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RESEARCH INTO PRACTICE

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Symptomatic versus disease-modifying effects of psychiatric drugs

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Abstract

Objective: Drugs can be divided into two major categories, symptomatic and disease modifying. This review explores whether and how psychiatric drugs fall into one or the other of those categories, and the implications of those results for clinical practice and research in psychopharmacology.

Method: Narrative review.

Results: Most psychiatric drugs have only short-term effects of improving active symptoms. They do not show long-term benefits for the underlying disease, such as improving the course of illness and improving mortality. Evidence is provided for this claim in the treatment literature of antidepressants for depressive illness and antipsychotics for schizophrenia. Developing truly beneficial drugs for disease modification also is limited by the poor clinical and biological validity of Diagnostic and Statistical Manual diagnoses as well as the use of invalid falsely positive maintenance efficacy randomized discontinuation trial designs.

Conclusions: Current psychopharmacology is limited mostly to symptomatic effects, not transformative treatments for the diseases underlying those symptoms. A change in approach is needed in psychopharmacology practice and research, focusing on long-term disease modification rather than short-term symptom improvement.

KEYWORDS

antidepressants, antipsychotics, lithium, major depressive disorder, maintenance trial designs, mortality, psychiatric drug development

1 | INTRODUCTION

It is a truism in modern drug development that all drugs can be divided into two basic classes: symptomatic and disease modifying. It is always preferable to develop disease modifying drugs, such as chemotherapy that cures cancer, rather than symptomatic drugs, such as pain relievers that reduce pain caused by cancer. Almost all psychiatric drugs are symptomatic, not disease modifying. In the course of this paper, the evidence will be provided for that statement. If correct, then a major limitation of psychiatric drugs is that they are like having many variations of aspirin, without chemotherapies or antibiotics or antihypertensives or anticholesterol agents that are able to improve the disease itself.

2 | STATE OF THE ART

2.1 | Symptomatic efficacy versus disease modification

The central problem with psychopharmacology 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 or to improve shortness of breath.

For new drugs in cardiovascular disease, researchers do not bother to measure chest pain or dyspnea. They simply measure time to myocardial infarction, or mortality; these are the primary outcomes for regulatory indication (by the Food and Drug Administration, FDA, or the European Medicines Agency, EMA), not symptoms of chest pain or dyspnea, or even blood pressure.[1] In psychiatry, we measure symptoms of depression and anxiety and psychosis as primary outcomes for FDA/EMA indication; studies usually do not even measure time to hospitalization, and mortality is not even on the radar.

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, but tentatively, following approaches taken in neurology,[2] it can be suggested that disease modification can be defined partly biologically and partly clinically.

Biologically, it would involve affecting the pathophysiology of the disease process itself. For instance, lipid lowering drugs and antihypertensive drugs are disease modifying for cardiovascular disease because they affect important aspects of biological changes that lead to myocardial infarction (coronary artery thickening and narrowing). Note that lipid lowering drugs and antihypertensive agents are completely asymptomatic: they do not improve any symptoms of cardiovascular disease. Yet they are disease modifying. In contrast, psychiatric drug development continues to focus on reducing symptoms, with an apparent lack of awareness that the most effective drugs would be disease-modifying drugs, without any relevance of their effects on symptoms.

A second aspect of disease modification is clinical. In most diseases, clinical 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.

Turning to examining these two aspects of disease modification, biological and clinical, in psychiatry, one could observe the following, with emphasis on the two major psychiatric diagnoses which are the focus of current drug development: schizophrenia and "major depressive disorder" (MDD).

Biologically, antipsychotics are mainly dopamine blockers, and standard antidepressants are mainly monoamine agonists. After their introduction in the 1960s, corresponding theories arose regarding the dopamine hypothesis of schizophrenia[3] and the monoamine hypothesis for depression.[4] Half a century of research has disproven these hypotheses: dopamine overactivity and monoamine depletion are not parts of the pathogenesis of schizophrenia and depression, respectively. Those biological states may be final common pathways of the pathophysiology of those diseases, but even then, they affect only the acute symptoms, not the course of the disease itself. Hence, from a biological perspective, antipsychotics and antidepressants are not disease-modifying drugs.

