The Need for Non-profit Psychiatric Drug Discovery and Development

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Abstract:

Background: Current psychiatric drug discovery and development has not produced very effective medications in the past few decades. Conventional wisdom provides reasons for failure that do not address major structural obstacles to true innovation for psychiatric drugs.

Method: Narrative review based on analysis of the scientific literature augmented by personal experience in academic clinical research as well as in the pharmaceutical industry.

Results: The largest obstacles to drug discovery and development are the biological invalidity of most DSM diagnoses, the economic incentives to produce short-term symptomatic treatments with blockbuster profit potential, and very low thresholds set by the FDA for ending drug discovery due to toxicity. Since these larger structural socio-economic obstacles to drug development will be difficult to change, a new proposal is made for a parallel non-profit drug discovery paradigm, to be funded by governments, akin to the development of vaccines for the Covid-19 pandemic. The key public health implications are highlighted in the example of developing new drugs for Alzheimer dementia, and the potential utility of an anti-tau agent like lithium, currently ignored in drug development in favor of much more expensive and questionably effective amyloid-reducing agents.

Conclusions: Given the key structural problems of psychiatric drug discovery and development, a parallel non-profit drug discovery paradigm is needed to meet all public health needs, as well as to reinvigorate truly innovative and transformative research.

Key Words: drug discovery, non-profit, pharmaceutical industry, lithium, dementia, psychopharmacology, healthcare policy, DSM, FDA

Most observers would agree that psychiatric drug discovery and development is not optimal. New drugs often are not transformative or truly innovative. Many major public health needs are addressed inadequately. For instance, depression remains among the highest causes of disability worldwide, yet new breakthroughs are insufficient.

The reasons behind these limitations are less well appreciated. There is a consensus that we need better psychiatric drugs. But the conventional wisdom blames factors that have not been productively solved: high placebo responses, the difficulty of identifying target brain mechanisms, and the lack of biomarkers. This article proposes other alternative explanations that often are ignored, and are structural in nature. It argues that to address those obstacles in psychiatric drug discovery, the current for-profit system would need to be augmented with a systematic non-profit system of psychiatric drug discovery and development.

Readers should appreciate that the argument made here is not intended to deny aspects of the current system that try to achieve similar goals. For instance, this article argues for a major increased role of government funding for psychiatric drug discovery and development. Some such efforts have been made and exist, but they are unsystematic and woefully insufficient to meet public health needs. There is increased activity of advocacy groups, which is much needed, but it is hampered by needing to function within the current for-profit pharmaceutical industry. Private foundations have begun to look for non-profit based roles in the pharmaceutical system, but they tend to be limited to price concerns and access, not drug discovery and creation of new transformative treatments.

This article calls for non-profit based drug discovery and development, either within existing government institutions like the National Institutes of Health, or with government funding for new agencies, or with government and private foundation funding to private non-profit organizations dedicated to psychiatric drug discovery and development. The proposed system would be parallel to the current for-profit pharmaceutical and biotechnology industries. The goal would not be to replace the latter, but to fill huge gaps in public health that the latter do not address.

STRUCTURAL OBSTACLES

Alternative explanations for the limitations of current psychiatric drug discovery and development are provided on Table 1, the most important of which, and the most controversial, is the poor validity of

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psychiatric diagnosis using the official nomenclature of the American Psychiatry Association (APA), the Diagnostic and Statistical Manual 5th edition (DSM-5). As discussed elsewhere, the process of defining DSM-5 definitions is mostly unscientific, and has led to decades of failure in biological and pharmacological research.[1,2] Few now would defend DSM as being effective in biological research. However, some might deny ascribing blame to it, blaming instead the failures of scientific researchers themselves. Contrary to those who would defend DSM, the reference cited provides evidence that DSM leaders explicitly opposed scientific criteria as the main standard for diagnostic criteria. This fact is a major reason why scientific research using those criteria could not succeed. The APA is fully committed to the DSM-5 ideology, and unwilling to allow more scientific approaches to diagnosis. The National Institute of Mental Health (NIMH) has acknowledged this problem, and no longer uses DSM criteria for biological research.[3]

Another major obstacle, which is more general, is that private profit-based pharmaceutical drug discovery and development entails very high initial costs, well-documented to be in the range of over $2 billion per drug,[4] resulting in a strong economic incentive to limit development to potential blockbusters, with resulting high drug prices. Many public health needs are not met in this process. Further, to minimize costs, pharmaceutical companies mostly do short-term acute symptom improvement studies in psychiatry, unlike other specialties, like cardiology and oncology, where long-term studies lasting years are common. Hence, in psychiatry, long-term outcomes and effect on course of illness or mortality are not studied at all in typical industry trials. These disease-modifying effects are not proven with psychiatric drugs, and appear to be absent. For instance, randomized studies do not exist to show that standard antidepressants reduce suicide overall or reduce general mortality with long-term treatment.

