Off-Label Use of Pharmaceutical Agents in Children: The Drumbeat Quickeens

Lee and colleagues have highlighted an insidious and worrisome aspect of off-label prescription practices for patients in pediatric age groups. However, before discussing their findings, let’s recapitulate the regulatory history that provides the context for their work, which we are excited to publish in this month’s issue of *Clinical Therapeutics*.

The road to institutionalizing equitable opportunities for the development of drugs for patients in pediatric age groups has been long and tortuous. The topic has been well reviewed. Beginning in the early 1990s, the US Food and Drug Administration (FDA) began to make concerted efforts to encourage pharmaceutical companies to conduct studies in children, with no effect. Next, the FDA tried to promulgate regulations, the Pediatric Rule, to require companies to conduct studies in limited circumstances. The FDA was challenged in federal court and was found not to have the authority to enforce such a rule. In 2003, the executive branch worked with the US Congress to convert the Pediatric Rule into legislation, the Pediatric Research Equity Act (PREA), granting the FDA authority to require pharmaceutical companies to conduct pediatric studies for drugs and biologics under development. Thus, paired with the Best Pharmaceuticals for Children Act (BPCA) of 2002 that provided the FDA with authority to provide a financial incentive, pediatric exclusivity, to conduct pediatric studies, the FDA now had the classic carrot-and-stick to encourage pharmaceutical companies to conduct pediatric studies.

Other provisions in the BPCA have been instrumental in expanding infrastructure for conducting studies and developing data that have led to > 800 changes in drug labels. In collaboration with the FDA, the National Institutes of Health has had responsibility for most of these activities: to identify drugs that require additional study, to prioritize these drugs for pediatric therapeutic use, and to sponsor clinical studies of these drugs. Some of the achievements include the following: (1) creation, annual prioritization, and continued maintenance of a list of drugs for which pediatric studies are needed these responsibilities ended in 2012 with permanent enactment of the BPCA and PREA through the Food and Drug Administration Safety and Innovation Act; (2) conduct of workshops in fulfillment of the Newborn Drug Development Initiative; (3) support for the pediatric pharmacology research units that were operational from 1994, before passage of the BPCA, through 2010; (4) sponsorship of pediatric clinical trials for the evaluation of 38 drugs or categories of drugs; and (5) creation of the T32 Pediatric Clinical and Developmental Pharmacology Training Network, which began in 2011 and has resulted in sponsorship of 15 fellows in 11 institutions for 2021-2022, in addition to the > 70 participants who have graduated from T32 training programs.

So, a lot has been achieved since enactment of the BPCA (2002) and PREA (2003), both of which became permanently reauthorized in 2012. However, some publications suggest that there is still much to do. Starting with a hospital-based experience, Czaja and colleagues reported in 2015 that, for 66,896 children who were admitted to pediatric intensive care units in 39 hospitals during 2010, 85% were prescribed ≥1 drugs off-label, with a median of 3 drugs (interquartile range, 2-6) during their stays in the pediatric intensive care unit. They note, “Half of all prescribed medications (n=84) were used off-label: 26 with significant off-label use, 30 high-risk medications, and 47 with high FDA/BPCA priority. The highest impact medications were: dexmedetomidine, dopamine, hydromorphone, ketamine, lorazepam, methadone, milrinone, and oxycodone.” Considering office-based practices, Hoon and colleagues reported in 2019 that, based on surveys between 2006 and 2015 of office-based physicians, they ordered ≥1 off-label systemic drugs at 18.5% of office visits 75% of the time because of unapproved uses. Off-label ordering was most common for neonates (83%).

Closer to the topic at hand, Sohn and colleagues reported in 2016 that the rate of prescriptions for atypical antipsychotic drugs increased from 0.0 prescriptions per 100 office visits in 1995 at the time of market introduction to 1.3 to 2.0 prescriptions per 100 office visits in 2003-2010, with a remarkable 70% to 80% for off-label diagnoses. Attention-deficit/hyperactivity disorder (ADHD) was the most common primary mental diagnosis (24%)...
for antipsychotic prescriptions at pediatric visits, and another 15% of total pediatric visits with antipsychotic prescriptions had no mental disorder diagnosis.

Lee and colleagues\(^1\) conducted a cohort study on data from 2007 to 2020, using a longitudinal health insurance plan database of adjudicated pharmacy and medical claims. They selected youth 5 to 15 years of age at an index visit that included a diagnosis of ADHD and excluded a diagnosis of disruptive behavior disorder (DBD). The authors identified 41,098 youth who met the eligibility criteria, 4557 of whom were subsequently diagnosed with DBD. The incidence of initiation of use of an antipsychotic drug was 19.6 per 1000 person-years (95% CI, 18.7–20.5). The hazard ratio was 4.64 (95% CI, 4.15–5.18). The authors noted that (1) none of the prescribed atypical antipsychotic drugs have an FDA-approved indicated for managing aggressive behaviors in youth, (2) risperidone use is supported by most of the available evidence, (3) aripiprazole use is supported by smaller studies, but (4) “[e]vidence for other antipsychotic medications in managing aggressive behaviors in youth is lacking, yet our data show that use of these agents is not trivial.”

Thus, for most pediatric prescription drug use of established, though off-label, drugs, the build-out of professional infrastructure is well underway for training the inaugural generation of pediatric clinical pharmacology investigators in the conduct of the needed studies. Although the twin pediatric legislative drivers, BPCA and PREA, continue to shape industry thinking and practices about drug development in children and adolescents and pediatric labeling continues to have its gaps filled and continues to catch up to adult labeling, use of nonlabeled sources, such as peer-reviewed literature, consensus statements and practice guidelines from professional organizations, and collected experience in such sources as the Harriet Lane Handbook, will likewise continue to provide a soft work-around of needed information. For example, the Substance Abuse and Mental Health Services Administration provides thorough guidance on best practices for prescribing antipsychotic drugs to children and adolescents.\(^17\) Centralizing these sources may be a useful next step to lessen the redundant workload of searchers and thereby improve efficiency.

However, for drugs that are subject to the slippery slope of commercial pressures, such as use of atypical antipsychotics for treating pediatric patients with ADHD and DBD, another strategy may be needed. One proposal is to borrow conservative prescribing practices from adult medicine, such as

“[E]xercise caution and skepticism regarding new drugs (seek out unbiased information; wait until drugs have sufficient time on the market; be skeptical about surrogate rather than true clinical outcomes; avoid stretching indications; avoid seduction by elegant molecular pharmacology; beware of selective drug trial reporting).”\(^18(p\ 1433)\)

Until there is sufficient time on the market, the adverse event profile is particularly uncertain because only 60% to 80% of the eventual safety profile is known at the time of approval. Thus, it is essential to have a clear rationale that includes risk as well as benefit when prescribing a new drug, especially when the indication is off-label. From a comparative effective analysis of 84 published studies conducted by Agency for Healthcare Research and Quality, the adverse event profile of atypical antipsychotic drugs includes weight gain and metabolic syndrome.\(^19\) However, it is still early in the use of these drugs in pediatrics.

There are a lot of moving parts in the world of off-label use in pediatric drug development. It takes concerted attention to keep up with developments. And the drug beat is only quickening.

Paul Beninger, MD, MBA

Tufts University, Public Health & Community Medicine, 136 Harrison Avenue, 02111, Boston, Massachusetts, USA

E-mail address: paul.beninger@tufts.edu

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