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The diminished pipeline for medications to treat mental health and substance use disorders

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Abstract

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 article examines the state of the current psychotropic drug pipeline and potential barriers to psychotropic drug development.

Methods—We scanned the recent academic and "grey" literature to evaluate the current state of psychotropic drug development and to identify experts in the fields of psychiatry and substance use disorder treatment and psychotropic drug development. Based on that preliminary research, we interviewed six identified experts and then analyzed drugs in Phase III development for major psychiatric disorders.

Results—Our interviews and review of clinical trials for drugs in Phase III of development confirm that the psychotropic pipeline is slim and that the majority of drugs presently 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 taking risks on radically new approaches. Other barriers include human brain complexity, failure of animal trials to translate well into human trials, and a drug approval threshold that is perceived to be so high as to discourage 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 and substance use disorders directly affect a large segment of the population of the United States with even larger indirect effects (1–4). The economic burden of serious mental illness was estimated to be at least $317 billion in 2002 (5) and that of substance abuse was estimated at $511 billion in 1999 (6–8). Given recent estimates that current antidepressants are effective in only about 54% of those treated (9) and 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. The process by which drug approval occurs often begins with pre-clinical trials that rely on animal testing. Most of these do not proceed further into human testing that is overseen by the Food and Drug Administration (FDA), the agency responsible for assuring safety and efficacy in humans. For drug development that reaches the purview of the FDA, the first step is an application filed by the sponsor seeking to test the drug in humans. Drugs subsequently pass through a series of human trials regulated by the FDA which examine safety, side effects and effectiveness in increasingly large and diverse samples (Phases I through III). Upon successful completion of Phase III, the drug sponsor seeks FDA approval, which may or may not be granted (13–15).

The time from pre-clinical trials to marketing may range from 9 to 15 years; for every 5000 compounds that begin development, on average, five enter Phase I testing and only 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 time and resources required to bring a drug to market, drug development costs are high. Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that, in 2011, their members spent $49.5 billion on research and development (16). Adjusting recent estimates for inflation, the estimated average cost to bring a new drug to market ranges from $1.349 billion (17) to $1.706 billion (13) ($US 2013 values).

After a drug is approved by the FDA, the drug's sponsor has the exclusive right to market it in the United States until applicable patent and exclusivity rights expire. Patents are granted by the United States Patent and Trademark Office and typically last 20 years from application; exclusive marketing rights are granted by the FDA for lengths of time that vary depending on the nature of the application (e.g. "orphan drugs" (seven years), pediatric exclusivity (six months in addition to existing rights)) (18). As exclusivity ends, competitors seek to enter the market with bioequivalent (generic) drugs by filing an application with the FDA. If the application is granted, the generic manufacturer typically has 180 days of exclusivity before other manufacturers may compete (19). Seeking to "jump-start" this process and obtain advantage over other challengers, these applications increasingly are filed prior to patent expiration, challenging either the validity of the existing patent or arguing that the drug the challenger seeks to market does not infringe the patent (20, 21), a process known as "prospecting" (21). In addition, the patent holder for the original drug often challenges submission of the application and may even market their own "authorized generic" (20), with the entire process muddied by increasingly common and aggressive litigation (20–22).

The lengthy and costly development process and the lost revenue associated with eventual loss of patent has led to tactics designed to prolong patents and market exclusivity on existing drugs via 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" (p. 435) (23)) for which patents are weaker and more easily "prospected." Another tactic is to obtain FDA approval and/or new patents for new formulations of existing drugs (e.g., sustained release) or for new uses of existing drugs (e.g., for a new indication) (21). Because it is much 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 on development of new pharmacological approaches to treatment.

Current drug development for mental health and substance use disorders is purported to lag behind other pharmaceutical development. A recent publication by PhRMA reported that, as of December 2011, only 240 drugs were in the "pipeline" for mental health, in contrast to more than 3000 for cancer and 750 for infectious disease (24). This parallels a general consensus seen in both 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 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 as to the state of psychotropic drug development, and why it may lag behind development in other drug classes. Our findings are based on interviews with experts and analysis of on-going clinical trials.