Clinically, long-term course of illness has to do with future episodes, or chronic deterioration. In most studies of antipsychotics, if schizophrenia is defined using Kraepelinian criteria (studies suggesting otherwise use much broader definitions), the course of illness remains chronic and deteriorating. It is not reversed with long-term antipsychotic treatment.[5] Pathophysiologically, antipsychotics, both older and newer, have a neurotoxic effect in reduction of brain volume with long-term treatment.[6–8] This effect would not be consistent with disease modification benefit. Further, most maintenance randomized clinical trials do not show improvement in the chronic declining course of schizophrenia with antipsychotics. A review of 32 maintenance RCTs claimed benefit, but the overall effect size was just below the cut-

Clinical recommendations

- Short-term symptomatic benefit should not be presumed to provide long-term disease-modifying benefits in psychiatry.
- Since most psychiatric drugs are symptomatic, they should be used mostly short-term rather than long-term, and at lower doses.
- Lithium and some mood stabilizers are distinguished from other psychiatric drugs because they are disease modifying, and should be used more frequently and consistently than in current practice.

Limitations

- This paper is a narrative review and may not have included relevant studies that might have been identified in systematic review.
- The concept of disease modification is new to the psychiatric literature and has not been studied or discussed systematically in the past.

off for a clinically meaningful benefit (Cohen's $d = 0.5$), and most studies were far below that cut-off individually.[9] Even with this small effect size of benefit, the outcome measured was relapse into an acute exacerbation, not gradual improvement in the course of schizophrenia, which reflects chronic psychosis and declining function. The largest randomized maintenance study in schizophrenia, the CATIE trial, found that 74% of antipsychotic-treated patients discontinued treatment at 1 year.[10] Thus very little benefit, even at the minimal standard of tolerating and continuing medication, could be shown at the 1 year endpoint. 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.[11] Given such limited, absent, or negative data, one at least cannot assume that antipsychotics produce long-term course recovery. Except for clozapine, antipsychotics do not reduce mortality or suicide in schizophrenia.[12]

It is well known that standard antidepressants do not reduce overall suicide rates in so-called major depressive disorder (MDD), and in fact increase suicidal ideation and attempts in younger adults and children, based on randomized data.[13] Oft-cited epidemiological studies to the contrary[14] do not contradict those randomized data, which are more valid than non-randomized epidemiological reports.[15] Regarding course of illness, there are around a dozen randomized clinical trials (RCTs) reporting benefit with standard antidepressants in MDD.[16] These dozen or so trials are notably fewer than over 500 acute trials of short-term symptomatic benefit.[17] So the first point to note is that there are far fewer studies of long-term course benefit with standard antidepressants than for acute symptomatic efficacy. Further, an FDA meta-analysis of those maintenance trials found no benefit with antidepressants versus placebo after 6 months of treatment.[16] Lastly, as explained further below, the apparent efficacy in those maintenance trials was driven by short-term relapse, not long-term prevention, based on the randomized discontinuation design. Given that result and the critique below, one could conclude that antidepressants in MDD do not have proven long-term efficacy.

2.2 | Effect size comparisons

Many authors long have raised the problem of limited effect size of benefit with antidepressants in MDD,[18,19] but they have not made the key distinction that even such limited benefits are purely symptomatic, and do not show any disease-modifying benefits. The absence of awareness of this distinction has led to mistaken claims, such as in a highly-cited meta-analysis.[20] That study compared effect sizes of antidepressants with those of drugs for other medical conditions like cardiovascular and infectious diseases. The authors claimed that the effect sizes of psychiatric drugs were similar to non-psychiatric drugs.

