The Diminished Pipeline for Medications to Treat Mental Health and Substance Use Disorders

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Objective: **Psychotropic drug development is perceived to be lagging behind other pharmaceutical development, even though there is a need for more effective psychotropic medications. This study examined the state of the current psychotropic drug pipeline and potential barriers to psychotropic drug development.** ***Methods:*** **The authors scanned the recent academic and "grey" literature to evaluate psychotropic drug development and to identify experts in the fields of psychiatry and substance use disorder treatment and psychotropic drug development. On the basis of that preliminary research, the authors interviewed six experts and analyzed drugs being studied for treatment of major psychiatric disorders in phase III clinical trials.** ***Results:*** **Interviews and review of clinical trials of drugs in phase III of development confirmed that the psychotropic pipeline is slim and that a majority of the drugs in phase III trials are not very innovative. Among the barriers to development are incentives that encourage firms to focus on incremental innovation rather than take risks on radically new approaches. Other barriers include human brain complexity, failure of animal trials to translate well to human trials, and a drug approval threshold that is perceived as so high that it discourages development.** ***Conclusions:*** **Drivers of innovation in psychotropic drug development largely parallel those for other drugs, yet crucial distinctions have led to slowing psychotropic development after a period of innovation and growth. Various factors have acted to dry up the pipeline for psychotropic drugs, with expert opinion suggesting that in the near term, this trend is likely to continue. (*Psychiatric Services* 65:1433–1438, 2014; doi: 10.1176/appi.ps.201400044)**

Psychiatric and substance use disorders directly and indirectly affect a large segment of the U.S. population (1–4). The economic burden of these disorders was estimated to be $317 billion in 2002 for serious mental illness (5) and $511 billion in 1999 for substance use disorders (6–8). Given recent estimates that current antidepressants are effective for only about 54% of those treated (9) and given that schizophrenia is treatment refractory for one-fifth to one-third of those affected (10–12), the need to develop innovative treatment is apparent.

The drug development and approval process is complex. It often begins with preclinical trials that rely on animal testing. Most of these do not proceed further into human testing, which is overseen by the U.S. Food and Drug Administration (FDA), the agency responsible for ensuring the safety and efficacy of drugs in humans. For drug development that reaches the purview of the FDA, the first step is an application for testing the drug in humans. Drugs subsequently pass through a series of human trials regulated by the FDA that examine safety, side effects, and effectiveness in increasingly large and diverse samples (phases I–III). Once phase III is successfully completed, the drug's sponsor seeks FDA approval, which may or may not be granted (13–15).

The time from preclinical trials to marketing ranges from nine to 15 years; for every 5,000 compounds that begin development, on average, five enter phase I testing and one is approved by the FDA (16). Mean duration in each clinical phase for successful trials is 16.58 months in phase I, 30.65 months in phase II, and 27.15 months in phase III (13). Given the resources required to bring a drug to market, drug development costs are high. Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that its members spent $49.5 billion on research and development in 2011 (16).

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After adjustment for inflation, the estimated average cost to bring a new drug to market ranges from $1.349 billion (17) to $1.706 billion (13) in 2013 dollars.

After a drug's approval by the FDA, the drug's sponsor has the exclusive right to market it in the United States until patent and exclusivity rights expire. Patents are granted by the U.S. Patent and Trademark Office and typically last 20 years. The FDA grants exclusive marketing rights for varying amounts of time depending on the nature of the application. For example, marketing rights for orphan drugs last seven years, and for pediatric drugs they are extended beyond existing rights for an additional six months (18). As exclusivity ends, competitors seek to enter the market with bioequivalent (generic) drugs. If its application with the FDA is granted, a generic manufacturer typically has 180 days of exclusivity before others may compete (19). Seeking to jump-start this process and obtain advantage over others, manufacturers increasingly file these applications prior to patent expiration, challenging either the validity of the existing patent or arguing that the drug they seek to market does not infringe the patent (20,21), a process known as "prospecting" (21). The original patent holder may challenge submission of the application and even market its own "authorized generic" (20), with the entire process increasingly muddied by litigation (20–22).

The lengthy and costly development process and the lost revenue associated with eventual loss of patent have led to tactics designed to prolong patents and market exclusivity for existing drugs through what is commonly known as "evergreening." One tactic involves seeking new patents for aspects of an existing drug (typically not the active ingredient but "peripheral aspects such as their coating or normal metabolites" [23]). Another tactic is to obtain FDA approval or a new patent for new formulations (for example, sustained release) or new uses of existing drugs (21). Because it is less costly to develop new formulations of existing drugs than to develop a new drug (13), development dollars and research efforts often are spent developing new versions of existing drugs rather than new pharmacological approaches to treatment.

