-stressed (NH) dapagliflozin tablets were conducted in healthy subjects. The first assessed fasted-state bioequivalence of 10 mg tablets (N = 29). The second evaluated fed and fasted-state effect on 2.5 mg tablets (N = 28).

**Results:** Under fasting conditions, 90% CIs of the geometric mean ratios of AUC0-∞, AUC0-t, and Cmax for the HS 2.5 and 10 mg tablets were within 80%–125%, indicating bioequivalence with NH tablets (Table). In the fed versus fasting state for the 2.5 mg tablets, AUCs were similar, time to Cmax was prolonged by 1.25 hours and Cmax decreased by approximately 50% for HS and NH tablets; this is not clinically significant. No serious adverse events were reported.

**Conclusions:** Under fasting conditions, HS and NH 2.5 mg and 10 mg dapagliflozin tablets are bioequivalent. The non-meaningful food effect may support patients’ adherence to diabetes treatment through convenience of administration irrespective of meals.

**SMALL GENDER DIFFERENCES IN DRUG CONCENTRATIONS STORED IN A TDM DATABASE**

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Several recent reviews on pharmacological gender differences suggest important effects on pharmacokinetics, with females having slower drug elimination compared to men. However, the evidence referred to is not convincing. Our department has been involved in therapeutic drug monitoring (TDM) since 1970 and presently analyzes 75,000 TDM samples of 100 different drugs annually. Over the years, the methods have been successively refined and now mostly involve LC-mass spectrometry. The drug concentrations are stored in a TDM database.

We have used this source to trace possible gender differences in dose-adjusted plasma concentrations of commonly used drugs. Men and women did not differ in age.

The most frequently analyzed drugs were immunosuppressants, antiepileptics, antibiotics, antivirals, antipsychotics, and antidepressants.

For a large number of these drugs, women achieved higher dose-adjusted concentrations compared to men but after adjustment for differences in body-weight, only a small number of drugs (geno-tacicin, hydroxyureabepine, isoniazid, perfenazine, and valproic acid) exhibited this pattern. For a majority of drugs (in particular amikacin, ciscoplin, gancliovir, mycophenolic acid, sertraline, and tacrolimus) the opposite tendency was observed, with slightly lower weight- and dose-adjusted concentrations in women.

The overall data, which will be further analyzed statistically, suggest that previously made claims of lower drug clearance in women may be incorrect. If gender differences in drug elimination exist, they are probably negligible compared to interindividual differences due to other genetic and environmental factors.

IMPACT OF MEDICATION USE ON MORTALITY IN BELGIAN COMMUNITY-DWELLING OLDEST OLD
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Background: High drug use in older adults is associated with adverse outcomes. The association between medication use as a risk factor for mortality is investigated in a Belgian community-dwelling cohort of oldest old (80+).

Methods: Data was collected between November 2008 and July 2011 of the Belfrail-med cohort. Baseline predictors included medication data, and personal, clinical, and functional characteristics. Medications were coded by the Anatomic Therapeutic Chemical classification. Survival analysis included Kaplan-Meier and Cox regression analysis.

Results: Participants (n = 503) mean age was 84.4 years (range 80 – 102) and 62.2% was female. The mean medication use was 5.4 (range 0 – 16). Mortality rate after 18 months was 8.9% (n = 45).

The mortality group was significantly older (85.7 vs 84.3 years), received more nursing care (53.3% vs 35.2%), had a higher multimorbidity (CIRS 4.6 vs 3.7), and used more medications (6.4 vs 5.3).

Usage of antidepressants (Hazard Ratio 2.0, 95% CI 1.0 – 3.9), loop diuretics (HR 2.6, 95% CI 1.4 – 4.9), verapamil/diltiazem (HR 3.5, 95% CI 1.4 – 8.9), or anticholinergics (HR 2.4, 95% CI 1.3 – 4.4) were independent risk factors for mortality. Corrected for gender and age, loop diuretics (HR 2.8, 95% CI 1.2 – 4.3), anticholinergics (HR 2.05, 95% CI 1.1 – 3.8), and verapamil/diltiazem (HR 2.7, 95% CI 1.0 – 7.1) proved risk factors for mortality in a multivariate model.

Conclusions: Medication use is a risk factor for mortality in the oldest old. Usage of loop diuretics, verapamil/diltiazem, or anticholinergics by the oldest old requires close follow-up and further analysis for comorbidities.

PHASE I, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL WITH THE PROBIOTIC NYADITUM RESAE® IN ADULTS WITH OR WITHOUT LATENT TUBERCULOSIS INFECTION
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Background or Introduction: Tuberculosis could be induced by an exaggerated inflammatory response against Mycobacterium tuberculosis (MtB) in people with Latent Tuberculosis Infection. A probiotic containing heat-killed environmental Mycobacterium marcessens (Nyaditum resae®) (NR) was developed to induce a Treg-cells-mediated tolerance process, generating cross-immunity with MtB. To evaluate its safety and immunogenicity a phase I clinical trial was conducted.

Material and Methods: A double-blind placebo-controlled, randomized trial stratified by tuberculosis skin test (TST) response was performed. Inclusion criteria: ≥ 18 years. Main exclusion criteria: active tuberculosis, immunodeficiency and pregnancy. Primary endpoints were adverse events (AE) and immunogenicity.

Volunteers received either placebo, NR low [104 Colony Forming Units (CFU)] or high [105 CFU] dose vials, orally daily during 14 days. Four control visits including physical exploration, blood analysis, and a volunteer’s log register were performed in a 6 weeks period.

Results: Of 76 volunteers screened, 51 were enrolled (18 received placebo, 16 low dose NR, and 17 high dose NR). They were mainly female (62%) with a mean (SD) age of 31.8 years (12). No loss to follow-up or discontinued intervention occurred.

A total of 322 AE were reported in 49 volunteers (96%), and 46.3% (149) considered possibly or probably related to the treatment. Most of AE were gastrointestinal (82%) and mild. None of them were severe. There were no significant statistical differences when comparing safety between groups.

A statistically significant increase on the Treg response (factor CD25+CD39+ and memory cells CD25+CD19+) was observed in those groups treated with NR, higher in TST positive volunteers and in the high dose NR group.

Conclusions: Data support that NR administration has a good safety profile, and is able to induce an immunologic response through increasing Treg cell population. Future clinical trials are needed to assess the efficacy of NR in lowering the risk of the progression from latent infection to tuberculosis.

LIVER INJURY WITH DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS (GLITPIINS): SIGNALS EMERGING FROM THE US-FDA ADVERSE EVENT REPORTING SYSTEM
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Background: The recent debate on alogliptin hepatotoxicity has aroused interest on liver injury as a class effect of dipeptidyl peptidase-4 (DPP-4) inhibitors, known as glitpiins. Considering that drug-induced
liver injury (DILI) is unpredictable and clinical trials underpowered, we analysed the largest publicly available database of spontaneous reports, the US-FDA Adverse Event Reporting System (FAERS).

**Material and Methods:** We extracted FAERS reports (up to December 2013) where DDP-4 inhibitors were recorded as suspect and performed a case/non case study by calculating the Reporting Odds Ratio (ROR) with 95% CI, as a measure of disproportionality. A list of Preferred Terms (PTs) was compiled according to the Medical Dictionary for Regulatory Activities terminology to identify the following clinical events (i.e., cases): (a) Overall Liver Injuries (OILI, including acute and chronic damage); (b) Acute Liver Failure (ALF, a subcategory including only acute severe hepatic injuries).

Non cases were all other reports without pre-specified PTs of interest. A signal was defined by statistical significant ROR (lower limit of the 95% CI > 1).

**Results:** During the study period, no signal of DILI emerged for alglaptin (no OILI cases; number of OILI cases=100; ROR = 1.73; 95% CI = 0.55-4.20) and lianglaptin (no OILI cases; OILI cases = 18; ROR = 1.20; 95% CI = 0.71-1.92). Conversely, statistically significant associations were found for OILI with the first-in-class DDP-4 inhibitor sitagliptin (234; 1.33; 1.16-1.52), and also for saxagliptin (38; 1.47; 1.03-2.03) and vildagliptin (22; 6.51; 3.92-10.35).

**Conclusions:** The heterogeneous marketing life, penetration and utilization of DDP-4 inhibitors may explain signals originated from FAERS, and justify population-based studies to assess actual clinical effect of glitamins. Notably, while the European label does not address DILI risk, the US label recommends mandatory hepatic monitoring before and during alglaptin (the latest DDP-4 inhibitors receiving US approval): this mandatory recommendation may have contributed to minimize DILI risk by excluding diabetic patients with baseline hepatic enzyme elevation.

**H1 ANTIHISTAMINES’ EFFECT ON PRO-INFLAMMATORY CYTOKINES IN ALLERGIC RHINITIS TO HOUSE DUST MITES**

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**Background:** Allergic rhinitis to house dust mites is characterized by a chronic inflammation of nasal mucosa. H1 antihistamines from second generation reduce the rhinitis’ symptoms, but may also have anti-inflammatory properties. This study aims to evaluate some pro-inflammatory cytokines in patients with allergic rhinitis to house dust mites and their evolution during treatment with H1 antihistamines.

**Material and Methods:** Fifty-eight patients with persistent allergic rhinitis to house dust mites were included in the study. They were clinically evaluated before and after 4 week-treatment with 2nd generation H1 antihistamines, Levocetirizine 5 mg/day or Desloratadine 5 mg/day. The clinical evaluation includes: symptoms scores and total symptoms score (TSS), type of sensitization. Plasmatic levels of IL-6 and TNF-α were determined before and after treatment.

**Results:** A total of 20.7% of the patients were sensitized only to house dust mite, while 79.3% were polysensitized (house dust mites and pollen). Most of the patients with moderate severe forms of allergic rhinitis were polysensitized (9.8% vs 90.2%, P = 0.003). The total symptoms score was significantly higher in patients with polisensitization (P = 0.045), Plasmatic level of TNF-α was significantly higher in patients with allergic rhinitis (1.92 vs 1.206, P = 0.003), while IL-6 was similar to healthy volunteers. Both Levocetirizine and Desloratadine improved the rhinitis’ symptoms and significantly reduced total symptoms score (8.62 ± 3.47 vs 2.18 ± 2.3, P = 0.000) after 4 weeks of treatment. Levocetirizine improves better the nasal congestion (P = 0.048) than Desloratadine. Both H1 antihistamines significantly reduced plasmatic level of IL-6 and TNF-α after 4 weeks of treatment. Levocetirizine reduced more significantly the value of IL-6 compared to Desloratadine (P = 0.03).

**Conclusions:** There were observed high plasmatic values of TNF-α in patients with persistent allergic rhinitis to house dust mites. H1 antihistamines reduce the severity of symptoms and the level of some pro-inflammatory mediator.

**TRANSPORTER CHEMOEMBOLIZATION TO THE TREATMENT OF HEPATOCELLULAR CARCINOMA – PREPARATION PROCEDURES**

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**Background:** The liver is a vital organ to our organism and an hepatocellular cancer brings several complications and problems in patient’s life quality. Nowadays, hepatocellular carcinoma is one of the most diagnosed in the world and the third cause of death related to oncologic disease. Its treatment is mostly based in cytotoxic therapeutics. One of the drugs is doxorubicin, an anthimer drug belonging to anthracyclines that acts by intercalating into DNA of tumor cells. Transarterial chemoembolization (TACE) is a method that takes advantage of arterial and hepatic vascularization, which exists near the hepatic tumors. Recently, conventional TACE has suffered some developments, using beads that transport the drug – transarterial chemoembolization with drug-eluting bead. The objective of this review was to understand the different steps of the preparation procedure of the transarterial chemoembolization with drug-eluting beads, specifically, to doxorubicin in hepatic cancer treatment, and its administration path.

**Material and Methods:** We conducted a research of articles published, in PubMed and Google Scholar, in English and Portuguese, using key words like chemoembolization, hepatocellular carcinoma, doxorubicin and TACE-DEB.

**Results:** This method uses microspheres (TACE-DEB), which are loaded with the drug in question and subsequently dropped by catheter to the tumor site. This procedure is made in aseptic conditions, with all necessary precautions due to the nature of the drug.

**Conclusions:** TACE-DEB with doxorubicin brings higher results and favorable improvements in evolution of hepatocellular carcinoma. There are many studies ongoing to discover more things about this important thematic.

**AN ACENOCOUMAROL DOSE ALGORITHM IN A ROMANIAN POPULATION**

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**Background or Introduction:** A stable therapeutic dosing of vitamin K antagonist such as acenocoumarol or warfarin is a difficult task due to a high inter- and intra-individual variability. This variability is determined by several genetic and environmental factors. Our study aimed to develop an algorithm for stable acenocoumarol therapeutic dose prediction in Romanian patients.

**Material and Methods:** We recruited 301 patients who necessitated treatment with acenocoumarol for one or two concomitant diseases: acute deep vein thrombosis, permanent atrial fibrillation or valvular prostheses. The patients were selected from those admitted within the Municipal Hospital of Cluj-Napoca and the Heart Institute.
“Niculae St ncioiu” in Cluj-Napoca, Romania, between 2009 and 2011. Clinical and demographic data that could influence the acenocoumarol stable dose were recorded for each patient. Genetic analysis included the genotyping of CYP2C9 gene and the -1693 G>A polymorphism of the VKORC1 (vitamin K epoxide reductase) gene. The patients were randomly divided into two groups: 200 patients (66.4%) formed the main group designed to develop clinical and genetic algorithms for acenocoumarol dose prediction, and 101 patients (33.6%) formed the validation group.

Results: Age and body mass index explained 18.8% (R²) of the acenocoumarol weekly dose variability in patients from the main group. When we added the genetic data to the algorithm, CYP2C9 mutations account for 4.7% of acenocoumarol dose variability and VKORC1 -1693 G>A polymorphism explained 19.6% of dose variation. In the validation group, clinical parameters explained 22.2% of the weekly acenocoumarol dose variability. Genetic variants increased the R² coefficient to 32.8%.

Conclusion: We created and validated an accurate algorithm for prediction of stable therapeutic dose of acenocoumarol.

VANCOMYCIN THERAPEUTIC DRUG MONITORING IN CLINICAL PRACTICE
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Introduction: Vancomycin has a particular importance in treatment of Gram-positive bacterial infections. Recent TDM guidelines recommend monitoring of only trough concentrations for dosage adjustment with target Cₘₜ between 15mg/l and 20mg/l in patients with invasive infections (or) where less sensitive pathogen is involved, and between 10mg/l and 15 mg/l in other infections. This study evaluated the practice of vancomycin TDM in University Hospital in Olomouc and the influence of new recommendations on dosing strategies.

Patients and Methods: A retrospective analysis of vancomycin plasma levels determined in patients treated with i.v. vancomycin was performed. Values with uncertain sample timing and haemodialysed patients were excluded. Each trough value was compared with the value of MIC of the pathogen involved. Consecutively, pharmacokinetic modelling using MWPharm 3.3 software was performed for every patient to assess individual PK/PD indices.

Results: A total of 250 vancomycin concentrations were included, which represented 143 events of monitoring performed in 74 patients. Vancomycin was mostly used for suspected or proven sepsis (44% of all patients). Pathogens with MIC >1 mg/l were responsible for 24% of all infections. Clinical pharmacologist trained in TDM was consulted in 23.8% of all events. According to the new guidelines, 44% patients were underdosed, and 34% overdosed. PK simulations showed suboptimal concentrations in 34% and too high concentrations in 34% of the patients.

Conclusion: Dosage adjustments based only upon pre-dose concentrations may increase the risk of toxicity or therapeutic failure, especially if the value is not interpreted with regard to the timing of the sampling.

Disclosure of Interest: None declared.
Introduction: Hypertension (HTN) developing during antiangiogenic (AAg) treatment in cancer patients (pts) is a well-recognised “class-effect” whose prevalence has recently been re-evaluated according to new guidelines from international Societies of Hypertension and Cardiology. Its management and outcome implications have not been yet completely investigated.

Materials and Methods: Between March 2012 and January 2015, 41 consecutive AAG-treated pts were evaluated. Clinical and instrumental follow-up was performed according to the ESH/ESC guidelines, from 1 week before starting AAG to 4 weeks after its withdrawal.

All pts underwent Home, Ambulatory and Office blood pressure measurements (HBPM, ABPM, OBPM, respectively), echocardiography and complete laboratory examination.

Results: Median age was 67 yrs (mean = 66.6, range = 49-84yrs) and male/female = 27/14. Five pts, with disease progression after one AAG, received a second AAG. The AAG employed were: bevacizumab (N = 18), sorafenib (N = 11), sunitinib (N = 10), axitinib (N = 3), pazopanib (N = 2), and regorafenib (N = 2). Before starting AAG 33 out of 41 pts had a history of HTN (in 3 of them it was diagnosed ex novo at basal evaluation; in 7 it was uncontrolled thus requiring an adjustment of anti-hypertensive therapy). AAG-related HTN (BP >140/90 mm Hg) was observed in 21 (61.8%) out of 34 evaluable pts (7 not evaluable). Among pts receiving AAG as second line, all the 4 evaluable developed AAG-HTN. AAG-HTN was treated according to the current guidelines and, considering both first and second line of AAG, 1, 2, 3, ≥4 antihypertensive drugs were employed in 3, 11, 6, 5 pts respectively.

Discussion: Despite the small number of evaluated pts, our data seem to confirm that prevalence of AAG-HTN is higher than previously reported, probably due to different criteria used to define HTN in AAG regenerative studies. Moreover, as AAG-HTN presents peculiar features compared to HTN in general population, a careful evaluation before starting AAG is essential and a tailored management should be considered.

MISmatches IN MedICines RECONCiliation IN ACUte medICal IN-patienTS AT THE ChUK TERTIARY REfERRAL HOSPITAL IN rwanda

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Background: Accurate medicines reconciliation is important for continuity of medical care and for recognizing Adverse Drug Reactions (ADRs) as a contribution to hospital admission. We assessed medicines reconciliation in the Internal Medicine Department by comparing recorded information about medications and allergy on admission with results of direct questioning of patients or carers.

Methods: Data were audited prospectively for Internal Medicine inpatients during a continuous 8 day period in October 2014, as part of quality improvement for patient safety in relation to medicines. Patients were asked to provide indications, names, and doses for their treatment(s) on admission, including over the counter products (OTC) and traditional medicines, and to report allergies.

Results: Results were obtained for 44 patients (19 female; mean age 45, range 19-88 years). There were 14 patients concordant for no drug history in the notes and on direct questioning (5 female; age 51 ± 6 (SE) years). Ten (23%) of these patients had important pre-admission drugs not recorded in case notes (3 female; age 46 ± 6 years). For 24 patients recorded as being on no treatment, 10 on review were found to have been on pre-admission treatment – one each for cloxacinil, amoxicillin, clarithromycin, arteether and lumezantrine, paracetamol and captopril and 4 on unknown treatments. Notes also recorded 20 patients (11 female; mean age 41 ± 4 years) as on pre-admission treatment. One 46 year old male did not recall pre-admission treatment with aspirin. Recording of medicines reconciliation by a combined pharmacy and internal medicine team identified that prior treatments were not identified on admission to hospital in 1 in 4 patients assessed. Absence of prior treatment in the notes appears a strong cue for the medicines history to be revisited.
PHARMACOECONOMICS BIOSIMILARS IN ONCOLOGY
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Background: Population growth, long life spans, an increased morbidity cause an increased incidence of cancer diseases. Bio-similar drugs come to the market after the patent protection of biological drugs expires. In general, they reduce the price of the original drugs by 20%. Prior to a practical use they require clinical studies that demonstrate the quality, safety and efficacy biosimilar to that of the original. The price of development and production is 10 times higher than the price of generics.

Material and Methods: For the treatment and prophylaxis of febrile neutropenia the original drugs are used; such as pegfilgrastim and filgrastim and filgrastim biosimilars. The study compared the cost-effectiveness of 5 EU countries of filgrastim, pegfilgrastim and bio-similar filgrastim in different modes with cost efficiency in the Slovak Republic with a differentiating pricing policy of drugs over the years 2011–2013.

Results: The prophylaxis and therapy of febrile neutropenia with biosimilar filgrastim is cost-effective when related to filgrastim and pegfilgrastim. Both the international and internal analysis puts the biosimilar filgrastim to a position of a cost-effective treatment even in with the absence of evidence provided by a pharmacological and therapeutic priority.

Conclusions: The administration of an adequate treatment using pegfilgrastim and biosimilar filgrastim is a cost difference of 289 Euros in the Slovak Republic. Savings during the administration of the biosimilar drug for years: 2011 is 3703 thousand Euro thus, 70% of expenditure, in 2012 it was 4079 thousand. 68%. In 2013 it is 3847 thousand Euro, which is 60% of the cost for treating febrile neutropenia. Biosimilar drugs are the solution for oncologists as how increased focus on ADR reporting may reduce preventable morbidity cause an increased incidence of cancer diseases.

Drug-illness interactions were observed in 3: lower GI bleed in a 57M with proximal DVT, metastatic colon cancer, and HIV/AIDS, on warfarin for 8 months; acute gouty arthritis, hyperkalemia, and severe chronic haloperidol use for treating psychosis (52M); lip swelling and pruritus after 1st dose of nifedipine for hypertension (51M); recurrent hypoglycaemia on metformin and glibenclamide (58F); and generalized rash and pruritus on first dose carvedilol and losartan (51M), resolving during continued treatment with the drugs.

Conclusions: We were effective in improving ADR reporting by many departments at this major centre and in identifying an important contribution of ADRs to serious morbidity at CHUB, including unrecognized use of traditional medicine as a cause of hospital admissions and delayed detection of serious medical conditions.

PATTERNS OF SUSPECTED ADVERSE DRUG REACTIONS AMONG IN-PATIENTS AT KING FAISAL REFERRAL HOSPITAL, RWANDA
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Background: Pharmacovigilance is important for patient safety however adverse drug reactions (ADRs) are under-reported in Sub-Saharan Africa.

Aims: We aimed to encourage ADR reporting and to assess ADR patterns at our major referral hospital.

Methods: We used WHO and Ministry of Health ADR reporting protocols, including causality reviews, to identify suspected harmful responses to one or more medicines, prescribed, OTC or traditional, known or new.

Results: We audited ADRs prospectively over four weeks in October 2014. We identified ADRs in 9 in-patients (age 25–62 years, median 43.5 years; 4 females) from Internal Medicine, Surgery and ICU. A single drug-associated ADR was seen in five: chlorpromazine-hypertension, colchicine-vomiting, clocaxillin-bromochasmp, amphotericin B-severe hypomagnesemia; hypokalemia and indapamide causing severe hypokalemia. Implicated drugs were stopped (and replaced if necessary), and symptomatic treatment was provided.

Drug-illness interactions were observed in 3: lower GI bleed in a 57M with proximal DVT, metastatic colon cancer, and HIV/AIDS, on warfarin for 8 months; acute gouty arthritis, hyperkalemia, and severe acute on chronic kidney injury in a 51M with dilated cardiomypathy and cardio-renal syndrome, on furosemide, hydrochlorothiazide, carvedilol, losartan and spironolactone; renal failure (normal sized kidneys) after 2 weeks high dose diaclofenac postoperatively in an ANA +ve SLE. Drug-drug interactions were suspected in 3: 57M – flunoxazol interacting with new HAART (atavanan/ritonavir/ abacavir) to cause acute liver failure; furosemide and hydrochlorothiazide-associated hyperuricemia in 51M; elevated liver transaminases in 41F on flunoxazol and anti-TB therapy (rifampinc, isoniazid, pyrazinamide, ethambutol).

Conclusions: We raised awareness of ADR reporting at our centre. Key patterns for suspected ADRs included drug-drug interactions and drug-illness synergistic adverse effects. We aim next to assess impact of ADRs on morbidity, length of hospital stay, and associated costs, and how increased focus on ADR reporting may reduce preventable morbidity and costs.

PHARMACOVIGILANCE IN KYRGYZSTAN: THE CURRENT SITUATION
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Introduction: Well-known that the medicines safety issues has been required increasing attention worldwide. For Kyrgyz pharmacovigilance has been established since 2002 only. Well organized pharmacovigilance system is the base for rational and safely use of medicines and more over is the base for optimization of health facility’s operation. Objective of this work is to evaluation of frequency and severity of adverse drug reactions (ADRs) and highlighting the importance of medicines safety issues in health system.

Methods: Spontaneous reporting method and retrospective analysis of medical cards of hospital patients have been used. Statistical analysis has been done by MS Excel 2010.

Results: A total of 11,630 medical cards of patients in 10 hospitals of country were analyzed; only 5 cases of ADR were registered, that is the proof of apparent lack of doctor’s activities on that direction. From our view it is due to the low awareness of majority medical professionals on the need to informing about ADR (91%). Also, another reason of low registration of ADRs is the limited knowledge on recognition the events associated with use of medicines (72%). It must be noted that the active implementation of pharmacovigilance has been initiated since 2013. Out of total 666 reports have been received from the period of 2002 to 2014, 30% have been received in 2013-2014. The main parts of ADRs were due to use of antibiotics (37%), anti-TB drugs (10.5%), vaccines (10.3%). 40.4% of reports has been initiated since 2013. Out of total 666 reports have been received from the period of 2002 to 2014, 30% have been received in 2013-2014. The main parts of ADRs were due to use of antibiotics (37%), anti-TB drugs (10.5%), vaccines (10.3%). 40.4% of reports due to use of injection medicines.

Conclusion: The current situation of pharmacovigilance is not fully effective, so by nowadays there is no reliable statistical data on ADRs. The situation on pharmacovigilance has been improving since 2013 as a result of organizational and educational activities held, that is proving there is a need of further more focused and regular activities at all levels of health care system.

EARLY USE OF ULINASTATIN REDUCES MULTIORGAN DYSFUNCTION (MODS) IN SEPTIC SHOCK FOLLOWING ANASTOMOTIC FAILURE

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Introduction: Anastomotic failure is a serious complication after major abdominal surgery resulting in septic shock and death. Early intervention can reduce the adverse outcomes in septic shock. Ulinastatin is a potentially effective intervention to attenuate the systemic inflammatory response induced by sepsis.

The aim of the present study was to compare the effects of early (<48 hours) versus late (>48 hours) use of Ulinastatin on the outcome of septic shock following anastomotic failure after major abdominal surgery.

Methods: One hundred four patients developing anastomotic failure after major abdominal surgery in two multispeciality hospitals in India between October 2012 and May 2014 were included in the study. The patients receiving Ulinastatin within 48 hours of the onset of septic shock (Group A; n = 37) were compared against those receiving Ulinastatin after 48 hours of the onset of septic shock (Group B; n = 31) and control (Group C; n = 36). The primary outcome was mortality at 28 days. The secondary outcomes were duration of mechanical ventilation, length of ICU stay, use of vasopressors and occurrence of MODS according to the SOFA (sequential organ failure assessment) score. Intention to treat (ITT) analysis was performed. Comparisons between groups of categorical data were performed using the two-tailed Fisher’s exact test and comparisons between groups of continuous data were performed using the Mann-Whitney U test. The data were analyzed using SPSS Version 15 for Windows (SPSS Inc., Chicago, IL, USA).

Results: Demographics and illness severity were similar between the groups. The 28 day mortality was similar in all the groups (37.2% vs. 37.8% vs. 40.5%), as were ICU length of stay (8.7 days vs. 8.9 days vs. 10.2 days) and duration of mechanical ventilation (4.2 days vs. 4.0 days vs. 4.9 days). More patients in the late Ulinastatin and control groups developed MODS (52.9% vs. 44.5% vs. 24.7%, P < 0.001) than early Ulinastatin group. There was also overall reduction in the total vasopressors usage in both early and late Ulinastatin groups over control group (54.3 % vs. 56.7% vs. 79.8%; P < 0.001). There were no increases in the overall side-effects between the groups.

Conclusion: Our study found that early use of Ulinastatin (<48 hours) reduces the occurrence of MODS in patients with septic shock following anastomotic failure.

TOWARDS A MORE EFFICIENT AND EFFECTIVE USE OF PSYCHOTROPIC DRUGS IN NURSING HOMES: A QUALITY IMPROVEMENT PROJECT IN BELGIUM

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Introduction: ‘Working towards a more efficient and effective use of psychotropic drugs’ was a quality improvement project, funded by the Belgian government. The goal was to reduce the high psychotropic drug use through education and sensitization of all actors.

Methods: This was a pilot project (2013-2014) with a pre-post design in two residential care centers. The intervention group received an educational trilogy given by experts on psychotropic drugs, as well as one-on-one professional support. The control group received education-only without professional support afterwards. Drug use was recorded and coded according to the Anatomical Therapeutic Chemical classification. Included psychotropics were antipsychotics, antidepressants and benzodiazepines. Measurements were done at 3 time-points: at baseline (pre), after 10 months (post) and after 1 year (follow-up).

Results: Residents’ (n = 119) had a mean age of 82 years, of which 71% were female. The mean drug use was 9 (range 1-21). Most commonly used drugs were central nervous system drugs (88%). At baseline (intervention group), the prevalence of psychotropic use was 72.3% (range 1-6). There was a significant reduction (<0.001) after the intervention, with a remaining prevalence of 60.5%. The overall mean drug use decreased to 8 (range 0-20). The comparison of pre versus post-measurements (intervention group) showed a strong decrease for benzodiazepines: 50% vs. 38%, followed by antidepressants 42% vs. 36%. The decrease of antipsychotics was less strong: 21% vs. 17%. In the control group (with education-only), there was a modest reduction of the psychotropic drug use: benzodiazepines 58% vs. 53%, antidepressants 44% vs. 41%, and antipsychotics 30% vs. 28%.

Conclusion: This improvement project led to a significant decrease in the use of psychotropic drugs, even after 1 year follow-up. Education only had a very limited effect. The person-centered approach offered by the project staff was of a great value.
ASSESSMENT OF COMORBIDITIES IN PATIENTS WITH SYMPTOMATIC KNEE OSTEOARTHRITIS IN SPAIN: THE EMARTRO STUDY

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Introduction: The primary outcome of the study is to assess the prevalence of comorbidities in symptomatic knee osteoarthritis (KOA) patients. Additionally, potential differentiating factors between KOA and non-osteoarthritic subjects will be assessed to detect a possible prognosis effect complementary to osteoarthritis.

Here we present the protocol of the study that is being conducted at the moment.

Material and Methods: It’s an observational, epidemiologic, multicenter, transversal study comparing comorbidities between subjects with and without KOA. The recruitment will be carried out by 65 investigators from different Spanish’s healthcare centers. 1150 subjects will be enrolled distributed in two groups: 575 KOA subjects selected and 575 sex and age-matched control subjects, without neither knee pain nor osteoarthritis. The results will be analyzed using descriptive statistics.

Results: This study will provide new information about comorbidities in osteoarthritis which has become the leading cause of disability in the elderly and permanent disability caused by a rheumatic disease (RD) and one of the most frequent reasons for consultation. In other studies, it has been observed that the prevalence of comorbidities was significantly higher in osteoarthritis patients than controls (P < 0.0001) being hypertension, diabetes mellitus, chronic obstructive pulmonary disease, stroke and myocardial infarction the most prevalent osteoarthritic comorbidities.

The ongoing study is in the follow-up period.

Conclusions: Osteoarthritis is the most common RD, affecting 28% of those over 60 years, enduring pain, functional disability, decreased quality of life and causing significant social and economic burden. However, an important proportion of the economical costs of osteoarthritis compared to non-osteoarthritic population is due to an excessive use of sanitary resources which includes not only pharmacological treatment but also image and laboratory tests, management of treatment adverse reactions or rehabilitation and surgical interventions. The knowledge of comorbidities and concomitant medications in KOA patients will provide useful information to manage the disease more effectively and reduce its social and economic burden.

VALPROIC ACID AND CARBAPENEMS INTERACTION: CLINICAL OUTCOMES

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Background or Introduction: One of the setbacks of the valproic acid (VPA) is the potential for pharmacological interactions. Although the decrease in the VPA serum concentrations in patients receiving carbapenems is well known, the available data are focused on pharmacokinetic studies rather than clinical implications.

Objective: to evaluate the clinical outcome due to interaction between VPA and carbapenems.

Material and Methods: An observational, retrospective and unicentric study was performed. Patients whose VPA plasma levels were closely monitored by our department and that had been simultaneously treated with a carbapenem from 2011 to 2014 were included. Demographic variables, VPA plasma levels, changes in prescription, electroencephalogram (EEG), and seizures were analyzed.

Results: Of 66 patients with VPA plasma levels closely monitored, 9 (14%) had an interaction with a carbapenem. Of these nine, 56% (5) were female, with a median age of 47 years, range 18-76.

All of the patients were hospitalized in the intensive care unit and received meropenem concomitantly to VPA. After the introduction of meropenem, the mean decrease of the VPA plasmatic levels was 29.3 mg/L, range from 5 to 48 mg/L. In four patients (44.4%) the meropenem was stopped, in three (33.3%) was switched to another antibiotic and in 2 (22.2%) was continued. All the patients required an increase of the VPA dosage. In three patients (33.3%) the drug interaction had clinical consequences (in one patient the VPA level dropped 40 mg/L causing a seizure, and in the other two their EEGs showed seizure activity without clinical convulsions, probably due to general sedation).

Conclusions: A third of the patients treated concomitantly with VPA and meropenem had clinical implications such as seizures (one patient) and EEGs with seizure activity (two patients). Simultaneous administration of both drugs should be avoided when possible. If not, VPA plasmatic levels should be closely monitored.

DRUG INDUCED PATHOLOGICAL GAMBLING

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Introduction: Pathological gambling is a severe impulse control disorder. It has been associated with dopaminergic drugs prescribed to treat Parkinson’s disease (PD). In recent years, it also has been reported cases with aripiprazole. We aimed to describe the main characteristics of spontaneous reports about pathological gambling received by the Spanish Pharmacovigilance System (SPvS).