The central flaw to that analysis was that it completely failed to make any distinction between symptomatic and disease-modifying effects. The antidepressant effect size was simply symptomatic improvement on a depression rating scale. But it was not compared with antihypertensives for symptomatic improvement of high blood pressure, which is impossible since there are no or few symptoms in hypertension. Rather, the effect size of antihypertensive drugs was based on prevention of future strokes or heart attacks, or mortality. The equivalent comparison for antidepressants would have been prevention of future depressive episodes, and prevention of suicide mortality. Yet such data, as we have shown, indicate no or very limited efficacy for antidepressants. The same considerations would apply for many of the other non-psychiatric medications examined in the meta-analysis, such as treatments for acute stroke (death), chronic heart failure (mortality), diabetes (FBS and mortality), chronic hepatitis (virological response), multiple sclerosis (episode recurrence), breast cancer (mortality), non-small lung cell cancer (mortality), and antibotics for cystitis ("cure"). These outcomes clearly are disease-modifying, not symptomatic.

In short, that meta-analysis compared apples and oranges: symptomatic effect sizes of psychiatric drugs with disease-modifying effect sizes of non-psychiatric drugs. This comparison is illegitimate. Psychiatric drug effect sizes are for symptoms only, not mortality or "hard" outcomes like hospitalizations or future disease episodes or mortality, whereas non-psychiatric outcomes are for the latter, which psychiatric drugs have not been shown to improve.

In current psychiatric drug development, with a focus on ketamine-like agents and psychedelic-type drugs, excitement centers around rapid and large improvement in depressive symptoms over weeks.[21] Yet these claims remain limited to acute symptomatic benefit, not long-term disease modification. Suicidality is not markedly reduced, but only modestly based so in the largest recent studies.[22] Such benefit in suicidal ideation, however limited, has not been shown to translate into prevention of completed suicide or decreased mortality. Until such agents show improvement in course of illness over years, meaning prevention of depressive episodes, and reduction in completed suicide and mortality, disease-modifying benefit cannot be claimed.

2.3 | Disease modification in psychiatry defined

The claim of this paper is that disease modification in psychiatry should require both clinical and biological evidence. The hallmark of clinical evidence for disease modification is improvement in the long-term course of the illness. This effect usually involves prevention of illness episodes (mood episodes for manic-depressive illness) or improvement in chronic disease features (chronic delusions/hallucinations along with chronic poor function for schizophrenia). A common feature of long-term course of illness also is mortality, usually reflected in psychiatry as death by suicide. If this long-term course of illness improvement is not proven clinically, then a drug cannot be said to have disease modification. It is necessary, though not sufficient, to make that claim.

The second criterion would be to affect the biological pathophysiology of the disease. In psychiatry, this effect would depend on the disease. In manic-depressive illness, the basic pathophysiology is known to involve biology of recurrence,[23] which includes second messenger systems and circadian rhythms. Lithium is known to have direct effects on these mechanisms.[24] Standard antidepressants do not affect those mechanisms.[24] In schizophrenia, the basic pathophysiology involves neurodevelopmental disarray of cortical architecture in the frontal lobe, which is thought to include the glutamatergic system in particular, leading to neurotoxicity and a range of consequent later clinical features.[25] Current dopamine blockers do not affect those mechanisms.[26]

Neuroprotective effects alone, as often claimed for antidepressants or antipsychotics, are not equal to or sufficient for the claim of disease modification. At one level, the clinical feature, long-term improvement in the course of the illness, is missing. At another level, even the biological claim is misleading. To claim neuroprotective benefits, it is not sufficient to cite one study where such a claim is shown, but rather the benefit should be replicated in multiple studies and it should be consistent. Further, neuroprotective benefit, like most biological effects, cannot be assumed to translate from an animal species to another animal species or to humans. Such benefit would need to be shown not only in vitro but in vivo; not only in smaller mammals like rodents, but larger mammals like dogs; not only in primates but also in humans. Further not just one neuroprotective marker, like the most commonly cited brain derived neurotrophic factor (BDNF), but a range of neuroprotective markers should be shown to improve. BDNF is nonspecific, and a final stage marker; it correlates with treatment response, so it is not an independent marker of neuroprotection irrespective of the secondary benefits of treatment response.[27] Hence, by itself, it is not sufficient proof of an independent effect of neuroprotection.

