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UPDATE ARTICLE

Industry withdrawal from psychiatric medication development

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Between 1950 and 1969, on a serendipitous basis, psychiatric drug development flourished. However, there has been a steep decline in the development of new medication classes. Instead of new molecular entities, slight molecular modifications producing ''me-too'' drugs attempted to garner market share. With failing profitability, industry is now withdrawing from psychiatric medication development. Managed care drastically shortened contact between patients and clinicians, so the possible observation of unexpected benefits has been nullified. The randomized, parallel-groups design met FDA requirements for specific pharmacological efficacy. However, it does not determine whether a patient who improved while drug-treated required the drug or would have gotten better on his own. Further, pathophysiology benefit remains obscure. The major psychotropic drugs have no benefits for normal subjects. Their remarkable benefits must stem from a necessary interaction with a pathophysiological state. Therefore, understanding therapeutic benefit by treating normal subjects becomes unlikely. The claim that therapeutic knowledge in psychiatry proceeds from bench to bedside has proven vacuous, primarily because of our limited understanding of brain pathophysiology. The utility of the alternative intensive design for understanding diagnosis, therapeutic benefit, and pathophysiology is emphasized.

Keywords: Psychotropic drugs; psychopharmacology; psychopathology; antidepressant; antipsychotic

Introduction

Fueled mostly by benefits from psychopharmacology, psychiatry flourished over the past six decades. Efficacy advances brought psychiatry squarely into ''medicine'' as a full partner, while struggling how to translate genetic and neuroscience discoveries into clinically useful treatments. However, even given the enormous unique opportunities apparently opened by molecular biology, genomics, proteomics, epigenetics, etc., the pharmaceutical industry has shut down its laboratories investigating central nervous system (CNS) drugs. Two recent commentaries from National Institute of Mental Health (NIMH) directors agree that the situation is catastrophic.[1,2]

In announcing the move to investors and analysts, GlaxoSmithKline Chief Executive Andrew Witty explained that pain, depression, and anxiety were areas where ''the probability of success is relatively low… the cost of attaining success is disproportionately high.''[3]

CNS drugs cost more and take longer to bring to market than other types of drugs. CNS drugs often fail in late-stage clinical trials, after significant investment has been made; only 8% of CNS drugs that make it to clinical trials end up being approved.[4]

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Background

The current deficit in novel agents contrasts sharply with the 1950s. Then, there was a sudden efflorescence of potent psychiatric therapeutic agents. The pace of discovery of entirely new classes of psychotropic drugs was dizzying. These included lithium, lysergic acid diethylamide (LSD), chlorpromazine, iproniazid, reserpine, imipramine, chlordiazepoxide, haloperidol, and clozapine.

These discoveries resulted from chance observations of unexpected clinical benefits rather than being derived from basic neuroscience. All major classes were serendipitously discovered by 1969. For instance, chlorpromazine was a pre-surgical antihistamine sedative whose antipsychotic properties were completely unsuspected. Imipramine was developed as a chlorpromazine ''me-too,'' but turned out to be an antidepressant. Conversely, clozapine was a potential antidepressant, but turned out to be an antipsychotic with remarkably low extrapyramidal toxicity and superior efficacy.

What stymied generative serendipity over the next 40 years? A number of elements came together. The most important factor may have been the drastic change in medical practice economics. Hospital-based academic research was supported from clinical income. That freed up clinicians

for therapeutic explorations. However, "managed care" declared this irrelevant to patient care and markedly shortened hospital stays. Second, often patients were discharged before the effects of a new therapeutic regimen became clear. Third, industry became concerned with immediate return on their investments, which were limited by extensive regulations, liability concerns, and exhaustive preclinical animal model testing. Fourth, the growth of clinical research organizations (CROs) diverted industrial support from investigator-initiated academic research to relatively inexpensive, pre-set industrial protocols.

Pasteur famously stated that, for discovery, "chance favors the prepared mind." However, there must be environments that foster chance clinical observations and support prepared minds. The anti-serendipity of the past 40 years may be largely due to the radical constriction of time for informed clinical observations. Shortening clinicians' treatment time per patient visit and preventing continuity in long-term care subverted opportunity for serendipitous discovery.