Current development of drugs for mental and substance use disorders is purported to lag behind other pharmaceutical development. A recent publication by PhRMA reported that in late 2011, only 240 drugs for mental health were in the "pipeline," compared with more than 3,000 for cancer and 750 for infectious disease (24). This report parallels a general consensus in the academic and popular literature that psychotropic drug development, after considerable growth between 1980 and 2000, has slowed (25–29). The contrast between development prospects for psychotropic drugs and other drugs is striking, in that both groups are largely subject to the same markets, reimbursement and care management mechanisms, patent laws, and growing interest in comparative effectiveness and treatment efficacy.

This article reports on our research on psychotropic drug development and why it lags behind development in other drug classes. Our findings were based on interviews with experts and analysis of clinical trials.

Methods

This study drew on information from three primary sources: a preliminary scan of nonacademic sources, such as industry reports and articles in the news media, and the academic literature; interviews with experts in clinical treatment of psychiatric and substance use disorders and psychotropic drug development; and an analysis of trials listed on the government's clinical trials Web site.

We began by scanning the Internet and other nonacademic sources to identify medications in development and then examined the academic literature to more fully understand the state of psychotropic drug development and identify experts for interviews. Our examination of the academic literature involved multiple searches of PubMed to identify English-language articles published after 2010 that addressed the psychotropic drug pipeline, particularly literature that examined the subject broadly. All searches included the terms "drug" or "pharmaceutical" and "development." These terms were supplemented by combinations of the following terms: "pipeline," "psychotropic," "depression," "bipolar," "ADHD," "attention deficit," "schizophrenia," "schizoaffective," "psycho*," "sleep," "insomnia," "anxiety," "substance use," "alcohol," "drug," and "disorder." These searches identified several hundred articles, with fewer than 50 of direct relevance to our subject matter.

On the basis of the literature search, we identified multiple experts in the area of drug development and clinical treatment of psychiatric and substance use disorders. Between April and May 2013, we interviewed six individuals with expertise in the areas of psychotropic drug development and treatment of mood and anxiety disorders, psychotic disorders, and substance use disorders. We utilized interview questions that focused on the general state of the psychotropic pipeline, specific drugs in phase III development, and areas of promise and barriers to development. The results of these semistructured interviews were categorized into overarching themes, including the state of the pipeline, reasons why the pipeline is depleted, and factors affecting future drug development.

Our analysis of the National Institutes of Health (NIH) clinical trials Web site (www.clinicaltrials.gov) entailed searches for all phase III interventional clinical drug trials that were either open for recruitment or active but no longer recruiting, involving subjects 18 or older, and that were being conducted in the United States as of the final search date (November 14, 2013), which were updated on the Web site between January 1, 2013, and November 10, 2013. We examined the Web site for clinical trials involving the following conditions: anxiety, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, depression, insomnia, schizophrenia or schizoaffective disorder, and substance use disorders. Drug trials meeting these criteria were analyzed to determine whether they involved existing drugs already approved for some purpose or drugs not yet approved for any purpose. From the latter group, we identified drugs that represented a substantial departure from existing treatment by targeting brain mechanisms for which there presently is no approved drug. We relied on literature discussing the psychotropic pipeline to ascertain drugs with that status (9–12,30–33).

Results

Phase III clinical trials

Our analysis of the clinical trials Web site revealed limited development of new drugs in phase III and even less drug development that was truly innovative (Table 1). For most of the disorder categories examined, a majority of drugs in phase III trials were either already approved drugs that were being tested for new indications or delivery system approaches or, in a few cases, supplements that are already on the market, such as folic acid. New drugs were being tested for depression, insomnia, and schizophrenia, and, of these, only three represented substantial departures from existing medications. These included a serotonin-norepinephrine-dopamine reuptake inhibitor for treatment of depression (amitifadine), a drug targeting glycine receptors to address negative symptoms of schizophrenia (bitopertin), and a nicotinic alpha-7 agonist for adjunctive treatment for cognition in schizophrenia (EVP-6124).

Drugs that are already approved for nonpsychiatric purposes that were being tested for psychiatric disorders included, among others, estradiol for depression in perimenopausal women and a combination of the antibiotic minocycline and aspirin for bipolar depression. Many drugs already approved for psychiatric purposes were being studied for new indications, such as topiramate for comorbid alcohol use disorders and cocaine or nicotine dependence and lisdexamfetamine for depression and bipolar disorder. In a number of trials, different forms of drugs currently approved for specific psychiatric disorders were being tested, such as depot aripiprazole, a longer-acting, injectable version of an existing antipsychotic.