Putting all these factors together, contrary to common belief,[28] antidepressants and antipsychotics do not have neuroprotective benefits in all species in animals, nor replicated and consistent studies in humans, nor benefits beyond BDNF that is independent of treatment response. For instance, some animal studies do not find neuroprotective benefits with standard antidepressants at higher doses,[29] or find neurotoxicity in human brain tissue,[30] or cortical atrophy in nondepressed primates.[31] In short, the antidepressant data are inconsistent and not definitive.

In contrast, lithium has proven to have all of the above benefits at standard or low doses in vivo and in vitro, in all animal species and in humans, with clear replication.[24,32,33]

2.4 | Biological invalidity of diagnostic and statistical manual diagnoses

Another feature of the inability to develop drugs for psychiatric diseases, as opposed to purely symptomatic benefit, has to do with the poor validity of psychiatric diagnosis using the official nomenclature of the American Psychiatry Association (APA), the Diagnostic and Statistical Manual 5th edition (DSM-5). As discussed in more detail elsewhere, the process of defining DSM-5 definitions has been influenced heavily by non-scientific factors, and has not proven successful in biological and pharmacological research.[34–36] However, 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.[37]

2.5 | Invalidity of current maintenance clinical trials

Another important aspect of the poor quality of current psychiatric drug development involves the probable invalidity of current maintenance trials accepted by the FDA.[38] Such trials use a randomized discontinuation design. On this design, patients initially are treated with the experimental drug on an open-label basis for acute symptoms (e.g., olanzapine for acute mania, or sertraline for acute depression), and then those who respond to the experimental drug are randomized to continue on it or come off (switch to placebo) in a usually one-year

maintenance trial. Non-responders to the acute treatment are not included in the maintenance phase.

Hence this design is biased from the start by excluding acute symptomatic non-responders. A drug with long-term efficacy for prevention of new episodes does not need to have acute symptomatic efficacy to show such benefit (e.g., antihypertensives, lipid-lowering drugs), which is one reason why this exclusion is not necessary.

Further, this design ensures that the maintenance study is not an all-comers study of future prevention, but rather a study of continuation phase symptomatic relapse after acute symptomatic benefit.[38] The study thus remains a symptomatic study, rather than a study of disease-modifying prevention of new episodes. This aspect of such studies is proven by the fact that almost all "relapses" occur within 3–6 months or earlier after randomized continuation or discontinuation of the acutely effective drug. This is the case with the studies of standard antidepressants in MDD,[16] and it has been shown with studies of antipsychotics in bipolar illness where such data are available.[39] Other lines of evidence also exist to throw doubt on the validity of this design, as described in much more detail elsewhere.[38]

A final feature of relevance is that the randomized discontinuation design almost never has failed to show benefit for any drug in which it is used.[38] A design which provides efficacy for any drug under any condition is not a scientifically valid design, since it cannot falsify its hypothesis. This aspect of the invalidity of this design became relevant in the FDA approval of esketamine in refractory MDD. That agent was effective in only one of three acute trials; usually two such trials are needed to receive FDA indication. However a maintenance randomized discontinuation trial was, not surprisingly, effective, and the FDA accepted that second trial to provide an indication for refractory MDD.[40]

No other FDA branch for any other medical discipline accepts randomized discontinuation trials as the sole basis to demonstrate maintenance efficacy. Only the FDA psychiatry branch does so. In oncology, such designs are used as proof-of-concept phase II studies, to be confirmed with more traditional prophylaxis studies. Psychiatry should do the same. The only prophylaxis design which is unbiased is one in which all-comers, not preselected for acute drug response, are randomized to take or not take a drug and followed for course improvement.[38]

Using this definition, only lithium has been proven to improve the course of any psychiatric illness.[41] Further only lithium has been proven to prevent completed suicide in randomized clinical trials in psychiatry (clozapine reduced suicide attempts but not completed suicide in one randomized trial).[12,42] Thus, only lithium has been proven to improve course of illness and mortality in psychiatry in randomized trials. It is the only drug in psychiatry which is proven to be disease-modifying.