The bench to bedside model

Hyman states that industrial drug development turned away from novelty to market share by imitation.[1] Molecular "targets" such as the serotonin and norepinephrine receptors are affected within minutes by psychotropic agents, whereas clinical benefit takes several weeks. Such "targets" are only the first domino. However, many compounds constructed by copying prototypes with similar receptor effects proved ineffective or toxic. The relation of molecular structure to therapeutic benefit remains unclear.

Hyman asserts that, "given such important properties as gene expression, synaptic connectivity, and neurotransmitter and receptor utilization, the next stage of progress will require genetic engineering of cultured human neurons using elements that encode functional protein domains" (p. 4).[1]

This idea remains well within the current bench to bedside paradigm. Insel takes a different tack[2] by optimistically emphasizing that many unexplored targets remain: "…one conspicuous observation from the genetics of mental disorders is that none of the scores of candidates from genome-wide association studies (GWAS) involve the usual psychopharmacologic suspects, monoamine transporters or receptors… interesting candidates emerge. The calcium channel *CACNA1*…, the potassium channel *KCNH2*…, Vasoactive intestinal peptide receptor 2…, *DISC1* (and other pathways leading to AKT-mTOR signaling)… and Ankyrin-3… could serve as portals to explore druggable targets" (p. 2).[2] Insel proclaims, "genomics is delivering potential new molecular targets almost monthly" (p. 5).[2]

Although the promise of new knowledge is intoxicating, the relation of these "targets" to therapeutics remains unclear. In part, senior scientists/administrators continue to argue that therapeutic research should be "translational," that is, remain in the "bench to bedside" model. The early, remarkable, multiple, novel therapeutic advances are viewed as lucky accidents irrelevant to current science.

Also ignored is the peculiar fact that these powerful agents have so little beneficial impact on normal humans. They do have therapeutically irrelevant side effects. Antidepressants do not make normal humans happier and antipsychotics do not clarify their thoughts. This suggests that benefits are due to a therapeutic normalizing of a pathological state. Therefore, studies of pharmacological impact on normal animal behavior, or cells, are unlikely to be directly relevant to illness or therapeutics.

The 1962 Kefauver-Harris FDA amendment required the statistical demonstration of acute drug efficacy before marketing. This clear advance had unintended consequences. Industry-supported scientific effort narrowed to testing whether putative medications were really active. Statistical superiority to the double-blind, average randomized, parallel placebo group, as measured by average outcome scale scores, established specific drug activity. Understanding the mechanisms of disease was not necessary for FDA approval. Any and all differences peculiar to clinical samples were affirmed as "biomarkers" – targets for therapeutic intervention. Such claims have not been modified by the disheartening realization that even in the objectively diagnosable, monogenic Huntington's disease, no therapeutic advance has occurred. Sickle cell anemia and cystic fibrosis have yielded parallel disappointments.

The standard randomized parallel-group design leaves a crucial causal ambiguity. If 60% of those treated with medication have substantial improvements, while only 30% of those on placebo improve (assuming statistical significance), then in about half of those who seemed to have a direct drug benefit, the drug was actually not required. Identifying individuals who actually require medication to improve and maintain their gains remains obscure. Therefore, attempts to determine how a drug brought about its benefits by studying those who improved during drug treatment are handicapped by study of a causally heterogeneous mixture.

The attempt to understand the causes of psychiatric illness by studying distal genetic determinants has faltered, finding only slight effects. This emphasizes our ignorance about pathophysiology. However, that major psychotropic agents can induce remissions in certain syndromes – e.g., retarded unipolar depressions, manic states, angry hyperactive paranoid states, panic disorder, and psychoses approximating bipolar disorder – suggests an experimental approach to the proximal pathogenic process.

We hypothesize that drug-induced remission may be due to normalizing episodically dysfunctional cybernetic feedback controls, e.g., decreased negative feedback or pathologically induced positive feedback. Such episodic defects could engender syndromes where defect correction can lead to remission. Patients who require specific pharmacotherapy to remit may share a common cybernetic dysfunction that arises from a variety of causes.

However, studies reducing syndromal heterogeneity by pharmacological dissection failed to thrive as the two major funding sources turned away. NIMH abandoned support for placebo-controlled drug studies, arguing this

was the proper province of industry. NIMH and academia were to focus on basic processes.