Some might claim that drugs like serotonin reuptake inhibitors (SRIs) were blockbusters and reflect new mechanisms, thus representing innovation in the pharmaceutical industry. However, SRIs are symptomatic drugs, not disease-modifying drugs, and thus were not truly transformative. They were just better tolerated agents for reducing the acute symptom burden of depression. They were not even as effective as their predecessors,[5] nor did they improve the course of unipolar depressive illness and provide disease-modifying effects such as clearly preventing suicide.[6] Hence they are a poor example for claims of truly transformative scientific innovation. Some may disagree with these statements, and space precludes full discussion here, but such discussion is provided elsewhere.[7]

These high costs also are reflected in high attrition rates. Around 90% of drugs in early discovery eventually fail in the course of development.[8] This failure rate often has to do with ending projects for commercial reasons, such as low blockbuster likelihood, as opposed to purely scientific reasons.

Further the United States Food and Drug Administration (FDA) has very strict safety standards[9] that lead to rejection of potentially effective drugs early in the process of drug discovery, often even before any human studies, at the level of animal toxicology. For instance, a standard requirement is that serious toxicity in animals should occur at doses that at least 10-fold lower than the doses planned for humans. Such toxicity includes adverse events like seizures. Highly effective drugs like lithium and clozapine would never make it past preclinical laboratory studies today, dying in animal toxicology studies showing nephrotoxicity and seizures. Some may ask for evidence of examples where drugs have been dropped early in development for these reasons. But that is exactly the point. Such drugs never see the light of day. Further, one cannot even identify them usually because they never reach the point of being identified for further research or even for filing patent protection. Those who never have worked for the pharmaceutical industry will ask for examples, which cannot be provided for the reasons given. This process is well known to occur by those who work in the pharmaceutical industry, for which I can vouch with my personal experience.

TABLE 1. Alternative explanations for failures in current psychiatric drug development

Triad of "macro" socioeconomic explanations
1. The DSM diagnostic system
2. Commercial incentives of the pharmaceutical and biotech industries
3. Harmful effects of some government regulations

Some might claim that the FDA standards would be no different for non-profit drug discovery as opposed to profit-based discovery. That view could be questioned. The FDA sets the high standards we have now in part because it knows it is dealing with a for-profit enterprise whose main motivation is economic. If faced with non-profit enterprises, especially when dealing with major public health hazards, the FDA likely would loosen some standards, as it has in the past with HIV drugs, and recently with COVID vaccines and medications for Alzheimer's dementia.

The FDA is sensitive to public perception that it either is too strict or too lax in its willingness to approve drugs for the US market. Another example is the opioid crisis, where the FDA has been criticized, justly, for being too liberal with approval of Oxycontin as supposedly less addictive than other versions of opioids.

The issue is not whether the FDA is too liberal or too strict, in a general sense, but rather whether it is correct. For opioids, it should have been more strict; for HIV and COVID, it was correctly more liberal.

The point made here is that the preclinical toxicity guidelines of the FDA, such as the 10-fold dosing rule described above, are being taken by the pharmaceutical industry in a strict sense. If the FDA was more flexible on such toxicity rules, pharmaceutical discovery could lean more in the direction of efficacy than has been the case hitherto. Of course, critics will worry that unsafe drugs will then be produced; if not outweighed by strong efficacy data, the FDA could block further development later in the lifecycle. As it is, such drugs never even make it to the point of testing for clinical efficacy.

This paper would encourage the FDA to be more flexible regarding safety earlier in the drug discovery process, and perhaps more conservative later in the drug development process after clinical efficacy data also have become available.