Material and Methods: Spontaneous reports of PG received by the SPvS from 1983 to 2014 were selected. The variables analyzed were age and sex of the patients, suspect drugs and therapeutic indication, spontaneous reports of PG received by the SPvS from 1983 to 2014 were selected. The variables analyzed were age and sex of the patients, suspect drugs and therapeutic indication, concomitant adverse drug reactions (ADRs), severity and outcome, latency period, rechallenge, underlying conditions and alternative causes.

Results: Until December 2014 the SPvS database had gathered 203,582 spontaneous reports of ADRs, 15 of them described pathological gambling. All cases were male with a median age of 60 years (46 to 84 years). The total number of suspect drugs was 24; all of them were dopaminergic agents, mainly dopamine agonists (15). The drug most frequently reported was pramipexole (10 cases) followed by andropirone (3). All patients were treated of PD, The latency period ranged from 1 month to 3 years. Besides pathological gambling, in three cases other ADRs were described; suicidal ideation (1 case), hypersexuality, dopamine dysregulation syndrome and drug abuse (1) and alcoholism (1). Thirteen reports were serious (86.6%); 6 patients improved after withdrawal of the suspect drug. Only one patient had history of previous gambling. Alternative explanations were excluded in 9 cases; there were no cases with a positive rechallenge.
Conclusions: Drug-induced pathological gambling is a serious adverse reaction. Affected patients were treated for PD. Dopaminergic agents appear to be the only drugs involved, mainly pramipexole. Prescribing physicians should warn patients and their families in order to allow for early diagnosis of this condition, which would allow early intervention and thus avoid possible medical and social complications.

BRAND-NAME TO GENERIC SUBSTITUTION OF ANTIEPILEPTIC DRUGS (AED) DOES NOT LEAD TO SEIZURE-RELATED HOSPITALIZATION: A POPULATION-BASED CASE-CROSSOVER STUDY

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Introduction: There are still controversies over pill substitution among AEDs. We aimed at further estimating the association between generic substitution and loss of seizure control.

Patients and Methods: We used data from the French National Health Insurance Information System linked with the French Hospital Discharge Database. We identified a cohort of adult patients who filled a prescription in 2009–2011 for AEDs that had at least one brand-name and one generic form available on the French market. Patients with a medical history of cancer and women who gave birth in 2009–2011 were excluded. We designed a case-crossover study; three months were used for the case- and the control-periods. The outcome date was defined as the date of first occurrence of hospitalization for seizure, code G40.x or G41.x, pending being G40/G41 hospitalization-free period in the preceding year. We required individuals to have regular dispensations of AEDs within the year preceding the outcome date. Free patients were defined as patients who had only brand-name dispensations before the control period. B-G substitution was defined as a filled prescription for a generic AED that was preceded by a filled prescription for a brand-name counterpart. ORs and 95% CIs were estimated using conditional logistic regression model.

Results: A total of 8,384 patients (mean age ± SD, 52.7 ± 18.8 years; sex ratio male/female, 1.27) were analyzed. Discordant pairs were 491 with B-G substitution in the control period only and 478 with B-G substitution in the case period only; OR (95% CI) 0.97 (0.86–1.10). No statistically significant interaction was detected among four pre-specified subgroup analyses (gender, age strata, free or non-free patients and strict AED monotherapy or not). Controlling for non-seizure-related hospitalizations made no material difference. Sensitivity analyses yielded similar results.

Conclusion: B-G AED substitution was not associated with an elevated risk of seizure-related hospitalization.

THE MAPK-ACTIVATED PROTEIN KINASE 2 (MK2) INHIBITOR CMPD1 IS A NOVEL MICROTUBULE TARGETING AGENT FOR GliOBLASTOMA THERAPY

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Introduction: Glioblastoma is among the most lethal and least successfully treated solid tumours. A suitable agent for brain tumour treatment must cross the blood-brain barrier and lack neurotoxicity.

MAPK-activated protein kinase 2 (MK2) is a cell cycle checkpoint kinase involved in DNA damage response. MK2 inhibitors enhance efficacy of conventional chemotherapeutic agents, but their effectiveness as a single agent has not been investigated.

Material and Methods: The anti-cancer effectiveness of an MK2a substrate-selective p38 inhibitor CMPD1 (Boehringer-Ingelheim; Davidson et al., Biochemistry 2004; 43(37):11638-71) was determined in a panel of glioblastoma cell lines and normal cells (primary human microglia, astrocytes and neurons) using cell viability, Annexin-V staining and cell cycle analysis. Immunofluorescence and tubulin polymerization assays were conducted to study the effect of CMPD1 on microtubules.

Results: The MK2 inhibitor CMPD1 demonstrated single agent anti-cancer efficacy with a submicro-molar IC50 in glioblastoma cells yet exhibited minimal toxicity on normal cells. Treatment of U87 cells with CMPD1 resulted in G2/M arrest and accumulation of a poly-(>4)n population. Moreover, CMPD1 induced apoptosis and affected the expression of anti-apoptotic proteins in glioblastoma cells. However, these observations were less evident in primary astrocytes. Interestingly, while reported to be MK2a substrate-selective p38 inhibitor, CMPD1 did not inhibit MK2 or its downstream target Hsp27 at doses that are cytotoxic in U87 cells. siRNA knockdown of MK2 did not alter the IC50 of CMPD1 suggesting that MK2 is not involved in cell death. Instead, we identified CMPD1 as a tubulin depolymerizing agent causing microtubule disruption in glioblastoma cells. Furthermore, we discovered that CMPD1 reduces the expression of tubulin in U87 cells and inhibited the self-renewal capacity of glioblastoma cells.

Conclusions: Collectively, we have discovered a novel microtubule targeting drug candidate with selective toxicity for glioblastoma therapy. We are currently developing analogues with enhanced blood-brain barrier permeable properties.

ADVERSE EVENTS ASSOCIATED WITH ANTI-TNF THERAPY IN INFLAMMATORY BOWEL DISEASE COHORT GROUP IN A CROATIAN TERTIARY CENTRE

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Introduction: Biological therapy has significantly improved the treatment of patients with inflammatory bowel disease (IBD). Anti-Tumor Necrosis Factor (anti-TNF) agents infliximab (IFX) and adalimumab (ADA) are biologics most commonly used for the treatment of IBD, but with a burden of possible severe adverse events (AEs). Our objective was to present the evaluation of safety data on anti-TNF therapy in the cohort of IBD patients in our centre.

Methods: We included patients treated with anti-TNF therapy at the Department of Gastroenterology and Hepatology of Clinical Hospital Centre Osijek from 2005 to 2013. Data were collected from patient’s medical records and presented according to the Common Terminology Criteria for AEs. Patients with incomplete medical records were excluded.

Results: We included 60 patients treated for Crohn’s disease and 22 for ulcerative colitis. Of those, 37 patients were on IFX, 25 patients on ADA, while 20 patients were treated with both medications during different intervals. Median follow-up of an individual patient was 36.5 months (range 1-99). At least one AE was reported for 27 patients (47.4%) on IFX and 16 patients (35.6%) on ADA. The overall number of observed AEs was 67, of which 63 (94.03%) were mild to moderate, and 4 (5.97%) were severe. The most common
**Background:** Patients with cancer have a high inherent risk of infectious complications. In addition, the incidence of acute and chronic kidney dysfunction rises in this population. Infections need immediate treatment; during the further course, kidney function must be taken into account. Anti-infective drugs often require dosing modifications based on an estimate of kidney function, usually the glomerular filtration rate (GFR). However, there is still no preferential GFR formula to be used, and in acute kidney injury there is always a considerable time delay between true kidney function and estimated GFR.

**Conclusion:** To avoid the risk of either too low or too infrequent peak concentrations, we prefer the eliminated fraction rule for dose adjustment calculations. When in doubt, the peak should be the target.

**PHARMACOKINETICS, PHARMACODYNAMICS, AND ANTIMICROBIALS IN CANCER PATIENTS WITH KIDNEY DYSFUNCTION**

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**Background:** Patients with cancer have a high inherent risk of infectious complications. In addition, the incidence of acute and chronic

kidney dysfunction rises in this population. Infections need immediate treatment; during the further course, kidney function must be taken into account. Anti-infective drugs often require dosing modifications based on an estimate of kidney function, usually the glomerular filtration rate (GFR). However, there is still no preferential GFR formula to be used, and in acute kidney injury there is always a considerable time delay between true kidney function and estimated GFR.

**Conclusion:** To avoid the risk of either too low or too infrequent peak concentrations, we prefer the eliminated fraction rule for dose adjustment calculations. When in doubt, the peak should be the target.

**DISTINGUISHING DRUG-INDUCED AUTOIMMUNE HEPATITIS FROM IDIOPATHIC AUTOIMMUNE HEPATITIS AND DILI WITH AUTOANTIBODIES**

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**Aim:** Drug-induced liver injury (DILI) may be associated with an autoimmune phenotype (DILI-AIH). We aimed to characterize phenotypes, outcomes and culprit drugs in idiopathic autoimmune hepatitis (AIH), DI-AIH and DILI with/without autoantibodies (AAB) in a large cohort of DILI patients.

**Methods:** Demographic variables in 21 of 1013 (2.1%) patients from the Spanish-Latin DILI Registries diagnosed with DI-AIH (detectable ANA/ASMA titres and high gammaglobulin levels) were compared to 51 idiopathic AIH patients and 129 (12.7%) DILI AAB+ and 371 AAB−.
Clinical Therapeutics

Results: DILI-AIH and AIH patients had similar age and gender distribution, 38% males (mean 58 y) in the DILI-AIH cohort. The DILI AAB+ were older (mean 53 years vs 49, \( P = 0.025 \)) and female predominated (37% vs 52%, \( P = 0.306 \)) than DILI AAB-. Among drugs triggering DILI-AIH and concomitant drugs in AHB patients statins (19% vs 12%), NSAIDs (10% vs 12%) and antibiotics (24% vs 2%) featured more frequently. Statins were also more frequent in DILI-AIH than in AHB (4.6% vs 3.6%). Compared to AIH, DILI-AIH patients were more frequently jaundiced (62% vs 31%) and had higher AST (23 × ULN vs 11 × ULN, \( P = 0.001 \)) and ALT values (27 × ULN vs 14 × ULN, \( P = 0.001 \)) at presentation. DILI AAB+ and DILI-AIH did not differ. DILI-AIH patients required less often immunosuppressant treatment than the AHB group (81% vs 93%), but more frequently than DILI AAB+ (81% vs 24%, \( P = 0.00 \)). DILI with autoimmune features responded better to treatment (100% vs 92% AHB).

Conclusions: DILI-AIH and DILI AAB+ typically affects older females and less often necessitates steroid therapy than AHB cases despite exhibiting a more severe phenotype at onset. Statins are likely to unmask DILI-AIH and DILI AAB+ and could be the unidentified trigger in cases of “idiopathic” AIH suggesting a continuum across the spectrum of drug-induced autoimmune liver disease.

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INDIVIDUAL VARIABILITY IN THE PHARMACOKINETIC OF TEA POLYPHENOLS AND GENE EXPRESSION AFTER ORAL INTAKE OF GREEN TEA EXTRAKT

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Background: Green tea from the plant Camellia Sinensis is one of the most widely consumed beverages in the world. Furthermore, dry extract of green tea is recently marketed as nutritional supplement. Epidemiological studies on green tea show a reduction of the cancer risk and a protective effect on the cardio-vascular system. These effects seem to be governed particularly by green tea polyphenols, with epigallocatechin-3-gallat (EGCG) as the main compound.

We investigate the influence of individual genetic predisposition on the pharmacokinetic of EGCG in order to gain information on the individual consequences of green tea consumption.

Material and Methods: We carried out a clinical trial with 100 healthy participants taking green tea extract capsules (300mg EGCG/d) for 5 days. The study protocol was approved by the Ethical Committee of the University of Ulm; participating patients gave oral and written consent. We determined the plasma concentration of EGCG and other common green tea polyphenols on the last day of study. Further, genome-wide expression profiles from participants before and after green tea extract treatment were analyzed.

Results: We determined an individual variability in the pharmacokinetics of the measured green tea polyphenols and the gene expression after intake of green tea extract capsules. Several genes related to oxidative stress and immunomodulation were significant regulated within the study population after intake of green tea extract capsules. Here, we will present our recent results and discuss the individual consequences of the consumption of green tea extract.

POSITIONING THE NEW ORAL ANTICOAGULANTS FOR PREVENTION OF STROKE IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

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Introduction: Non-valvular atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, being the cause of considerable morbidity (i.e. stroke) and mortality. Vitamin K antagonists (VKA) have been the back-bone of oral anticoagulation for decades in the prevention of stroke in patients with moderate to high risk of stroke. In the last few years, a new group of drugs, called new oral anticoagulants (NOACs) have been introduced; acting directly on thrombin ( dabigatran) or factor X ( rivaroxaban, apixaban, edoxaban). In comparative clinical trials of NOAC and AVK apparent advantages have been described with non-inferiority designs, like fixed-dose administration, a wide therapeutic window and the lack of requirement for regular monitoring. However, there is a need to assess their relative benefit/risk ratio in real clinical practice conditions in order to be able to position them in therapeutics.

Objective: To review all published clinical trials of NOACs in non-valvular AF assessing their internal and external validity and to update all the relevant literature related to their efficacy and safety in real clinical practice conditions.

Materials and Methods: An up-to-date review and analysis of the most relevant clinical data in patients with non-valvu lar AF treated with VKAs and NOACs.

Results
• Results of comparative head-to-head trials with NOAC show a trend towards dependence on the time that patients on the arm of VKA are in the therapeutic range.
• The risks of bleeding for NOACs are greater in clinical practice than those observed in published clinical trials.
• Treatment with NOAC (to start with or to switch on) should be carefully assessed in a case by case basis.

Conclusions: In patients with non-valvular AF at moderate/high risk of stroke, with good compliance and good INR, VKA must be considered as the treatment of choice.

A TWIN STUDY OF THE TROUGH PLASMA STEADY STATE CONCENTRATION OF METFORMIN

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Background: Metformin is a glucose-lowering drug, which is used in the treatment of type 2 diabetes. During the last decade the pharmacogenetics of both the pharmacokinetics and –dynamics of metformin has been extensively investigated. Due to conflicting results no consensus has been reached regarding the impact of pharmacogenetics. Thus, the aim of this study was to determine the heritability of the trough concentration of metformin at steady state in twins.

Material and Methods: We included 16 twin pairs (8 mono- and 8 dizygotic twin pairs) for this study, after contacting 524 twin pairs. They were dosed with metformin to steady state (1 g twice daily) for 6 days and on day 7 the trough concentration of metformin was determined 12 hours after the last dose.

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Results: The correlation of age and weight was higher in monozygotic twin pairs than in dizygotic twin pairs. However, the correlation of the trough concentration in the monoyzygotic twin pairs was equal to that of the dizygotic twin pairs.

Conclusions: This indicates that the trough concentration of metformin is not regulated to a major extent by genetic factors.


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Introduction: Fifty years have passed since the 18th WMA Assembly adopted the original version of the Declaration of Helsinki (DoH). Since then it has been amended seven times (in the years 1973, 1983, 1989, 1996, 2000, 2008 and 2013). In the 2000 version, two notes of clarification were added (in the years 2002 and 2004), due to hot debate and lack of consensus.

Material and Methods: We have compared the different versions of the DoH, searching for the main changes introduced in the different topics in each of the new versions in relation to the previous ones, aiming at describing the main ethical discussions of that time.

Our objective has been to draw a historical perspective of the most prevalent ethical dilemmas in relation to clinical research within the scientific and bioethical community over time.

Results: Main changes in each version which reflect the most debated topics per year were:

1st (1975):
- Primacy of the individual over society
- Independence of Research Ethics Committees (RECs).
- No major changes
4th (1996):
- Ethical universalism vs ethical pluralism
- Use of placebo.
- Post trial access of studied drugs
6th (2008):
- Clinical Trials registry in a publicly accessible database
- Source of funding and conflicts of interest
7th (2013):
- Continuous monitoring of the risks by the researcher
- Qualification of REC members
- Use of placebo
- Post-trial provisions (access of studied drugs).

Conclusions: The most prevalent topics in the ethical debate have been: General concepts in the early 70s & 80s, use of placebo and post-trial provisions since early 90s onwards, and the issue of transparency and qualification of RECs in the late 2000s.

MEDICAL RECONCILIATION: DOES THE SERVICE MATTER?
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Background: The drug treatments conciliation is an interactive process which guarantees the continuity of care by integrating in a new global prescription all the chronic treatments of a patient. This process minimizes prescription’s gap at critical points of transition (admission, service transfer, end of hospitalization). The interest to secure medical care don’t have to be proved anymore, but does it have the same impact according to the department? What are the feedbacks about the implementation in an oncology department?

Material and Methods: The experience is made on one month, all the drug conciliations have been treated retroactively (72 h) about all entrants in a 30 beds oncology department. An exhaustive treatments list is establish (by crossing different sources like family, regular doctors, pharmacy, report..) and compared to the admission’s prescriptions, differences obtained are highlighted and characterized.

Following, this study conclusion is compared with existing literature and results obtained by other way (other department, entry mode of patients).

Results: Results of conciliation in an conventional hospitalization service versus emergencies downstream or surgery department in literature

- On average 0.6 differences by patients (forgotten medication) versus 1.7 [0.5-3.3] (comparative board)
- More than 80% of the entrants in our department are already known
  - Hospitalizations in the last 6 months (37%)
  - Consultations and followed in day hospital (47%)
- 16% come via emergency for a first support.

Conclusion: Oncological patient regularly followed for chronic disease in day consultations at hospital get their chronic treatments frequently reassessed, and multiple hospitalizations have solved their acute problems. The patients’ profile is significantly different from those from emergency downstream departments who are followed by different actors. This explains the number of discrepancies less important observed in relation to the literature. However this number is not nil and encourages us to pursue our approach.

OFF-LABEL USES OF LOW-DOSE RITUXUMAB: A SYSTEMATIC REVIEW OF THE LITERATURE
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Background: Rituximab is frequently used in off-label indications.

Recently, there has been reported that its use in low-dosage might also be effective in approved indications such as rheumatoid arthritis. Therefore, our objective was to review the efficacy of low-dose courses of rituximab in off-label indications.

Material and Methods: A search of Pubmed database together with a reference screening was performed from January 1999 to December 2014 in order to identify all the studies that examined the effectiveness of low-dose rituximab in off-label indications.

Results: Among 245 publications identified, 51 (n = 1049) fulfilled the eligibility criteria (4 clinical trials, 10 prospective cohorts, 9 retrospective cohorts, 15 case-series and 13 case reports). Rituximab was used in 30 off-label diseases, being kidney transplant (n = 646), immune thrombocytopenia (PTI, n = 146), pemphigus (PnP, n = 45) and autoimmune haemolytic anaemia (AIHA, n = 43) the main indications. Most frequently used dosages were 500mg twice given 1-2 weeks apart for musculoskeletal system, nervous system and skin diseases, 100mg weekly for 4 weeks in hematological diseases and a single dose of rituximab 200mg (range 35-500mg) in KT. The overall response OR observed was 80.5% with a 67.9% of complete responses CR. Among the most frequent diseases, the OR and CR were 100% and 66.6% in PnP, 97.7% and 65.1% in AIHA, 82.2% and 81.3% for KT and 70.5% and 50% in PTI, respectively. The relapse rate and follow-up -median in months- were described
INHIBITORY EFFECTS OF POMEGRANATE CONCENTRATED SOLUTION ON THE ACTIVITIES OF HYALURONIDASE, TYROSINASE, AND METALLOPROTEINASE 1

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Background: Botanical antioxidants have attracted much attention as useful preventatives of skin damage. Pomegranate is consumed throughout the world for its beneficial health effects, including its anti-oxidant and anti-inflammatory activities.

Objectives: We investigated whether pomegranate concentrated solution (PCS) could serve as a potential functional cosmetic ingredient that exerts a skin-whitening effect and anti-wrinkle activity.

Methods: To investigate the moisturizing effect of PCS, hyaluronidase activity was examined in human keratinocytes (HaCaT). Elastase and pro-collagenase activities were assessed in normal human primary dermal fibroblast-neonatal (HDF-N) cells to determine their anti-wrinkle effects. Metalloproteinase 1 (MMP-1) activity was also assessed following UVA irradiation. Whitening effects were measured by a tyrosinase inhibition assay and melanin formation test in murine melanocytes (Melan-A). In addition, histopathological analysis was performed to determine the number of microfolds formed on the epithelial surface, mean epithelial thickness, mean number of inflammatory cells infiltrating the dermis, and collagen fiber-occupied regions within the dermis.

Results: Hyaluronan synthesis was significantly increased by PCS in HaCaT cells, while pro-collagenase and elastase activities were decreased in HDF-N cells. A significant decrease in UVA-induced MMP-1 activity was also observed in PCS-treated HDF-N cells, compared with UVA-exposed cells. PCS effectively reduced melanin production and mushroom tyrosinase activity in Melan-a cells. Moreover, UBV-induced histopathological dermal sclerosis and inflammatory signs were significantly attenuated in PCS-administered mice compared with UBV-exposed mice.

Conclusions: Our results suggest that PCS prevents signs of aging, including those related to photo-aging. These effects are associated with enhanced hyaluronan synthesis, as well as suppressed elastase, collagenase, MMP-1, and tyrosinase activities and melanin production. UVB-induced photo-aging, such as histopathological dermal sclerosis and inflammatory signs, were effectively reduced upon the addition of PCS. These results also suggest that skin aging can be prevented and reduced by the antioxidant effects of PCS.

Key words: pomegranate concentration solution, hyaluronan, melanin, tyrosinase, photo-aging.
1 the Danish nationwide registers. The most common drugs leading to
2 hospital admission will be identified and nationwide estimated rates of
3 hospitalization will be calculated, adjusted for regional confounders.
4 The study has been approved by the Danish Data Protection
5 Agency (Id BBH-2015-005).
6 Conclusions: The present study will yield an updated estimate of the
7 rate of ADRs leading to hospital admissions and valuable information
8 on high risk drugs and high risk patient characteristics. Furthermore,
9 it will identify the frequency of ADRs leading to hospitalization in a
10 post-marketing setting.

IS DEVOLUTION OF PRESCRIPTIONS
CONTRIBUTING TO COMMUNITY PHARMACIES’ FINANCIAL CRISIS?
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Introduction: Portuguese community pharmacies were already
affected by the global economic crisis. Pharmacies have experienced
successive legislative amendments, including: the implementation
of International Non-Proprietary Name (INN) prescription, the
introduction of the National Code for the Electronic Prescription
of Medicines (NCEPM) and the use of technical justifications by
physicians. Devolution of prescriptions containing errors, by the
Conference Center of Bills (CCB), represents an additional obstacle
to the financial management of pharmacies. The aim of the study
was to evaluate the economic impact caused by the devolution
of prescriptions to pharmacies and to assess how the referred measures
affected the drug dispensing process.

Methodology: A longitudinal descriptive-correlational study was
performed, based on a self-administered questionnaire delivered to
each of the fifty pharmacies of Coimbra municipality. Software: SPSS
20.0®. Statistical tests: Friedman, Spearman’s Rho, Wilcoxon and
Mann-Whitney U (significance level = 0.05).

Results: The response rate was 58%. In September, the maximum
value not paid to pharmacies was €1,202.37. Statistically signifi-
cant differences detected between the months analyzed showed a
bigger impact of devolutions in September (maximum = 4.36%),
mainly due to technical justifications, but also to implementation of
NCEPM. In March, there was a reduction of the value not paid by
CCB (maximum = €603.09). After correction and resend of returned
prescriptions, maximum impact was 0.8%. Patient’s health was not
affected by the errors.

Conclusions: INN prescription contributed to the reduction of
returned prescriptions. Due to recent implementation, NCEPM
contributed to increase devolutions. Technical justifications created
difficulties in drugs dispensing process and actively contributed to
increase the number of returned prescriptions. Values not paid by
CCB have a significant impact on financial management of pharma-
cies. However, pharmacies can recover the majority of this value,
after correction and resend of prescriptions. Electronic prescribing
could be an effective measure, regarding the reduction of this impact.

MEDICATION ERRORS IN COMMUNITY
PHARMACY: POTENTIAL CAUSES AND
STRATEGIES FOR PREVENTION
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Introduction: Medication errors are serious safety concerns that have
existed for as long as medications have been available to patients.
They are a widespread problem, a major cause of adverse drug events
and one of the most preventable causes of patient injury. The aim of this
study was to investigate pharmacy professionals’ perception and
opinions about potential causes of dispensing errors and the strategies
to prevent them in community pharmacies.

Material and Methods: Through a cross-sectional and descriptive-
correlational study, a survey was handed to all pharmacists and phar-
mcy technicians working in one of the 49 community pharmacies
of a central Portuguese region.

Results: The response rate was 90.9%. “Prescription” category
assembled the largest number of causes of medication errors (26%). “Drugs” category was second with 23% of causes of
errors. “Handwriting prescriptions” appear as the most frequent
single cause of medication errors (51.5%). Besides this “source of
errors”, the most frequent cause was “Patient in a hurry” (47.3%);
“Outdated prescriptions” (46.4%) and “Drugs with similar pack-
ages” (45.6%). “Prescription” category assembled the largest number of preventive methods (34%). “Professional” category was second
with 28%. The single prevention methods that generated the high-
est percentage of agreement were “Check of dubious prescriptions”
and “Confirmation of the respective drugs through the barcodes”
(97%). Besides these two preventive factors, “Constant updating and
searching for knowledge” (96.5%), “Increased communication with
the medical class” (95.9%) and “Electronic prescribing” (95.3%) yielded the highest agreement rate.

Conclusions: Community pharmacy professionals identified some
sources of medication errors, as well as some strategies to prevent them. Pharmacists and pharmacy technicians are key players in
reducing the number of medication errors and in the consequent
increase of patients’ safety. An appropriate educational intervention
based on the findings of this study could improve the risk perception
among pharmacy professionals.

AUTOANTIBODY PRESENTATION IN
DRUG-INDUCED LIVER INJURY (DILI) AND
IDIOPATHIC AUTOIMMUNE HEPATITIS (AIH): THE INFLUENCE OF HLA ALLELES
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Background: Positive autoantibody (AAB) titres are seen in a propor-
tion of DILI patients, resembling AIH. The underlying mechanism for
selective AAB occurrence in DILI is unknown, but could be associated
with variations in immune-associated genes. Hence, we aimed to
analyse HLA allele compositions in DILI with positive (AAB+) and
negative (AAB-) AAB titres and AIH patients.

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Material and Methods: High resolution genotyping of HLA class I (A, B, C) and II (DRB1, DQB1) loci were performed on 178 DILI patients (drug-induced autoimmune hepatitis excluded) and 51 AIH patients and compared to 883 Spanish healthy controls.

Results: Fifty-one of the 178 DILI patients presented positive titres for at least one AAB (ANA 76%, ASMA 26%, AMA 8% or LKM-1 3%) during the DILI episode, while 127 were negative for all four AABs. Compared to controls, HLA alleles B*08:01 (43% vs 10%, p=4.4E-14/p<0.0001), C*07:01 (47% vs 24%, p=3.0E-04/p<0.006), DRB1*03:01 (59% vs 26%, p=3.8E-07/p<0.0005) and DQB1*02:01 (57% vs 22%, p=3.2E-06/p<0.0007) were significantly more frequent in AIH patients. The frequency of HLA-A*01:01 was increased in the same population, but did not reach significance after Bonferroni’s correction (33% vs 19%, p=0.02/p=0.37). There was a tendency for higher representation of DRB1*14:01 and DQB1*05:03 in DILI AAB+ compared to DILI AAB- (16% vs 4%, p=0.01/p<0.02; 16% vs 5%, p=0.02/p<0.03) and controls (16%vs5%, p=0.002/p<0.05; 16% vs 5%, p=0.004/p<0.06). No significant differences in HLA allele frequencies were found when stratifying the AAB+ and AAB- populations into hepatocellular and cholestatic/mixed type of liver injury.

Conclusions: The presence of HLA alleles B*08:01, C*07:01, DRB1*03:01 and DQB1*02:01 and possibly A*01:01 appear to enhance the risk of AIH in Caucasians with Spanish inheritance. These alleles form part of the conserved extended haplotype 8.1. However, haplotype formations in the study cohort are currently unknown. HLA alleles DRB1*14:01 and DQB1*05:03 could potentially increase the risk of positive AAB (particularly ANA) in Spanish DILI patients.

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UNWITTING INDUCEMENT TO PARTICIPATE IN CLINICAL TRIALS

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Introduction: Informed consent process is the means to guarantee that the respect for persons (autonomy) is preserved when humans are involved in research. Subjects must be given fair the information they need to decide to enter a study or not. There should neither be pressure to participate nor undue inducement. The aim of this study (approved by the Research Ethics Committee) was to demonstrate that some kind of unwitting inducement cannot be avoided. Our hypothesis is that the relationship between the participant and the person who delivers the study information (usually the participant’s doctor) can unconsciously influence the subjects’ decision.

Material and Methods: Subjects (healthy volunteers) attending an information meeting about a clinical trial with drugs were randomized (1:1) in two different lecture rooms: one (control group) receiving the trial information from a speaker who knew the study and the other (test group) would agree to enter the study, 77 wouldn’t and 2 didn’t answer; 72 subjects stated that they knew the speaker before the session, 83 didn’t. From the test group, 42 subjects would accept but only 22 knew the speaker. From the control group, 34 subjects would accept and 50 knew the speaker.

Conclusion: No differences were found between groups for the main endpoint. The study failed to demonstrate an unwitting inducement: the eminent scientist wasn’t really known by the study subjects.

ATTENUATION OF HYALURONAN FRAGMENT INDUCED INFLAMMATORY RESPONSE IN MACROPHAGES BY CHONDROITIN SULPHATE

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Background: Hyaluronan (HA) fragments (≤500 kDa) are known to be able to induce an inflammatory response from macrophages. We have previously shown that chondroitin sulphate (CS) can attenuate the monosodium urate crystal mediated release of inflammatory cytokines from activated macrophages in culture.

Materials and Methods: Mature macrophages were primed with 10 ng/mL of LPS for 24 hours with CS in various physiologically relevant concentrations (0, 10-200 µg/mL). After 24 hours, cells were incubated for 24 hours more with the previously mentioned concentrations of CS and with various molecular weights (sizes) (from 7.5 kDa to 1.54 × 10⁶ kDa) and concentrations (0, 1, 10, and 100 µg/mL) of HA fragments. IL-1β and proIL-1β were analysed by ELISA. Caspase-1 activity was determined by fluorometric assay. One-way ANOVA with Dunnett’s post-hoc test and post-hoc linear trend were performed using Graphpad Prism software.

Results: As expected, HA fragments produced large increases (P < 0.0001) in IL-1β release at 10 and 100 µg/mL, with a decreasing gradient effect (P < 0.0001) seen from ULMW to MMW and no effect seen for HMW HA. CS (100-200 µg/mL) produced a dose dependent reduction in IL-1β release in cells treated with 10 µg/mL of the 3 HA lower MW fragment types. While ULMW HA fragments induced a significant increase (P < 0.0001) in intracellular caspase-1 activity, CS had no effect on this activity. CS reduced intracellular IL-1β and proIL-1β in cells treated with ULMW HA, however, the ratio between the 2 was unchanged.

Conclusions: HA fragments (≤289 kDa) induced an inflammatory response in TFP-1 macrophages which could be attenuated by CS. An anti-inflammatory effect at the level of the inflammasome would be expected to decrease intracellular caspase-1 activity thereby decreasing the ratio of IL-1β to proIL-1β. Since we did not observe this, it can be concluded that the anti-inflammatory effect of CS is upstream of the inflammasome.

MITOCHONDRIA: A NEW CHONDROITIN SULPHATE THERAPEUTIC TARGET FOR OSTEOARTHRITIS

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Background: In a recent proteomic study, we have demonstrated that mitochondrial dysregulation occurs in cartilage cells during osteoarthritis (OA). In this study we have investigated the mitochondrial activity of OA human articular chondrocytes treated with chondroitin sulphate (CS).

Materials and Methods: OA human chondrocytes were treated with CS (Biofércia, Spain) with or without IL-1β 5 ng/mL, TNFα 10 ng/mL and LPS 100 µg/mL. SPSS statistical software was used to determine statistical significance by using U-Mann Whitney test (P ≤ 0.05).
Results: At basal condition, a 64% increase in chondrocytes $\Delta \psi_m$ was observed after 48 hours treatment with CS 200 µg/mL. A significant depolarization was induced with TNFa ($\Delta \psi_m$ decreased up to 41% and 39% respectively). CS was also able to increase chondrocytes $\Delta \psi_m$ up to 66%, partially counteracting the effect of TNFa. CS significantly increased ATP production compared to basal condition (0.53 µM vs 0.65 µM). After TNFa stimulation, ATP production fell to 0.40 µM; but also in this case, CS was able to inhibit TNFa effect increasing the ATP synthesis up to 0.62 µM. CS was able to reduce NO synthesis induced by IL1β, TNFa or LPS. The NO levels were reduced after cytokine stimulation up to 21%, 32% and 31% respectively. On the other hand, in presence of IL1β, ROS production and SOD2 activity were increased. In this case, intracellular ROS production as well as SOD activity decreased in CS treated chondrocytes at an average of 80%.

Conclusions: CS improves mitochondrial activity in human OA chondrocytes by affecting several mitochondrial processes. The mitochondrial membrane hyperpolarization and the increased ATP production could correlate with a greater resistance of CS treated chondrocytes to apoptosis. Moreover, the reduction of NO and ROS levels, as well as the reduction in SOD2 activity, provide evidence of the effect of CS on oxidative stress regulation.

SEXUAL DYSFUNCTION ASSOCIATED WITH DAILY OPIOID USE

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Introduction: Sexual dysfunction (SD) is highly prevalent associated to long-term treatment with opioids in chronic non-cancer pain (CNP). Furthermore, many patients do not report their symptoms, thus causing this adverse effect to go unnoticed and without clinical monitoring. The purpose of this study was to investigate the occurrence of male and female sexual dysfunction in our population.