Industry did not pursue such diagnostically informative studies, since finding statistically significant benefits was sufficient for the primary goal of FDA marketing approval. Since profitability would drop by narrowing marketing for a broad syndrome to sub-syndromes, this is not an industry priority.

An alternative design for drug discovery

Five decades ago, Chassan addressed whether a treatment intervention was actually required by an individual patient to respond.[5] He recommended "intensive design" – that is, repeated periods of intervening and non-intervening, judging whether the benefit synchronized with the intervention. This suggests an alternative clinical trial design, as relapse rates are usually high if psychotropic drugs are discontinued immediately after remission. Only among those who require medication for benefit should double-blind placebo substitution incur relapse.

Therefore, an alternative design would be to initially and openly treat all patients with the putative medication, titrating for the individual's optimal dose, until it is clear if the patient was not a treatment responder. These subjects would leave the trial. Apparent responders would be maintained on medication for a period, but then randomly, and in double-blind fashion, switched to placebo or remain on medication. All patients would be followed independently and closely, blind to treatment status, for defined signs of worsening. At a predetermined level of modest worsening, double-blind medication re-treatment would start. A worsening rate higher in the placebo-substituted group than in the medication-maintained group would provide clear evidence of medication efficacy. Those individuals who worsened on slow placebo substitution and then improved on medication re-treatment are very likely specific drug responders. Those who switched to placebo and nevertheless continued to do well would be far less likely to be specific medication responders.

To summarize, this design would determine individuals very likely to be medication-specific responders, very likely non-specific responders, and non-responders.

Other practical benefits are that all patients initially receive active treatment. This fosters recruitment, since many patients will not risk being initially assigned to placebo. In addition, patients will learn if medication is necessary for them to remit or that they have sufficient resources. In fact, academic investigators have successfully used this design.[6]

Extending the intensive clinical trial design by including objective baseline measures can isolate objective diagnostic criteria for the sub-syndrome of specific responders. Further, if such measures normalize prior to syndrome remission, they must be tightly tied to the causation of dysfunction rather than a mere correlate. This argues that embedding objective measures (such as brain imaging) within intensive clinical trials of already known specific therapeutic agents would yield the long-sought goal of objective, clinically relevant, psychiatric diagnostic criteria. However, this requires a long-term programmatic approach that substantially exceeds current National Institutes of Health (NIH) roadmaps or DSM discussions.

Summary and conclusion

Since the American Psychiatric Association's (APA) DSM is primarily a diagnostic manual for practitioners, the threshold for including objective findings should depend on clearly demonstrated practical value related to differential diagnosis. Our suggested approach for the objective investigation of the pathophysiologies manifested as psychiatric syndromes requires expensive, long-term, programmatic support. It is not likely to affect any DSM for quite a while. The large difficulty is that neither NIH nor industry – nor, in fact, the APA's DSM process – supports such studies, especially of marketed medications.

Achieving the necessary long-term support may depend on the realization that casting a wide net that includes genomic and brain-imaging efforts is unlikely to succeed in resolving nosological ambiguities or advancing neuroscience, because heterogeneity defeats clustering and correlative studies. Our suggestion is to substantially diminish heterogeneity by intensive design. Further, using known effective agents hastens this goal. This is worth emphasizing, as it affords a strong basis for programmatic support.

The withdrawal of industry funds for CNS research is widely viewed as a catastrophe, but could be a wake-up call. It is a signal that should not be ignored. We eventually realize that a certain strategy is wrong because of lack of payoff. The question is: how long to wait before abandoning major theoretical investments, such as bench to bedside for psychiatric medication? Industry actions suggest that 40 years is enough.

Disclosure

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References

1 Hyman SE. Revolution stalled. Sci Transl Med. 2012;4:155cm11.
2 Insel TR. Next generation treatments for mental disorders. Sci Transl Med. 2012;4:155ps19.
3 Miller G. Is pharma running out of brainy ideas? Science. 2010; 329:502-4.
4 Abbott A. Novartis to shut brain research facility. Nature. 2011; 480:161-2.
5 Chassan J. Research design in clinical psychology and psychiatry. New York: Appleton-Century-Crofts; 1967.
6 McGrath PJ, Stewart JW, Petkova E, Quitkin FM, Amsterdam JD, Fawcett J, et al. Predictors of relapse during fluoxetine continuation or maintenance treatment of major depression. J Clin Psychiatry. 2000;61:518-24.