These obstacles to drug development in psychiatry are difficult. Overcoming them would require a revolution in psychiatric diagnosis, and structural changes in government regulations and economic incentives. Those changes are needed but are unlikely to happen in the United States for political and cultural reasons.

It is obvious that none of these solutions will be met with any great enthusiasm by the major players in drug development. The academic profession of psychiatry is fully wedded to the DSM system of nosology as its Bible, a common metaphor. People do not give up the Bible very easily. The FDA is fully committed to restrictive safety standards, given the profit-based motivations of the pharmaceutical industry. The public and advocacy groups are likely to resist lowering of safety restrictions in drug development, since one of the most common complaints and fears about drugs is that they are unsafe or have harmful known or unknown side effects. Pharmaceutical companies would resist such changes too in the interest of avoiding future lawsuits.

In short, most of the players in drug discovery and development have strong motivations to maintain the failed status quo,

and few motivations to make the somewhat radical changes needed. Everyone says they want better drugs. Lip service is provided to the goal of curing mental illness, or at least making a real transformation. But those who state these goals are unwilling to make the difficult, uncertain, and unpopular decisions needed to reach those goals by reforming the current drug discovery and development process.

AN ALTERNATIVE

There is another alternative.

In psychiatry, the current status quo meets some needs, but not others. It meets the needs of those drugs that can be blockbusters, that are relatively safe, and that have mainly short-term symptomatic benefits (like better variations on aspirin or ibuprofen). It does not meet the needs of those drugs that might have less financial gain, that might have some toxicities that will need to be handled well medically, but that have long-term disease modification benefits.

For the first set of needs, the current private pharmaceutical industry system and current government regulations suffice. For the second set of needs, since the players likely would not agree to radical changes, a second alternative can be proposed: parallel non-profit government-supported drug development (Table 2). Without economic profit motivation, the incentive to seek blockbusters to recoup costs of early drug discovery would be removed. Further, the FDA could loosen safety restrictions and the public might be more forgiving of potential risks if the suspicion about economic motivations was removed. The higher costs of disease modification drug development, as opposed to short-term symptomatic objectives, would not be an obstacle once the profit motivation was replaced by government funding.

The concept of non-profit drug discovery is novel and hardly can be found in the scientific literature. Where mentioned, editorials have focused on drug costs, with non-profit activity focused on distribution of cheaper generic drugs.[10] Here the focus is on production, not distribution. The concept here is about non-profit drug *discovery*, not just marketing and commercial aspects of drugs. The view here is that unless we engage in non-profit drug discovery, we likely will not be able to overcome the structural obstacles that prevent true transformation in psychiatric drug discovery and development.

There is precedent for such work, quite recently. During the coronavirus pandemic, much attention has been given to the incredibly rapid development of effective and safe vaccines via the private pharmaceutical industry (spearheaded by two biotechnology companies, Biontech and Moderna). Those companies developed their novel mRNA vaccines within about 9 months from initiation of their efforts. Less attention has been paid to the development of quite effective vaccines, using more traditional methods, by non-profit government sponsored programs in Russia and China (among other countries). Those vaccines, which are proven effective and safe (with marginally less efficacy than the mRNA vaccines), were developed in about 12-15 months, which is still extremely rapid. The point here is that this effective vaccine work was done by government scientists, with government funding, without any involvement of private companies.[11] The purpose was a clear public health need; there was no economic motivation. There is no inherent reason why a similar process cannot be applied to other public health needs and other treatments, besides vaccines. The Covid-19 example provides evidence that there is a possibility of realistic success with non-profit drug development.

TABLE 2. Characteristics of current drug development versus proposed alternative non-profit drug development

Current private industry drug development
High initial research costs
Need high prices with blockbuster profits to offset costs
Strict FDA safety standards lead to less innovation or risk-taking
Meets some public health needs, mainly acute symptom improvement
Limited to patented molecules
Alternative non-profit drug development
Lower initial research costs
Low drug prices on market
Looser FDA safety standards allows more innovation or risk-taking
Not limited by patent life
Meets unmet public health needs, mainly long-term disease modification

TABLE 3. Comparison of non-profit lithium drug development for dementia with private industry drug development of Aduhelm

Current private industry drug development
High drug price: $56,000 per year
Intravenous route of administration
Questionable efficacy, unknown long-term harms
Alternative non-profit drug development of lithium
Low drug price: $100 per year
Oral route of administration
Well-defined long-term risks