Material and Methods: A cross-sectional pilot study was carried out in moderate-severe CNP patients (n = 223, 143 women, 90 men) treated with long-term opioids (>12 months) in our Pain Unit, along 2 years. Standardized questionnaires and medical record reviews were used to assess rates of pain diagnosis, opioid adverse effects (ADRs) including sexual function by Female Sexual Function Index (FSFI) and International Index of Erectile Function (IIEF) questionnaires and drug use.

Results: A prevalence of 4% of SD was found in CNP patients. In total, 143 females were included (mean age 58 ± 12.3 years, VAS 6.2 ± 2.7, 65% married), 43% were sexually active, 81% of who reported FSD (IFSF total 15 ± 5 scores), resulting in 19% who were sexually active without impairment (IFSF total 21 ± 8 scores). In 90 males (mean age 56 ± 10.6 years, VAS 5.7 ± 1 ± 23 married 76%), IIEF scores were divided in two groups: (I) normal or mild ED>16 scores (34.17 ± 11.67); (ii) moderate or severe: IIEF <16 scores (6.32 ± 3.67), resulting in 20% who were sexually active without impairment. Drug use was: 20% analgesic, 41% tramadole, 74% opioids and 70% some adjuvants.

Conclusions: Sexual functioning is a problem in CNP. Evidence-based interventions to support sexual activity and function in women and men with CNP are needed.

COMBINED CHONDROITIN SULFATE AND GLUCOSAMINE IS MORE EFFICIENT THAN CELEBREX IN REDUCING SERUM LEVELS OF COLL2-1, A CARTILAGE DEGRADATION BIOMARKER, IN PATIENTS WITH SEVERE OA: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, MULTICENTRIC CLINICAL TRIAL

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Background: Coll2-1 is a peptide located in the triple helical part of type II collagen and Coll2-1NO2 is the nitrated form. Fib3-2 (fragment of fibulin-3) is an extracellular glycoprotein highly expressed in osteoarthritic cartilage. The levels of these biomarkers have been found to be elevated in serum of osteoarthritic patients and to vary with severity. The objective of the study was to investigate soluble osteoarthitis (OA) biomarkers in the patients of the double-blind Multicentre Osteoarthritis interVEntion trial with CelebreX in reducing serum levels of Coll2-1, particularly in a subgroup of patients with severe OA. This data indicates that CS+GH may down-regulate cartilage catabolism.
and are in accordance with the symptomatic benefits observed in clinical trials.

**CILOSTAZOL IN PERIPHERAL ARTERY DISEASE: CARdiovascular and BLEeding EVENTS IN REAL-USE CONDITIONS**

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**Background:** On 2013, the European Medicines Agency’s Committee on Medicinal Products for Human Use (CHMP) recommended that the use of cilostazol should be restricted. The Spanish Agency for Medicines and Health Products (AEMPS) asked the CHMP to carry out a review following reports of serious suspected side effects such as coronary heart disease (CHD), arrhythmias and haemorrhages.

**Objectives:** To estimate the risk for ischemic events, arrhythmias and haemorrhages in patients with peripheral artery disease treated with cilostazol vs pentoxifylline.

**Material and Methods:**

**Design:** Retrospective observational cohort study.

**Population:** ≥40 years-old individuals initiating cilostazol or pentoxifylline for peripheral artery disease between 01/04/2009-30/09/2011, not previously treated. End of follow-up: 31/12/2013.

**Data Sources:** SIDIAP database; contains anonymized clinical information from electronic clinical records in Primary Care of 5.8 million people from Catalonia on sociodemographic data, comorbidities, medical procedures, clinical parameters, laboratory data and pharmacy invoicing data. Diagnoses of CHD events, arrhythmias and haemorrhages were linked from hospital discharge database.

**Statistical Analysis:** Two cohorts (cilostazol and pentoxifylline) were matched 1:1 using propensity-score methods to ensure comparability among groups and then followed-up from treatment initiation until event, end of follow-up or death. Survival analysis was performed and cumulative incidence rates of events were obtained for each cohort. Cox proportional-hazards regression models were performed to estimate hazard ratios and 95% confidence intervals (HR; 95% CI).

**Results:** We included 2,953 patients per cohort. They were 68.9 years-old, 76.1% were men. Median follow-up were 1217 days. Preliminary analysis showed no statistically significant differences in the cumulative incidence rates between cohorts: 10.5% vs 11.0% CHD events with cilostazol and pentoxifylline respectively (HR=0.97; 95% CI: 0.83–1.13), 7.1% vs 8.1% arrhythmias (HR=0.88; 95% CI: 0.73–1.06), and 0.7% cerebral haemorrhages in both cohorts (HR=1.1; 95% CI: 0.63–2.15) and 3.6% vs 3.4% digestive haemorrhages (HR=1.07; 95% CI: 0.81–1.40).

**Conclusions:** We found no differences between our cilostazol and pentoxifylline patients in CHD, arrhythmias and bleeding events.

**COMBINED CHONDROITIN SULFATE AND GLUCOSAMINE VERSUS CELECOXIB FOR PAINFUL KNEE OSTEOARTHRITIS: POST-HOC ANALYSES BY KELLGREN AND LAWRENCE GRADE AND C-REA CTIVE PROTEIN LEVEL FROM A RANDOMIZED, DOUBLE-BLIND, MULTICENTRE CLINICAL TRIAL**

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**Background:** The Multicentre Osteoarthritis interVention trial with Sysadoa (MOVES) was a phase 4, noninferiority, double-blind study comparing the efficacy and safety of chondroitin sulfate (CS) plus glucosamine hydrochloride (GH) with that of celecoxib (CE) in 606 patients with knee osteoarthritis (OA) and severe knee pain. Patients were randomized to receive 400 mg of CS plus 500 mg of GHtid or 200 mg of CEqqd. Both treatments elicited a 50% reduction in WOMAC pain (primary outcome) at 6 months, without differences between them.

**Material and Methods:** To further analyze the results obtained according to different patient subsets, we sought to compare, as a post-hoc analysis, the efficacy of CS+GH with that of CE in reducing severe pain (WOMAC pain >30) according to Kellgren-Lawrence (KL) grade (2 or 3) and C-reactive protein (CRP) levels (≤3 vs >3 mg/L) in the MOVES study population, to determine whether they presented different treatment responses.

**Results:** In patients with CRP >3 mg/mL, there were no statistically significant differences between CS + GH (n = 85) and CE (n = 81) on WOMAC pain reduction at all time points, after 1, 2, 4 and 6 months (Table 1). Equally, there were no statistically significant differences between CS + GH (n = 99) and CE (n = 86) in patients with KL grade 3 at all time points (Table 2). Consumption of rescue medication was the same in both treatment groups for KL grade 3 and CRP >3 mg/L (P = ns for all between-group comparisons). An analysis for the values of interaction of treatment by group was made for these subsets. There was differences statistically significant in the interaction of treatment by CRP groups (P = 0.038) but not in treatment by KL group (P = 0.581). As results of the analysis KL is presented as descriptive rather than confirmatory results.

**Conclusions:** This post-hoc analyses indicate that CS + GH has equivalent efficacy to CE in reducing pain after 1 month in patients with painful knee OA and KL grade 3 or with CRP >3 mg/L. These data from a double-blind, randomized trial demonstrate that there are no statistically significant differences between a SYSADOA and a COX-2i in patients with Kellgren-Lawrence grade 3 knee osteoarthritis and patients with CRP >3 mg/L, as early as 1 month and throughout all the study period, as measured by WOMAC pain subscale.
HEPATOTOXICITY RELATED TO HERBAL AND DIETARY SUPPLEMENTS (HDS): A CAUSE FOR CONCERN

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Background: Widespread use of HDS, their weak regulatory framework and unawareness of health risks, particularly liver injury, are main causes for the growing health problem related to HDS hepatotoxicity. We aim to evaluate incidence and clinical phenotype associated with HDS-DILI.

Results: Sixty-eight DILI cases of 1025 (7%) included were attributed to herbal and dietary supplements, 26 (38%) by anabolic steroid (AAS) and 42 (62%) by herbal products and other dietary supplements (HDS). Women (57%) were more frequent among HDS-DILI cases, while AAS-DILI patients were all males. The mean age of HDS-DILI was significantly higher than that of AAS-DILI cases (47 vs 33y) (P < 0.001), but lower than those caused by conventional drugs (47 vs 56y) (P = 0.004). Jaundice and hospitalization were higher in AAS cases (92%/76%) than HDS (78%/53%) and conventional drugs (68%/57%), respectively. Although hepatocellular damage predominated in all groups, HDS had more hepatocellular cases than conventional medications and AAS-DILI (86% vs 62% and 58%). The HDS cases presented higher ALT and AST mean values (33 and 27xULN) compared to AAS (13 and 6xULN) (P = 0.004, P < 0.001) and conventional medications (19 and 18xULN) (P < 0.001, P = 0.2) respectively, but lower total bilirubin values than AAS cases (9 vs 14xULN) (P = 0.021). HDS-DILI patients went more frequently into acute liver failure (ALF) than DILI patients associated with conventional drugs (7.3% vs 4%). No AAS cases developed ALF.

Conclusions: In comparison to conventional drugs, HDS-DILI affects mainly to young women, presenting with hepatocellular injury, higher transaminase values, worst outcome leading to ALF and inadvertent re-exposure. Greater awareness and stricter regulation are required to prevent HDS-related severe adverse effects to the liver.

Funding: AEMPS,FISS-PI12-00620;AC-0073-2013.CIBERehd-ISCIII.
Introduction: DKP.TRIS 25 mg single dose, TRAM.HCl 100 mg concomitantly administered in healthy subjects. The study investigated any effect on the pharmacokinetics (PK) of DKP.TRIS and TRAM.HCl when concomitantly administered in healthy subjects. Plasma samples collected up to 48 hours post-dose were analyzed for each enantiomer of ketoprofen, tramadol and its O-demethyl metabolite (M1) using chiral HPLC methods. The PK properties of each analyte were compared when DKP.TRIS and TRAM.HCl were not administered as single agents and in combination. Results: Mean Cmax [ng/mL] and AUC [ng*h/mL] of analytes for the combination treatment were respectively: (+)TRAM: 177.7, 1213.6; (+)M1: 22.0, 250.3; and DKP: 2816.5, 3935.7. The 90% CIs of geometric mean ratio of AUC and Cmax of all the analytes were within the accepted bioequivalence range (80.00-125.00%), when DKP.TRIS and TRAM.HCl were given alone or in combination. Other relevant PK parameters (tmax, Vz/F, CL/F, t1/2 and MRT) were not affected by the co-administration.

Conclusions: This study indicated the absence of any drug-drug interaction between DKP.TRIS 25 mg and TRAM.HCl 100 mg concomitantly administered in healthy subjects.

PHARMACOVIGILANCE IN A HOSPITAL PAIN RELIEF UNIT

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Introduction: It is known that prolonged use of opioids chronic non-cancer related pain (NCP) can lead to a number of adverse reactions, normally associated with gastrointestinal tract, central nervous system or dermatological effects. The aim of this study was to document the types and severity of adverse drug reactions of chronic opioid therapy.

Methods: A total of 650 patients NCP chronically treated with opioids (1350 outpatient visits) were evaluated using validated pain intensity and relief scales (Visual Analog Scale, VAS: 0-10 cm), quality of life (EQ-VAS, 0-100%), presence of adverse events (AE reported in form model to be filled by patients) and adverse drug reactions (ADR reported by physicians) and drug use, along 24 months. Results: Our sample (mean age 63 ± 14 years old, 67%, 27 ± 6 kg/m²) shows a moderate mean pain intensity (VAS 6 cm), pain relief (VAS 4 cm) and quality of life (EQ-VAS 43%). A mean of 4-5 AEs were reported by each patient visit (a total of 6719 AEs, most common were: 12% dry mouth, 10% constipation, 9% nervousness, 7% sleepiness, 6% depression, 6% insomnia, 6% dry skin and 5% sexual dysfunctions), being reported to Spanish Pharmacovigilance System 140 ADRs (most common: 47% related to central nervous system, 15% dermatological and 13% gastrointestinal). All were predominantly mild side effects.

Conclusions: In our study, a higher prevalence of CNS ADRs was found, being gastrointestinal system ADRs significantly lower than in previous researches. Control of adverse effects is needed to conduct a proper drug prescription plan, even more, for long-term management of chronic non-malignant pain.
INDEPENDENT CLINICAL RESEARCH. WHAT MAY CONTRIBUTE TO SUCCESS? THE EXPERIENCE AT THE CLINICAL RESEARCH UNIT OF HOSPITAL RAMÓN Y CAJAL

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The Clinical Research Unit at Hospital Ramón y Cajal (included in SCReN since 2014) has supported 48 Clinical Trials (phase I to IV) and 4 Observational Studies with independent sponsors between 2010 and 2015. Of these 52 studies, 43 got public funding and only 9 were supported by industry. About recruitment:

- 11 of these trials were completed in compliance with the planned recruitment:
  - 7 were sponsored by the Ramón y Cajal Hospital Foundation (FIBio-HRC) and 4 by researchers.
  - 9 were single-center trials and 2 multi-center trials.
  - Overall, these trials resulted in 3 theses, 6 international publications and 14 conference communications.
- 11 were closed without reaching the planned recruitment:
  - 5 sponsored by different Foundations and 6 by researchers.
  - 7 were multi-center trials and 4 single-center trials.
- 19 ongoing trials:
  - 11 sponsored by Foundations (10 of them sponsored by the FIBio-HRC)
  - 9 are single-center and 10 are multi-center trials.
  - Currently 9 of this 19 trials have reached 60% of the planned recruitment and 6 of them have not needed to extend the planned recruitment timing.
- 4 were transferred to CROs in recruitment phase.
- 7 failed to initiate the recruitment phase.

Conclusions: These data show that for independent clinical research, the most successful trials were those sponsored and developed in the own center (single-center) which generate relevant scientific publications. Public-funding supported staff is a positive factor for this success. However, recruitment is a caveat for these studies since many of them were closed for lack of recruitment (21.5%) or failed to initiate (13%) probably due to a wrong version. This overview highlights the importance to develop good feasibility studies and to get funding ensuring both, material and human resources, for the study success.

NEW ANTIVIRAL TREATMENT FOR CHRONIC HEPATITIS C (HCV): LEARNING FROM EXPERIENCE, THE ROLE OF THE PHARMACIST IN IMPROVING ADHERENCE

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Background: Treatment of chronic HCV is undergoing a revolution. Several direct acting antivirals (DAAs) have reached the market (boceprevir, telaprevir and sofosbuvir) and many others are in development.

Poor adherence is a major medical problem which leads to failure of therapy and increased healthcare cost.

The course of treatment with first generation protease inhibitors (boceprevir, telaprevir) has been monitored in order to adopt the best multidisciplinary approach in the management of sofosbuvir and other costly second generation DAAs.

Material and Methods: Between 2013 and 2014, overall 31 patients (27 with cirrhosis and 4 with advanced fibrosis) at the Hospital underwent triple therapies with either boceprevir or telaprevir in combination with peg-interferon (PEG) and ribavirin (RBV). Medical prescriptions were analysed using an administrative database and the Italian Medicines Agency (AIFA) Monitoring Registry.

Results: The data showed that 52% of patients treated with first generation protease inhibitors did not achieve sustained virological response (SVR) due to side effects or treatment failure. Therefore, a procedural guideline between Pharmacists and Hepatologists has been endorsed to assure safe dispensing and monitoring of these new costly agents. “Patient Information Leaflets” have been developed as a monitoring tool for patients in therapy with sofosbuvir in association with PEG and RBV. When sofosbuvir is dispensed at the Hospital Pharmacy counter, a leaflet is given to each patient monthly containing main information about the drug (administration, conservation, drug interactions, special warnings and side effects) and a compliance diary where the patient must fill in daily when medication is taken.

Conclusions: Pharmacist expertise can contribute to properly assess and respond to patients’ medication needs, thereby contributing to inter-professional management of patient care to achieve better therapy adherence and clinical outcomes.

USE OF PSYCHOTROPIC DRUGS IN OLDER PATIENTS: PREVALENCE AND CHARACTERISTICS OF PATIENTS

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2015
Background: Psychotropic drugs are frequently prescribed to older patients. This study aimed to describe their prevalence of use and to compare the characteristics of patients treated with different psychotropic drugs.

Material and Methods: From a prospective and multicentric study of a cohort of patients aged 75 or older admitted to seven Spanish hospitals for a year (March 2011 to March 2012), a sub-analysis of those treated with psychotropic drugs (antipsychotics, anxiolytics or hypnotics-sedatives and antidepressants) was performed. Information on patients’ characteristics and on prescribing medicines the month before admission was obtained from the hospital and the primary care electronic medical records and from interviews with the patients and/or relatives.

Results: A total of 672 patients [median age (Q1-Q3): 82 (79-86) years, 55.9% female] were included. 44.2% of them were treated with anxiolytics or hypnotics-sedatives, 22.6% with antidepressants and 10.8% with antipsychotics. A total of 12.4% were treated with a combination of anxiolytics or hypnotics-sedatives and antidepressants. The most frequently prescribed psychotropic medicines were: anxiolytics (lorazepam [17.4%] and potassium clorazepate [7.2%]), antidepressants (citalopram [6.6%] and paroxetine [3.3%]) and antipsychotics (haloperidol [4.7%], risperidone [3.4%] and quetiapine [2.3%]). Patients treated with some kind of psychotropic drug were more frequently women, especially those treated with antidepressants. In addition, those treated with antipsychotics were older, and less often visited by a GP but were more often admitted to hospital the month prior to admission. Both, those treated with antipsychotics and those treated with antidepressants more often lived in and were discharged to nursing home facilities. Furthermore, those treated with antipsychotics more often died during admission.

Conclusions: The prevalence of psychotropic medicines prescription was high in the elderly, especially the prescription of anxiolytics or hypnotics-sedatives and antidepressants. Women were more frequently prescribed than men, especially for antidepressants, and patients treated with antipsychotics had worse outcomes.

OSTEOARTHRITIS, DRUG USE AND RISK OF CARDIAC ISCHAEMIC EVENTS: A CASE-CONTROL STUDY

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Background: Recent controversies on the safety profile of drugs used to treat osteoarthritis (OA) have led to changes in clinical guidance for management (1). The objective of the study was to describe associations between the use of different OA drug therapies and the risk of cardiac ischemic events (CIE).

Material and Methods: We conducted a nested case-control study within a cohort of patients with clinically diagnosed OA (according to ICD10 codes in the SIDIAP database of primary care records for over 5 million people in Catalonia, Spain (2)). Study was approved by the corresponding Ethic’s Committee. Cases were identified in the period 2008-2012 through ICD10 codes of cardiac ischemic events (CIE) (AIM or unstable angina, fatal or not) and cross-checked with hospital discharge diagnosis; 3 controls without CIE were matched to each case by sex, age (±5 years), area and year (±2 years) of first diagnosis of OA. Data were linked with pharmacy invoicing information, encrypted and extracted for analysis. Exposure to NSAIDs, SYSADOAs, opioids, paracetamol and metamizole were analysed. Adjusted multivariate conditional logistic regression models were fitted to estimate odds ratio (OR) for CIE according to drug use.

Results: We studied 5663 cases and 16989 matched controls. Cases had more morbidity and cardiovascular risk factors, but similar characteristics for OA and joint involvement. Significantly increased risks (OR 95%CI) were observed related to the use of non-selective NSAIDs (1.10(95%CI 1.01 to 1.19)), in particular for diclofenac (1.16(1.07 to 1.25) and naproxen (1.14(1.01 to 1.29), and for opioid analgesics (1.13(1.04 to 1.24). SYSADOAs, paracetamol and metamizole showed no significant associations with CIE.

Conclusions: In patients with OA, non-selective NSAIDs (diclofenac, naproxen) and opioid analgesics are associated to an increased risk of CV events. This should be considered for the management of OA patients with a high cardiovascular risk profile.

References

METABOLIC RISK FACTORS AFFECT CLINICAL PHENOTYPE AND OUTCOME OF HEPATOTOXICITY (DILI)

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Background: It has been suggested that metabolic risk factors may play a role in drug-induced liver injury (DILI) presentation. Hence,
the aim of this study was to determine the influence of diabetes and dyslipidemia on the clinical profile of DILI.

Material and Methods: Clinical profiles of 864 DILI cases included in the Spanish DILI Registry were compared according to the presence or absence of diabetes and dyslipidemia. Patients with hepatic underlying diseases were excluded.

Results: Comparing patients with (n = 121) and without (n = 743) dyslipidemia, the mean age was significantly higher in the former group, 64 vs 52 years (P < 0.001); 38% of the patients with dyslipidemia were treated with statins. Duration of treatment of DILI causative agents and latency did not differ between the groups. Patients with dyslipidemia had significantly better outcomes (severe and fatal cases: 3% vs 13%, P = 0.009). In the dyslipidemia group, 30% of the patients had persisting liver damage after one year from DILI onset, compared to 22% in the non-dyslipidemia group. Comparing diabetic (n = 103) with non-diabetic (n = 737) DILI patients, higher mean age (66 vs 52, P < 0.001), higher mean BMI value (28 vs 25, P < 0.001) longer duration of treatment (158 vs 78 days, P = 0.001) and latency (140 vs 71 days, P = 0.002) were found in the former group. No differences in severity were observed. Among the diabetics, 28% had persisting liver damage >1 year from DILI onset versus 22% of the non-diabetics.

Conclusions: Dyslipidemia appears to play a protective role in DILI severity, although persistent liver damage >1 year from DILI onset is more frequent in patients with metabolic risk factors (diabetes and dyslipidemia). Diabetic patients presented longer treatment and latency prior to DILI development.

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ASSESSMENT OF THE ACQUIRED KNOWLEDGE DURING THE MEDICAL RESIDENCY OF CLINICAL PHARMACOLOGY

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Introduction: The medical residency is an important training to become a competent specialist. Few efforts are focused on the acquisition of new knowledge and capacities as well as the evaluation of learning results. Clinical Pharmacology’s residents in our service have training on general medicine during the first year, before starting the specific specialist period.

Material and Methods: A test with 65 binary questions was designed to assess knowledge about patient’s selection drug (10 items), pharmacovigilance (15 items), drug monitoring (10), phase I clinical trial (15), and clinical trials or Ethic Committee (15). The residents answered the test before starting the residency (basal), and then annually during residency (totally 5 times). For comparison of means we used the T test for independent data.

Results: From 2008 to 2014, eight residents performed a total of 20 tests. Only two of them have carried out all the 5 tests, the rest of them have previously started the residency (2-3 test performed) or dropped out within the second year (1 test performed). The mean global score was 36.8 (range 16-54). The mean scores of each test were: basal 26, first year 28.7, second year 38, third year 46, and fourth year (specialist) 48. Individual score evolution though residency period showed a progressive improvement (increase from basal range from 12 to 33 when all tests were performed). Statistically significant differences of means were observed when comparing before starting the specific specialty training (basal and first year tests) with the third and/or fourth years tests.

Conclusions: This test is a useful tool to assess individually the acquired knowledge during the training period of specialty. However, its external validation has not yet assessed. A test to certify a level of knowledge acquired during training on Clinical Pharmacology validated and accepted by European countries is urgently needed.

RITUXIMAB AS TREATMENT OF IMMUNE THROMBOCYTOPENIC PURPURA

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Background: Immune thrombocytopenia purpura (ITP) is an autoimmune disease characterized by auto-antiplatelet antibody-mediated thrombocytopenia. These antibodies mediate thrombocytopenia by accelerating the destruction of platelets in the peripheral blood, and binding to megakaryocytes and impairing platelet production. In Europe, the annual ITP incidence is around 3 per 100,000 people. ITP tends to have a higher incidence in middle-aged females and male children.

Rituximab (RTX) is a chimeric monoclonal antibody directed against CD20, an antigen expressed on the surface of B-lymphocytes but not present on most plasma cells.

The objective of this work was to better understand the treatment of ITP, specifically with rituximab.

Material and Methods: Was conducted a research of articles published, in PubMed and Google Scholar, in English and Portuguese, using key words like rituximab, immune thrombocytopenic purpura, mechanism and treatment.

Results: The aim of this treatment is to stop ongoing bleeding and also decrease the risk of developing clinical-significant bleeding in the future. There are lots of strategies in this treatment between first, second and third line with steroids, intravenous immunoglobulin, splenectomy or immunosuppressive drugs. The decisions are guided by physicians’ personal preferences, cost considerations and various regulatory.

Conclusions: Several studies refer that the administration of RTX leads to the rapid and complete depletion of circulating B cells. However, the mechanism of action of RTX on immune cells in ITP has not yet been completely elucidated.

MULTIPLE ADVERSE REACTIONS DUE TO NEUROVAX SYSTEM DRUGS METABOLIZED THROUGH CYP2D6

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Background or Introduction: The CYP2D6 is a highly polymorphic isoenzyme with more than 100 allelic variants and subvariants. It is involved in the metabolism of at least 25% of commonly prescribed drugs (such as antidepressants, antipsychotics, and analgesics).

Material and Methods: In a period of two years, a 56 year old female with neuropathic pain due to T2-T3 transverse myelitis had multiple adverse drug reactions (ADR) related to nervous system drugs. The patient had visual hallucinations due to amitryptiline (10 mg/ day) and then organic psychosis related to tramadol. Tramadol was withdrawn by the psychiatrist and treatment with olanzapine was started. The patient presented a generalized rash with itching due to an increase in the dose of gabapentin (2200 mg/day) that disappeared
within 2 weeks after a reduction of half the dose. The last ADR of
the patient was symptomatic hypertension (BP up to 166/105 mm
Hg) due to duloxetine (30 mg/day) which was prescribed for anxiety
and depression.
Results: After accurately assessing each ADR, the same metabolic
pathway (CYP2D6) was seen for three of the drugs (amitriptyline,
tramadol, and duloxetine). Gabapentin is not metabolized by the
liver. Therefore, slow metabolism of the isoenzyme was suspected
for psychosis and hypertension. Pharmacogenetic test (PGT) was
performed in search of polymorphisms by including: CYP2D6 (*2,
and *6) and CYP2C19 (*2, *3, *4, *5 and *17). The results of the
PGT analyses revealed that the patient was homocigous (wild type).
Conclusions: Genetic polymorphisms that could explain the ADRs
were not found in this patient. However, further studies assessing the
involvement of some other gene or protein in the metabolic process
or transport could elucidate our preliminary suspicion.

SPONTANEOUS ADVERSE DRUG EVENT REPORTS
TO THE ADVERSE DRUG EVENT MANAGER
(ADEM)
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Introduction: The “Adverse Drug Event Manager” (ADEM) is a
service offered to health care professionals (HCPs) employed at a hos-
pital in the Capital Region of Denmark. The purpose of the ADEM
is to assist HCPs report suspected adverse drug events (ADEs) to the
Danish health authorities, and to raise awareness of ADEs in general.
In the present study, we describe the ADEs reported through the
ADEM in 2014 with respect to reporter, patient, drug and symptom
characteristics.
Materials and methods: All ADE reports handled by the ADEM were
recorded prospectively and anonymously. For this descriptive analy-
sis, we included data from 2014, and assessed drugs and symptoms
for each report made by the clinician.
Results: In 2014, the ADEM handled 484 ADE reports from the
Capital Region of Denmark (1.6 million inhabitants). The median
number of reports per month was 37 (range 17-78). The majority of
reports came from departments of internal medicine (63%), followed
by psychiatry (14%) and surgery (7%). The most frequently reported
drugs were lisdexamphetamine (n = 40), dabigatran (n = 37) and
aspirin (n = 33). The most frequently reported adverse events were
nausea (n = 42), hyponatremia (n = 40) and dyspnoea (n = 36). The
proportion of ADEs with a fatal outcome was 11/484 (2.3%). In four
of these cases, the suspected drug was an anticoagulant, and in seven
cases, the adverse event was cerebral bleeding.
Conclusion: The ADEM is a unique source for evaluating reporter
and ADE characteristics, in a clinical pharmacological setting,
contributing to an increased knowledge on ADEs. Based on our expe-
rience we strongly encourage other regions to establish an ADEM.

SAT-HULP TOXICOVIGILANCE PROGRAM:
RESULTS OF 30 MONTHS
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Background: SAT-HULP toxicovigilance program is a validated
tool (R. Muñoz et al, 2013) that allows a semi-automated detec-
tion of acute intoxication for patients attending to the Emergency
Department of La Paz University Hospital. We describe the cases of
acute poisoning detected by this system since its introduction in 2011.
Material and Methods: This is a descriptive epidemiological study
(April 2011-October 2013). We analyse all cases of acute poisoning
detected by SAT-HULP program. This system performs a daily search
for cases in the hospital’s computerized case records. The tool uses a
truncated keyword list to systematically look for the reasons patients
come to the emergency department and the clinical decisions made.
Found cases are entered into a database for recording of type of
poisoning episode, reasons for exposure, causative agent, signs and
symptoms, and treatment.
Results: In the study period (30 months) 3,195 acute poisoning
cases were identified, among 182,502 patients attending to the ED
(1.75%); this represents a rate of 143/100,000/year if we consider that
the reference population is 725,006 people. The mean age was
41 years (51.2% male). Abusive and/or recreational poisoning were
the most frequent (47.5%), followed by suicide (38.1%) and acciden-
tal (14.0%) poisoning. Forty seven percent of subjects had previous
psychiatric pathology and 36.8% alcoholism or previous addictions.
81.8% had symptoms at admission. Drug abuse accounted for 51.7%
of the cases (alcohol: 86.5%); Most patients were discharge from the
emergency department (84.1%), followed by patients admitted to
psychiatry unit (6.7%), internal medicine (4.9%) and intensive care
unit (1.5%). Six patients (0.2%) died.
Conclusions: The results after 30 months confirm that SAT-HULP
toxicovigilance program is a tool that provides continuous informa-
tion and allows quick data management of acute poisoning.
SCREENING AND RECRUITMENT PROCEDURES OF HEALTHY VOLUNTEERS IN A PHASE I CLINICAL TRIAL UNIT: EXPERIENCE IN 64 BIOEQUIVALENCE STUDIES

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Background: This study reports and analyses screening and recruitment procedures carried out in 64 bioequivalence (BE) studies.

Material and Methods: All the studies were designed and conducted following the requirements of EMA for BE studies and carried out in the Phase I Clinical Trial Unit of the Pharmacology Department (School of Medicine, Universidad Autónoma de Madrid). For each trial calculated sample size, number of volunteers and reasons for exclusion, withdrawal and dropping were recorded.

Results: For the included 64 trials, a total of 3575 healthy volunteers signed the informed consent form. During the screening period 1076 volunteers (30.1%) were found not to be suitable for the study. The main reasons were: 508 volunteers withdrew the informed consent (47.3%), 251 showed analytical abnormalities (23.3%) and 80 gave a positive result in urine abuse drug test (7.4%). Therefore, a total of 2500 fulfilled inclusion criteria (69.9%) and 2339 were included (158 volunteers were considered as reserves). During the study, 52 volunteers (2.2%) dropped for personal reason and 40 were excluded (1.7%). A total of 2252 volunteers were suitable for the main analysis.

Conclusions: To select 2252 valid participants in BE trials we needed to obtain the signed informed consent form from 3575 potential participants and to make the initiation visit in 3282 volunteers. Only a 6.3% of the healthy volunteers interviewed and fulfilling selection criteria were finally not included. Post-randomization losses were also low (3.9%).

UAM COURSE ON GOOD CLINICAL PRACTICE (GCPS) FOR INVESTIGATORS: A 3 YEARS EXPERIENCE

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Background: The Department of Pharmacology and Therapeutics from the School of Medicine at Universidad Autónoma de Madrid (UAM) has designed an on-line course to provide investigators with basic training in GCPS. It also aims to update investigators in ethical issues and Spanish legislation concerning the conduct of clinical trials.

Methods: Based in ICH-E6-GCP guideline and Spanish regulation, the course is organized into 9 modules and 3 sections each (a theoretical part, an exam and a section of questions and answers). The course is implemented within the tool “e-learning Moodle” of the UAM (https://formacion.uam.es/). It also includes complementary bibliography and a satisfaction survey that students can voluntarily fill out.

In order to obtain the certificate students must pass the exams with a score of 100%. The Course is credited with 3.8 credits by the Health Commission for Continuing Education in the Health Professions of the Community of Madrid/National Health System.

Results: In 3 years, 963 subjects have been registered in the course. Among them, 779 completed the course and have already obtained the certification. We had 380 students from Governmental institutions, 274 students from different pharmaceutical companies and CROs, and 309 individual registrations. Finally, 271 students (34.7% of those completing the course) filled the anonymous satisfaction survey and voted on the following aspects: for 95.2% the e-learning tool is easy to use, 92.2% consider that the contents is adjusted to his/her formative needs, 93.6% said that in general the course has fulfilled his/her expectations and for 94.8% the course has given them the expected knowledge level.

Conclusions: The course has been completed (80.9%) by the most important target groups involved in clinical trials. Our Course is being well received for the students because it is clear and concise and has no time restriction to follow it.

IMPLEMENTING PHARMACOGENETICS: PHARMAARRAY® AND PHARMACOGENETIC CONSULTATION

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Background: The important growth in pharmacogenetics (PGx) information has not been paralleled by its application in clinical practice, due to some barriers related to the interpretation of PGx information and the costs of implementation. Our objective is to describe the strategy adopted in La Paz University Hospital to facilitate the implementation of PGx in clinical practice.

Material and Methods: A Clinical Pharmacogenetics Unit (CPSxU) has been set up by the Clinical Pharmacology Service and the Institute of Medical and Molecular Genetics. Through this functional unit, we have proposed: 1) to design a cost-effective genotyping tool for healthcare purposes; and 2) to set up a pharmacogenetic counseling service aimed to integrate clinical and genetic information and provide evidence-based therapeutic advice to the attending physicians which requested it.

