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Drug Discovery in Psychiatry: Rethinking Conventional Wisdom
Découverte de médicaments en psychiatrie: Repenser les idees conventionnelles

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Why do we not have better drugs? This question is the core concern of this paper, based on an assessment of the scientific literature and personal experience inside and outside the pharmaceutical industry.

I will examine standard and alternate explanations for the challenges of psychiatric drug discovery and development (Table 1) and provide my interpretation based on scientific studies and historical processes.

The Conventional Wisdom

The usual explanations given for the limitations of current drug discovery and development are that placebo responses are too high, that drug mechanisms need to be more innovative, that brain structure and genetics are important, that outcome endpoints are poor, and that biological markers are needed.

Placebo is blamed most frequently. But this claim is based on a false assumption that psychotropic drugs are highly effective; they show little difference from placebo because placebo response is too high. Yet it could be that psychotropic drug response is just low, and that placebo is demonstrating limited drug efficacy, especially because of its purely symptomatic nature, as explained later.

A second explanation is that psychotropic drug mechanisms simply are inadequate. Better mechanisms will produce more effective drugs. This attitude is very common,[1] but historically reflects fads, not science. First dopamine was seen as important, then norepinephrine, then serotonin. Now all monoamines are being rejected in favor of the NMDA receptor.[2] The next mechanism to generate passion involves psychedelic drugs. Hundreds of millions of dollars are invested in the hope that a new mechanism will produce even bigger profits. In fact, these mechanisms are just variations in producing symptomatic effects; they have no disease-modifying influence. They remain variations on aspirin. A better aspirin is still aspirin. There is no real innovation.

A third explanation is to focus on brain anatomy, genetics, or biomarkers. This approach is exemplified in the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC).[3] NIMH leadership correctly judged that DSM had failed for the past 40 years, but it incorrectly judged that the cause of this failure was the clinical approach to research, working from the outside in, from symptoms to the brain. In fact, DSM failed because it was inherently unscientific, as explained further below. By incorrectly rejecting all clinical research, the NIMH proposed to work from the inside out, from the brain to symptoms. Further, the RDoC approach assumes that there is a necessary one-to-one correlation between brain mechanism and disease, which is a false assumption.[4]

Regarding genetics and biological markers, any single genetic effect is likely to be small given the polygenic nature of psychiatric diseases. As for biological markers and laboratory tests, the problem is that if the phenotype is false, then any genotype or biological marker also will be false. Since psychiatric phenotypes are DSM-based, if DSM is mostly false, then biological markers for such phenotypes will not prove successful.[5] Instead of these standard explanations, in this paper an alternative set of four major reasons are offered to explain why psychiatric drug development is failing.

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Table 1. Standard and Alternative Explanations for Psychiatric Drug Development Failure.

Standard explanations
High placebo responses
Need for better drug mechanisms
Need for focus on brain structure and genetics
Need for biological markers
Need for better outcome endpoints
Alternate explanations
Focus on symptomatic, not disease-modifying, drugs
Biological invalidity of the DSM diagnostic system
Economic incentives of the commercial system
Excessive focus on safety in government regulations

Symptomatic versus Disease-Modifying Drugs

The central problem with psychiatric drug development today is that it is symptomatic. Drugs are being developed for symptoms only, like fever during an infection, instead of the underlying disease process. This situation would be as if all drugs for cardiovascular disease were being developed to improve chest pain symptoms only, or to improve shortness of breath, as opposed to myocardial infarction, or mortality.[7]

As a result, most psychiatric medications are purely symptomatic, with no known or proven effect on the underlying disease. They are like 50 variations of aspirin, used for fever or headache, rather than drugs that treat the causes of fever or headache.

The concept of disease modification in psychiatry is another topic that requires separate full-length discussion, provided in more detail elsewhere.[8] Briefly, following approaches taken in neurology,[9] it can be suggested that disease modification can be defined partly biologically and partly clinically.

Biologically, it might involve affecting the pathophysiology of the disease process itself. For instance, the pathophysiology of multiple sclerosis involves autoimmune demyelination of axons; disease-modifying treatments have been developed which target the immune system. In cardiology, lipid-lowering drugs and antihypertensive drugs are disease-modifying because they affect important aspects of biological changes that lead to myocardial infarction (coronary artery thickening and narrowing). In psychiatry, such knowledge would involve the pathophysiology of bipolar illness involving abnormal circadian rhythms, for instance, with their consequent clinical effects. Or in schizophrenia, it would involve abnormal neurodevelopment of frontal cortical cytoarchitecture, with later clinical effects involving apathy and amotivation.