THE EXAMPLE OF LITHIUM AND DEMENTIA

As an example, it is clear that dementia is a major public health problem, with huge personal and societal costs. Pharmaceutical companies have spent at least two decades and likely billions of dollars on failed drug development using the amyloid hypothesis. Recently they have begun to turn to the tau hypothesis; one difficulty with the latter is that it is difficult to influence tau in the brain.[12] Intrathecal anti-sense antibodies are the most common intervention, but they have potential safety risks such as increased risk of infections or autoimmune reactions. They also have failed in recent trials partly perhaps because the antibody vehicle cannot impact tau inside neurons.[13] These risks likely are leading to many possible treatments being dropped in early drug discovery.

An alternative treatment is an oral agent with strong anti-tau effects which has well-proven neuroprotective effects biologically and has shown impressive pilot evidence of dementia protection: lithium (Table 3).[14] But since it is given orally, lithium's range of effects can cause many side effects, including well-known kidney and thyroid harm. In older persons, its therapeutic range is small.[15] Hence it is rarely considered in clinical practice and in research. Besides these limitations, it is a generic drug and costs pennies per pill. Thus, there has been no economic motivation for any pharmaceutical company to study it.

There is some evidence that it may have dementia prevention benefit, however, at very low doses, which likely would be safe in older persons.[14] To test this hypothesis, a non-profit government-funded drug development program would be needed. The cost-benefit ratio of such a program would be highly attractive. To give ballpark figures, the low dose lithium for dementia hypothesis could be studied in a generous phase II proof-of-concept trial in about 500 older subjects followed for about 5 years, randomized to

lithium versus placebo. Such a trial likely could be conducted in the US at a cost, liberally estimated, of about $10–20 million.[16] If positive, two large phase III trials with 1000 subjects for 5 years each, using standard industry expenses, could cost around $100 million overall. In short, this potentially effective treatment could be studied for around $100 million. The commonly cited number for the cost of full development of a new drug in medicine is about $2.6 billion.[4] Hence, the major cost savings in non-profit development is obvious. Further, if effective for dementia, lithium could enter the market at minimal cost to the public, insurance companies, and governments – likely less than actual drug costs of $100 per person per year (estimated very liberally). In contrast, current debate about the recently FDA-approved Biogen drug for Alzheimer's dementia, Aduhelm, has intensified around projected costs of about $56,000 per year per person.[17] The actual costs of dementia to society, of course, is very high, estimated at about $604 billion per year in the US.[18]

It would seem to be entirely in the interest of public health for a government to support non-profit drug development of a potentially effective treatment that may require $100 million to prove or disprove, for a potential benefit of $100 per year in the marketplace, to treat a condition causing $600 billion per year of societal damage. This process is contrasted with the current private industry drug development process where drugs costs billions to study, and even if effective they would cost billions to the public, insurers, and governments – all in the context of actual failure of such private industry drug development for dementia in the past two decades, and no incentive to study a possibly effective generic medication.

If the concept of non-profit drug development is attractive, readers might wonder if it is needed since we already have government-funded psychiatric research agencies, such as the US National Institute of Mental Health (NIMH). Unfortunately, most clinicians and the public do not realize that the NIMH does not fund clinical psychopharmacology research to any appreciable extent. Various analyses of NIMH budgets find that not more than 5% of those budgets is assigned to grants for clinical psychopharmacology research, meaning studies of drugs in humans.[19] The other 95% is given over mostly to preclinical animal research, or to biological research in humans that is not testing drug efficacy for specific conditions, or to non-drug clinical studies. Recent total NIMH budgets are about $1.5 billion.[20] The amount spent on clinical research in 2014 was $145 million, of which only about $40 million was spent on studies of the two major disease categories of schizophrenia and mood disorders.[19] This amount would be insufficient for drug development of even one drug for those major diseases. In the pharmaceutical industry, in contrast, companies spend about $5–10 million per drug in early development (discovery to phase II) and about $50–100 million per drug in late development (phase III).[21] Thus, the entire yearly NIMH budget for clinical treatment studies is less than a single large pharmaceutical company would spend on developing one drug (one phase I trial plus one phase II trial plus two phase III trials). Given that there are about a dozen large pharmaceutical companies, it is clear that NIMH spending is dwarfed by pharmaceutical industry spending for drug development.

