In this issue of *Clinical Therapeutics*, under the topic area of Pharmacology, Pharmacokinetics, and Pharmacodynamics, we discuss a diverse group of therapeutic agents that fall into the broad category of central nervous system (CNS) agents. These are drugs that affect the CNS (the brain and the spinal cord) and produce a response that serves to alleviate or treat a particular medical or psychiatric condition. In a broader definition, CNS agents include almost all of the major classes of prescription medications routinely used by neurologists and psychiatrists (eg, anticonvulsants and antidepressants, respectively). Recent data regarding psychiatric medications in particular suggest that primary care physicians, obstetrician/gynecologists, and pediatricians account for the overwhelming majority of the prescribing of psychotropic drugs. In any case, this category extends to analgesics, anesthetics, emetics, muscle relaxants, and others. In addition, a number of CNS-active agents are available for over-the-counter use; they are taken daily by millions of people who self-medicate for conditions such as insomnia or “decreased energy.” Medications with CNS indications are among the most frequently prescribed in medicine and comprise 20% to 25% of all prescriptions dispensed annually in the United States. Furthermore, their use is increasing. In the United States in 2013 alone, 22.3 million prescriptions were dispensed for antidepressants, 14.9 million for narcotic analgesics, and 11.4 million for anticonvulsants. Indeed, most dispensing pharmacists who have been practicing in the last 30 years can attest to the startling change in the community-prescribing patterns of CNS agents in the early to mid-90s. These changes resulted in the literal movement of CNS agents such as selective serotonin reuptake inhibitor antidepressants out of their alphabetical arrangement on pharmacy stock shelves and onto the smaller “fast mover” section directly on the pharmacy counter. This area was at the time typically populated by high-volume non-CNS pharmaceuticals such as thiazide diuretics, broad-spectrum antibiotics, and conjugated estrogens.

Fast-forward to 2015, and we find that demand for existing CNS agents remains high, and novel treatments are sorely needed in essentially every disease state potentially benefitting from intervention with a CNS agent. Compared with other therapeutic areas, the CNS category has an exceedingly slow approval of novel therapeutic agents, and breakthroughs are rare. An estimated 5.2 million people in the United States have Alzheimer’s disease, and this number is expected to be as high as 16 million by 2050. However, only 4 drugs have received approval by the US Food and Drug Administration for this devastating illness in the last 20 years, and none is effective at halting the disorder.

Why, therefore, is the development of novel CNS therapeutic agents so slow relative to all other drug classes? The answer is multifactorial and beyond the scope of this commentary, but the most oft-cited impediments include the fundamental uncertainties surrounding the pathophysiology of neuropsychiatric disorders, the lack of reliable biomarkers with which to gauge pharmacologic response or even target engagement, and the lack of adequate...
animal disease models. A further obstacle uniquely problematic to the CNS therapeutic area (and perhaps with some chemotherapeutic agents targeting CNS tumors) is reaching the pharmacologic target in adequate concentrations. For any drug or drug candidate to achieve even a modicum of therapeutic efficacy, it must be able to attain sufficient target tissue concentrations that are above a certain threshold value. In the case of CNS therapeutics, in addition to the specific absorption, distribution, metabolism, and excretion considerations fundamental to all therapeutic agent development, additional challenges are posed by the unique protective barriers of the CNS. These include the blood–brain barrier and the blood–cerebrospinal fluid barrier. In addition to playing vital roles in protecting the CNS against potentially toxic agents while maintaining a homeostatic environment, these barriers represent major pharmacokinetic obstacles for sufficient systemic drug delivery to the CNS. Thus, the challenges to CNS drug development are substantial.

Relative to other industries, pharmaceutical development in general is an expensive and slow process. It is estimated that between 1994 and 2001, only 15% of compounds tested in clinical trials from all disease areas reached the marketplace. During this same time frame, however, for the specialty area of psychiatry, <7% of compounds developed for a psychiatric indication were ultimately approved for clinical use. In addition, the time investment in the development of a drug for a psychiatric indication (ie, ~13 years) is the longest of all therapeutic areas; for example, it is twice that of the development of drugs for cardiovascular indications. In addition, the overall failure rate of CNS candidate molecules during development is the highest of any therapeutic area. Even as promising CNS compounds emerge from preclinical assessments and Phase I studies in an intact and forward-looking manner, they are unique in that Phase II and III developmental studies, such as those presented in this issue, take on average >2 years longer than drugs in other therapeutic areas. Last, it is well known that even regulatory approval is ~2 years longer for drugs with CNS indications. Existing CNS drugs are also among the agents most commonly associated with significant adverse effects and among the most frequently implicated in drug–drug interactions.

Sadly, despite the dire need for improved therapeutic agents, there is now a worrisome trend from the pharmaceutical industry: a number of major companies have announced that they are selectively downsizing their neuroscience research divisions. This trend reflects the present reality that developing drugs to treat brain disease is more difficult and resource-consuming than developing drugs for other therapeutic areas, and it thus represents a poor area for investment returns on research and development.

The development of drugs with CNS indications requires contributions from a wide array of scientists and researchers from the basic science disciplines of chemistry, physiology, pharmacology, toxicology, and psychology. With regard to neuropsychiatric agents, it also requires the critical and uniquely personal interface between clinician and patient, as well as the efforts to relieve both the physical and emotional distress associated with a brain disease. Let us hope this last and uniquely human factor prevails and that research efforts will be redoubled to find improved CNS agents rather than a nonstrategic retreat.

This issue of Clinical Therapeutics offers a collection of CNS articles. First, Nam et al present a randomized, 2-way crossover investigation comparing the pharmacokinetics profile of 2 dosage strengths of the tricyclic antidepressant amitriptyline; this drug was 1 of the earliest clinically useful antidepressants developed and remains in clinical use today. Next, Chen et al report the results of a study assessing the pharmacokinetics and tolerability of gabapentin enacarbil, a prodrug of gabapentin indicated for restless legs syndrome and for the management of postherpetic neuralgia, and the opioid morphine administered in combination versus alone. Darwish et al then present an evaluation of the potential for a drug–drug interaction between another anticonvulsant, carbamazepine, and the wakefulness-promoting agent armodafinil, the R-enantiomer of modafinil (a mixture of the R- and S-enantiomers). Armodafinil is currently approved by the US Food and Drug Administration for the treatment of obstructive sleep apnea, narcolepsy, and shift work disorder. Turncliff et al report the results of a single- and multiple-dose pharmacokinetic assessment of samidorphan, a selective opioid antagonist that blocks the μ-opioid receptor without affecting the δ-opioid or κ-opioid receptors. Barbier et al present an article assessing the pharmacodynamics, pharmacokinetics, safety, and tolerability of the investigational compound encenicline. Encenicline is a partial, selective agonist of the α7 nicotinic acetylcholine receptor being developed for the treatment of cognitive deficits in schizophrenia and Alzheimer’s disease. Lastly, Gurley et al have contributed a timely and exhaustive review of multi-ingredient, caffeine-containing dietary supplements. Caffeine is most certainly
a drug and most assuredly a CNS-active one at that, although it is not subject to regulatory requirements and the rigors of the drug development process inclusive of safety and efficacy assessments required of the other prescriptive medications discussed in this issue; such reviews, however, provide otherwise unavailable appraisals of drug safety.

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REFERENCES