Themes of expert interviews

Our interviews with experts highlighted several themes. Given that the themes are derived from qualitative interviews with multiple experts who approached the questions from different perspectives, we cannot rank the importance of the themes with certainty. However, the first theme is certainly one of the most significant, and our earlier analysis of drugs in phase III development confirmed the paucity of clinical trials of drugs targeting brain mechanisms for which there presently is no approved drug.

Table 1

Status of drugs in open or active phase III drug trials for treatment of psychiatric disorders

Disorder	Open or active phase III drug trials[a]	All drugs[b]	New drug[c]	New drug that substantially departs from existing treatment
Alcohol use disorders	11	9	0	0
Anxiety	8	7	0	0
ADHD	3	2	0	0
Bipolar disorder	17	13	0	0
Depression	23	18	4	1
Insomnia	5	9	1	0
Schizophrenia	32	10	5	2

[a] Some trials were listed in the clinical trials Web site under multiple disorders, such as comorbid alcohol use disorders and PTSD, which is considered an anxiety disorder.

[b] Includes drugs that were studied in combination

[c] Includes drugs that had not yet been approved by the U.S. Food and Drug Administration for any purpose, excluding drugs that are marketed as supplements

Most psychotropic drugs in phase III development are not fundamentally different from existing drugs. Psychotropic drugs in phase III development tend to be either very similar to existing medications, for example, antipsychotics that block D_2 receptors; new formulations of existing drugs, for example, depot aripiprazole; combinations of existing drugs; or drugs being studied for new indications, such as lurasidone, a second-generation antipsychotic, for treatment of bipolar depression, and topiramate, an antiseizure and mood stabilizer medication, for treatment of alcoholism. Although reformulations are useful—for example, depot formulations may improve adherence—this approach permits the manufacturer to command a price premium and prolong patent protection (34) for existing medications.

Most new medications offer innovation in the form of increased tolerability. New drugs that are closely akin to existing drugs may provide improved tolerability or reduced side effects. These benefits may lead to greater acceptance of medication and greater adherence. For example, acceptance of antidepressant treatment expanded once selective serotonin reuptake inhibitors became available in lieu of monoamine oxidase inhibitors. Development costs for improvements of drugs that are already on the market are lower than for new drugs. A predominant focus on bringing similar drugs to market, however, detracts from efforts to develop innovate psychotropic treatments with greater efficacy.

Off-label use of existing medications fuels trials of new indications for existing medications. Many drugs are used off label for unapproved indications—for example, ketamine for acutely suicidal depression—with an increase in off-label prescribing among younger cohorts. The National Institute of Mental Health is interested in the implications of off-label use of medications, and the Division of Adult Translational Research and Treatment Development has focused on evaluating "existing therapeutics for new indications" (35). This focus encourages the exploration of new uses for old drugs. Admittedly, this approach is a cost-effective way to improve treatment and to utilize drugs with known side effects and safety. Such endeavors, however, also may have the consequence of discouraging more costly but innovative drug development.

Results from animal trials may not translate well for human trials. Success in animal trials does not necessarily mean success in human trials. For instance, models of depression among animals are not good indicators of depression among humans. The complicated nature of the human brain and of psychotropic drug development has led companies to avoid development of drugs when translation from animal studies is unpredictable. One area of great disappointment among experts interviewed was the failure, to date, of glutamatergic drugs for schizophrenia,

with one recent stifled effort involving a Lilly drug (LY2140023) for which there was "great hope." The drug was potentially the first in its class to target negative symptoms of schizophrenia. It showed promise in preclinical animal trials (36) and progressed further in clinical trials than had similar drugs, but it was withdrawn from phase III trials in late 2012.

Development efforts are suppressed by an uncertain path to drug approval. The interviews with experts indicated that the lengthy process leading to approval for new psychotropic drugs is seen as so uncertain, relative to associated costs, that innovation may be thwarted. Although a rigorous drug development process is both necessary and desirable, the current lack of payoff means that many companies have abandoned development in the psychotropic field. It has been suggested that the small effect sizes that often appear in early trials are partially responsible for hampering drug development because they discourage funding of later-stage trials (37). The current inability to more precisely match drugs to trial participants at an early stage, however, might be alleviated with further development of genomic and brain research permitting targeted early trials. Thus relying on biomarkers to distinguish between different "types" of people with the same condition might result in more positive early results for specific populations, permitting targeted diagnosis and treatment and preventing investment from fading because of limited effect in early samples (37).