Results: We have designed and patented an array (PharmArray®, Application-MC011608403) using an Open-Array® technology (Life Technologies Corporation). It allows genotyping 192 SNPs from 57 genes, including drug metabolism enzymes and transporters genes, in about 12 hours. The cost of genotyping 192 SNPs per patient, including DNA extraction, is 23 €. We have implemented for clinical use an electronic medical history and pharmacogenetic protocols for treatment selection and dose adjustments. In addition, we are running a PGxU providing advice both by means of an electronic platform or direct patient consultation. This unit makes a mean of 450 PGx determinations per year, 312 online consultations and a mean of 200 patients were attended in person.

Conclusions: The implementation of Pharmarray® and a PGxU in a tertiary hospital aiming to provide clinically useful information is feasible and it will avoid adverse drug reactions and improve drug selection at limited cost.

PHARMACOGENETIC IMPLEMENTATION IN THE ROUTINE CLINICAL PRACTICE: DESIGN OF A MULTICENTER PILOT CLINICAL TRIAL

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   3 | Introduction: The aim of this study was to give an overall picture of the utilization trends of oral antidiabetics in Serbia between 2010 and 2012.

Material and Methods: The study examined consumption of oral antidiabetics during the 3-year period. The data were retrieved from the annual reports of the Agency for Drugs and Medical Devices of the Republic of Serbia. Consumption was calculated using the ATC/DDM methodology and results were expressed in DDD/1000 inhabitants/day (DDDs/TID).

Results: The total consumption of antidiabetic drugs varied 1.5 fold, ranging from 34.89 DDDs/TID in 2010 to 50.33 DDDs/TID in 2012. Biguanides (metformin) were the most frequently used class of OAD during the three examined years (ranging from 19.08 DDDs/TID in 2010 to 26.56 DDDs/TID in 2012). Sulphonylureas were the next frequently used class and among them gliclazide was the most frequently used drug (ranging from 12.03 DDDs/TID in 2010 to 16.51 DDDs/TID in 2012). The use of thiazolidinediones, DPP-4 inhibitors, meglitinides as well as acarbose remained marginal.

Conclusion: Diabetologists and clinical pharmacologists should explain causes leading to these increase in consumption of OADs and determine side effects of available antidiabetic drugs, either positive or negative, in order to enable their optimum utilization. This work was supported by the Ministry of Science and Technological Development, Republic of Serbia, project No. 41012.

A COMPARISON OF THE CLINICAL ABUSE LIABILITY OF MDMA AND MEPHEDRONE

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Introduction: Mephedrone is a synthetic cathinone derivative included in the class of “New-Novel Psychoactive Substances”. Interestingly, synthetic cathinones are marketed as “bath salts” or “plant food” and have gained notable popularity for their similar effects to 4-methylendioxymethamphetamine (MDMA, ecstasy), amphetamine or cocaine. The aim of the present study was to evaluate the clinical abuse liability of mephedrone in comparison to MDMA.

Materials and Methods: The protocol was approved by the local Research Ethics Committee and registered with ClinicalTrials.gov, number NCT02232789. Participants signed an informed consent before inclusion. Twelve healthy male, recreational users of psycho-stimulants participated as outpatients in three experimental sessions. They received a single oral dose of mephedrone (200 mg), MDMA (100 mg) and placebo. Design was double-blind, randomized, crossover and controlled with placebo. Study variables included: vital signs (blood pressure, heart rate, temperature, and pupil diameter), subjective effects (visual analogue scales-VAS, ARCI-49 item short form, VESSPA questionnaire, and identification class questionnaire). Blood and urine samples were obtained.

Results: Both mephedrone and MDMA produced similar increases in blood pressure, heart rate and temperature, but MDMA produced more mydriasis. Mephedrone and MDMA induced euphoria and pleasurable effects, slight changes in perceptions but nor hallucinations. Mephedrone effects appeared earlier, were less intense and dissipate faster. Mephedrone was classified as similar to MDMA. Both substances were well tolerated and no serious side effects were observed. Mephedrone and MDMA plasma concentrations peaked at 1.25 and 2 hours, and its elimination half-life were 2.15 and 7.9 hours, respectively.

Conclusions: Mephedrone presents an abuse liability similar to MDMA but its shorter duration of effects could explain a more compulsive pattern of use.

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WHAT DO YOU THINK ABOUT GENERIC DRUGS PRODUCTS? RESULTS FROM A SURVEY

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Background or Introduction: Generic Drugs Products (GDP) have been subject of discussion for many years, and still now there is some controversy about their quality, effectiveness and safety compared to Innovators drugs. This survey tried to find what is the general perception and opinion from physicians and medical students about generic drugs products.

Material and Methods: A questionnaire of 12 items focused mainly in effectiveness, safety, quality and adverse event occurrence was sent to physicians of a third level health care hospital and to medicine students. Individual demographic information and clinical practice data (specialty, years of experience, pharmaceutical sale representative visits, etc.) was asked.

Results: One hundred fifty-five subjects answered the survey (n = 157). Physicians from specialties that are less related with clinical practice (who do not prescribe daily) showed to be more agreed with the affirmation that Innovators and GDP products have the same quality, effectiveness and adverse event occurrence compare with physician’s that prescribe daily. Internal medicine specialist tends to be more agreed with equivalence in term of effectiveness and adverse events occurrence than surgical specialist. Years of experience, number of patients by day and number of pharmaceutical sales representative’s visits by month showed an inversely proportional relationship to be in agreement with equivalence in quality, effectiveness and safety. Difference between medicine students and physician were found in questions related to quality, effectiveness and safety. Physicians tend to be more in disagreement with the equivalence in those aspects between GDP and Innovators ones. All commented results were statistically significant (P values <0.05).

Conclusions: We found that physicians have some concerns about equivalence between GDP and Innovators ones regarding the quality, efficacy and safety of generic drugs, this concerns increase with years’ experience, number of patients visited and number of sales representatives visits, the fact of prescribing daily and to be surgical specialist. Students tend to be more agreed with equivalence between GDP and Innovators drugs. Nevertheless the response rate is a limitation of this study.

CYTOCHROME P450 OXIDOREDUCTASE CONTRIBUTION ON AN ACENOCOUMAROL DOSING ALGORITHM

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Background: The great majority of clinically used drugs are metabolized by hepatic type II cytochrome P450 enzymes and require the activity of P450 oxidoreductase (POR). The presence of POR polymorphism can modify the activity of CYP450. Studies about POR influence on the stable dose of warfarin are not conclusive while there are no studies about its influence on acenocoumarol dosing. Material and Methods: This was an observational, prospective study. We recruited 341 patients in La Paz University Hospital between 2008 and 2013 in stable anticoagulant treatment with acenocoumarol for atrial fibrillation, thromboembolic disease and valve replacement. Data collection included age, gender, race, body weight and height, INR results and acenocoumarol dose administered in the last 3 months and concomitant medications. A blood sample was prospectively collected for CYP2C9, VKORC1, CYP4F2, APOE and 2 variant of POR rs2868177 and rs1057868 (POR*28). Multiple linear regression was performed to determine the influence of POR SNPs on the acenocoumarol dosing algorithm previously developed by our group.

Results: The real dose of acenocoumarol did not differed significantly among carriers of the different polymorphisms of the two POR variants evaluated (POR*28, P = 0.176) and (POR rs2868177, P = 0.534). In the simple regression analysis, none of the POR SNPs was identified as being significantly associated with acenocoumarol dose variation. In the multiple regression analysis, $R^2$ obtained with the acenocoumarol dosing algorithm was 48.5%; adding POR*28 or POR rs2868177 just increase $R^2$ in 0.1%.

Conclusions: None of the 2 POR variants evaluated are associated with the interindividual variability of acenocoumarol.

MANIFESTATIONS OF UNETHICAL MARKETING IN HEALTH CARE OF THE KYRGYZ REPUBLIC

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Unethical marketing of drug is hot topic around the world. It is necessary to study the actual practice, the implementation of technical regulations.

Objective: Identification of unethical marketing of medicines among 29 clinics in Kyrgyzstan.

There were seized 412 forms of an unknown sample, self-pads with advertising for drug prescribing, pharmacy network, engaged in unethical marketing during the checking of 94 doctors. The lists of patients indicated name, phone, address, sheets rewards prizes and bonuses for prescription drugs. Doctors for prescription drugs were provided with bonuses in monetary terms from 10% to 26% of the cost of prescribed drug, household and office equipment, cookware sets, 5% discount cards, vouchers for petroleum products, mobile communications, and trips to luxury resorts.

During one month 6 pharmaceutical companies have been presented one workshop, at one of the institutions for the promotion of 6 drugs. In violation of the technical regulations medical representatives visit doctors during medical reception, distribute handouts, prescription forms unknown sample, loose-leaf notebooks with advertising of medicines, conduct workshops without the consent of Department of Drug Provision and Medical Equipment Ministry of Health. Managers and medical representatives of pharmaceutical companies have received official letters on these violations of the ethical principles of promotion of drugs directed newsletters. To reduce the harm of unethical marketing of drugs in Kyrgyzstan it is very important to regulating the monitoring of medical institutions. Repeated violations, by law, must revoke licenses for pharmaceutical activity and registration certificates for drugs. To improve the situation we need to restore the system of professional information about drug and of keeping the medical staff.
Clinical Therapeutics

AN INTERNAL SYSTEM FOR QUALITY ASSURE WITH EXTERNAL AUDIT (AENOR) IN A CLINICAL PHARMACOLOGY SERVICE: A POSITIVE EXPERIENCE

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The internal systems for quality assure are being introduced in the health care environment, and especially in hospitals. The Clinical Pharmacology Service (CPS) at a University Hospital has implemented a quality management system, consistently with ISO 9001:2008 requirements and subjected to external audits by AENOR. The CPS defined 6 processes representing its activity in the hospital, and within each of those processes defined a number of indicators of the performance and its quality (process/n indicators): Clinical consultations (6), Safety of medicines and pharmacovigilance (7), Therapeutic Drug Monitoring (3), Policy and medicines selection (5), Clinical trials (4) and Clinical research (2). Three of the indicators were satisfaction surveys. The implantation period lasted 10 months. In a first phase (4 months), the design and documentation of the processes were developed; 24 procedures, 9 work instructions and 67 forms (or records) were documented and incorporated into the management system. In a second phase (6 months) the system was implemented. The internal and the external audits valued the performance and gave the higher standards to the CPS. The certification improved the activity of the CPS by using a structured process, analyzing the results, and introducing improvements. Furthermore the activity of the CPS was clearly visible for the rest of the Hospital and especially for the head physician team. The extra bureaucratic work pays off for the results obtained.

APPLICATION OF PHARMACODYNAMIC PRINCIPLES (AUC/MIC) TO IMPROVE THE CLINICAL EFFICACY OF INDIVIDUALIZED TREATMENT WITH VANCOMYCIN

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Introduction: Vancomycin monitoring is based on determining trough levels (Cmin) before administering next dose; however, the bactericidal effect of in vitro vancomycin and its clinical efficacy has been related to the pharmacodynamic parameter AUC/MIC ≥ 400 μg.h/mL. The aim was to analyse the AUC/MIC availability in patients monitored during 2012 to 2013 and to evaluate if we have reached the therapeutic objective proposed in literature.

Materials and Methods: A patient sample (100) with stable values for Cmin and AUC were obtained. Pharmacokinetic parameters were calculated. In cases with presence of MIC for gram-positive microorganisms in the antibiogram, AUC/MIC ratio was calculated. The study was approved by an Ethics Committee.

Results: Diagnoses in the patient cohort (77 men and 23 women, median age 63) were as follows: pneumonia (36%), heart infections (10%), abdominal (15%), musculoskeletal (4%), CNS (5%), MRSA bacteremia (2%), coagulase-negative staphylococcal bacteremia (7%), Urinary-tract (4%), and others (13%). Susceptible organisms (Coagulase-negative staphylococci, Enterococci, MRSA, MSSA and Streptococcus spp.) were isolated in 79 patients, in 44 patients cultures became negative after 8.5 days (median). In 69 cases, MIC was available. Median treatment lasted 10 days; 1000 mg/12h was the most frequently prescribed dose (71%). According to administered doses, Cmin achieved (5–10, 10–15, 15–20 and >20), and AUC/MIC (<400 or ≥400), there was no relationship between Cmin and AUC/MIC parameter. Of 50 patients with both measures, 58% achieved AUC/MIC ≥400; 2 patients did not exceed 400 μg/mL AUC/MIC despite reaching Cmin 15 to 20 μg/mL, whereas 11 achieved an AUC/MIC ≥400 μg.h/mL with Cmin 5 to 10 μg/mL.

Conclusions: Therapeutic trough levels do not always correlate with AUC/MIC ≥400 μg.h/mL, as they depend on patients’ PK parameters and the microorganisms’ MIC. Furthermore, other studies only mention the role of AUC/MIC in lower respiratory-tract infections and MRSA bacteremia. Therefore, studies with larger number of patients and different locations are needed to assess the clinical efficacy of this parameter.

MILESTONES ON ORPHAN MEDICINAL PRODUCTS DEVELOPMENT: THE 100 FIRST DRUGS FOR RARE DISEASES APPROVED THROUGHOUT EUROPE

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Background: More than 10 years have lapsed since the issue of the EU orphan drug Regulation (EC No 141/2000), and along this pathway, substantial experience has been gained on the assessment of orphan medicinal product (OMP) marketing applications. In the framework of an international FP7 collaboration (FP7-HEALTH-2013-INNOVATION-1, ASTERIX), a review of European Public Assessment Reports (EPAR) for approved OMP is being conducted to describe the amount and type of information submitted to the European Medicines Agency (EMA) to support a positive opinion for an orphan drug.

Material and Methods: A review of the EPAR for first 100 OMP approved in Europe has been performed. Administrative, regulatory and clinical data in which the approval was based on have been extracted from the public information available and have been systematized.

Results: From 2000 to January 2015, 100 OMP including 98 different molecules have been authorised for 125 different therapeutic indications. Small molecules represented 76% of OMP, biologicals 23% and there was 1 advanced therapy OMP. According to ATC code, oncology accounted for 41.6% of indications, and endocrine and metabolic diseases for 28%. Most indications had prevalences <1/10.000 (58.4%), while 8 indications (6.4%) had prevalences >3/10.000. Small and medium-sized enterprises (SME) hold the marketing authorisation for 13/125 applications; 5 companies were applicant for 45 (36%) out of all OMP applications. Average (range) time between orphan designation and approval was 4.1 (0.5–12.9) years. Nineteen OMP were transferred between companies between the orphan designation and the application, once (15 OMP), twice (2 OMP), 4 (1 OMP) or 6 times (1 OMP).

Conclusions: Preliminary description of the first 100 orphan drugs approved in EU showed that most of drugs approved are chemical substances, most of OMP are aimed to treat neoplastic diseases and for conditions with prevalence on the low range, and SMEs account for a very small part of applications.

AGOMELATINE EFFECTIVENESS IN SLEEP DISTURBANCES IN AUTISM SPECTRUM DISORDER

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European Medicines Agency, London, United Kingdom; and 2European Medicines Agency, London, United Kingdom

PrINCiPLES (auC/miC) To ImProVe THe PHarma Cology Ser ViCe: a PoSiTiVe iNteRnAl SySTem for qualiT y aSSure and drugS for rare diSeaSeS aPPro Ved milestoneS oN orPHaN mediCiNal

P. Ballester; M.J. Martínez; E.J. Sanz Álvarez; M.C. García Sáiz; J. Herrera Herrera; and C. Rodriguez Jiménez
Hospital Universitario de Canarias, Tenerife, Spain

Background: In the development of orphan medicinal products (OMPs), the European Medicines Agency (EMA) to support a positive opinion for a very small part of applications.

Conclusions: Preliminary description of the first 100 orphan drugs approved in EU showed that most of drugs approved are chemical substances, most of OMP are aimed to treat neoplastic diseases and for conditions with prevalence on the low range, and SMEs account for a very small part of applications.
Introduction: Sleep disorders (SD) affect up to the 84% of subjects with autism spectrum disorders (ASD) increasing cognitive and behavioural impairments. Even more, SD is a marker of family stress and one of the main reasons for drug treatment. Our aim was to evaluate the effectiveness of the antidepressant agomelatine improving sleep quality by actimetry in ASD.

Methods: A randomized, crossover, double-blind, placebo-controlled and multicenter clinical trial, was performed in 25 subjects with ASD. Participants along two periods of 3 months received (A) agomelatine 25 mg/day or (B) placebo. Functional circadian rhythm markers (wrist temperature, actimetry and position [TAP]) and salivary cortisol, were measured during a week at the beginning and at the end of each period (random drug sequence: AB or BA).

Results: Participants were 25 adults with low-functioning ASD (20♂S♀, mean age of 32 ± 2 years). We found significantly differences improving circadian rhythms in agomelatine versus placebo (P = 0.018). We observed an absence of difference in cortisol levels between groups suggesting that hypothalamic–pituitary–adrenal axis functioning was unaltered.

Conclusions: Actigraphy is an objective and useful tool to analyze SD in ASD population, where preliminary, agomelatine seems effective in improving sleep patterns compared to placebo. Further analyses will focus on correlation between actigraphy and genetic and epigenetic analyses from sleep genes data.

DETECTION OF UNNOTIFIED ADVERSE DRUG REACTIONS (ADR). ACTIVE PHARMACOVIGILANCE (APV)

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Introduction: Cases of ADR, which are attended and occur while hospitalized, are important due to the severity of these reactions. Nevertheless, many of these cases are not notified spontaneously. Different methods have been proposed to obtain this information, however, their sensitivity and/or specificity is low. Therefore, a programme of Active Pharmacovigilance (APV) was launched in our hospital in 2011.

Materials and Methods: The Department of Clinical Pharmacology performs a systematic review of patients’ clinical records which serve to detect suspected ADR cases. This information is completed with other clinical data (laboratory and imaging tests, primary care history, etc.) for validation purposes and to proceed to its notification. Hospital discharge reports are reviewed weekly, filtering for departments (Internal Medicine and Nephrology) instead of diagnoses. Furthermore, progress report of patients attended in the Emergency Department, selected by diagnoses and age, are assessed daily.

All reports obtained are digitally available to the evaluating physicians, to facilitate identification of suspected ADR, and to enable notification to the National Pharmacovigilance System.

Results: Six thousand five hundred five cases have been reviewed since implementation of this activity, 587 ADR detected, and 232 notified. Evaluation of 40 cases per week consumed 3 hours on average. In the period 2011 to 2014, notification went up from <50 cases to >130 per annum, representing easily more than 50% of all notifications in our hospital; 80.7% are severe.

Conclusions: APV programme more than doubled the notifications in our hospital since its implementation, demonstrating the feasibility and effectiveness of the active and systematic search for ADR cases. It also encourages interaction with other hospital services and promotes a habit of notifying among health professionals. These results highlight the importance of joint work between pharmacovigilance centres and clinical services, and therefore this activity should be encompassed among the tasks of Clinical Pharmacology Departments.

IMMUNOSUPPRESSIVE DRUG USE IN SOLID ORGAN TRANSPLANTATION: OFF LABEL USE CHARACTERIZATION

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Introduction: Immunosuppressive (IS) treatment in solid-organ transplantation should prevent acute-chronic rejection without increasing infections and malignancies through the combination of drugs with different action mechanism in three differentiated phases: induction, maintenance and rejection. Off label use is frequent in induction and maintenance phases. Utilization studies to characterize these uses are necessary.

Material and Methods: We conducted a prospective observational study in 2 hospitals experienced in transplantation. The principal objective was to describe IS use in solid-organ transplantation. Clinical-Pharmacology Services identified patients and will follow them up to three years. Clinical, laboratory and pharmacological data were collected from clinical history.

Results: At our data cut-off date 108 patients were included and followed for 3 months.

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Heart</th>
<th>Liver</th>
<th>Lung</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients: n (%)</td>
<td>23 (21.3)</td>
<td>14 (13.0)</td>
<td>41 (38.0)</td>
<td>30 (27.9)</td>
</tr>
<tr>
<td>Age: median (P25-P75)</td>
<td>60 (34-64)</td>
<td>51 (46-57)</td>
<td>62 (57-65)</td>
<td>50 (34-59)</td>
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<tr>
<td>Acute rejection: n (%)</td>
<td>5 (21.7)</td>
<td>1 (7.1)</td>
<td>17 (41.5)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Cellular: n (%)</td>
<td>3 (13.0)</td>
<td>1 (7.1)</td>
<td>17 (41.5)</td>
<td>5 (16.7)</td>
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<td>Humoral: n (%)</td>
<td>2 (8.7)</td>
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<td>0</td>
<td>1 (3.3)</td>
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<td>Adverse events: n (%)</td>
<td>4 (17.4)</td>
<td>2 (14.3)</td>
<td>11 (26.8)</td>
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</tr>
<tr>
<td>Required treatment</td>
<td>3 (13.0)</td>
<td>1 (7.1)</td>
<td>2 (4.9)</td>
<td>0</td>
</tr>
<tr>
<td>Required hospitalization</td>
<td>2 (8.7)</td>
<td>1 (7.1)</td>
<td>5 (12.2)</td>
<td>0</td>
</tr>
<tr>
<td>Infections: n (%)</td>
<td>4 (17.4)</td>
<td>8 (57.1)</td>
<td>15 (36.6)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Bacterial: n (%)</td>
<td>3 (13.0)</td>
<td>7 (50)</td>
<td>13 (31.7)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Induction: n (%)</td>
<td>4*</td>
<td>0</td>
<td>0</td>
<td>18</td>
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<tr>
<td>Thymoglobulin: n (%)</td>
<td>19*</td>
<td>4*</td>
<td>0</td>
<td>12</td>
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<tr>
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<td>Tacrolimus + Mycophenolate</td>
<td>Tacrolimus + Mycophenolate</td>
<td>Tacrolimus + Mycophenolate</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>14</td>
<td>41</td>
<td>30</td>
</tr>
<tr>
<td>IS changes</td>
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<td>TAC-EVE 1</td>
<td>TAC-C6 6</td>
<td>TAC-SIR 4</td>
</tr>
</tbody>
</table>

* Off label
Conclusions: Following EPARs, off label use accounted for 91.3% of Heart-T and 28.6% of Liver-T in induction phase and 100% of Lung transplanted patients.

VINCRI STINE-INDUCED NEUROPATHIC PAIN IN A CYP3A5 NON-EXPRESSER WITH REDUCED CYP3A4 ACTIVITY

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Background: Vincristine is metabolised by CYP3A5 and CYP3A4 isoforms with CYP3A5 contributing to 75% of vincristine intrinsic clearance. Vincristine is a substrate of the P-glycoprotein (P-gp) transporter. An increase in vincristine neurotoxicity in CYP3A5 non-expressers has been observed. The severity of neuropathy was found to be inversely correlated to vincristine metabolite concentrations.

However, a clear correlation between genetic polymorphisms and vincristine toxicity has not been established.

Case Presentation: We report the case of a 21-year old African male patient who received vincristine 2 mg on 3 occasions (on 14.10, 30.10 and 06.11.14) for the treatment of pre-B acute lymphoblastic leukaemia. Six weeks after the last vincristine dose the patient complained of bilateral severe burning pain in the toes and allodynia, suggestive of neuropathic pain.

The patient was genotyped for CYP3A5 using a real-time PCR method as well as for ABCB1 (coding for P-gp) G2677T/A and C3435T SNPs. The results showed that the patient presented a CYP3A5*3/*3 polymorphism indicating that he did not express CYP3A5 enzyme. He was a homozygous ‘wild type’ carrier for ABCB1 SNPs.

Furthermore, CYP activity was evaluated using the Geneva phenotyping cocktail including midazolam as a probe for CYP3A4. The patient had a decreased CYP3A activity which could not be explained by the concomitant medication. Similarly he had no CYP3A inhibitor in his medication at the time he received vincristine.

Conclusion: The lack of CYP3A5 expression together with decreased CYP3A4 activity probably led to a decrease in vincristine clearance and to an increase in its plasma concentrations. It is a likely explanation for the occurrence of neurotoxicity in our patient despite the low doses of vincristine he received. In patients treated with vincristine, CYP phenotyping and genotyping could be crucial in preventing serious side effects.

ROLE OF CPS AND CRP IN DETERMINATION OF EFFICACY OF CHEMOTHERAPY IN MANAGEMENT OF ENTEROBACTERIACEAE INFECTION

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Background: Patients in intensive care unit (ICU) are at risk for death not only from their critical illness but also from secondary processes such as nosocomial infection. Pneumonia is the second most common nosocomial infection in critically ill patients.

Aim of the Work: The present study was conducted to evaluate the role of the clinical pulmonary infection score (CPS) and C-reactive protein (CRP) in measurement the efficacy of antibiotic therapy against nosocomial enterobacter pneumonia.

Patients and Methods: After approval of the study by the Research Ethics Committee, 200 patients with manifestation of pneumonia as assessed at the onset of ICU administration by calculation the CPS and daily by CRP detection during the first 8 days of intubation.

According to the culture and sensitivity, 48 patients were positive for enterobacter aerogenes, 34 patients from the 48 were sensitive to amikacin and levofloxacin. So, firstly we began with amikacin and noticed that only sixteen patients were respond. On the other hand addition of levofloxacin to amikacin on the fourth day to treat the remaining patients showed complete recovery of the patients as reported by CPS and CRP.

Results: There is a significant change in both CPS and CRP in first day versus fourth day in 16 patients that responded to single antibiotic amikacin, however, the remaining 18 patients not response to single antibiotic. On the other hand, adding other antibiotic (levofloxacin) for the remaining eighteen patients showed a significant changes in both CPS and CRP in fifth day versus ninth day.

Conclusions: It can be concluded that CPS and CRP play an important role in determination the efficacy of antibiotics that used in treatment in nosocomial pneumonia.

Key words: nosocomial pneumonia, CPS, CRP, amikacin and levofloxacin.

RETROSPECTIVE STUDY OF LACOSAMIDE IN THE ELDERLY (≥ 60 YEARS OF AGE)

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Background: Lacosamide was FDA approved in 2008 for partial onset seizures. Few studies evaluated its effectiveness in the elderly. This multi-center study documented the use of lacosamide for patients ≥60 years in a naturalistic setting. We evaluated the efficacy, safety, tolerability and dosing requirement in this population.

Methods: Patients with a diagnosis of epilepsy, ≥60 years of age and started lacosamide between October 2008 and December 2014, were identified at the study sites. Patients’ medical history, treatment efficacy and safety measures were retrospectively reviewed. Primary outcome measure was retention rates at 3, 6, and 12 months. Secondary outcome measures were seizure freedom and 50% seizure reduction at final maintenance dose, final effective total daily dose, and days to achieve effective dose.

Results: Fifty-two patients were evaluated: 18 were between 60 to 64 years, 16 were between 65 to 69 years, and 18 were 70 years or older. The average time since diagnosis was 24.7 years (SD 23.5). The main seizure type was complex partial seizure (78.8%). Forty-four percent of patients were using lacosamide as monotherapy. Overall 3, 6 and 12-month retention rates were 94.2%, 84.6% and 51.9% respectively. Seizure freedom was achieved in 28.8% of patients. Median maintenance total daily dose was 300mg/day (range 100–600mg/day) in those 60 to 64 years and 65 to 69 years; 200mg/day (range 50–400mg/d) in those ≥70 years. Average time to maintenance dose was 207 days for those 60 to 64 years, 195 days for those 65 to 69 years and 89 days for those ≥70 years. During titration phase, 53.6% of those ≥70 years, 62.5% of the 65 to 69 years, and 22.2% of the 60 to 64 years experienced neurological side effects. The most common neurological adverse effects were dizziness and balance issues.

Conclusions: Lacosamide was effective and well-tolerated in our elderly population. Our findings suggest that this population may require a lower dose and an extended titration schedule.
THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICATIONS AMONG DIALYSIS PATIENTS

THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICATIONS AMONG DIALYSIS PATIENTS

The use of CAM among dialysis patients has increased in the past decade. CAM includes the use of herbal medications, dietary supplements, and alternative therapies. The prevalence of CAM use among dialysis patients is higher than the general population, with around 30% of dialysis patients reporting CAM use in a recent study.

METHODS:

A cross-sectional study was conducted at a large dialysis center in a major city in Israel. A total of 200 dialysis patients were included in the study. CAM use was assessed using a validated questionnaire. The questionnaire included questions about the type of CAM used, the frequency of use, and the reasons for using CAM.

RESULTS:

The overall prevalence of CAM use among dialysis patients was 30%. The most commonly used CAM types were herbal supplements (20%), dietary supplements (15%), and massage therapy (10%). The most frequently used herbal supplements were ginseng, garlic, and echinacea. The most frequently used dietary supplements were multivitamins, calcium supplements, and fish oil.

CONCLUSIONS:

CAM use among dialysis patients is prevalent and varies widely. Healthcare providers should be aware of the potential interactions between CAM and conventional medications and the need to monitor patients who use CAM. Further research is needed to better understand the impact of CAM use on patient outcomes.

Impact of Cyclosporine Dosing Regimen and Infection on Voriconazole Pharmacodynamics in an Experimental Model of Cerebral Scedosporiosis

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The use of complementary and alternative medicine (CAM) is on the rise in last decade. Subpopulations of patients with chronic diseases are at risk for adverse events and potential drug-herb interactions, among them dialysis patients. This study aimed to evaluate the prevalence of CAM consumption among dialysis patients and search for potential interactions.

METHODS: This is a Cross Sectional study based on questionnaires. The study included patients at the hemodialysis unit at “Asaf Harofe” medical center, Zerifin, Israel. Questionnaires included demographic data, information about medical history and the use of prescription medication (PM) and all relevant history of CAM use, including the interest of the medical team in the supplements. Possible interactions between CAM and PM were evaluated by a clinical pharmacist and a clinical pharmacologist.

RESULTS: Eighty-four patients participated in the study. Eight patients (9.5%) used CAM, 5 (62.5%) of them women. They tend to be more educated (50% of CAM consumers had academic education vs. 18.4% in the nonconsumers group (P = 0.061)). Most of consumers had free professions (75%) in comparison with 39.5% of the nonconsumers, although this was not statistically significant (P = 0.22).

No differences were found regarding smoking, alcohol consumption and physical activity habits between consumers and nonconsumers.

We found a potential drug-herb interaction in 50% of the CAM consumers. Moderate interactions between aloe vera and diuretics, aloe vera (as part of Kalgo) and insulin, niacin (vitamin B3), and pyridoxine (B6 as part of Nephrotive) with calcium channel blockers and diuretics. These interactions may result with hypoglycemia, hyperglycemia, hypokalemia and lower blood pressure.

CONCLUSIONS: We found a lower prevalence of CAM consumption in dialysis patients than is found in other studies in the general population. Still, unawareness of the harm and potential interactions, lack of data sharing between the patient and caregiver might have disastrous consequences. Therefore, care givers need to inquire their patients specifically of the use of CAM, especially in populations with chronic diseases, let alone patients undergoing dialysis.

ADVERSE EFFECT PROFILE OF ANTI EPILEPTIC DRUGS IN PERSONS WITH EPILEPSY IN INDIA: A CROSS SECTIONAL STUDY

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Background: Epilepsy has an annual incidence of 27.27 and prevalence of 572.8 per 1 lakh population in India. Half the persons with epilepsy (PWEs) on antiepileptic drugs (AEDs) experience troublesome adverse effects (AEs) with the potential to affect compliance. AEs may vary among population and with the type of AED used. The study was planned to map the adverse effect profile of antiepileptic drugs in patients with epilepsy attending the neurology OPD of a tertiary care centre in North India.

METHODS: Adult PWEs attending the neurology OPD of a tertiary care centre in North India were questioned for AEs after the study was approved by the Institute Ethics Committee. A 19-item Liverpool Adverse Effect Profile (LAEF) dataset was administered to all the participants. In addition, demographic profile and treatment history were captured in separate case record form. The global LAEF score was calculated and the AEs were classified as frequently problematic (Likert scale 3&4) and rarely problematic (Likert scale 1&2).

RESULTS: One hundred PWE (mean age 30.8 ± 8.9; 43.2% females). Median no of drugs prescribed was 2 (range 1–5). Average Global LAEF score was 36.1 ± 7.9. Memory loss (68%), anger (68%), nervousness (56%), sleepiness (49%) and difficulty in concentration (41%) were the most frequently problematic AEs. The least problematic AEs were blurred vision (2%), trouble with mouth or gums (3%), unsteadiness (10%), problems with skin (10%) and dizziness (11%). Loss of libido was reported by 12% male PWEs as a problematic AE. Global LAEP score correlated poorly with the BMI (Pearson r = 0.053). It increased with the total number of AEDs (P = 0.053).

CONCLUSION: Presence of frequently problematic AEs in nearly all the patients suggests a substantial burden of AED related adverse effects.
Clinical Therapeutics

1 in Indian population. Larger studies are needed to assign causality
2 on individual AEDs and their combinations.

5 INFORMED CONSENT (IC) IN CLINICAL TRIALS
6 (CT): AN ASSESSMENT OF UNDERSTANDING BY
7 PATIENTS AND VOLUNTEERS AND ANALYSIS OF
8 IC FOR SUBSTUDIES WITH BIOLOGICAL SAMPLES
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12 Spain
13 Objective: Documenting how patients included in CT and external
14 volunteers understand ICs and the reasons for participating in CT.
15 Evaluating the IC of sub-studies collecting biological samples accord-
16 ing to Spanish legislation.
17 Material and Methods: We gave a survey to patients receiving treat-
18 ment at the clinical trials unit and to external volunteers. These ICs
19 were also evaluated by 3 clinical pharmacologists (CPs). CPs also
20 evaluated how the ICs corresponding to sub-studies involving bio-
21 logical samples fulfilled the requirements described in the 14/2007
22 Investigation law.
23 Results: Fifty-four patients (from 27 CT) and 27 volunteers filled
24 the survey. Median age was 54 and 59 years, respectively. Most of
25 participants answered they understood correctly what it means to
26 participate in a CT and that their participation was voluntary. In both
groups, about 65% took the decision after consulting with relatives
and 20% not understood well the risks. For patients, the most fre-
quent reason for participating was confidence in the physician and for
volunteers the progress in research. Fifty percent of volunteers
commented that IC was too long. The review by the CP detected that:
65% of IC were too long, 58% contained numerous technical terms
and the risk section was excessively long in 35%. About the 20 IC
for sub-studies (74% of trials), 85% were considered adapted to our
legislation only in some aspects.
26 Conclusions: In general, all sections of the IC document were well
understood but many participants did not understand well the risks.
Outcomes from patients and volunteers were similar except for the
reason for participation: the most frequent reason for patients was
confidence in the physician and for volunteers’ progress in research.
Regarding trials containing sub-studies with biological samples:
Despite the fact there is an increasing number of CT including these
sub-studies, its ICs do not fulfill entirely the 2007 law requirements.