Methods

This article draws on information gathered from three primary sources: a preliminary scan of nonacademic sources (e.g., industry reports, media articles) and of the academic literature; interviews with experts in the field of clinical treatment of psychiatric and substance use disorders and psychotropic drug development; and an analysis of trials listed on the government's clinical trials website.

We began by scanning the Internet and other non-academic sources to identify medications in development, and then examined the academic literature to more fully understand the state of psychtropic drug development and identify potential experts for interviews. Our examination of the academic literature involved multiple searches of PubMed, identifying English-language articles published in 2011 or later that addressed the psychotropic drug pipeline, paying particular attention to literature that examined the subject broadly, rather than focusing on specific trials. All searches included the terms (drug OR pharmaceutical) and development. These terms were supplemented by various combinations of the following terms: pipeline, psychotropic, depression, bipolar, (ADHD OR "attention deficit"), (schizophrenia OR schizoaffective OR psycho*), (sleep OR insomnia), anxiety "substance use", (alcohol OR drug) and disorder. These searches identified several hundred potential articles, of which fewer than 50 were directly relevant to our subject matter.

Based upon the literature search, we identified a number of experts in the area of drug development and clinical treatment of psychiatric and substance use disorders, contact with whom led to identification of others. Between April and May 2013, we interviewed six of those experts, with expertise in the areas of psychotropic drug development and of treatment of mood and anxiety disorders, psychotic disorders and substance use disorders. We utilized a set of interview questions focused on the general state of the psychotropic pipeline,

specific drugs in Phase III development, areas of promise and potential barriers to development. The results of these semi-structured interviews were categorized into themes that emerged both from the structure and the results of the interviews. Over-arching themes identified included: the state of the pipeline, reasons that the pipeline is depleted, and factors that might affect future drug development.

Our analysis of the National Institutes of Health (NIH) clinical trials website (30) entailed searches for all Phase III interventional clinical drug trials listed as being conducted in the United States as of the final search date (November 14, 2013) that met certain criteria. Specifically, we examined open or active trials with subjects who were 18 or older (excluding any focused primarily on children and adolescents that included subjects who were age 18) and that were updated on the clinical trials website between January 1, 2013 and November 10, 2013. We examined the following categories of condition: alcohol use disorders, anxiety (including OCD and PTSD), ADHD, bipolar disorder, depression, insomnia (excluding trials related to sleep apnea and sleep-wake disorder), and schizophrenia (including schizoaffective disorder). Drugs that met these criteria were analyzed to determine whether they were: existing drugs that were already approved for some purpose, or drugs not yet approved for any purpose. From the latter we identified drugs representing a substantial departure from existing treatment (never approved and targeted at brain mechanisms for which there presently is no approved drug). We relied on literature discussing the psychotropic development pipeline to ascertain that status (9–12, 31–34).

Results

Phase III Clinical Trials

Our analysis of the NIH clinical trials website (30) revealed limited new drug development in Phase III and even less drug development that is truly innovative. In most of the disorder categories examined (Table 1), the majority of drugs involved in Phase III trials were ones that were either already approved and being tested for new indications or delivery system approaches or were, in a few cases, supplements already on the market (e.g., 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 triple reuptake inhibitor or SNDRI being tested for depression (EB-1010 (amitifadine)), a drug targeting glycine receptors to address negative symptoms of schizophrenia (RO4917838 (bitopertin)), and a nicotinic alpha-7 agonist to be used as adjunctive treatment for cognition in schizophrenia (EVP-6124). Examples of drugs being tested that were already approved for non-psychiatric purposes included estradiol for depression in perimenopausal women, a combination of the antibiotic minocycline and aspirin for bipolar depression, and the antibiotic D-cycloserine for PTSD and bipolar disorder. Many drugs already approved for psychiatric purposes were being studied for new indications, such as topiramate for treatment of alcohol use disorders co-morbid with cocaine or nicotine dependence, aripiprazole for alcohol use disorders, and lisdexamfetamine for depression and bipolar disorder. Drugs currently approved for specific psychiatric disorders are also being tested in

different forms in a number of trials (e.g., depot aripiprazole, a longer acting injectable version of the existing antipsychotic designed to improve adherence).