Clinically, disease-modifying benefit is shown by improvement in the course of illness and mortality: in cardiovascular disease, there are fewer myocardial infarctions; in oncology, there are fewer malignant recurrences. Mortality is the ultimate arbiter of clinical disease modification. In psychiatry, clinical disease modification would be shown by improving the course of illness. In bipolar illness, there is obvious consensus that such improvement involves the prevention of mood episodes, as clearly provided by lithium. In schizophrenia, it would involve arresting the chronic declining function along with chronic psychosis, which dopamine blockers have not been shown to do, as explained below.

In psychiatry, one could argue that standard treatments for two major diagnoses of schizophrenia and "major depressive disorder" (i.e., dopamine blockers and monoamine agonists) are not disease-modifying because they do not improve the course of illness, nor are they part of known pathogenetic biological processes. This statement is complex and will be challenged, and space does not allow it to be addressed fully here, but it has been defended with further detail elsewhere.[10] To provide one brief example in schizophrenia, a review of 32 maintenance RCTs claimed benefit, but the overall effect size was just below the cut-off for a clinically meaningful benefit (Cohen's $d = 0.5$), and most studies were far below that cut-off individually.[11] In other words, a small effect size of benefit was seen, and the outcome was relapse into an acute exacerbation. That outcome did not measure gradual improvement in the course of schizophrenia, which reflects chronic psychosis and declining function. The largest maintenance study, the CATIE trial, found that 74% of antipsychotic-treated patients discontinued treatment at one year.[12] Thus very little benefit, even at the minimal standard of tolerating and continuing medication, could be shown at the one year end point. A consensus of schizophrenia experts has reviewed the current literature and concluded that antipsychotics do not worsen the course of schizophrenia, but they were not able to show that these agents improve that course either.[13]

In current psychiatric drug development, with the focus on ketamine-like agents and psychedelic-type drugs, all the excitement is about more rapid and greater improvement in depressive symptoms over weeks, or at the longest months.[14] Yet these claims remain limited to acute symptomatic benefit, not long-term disease modification.[15]

Biological Invalidity of DSM

The full extent of the reasoning for this viewpoint has been expressed elsewhere,[16-18] and again only a brief summary can be provided here. DSM-III leaders claimed that the consensus opinion-based approach would establish reliability, like agreeing on dictionary definitions, later leading to validity, after a research-based evaluation of those initial guesses.[19] But the fourth (1994) and fifth (2013) editions made few and usually minor changes. A conservative overtook the profession whereby DSM committees were told explicitly not to make any major changes unless scientific data were overwhelming (which rarely is the case), and even minor changes were debated in detail.[20] DSM leaders admitted that scientific data were not the primary reason for making changes, but rather

"pragmatism,"[21] which meant what they thought was best for the profession and society. For instance, insurance reimbursement and lawsuit implications were taken into account.[21] Such social factors of course would have no direct concordance with pharmacological mechanisms of psychiatric diseases.

In short, DSM is a "social construction,"[22] a creation of late 20th century American psychiatry meant to meet economic, insurance, legal, and practical needs. It is not our best research-based definition of psychiatric illnesses. Hence, if used for biological research, it fails, because nature did not devise genetics, pharmacology, and brain anatomy to correspond to American psychiatry's socioeconomic preferences. The NIMH leadership finally admitted such invalidity of DSM for biological research in 2013,[23] when the fifth edition repeated the errors of two decades earlier with little change. In short, if DSM is invalid for genetics research, or for neuroimaging research – as the NIMH now admits – then it also is invalid for psychopharmacology research and drug development.

Errors of Conventional Wisdom

Common errors of conventional wisdom regarding these matters exist, two of which are mentioned here: "the brain is complex" counterargument, and the "we don't know the cause" counterargument.

Drug development in neurology is difficult, not just in psychiatry. The problem, many claims, is that the target organ of the brain is "hard"; it is complex and difficult to fix when broken. This piece of conventional wisdom is partly true – the brain is indeed more complex than many organs – but also partly false. Witness multiple sclerosis, a neurological condition that for many decades was treated only symptomatically with steroids. In recent years, disease-modifying treatments have been developed (and in fact the class of treatments is called "Disease-modifying therapies"), with major progress in results.

The brain is difficult, but it is not impossible to produce disease-modifying treatments for it. However, if diagnoses are biologically false, as in much of psychiatry, it is indeed impossible.