THE REVERSAL EFFECT OF ONDANSETRON ON LOCAL ANESTHESIA IN THE THERMAL PAIN
MODEL OF RATS

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Background: Up to date there is no agent described as local anaes-
thesia antagonist that can reverse the local anesthesia. Ondansetron
is a 5-HT3 receptor antagonists interfere with both peripheral and spi-
nal serotonin effects on nociception. The aim of this study was to
evaluate the effect of ondansetron on thermal antinociceptive effect
of local anesthetic when injected into a rat hind paw.

Material and Methods: The experimental protocols were
approved by the Institutional Animal Care and Use Committee.
Sprague-Dawley rats received a 50 μL left intraplantar injection of
commercially available 0.4% articaine (combined with epinephrine).
Local anesthetic effect was determined as achieve cut-off latency by
the paw withdrawal latency (PWL) measurements at 20 minutes later
articaine injection. Group I (local ondansetron group, n = 7); 50 μL
ondansetron was injected in the same area of articaine. Group II
(systemic ondansetron group, n = 7); 50 μL ondansetron was injected
intrapерitoneally. Group III (placebo group, n = 7); 50 μL saline
was injected into the same area of articaine. Observers who performed
to PWL measurements were blind to the drug administrations. The
data are reported in terms of duration of block. Statistical compari-
sions were made using the Mann-Whitney U test. A P < 0.05 were
considered statistically significant.

Results: Locally injected ondansetron significantly decrease in dura-
ton of block when compared to systemic ondansetron and placebo
group (92 ± 37 min vs. 176 ± 40 min, and 181 ± 28 min respectively).

Conclusions: We found that ondansetron significantly reduce the
duration of antinociceptive effect of articaine in thermal pain model
when applied with the same area of local anesthetics. These data
does not indicate that ondansetron, a selective 5-HT3-receptor antagonist,
might serve as a prototype molecule for development of a novel series
of antagonist of local anesthetics. Future studies should be carrying
out to clarify the effects on Ondansetron on effect of local anesthetics.

STOPP/START CRITERIA 2014: COMPARISON OF APPROACH, PATHOLOGY AND THERAPEUTIC
CHANGES

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Introduction: the 2008 STOPP/START criteria for optimization of
drug prescription in elderly patients have been reviewed in 2014.
The aim of the present study is to describe the differences between
the previous version in terms of general structure, relevance of the
different pathologies and pharmacologic groups.

Materials and Methods: Both the 2008 and 2014 STOPP/START
criteria have been revised in terms of the established criteria, number
of pathologies included and pharmacological groups. The different
criteria within each disease and pharmacological group have been
defined.

Results: Fifty-six percent of the STOPP criteria and 53% of the
START criteria are new. There has been an increase of 16 and 12
STOPP and START criteria, respectively, throughout the differ-
ent sections of the 2008 article, to which 6 new sections are added
in the 2014 version (STOPP: Coagulation System, Renal system,
Antimuscarinic/anticholinergic drug burden; START: Urogenital
System, Analgesics and Vaccines). The new criteria include 10 new
pathologies and 14 new therapeutic groups. The pathologies that
summed more criteria in the 2008 version were pain (10), hyperco-
agulability (9) and depression (8), with respect to the 2014 version
that include hypercoagulability (13), pain (12) and arterial hyperten-
sion (7). The drugs that accumulate more criteria in the 2008 article
are NSAIDs (14), antipatelet agents (10) and anticholinergic (8) and
in the 2014 version are blood thinners (11), antipatelet agents (10),
NSAIDs (6), and beta-blockers (6).

Conclusions: the new STOPP/START criteria have introduced
quantitative and qualitative changes, covering a greater number of
pathologies and pharmaceutical groups in consonance with the new
scientific evidence with elderly patients. A periodic revision of the
criteria is crucial for prescription optimization.
A COMPUTERIZED SYSTEM FOR REPORTING
AND ANALYSIS OF INCIDENTS, ERRORS OR
ADVERSE EVENTS: RESULTS OF 2014

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Background: Incidents, errors or adverse events affect 10 to 17% of hospitalized patients; more than half are related to drugs. The Functional Unit of Risk Management (FURM) has developed a Computerized System for Reporting Incidents, errors or adverse events (SINORES) for its acronym in Spanish) which is voluntary, anonymous and confidential, allowing the analysis through online collaboration with Responsible of Clinical Safety (RCS) of the units involved. We described the results of the first year of work.

Methods: SINORES has been developed as a project of JAVA programing Struts frame work as a database using Microsoft SQL Server with functionalities: (i) reporting form, and subsequent consult by the notifier by an identification code, (ii) information of method, characteristics and conditions of the system, (iii) management of incidents with 3 profiles: administrator, manager and RCS, (iv) communication between users of the system. Procedure: managers (4 FURM’s members) access to the notifications assign state (open, in process, implementing improvements, closed), priority (high, medium, low), and assigned 2 or 3 RCS that analyse the notification. Once the analysis (not visible to the notifier) has been completed, managers decided the actions (visible to the notifier) and together with RCS monitoring the recommendations.

Results: SINORES received 203 notifications in 2014: medication/vaccine (63 notifications), continuity of care (18), infrastructure (17), diagnostic test (17), patient monitoring and care (16), patient identification (13), therapeutic procedure (10), clinical/diagnosis assessment (10), rest of phases (39). Were decided 104 systemic actions, of them one generalizable action to improve “the prescription and administration of intravenous paracetamol”.

Conclusions: SINORES facilitates the notification and the study of incidents, allowing standardization of the procedure in the hospital, keeping the main features of confidentiality and feedback from the notifier. The system allows knowing the circumstances that favour the occurrence of human errors and system failures, to improve the defenses of the organization.

A PHARMACOVIGILANCE PROGRAM FROM
LABORATORY SIGNALS IN HOSPITALIZED PATIENTS: RESULTS OF 2014

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Background: Adverse drug reactions (ADR) are considered to be among the leading cause of morbidity and mortality. Detection, diagnosis and reporting of serious ADR (SADR) have become important components of activities performed in hospitals. A prospective Pharmaco vigilance Program from Laboratory Signals (PVPLS) at a Hospital (PPLSH) was developed in 2007, method and results published (Ramirez et al. CPT 2010; 87:74–86). We present the results of an improved PPLSH in 2014.

Methods: Fourteen Automatic Laboratory Signals (ALS) (agranulocytosis (neutrophils <300 mm3), pancytopenia (white blood cell count <3.5 × 109/μL), hemoglobin <10 g/dL, and platelet count <50 × 109/μL), thrombocytopenia (platelet count <20 × 109/μL), anemia (hemoglobin <6.5 g/dL), coagulopathy (prothrombin activity <14% or cephalin ratio <3ULN), eosinophilia (eosinophils account and percentage >15%), liver injury (ALAT >500 μL), pancreatitis (amylase x3ULN or lipase x3ULN), acute kidney injury (creatinine >4 mg/dL), rhabdomyolysis (creatinine-kinase x5ULN), hyponatremia (<122 mmol/L), hypokalemia (<2 mmol/L), hyperkalemia (>7 mmol/L), and hypoglucremia (<30 mg/dL)) were monitored at admission and during hospitalization of all wards. Patients who died in the emergency were also included.

Results: At least 4926 patients experienced at least 1 ALS. The review of electronic medical records (EMR) showed that no alternative cause (i.e. no non-SADR explanation) for ALS was identified in 955 (20%) of the patients. After the individual ALS-patient revaluation, a total of 702 SADR (14% of those identified after reviewing EMR and 71% of those requiring individual patient evaluation) were identified: agranulocytosis (29 cases), pancytopenia (21 cases), thrombocytopenia (10 cases), anemia (71 cases), coagulopathy (44 cases), eosinophilia (29 cases), liver injury (261 cases), pancreatitis (32 cases), acute kidney injury (71 cases), rhabdomyolysis (28 cases), hyponatremia (32 cases), hypokalemia (23 cases), hyperkalemia (13 cases), and hypoglucremia (18 cases). In order to identify a single SADR, we had to review the EMR of 7 patients and personally visit 1.4 patients.

Conclusions: The implementation of PPLSH allowed the detection and diagnosis of 702 SADR. The election of the ALS and the quality of EMR allowed an improvement in the effort to detection and diagnosis of SADR.

DOING CIPROFLOXACIN IN UNCOMPLICATED URINARY TRACT INFECTIONS
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Introduction and Background: Uncomplicated urinary tract infection (UTI) infections are the commonest bacterial infections in community. Recently ciprofloxacin has become a popular treatment option. However, with increasing resistance to ciprofloxacin, adequacy of current dosing regimens became questionable.

Methods: Ciprofloxacin sensitivity was tested on 4 urinary bacterial isolates. Pharmacodynamic parameters (minimum inhibitory concentrations (MIC) and postantibiotic effect) were determined. MIC values were incorporated with ciprofloxacin pharmacokinetic profile using pharmacokinetic/pharmacodynamic efficacy index, Cmax/MIC, which is known to correlate with therapeutic response, in order to compare two dosing regimens of ciprofloxacin: 250mg/12h and 500mg/24h, usually used in treatment of uncomplicated UTI.

Results: Urinary concentrations of ciprofloxacin are twice higher after a single 500 mg dose (15, 16) than after a 250 mg one (236 and 518 μg/mL, respectively) and are still high at the end of dosing interval (23 and 32 μg/mL). When PK/PD ratios were calculated, both dosing regimen produced Cmax/MIC values high above the desired threshold of 10 for all tested bacteria and for both dosing regimens, concentrations stay above the MIC (T>MIC) through whole dosing
interval. Dosing regimen of 500mg/24h showed supremacy over 250 mg/12h producing higher peak concentrations in urine.

Conclusion: The 500mg/24h dose should produce faster eradication rate and slow the development of resistant strains. With the advantage of higher compliance once daily, 500mg ciprofloxacin seems a better option for treatment of uncomplicated UTI.

The work is part of Republic project No 41012.

USE OF DRUGS FOR MALIGNANCY IN EU VS NON-EU EUROPEAN COUNTRIES

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Background and Introduction: Consumption of drugs for malignancy treatment varies between countries. Developed countries have higher allocations for health protection, more resources for the treatment of malignant diseases and better access to expensive drugs.

Material and Methods: The authors have used the available data on consumption of anticancer medicines in Serbia, Slovakia and Norway during the year 2012. Data, analyzed using Microsoft Excel, are expressed in grams of active ingredient per million in one year as well as in Euro spent for this drugs.

Results: Demographic data indicate that mortality due to malignant diseases in Slovakia and Norway was 2100 deaths per million inhabitants, while in Serbia mortality was slightly higher, 3050 deaths per million inhabitants. In Slovakia 190 million Euros was allocated for drugs for malignancies, or about 37 million Euros per million. In Serbia, only 73 million Euros for anticancer medicines, or about 10 million Euros per million was allocated, which is much less compared to the Slovak republic and Norway. Data on consumption of 10 most expensive oncology drugs show that the least of these drugs are consumed in Serbia regard to the consumption in Slovakia and Norway. Among them, the most consumed oncology drug in Serbia is trastuzumab, used in the treatment of metastatic breast cancer. For this indication is also used cheaper lapatinib, which has the highest consumption among the most expensive drugs in Slovakia.

Conclusion: Countries with lower GDP have less availability of anticancer medicines in amount and in quantity. Despite this fact, between the selected countries there are not drastic differences in mortality. Countries with lower GDP, must use wisely oncology drugs if they want to allocate their resources for treatment of other diseases as well.

The work is part of Serbian Republic project No 41012.

INTERACTIONS BETWEEN ANTIBIOTICS AND ORAL CONTRACEPTIVES – A NEED FOR CLARIFICATION

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Introduction: The discussion about the possible interactions between oral antibiotics and oral contraceptives (OCs) is not new. However, it remains a subject that generates controversy among the scientific community. There are several mechanisms proposed that explain these antibiotic-associated interactions. Although the general risk of interaction is low, sporadic cases of oral contraceptive failure during antibiotic therapy continue to be reported. The objective of this study was to determine the effect of the antibiotic therapy in OC’s efficacy and which mechanisms are involved in this process.

Material and Methods: Literature search in PubMed and in Google Scholar. A total of 52 articles were selected for analysis and other 21 articles were identified by review of the references cited in these publications. Articles were selected based on information related to antibiotic therapy and OC’s efficacy relationship. All different classes of antibiotics were analyzed, including 40 different antibiotics, which were crossed with 10 OC data, searching for possible interactions between antibiotics and OCs and loss or commitment of efficacy.

Results: Most of the analyzed antibiotics decreased the level or effect of OC indirectly by altering intestinal flora, remaining a low risk of contraceptive failure. However, the main adverse reactions reported with the use of antibiotics include: nausea, vomiting and diarrhea, which could also have interference on the efficacy of OC’s. Furthermore, some antibiotics can modify the level or effect of OC’s by affecting hepatic/ intestinal enzymes metabolism or by P-glycoprotein (MDR1) efflux transporter.

Conclusions: Some potential severe interactions were identified and the mechanisms involved were detected. Pharmacy professionals play an essential role regarding the communication of information to women consuming OC’s that will start antibiotic therapy. Patients should be advised to add extra precautions during the therapy and for seven days after finish the antibiotic.

SIGNIFICANT DRUG-DRUG INTERACTION BETWEEN ZOLPIDEM AND CLARITHROMYCIN

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Introduction: Zolpidem is indicated for the short-term treatment of insomnia and belongs to a class of medications called sedative-hypnotics. Zolpidem is mainly metabolized by CYP3A4. Clarithromycin, which is used to treat bacterial infections including pneumonia and bronchitis, is known as a potent CYP3A4 inhibitor. Therefore, the aim of the study was to investigate the effect of clarithromycin on the pharmacokinetic parameters of zolpidem.

Material and Methods: Twenty-four healthy Korean subjects were volunteered in the our study. All subject received a single 5 mg oral dose of zolpidem after overnight fasting in the control phase. In the clarithromycin phase, a single 500 mg oral dose of clarithromycin was administered to every subject twice in a day for 5 consecutive days. Each subject received a single oral dose of zolpidem and clarithromycin on a study day. Blood samples were collected up to 12 hours after drug administration and LC-MS/MS was used to validate the plasma concentrations of zolpidem.

Results: AUC∞ of zolpidem in clarithromycin phase increased by 1.66-fold, compared to control phase (P < 0.001). t½ of zolpidem in clarithromycin was significantly prolonged after the administration of clarithromycin (P < 0.001). Also, the apparent oral clearance (CL/F) zolpidem in clarithromycin phase decreased by 34.8%, compared to control phase (P < 0.001).

Conclusions: Therefore, clarithromycin had significant impacts on the pharmacokinetics of zolpidem, leading to prolong the plasma exposure of zolpidem.

PHARMACOKINETICS OF ZOLPIDEM IN RELATION TO CYP2C19 GENOTYPE AFTER ADMINISTRATION OF CYP3A4 INHIBITOR

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Introduction: Zolpidem is indicated to treat sleeping problems. Zolpidem is predominantly metabolized to its inactive metabolite...
**THE INFLUENCE OF ELECTROLYTE STATUS AND CONCOMITANTLY USED MEDICATIONS ON CORRECTED QT INTERVALS IN METHADONE MAINTENANCE TREATMENT PATIENTS – A CROSS SECTIONAL STUDY**

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**Introduction:** Methadone is a synthetic agonist of opioid receptors which is used in methadone maintenance treatment (MMT) of opiate addicts. It belongs to a group of medications which can provoke a prolongation of the QTc (corrected QT) interval in the electrocardiogram (ECG) and thus increase the risk of the development of potentially fatal arrhythmias - *tossades de pointes*. The aim of the study was to assess the influence of the electrolyte status and concomitantly used medications on QTc in MMT patients.

**Material and Methods:** During January 2015, 40 MMT patients were recruited from the outpatient MMT centre. ECG (to calculate QTc interval) and blood sampling (to determine potassium, magnesium and calcium levels) were performed in all study participants at one time point. Patients were also interviewed about their current methadone dose, duration of MMT, recent increase in methadone dose, and other drugs used in combination with methadone.

**Results:** Mean QTc interval was 430.66 ± 29.76 ms. Mean levels of potassium, magnesium and calcium were 4.51 ± 0.41 mmol/L, 0.87 ± 0.06 mmol/L and 2.40 ± 0.10 mmol/L, respectively. Mean methadone dose was 64.74 ± 18.12 mg, while mean duration of MMT was 1086.24 ± 1222.78 days. In the univariate analysis, QTc correlated significantly with methadone doses and the duration of MMT (r = 0.40, P = 0.01 and r = 0.33, P = 0.04, respectively), while no significant correlation was observed between QTc and electrolyte levels (r = 0.06, P = 0.75; r = 0.13, P = 0.46; r = 0.06, P = 0.72, respectively). Thirty-three patients used methadone in combination with other drugs. The mean number of concomitants was 1.97 ± 0.21. The most commonly used drug was diazepam, taken by 24 patients. Neither recent increase in methadone dose, nor concomitantly used medications influenced QTc (436.25 ± 29.9 vs 427.56 ± 29.82 ms, P = 0.41 and 433.55 ± 23.9 vs 415.07 ± 44.13 ms, P = 0.35, respectively).

**Conclusion:** It is highly advisable for health care professionals to be informed about risk factors for the development of arrhythmias in MMT users, particularly in those receiving higher methadone doses.

**Acknowledgement:** The Ministry of Education and Science of the Republic of Serbia (grant numbered 172050) supported this research work.

**DRUG INTOXICATIONS TREATED AT THE EMERGENCY CENTER OF CLINICAL CENTRE OF VOJvodina in 2013**

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**Introduction:** Intoxications caused by the large number of xenobiotics have become an increasingly important issue in the emergency medicine. In the etiology of 60 to 80% of intoxications are various drugs. The aim of this survey was to determine the incidence and characteristics of drug intoxications in 2013 at the territory of South Baćka district.
**Materials and Methods:** Data were collected from medical records of patients hospitalized under suspicion of drug intoxications at the Emergency Centre of Clinical Centre of Vojvodina during observed period.

**Results:** During 2013, 1078 patients were hospitalized under suspicion of drug intoxication, which was confirmed in 47.22% of them. The largest number of patients was hospitalized in January and December, and most of them were females (62.87%). The average age of patients was 40 years. The most commonly found drugs were benzodiazepines (89.9%), followed by analgesics (23.18%), antiepileptics (14.15%), antidepressants (13.9%) and antipsychotics (10.6%). All the patients took drugs orally. Suicidal intention of drug intake was recognized in 72.89% of patients, while 27.11% of them took drugs accidentally. A majority of patients (76.23%) coingested drugs with alcohol, while 23.77% consumed only drugs.

**Conclusions:** Health and education directives are needed in order to prevent drug intoxications, as a significant medico-social problem.

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**SCReN: SPANISH RESEARCH NETWORK; ONE-YEAR EXPERIENCE**

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**Background or Introduction:** The Spanish Clinical Research Network (SCReN) is transversal in structure with a decentralized organization supported by the Spanish institute of health (Instituto de Salud Carlos III), and cofinanced by European Federation FEDERs. As a professional network provides service for the implementation of cooperative clinical research projects, (national or international) initiated within the integrated sites, co-operative research groups, academic institutions, health authorities and other fundamental players on the scene of biomedical research. SCReN is a network of 29 Clinical Trials Units integrated in healthcare centres across Spain at both hospital and primary healthcare levels. Clinical Pharmacologists play a central role in running the network and coordinating activities, in close coordination with other healthcare professionals.

**Material and Methods:** During its first year of life (2014) SCReN core activity was focused on building a solid network structure.

- Definition and acceptance of a strategic model with four main areas: Coordination; Regulatory and Monitoring; Pharmacovigilance; Statistics and Data Management.
- Harmonization through the approval and implementation of the quality plan (SOPs).
- Nodes interconnection by the definition of the technology architecture model.
- Capacitation of the network.

**Results:** The resources and efforts invested in the development of the infrastructure enabled the network to conduct 19 clinical trials, with a total of 219 individual sites collaboration. Additionally, the executive committee identified 10 high quality trials to be initiated in 2015. SCReN was born with the aim to empower the development of clinical trials providing a professional network focused on no commercial research. SCReN successfully make the first step in achieving our goals with the inclusion of 19 complex clinical trials, providing infrastructures to guarantee and preserve the quality of the studies, the patient safety and data reliability. 2015 will be the consolidation year, when the project related activity would increase.

**COMMERCIAL MOVIES TO TEACH NON-MEDICAL AND UNDESIRABLE USE OF DRUGS**

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Screening And Recruitment Procedures of Healthy Volunteers In A Phase I Clinical Trial Unit

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Introduction: The use of commercial films to illustrate a health problem is a common experience in university teaching of health sciences. The objective was to illustrate nonmedical or undesirable use of drugs using different commercial films in teaching of clinical pharmacology.

Materials and Methods: We selected the following non-medical and undesirable uses: chemical submission, induction of addiction, poisoning, lethal injection (death penalty), improved sexual performance, neuroenhancement (smart drugs) and drugs and crime. Search for films that had scenes corresponding to these uses were collected using the New York University’s School of Medicine (NYU) literature, arts and medicine database, and the Film Affinity and Internet Movie Databases (IMDb). In addition we used our own archives and memories to select the adequate movies.

Results: We chose the following movies to illustrate such use: Seeking Miguel (2007) for chemical submission, Revenge (1990) for the induction of addiction, Murder my sweet (1944) for poisoning, Dead Man Walking (1995) for lethal injection, Something’s Gotta Give (2003) for the use of drugs enhancing sexual performance, Limitless (2011) for neuroenhancement, and Zulu (2013) for drugs and crime. For each film we redacted a list of learning objectives and a list of questions that could be answered by the students the end of the session.

We have introduced some of films in seminars of clinical pharmacology and drug addictions.

Conclusions: It is concluded that the films are of interest to illustrate such practices in the domain of medicine and clinical pharmacology.

Acknowledgements: Clara Pérez-Maná, Esther Papase and Liliana Galindo are Rio Hortega fellowship (Instituto de Salud Carlos III-SCIII, CM12/00085, CM13/00016, CM14/0011).

RECENT DEVELOPMENTS IN CLINICAL TRIAL REGULATIONS IN INDIA

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Clinical research was rapidly growing in India because of cost advantage, treatment naive patient, qualified doctors conversant in English etc. However isolated unethical incidences resulted in trust deficit amongst stake holders. The fluid situation lead to a sharp decline in trials during last three years. India accounts for 20% of global disease burden but hosted only 1.5% of global clinical trials in the past 2 years. A series of corrective measures, some due to judicial intervention, lead to sweeping changes in drug regulatory scenario. These directives include 1) Mandatory registration of clinical trials from February 2013. 2) Compulsory audio–visual recording of informed consent process since Jun 2013. 3) Registration of Institutional Ethics Committees (IEC) since February 2013. IECs have to monitor and report serious adverse events (SAEs) under strict timelines and opinion on compensation. 4) The drug regulator (DCGI) is required to forward the reports by investigators, sponsors and ethics committees to the national expert committee within 150 days of SAE occurrence. This committee has to analyze and give final recommendations regarding causality and compensation. 5) Financial compensation for trial related injuries or death, calculated as per a comprehensive formula, is now a mandatory responsibility of sponsor. The formula ensures that younger participants get more compensation as compared to older participants. The final order of the DCGI has to be complied within 30 days. 6) Accreditation of principal investigators (PIs), IECs and the trial sites has been recommended to ensure competence. To ensure adequate trial supervision, number of trials per investigator is being restricted. This regulatory overhaul highlights the national commitment to patient safety, ethics and confidentiality. However, there is some apprehension regarding some grey areas. Once, more clarity emerges, it is envisaged that clinical research in India will quickly scale up in a much safer, regulated and enabling environment.

THE ANALYZE OF CONSUMPTION OF DRUGS FOR THE TREATMENT OF CHRONIC RESPIRATORY DISEASES IN THE REPUBLIC OF SERBIA, CROATIA, NORWAY AND FINLAND FROM 2009 TO 2012

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Introduction: Chronic respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD), are responsible for 4 million deaths globally in 2012. Drugs for the treatment of chronic respiratory diseases are often used group of drugs.

Aim: The aim of this study was to analyze consumption of drugs for the treatment of chronic respiratory diseases in the Republic of Serbia, Croatia, Norway, and Finland from 2009 to 2012.

Material and Methods: Data about use of drugs were taken from the Agency for drugs and medical devices of Serbia, Agency for medicinal products and medical devices of Croatia, Finnish Medicines Agency Fimea and Norwegian Institute of Public Health.

Results: Drugs which are used in therapy of respiratory diseases are, in Serbia, in the sixth place, in Croatia in the fifth, in Norway and Finland they are in the fourth place of total consumption of drugs for the period that we observed. In all of the 4 countries the highest consumption of drugs is the one that is used in therapy of chronic obstructive pulmonary disease (R03 group). The most used drugs from this group in Serbia and Croatia are Xanthishes but in Norway and Finland those are the drugs of new generations-R03AK (Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics).

Conclusion: The drugs are unequally used in therapy of respiratory diseases in the mentioned countries. In the first place are the drugs in therapy of COPD. In Serbia and Croatia the most used drugs of R group are much different in regard to Norway and Finland.

Acknowledgement: This research was supported by Provincial Secretariat for Science and Technological Development, Autonomous Province of Vojvodina project No 114-451-2458/2011 and by Ministry of Science, Republic of Serbia, project no 41012

Key words: COPD, consumption of drugs, pharmacoepidemiology

REGULATORY GUIDELINES FOR THE DEVELOPMENT OF TOPICALLY APPLIED PRODUCTS IN ATOPIC DERMATITIS AND PSORIASIS

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Background: Obtaining an early proof of activity is one of the key milestones in drug development. The early development of products for the topical treatment of dermatological inflamma-
Clinical Therapeutics

TOLERABILITY OF PREDNISONE AND DEXAMETHASONE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Therapy of acute lymphoblastic leukemia includes the use of high doses of glucocorticoids (prednisone and dexamethasone), which significantly increase the success of therapy because of its lipophilicity.

Aim: The aim of the study was to determine tolerability of high doses of prednisone and dexamethasone in children with acute lymphoblastic leukemia and the structure and the intensity of adverse effects, occurred following these medicines.

Material and Methods: In a prospective study, histories of the children suffering acute lymphoblastic leukemia treated in the Institute for Child and Youth Health Care of Vojvodina, since December 2010 until October 2014, were analyzed. This study includes 18 patients, aged from 2 to 15 years.

Results: Hyperglycemia appeared in 89% of patients treated with prednisone and in 61% of patients treated with dexamethasone. To control the high blood glucose above 10 mmol/L, in 11% of patients insulin was used. Hypertension appeared in 28% patients treated with prednisone and dexamethasone. Anthypertensives were needed for regulation in 11% patients. Hypopotassemia and hypocalcaemia were significantly more expressed after the use of prednisone in comparison to dexamethasone. In 11% of patients, the treatment with dexamethasone caused depressive behavior, followed by agitation.

Conclusion: Adverse effects of dexamethasone and prednisone, administered in high doses in children with ALL, were known, expected and reversible. Adverse reaction were usually disappeared spontaneously or after short-term symptomatic therapy.

Acknowledgement: This research was supported by Provincial Secretariat for Science and Technological Development, Autonomous Province of Vojvodina project No 114-451-2458/2011 and by Ministry of Science, Republic of Serbia, project no 41012.

Key words: prednisone, dexamethasone, acute lymphoblastic leukemia, adverse effects, children.

ANTI-HISTONE ANTIBODIES IN HIV-INFECTED PATIENTS ON NEVIRAPINE-CONTAINING ANTIRETROVIRAL THERAPY

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Background: The anti-HIV drug Nevirapine (NVP) has been associated with severe liver and skin toxicity. NVP bioactivation in man leads to the formation of electrophilic metabolites that generate covalent adducts with proteins (1), a mechanism proposed to be at the genesis of NVP toxicity. These results, combined with our reports of NVP-induced genic alterations in rat(2) and in vitro evidence of histone adduct formation (3), led us to screen anti-histone antibodies (AHA) in patients and explore their relationship with NVP metabolites.

Methods: This study was approved by the Hospitals’ Ethics Committees and subjects have signed an informed consent. A comparison was performed between AHA titres in 2 cohorts of patients: naive versus treated with NVP for more than 12 weeks. Moreover, we explored the association between the concentrations of NVP and metabolites and AHA titres. A prospective exploratory study (weeks 0, 2 and 12) was also conducted to investigate AHA titres in patients initiating treatment with NVP (200mg PO qDay for 2 weeks and 400mg PO qDay thereafter). The concentrations of NVP and its phase I metabolites were quantified by HPLC (4) and IgG class autoantibodies to histone H2A-H2B dimers by ELISA.

Results: AHA titres were higher in naive patients [n = 29, 15 (10-22) U/mL] than in patients on chronic NVP use [n = 37, 10 (5-15) U/mL, P = 0.0064]. Patients with undetectable 2OH-NVP had higher AHA [n = 14, 15 (12-18) U/mL] than those with detectable concentrations [n = 23, 9 (4-14) U/mL, P = 0.007]. AHAs were inversely correlated with the concentration of 2OH-NVP (r = 0.5776, P = 0.0049). AHAs (n = 8) in weeks 0, 2 and 12 were respectively 20 (16-21); 4 (3-5) (P = 0.0001) and 17 (14-20) U/mL.

Conclusions: Low doses of NVP caused a rapid but short-lasting decrease in AHAs. In chronic treatment with therapeutic doses, AHAs were negatively associated with the 2OH-NVP levels in a dose-dependent manner. The significance of these findings is presently unknown and warrants further investigation.

References:

Acknowledgments: FCT, PORTUGAL (RECI/QEQMED/0330/2012), (IF/01091/2013/CP1163/CT0001).
POST-ANESTHETIC APNEA PREDICTIVE OF
THE TERMINAL PHASE OF A CONVULSIVE
ENCEPHALOPATHY WITH A CHROMOSOME
1q21.1 MICRO-DUPPLICATION

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France; 3Néonatalogie, CHU de Caen, France; and 4Génétique
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In postoperative periods apnea can be attributed to excessive doses
of opioids and/or sedative drugs or pharmacokinetic or pharmacody-
namic abnormalities, or even dosing errors. Generally the frequency
and respiratory rate are returned to normal after a short time with
help of naloxone administration.

Clinical History: Third child in a family without inbreeding nor
hereditary disease. Pregnancy and birth were normal. Apgar’s scores:
10 all the time. Weight, size, and cranial perimeter were normal. For
the third month there was a major psychomotor retardation with
convulsive encephalopathy. He had amblyopia with major altera-
tion of visual and auditory evoked potentials. At 5 years old, a MRI
displayed diffuse cortico-subcortical atrophy, major lesions of puta-
men and thalamus. MR spectroscopy: increase in lactate in putamen,
and fluctuations in N-acetyl aspartate decreased in putamen and
increased in periaqueductal cortex. De novo genetic abnormality
could be characterized: microduplication (1.2-3 Mb) in chromo-
some 1q21.1. Epilepsy was treated with valproic acid 520 mg/d,
Gabapentin 1000/1000/day, Levetiracetam 900 mg/d (usual doses for the
weight). The child had few surgical interventions for gastrosomy
and dental extractions.

Last anesthesia was made by sufentanil and propofol; 1 hour after
lack of spontaneous breathing despite the injection of naloxone. He
suffered of episodes of hypventilation with hypercapnia but can
be slowly weaned respirators; and returned home at postoperative
D6; the days after appeared anachoric respiration and he was again
admitted to pediatric intensive care. The neurological exploration
confirms the failure of the respiratory drive. His status gradually
worsens and the child died 6 weeks later. Postoperative apnea was
considered not related to epileptic equivalents and neither linked to
opiate or sedative overdose.

Conclusion: several weeks before the final brainstem failure drug
induced apnea revealed the final phase of this encephalopathy whose
etiology remains unknown.

COMPARATIVE BIOAVAILABILITY OF
ARIPIPRAZOLE TABLETS AND ORALLY
DISINTEGRATING TABLETS IN YOUNG HEALTHY
VOLUNTEERS

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Introduction: Aripiprazole is a third-generation antipsychotic used
in the treatment of schizophrenia and moderate to severe manic epi-
sodes in bipolar I disorder and for the prevention of a new manic
episode in patients who experienced predominantly manic episodes
and whose manic episodes responded to aripiprazole treatment. The
aim of our study was to compare the bioavailability of tablets and
orally disintegrating tablets (ODT), both in men and women.

Methods: The study population included 167 healthy volunteers
receiving 10 mg aripiprazole in 6 single dose clinical trials (3 Abilify®
tables and 3 Abilify® ODT) under fasting conditions. Seventy-five
subjects (48 male and 27 female) received tablets and 90 subjects
(49 male and 41 female) received ODT. Plasma concentrations were
measured by HPLC coupled to mass spectrometry. The pharmacoki-
netic parameters were calculated by a non-compartmental method
using WinNolin program and adjusted for weight. The difference
between pharmacokinetics data of tablets versus ODT; and male
versus females were compared by T test using SPSS.