Even smaller companies are increasingly less likely to attempt development of innovative drugs. Small drug companies are more likely than larger companies to invest in developing novel mechanisms, but presently development efforts by smaller companies tend to be in an early phase or in clinical trials preceding human trials. Smaller companies have a history of being purchased by larger pharmaceutical companies once they have shepherded an innovative drug to the point of being considered a reasonable risk. As larger companies leave the psychotropic drug development market, venture capital is less likely to invest in small companies, making the advent of innovative trials less likely for any type of drug.

Discussion

Our interviews with experts and our analysis of phase III drugs confirm that the psychotropic pipeline is depleted, at least for drugs in phase III development, with little resembling innovative drug development. Although more innovative "first in class" drugs may be seen in early phases (24), the prospect of many of those drugs emerging successfully is limited.

Late-stage development commonly involves trials of new drugs from an existing class, such as monoamine-focused antidepressants and antipsychotics that target dopamine receptors, rather than innovative drugs. It also commonly involves trials of existing drugs for new populations or indications, combinations of existing drugs, or new mechanisms for delivery. This pattern contrasts with other areas of pharmaceutical development, such as Alzheimer's disease (24,38), cancer (24,39), and infectious disease (24,40), where large-scale efforts exist to develop innovative treatment. Certainly, incremental developments in psychotropic medication may lead to better outcomes at lower cost (41), and improved tolerability or marginal improvement in symptoms may have substantial value for some patients. However, opportunities for innovative treatments may suffer if development is too narrowly focused on expanding the use of existing drugs.

Several factors might encourage investment in new products. Prescribing of psychotropic medications will increase because of population growth, particularly of the elderly cohort (42–44), continued increased prescribing for younger cohorts (45–47), and increased insurance coverage with the advent of the Affordable Care Act (48). Further, increased availability of generics (49,50) might motivate the search for innovative drugs. In addition, the evolution of personalized medicine (25,26,37,51,52) and innovative research approaches undertaken by NIH (37) might contribute to innovative development.

Despite these trends, innovation barriers clearly exist. As mentioned earlier, human brain complexity makes the transition from animal studies to marketable drugs a difficult and uncertain proposition, more so than for other disorders (25). One example of the difficulty of translation from animal to human studies involves failures of glutamatergic drugs for schizophrenia. Although the translation from animal to human studies is likely more difficult for psychiatric illnesses compared with many conditions, surely other conditions, such as Alzheimer's disease, present a similar challenge and offer equal uncertainty. One distinction, however, may be that dementia-related disorders and cancer, which also increase with age (53), are linked to an upcoming bulge in elderly cohorts. The financial rewards of innovation may seem greater, motivating new treatments for these disorders in lieu of less lucrative psychiatric disorders.

It also may be that some medications, such as procognitive drugs for schizophrenia, might be more effective if linked with cognitive retraining, with clinical trials considering dual avenues of treatment (54). Coordinated treatment that reaches beyond pharmacotherapy may be more essential with psychiatric disorders, further limiting investment in psychotropic development.

Furthermore, existing classes of drugs, even if not optimally effective or free of side effects, provide relief for many patients. This relief may suffice to reduce the pressure on companies to make major investments in new molecules, if prescribers and patients are satisfied with the promise of new but similar drugs. If prescribers can continue to hope, for instance, that the latest permutation of an antipsychotic targeting the dopamine system may bring some improvement of symptoms and reduction in side effects, pressure to develop drugs that take different approaches may be limited.

Finally, because marketing exclusivity and the patent system reward modifications of existing drugs or variations of current classes of drugs, and because those efforts involve less investment, there is limited incentive to develop innovative medications that might truly alter treatment. This circumstance alone should not disproportionately affect the development of psychotropic drugs in conjunction with other factors discussed above, however, it may contribute to shifting investment in innovative drug development to other areas of medicine.

Conclusions

Drivers of innovation in psychotropic drug development largely parallel those

for other drugs, yet crucial distinctions have led to slowing psychotropic development after a period of innovative growth. Although this study did not explore options for increasing innovative psychotropic drug development, there are methods of incentivizing targeted drug development (55,56), including prizes for innovation (56) or government-industry partnerships, such as the National Institute on Alcohol Abuse and Alcoholism clinical investigations group (37). Other approaches include encouraging comparative effectiveness research to ensure adequate differentiation of "me too" drugs from existing offerings (57) and increasing basic research on brain functioning. As we achieve improved understanding from expanded brain and genetics research, one option might be to provide incentives to apply that knowledge in the development of treatment innovations.

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