3 | FROM RESEARCH TO CLINICAL PRACTICE

It might be claimed that all chronic or recurrent illnesses, like psychiatric illnesses, are treated with drugs that do not reverse the causes (usually unknown) of disease but that help with symptoms, improve quality of life, prevent hospitalization, and extend life. Psychiatric drugs are believed to have these effects by most clinicians. Lithium has similar effects, clinicians often believe, but it is not seen as different from the others.

This perspective does not appreciate the concept of disease modification. Disease modification does not require improvement of symptoms. Many disease-modifying drugs for hypertension, multiple sclerosis, migraine (like valproate or beta-blockers), or gout (like colchicine) do not affect current symptoms at all. They do improve the long-term course of those illnesses (preventing episodes usually), which is the clinical hallmark of disease modification. In psychiatry, lamotrigine does not improve current symptoms at all,[43] but has long-term disease-modifying effects (prevention of mood episodes). So it is not true that all drugs for all illnesses improve symptoms. That is the central point of this paper: some drugs improve symptoms and often are not disease-modifying; some drugs improve diseases, and often do not improve symptoms.

Further, as documented above, most psychiatric drugs have not been proven, in properly designed randomized trials, to improve the course of any illnesses they are purported to treat; specifically they have not been shown to prevent hospitalization or extend life, as many clinicians believe.

Even quality of life on most psychiatric drugs is much more limited than many clinicians might believe. For instance, past randomized trials of most antidepressants did not study quality of life, and thus most of those agents have not been proven to improve quality of life in short-term 8 weeks randomized trials, much less in 1 year or longer maintenance randomized trials. Hence proof via randomized data is missing. Some observational data on quality of life do not show notable benefit with antidepressants.[44]

Lithium is different from most other psychiatric drugs (outside of the mood stabilizer class of lamotrigine and valproate and carbamazepine) in that it has clear randomized data that it improves course of illness (prevents

episodes), extends life, and prevents hospitalizations.[33] Such randomized data do not exist in long-term studies, meaning 1 year or longer, with antidepressants for unipolar depression, antipsychotics for schizophrenia, or anxiolytics for anxiety conditions.[45]

Current psychiatric drug development has failed and will not succeed for structural reasons. The current system develops many variations on psychiatric aspirin for symptoms akin to headache or fever, but no transformative treatments for the diseases underlying those symptoms. A change in approach is needed in drug development, focusing on long-term disease modification rather than short-term symptom improvement.

4 | LIMITATIONS

Academic analyses of the drug development process are hindered by the fact that most academic experts never work in the pharmaceutical industry, and thus are not knowledgeable about the internal processes of decision-making there. Further, most pharmaceutical industry researchers are limited in their ability to discuss these topics due to non-disclosure agreements and contractual restrictions of employment. This critique of psychiatric drug discovery and development is based on personal experience working in the pharmaceutical industry after having worked in academia. Further interaction and interchange in employment between both groups would help all sides understand and improve the drug development process.

Limitations include that this paper is a narrative review and may not have included relevant studies that might have been identified in systematic review. Further, the concept of disease modification is new to the psychiatric literature and has not been studied or discussed systematically in the past.

CONFLICT OF INTEREST

Until June 2021, Dr. Ghaemi was an employee of Novartis Institutes for Biomedical Research (NIBR), Cambridge MA. All views expressed here are his own alone, and do not reflect those of his employers.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13459.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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