Results: Pharmacokinetics data were similar for both formulations:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ODT</th>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t</td>
<td>55.10 (25.63)</td>
<td>59.92 (28.73)</td>
</tr>
<tr>
<td>Cmax</td>
<td>32.70 (14.66)</td>
<td>32.02 (12.97)</td>
</tr>
<tr>
<td>T1/2</td>
<td>4.02 (2.33)</td>
<td>3.12 (2.00)</td>
</tr>
<tr>
<td>T1/2</td>
<td>53.50 (25.63)</td>
<td>54.21 (30.27)</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters were calculated by a non-compartmental method
using WinNolin program and adjusted for weight. The difference
between pharmacokinetics data of tablets versus ODT; and male
versus females were compared by T test using SPSS.

The results only showed differences in Cmax and T1/2 between
males and females for orally disintegrating tablets formulation.

Conclusion: Bioavailability of both formulations, standard and
orally disintegrating tablets of Abilify® were similar. There were no
gender differences in pharmacokinetics for tablets. Only appeared
differences for ODT formulation, Cmax was higher in males than
females and T1/2 is higher in females than males and tablets
formulation.

Epidural Methyldprednisolone Versus
Transdermal Fentanyl in Treatment
And Prevention Complication of Acute
Herpetic Lesion

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Background: Herpes zoster (HZ) results from reactivation of var-
cella-zoster virus and spreads from a single ganglion to the neural
tissue of the affected segment and the corresponding cutaneous
dermatome. Currently, there are no preventative drug treatments for HZ
or postherpetic neuralgia (PHN), and although some treatments are
available, pain control is often difficult and unsatisfactory.

Patients and Method: This study was performed on 40 outpatients
suffering from acute herpetic pain below dermatome L1 and skin
 rash. They were classified into 2 groups (D group, group E) accord-
ing to regimen of treatment as following. Group D received acylo-
vir with gabapentin with fentanyl transdermal patch 75 µg every
3 days for 14 days. Group E received acyclovir with gabapentin
with epidural injection of bupivacaine 6 to 12 mL (0.25%) with 40
mg methylprednisolone as 3 separate injection for 14 days. In both
groups, patients followed up by the Wong/Baker faces rating scale
for pain assessment, and if the pain was continuous after 14 days, the
treatment was continuous until pain sensation disappeared.

Results: In group E, there were no significant changes regarding
analgescic effect when comparing first day pain score with that of
fourth day. On other hand, there is a significant change between 1st
day score and that of the 15th day, 1st, 3rd and 6th months. In group
D, there was significant change between first day score and that of
day fourth, 15th day, first, third and sixth months. The incidence of
PHN is high in group D (40%) as compared with group E (10%).

Conclusions: We concluded that regimen used in group D provides
an adequate analgesia but carries high risk of developing PHN; on
AN EDUCATIONAL INTERVENTION TO IMPROVE ANTIBIOTIC USE IN THE CENTER REGION OF PORTUGAL

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Background: Microbial resistances are one of the most important problems of public health, and it has been associated to the misuse of antibiotics. Inadequate antibiotic prescription and self-medication (with antibiotic leftover or by acquiring antibiotics directly in the pharmacy without a prescription), are behaviours directly related with this misuse, revealing the necessity of interventions directed to health professionals. The aim of this study is to improve the consumption of antibiotics through an educational intervention directed to community pharmacists and primary care physicians.

Material and Methods: A cluster randomized trial in the region center of Portugal. Of the 8 clusters, 4 clusters received an educational intervention and the other four clusters did not receive any intervention and were included in the control group. Educational intervention consisted of group sessions with physicians and group sessions with pharmacists. In the sessions groups it was presented information about the problem of microbial resistances and each session was focused in the identified attitudes that influence the behaviour of physician during antibiotic prescription or the behaviour of pharmacist during the dispensation of antibiotics in pharmacies. At the end of each group session, were distributed flyers and poster about the importance of the adequate use of antibiotics to be diverted to the patients. The data of antibiotics consumption was compared between the intervention group and the control group.

Results: The intervention was well received for the pharmacists and the trend in expenditure for the 22 regions ranged from –£3106 per 1000 PUs per year to £229 per 1000 PUs per year. There was significant positive association between trend in expenditure and deprivation (Spearman’s rho = 0.50, P = 0.018). There was also a significant relationship between expenditure for the financial year 2013–2014 and deprivation index (Spearman’s rho = 0.56, P = 0.007).

Conclusions: This study indicated that although deprivation appeared to be related both to absolute primary care expenditure and the trend in expenditure between geographical regions of Wales, other factors may also be associated with variation in prescribing costs and trends. Further work is needed to ascertain the nature of these factors and their relative influence.

OFF-LABEL PRESCRIPTIONS IN PALLIATIVE CARE PATIENTS AT HOME CARE UNIT*

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The use of off-label drugs is considered to be frequent. This study aims to describe and to quantify the off-label use of drugs prescribed to palliative-care patients just before admission in a Home Care Unit and explore the motives of off-label use. The secondary aim was to study if the off-label prescriptions were according to the most used guides in our environment (we tried four of them).

Methods: A cross-sectional study was carried out. Informed consent was obtained from patients admitted to 20 beds at a Home Care Unit for a 6 month period. Demographic and anthropometric characteristics, clinical background, current disease, and prescriptions just before admission were registered. Medications were analysed to determine whether they had been used according to the terms of the summary of product characteristics (SmPC).

Results: Eighty-seven patients (52 women) were included; mean age 67,2; IC95% 64,7–70,1. They received 678 prescriptions (315 different pharmaceutical products). Patients received from 2 to 15 (mean = 7,8) medications for treating 553 health problems (113 different diagnoses). Opioid analgesics were the most commonly used drugs according to the pain which was suffered by 86,2% of the patients. One hundred eight prescriptions (15.9%) involving 67 (77.0%) patients were off-label due to their use in disagreement with the indications authorised in the SmPC. Ten medications affecting 7 patients were off-label due to the lack of SmPC. The prophylaxis of ulcer by proton pump inhibitors and the palliative care in patients with terminal cancer by corticosteroids were the most frequently used off-label drugs. According to the 4 guides included in this study, just 24 of the off-label prescriptions were not suggested by the authors.

ANALYSIS OF PRIMARY CARE MEDICINES EXPENDITURE IN RELATION TO MEASURES OF DEPRIVATION IN WALES UK

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Background: The National Health Service in Wales (UK) provided healthcare to a population of approximately 3.1 million during the financial year 2013 to 2014. Services were delivered by 7 health boards (subdivided into 22 geographical regions) and 1 hospital trust. The combined routine drug expenditure was approximately £800m, of which primary care accounted for approximately £569m. Considerable variation was observed in primary care spend across the geographical regions. We examined trends in primary care expenditure in the 22 regions to determine whether any of the variation in prescribing might be associated with differences in deprivation measures between regions.

Methods: Annual primary care drug usage data (measured as cost per 1000 prescribing units [PUs]) for the 22 regions were obtained for the period June 2004 to March 2014. Deprivation rank was obtained from the Welsh Index of Multiple Deprivation 2014. Trend in expenditure was determined using linear regression analysis and the slopes of the regression lines (as well as absolute expenditure for 2013–2014) ranked and correlated with deprivation for each region using Spearman’s correlation analysis.

Results: The trends in expenditure for the 22 regions ranged from –£3106 per 1000 PUs per year to £229 per 1000 PUs per year. There was significant positive association between trend in expenditure and deprivation (Spearman’s rho = 0.50, P = 0.018). There was also a significant relationship between expenditure for the financial year 2013–2014 and deprivation index (Spearman’s rho = 0.56, P = 0.007).

Conclusions: This analysis indicated that although deprivation appeared to be related both to absolute primary care expenditure and the trend in expenditure between geographical regions of Wales, other factors may also be associated with variation in prescribing costs and trends. Further work is needed to ascertain the nature of these factors and their relative influence.
CYP2C9 GENOTYPE AND CLINICAL EFFECTS OF GLICLAZIDE

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Introduction: Gliclazide is an oral antidiabetic agent. It belongs to sulfonurea derivatives and may be used as a second choice agent. It is known to be metabolized by cytochromes P450 (CYP) 2C9 and 2C19. Clinical data showing influence of genetic polymorphisms on patient's individual outcomes are scarce. We evaluated effects of CYP2C9*2 and CYP2C9*3 polymorphisms on clinical response to gliclazide in Russian diabetic patients.

Material and Methods: Seventy-four patients who were diagnosed with type 2 diabetes mellitus, did not have obesity and did not have contraindications were prescribed gliclazide in the initial dose of 30 or 60 mg/day based on clinical judgement of endocrinologist. During clinical observation the dose could be adjusted, or the medication could be changed in case of insufficient clinical effect or intolerance. After initial treatment adjustments, patients were followed up to 6 month. Glycated haemoglobin (HbA1c) and 24-hour monitoring of glucose levels were registered. Blood samples for genotyping were collected, and analysed after collection of all clinical data.

Results: Twenty-eight patients (38%) were carrying mutated CYP2C9 alleles *2 or *3. By the end of the observation all patients had target HbA1c levels. In the group of mutant alleles carriers 21 patients (86%) achieved target levels on initial dose of gliclazide, compared to 14 patients (37%) in the group of noncarriers (P < 0.001). Mean effective gliclazide dose in mutation carriers was 53 ± 13 mg; in non-carriers − 84 ± 26 mg (P < 0.01). Mild hypoglycemic episodes were observed in only 1 patient in the group of mutations non-carriers and in 4 patients carrying CYP2C9*2 or *3. The difference was not significant.

Conclusions: Patients carrying CYP2C9*2 or *3 alleles achieved clinical effect on gliclazide alone more frequently, and required smaller doses. Frequency of hypoglycaemic episodes was not significantly different between the groups.

ESTIMATED PREVALENCE OF CONTRAINDIкатED, SEVERE AND MODERATE INTERACTIONS IN AMBULATORY PATIENTS WITH POLYPHARMACY IN A HEALTHCARE PROVIDER IN URUGUAY

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In this paper we present an estimate of the prevalence of contraindicated, severe and moderate interactions in ambulatory patients in a healthcare provider in Uruguay. We also present the most problematic drugs in this population, which will be used to make interventions to inform the results to the medical staff. In Uruguay, healthcare providers must dispense medication to outpatients. This healthcare provider has 60,000 members and dispenses more than 61,000 drugs to outpatients per month. Polymedication is defined as the set and daily use of 4 or more drugs. This usually provokes administration errors, low adherence or compliance, increased risk of drug interactions between other consequences. By an informatic system we identified 4293 patients (2843 women and 1451 men) who had taken out four or more drugs during the month of December 2014. 1,863 of them were <65 years old, which represent 66% of the population, and 2430 were >65 years old and represent 34%). After identifying the drugs involved we used an informatic system to seek incompatibilities, severe or moderate interactions. In 600 drugs involved in polypharmacy, we found 192 contraindications, 1979 severe and 2497 moderate interactions. The crossing of these data with the polymedicated patients profile is under study in order to identify which of these interactions actually happen. Once we detect the patients involved, we will analyze the status by studying the clinical history. If interactions are occurring, an intervention will take place in the patient's medical history alerting and explaining the interaction detected to carers physicians.
EFFECT OF SEX AND FORMULATION ON SINGLE-DOSE PHARMACODYNAMICS OF ARIPIPRAZOLE

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Introduction: Aripiprazole is a third-generation antipsychotic agent that possesses a unique mechanism of action. Orthostatic hypotension, QT prolongation, bradycardia and syncope are some of adverse events associated with aripiprazole. The objective of this study was to determine the effects of aripiprazole on blood pressure and electrocardiogram on single-dose studies in healthy volunteers.

Material and Methods: A total of 180 healthy volunteers participating in six crossover bioequivalence clinical trials were included after giving informed consent (102 men and 78 women). They received a single aripiprazole 10 mg tablet or orodispersable tablet twice. Blood pressure and heart rate were measured lying down on the days of admission before taking the medication, 30 minutes, 2, 4, 6 and 8 hours after the dose. Electrocardiogram was performed before the administration of the drug, and 4 and 8 hours after.

Results: Mean blood pressure [systolic blood pressure (SBP)/diastolic blood pressure (DBP)] at baseline, 30 minutes, 2, 4, 6 and 8 hours were 116/65, 110/63, 107/59, 109/59, 111/59 and 117/59 mm Hg, respectively. A decrease between 5 and 9 mm Hg in SBP and 2 and 6 mm Hg in DBP were showed at all times after administration of drug (P < 0.05) and in all subjects, but no differences were apparent in heart rate or between males and females. Moreover, the differences between tablet and orodispersable was only showed at 4 hours (P < 0.05) post-dose. Mean QTc prolongation was 8 ms at 4 and 8 hours after dosing (P < 0.05).

Conclusions: Our data show that a single dose of aripiprazole produces a small decrease in blood pressure and a small increase in QTc, but there was no change in heart rate. There were no differences between males and females.

ESTABLISHING CLINICAL PHARMACOLOGY IN SLOVAKIA: PAST, PRESENT AND FUTURE PERSPECTIVES

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Clinical pharmacology (CP) was successfully developed in Slovakia (SR) since 1970ies as an interdisciplinary medical specialty, endowed (SR) since 1970ies as an interdisciplinary medical specialty, endowed

INFLUENCE OF SOCIODEMOGRAPHIC AND PROFESSIONAL CHARACTERISTICS ON ANTIBIOTIC PRESCRIBING: A CROSS-SECTIONAL STUDY IN THE CENTER REGION OF PORTUGAL

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Antibiotic prescribing is a complex process influenced by medical and non-medical aspects. Our aim was to evaluate the influence of GPs’ sociodemographic and professional characteristics on the quality of antibiotic prescribing in Portugal.

**Material and Methods:** An observational cross-sectional study was conducted (November 2011 to February 2012) in the catchment area covered by Portugal’s Centre Regional Health Administration (1094 General Practitioners (GPs) working at 84 primary care facilities). A validated, self-administered questionnaire was used to assess sociodemographic and clinical practice information. 

**Introduction:** Socioeconomic and clinical practice information were evaluated. Logistic regression analysis was performed.

**Results:** The response rate was 46.6%. Older GPs revealed to have better performance of antibiotic prescribing [OR (95% CI) = 2.21; 1.08 – 4.54; P < 0.05]. About GPs who also work at the emergency department, the statistical significance was found on their relation with poor prescribing [OR (95% CI) = 0.29; 0.16 – 0.54; P < 0.05]. Workload also revealed to influence the quality of antibiotic prescribing: more patients seen per day [OR (95% CI) = 0.97; 0.94 – 1.00; P < 0.05] and more patients seen per week in the emergency department [OR (95% CI) = 0.98; 0.97 – 0.99; P < 0.05] were related with lower quality on antibiotic prescribing.

**Conclusions:** These findings revealed that socioeconomic and professional characteristics can influence the quality of antibiotic prescribing, which is a very important step to understand this complex process aiming to tackle a global concern: the misprescription of antibiotics.

**COMPARISON BETWEEN DRIED BLOOD SPOT AND PLASMA BOSENTAN PHARMACOKINETICS IN PAEDIATRIC PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION**

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**Actelion Pharmaceuticals Ltd, Allschwil, Switzerland**

**Background:** Plasma has been the historic matrix used for the determination of bosentan pharmacokinetic (PK) parameters. The FUTURE-3 study (NCT01223352) was a phase III paediatric PK trial conducted primarily to compare 2 bosentan dosing regimens in children aged from 3 months to 12 years. It offered the opportunity of sampling and analysis by the dried blood spot (DBS) method and to compare the results to plasma data.

**Material and Methods:** At steady-state, for each of the six time points of the PK profile, approximately 1.2 mL of venous blood was collected in an EDTA-coated tube. Prior to centrifugation, blood aliquots were taken from each tube and spotted on FTA DMPK-A cards (Whatman). To compare whole blood to plasma concentrations of bosentan, a blood-to-plasma distribution ratio of 0.6 was applied.

**Conclusions:** Bosentan concentrations measured by DBS are good estimations of bosentan plasma concentrations. DBS can be considered as a valid alternative to the plasma method for the analysis of bosentan PK in children with pulmonary arterial hypertension. Moreover DBS has the advantage of requiring a very low blood volume and the samples can be stored at room temperature.

**RESEARCH ETHICS COMMITTEES IN SLOVAKIA: 25 YEARS OF DEVELOPMENTS AND NEW CHALLENGES**

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**Introduction:** Ethics review in Slovakia (SR) was gradually established since 1990. It consists of the National Ethics Committee (working at the Ministry of Health), and of the mutually independent local (hospital) and regional (research) ethics committees - (R)ECs. It is based on a specific law (laws No. 576/2004 and No. 362/2011 Coll.) and decentralized. A lot is being done for systemic education, training and information sharing among SR (R)ECs: national meetings of (R)ECs are held once/twice a year, national centre for (R)ECs education and consulting operates at the Institute of Medical Ethics and Bioethics (IMEB) in Bratislava (partially supported under EC FP7 EURECNET Project), state accredited education program in GCP is established for almost 2 decades at the Slovak Medical University in Bratislava, dedicated web page is maintained (www.bioetika.sk/www.bioethics.sk), and an international bioethics journal is published (IMEB, since 1994: Medical Ethics & Bioethics). There are both positives and negatives of the current SR ER system. Among positives: nation-wide RECs network in health care and in clinical research facilities; good contact with researchers and (if appropriate) with patients, volunteers and their relatives; positive local reputation and impact; support of local ethics education. Among negatives: lower experience/competence of some (R)ECs (small facilities); problems in sustaining appropriate membership; longer review periods; unexpected differences of opinion; possible hidden local agendas. The present developments in biomedical sciences, bio- and converging technologies, health policies, as well as the need of effective implementation of the New EU CTs Regulation in SR, pose rather new, complex challenges for RECs competence and work management. To meet these new demands and responsibility, RECs would need adequate support and practical action of respective regulatory authorities, academic and research community (including expertise in ethics and other humanities), as well as from a better educated general public.

**GENERIC USE IN STATIN SALES IN THE COMMUNITY OF THESALONIKI, GREECE**

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**Introduction:** Under the current financial crisis in Greece, an effort has been made by Health authorities to encourage generic prescribing, in order to lower medicinal cost. The purpose of this work was to use the newly established Electronic Health Records to study trends in
in statins use, and to calculate the use of generics in statins sales in
a sample from the medicines market of Thessaloniki, the second
largest city in Greece.

Material and Methods: A sample of statins registered sales was
collected using the new Electronic Health Records, which has been
applied during the last years in Greece. The sample corresponded to
a small amount of sales from the market of Thessaloniki during the
years 2012 and 2013, including only community and no hospital
sales. All brand names (reference and generics) of statins and their
relative ratios in the sales were estimated, and the percentage of
generics in the sale of each medicine was calculated. The amount
of medicines was estimated in Defined Daily Doses (DDDs) of the
reference drug and its generics.

Results: Simvastatin and atorvastatin sales correspond to 81% of
total statins sales with almost equal share in the market (41% and
40% respectively). Generic use corresponded to 66% of total sales
(56,795 DDDs out of 86,103 DDDs), being 99.7% for simvastatin
(35,442 DDDs out of 35,555 DDDs), 54% for atorvastatin (18,274
DDDs out of 33,856 DDDs) and 78% for pravastatin (3,066 DDDs
out of 3,913 DDDs).

Conclusions: Although the use of generics is generally low in Greece,
the use of generics in statins sales was very high in the study sample.

UTILITY OF PILOT STUDIES FOR PREDICTION OF
BIOEQUIVALENCE RATIO AND INTRASUBJECT
VARIABILITY

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Introduction: Sometimes pilot studies are performed to decide if
a new generic formulation is adequate for evaluation in a pivotal
bioequivalence trial and to calculate the number of subjects needed
in this trial. We aim to analyse if a pilot study can predict the ratio
between test and reference formulations and the intrasubject vari-
ability, that is the main parameter to calculate the sample size.

Material and Methods: We selected seven replicated crossover
(4 periods x 4 sequences) trials, with 24 to 36 volunteers each. A
hundred simulations of pilot studies with a 2x2 crossover design
were carried out including 6 or 12 volunteers randomly selected from
these trials keeping a balanced sequence. ANOVA was performed of
logarithmically transformed AUC and Cmax, considering sequence,
subjects within sequence, period and formulation, to obtain the ratios
and 90% confidence intervals. Intrasubject variability, expressed as
percent coefficient of variation (CV), was approximated by the square
root of the error mean square of ANOVA. We calculated the per-
centage of pilot studies giving a result within ±10% the real value
obtained in the replicated study.

Results: Prediction of ratio of AUC was quite good, especially for
12-subjects pilot studies, but prediction of Cmax ratio or CV was poor.
Percentage of pilot studies obtaining a value ±10% of real value
(median and range):

<table>
<thead>
<tr>
<th>Pilot study</th>
<th>AUC ratio</th>
<th>Cmax ratio</th>
<th>AUC CV</th>
<th>Cmax CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 subjects</td>
<td>68 (40–92)</td>
<td>35 (26–55)</td>
<td>18 (8–19)</td>
<td>22 (11–25)</td>
</tr>
<tr>
<td>12 subjects</td>
<td>87 (68–99)</td>
<td>35 (38–75)</td>
<td>27 (20–40)</td>
<td>30 (23–44)</td>
</tr>
</tbody>
</table>

Conclusions: The predictability of pilot studies is greater for AUC
ratio than for Cmax. Possibly due to higher variability of this param-
eter. The value of pilot studies to decide if a formulation is good
enough to proceed with pivotal study is quite low. Pilot studies should
include at least 12 subjects.

IMPLEMENTATION OF THE NEW EU CLINICAL
TRIALS REGULATION IN SLOVAKIA: TASKS AND
CHALLENGES FOR THE DISCIPLINE OF CLINICAL
PHARMACOLOGY

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Implementation of the new EU Clinical Trials (CTs) Regulation
(No.536/2014) poses numerous challenges for all parties con-
cerned, be it national regulators, drug agencies/competent authori-
ties, sponsors, contract research organizations (CROs), investigators,
or research ethics committees (RECs). In Slovakia, the existing CTs
law (leg No. 362/2013 Coll.) and existing procedural, pro-
fessional and scientific background provide a good basis to achieve
smooth and effective transition to the new procedural environment
provided for by the Regulation. To facilitate the necessary collabora-
tion, representative stakeholders’ working groups were established,
involving state authorities, professional medical associations, indus-
try and CROs to deal with concrete problems encountered within
the implementation processes. Clinical pharmacology (CP), as an
interdisciplinary medical discipline integrating the relevant clinical,
methodological, ethical and procedural expertise concerning CTs
of medicinal products and medicinal drugs for human use, seems to be
especially well positioned to be useful in providing necessary exper-
tsise, and even in professionally coordinating these efforts. That’s
why the Slovak Society of CP (SSCP, branch of the Slovak Medical
Association) has initiated and been involved, together with respective
partners, in several ongoing activities at the professional and regu-
larly levels, as well as in novel education and teaching initiatives
aimed at providing and disseminating the necessary know how to the
implementation process parties concerned. Among those, national
CTs and GCP conferences, national meetings of RECs, and an active
involvement of physicians – clinical pharmacologists (together with
other medical specialties, clinical pharmacists, lawyers, and others)
in the working groups mentioned above may be the most prominent
examples. Hopefully, active involvement of CP in re-creating effect-
ive and safe environment for conducting of high quality CTs (and,
indirectly, also for other clinical research), brings also new opportu-

SYSTEM OF POSTGRADUATE EDUCATION AND
TRAINING IN CLINICAL PHARMACOLOGY IN
SLOVAKIA: FOCUS ON THE PATIENT’S CARE AND
GOOD THERAPEUTIC PRACTICE

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System of postgraduate education and training in clinical phar-
macology (CP) has been developed gradually in Slovakia (SR) in
parallel with the continuous efforts aimed at establishing CP as an
independent, but interdisciplinary medical discipline, providing
necessary expertise and knowledge integration regarding safe and
effective medicinal drug use and research, and thus improving the
quality of practical pharmacotherapy and patients care. The first teaching/research unit devoted specifically to CP was founded at the present Slovak Medical University (SMU) in Bratislava in 1983. It led, in the subsequent period, the development and efforts for a full state recognition of a comprehensive system of postgraduate education and training for medical specialists – clinical pharmacologists (physicians). It also took an active, albeit relatively minor part in the postgraduate education and training of other medical specialists, and also in the continuous medical education. In this work, it was greatly helped by the Slovak Society of CP (SSCP, established in 1990). Already since 1993, CP has been recognized in SR as a medical sub-speciality and since 2004 as a self-standing medical specialty. In the meantime, the original CP unit has been developed into the SMU Institute of Pharmacology, Clinical and Experimental Pharmacology, involved nowadays also in the undergraduate CP education of medical students, nurses and other health care professionals, and in numerous other research, clinical and consultation activities. It still serves as a national CP education, training (and examination) centre. At present, the state accredited, comprehensive specialization program in CP lasts at minimum 5 years, while the first 2-3 years of a physician’s education/training are devoted to the so-called internal medicine (IM) common stem (compulsory for all IM specialties). The state accredited certification training programs are available at PPCEP SMU also in the specific field of clinical trials (CTs) methodology and Good Clinical Practice, and in pharmaco-economics.

A CASE-NON CASE EVALUATION OF THE PSYCHIATRIC DISORDER AND STATINS ASSOCIATION IN FEDRA DATABASE

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Background and Introduction: The association of neuropsychiatric reactions and statins have been assessed over the years, by using case series and national registries of spontaneous adverse drug reaction reports. However, the available studies have not analyzed the risk in different age groups. The objective is to investigate the disproportionality in young adults with less probability to suffer comorbidities than older adults.

Materials and Methods: Association between psychiatric disorders (SOC) and statins was assessed in FEDRA database (analysis of the Spanish drug safety database up to October 2014) by the case/non-case methodology, calculating Reporting Odds Ratio (ROR) as a measure of disproportionality. Case was defined as patients less than 45 years (young adults) who experienced at least one psychiatric reaction (PT, HLGT, HLT) related to the drugs included in the C10AA ATC group.

Results: A total of 72 ICSR were notified (81% from 35-45 years aged; 69% male). Atorvastatin and simvastatin were involved in 36% and 33% cases, respectively. The most reported psychiatric reactions were related with sexual dysfunction (26%), the altered level of consciousness (24%) and mood disorders (12%). The ROR values, considering the psychiatric disorders in all aged groups, was 0.93 (95% CI, 0.87-1) and 1.31 (95% CI, 1.04-1.65) in young adults. The ROR for the HLGT Sleep disorders and disturbances and HLT Erection and ejaculation conditions and disorders, were 1.53 (95% CI, 1.08-2.15) and 11.32 (95% CI, 7.54-16.98), respectively. Insomnia PT and erectile dysfunction PT had ROR significantly over than 1. The ROR for nervousness PT was 0.37 (95% CI, 0.14-0.99).

Conclusions: An association of statins with insomnia and erectile dysfunction was found. These ADR are included in the SmPC. As he information obtained from this database does not allow to conclude about causality, other pharmacoepidemiological studies should be performed.

PROFILE OF PEDIATRIC CLINICAL TRIALS PHASE III CARRIED OUT IN SPAIN AT OCTOBER 2014

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Background and Introduction: Only a limited number of medicinal products, such as vaccines, had been developed specifically for children, or have been tested in children, before the clinical trial Regulation implementation. With those obligations introduced, the companies have to screen every new product for its potential pediatric use. The aim is to analyze the profile of Phase III clinical trials carried out in Spain and available in the EU CT register.

Material and Methods: The available information from the ongoing clinical trials (Phase III) within the European Clinical Trial register at October 2014 was used to evaluate the therapeutic areas and drugs studied eight years after the new Regulation was implemented.

Results: There were 412 ongoing clinical trials in pediatric population in Spain at October 2014. It represents the 16% of the CT with all age groups. In the pediatric CT, 78% were included the adolescents (66 of 323 CT were in the Pediatric Investigation Plan (PIP)), in 56% the children (68 of 229 CT were included in PIP), in 6% the newborn (11 of 25 were in PIP) and in 4% the preterm newborn and infants (6 of 15 CT were in PIP).

The most frequent therapeutic areas studied were congenital disease in newborn, and infections and neurological disorders in children and adolescents. The vaccines were represented in 6% and in 2% of the clinical trials in children and adolescents, respectively.

Conclusions: The number of pediatric clinical trials continued to be still low in relation to the total number of clinical trials. The promoters continued studying vaccines but the number of clinical trials focused on the congenital abnormalities and on drugs for infectious diseases, were predominant.

ADVERSE DRUG REACTIONS AS A CAUSE OF HOSPITAL ADMISSION HOSPITAL UNIVERSITARIO DE LA PRINCESA – MADRID

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Objective: To detect the incidence of adverse drug reactions as cause of admission to the Hospital Universitario de la Princesa in Madrid.

Materials and Methods: Transversal study, between June to December of May 2014. An electronic medical records review of patients admitted through the emergency was performed. We assessed whether the cause of admission was secondary to medication use. Causality was assessed according to the Naranjo algorithm and WHO criteria.

Results: There were 3917 admissions in that period, with a mean age of 77 years. In a preliminary analysis, we found 222 (being the sample size 195 subjects, 45.1% male and 54.9 female) the most representative: NSAID gastrointestinal bleeding/gastrointestinal bleeding on antiplatelet/anticoagulated patient: 37 (16.7%), Renal Insufficiency: 21 (9.5%), hyponatremia: 21 (9.5%), intracranial haemorrhage on antiplatelet/anticoagulated patient: 31 (14%), serotoninergic syndrome: 2 (0.9%), neutropenic fever: 18
MOLECULAR MECHANISMS THAT UNDERLIE THE [Cl]-SENSITIVE KINASES-MEDIATED REGULATION OF CFTR ANION SELECTIVITY

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Introduction: CFTR is a chloride channel that secretes chloride and bicarbonate in airway, exocrine pancreas, intestine, and genitourinary systems. Human pancreas secretes pancreatic juice which contains as much as 140 mM bicarbonate (HCO3-). CFTR senses low [Cl-]i, then kinase domain is exposed and binds to cytosolic signaling at the molecular level. Furthermore, WNK1 is a [Cl-]-sensitive kinase. These findings suggest that WNK1 increases the size of CFTR at each state. WNK1 makes CFTR pore size larger. We figured out that WNK1 kinase domain binds to CFTR and truncated forms of WNK1 respond to low Cl- concentrations.

Material and Methods: Overexpression and knockdown of each kinase in HEK293T cells were performed. Using patch clamp, we measured permeability of bicarbonate and halide ions. We did pull-down assay between truncated WNK1 and CFTR at 150mM and 0mM Cl- concentrations.

Results: WNK1 affects permeability of other anions as well as bicarbonate in patch clamp recordings. Especially, the interval of relative permeabilities (Pxi/PCl) between each anion was greatly narrowed by WNK1. Consequently, WNK1 increased the dielectric constant of the hypothetical selectivity filter of CFTR. And we measured the pore size of CFTR at each state. WNK1 makes CFTR pore size larger. We figured out that WNK1 kinase domain binds to CFTR and truncated forms of WNK1 respond to low Cl- concentrations.

Conclusions: These findings suggest that WNK1 increases the bicarbonate permeability of CFTR by modulating the polarizability of anion selectivity filter and provide insight into the fundamental question of how ion selectivity of anion channels can be regulated by cytosolic signaling at the molecular level. Furthermore, WNK1 senses low [Cl-], then kinase domain is exposed and binds to CFTR.

TMEM16F (ANO6) ACTIVATION IS ACCELERATED BY SELECTIVE SEROTONIN REUPTAKE INHIBITORS

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Introduction: ANO6 acts as Ca2+-activated Cl- channels and generates outward-rectifying ionic currents in response to intracellular Ca2+ increase. ANO6 is involved in platelet function by phospholipid scrambling required for blood coagulation. Selective serotonin reuptake inhibitors (SSRIs) are used for the treatment of major depressive disorders. Although chronic treatment of SSRI can increase the risk of upper gastrointestinal bleeding, at the earlier stage of intake, which is 1–7 days after the treatment, the possibility of blood coagulation might also increase, but transiently. Therefore, in this study, we investigated whether SSRI affected the Cl- current or phospholipid scrambling activity of ANO6.

Material and Methods: HEK293T and PANC-1 cells were used. Plasmids expressing hAN06 were transfected to HEK293T cells. siRNA of hAN06 was transfected to PANC1 cells for knockdown of hAN06. We measured anion channel activities using whole cell and inside-out patch clamp techniques with and without treatment of SSRIs. Flow cytometry was performed to evaluate phospholipid scrambling.

Results: In the whole-cell patch mode, SSRIs facilitated Ca2+-dependent activation of IANO6 in ANO6-transfected cells, as evidenced by a significant decrease in the delay of IANO6 generation. On the other hand, in the inside-out patch clamp configuration, SSRIs showed an inhibitory effect on ANO6 currents, suggesting that SSRIs activate ANO6 via an indirect mechanism in intact cells. SSRIs also facilitated Ca2+-dependent PS exposure and α-thrombin-induced platelet aggregation.

Conclusions: SSRIs at clinically relevant concentrations promote Ca2+-dependent activation of ANO6, which may have potential clinical implications such as the underlying mechanism of SSRI induced adverse drug reactions.

A REVIEW OF NEW DRUGS APPROVED BY THE SPANISH AGENCY OF MEDICINES AND MEDICAL DEVICES (AEMPS): A QUICK METHOD TO EXPLORE THERAPEUTIC INNOVATION

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Introduction: It has been questioned whether drug innovation meets societal needs. We undertook a critical review of new approved drugs by the AEMPS from September 2013 to December 2014.

Methods: A revision of the monthly bulletin published at the AEMPS website was performed to gather information on new drugs approved from September 2013 to December 2014. Key features of new drugs approved were summarized. The following indicators of innovation were considered: Direct indicators: a) drugs with new mechanism of action and b) lack of therapeutic alternatives for the approved indication. Indirect indicators: a) advanced therapy; b) orphan designation; c) first line vs. second or further line therapies; d) pediatric indication.