Themes from Interviews with Experts

Our interviews with experts highlighted a number of themes related to the state of the psychotropic pipeline. While we cannot state with certainty the relative importance of these different themes, derived as they are from qualitative interviews with multiple experts approaching the questions from different perspectives, Theme 1 is certainly one of the most significant and our analysis of drugs in Phase III development confirms the paucity of "new" drugs in development.

Theme 1: Most psychotropic drugs in Phase III development are not fundamentally different from existing drugs—These drugs tend to be either very similar to existing medications (e.g., more D2 antipsychotics), new formulations of existing drugs (e.g., depot aripiprazole), combinations of existing drugs, or existing drugs being studied for new indications (e.g., lurasidone (a second generation antipsychotic)) for bipolar depression; ondansetron (an antiemetic) for alcoholism; topiramate (an antiseizure and mood stabilizer medication for alcoholism)). While reformulations are useful (e.g., depot formulations of existing antipsychotics may improve adherence), this approach permits the manufacturer to command a price premium and obtain prolonged patent protection (35) for what are essentially existing medications.

Theme 2: Most new medications offer innovation in the form of increased tolerability—New drugs that are closely akin to existing drugs may provide benefits of improved tolerability and reduced side effects. These benefits may lead to greater acceptance of medication and greater adherence once prescribed, as exemplified by the expanded acceptance of antidepressant treatment once selective serotonin reuptake inhibitors (SSRIs) became available in lieu of monoamine oxidase inhibitors (MAOIs). Such improvements have lower development costs than would new drugs unlike those already on the market. The predominant focus on bringing similar drugs to market, however, detracts from efforts to develop innovate psychotropic treatments with greater efficacy.

Theme 3: Off-label use of existing medications fuels trials of existing medications for new indications—Many drugs are used off-label for unapproved indications (e.g., topiramate for alcoholism; duloxetine Hcl for pain; ketamine for acutely suicidal depression) and there is increased off-label prescribing for younger cohorts. The National Institute of Mental Health is increasingly interested in the implications of off-label use of medications, with the Division of Adult Translational Research and Treatment Development focused on evaluating "existing therapeutics for new indications" (36). This focus encourages the exploration of new uses for old drugs. This may not only be a cost-effective way of improving treatment but, also, a way to effectively utilize drugs developed for other purposes which have known side effects and known safety. Such endeavors, however, also may have the unintended consequence of discouraging the pursuit of more costly but innovative drug development.

Theme 4: Results from animal trials for depression and schizophrenia have not translated well into human trials—For instance, models of depression in animals are not good indicators of depression in humans and success in animal trials does not necessarily mean success in subsequent human trials. The "complicated" nature of the human brain and psychotropic drug development has led companies to focus development elsewhere. One area of great disappointment has been failures of glutamatergic drugs for schizophrenia, with one recent stifled effort at innovation being the Lilly drug (LY2140023), for which there was "great hope" as it was a potential first in a class of glutamatergic drug targeting the negative symptoms of schizophrenia. It had shown promise in preclinical trials using animal models (37) and progressed further in clinical trials than similar drugs by the time it was withdrawn from Phase III trials in late 2012, to considerable disappointment in the field.

Theme 5: Development efforts are suppressed by a highly uncertain path to drug approval—Interviews with experts indicated that the lengthy process which leads to potential approval for new psychotropic drugs is seen as so uncertain, relative to associated costs, that innovation efforts may be thwarted. While 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 this, discouraging funding of later stage trials (38). 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 more targeted early trials. Thus, ultimately 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 the fading of investment due to limited effect in a broad-based sample (38).

Theme 6: Smaller companies are more likely to attempt development of innovative drugs and even that is not as likely as was once true—Small drug companies are more likely to invest in developing novel mechanisms, but those that are in development presently tend to be in early phases or pre-human trials. These smaller companies have a history of being purchased by larger pharmaceutical companies once they have moved an innovative drug to the point that it is considered a reasonable risk. With larger companies leaving the psychotropic drug development market, venture capital is less likely to invest in small companies, making the advent of innovative early trials for any type of drug less likely for any pharmaceutical company.