The proposal here could be conducted within the NIH or via a separate government agency or via non-profit drug discovery and development companies. It is likely that the FDA and government agencies are inadequate for full drug discovery and development, and thus the most effective approach could be the organization of non-profit drug discovery and development companies, supported with either government funds or private foundation funds, or both. For psychiatry, the proposal would be that at least 4–5 drugs per year should be studied in discovery and development. Assuming around $50 million devoted to each drug program (less for early discovery, more for later development) the overall cost could be around $250 million per year. This would be only about 15% of the current NIMH budget, and could be funded by reprioritizing current government funding. Or the current budgets could be kept with a new government outlay for non-profit drug development. Because decisions to end projects would be purely based on scientific grounds, and not economic ones, attrition rates would be expected to be lower. Even with a high attrition rate of 80%, which is slightly lower than in for-profit drug discovery and development, i.e, if one drug per year out 5 proved to be effective and safe enough, societal benefits would far outweigh research funding costs. The Covid-19 pandemic non-profit vaccine development experience shows that this proposal is realistic. It is a matter of awareness and will to implement it.

Finally, some might ask where are the current drug candidates to study in such non-profit discovery and development? The answer is that there are plenty of drug candidates that are ignored in current psychiatric drug development, mostly for the social and economic reasons advanced in this article. It is an open fact that many possible candidates sit on drug company shelves today. For instance, there are many agents which affect second messengers, with mechanisms similar to lithium, that are not studied in current psychiatric drug development, often because of concerns that they would be rejected or strictly controlled by the FDA due to safety concerns. Ironically, those agents are much safer than lithium, which entered the market in 1970 before the FDA instituted its increasingly stringent safety restrictions. Lithium itself, as mentioned, is not studied by the for-profit pharmaceutical industry since it is generic and cannot generate profits.

THE LARGER CONTEXT

This proposal for a non-profit approach to psychiatric drug discovery and development does not exist in a vacuum. It can only be effective in a larger context of a range of changes to the entire system of pharmaceutical and biotechnology-based drug discovery and development. This article cannot address the overall context in its limited space. It seeks to present the case for non-profit drug discovery as just one piece of a needed overhaul to the whole approach to psychiatric drug discovery and development, including within the current system of profit-based drug development. The many issues that come up are both complex and controversial, and beyond the ability of a single article to address. This piece of that larger conversation has not been presented previously, and is presented here as one step towards a better system for psychiatric drug discovery and development in general.

Even if the overall idea of a need for a non-profit approach to psychiatric drug discovery and development is accepted, one might ask whether and how sufficient motivation can be generated to revise the current system. The examples of HIV and COVID are both scenarios where immediate public health emergencies had to be addressed. Depression is a major cause of worldwide disability but its impact is constant and chronic, like a slow leak that fills a basement, rather than large and sudden, as with a hurricane that leads to flooding, or worldwide pandemics. Further, mental health is infamously stigmatized, and the world engages in denial about it.

There are no easy answers, but one factor that should be noted is that the world will not begin to pay more attention to psychiatric needs if the profession of psychiatry does not provide a reasoned critique of its problems and a viable alternative approach. Honesty is needed, admitting the profession's obstacles, such as the biological invalidity of DSM and the limitations of commercial motivation in drug discovery and development. This proposal of the need for a viable alternative for psychiatric drug discovery and development is a necessary initial step in what will be a long road, if ever taken, to real progress.

CONCLUSIONS

Current psychiatric drug development has failed and will not succeed for structural reasons: economic motivations for private pharmaceutical companies limit research to blockbusters given current marketplace conditions, which only require symptomatic benefit as opposed to disease modification. Current government restrictions on safety in early drug discovery increase the costs of private drug research, leading to later high pricing, as well as termination of potentially effective drugs that never get to be tested for efficacy. The DSM system of nosology is mostly biologically false; its diagnoses mostly do not reflect valid diseases, thereby limiting drug development to purely symptomatic effects.

The structural changes needed to solve these problems are difficult to achieve. An alternative non-profit drug discovery and development paradigm is proposed. Whether and how sufficient motivation can be generated to revise the current system remains unclear, but the proposal of a viable alternative is a necessary first step.

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