Results: A total of 82 drugs were approved. Indications fell into the following areas: (16, 19%) infectious diseases, (14, 17%) oncology, (10, 12%) endocrinology, (6, 7%) neurology and haematology each one, (5, 6%) pneumology, (4, 5%) cardiovascular diseases, (3, 4%) psychiatry, dermatology, digestive system, ophthalmology, gynecology and immunology each one, 1% (n = 1) nephrology, metabolism and urology each one. Most were single-active substance drugs (67, 82%). Fixed-dosed combinations were mainly antiretrovirals (n = 4) and hypoglycemic agents (n = 3). Only 2 drugs targeted specifically pediatric indications and 13 were addressed to both adult and pediatric population. Overall, 22 (27%) were orphan drugs. First-line agents accounted for 70% of the total (16% in restricted patient populations).

Conclusion: A detailed analysis of newly approved drugs may be used to conduct an at first glance analysis of therapeutic innovation. The innovative value of new drug development will be presented and discussed according to the indicators proposed.
TESTING THE INTRanasAL ROUTe FOR ADMINISTRATION OF HALOPERIDOL IN EMERGENCY ROOM: GENERATION OF EFFICACY DATA TO SUPPORT CLINICAL PRACTICE

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Background: Managing schizophrenic patients with agitation in the emergency room requires medications with a rapid onset of effect. Intravenous administration is impractical, and intramuscular dosing may be risky for both patients and health care professionals. The intranasal route may offer shorter *T*<sub>max</sub> with safer administration. Intranasal haloperidol has been reported to achieve similar plasma concentrations to intravenous dosing, but clinical data on the efficacy and safety of such approach is lacking. Psychiatrists contacted our Clinical Pharmacology Unit for methodological and logistic support to generate clinical information on the acceptability of haloperidol by the intranasal route. We present here the research protocol that was prepared.

Methods: An exploratory randomized parallel observer-blinded clinical trial was designed to compare the administration of 5mg haloperidol by either intranasal or intramuscular route. The trial will include 40 agitated schizophrenic patients visited in the emergency room of Corporació Parc Taulí who are candidates to receive haloperidol and provide previous informed consent (personally or through representative). Patients will be monitored up to 6 hours for agitation, cardiovascular parameters and adverse events. Treatments will be administered by unblinded nurses and agitation will be assessed in blind by an uninvolved psychiatrist. Main efficacy variable is the percentage of patients with score ≤9 in the 5 item PANSS-EC scale 20 minutes after dosing. Sample size is based on subject’s availability considering the exploratory nature of the trial. The study will be performed according to the Good Clinical Practice.

Results: The clinical trial obtained Ethic’s and regulatory approvals during 2014. The first patient was recruited on December 2014. Recruitment is ongoing and expected to last 12 months.

Conclusions: An exploratory trial has been prepared to help physicians to generate initial clinical information on the effectiveness of a simple intervention aimed to improve patient management by healthcare professionals in the emergency room.

ECRIN (EUROPEAN CLINICAL RESEARCH INFRASTRUCTURE NETWORK): THE ADDED VALUE OF INTEROPERABILITY AND PAN-EUROPEAN INTERCONNECTION ON CLINICAL RESEARCH

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Introduction: ECRIN is a pan-European infrastructure providing coordinated services to multinational academic clinical trials via its experienced staff. By connecting National Clinical Research Networks from different European countries, ECRIN supports the access to patients across Europe and enables academic-driven clinical trials to overcome cross-border barriers derived from the diversity in health and legislative national systems.

Objectives:

- To describe the implication of ECRIN in European multinational clinical trials and its added value in fostering the development and enrichment of academic clinical research.

Materials and Methods: ECRIN is involved in two main courses of action: The ECRIN integrated activity (ECRIN-IA), funded by the FP7 Infrastructure Programme and supported by nine Work Packages (WP) and involving 23 European Countries, and the Horizon 2020 Programme, both in the context of the European Commission (EC). The activity and results of ECRIN will be analyzed on the basis of the expected milestones and the reported outcomes achieved within each project.

Results: Seven Framework Programme:

- 21 academic clinical trials have been funded by the FP7 Programmes in the context of the ECRIN-PII, ECRIN-IA and other FP7 funded Projects.
- Of these, 4 clinical trials have concluded and their results have been published in high-impact scientific journals.

H2020 Programme:

- Four large academic ECRIN-supported clinical trials, submitted to PHC-13 and H2020 Calls, succeeded to obtain the Grant from the EC in 2014. In total, 15 countries will be involved in those trials.

Conclusions: ECRIN is an infrastructure dedicated to fostering competitiveness of academic multinational clinical research across Europe, with high ethical and scientific standards. This target is achieved by the interaction, interoperability and harmonized work between European countries and their respective National Clinical Research Networks with the coordinated support of ECRIN-ERIC.

CONVERSION FROM TACROLIMUS TWICE-DAILY TO TACROLIMUS ONCE-DAILY IN STABLE CYSTIC FIBROSIS LUNG TRANSPLANT RECIPIENTS: COMPARATIVE PHARMACOKINETICS

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Objectives: The switch for conversion from tacrolimus (TAC) twice-daily-once daily recommended 1:1. The aim of this PK study was to evaluate TAC exposure in stable cystic fibrosis (CF) lung transplant (LT) recipients, converted from TAC twice daily to TAC once daily in an open-label, prospective, single-centre study.

Methods: Eligible patients were post-transplant CF patients (18-65 years) with stable lung function on stable doses of TAC twice daily that were candidate to switch to TAC once daily. Twelve consecutive patients were included into the study. Patients had their first PK analysis on day 1, still under the stable TAC twice daily regimen and were converted to TAC once daily from day 2 onwards. The doses were adjusted according to clinical judgement to achieve target levels and a second 24h PK period profile was obtained once the patient was on stable dosage on therapeutic range.

Results: The mean total (SD) daily dose of TAC twice daily at baseline upon enrolment was 0.17 (0.10) mg/kg/day and for TAC once daily after adjustments was 0.22 (0.12) mg/kg/day. In order to achieve target similar in *C*<sub>min</sub> levels and AUC<sub>0-24hr</sub> eighty-two percent of subjects who were converted to TAC once daily required a mean increase of 28%, in a range of 9.1-66.7%.
sentia: a spanish systematic online monitoring registry for children and adolescents treated with antipsychotics: results from a 2-year, naturalistic follow-up study

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sentia (safety of neuroleptics in infancy and adolescence) (https://sentia.es), is an online spanish registry created to track antipsychotic adverse effects in youth. sentia is financed by public funds. sentia is included in the european network of centres for pharmacoepidemiology and pharmacovigilance.

objectives: sentia has the following aims: 1. early detection of adverse events. 2. close monitoring and long term follow-up of pediatric patients on antipsychotic treatment. 3. development of an extensive pharmacovigilance database of antipsychotic treatment in children and adolescents.

methods: children and adolescents, regardless of the diagnosis or clinical symptoms that motivate the antipsychotics prescription are monitored regularly. the gathered information is structured as follows: 1. sociodemographic data; 2. medical and psychiatric history; 3. clinical assessment; 4. pharmacological history; 5. therapeutic compliance; 6. health habits; 7. side effects (aims, sas, smurf); 8. physical examination; 9. biological parameters.

results: ninety-six patients have been enrolled, 11.4 ± 2.9 years old, 14% are under 8 years old, 75% male. the most frequent clinical syndromes that motivate prescription are conduct disorder (38.5%) and adhd (26.0%). the most frequently prescribed antipsychotics were risperidone (48.8%) and aripiprazole (30.2%). during the follow-up, 21% of patients changed at least once the antipsychotic.

in relation to safety assessments, 85.4% of patients had adverse events related to treatment (aes). the most frequent aes were: problems related to appetite/weight (59.4%), tiredness and weakness (28.1%), sleeping problems (22.9%) and abnormal movements (14.6%). thirty-six patients have been exposed to antipsychotics for longer than 18 months. regarding specific adverse events in this group, the most frequent aes were: headache, problems related to appetite, hypersalivation and gastrointestinal problem.

conclusions: the creation of an online pharmacovigilance registry (sentia) is a useful tool in the long-term systematic assessment of adverse events in the antipsychotic treatment of children and adolescents that contributes to the increase of knowledge about the still too limited knowledge about medium- and long-term safety evidence in real-world pediatric population. results of sentia 18-months follow-up shows persistence of mild-moderate but potentially risky aes that deserves and justify a close clinical monitoring of tolerability and safety of aps in children & adolescents.
Background: Controlled hypotension during anaesthesia may improve the quality of the surgical field in Ear-Nose-and-Throat (ENT) interventions. A number of drugs are used to that purpose, including alpha-2 adrenergic agonists (A2AA). A systematic review of efficacy data on the use of A2AA as part of hypotensive anaesthesia in ENT has been conducted.

Methods: A MEDLINE and Scopus search (1980-2015) was done to identify clinical trials comparing an A2AA as a part of hypotensive anaesthesia regimen in ENT. Additional references were identified through cross-link references. Abstracts were reviewed by two investigators for eligibility, and full papers were fully reviewed if reporting randomised trials comparing A2AA in adult patients undergoing ENT surgery. Data was extracted and synthesized for studied population, surgical procedure, type of anaesthesia, treatments compared, bleeding results and overall report quality. Due to heterogeneity in variables, synthesis of data was based on a qualitative description of trials characteristics, and also of results on the assessments of surgical field bleeding, because of the heterogeneity in the type of variables used for its assessment.

Results: A total of 79 publications were identified, from which 22 randomised clinical trials were selected (15 double-blind, 4 single-blind and 3 open-label) including information on 1278 patients undergoing either nasal, sinusal or ear surgeries and comparing A2AA (clonidine (n = 11) or dexmedetomidine (n = 11)) with placebo (n = 9), remifentanil (n = 3), esmolol (n = 2), midazolam (n = 2), magnesium sulphate (n = 2), fentanyl (n = 1) or no treatment (n = 3). Sixteen trials including 1168 patients measured surgical field bleeding, of which 14 showed better results for A2AA. None of the studies compared directly clonidine and dexmedetomidine.

Conclusions: Alpha-2 adrenergic agonists have repeatedly shown to improve surgical field bleeding during ENT surgery, there are no comparative data between different A2AA.

COST-EFFECTIVENESS ANALYSIS OF TRIPLE THERAPY WITH PEGINTERFERON, RIBAVIRIN, AND BOCEPREVIR FOR THE TREATMENT OF CHRONIC HEPATITIS C VIRUS GENOTYPE 1 WITH SEVERE FIBROSIS UNDER "REAL-LIFE" CONDITIONS

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Objectives: Studies based on the data of clinical trials have proved that the triple therapy for hepatitis C is cost-effective. This study we assessed the cost-effectiveness of triple therapy in treatment of Chronic Hepatitis C with Severe Fibrosis under "real-life" conditions.

Methods: The analysis was conducted from the data included in the prospective, multicentre Spanish registry that includes patients with HCV-genotype-1, and severe fibrosis treated with triple therapy (peginterferon alfa-2a-ribavirin+boceprevir). The cost-effectiveness analysis includes: costs of antiviral treatment, of concomitant treatments and costs related to health-care resources.

Results: One hundred seventy patients were included; 68.2% male, age 53 years; 36.5% of patients reported at least one SAE. SVR12 was 46.5%. The cost of triple therapy represented a total of 4,916,652€, the pharmacological cost (triple therapy + concomitant treatment) a total of 5,161,168€. The consumption of health resources an additional cost of 240,000€ (1,500€/patient). The total cost per patient cured was 70,262€. This cost varies greatly based on different baseline characteristics of the patients, with significant differences in patients with albumin <35,120,597€; prior null response 120,727€ and platelets <90,000,104,464€.

Conclusions: The current scenario of hepatitis C treatment is changing. Triple therapy is more costly for patients with severe fibrosis and predictors of poor response. However, keeping in mind that the timeframe for the release of IFN-free-regimens remains uncertain and considering that the actual access to the new DAA in the real-world setting could be delayed, boceprevir could remain as an option for patients with intact liver function and an unmet medical need, regardless of the degree of liver fibrosis, in locations where a delay in the access to the newer therapies is foreseen and hepatic transplant would not be readily available. Incorporating clinical criteria and definition of subgroups of patients by medical experts influences significantly the cost-effectiveness and should be taken into account in decisions on public health policies. Current decisions based on short-term budgetary impact lead to incorrect decisions. Medium-term decisions that consider clinical criteria against specific decisions based on short-term budgetary impact should be favored.

RANDOMIZED CLINICAL TRIAL, PLACEBO COMPARED TO EVALUATE THE EFFICACY AND SAFETY OF MINOCYCLINE IN ANGELMAN SYNDROME (A-MANECO STUDY)

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Angelman syndrome (AS) is a rare disease with serious developmental disorder. Until now, no cure for AS exists. Recently published studies show an improvement of motor function, cognition and increased synaptic function in animal models with minocycline administration. A non-controlled treatment initiative in children with AS has been reported.

Methods: Randomized, crossover, double-blind, placebo-controlled, independent clinical trial to explore the efficacy and safety of minocycline in AS. The primary objective was to compare the efficacy (in terms of increase in age of development) of 8-week treatment with minocycline or placebo. The efficacy assessment was performed with validated scales (Scale Marrill-Palmer-R) and EEG parameters. Safety analysis was conducted through direct collection of adverse events, physical examination and laboratory tests.

Results: Thirty-two subjects enrolled, median age of 12 (6–29) years, 50% male. No differences in basal characteristics were observed. A summary of key results is shown in Table 1.
Influence of Sociodemographic and Professional Characteristics on Antibiotic Prescribing

First-in-man dose escalation study of aspirin®inhaled for the clinical development of a new antiviral treatment of resistant influenza

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Introduction: D-L-lysine acetylhyalocyanate (ASA) glycine (LASAG, Aspirin i.v.) has antiviral activity including resistant viral strains: inhalation of nebulized LASAG leads to dose-dependent lung virus titer reduction in mice, decreases disease severity and weight loss. Mortality is reduced dose-dependently. Proof-of-concept (PoC) is planned by measuring viral load and clinical symptoms after influenza infection in patients.

Material and Methods: First-in-man dose escalation for evaluation of safety and pharmacokinetics (PK) of treatment was conducted as placebo-controlled dose escalation in healthy male subjects: Safety was evaluated by questioning for AEs, controlling vital parameters, ECG, lung function and laboratory. PK was measured in plasma and thromboxane B2 was analysed in serum. Thirty-eight subjects were treated with nebulized LASAG, in 5 subjects with 62.5 mg, 5 with 125 mg, 6 each with 250 mg, 500 mg or 750 mg ASA. Ten subjects received inactive control.

Results: Inhalative doses up to 750 mg ASA were safe and well tolerated without serious adverse events. Vital signs (heart rate, blood pressure), ECG and clinical laboratory parameters were not affected by study treatments. Lung function parameters did not decrease relevantly (>5%) for mean FEV1 after any treatment. Fifteen subjects experienced treatment-emergent AEs: 2 subjects after treatment 125 mg ASA, 3 after 250 mg, 5 after 500 mg and 5 after 750 mg ASA. Drug related treatment-emergent AEs were throat irritation in 14 subjects (36% of subjects) and productive cough in 3 subjects (7% of subjects).

PK analysis for ASA showed dose proportionality regarding AUC.

Conclusion: LASAG administered as a single oral inhalation up to 750 mg to 38 healthy male subjects was safe and well tolerated and showed dose proportional total (systemic) exposure for ASA. Based on these results the antiviral effects through a host cell-mediated mechanism may be evaluated in a PoC study.

The use of complementary and alternative medicine in hospitalized patients with type 2 diabetes mellitus in Israel

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This work was performed in partial fulfillment of the M.D. thesis requirements of the Sackler Faculty of Medicine, Tel Aviv University.

Ayellet Lerner and Ronit Koren contributed equally to this work.

Introduction: The use of complementary and alternative medicine (CAM) is on the rise in recent years in the general population, as well as among patients with chronic diseases such as diabetes mellitus. The aim of this study was to add information regarding the use of CAM in patients with type 2 diabetes mellitus (DM2) in Israel and explore possible interactions between CAM and prescription medication (PM).

Methods: This is a Cross Sectional study based on questionnaires. The study included type 2 diabetic patients who were hospitalized in an internal medicine department at "Assaf Harofe" medical center, Zerifin, Israel between 12.2013 and 12.2014. Possible interactions between CAM and PM were evaluated by a clinical pharmacist and a clinical pharmacologist.

Results: A total of 23.4% of 111 diabetic patients used CAM. There was no significant difference between the consumers and non-consumers in terms of age, education, income, smoking or alcohol habits. Only 11 of the 26 CAM consumers informed their physician regarding the use. We found possible drug-herb interactions in 19 of the 26 CAM consumers. A major interaction was found between omega-3 and anti-aggregates and was encountered in seven (26.9%) of the CAM consumers. Other minor and major interactions were found with Vitamin E, Ginkgo-biloba, Q10, Green tea, Fenugreek seeds, pyridoxine and dandelion.

Conclusions: Since CAM consumption is on the rise, it is desirable to improve our knowledge concerning their potential effects and adverse effects, especially in conjunction with PM. Given the complexity of...
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pharmacists in patients with chronic diseases, among them patients with DM, use of supplementary medicine cannot be ignored.

**SAMPLING STRATEGIES TO ESTIMATE CYPs PHENOTYPE: IMPLICATIONS FOR CEIBA COCKTAIL APPROACH**

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**Introduction:** According to EMA recommendations, development of phenotyping procedures for drug interactions studies and clinical research are highly recommended, due to the discordances found between genotypes determined of the main CYP enzymes and their actual enzymatic activity. Recently, CEIBA cocktail approach to measure metabolic activity of the main CYPs in just one experiment has been designed. However, its optimal design remains to be elucidated, which is the main objective of this research, in order to appropriately select the sample to be analyzed and an optimal single time point for the analysis, to avoid diminish costs and discomfort to the volunteers without compromising the reliability of the results.

**Material and Methods:** Thirteen healthy subjects were given low oral doses of 100mg caffeine, 25mg losartan, 20mg omeprazole and 30mg dextromethorphan, and blood and urine samples were taken at different time points (predose, 0.5, 1, 2, 3, 4, 6, 8, and 12h) to assay the concentration and pharmacokinetic parameters (AUC). The MRs for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 were calculated at each time point and their correlation with AUC ratios calculated. All subjects were genotyped.

**Results:** The cocktail was well tolerated and single time point MRs at 4h or 6h (only for CYP2C9) after dosing showed high correlations with corresponding AUC ratios and can, therefore, be proposed as simple phenotyping metrics. On the other hand, metabolic ratios in urine samples were not comparable to plasma ratios.

**Conclusion:** This cocktail was proven to reliably reflect the selected CYPs activities for the evaluation of CYPs hydroxylation capacity. The proposed simplified sampling scheme could facilitate clinical application of CYP phenotyping with one blood sample collection, in a single analysis.

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**Disclosure of Interest:** None Declared.

**References**


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**CYP450 GENO-PHENOTYPE ANALYSIS: APPLICATION OF CEIBA COCKTAIL TO MEXICAN POPULATIONS**

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**Introduction:** For the CYP450 enzymes, there is significant variability of actual activity within a genotype group, i.e. genotype does not always correlate with the functional phenotype. Therefore, the most relevant genetic variants should be analyzed, together with the simultaneous analysis of the CYP450 isoforms hydroxylation capacities. Considering this lack of accuracy and the void of pharmacogenetic information in ethnically specific regions, this study aimed to explore the relationship between the main CYP450 (i.e. CYP1A2, CYP2C9, CYP2C19, and CYP2D6) polymorphisms and the metabolic ratios (MRs) in a group of Mexican subjects.

**Material and Methods:** Six hundred fifty-four healthy native individuals from Mexico were genotyped and additionally phenotyped by the CEIBA cocktail. Plasma concentrations of the drugs and metabolites were quantified and MRs calculated to determine the actual CYPs metabolic capacity. The geno-phenotype relationship was evaluated by correlation analysis between ‘activity score (AS)’ and logMR.

**Results:** No adverse effects were reported. The prevalence of PM genotypes is ≤2%, whereas for CYP2C19 and CYP2D6, an ultrarrapid metabolizer prevalence of 3.7% and 12.8%, respectively, was found. MRs correlated with AS for CYP2C9, CYP2C19 and CYP2D6, and MRs varied across subjects with different AS. Those individuals with 2 or more active genes showed lower MRs than those with one or no active genes. The frequency histograms and probit analysis showed no clear bimodality. Not all the phenotypically PMs carried zero active genes, whereas those individuals whose metabolism is faster exhibit at least two active genes.

**Conclusion:** This is the first study of simultaneous determination of genotypes, phenotypes and its correlation analysis for different CYPs on a Mexican population. The influence of the genetics on the enzyme hydroxylation capacity is confirmed, though further research on genotype-phenotype relationship is required due to the overlap among different genotypes and that other factors can potentially influence the activity of these enzymes.

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**Disclosure of Interest:** None Declared

**References**

STUDENT VIEWS ON THE STUDENT-RUN PHARMACOVIGILANCE PROGRAM

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Background: Pharmacovigilance centers play a vital role in the monitoring of drug safety after approval for marketing, and depend mainly on the quantity and quality of reported adverse drug reactions (ADRs). To ensure future ADR-reporting and increase pharmacovigilance awareness among medical students, we developed and aim to evaluate student outcomes of participation in our Student-run Pharmacovigilance program.

Method: A pilot study was performed in which student attitudes, knowledge and skills on ADR-reporting were evaluated using an e-questionnaire before and after participation in the student-run pharmacovigilance program. Teams of (1st-4th year) medical students assessed real ADR-reports from healthcare-professionals/patients reported to Lareb. These student-assessments included a causality assessment, (scientific) pharmacological explanation, feedback letter to the reporter, and summary for the pharmacovigilance-databases of the European Medicines Agency and WHO.

Results: From May 2014-January 2015, 100 different ADR-reports selected by Lareb staff were handled by 43 students. Before participating in the pilot <25% knew how to report ADRs. After participation >70% knew how to report, and were even able to name important details for ADR-reporting. Intention towards ADR-reporting was assessed using a 7-point Likert scale (1: extremely unlikely-7: extremely likely). Students indicated they intend to report serious (6.44 SD 0.73) and unknown (6.44 SD 0.63) future encountered ADRs. On a 5 point Likert scale students disagreed (2.50 SD 1.15) their current curriculum covered pharmacovigilance well, found participation educational (4.56 SD 0.63) and more interesting than fictive casuistry (4.56 SD 0.73). Furthermore besides students reported they learned how to assess ADRs, they stated to have learned skills/knowledge regarding critical appraisal of information, understanding of pharmacological mechanisms and scientific writing.

Conclusion: The Student-run pharmacovigilance program is a valuable and novel educational experience. It creates awareness in future doctors with the potential to increase ADR-reporting, lets students practice in searching and writing scientifically and teaches the basics of pharmacovigilance in real life.
THERAPEUTIC INNOVATION: DOES INDUSTRY RESEARCH MEET THE NEEDS OF SOCIETY? DEFENDING NO

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Educational Objectives: The Holy Grail of a big Pharma CEO is to “address unmet medical needs” of the society. However this general objective should be specified: Which medical needs we refer to? and of which societies?

Purpose: The purpose of the debate is to make clear this general goal is being fulfilled, looking for the real medical needs that are not been currently addressed.

Methods: Literature review searching for terms like “medical needs”, “disease mongering”, “neglected diseases” or “poverty-related diseases”.

Results: There are different measures to decrease the burden of many diseases other than drugs. The term disease mongering has been used since 1992 to refer to clinical conditions that are not “real” medical needs. Neglected diseases and poverty-related diseases are also terms that have been used by WHO and other international bodies to define “real needs” from non-affluent societies. Rare diseases and elusive clinical conditions are also situations where big Pharma are reluctant to invest.

Conclusions:

▪ Pure market sources cannot meet the needs of society as a whole
▪ Bias towards profit or self-interest is universal
▪ Not only R&D but also availability of drugs is also a major issue
▪ Adequate and appropriate incentives are needed to ensure R&D for new medicines
▪ Problem-oriented research should balance the drug-oriented approach currently dominating the scene
▪ There is a strong need of academic, non-for-profit, problem oriented research networks.
CLINICAL DILI NETWORKS AND CONSORTIA: WHAT LESSONS HAVE WE LEARNT?

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Introduction: Over the last 2 decades there has been an increasing demand for pharmacological laboratory services in Norway, both for therapeutic drug monitoring and drugs-of-abuse testing. By 2012, more than 50 Norwegian laboratories offered analyses of >150 different therapeutic drugs (1) and >200 drugs-of-abuse (2). Since the repertoires vary between laboratories and over time, national overviews quickly become outdated and unreliable. Further, different reference ranges and interpretation algorithms between laboratories entail unnecessary sources of confusion. We developed a nationwide web-based database for all pharmacological analyses in Norway to ensure a continuously updated overview of the field and to stimulate cooperation and standardization between laboratories.

Materials and Methods: A user-friendly database was developed in cooperation with a professional web design company, with funding from the Norwegian Medical Association (approximately 500,000 NOK). The core of the database was a substance registry on which all published information converged. A group of editors (clinical pharmacologists) were responsible for the facts presented about each substance, such as substance class, trade names, pharmacokinetic properties, etc. The laboratories published and edited their own repertoires and linked them to the substance registry.

Results: The database is published online and made publicly available (www.farmakologiportalen.no). It provides detailed information on substances and a continuously updated national repertoire on each substance. Furthermore, each laboratory has its own subpage where all analyses performed are listed and to which common national details on substances are linked.

Conclusions: A web-based database of clinical pharmacological analyses in Norway has ensured access to a continuously updated national overview of the field and has led to increasing standardization and cooperation between the laboratories.

Literature

THE SFINX/PHARAO COMPUTERIZED DECISION SUPPORT SYSTEM (CDSS) ON DRUG-DRUG INTERACTIONS AND PHARMACODYNAMICS

Y. Böttiger
Linköping University, Linköping, Sweden

Educational Objectives: At the conclusion of this presentation, the participants should be able to recognize the special demands that have to be met for the collection, classification, and structure of drug information in connection with computerized decision support systems, as well as organizational aspects of implementation, education, and follow-up of such systems.

Summary: The presentation will include a background description of the development of the SFINX database on drug–drug interactions and the PHARAO database on pharmacodynamics. The latter database contains information on pharmacodynamic properties of active drug substances, such as anticholinergic, serotonergic, and sedative properties, as a basis for a summarized pharmacological risk profile for a patient's complete drug list. Data from epidemiological studies in connection with the use of the SFINX database will be presented, as well as results from pilot testing of the PHARAO system in geriatric and primary health care settings. The experience from the working group behind these systems will be discussed in the broader context of computerized decision support systems for rational drug treatment.

Literature Reference
1. SFINX-a drug-drug interaction database designed for clinical decision support systems.

HOW RISKS ARE PERCEIVED. RECENT RESEARCH FINDINGS

D. Way1; F. Bouder2; and R. Löfstedt1
1King’s College London; and 2Maastricht University

Educational Objectives: This research presents the opportunity to better understand the drivers affecting medical risk perception as well as concrete lessons and implication for policy.

Purpose: Pharmaceutical regulatory agencies across the Atlantic have been increasingly committed to releasing risk information, mainly via online portals or open access to regulatory data, yet few studies have critically examined the effectiveness of the regulators’ policies on the achievement of public policy objectives (eg, behavioural change, building trust, and empowering patients to make better decisions).
Clinical Therapeutics

Methods: The authors conducted a large European survey (N = 1010) comparing the views of medical doctors (N = 1005) from Spain, Germany, France, and the UK.

Results: The study adds empirical evidence on the effects of European pharmaceutical policies on the end-users of “disclosed” information (ie, doctors and patients). The study found that the types of transparency policies adopted by European regulators are likely to be ineffective in achieving its policy objectives: building doctor and patient trust and providing a better understanding of agency decision-making (eg, why a medicine was approved). The large majority of respondents were found to have poor knowledge of how the regulators assess the safety of medicines and would be unconﬁdent in interpreting what safety-related information means (eg, as contained in documents being made publically available). Doctors and patients were also found to differ signiﬁcantly over key transparency issues, including when safety information should be made publically available in the ﬁrst place.

Conclusions: There is an urgent need to better connect medical transparency and communication policies to perception studies. The presenter concludes by discussing recommendations on improving transparency discussions that centre on achieving positive outcomes for patients and healthcare professionals.

SGLT2 INHIBITORS

M. Brito
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Diabetes treatment is evolving fast in the last years. New algorithms are published frequently to cover all the new drug developments. We will review published data from the proof to the concept of the pharmacological development of different molecules. EMA approved SGLT2 inhibitors currently on the market are dapagliflozin, empagliflozin, and canagliflozin. Although the efficacy is considered modest, the strengths of the class are low risk of hypoglycaemia, promotion of weight loss, good tolerance, durability, and mechanism of action non-insulin dependent, so they can be used regardless of diabetes duration. There are some limitations to their use: renal failure and concomitant use of diuretics. This new class of antihyperglycemic drugs can be used through most of the natural history of the disease from early stages to long standing. There is a great chance that they become part of the treatment of most diabetic patients in a near future.

TRAINING COURSE ON MEDICINES REGULATION: HOW THE EU REGULATORY NETWORK DEALS WITH DIVERGENT VIEWS

J. Camarero1; A. Gomez Outes1; F. Torres2; M. Weise3; and A. Sancho4
1Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid, España; 2Biostatistics and Data Management Core Facility, IDIBAPS - Hospital Clinic Barcelona; Biostatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona (UAB), Barcelona, España; SAWP and BSWP member at EMA; 3Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Bonn, Germany, Alternate Member CHMP, Member of the BWP, CVWP; and 4Research Institute Hospital Puerta de Hierro Majadahonda, Madrid, España, Alternate Member CHMP, RIWP Member

Objectives: Despite the existence of common technical and scientiﬁc requirements, divergent opinions among MS may exist throughout European marketing authorisation procedures. Participants will understand the complexity of the EU regulatory network and will get a flavour of the discussions behind EU opinions on medicinal products.

Purpose: The aim of the training session is to provide important background information to participants interested in drug regulation to understand the complexity of the EU regulatory network and how the system deals with divergent opinions.

Methods: The training course will start with a 15-minute pre-presentation of the general aspects on the marketing authorisation of medicines, with particular attention to the community procedures and how opinions are reached within the EU network. This will be followed by two 35-min sessions where 2 recent examples, an anti-coagulant and an oncologic drug, will be presented in an informal way with the aim to stimulate questions and discussion within the audience. All participants, speakers and attendees, are expected to interact in these discussions.

Results: Despite common technical requirements within the EU Network, differences in the interpretation of data supporting marketing authorisation applications may lead to divergent opinions on the beneﬁt/risk balance of a given medicinal product. Attempts to reach opinions by consensus are done throughout every procedure, and this is usually reached. However, in a portion of cases this is not possible, and a public declaration of the motivations behind a divergent opinion will be signed by the representatives of the concerned member states.

Conclusions: The evaluation of marketing authorisation applications within the EU Regulatory Network is complex. Divergent views enrich the discussions behind every single opinion on medicinal products, and a ﬁnal decision is either reached by consensus or absolute majority. For transparency reasons, both discussions and where applicable divergent opinions are publicly available.

The authors of this paper declare not to have any conﬂict of interest that may affect the conduct of this training session. They have public Declarations of Interests that can be consulted at EMA website.

RATIONAL PHARMACOTHERAPY IN CHILDREN - ISSUES CONCERNING OFF-LABEL DRUG USE

I. Choonara
University of Nottingham, Derbyshire Childrens Hospital, Derby, UK

Review: Many medicines used in children are used in an off-label manner. This means they are used either at a greater dose than that recommended in the product licence, for an alternative indication, or in an age group for which the medicine was not originally authorised. The main issue with regards to the use of medicines is not whether they are off-label but whether there is an evidence basis to justify their use in that particular condition. This means, speciﬁcally, has the medicine been used in a rational manner or not. Rational prescribing has been recognised as an important issue in low-income and lower middle-income countries. It has not been considered a major issue in high-income countries. This is unfortunate as many medicines are used inappropriately. There is signiﬁcant variation in the utilisation of antibiotics. Broad-spectrum antibiotics in particular are often used inappropriately. Polypharmacy is often used when this is inappropriate. Other examples of inappropriate drug use include the overutilisation of medicines for infants with gastro-oesophageal reﬂux.

Literature Reference
Clinical Dili Networks and Consortia: What Lessons Have We Learnt?

M.B. Christensen; K.M. Harboc; J.P.K. Kampmann; A. Kobberø; G. Jürgens; J. Sonne; L. Reuther; and H.R. Christensen
Copenhagen University Hospital Bispebjerg and Frederiksberg, Copenhagen, Denmark
We have successfully implemented a multifaceted initiative to enhance rational pharmacotherapy, pharmacological focus, and clinical pharmacological decision making across health care systems in our region. The initiative promotes clinical pharmacology as a clinical discipline and consists of 4 key elements:

1. Primary practice and hospitals in the region are offered systematic reviews of a patient’s list of medicines forwarded by e-mail, fax, or phone. Medication reviews are aimed at optimising the combined list of medicines focusing on efficacy, interactions, adverse effects, collective drug burden, and cost-effectiveness of the medication. The medication review is performed by junior doctors and approved by a specialist in clinical pharmacology and returned to the inquirer within 2 days.

2. Acute medical ward medication review. Clinical pharmacists employed at the acute medicine department of the local hospital are supported with 1) patient-specific acute clinical pharmacological input when necessary and 2) evaluation and education based on appraisal and grading of the clinical pharmacist’s suggestions in relation to the individual patient charts. Clinical scientific projects concerning medication reviews as an alliance between clinical pharmacists and clinical pharmacologist are in development.

3. Psychiatric medication dialogues. Medication reviews of complex psychiatric patient’s medication. The cases, chosen beforehand and submitted by psychiatrists, are reviewed by a clinical pharmacologist. Problematic areas of the medication are subsequently discussed bilaterally at conference meeting held at the psychiatric department.