Regarding "we don't know the cause," it often is claimed that we just don't know the cause of psychiatric illnesses, so how can we know what diagnoses represent real diseases, and thus how can we modify them? Or, in a variant on this view, it is emphasized that psychiatric illnesses are multifactorial, and due to a multiplicity of causes or risk factors, it is claimed that disease modification is not feasible. This common opinion makes an assumption that is not held in general medicine, namely, that to achieve disease modification, one must know etiology. In many cases in medicine, the etiology is not known, and yet still disease-modifying treatments are implemented. For example, as noted previously, DMTs have been developed for multiple sclerosis without knowing its etiology or causes. Coronary artery disease is highly multifactorial in causation, yet disease-modifying treatments have been developed.

Commercial Economic Incentives

It is well known that drug development is difficult, whatever the illness. In general medicine, a rule of thumb is that new drugs, being studied for efficacy for the first time in humans (in "phase I" trials) are either unsafe or ineffective about 90% of the time.[24] Such is the case even with atherosclerosis or hypertension, diseases with clear validity in their diagnostic symptoms and course.

Consider psychiatry, where most DSM diagnoses, being "social constructions," do not correspond to biological realities. In fact, psychiatry has the second-lowest success rate of eventually reaching the marketplace after entering phase I, with a 94% likelihood of failure.[24]

It is an understatement, then, to say, as is common in the pharmaceutical industry, that psychiatric drug development is hard. A 94% failure rate means that pharmaceutical companies know that any true innovation is almost guaranteed to fail. The solution? Either avoid psychiatric drug development altogether, for which they are criticized; or stick with known effective mechanisms, that is, "me-too" drug discovery and development, for which they are criticized. The reason for this lack of innovation is economic; any true innovation is almost guaranteed to fail; me-too innovation is more likely to succeed.

Because of this DSM-influenced 94% failure rate, any drug that succeeds has to succeed big. If pharmaceutical and biotechnology companies spend money on new drugs, with most failing, they want to recoup those losses if any drug moves forward. A successful drug has to be a blockbuster or it is nothing at all. A consequence is that very high prices are given for the 6% that make it to the marketplace.

Me-too drug discovery is faddish. Companies are exquisitely sensitive to what other companies are doing. If other companies are studying a certain mechanism, a pharmaceutical company will conclude that something must be valid there, and follow suit. In the 1980s and 1990s, the fads were serotonin agonism and dopamine/serotonin blockade; in the 2000–2010s, it was NMDA antagonism; now it is psychedelic structures. If no other companies study a certain mechanism, doubt creeps in: why has not anyone else figured this out? And yet, since companies then pursue the same mechanisms, they get into bitter and harsh competition around minor differences between their drugs, marketing those claims to patients and doctors in an effort to "differentiate" themselves.

Safety Over Efficacy

The US Food and Drug Administration (FDA) was granted its current powers in the early 1960s after the thalidomide

crisis, where a new drug for anxiety proved to have terrible teratogenic effects.[25] The FDA's focus on safety then expanded. Preclinical research involves a standard set of toxicity studies that are required in vitro, in vivo, and in animals. If drugs have certain amounts of toxicity, they either will not be approved or they will have strict restrictions.

37% of experimental drugs fail phase I clinical safety studies in humans.[24] An untold number of drugs fail prior preclinical toxicity studies in animals. The threshold of safety required is clear and strict: the FDA requires that doses used in humans should be at least ten-fold lower than equivalent doses that produced any notable toxicity in animal studies (such as liver or kidney effects, seizures, or central nervous system harms).[26] In phase I studies, I have observed how concern about possible seizures led to the plan to discontinue the development of an experimental drug if any seizure occurred in a single human subject. Under these conditions, highly effective drugs like lithium and clozapine would never be developed.

In short, ever since the 1970s, the drug development process has privileged safety over efficacy. The FDA is ensuring that safe drugs come to the market, by and large, but it is sacrificing efficacy. With the exception of clozapine, the current labeling for these older drugs is much looser than for newer drugs because these agents, all initially marketed in the 1930s–1960s (except clozapine) were grandfathered for current use by the FDA in the late 1960s, after new safety and efficacy standards were rolled out.[27] How many lithiums are dying in drug development today, how many clozapines are dropped, without anyone hearing about it?

Conclusions

The standard explanations for psychiatric drug development failure are insufficient, and alternative explanations raise key structural problems in the socio-economic context of psychiatric drug development. At the very least, a shift in focus in drug discovery and development from acute symptom improvement to long-term disease modification is imperative.

Authors' Note

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