Discussion

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

In contrast to innovative drugs, what is commonly seen in late stage development are trials of: new drugs of an existing class (e.g., monoamine-focused antidepressants, antipsychotics targeting dopamine receptors); existing drugs focused on new populations; existing drugs focused on new indications; combinations of existing drugs; or new mechanisms for delivery of existing drugs. This contrasts with other areas of pharmaceutical development such as Alzheimer's Disease (24, 39), cancer (24, 40), and infectious disease (24, 41), where large-scale efforts have long been underway to develop innovative treatment. On one hand, many of these incremental developments in psychotropic medication may, in fact, lead to better outcomes at lower cost (42), 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 reach of existing drugs.

There are factors that will contribute to increased prescribing of psychotropic medications, such as population growth, particularly of the elderly cohort (43–45), continued increased prescribing for younger cohorts (46–48), and increased insurance coverage with the advent of the Affordable Care Act (49). However, this increased prescribing will not necessarily motivate innovative development. Further, while increased availability of generics (50, 51) might motivate the search for innovative drugs, and the evolution of personalized medicine (25, 26, 38, 52, 53) and innovative research approaches undertaken by NIH (38) might contribute to innovative drug development, barriers to innovation clearly exist.

Human brain complexity is believed to make the transition from animal studies into marketable drugs a difficult and uncertain proposition, more so than in the case of other disorders (25). One example of the difficulty of translation from animal to human studies that was cited during interviews involved failures of glutamatergic drugs for schizophrenia. While this difficult translation and limited understanding of psychiatric disorders likely is true compared to many conditions, surely other conditions such as Alzheimer's disease challenge the translation from animal to human and offer equal uncertainty. One distinction that may explain differences in research and development, however, may be that dementia-related disorders and cancer, the manifestation of which also increases with age (54), are linked to an upcoming bulge in our elderly cohort. The financial rewards of innovation may seem greater, reasonably motivating new treatments for these disorders in lieu of less lucrative mental health and substance use disorders. It also may be that potential medications such as pro-cognitive drugs for schizophrenia might be more effective if linked with cognitive retraining, with clinical trials considering dual avenues of treatment (55). Coordinated treatment that reaches beyond pharmacotherapy may be more essential with psychiatric disorders, further limiting investment in psychotropic development.

Additionally, existing classes of drugs, even if not optimally effective or free from side effects, do provide relief for many patients. This relief may be sufficient to reduce the pressure on pharmaceutical companies to make major investments in finding new molecules, if prescribers and patients can be satisfied with the promise of new but similar drugs. If prescribers can continue to hope that the latest permutation of an antipsychotic which targets the dopamine system or an antidepressant that targets the monoamine system will, perhaps,

bring some improvement in relief of symptoms and reduction in side effects, then pressure to develop drugs that take different approaches may be limited.

Finally, because exclusive marketing rights and the patent system reward minor modifications of existing drugs or variations on current classes of drugs, and because those efforts involve considerably less investment, there is limited incentive to develop innovative medications that have the possibility of truly altering treatment. Taken alone, this should not disproportionately affect psychotropics; in conjunction with the other factors discussed above, however, investment in innovative drug development is clearly focused elsewhere.

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. While this article does not explore options for increasing innovative psychotropic drug development, methods of incentivizing targeted drug development do exist (56, 57). Potential approaches include incentives for development such as prizes for innovation (57) or partnerships between government and industry (such as the NIAAA Clinical Investigations Group (38)). Other approaches include encouraging increased comparative effectiveness research for psychotropic drugs to assure adequate differentiation of "me too" drugs from existing offerings (58) and increasing basic research on brain functioning. With increased understanding provided by expanded brain and genetics research, provision of incentives to move that research forward into treatment innovations may be worthy of consideration.

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Table 1

Status of Drugs in Phase III Development for Selected Psychiatric Disorders

Disorder [a]	Total number of open or active Phase III drug trials	Classification of those drugs in open or active Phase III drug trials		
		Number of drugs under study [b]	Number of drugs not yet approved by the FDA for any purpose [c]	Number of new drugs representing substantial departure 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 are found under multiple disorders (e.g., treatment for comorbid alcohol and PTSD).)

[b] Some drugs are studied in combination with other drugs that are also counted.

[c] Also excluded from this count are any drugs currently marketed as supplements.