4. Primary practice medication dialogues. Medication reviews of primary practice patient’s medication. The cases, chosen beforehand and submitted by general practitioners, are reviewed by a pharmacist followed by a specialist in clinical pharmacology. Suggestions for change and optimisation are subsequently presented to the general practitioner at a dialogue based meeting held in the general practitioners private practice.

Clinical Research Networks as a Support to Independent Clinical Trials

J. Demotes-Mainard
ECRIN, Paris, France
Independent multinational trials are key instruments to optimise healthcare strategies and to promote evidence-based medical practice in Europe and globally. However, conducting multinational trials raises major obstacles for academic institutions, both on the trial management side and on the clinical investigation side.

Due to the fragmentation of health and legislative systems, infrastructure, tools, procedures, and funding, a majority of non-commercial sponsors and clinical trial units (CTUs) lack the capacity to initiate and manage trials in foreign countries. ECRIN (European Clinical Research Infrastructure Network, www.ecrin.org) was designed to overcome these barriers, as a distributed, non-profit infrastructure supporting multinational clinical trials in Europe. By connecting and coordinating national CTU networks, ECRIN supports the management of multinational trials. ECRIN is open to the whole clinical research community, covering any disease area. Support to the management of multinational trials is provided after scientific evaluation of the full protocol. Most ECRIN-supported trials are funded by the FP7 and H2020; however, other funding mechanisms are being explored.

Typical ECRIN users are multinational investigator consortia conducting independent trials. In our experience, structuring investigation capacity through the development of pan-European investigation networks has a tremendous impact on the development and the conduct of the project. For this reason, ECRIN also promotes the structuring of pan-European, disease-oriented investigation networks that become strategic partners, providing the scientific content and investigation capacity, whereas ECRIN supports the trial management. This is for instance achieved in the current FP7 ECRIN-IA project for the rare disease, medical device, and nutrition investigator communities, and similar partnerships are being developed with other disease areas.

Impact of Biosimilar Medicinal Products in the EU Pharmaceutical Market

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Faculty of Pharmacy, University Ss. Cyril and Methodius, Skopje, Macedonia
Biosimilar medicinal products marketed for almost a decade are still relatively small segment of the EU pharmaceutical market, but with strong annual growth. The presence of biosimilars has enhanced competition and offered a less costly alternative to existing biologicals. There is a strong interest by healthcare stakeholders in measuring the biosimilar utilization and impact on the market entry. Regulatory issues, manufacturing, safety, pricing, and physician and patient acceptance have a part in developing the biosimilar market much different from the generic market. The lack of automatic substitution and interchangeability made the entry of biosimilars even more difficult.

The purpose of this research was to evaluate the information related to impact of biosimilars and their potential to penetrate the EU market. The assessment of the biosimilar market uptake is done using data from several sources, measuring volume consumption and pricing information in EU countries where they are marketed.

Different types of biosimilars have different market penetration potential, with very limited data for biosimilar monoclonal antibodies and biosimilar insulins. Noticeable differences in the use of biosimilars across EU countries are reflection of national treatment practices and guidelines, which are influenced by funding decisions and payer actions. The theoretical prediction that biosimilar competition will lead to major price erosion in practice has not been so significant. Despite those difficulties, it is expected that the biosimilar market will develop, mainly driven by potential profits with patent expiration in the next years. Even though the most important conditions for market uptake of biosimilars are driven by commercial factors, still, real clinical evidence, clear regulatory framework, and postmarketing data on the use of biosimilars will influence their market access.

Personalised Pharmacotherapy in Routine Clinical Pharmacological Practice

M. Grundmann
Department of Clinical Pharmacology, Faculty of Medicine, University of Ostrava, Czech Republic
Personalised pharmacotherapy as a part of personalised medicine is looking for the right drug, right patient, right dose, and right dosage interval. Selection of the right drug given to the right patient can be solved a priori using pharmacogenetics (eg, warfarin, azathioprine, etc). A posteriori therapeutic drug monitoring (TDM) can be used for the selection of the right dose and dosage interval. TDM refers to the individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window for optimal patient benefit. Traditionally, TDM involves measuring drug concentrations in various biological fluids and interpreting these concentrations in terms of relevant clinical parameters. For >100 drugs (aminoglycosides, vancomycin, antimycotics, digoxin, amiodarone, theophylline, antiepileptic drugs, immunosuppressive drugs, psychopharmaceuticals, cytostatics, etc) with better relationship between plasma or blood concentration-response than dose-response, the measurement of plasma or blood concentrations has become a valuable surrogate index of drug exposure in the body.

Next step, advanced TDM includes the estimation of metabolites and probe drugs (phenotyping), free drug concentrations, and genotyping. The estimation of the phenotype shows actual metabolic status, and genotyping seems to be very useful for the explanation of some differences. Cohort studies and case reports from the routine clinical practice will be demonstrated.

COURSES IN CLINICAL PHARMACOLOGY FOR NURSES AND YOUNG DOCTORS – NARROWING THE GAP OF IGNORANCE?

K.M. Harboe1; E. Jimenez-Solem1; A. Bondesen2; C.B. Rasmussen3; L.O. Reuth4; M.V. Hansen5; and H.R. Christensen1

1Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; 2Medical Department, Gilead Sciences, San Francisco, USA; 3Center for Human Resources, Gentofte Hospital, Copenhagen, Denmark

Background: Young doctors and nurses in Denmark lack sufficient training in clinical pharmacology and knowledge of medicines in general due to a lower pregraduate priority. The Department of Clinical Pharmacology has therefore developed courses in clinical pharmacology for both nurses and doctors.

Material and Methods: The courses are planned in cooperation with the HR department and supported financially by the Capital Region of Copenhagen. The nurse’s course is a 3 × 2-day course, targeting experienced nurses and qualifying them as “medication responsible nurses” at their departments. The doctor’s course is a 1-day “crash-course” for residents and junior doctors. The doctor’s course is accessible to all residents in the region. The courses are mainly taught by junior doctors in specialist training for clinical pharmacology as part of their own education with feedback by experienced educators.

Results: The courses have been held 2 to 4 times yearly since 2011. Altogether, 270 nurses have completed the nurse’s course, and in a 2-year period 438 junior doctors have attended the crash-course. The doctor’s course is evaluated Part I independently. The EC participate in the consolidation of corrective measures. The responsible EC and drug authority shall evaluate Part I independently. The EC participate in the consolidation of the final assessment report, too. The EC finally has to provide a vote regarding the authorisation of the trial.

The text of the implementation law is not yet available, but there is considerable agreement to proceed as outlined here. The ECs in Germany are convinced that clinical research is urgently needed, that Europe should be an attractive location for clinical trials, and that it is possible to safeguard the autonomy, the safety, and the well-being of research participants and to foster research-friendly conditions at the same time.

A COMPUTERIZED PHYSICIAN ORDER ENTRY-BASED SYSTEM TO PREVENT HBV REACTIVATION IN PATIENTS TREATED WITH BIOLOGIC AGENTS. THE PRESCRIB PROJECT

C. Hernandez-Lopez1,2; and J. Crespo3

1Tauli Parc Hospital, Autonomous University of Barcelona, Sabadell, Barcelona, Spain; 2Medical Department, Gilead Sciences, Madrid, Spain; and 3Marques de Valdecilla Hospital, Santander, Spain

Educational Objectives: Demonstrate that a multifunctional team can design an effective strategy to minimize risk of hepatitis B virus reactivation (HBVr) of patients receiving immunosuppressive therapies.

Purpose: The aim of the PRESCRIB project was to create a simple and useful tool in an academic hospital to facilitate the HBV screening of all patients who were to be treated with biological drugs (BDs) by medical specialists.

Methods: In 2011 a preliminary phase was done to characterize routine practices in HBV screening of major specialties prescribing BDs by means of a physician survey and the analysis of patients’ records. After this, the project was structured into three phases. The first phase included educational activities in HBVr and the creation of the new CPOE (computerized physician order entry) application. Future evaluations will reveal if training in clinical pharmacology can improve the quality of patient care.

RESEARCH ETHICS COMMITTEES: ADAPTATION TO THE NEW EUROPEAN REGULATION OF CLINICAL TRIALS – A VIEWPOINT FROM GERMANY

J. Hasford

Association of Research Ethics Committees in Germany, Germany

By the end of 2016 the EU regulation 536/2014 will come into full force. By then the EU portal and its related databases, which are essential for the submission of the trial applications and the communication between the sponsors and the member states, shall be operational. According to Art. 4 of the regulation, the ethical review of the clinical trial has to be performed by an ethics committee (EC), but it is left to the individual member states to decide whether the EC reviews Part II (informed consent material and quality of the study centers and its staff) only or Part I (trial protocol and risk/benefit assessment), too. The ECs need an unrestricted access to the EU portal. The German ECs have asked the government to decide that the ECs are responsibly involved in the following aspects of the process: the review of the ethical and scientific aspects of Part I and II and of substantial modifications, review of the classification as low-intervention trial, notification relating to an end, early termination or temporary halt of a clinical trial, the receipt and review of safety reports, and initiation of corrective measures. The responsible EC and drug authority shall evaluate Part I independently. The EC participate in the consolidation of the final assessment report, too. The competent EC finally has to provide a vote regarding the authorisation of the trial.

The text of the implementation law is not yet available, but there is considerable agreement to proceed as outlined here. The ECs in Germany are convinced that clinical research is urgently needed, that Europe should be an attractive location for clinical trials, and that it is possible to safeguard the autonomy, the safety, and the well-being of research participants and to foster research-friendly conditions at the same time.

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The CPOE system allowed for the introduction of an alert of the risk for HBVr with a BD at the time the drug is prescribed. Together, the prescriber was prompted to enter the patient’s serological status. Alternatively, the program itself generates a test order for the patient’s HBV serological profile. After that, there was the implementation phase (May–Nov 2012) in which participation was voluntary. In the subsequent universalization phase (Nov 2012–May 2013), the participants were recruited with targeted screening conducted by the Hepatology Unit.

Results: A total of 1076 patients undergoing BD treatment were included in this project (May 2012–2013), resulting in the identification of 4 HBsAg-positive and 69 anti-HBc-positive/HBsAg-negative patients. Over 90% of patients who were prescribed a BD have undergone serological screening to detect HBV infection. The use of CPOE has increased the screening rate from less than 50% to 94% for HBsAg and from less than 30% to 85% for anti-HBc.

Conclusions: This study demonstrates the feasibility of implementing a CPOE system in a tertiary hospital increasing HBV screening among medical specialties prescribing BDs. It would be interesting to determine whether this experience can be extrapolated to other centers with CPOE systems and whether this is cost-effective for hospitals.

**THE DUTCH/FLEMISH PRESCRIBING ASSESSMENT PROJECT**

C. Kramer§; A. Maassen van den Brink2; M.H. Hess2; B. Janssen3; W. Knol4; W.M. Mulder5; R. Rissmann6; and J. Tichelaar7

1Radboud University Medical Center, Nijmegen, the Netherlands; 2Era. University Medical Center Rotterdam, the Netherlands; 3Leiden University Medical Center, Leiden, the Netherlands; 4Maastricht University Medical Center, Maastricht, the Netherlands; 5University Medical Center Utrecht, Utrecht, the Netherlands; 6Academic Medical Center, Amsterdam, the Netherlands; and 7VU Medical Center, Amsterdam, the Netherlands on behalf of the Dutch/Flemish pharmacotherapy end test initiative

Educational Objectives: To develop a pharmacotherapy end test aimed to improve safe prescribing in the Netherlands and Flanders. At the conclusion of this presentation, participants know about the philosophy behind and practical implications of this test.

Purpose: The project aims to develop a Dutch/Flemish pharmacotherapy end test.

Methods: Most preventable serious adverse events are due to a relative small list of drugs (eg, pain killers, anticoagulants, cardiovascular drugs, antidiabetics). Based on these drug-related problems and on basic pharmacological principles (pharmacokinetics, good prescribing, prescribing laws), a list of end terms has been formulated, which each prescriber has to know before starting to prescribe independently. A test has been developed covering these end terms. Education material to prepare for this pharmacotherapy end test has been developed. Ultimately, each medical student in the Netherlands and Flanders has to pass this test before graduating.

Results: End terms covering 11 different subjects have been developed. Educational material (youtube channel, pharmacotherapy reader, cases in www.pscribe.nl) has been made available. A total of 215 multiple choice questions covering the end terms have been provided.
developed. Based on these, the pharmacotherapy end test has been taken since September 2014 in Nijmegen, the Netherlands. About 30% of students fail per test; however, ultimately all students pass. The other universities in the Netherlands and Flanders are preparing to start the test.

Conclusions: A Dutch/Flemish pharmacotherapy end test has been developed based on end terms covering the most frequent preventable serious adverse events and basic pharmacotherapy principles. The test has been taken in Nijmegen, the Netherlands since September 2014. The other universities in the Netherlands and Flanders are preparing to start testing. Whether this test will lead to safe prescribing is subject of an oncoming study.

Reference

PHARMACOVIGILANCE AND RISK MANAGEMENT: HOW TO DETECT, EVALUATE AND MINIMIZE THE RISKS: A EUROPEAN POINT OF VIEW
H. Le Louet
Head of Pharmacovigilance Federation at Paris University Hospitals (APHP), Pharmacovigilance Risk Assessment Committee Member (PRAC/EMA)

In the seventies, use of thalidomide led to one of the most prominent disasters in the history of drug development. This catastrophe initiated a change of paradigm in the world with regard to drug safety. Quickly after, a global system called pharmacovigilance was implemented in different parts of the world. Pharmacovigilance concerns the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem (WHO 2002).

The pharmacovigilance system is mainly based on spontaneous reporting signal detection and methods for causality assessment. But the only use of spontaneous reporting may lead to extreme regulatory decisions with product withdrawal (today the DILI are one of the main cause of drug withdrawals), delay, or refusal of marketing.

There is no efficient or risky drug for the whole population. Therefore, the concept of global drug risk management with implementation of risk management plan appeared in the early 2000 and is mandatory for all new drugs in Europe since July 2012. The goal is to define an early (preapproval) and proactive approach in order to ensure that the benefit always outweigh the risks during all the lifecycle of the drug and to better target the drug in subpopulation with a high benefit risk balance.

Several approaches mainly from European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have been developed in the frame of ICH recommendations. This presentation will focus on EMA plan.

CLINICAL NETWORKS AND CONSORTIA IN DRUG-INDUCED LIVER INJURY (DILI): AN OPPORTUNITY FOR ADVANCING SAFETY SCIENCE
M. Isabel Lucena1,2
1Head, Department of Clinical Pharmacology, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain; and 2Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

The IUPHAR Clinical Division is contributing at the 12th Conference of the European Association for Clinical Pharmacology and Therapeutics (EACPT) to be held in Madrid, 27 to 30 June 2015, sponsoring a symposium along with the EACPT titled “Clinical Networks and Consortia in Drug-Induced Liver Injury (DILI): an opportunity for advancing Safety Science.

Over the past decade several concerted efforts have facilitated an unprecedented growth in clinical and translational research in DILI, which have certainly contributed to highlight the relevance of this safety concern among all stakeholders.

In this session we will update some of the most important steps set forward and the challenges that still remain. We will discuss the prospective networking initiatives that allow collecting well-verified DILI cases which have provided new insights in clinical phenotypes and severity. The systematic collection of biological samples has enabled to perform pharmacogenetic and mechanistic approaches, providing the rationale for future studies. The discovery, qualification, and validation of new mechanistic and liver specific biomarkers have become an unmet need that can now be dealt through the joined collaborative efforts of the respective hepatotoxicity working groups of the European IMI SAFE-T Consortium and the Predictive Safety Testing Consortium (PSTC) in the US.

Finally, the role of health regulatory agencies to address the major risk of DILI for new compounds to reduce drug attrition, improve safety assessment through risk minimization plans, support conditional approval of new chemical entities with toxicity potential and to move towards truly safety personalized medicine will be also addressed.

PROMOTING UTILITY OF PK/TDM PRINCIPLES AMONG PRACTITIONERS FACILITATES DIALOG TOWARDS RATIONALIZATION OF DRUG USE
R. Maciulaitis
Institute of Physiology and Pharmacology, Lithuanian University of Health Sciences

Clinical pharmacology has been an educational subject of during undergraduate studies for >20 years as a short course (2 ECTC credits) during sixth year of medical studies. This education showed certain limitation in employment and interpretation of various therapeutic drug monitoring options. We did analyze the practice of therapeutic drug monitoring (TDM) in our hospital and observed clear areas for possible improvements. As a consequence, we did initiate a soft interactive intervention by illustrating and summarizing problems observed in TDM and discussing possible ways of improvements of patient care with colleagues from intensive care unit. This friendly interaction was accepted quite positively by colleagues also showing certain positive trends in TDM improvements. The interaction event was a timely option also to update colleagues with innovations utilizing new PK/TDM knowledge and principles for rational drug use. We will share with the audience our findings and specific arguments used by us to encourage colleagues to seek for consultations and studies in clinical pharmacology area.

JUNIOR DOCTOR-LED “NEAR-PEER” EDUCATION
S. Maxwell
Clinical Pharmacology Unit, University of Edinburgh, United Kingdom

Near-peer teaching (NPT) provides a means of delivering training in practical skills to medical students by tapping into the large resource of junior doctors as an important and effective pool of teachers. Not only does this approach provide much needed teaching for students
but it also provided a vital introduction to teaching skills for the
 doctors of the future. This approach is particularly relevant to the
delivery of prescribing education, which has proved to be a major
challenge for many undergraduate programmes. This brief presenta-
tion will review the development of a NPT programme in prescribing
education based in the hospitals of South-East Scotland over the last 8
years based on one hour tutorials delivered by junior doctors to small
groups of students. It will address (i) the motivations for developing
the programme, (ii) the prerequisites for establishing such a pro-
grame, (iii) the barriers to implementation, (iv) the potential bene-
cfits for the tutors and students, (v) the limitations of this approach,
and (vi) the importance of addressing the need for sustainability.

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JOINT EFFORTS FOR THE DEVELOPMENT AND
QUALIFICATION OF BIOMARKERS IN DILI.
WHERE DO WE STAND NOW?
M. Merz
Discovery and Investigative Safety, Novartis Institutes for
BioMedical Research, Werk Klybeck, Bassell, Project Coordinator
IMI SAFE-T
Timely detection and in-depth assessment of drug-induced liver
injury (DILI), in particular of idiosyncratic forms, is still one of the
big safety challenges for clinical drug development. What is needed
urgently is a set of biomarkers of hepatic function more sensitive
than bilirubin and of hepatocellular injury more specific than ALT
and AST. As idiosyncratic DILI by nature is a rare, but serious event,
large prospective studies across different patient populations and
healthy volunteers are required for clinical qualification of new mark-
ers. The IMI SAFE-T (Safer And Faster Evidence-based Translation)
consortium has undertaken this effort in close collaboration with
Critical Path Institute’s Predictive Safety Testing Consortium (PSTC).
The talk will present an overview on SAFE-T’s objectives and quali-
fication program, discuss results of the program for a set of new
DILI biomarkers, share lessons learned from collaborating in a large
public-private partnership, and provide an outlook on planned future
activities.

UPDATE IN STRATEGIES FOR APPROPRIATE
PRESCRIPTION IN OLDER PATIENTS
B.M. Errasquín

Inappropriate drugs prescription may have severe impact on health
outcomes, especially in the elderly population. Older patients have
an increased risk of adverse drugs reactions, morbidity and mortal-
ity, adverse drug reaction-related hospital admissions, and increased
health care systems costs. This higher vulnerability is due to age-
related physiological changes, pharmacokinetics and pharma-
dynamics, the presence of comorbidities, geriatric syndromes, and
polypharmacy and health care by several specialists in different set-
tings. The use of explicit criteria to identify and prevent inappropriate
use of drugs can be done within a comprehensive geriatric assessment.
Among these criteria are the STOPP-START criteria, first published
in 2008 and revised in 2014. They are emerging as reference criteria
throughout Europe.

HETEROGENITY, THE PROBLEM WITH THE
AVERAGES AND THE NEW REGULATORY
CHALLENGE: “WHOM TO TREAT”
C. Pontes
unidad de Farmacologia Clinica, Hospital de Sabadell, institut
Universitari Parc Tauli - universitat Autonoma de Barcelona,
Spain
Any regulatory assessment has the ultimate aim to safeguard public
health, by ensuring that, for a given medicinal product, the potential
risks are outweighed by its therapeutic efficacy in the intended condi-
tions of use. Evidence is required to reliably predict how the observed
effects in a limited sample will translate into a wide population if the
product is commercialized, and such prediction requires to be pre-
cise, since any failure may potentially have a huge impact on public
health. Testing for homogeneity of the effects across different types
of subjects is then a necessary step, but may also serve as a useful tool
to find markers of risk or therapeutic response that may help to bet-
ter define the medical use of the compounds. However, risks derived
from multiplicity of assessments may lead to misleading conclusions,
and thus clear rules for a priori confirmatory testing of certain sources
of heterogeneity are required, as well as clear understanding on what
constitutes exploratory analysis of data aimed to hypothesis gener-
ation. Besides, the huge implications of the development of precision
medicine have to be considered, since a full new paradigm in which
indications become narrower while achieving higher response rates
may challenge the current methodology of regulatory assessments.
The enrichment of patient populations based on predictive biomark-
ers may allow an early obtaining of evidence on benefits, but also
represents a challenge to the current methods of assessing the risk of
new drugs. The consideration of new timings and sources of safety
information on medicinal products is required, but also the assess-
ment of their potential implications from many perspectives, includ-
ing the economic impact to healthcare systems and those derived from
a greater involvement of patients in decision making.

ROLE OF PHYSICIANS IN DRUG SELECTION
POLICIES. A NEGLECTED RESPONSIBILITY?
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Educational Objectives: At the end of this presentation, the partici-
pants should be able to understand how the French Transparency
Committee (TC) works to recommend the reimbursement (R) of new
drugs in France.

Purpose: To describe what Medical Value (SMR) and Added Medical
Value (ASMR) are and imply on a physician point of view.

Methods: Descriptive analysis of the criteria for the 4 levels of SMR
for reimbursement, and for the 5 levels of ASMR for price negotiation
in a second step. Some real examples will illustrate the presentation.

Results: Based on severity of the disease, type of the drug (preven-
tive, curative or symptomatic), unmet needs, available alternatives,
efficacy/tolerance balance (on relevant clinical outcomes), place in the
therapeutic strategy, and public health value, SMR can be important
(R = 65% or 100%), moderate (R = 30%), weak (R = 15%), or
insufficient (R = 0%).

Based on head to head comparison with an active and reimbursed
comparator in the same indication (and at the same line of treatment),
ASMR can be 1 (revolution = high price) to 5 (no added medical
value = low price). ASMR 1 (major improvement) to 5 (none) is
mainly based on magnitude of effect (NNT and/or NNH on relevant clinical outcomes) observed in direct comparative head to head trial(s). Medico-economic data are never taken into account in the procedure followed by the Transparency Committee. Improvement on clinical benefit and safety outcomes is the key driver of the final decision for reimbursement.

Conclusions: Advices launched by the TC are “scientific”, but 20 of the 25 members of the TC are first physicians with an everyday practice, and second highly skilled in methodology and clinical practice. Physicians are involved in drug selection policies in France.

THE DRUG INFORMATION CENTRE IN 2015 – STILL A VALID CONCEPT?
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Educational Objectives: Participants should be able to identify factors that may increase and/or decrease the quality of DICs’ written responses.

Purpose: To assess the quality of written responses to drug-related queries, in order to identify factors increasing and/or decreasing their quality.

Methods: During an 8-week period in 2013, 6 drug-related study queries were posed simultaneously by e-mail to 7 Scandinavian DICs. The DICs were informed about the study, but staff members were blinded in terms of which queries were study queries, as the study queries were sent from local general practitioners in their own names. Six general practitioners (external experts) and seven clinical pharmacologists (internal experts) assessed the responses individually using a registry form allowing qualitative assessment.

Results: Responses were generally concordant in terms of professional content, but varied in terms of quality of references, advice and conclusions. In total, internal and external experts gave 334 comments. With 3 to 4 exceptions, the 42 responses were assessed as satisfactorily to good. Both expert groups were concerned with whether specific conclusions and/or advice were given, especially in patient-specific queries. Use of secondary and tertiary sources as references, as opposed to primary sources, was criticised by some experts.

Conclusions: To our knowledge, this is the first study using qualitative data to identify factors increasing and/or decreasing the quality of DICs’ responses. The presentation of specific advices and conclusions seem to be especially important when responding to drug-related queries. The study has prompted discussions about quality of the written responses in the participating DICs, and the results may also attain a more general interest.

IMPACT OF BARIATRIC SURGERY ON DRUG TRANSPORT AND METABOLISM
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Bariatric surgery often provides for patients with morbid obesity the only alternative to achieve sustaining weight loss and substantial improvement or remission of obesity related comorbidity. The surgical intervention as the Roux-en-Y gastric bypass technique leads to substantial anatomical and physiological changes associated with micronutrient deficiency and changes in pharmacokinetics of drugs. However, the changes are complex and poorly understood, and long-lasting mucosal adaptation of intestinal functions may occur.

Therefore, potential transcriptional and posttranscriptional adaptation mechanisms in the small intestine of patients with morbid obesity one year after RYGB surgery will be discussed, primarily with reference to intestinal drug metabolizing enzymes and drug transporters. Data are provided as obtained by genome-wide mRNA, microRNA, and targeted proteom analysis in the jejunum and by a pharmacokinetic study using probe drugs before and after bypass surgery. The results are compared with data obtained from healthy subjects (organ donors). There is evidence that multiple adaptation processes may compensate initial changes in drug absorption after bypass surgery.

SYSTEMATIC INTRODUCTION OF NEW THERAPIES WITHIN THE STOCKHOLM COUNTY AND THE KAROLINSKA UNIVERSITY HOSPITAL
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Ten years ago, a model for structured introduction of new medicines in Stockholm County was suggested as these were concluded to drive drug expenditures in years to come. The model is led by the Stockholm Drug and Therapeutics Committee and has since been stepwise implemented including a) horizon scanning and early drug evaluations, b) forecasting of drug expenditures, and c) projects to secure a structured introduction and follow-up of new medicines. Part of the model is currently a national collaboration, whereby a couple of counties contribute and all has access to the findings and deliverables. Meanwhile, at the Karolinska University Hospital, strategic funds can, when available, be claimed for new drugs or indications through the Hospital Medicines Council that provides a recommendation to the Priority Council of the Hospital Board. Pivotal questions that need to be addressed in connection with these requests include type of indication, estimated number of patients, evidence for efficacy (symptoms, quality of life, survival, biomarker, etc) and responder rate, cost per treated patient, and priority of the drug in national and international guidelines, by the pharmaceutical benefits agency, and by the Regional Drug and Therapeutics committee. Based on the above information, the Hospital Medicines Council review and propose horizontal prioritization of any strategic resources available to Priority Council to decide how these are keyed out on operations. Further, the prerequisites for structured introduction of new medicines include a description of the treatment decision process and follow-up procedures and a treatment decision protocol including clinical criteria to fulfill for treatment. Inclusion and exclusion criteria are selected according to pivotal documentation for the approved indication, steps to avoid indication drift and uncontrolled introduction with unclear benefits/safety at an early stage. A protocol for each patient is completed, signed, and sent to the Hospital Medicines Council for the go-ahead, and subsequent registration and monitoring of a continued rigorous implementation process.

STUDENT-LED EDUCATION
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Educational Objectives: After this presentation participants should be able to recognize the value of a new concept of education.
Clinical Dili Networks and Consortia: What Lessons Have We Learnt?

Purpose: Pharmacotherapeutic skills are best learned in the context of clinical practice; learning by doing. By giving medical students responsibility and independence they will gain intrinsic motivation and this is associated with deep learning.

Methods: Evidence to support the concept of student-led education is discussed in part 1 of the presentation. It is illustrated by the project “student-run clinic,” presented by a student in part 2.

Results: Students reported improved skills and indicated that they had acquired knowledge they were unlikely to have gained elsewhere in the curriculum. The quality of specific aspects of care delivered by students was comparable with that of regular care.

Conclusions: Students should take the lead in their own education, coached by the senior teacher. Medical students should be trained as professionals with responsibility for patient care.

Literature Reference


2. Coleman J et al. On the alert: future priorities for alerts in clinical literature reference unknown. To gain optimal benefit of electronic prescribing with Alert fatigue is a ubiquitous problem and much is still to obtain. Clinical pharmacologists may play a role in determining reasons are an important source of information, but often difficult to obtain. Clinical pharmacologists may play a role in determining cut-off points for alert generation.

Conclusions: Alert fatigue is a ubiquitous problem and much is still unknown. To gain optimal benefit of electronic prescribing with clinical decision support, more research should be performed on this topic.

RENAL FUNCTION IN OLDER PEOPLE - VALIDITY OF THE GFR-ESTIMATING EQUATIONS AND IMPLICATION FOR CLINICAL PRACTICE

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Glomerular filtration rate (GFR) is the best marker of renal function. Its evaluation is mandatory for diagnosis and classification of chronic kidney disease (CKD), as well as for drug dosage adaptation. The prevalence of CKD is very high in the elderly, due to physiological aging of the kidney, to lifelong pathological insults, and to comorbidities. However, the GFR estimating equations, such as the Cockcroft-Gault, MDRD, and CKD-EPI equations, have not been developed specifically in elderly patients. The presentation will review the performances of the GFR estimating equations in studies which included elderly patients, and discuss which methodology should be preferred in this population.

VARIABILITY IN DRUG RESPONSE AND CLINICAL REALITY: THE EXAMPLE OF PSYCHIATRIC DISEASES

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Educational Objectives: At the conclusion of this presentation, the participants should be able to demonstrate a deep understanding of the major causes of heterogeneity and variability of drug response in clinical practice, and in particular in the area of psychiatry.

Purpose: To identify and summarize the main factors involved in drug response variability in patients with mental disorders, and its implications.

Methods: A systematic review of the topic was carried out using “variability”, “drug response” and mental disorders” as PubMed key words.

Results: The systematic review yielded 741 PubMed publications. After careful screening, 18 were considered truly relevant for the study purpose. The current evidence, based on the 18 selected publications, indicates that Psychiatry is an area with blurred borders between conditions and high variability of treatment response.

Conclusions: Drugs do not have the same effects in all patients. Part of that variability may be genetically mediated and part may be environment-dependent. Psychiatry is an area of medicine where variability of drug response is particularly high. The results of clinical trials cannot be directly extrapolated to individuals. Even drugs with very similar mechanism of action may work differently in the same patient and the same drug may work differently in the same patient across different illness episodes. Drugs for psychiatric conditions cannot be judged exclusively based on their efficacy and tolerability. Stratification is needed in psychiatry to identify specific subpopulations that may be more or less responsive to given drugs.

Literature Reference


Literature Reference


UK TRANSLATIONAL MEDICINE AND THERAPEUTICS (TMAT) PHD TRAINING
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Within the last 10 years, 2 major UK funding bodies (Medical Research Council [MRC] and Wellcome Trust) have supported clinical PhD programmes designed to build capacity in clinical pharmacology and therapeutics, focusing on the translational difficulties in getting laboratory findings, which might be exploited therapeutically, into the clinic (a major translational “block”). This model builds on a concept argued by Garret Fitzgerald (UPenn) that there is a need for physicians with skills including, but going beyond, those of the traditional clinical pharmacologist. These individuals will drive translational research, working in a pivotal role between the lab and the clinic [1]. They will need an understanding of the potential of omics, quantitative analysis, imaging and bioinformatics as well as skills in pharmacology, PK/PD, statistics, trial design and first-in-human studies. Such new training schemes gain from collaboration with industry, and create clinical pharmacologists well able to move from identifying a clinical problem and undertaking an enabling programme of laboratory science, to building a drug development programme. The Wellcome Trust funded four UK centres, in Cambridge, London, Newcastle and Scotland (led from Edinburgh), while MRC funded two, in Liverpool and Scotland (led from Glasgow). A link with pathology in the Glasgow scheme has particular attraction for identifying drug targets. Around 50 clinicians, many with considerable academic potential, have been attracted into these schemes, to enhance capacity in translational medicine and therapeutics, and contribute to drug development by working with (or indeed within) the pharmaceutical industry, ultimately to promote health and wealth.

Literature Reference

THE DILI-SIM INITIATIVE. INTEGRATED SYSTEMS PHARMACOLOGY MODELING TO EXPLAIN AND PREDICT DRUG HEPATOTOXICITY
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Drugs-induced liver injury (DILI) can occur through a variety of adverse outcome pathways. Understanding and predicting the effects of multiple toxicity pathways as a function of time and exposure are difficult without systematic organization. Quantitative systems modeling can combine multiple drug effects to address this challenge. The DILIsim Initiative is a public-private partnership involving scientists from 14 major pharmaceutical companies and the FDA; it is now entering its fourth year. In addition to financial support, companies provide often unpublished data and perform in kind research to fill gaps in knowledge. The software produced by the initiative, DILIsim®, is a highly specified, mechanistic, hepatic model that utilizes extensive kinetic information among interrelated biological processes to explore the hepatotoxic underpinnings via simulations. Mechanisms currently included in the model are oxidative stress, mitochondrial dysfunction, bile acid transporter inhibition, and lipotoxicity. The DILIsim® software was originally developed to explain and predict interspecies differences in dose dependent hepatotoxicity to help inform first in man dosing. However, the modeling effort has expanded to improve interpretation of traditional and mechanistic serum biomarkers including miR122, CK18 and its caspase-cleaved fragment, and HMGB1. It is now possible to utilize DILIsim® to predict the range of percent hepatocyte loss through necrosis or apoptosis from measurements of these biomarkers in serial serum samples archived from clinical trials. By varying parameters within DILIsim®, it is possible to create simulated patient populations that mimic selected clinical populations in terms of susceptibility to DILI. This approach successfully recently predicted the latency and incidence of serum ALT elevations that were observed in the clinical trials of troglitazone (ClinPharmacolTher. 96(5):589–598, 2014). Systems modeling tools such as DILIsim® will increasingly be used to support decision making throughout the life cycle of new drug candidates.