PSYCHIATRIC DRUG DISCOVERY

Revolution Stalled

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Drug discovery is at a near standstill for treating psychiatric disorders such as schizophrenia, bipolar disorder, depression, and common forms of autism. Despite high prevalence and unmet medical need, major pharmaceutical companies are deemphasizing or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines. In this Commentary, I develop a view of what has gone wrong scientifically and ask what can be done to address this parlous situation.

From an economic perspective, drugs for psychiatric disorders have historically been among the largest sources of revenue (Table 1) for the pharmaceutical industry. Given the high prevalence of psychiatric disorders (1), their massive effect on global disease burden (2), and limitations in the efficacy of current therapies, large markets for new and better therapies already exist, and current demographic and socioeconomic trends predict the development of expanded markets. Such projections are based on gains in global life expectancy, increasing attention to mental health and cognitive performance in the developed world, rapid unplanned urbanization in the developing world, and large numbers of individuals affected by conflict and postconflict situations worldwide.

Advances continue to be made in modes of cognitive psychotherapy (3) and in device-based psychiatric treatments (4); but despite the growing market opportunities, major pharmaceutical companies recently announced substantial cutbacks or complete discontinuation of efforts to discover new drugs for psychiatric disorders (5, 6). This exodus creates a dangerous gap in the public health ecosystem, because safe and effective drugs can be readily deployed in both primary care and specialist settings and, when generic, can be highly cost-effective. Although large companies may continue to in-license new drug candidates, their complete or near complete exits from psychiatric research deplete expertise and financial resources from therapeutics discovery. Here, I describe how we arrived at this crossroads and how we might get back on a productive path of discovery.

identified: the antipsychotic drugs (beginning with chlorpromazine), antidepressants [the tricyclic drug imipramine and the monoamine oxidase inhibitor (MAOI) iproniazid], and benzodiazepines (chlordiazepoxide). Each of these discoveries had an important component of serendipity but also motivated path-breaking research on neurotransmitter release, receptors, and transporters (7).

What has happened—or rather not happened—in the intervening half-century was as unexpected as the initial spate of discoveries. Many antidepressant drugs have been developed since the 1950s, but none has improved on the efficacy of imipramine or the first MAOIs, leaving many patients with modest benefits or none at all (8, 9). Antipsychotic drugs achieved a peak in efficacy—never equaled (10) and still not understood—with the discovery of clozapine in the mid-1960s. Although valproic acid and other drugs developed as anticonvulsants were shown in the early 1980s to be mood stabilizers, lithium remains a mainstay of treatment for bipolar disorder, despite its serious toxicities. There are still no broadly useful pharmacological treatments for the core symptoms of autism—social deficits, language delay, narrowed interests, and repetitive behaviors—or for the disabling negative (deficit) and cognitive symptoms of schizophrenia (11, 12). The molecular targets of all of today’s approved psychiatric drugs are the same as the targets of their pre-1960 prototypes (Table 2), and their mechanisms of action are not understood beyond a few initial molecular events (13). Indeed, the critical molecular target (or targets) for lithium have not been established with certainty (13).

There has been some progress, of course. Important advances have been made in the safety and tolerability of antidepressants. More recently, clinical observation and small clinical trials with ketamine have suggested that the N-methyl-D-aspartate (NMDA) glutamate receptor channel represents a possible new target for antidepressants associated with more rapid onset of therapeutic effects (14). A second generation of antipsychotic drugs was developed on the
basis of a subset of the receptor-binding properties of clozapine. As a result, the second-generation drugs cause fewer motor side effects than do the first-generation drugs but exhibit their own serious side effects—typically, significant weight gain and metabolic derangements such as elevated serum levels of glucose and lipids. In the main, the second-generation drugs are not more efficacious than the first-generation ones (15), and none is as efficacious as clozapine.

**HOSTAGE IMAGINATION**

The astonishing series of discoveries between 1949 and 1957 was a great blessing for psychiatric patients, who had previously lacked effective treatments, and helped move psychiatry from its focus on a disembodied psyche to biological models of disease and pharmacological interventions. By capturing the imagination of researchers to excess, however, and in the absence of other robust biological tools to probe brain function, these drugs may have proved something of a scientific curse. Although it was recognized that disease mechanisms could not simply be inferred from drug action, the newly discovered drugs of the 1950s and 1960s exerted a powerful influence over the development of animal models, biochemical and genetic hypotheses, and approaches to psychiatric diagnosis that continues to this day.

The newly discovered antidepressants, antipsychotic drugs, and benzodiazepines were used to develop animal-based screens, with the goal of identifying new drug candidates. It was recognized that screens based on existing drugs might fail to identify new therapeutic mechanisms, and unfortunately this risk has been fully borne out (16). More troubling, these screens occasionally became imposters for disease models in the academic literature as well as in industry, despite scant corroborative evidence. In the widely used forced-swim and tail-suspension tests, for example, a compound is considered to be an antidepressant when, compared with a control, it causes a rat or mouse to continue swimming or actively struggling longer. Forced-swim and tail-suspension tests do not even model the therapeutic action of antidepressants, because in these rodent screens, a single dose of antidepressant is active, whereas in depressed patients, antidepressant drugs require weeks of administration to exert a therapeutic effect. These screens may have taken on plausibility as depression models because of their theoretical relationship to learned helplessness, a phenomenon considered by some as a possible cause of depression. In learned helplessness paradigms, an organism subjected to loss of control over circumstances subsequently tolerates aversive conditions that could have been avoided (17). For example, forced-swim and tail-suspension tests have become commonly used methods for classifying laboriously developed transgenic mice and other animals as having “depression-like” or “antidepressant-like” phenotypes. There is, in fact, only a tenuous connection between human depression and these rodent assays, which perhaps predictably have not yielded durable mechanistic insights or novel therapeutic agents.

Pharmacological therapeutics influenced much other translational research, as exemplified by the selection of biological candidates for genetic association studies. A PubMed search using the terms “serotonin transporter polymorphism depression” yielded 715 papers (18), and a less-constrained search on the “serotonin transporter polymorphism” yielded 1943 papers (18). This is an extraordinary deployment of human capital and scarce research funds on a very large number of studies, many underpowered and all focused on the known target of moderately effective drugs. Despite the resource investment, this research has not substantially clarified the pathogenesis or pathophysiology of depression or other phenotypes characterized by negative affectivity, or the complex and interesting actions of serotonin in the human brain. A recent mega-analysis of genome-wide association studies in human subjects suffering from depression failed to confirm an association with serotonin transporter polymorphisms (19).

Although these examples do not do justice to the breadth of translational research in psychiatry, which includes much cognitive neuroscience and brain imaging unrelated to monoamine pharmacology, they do demonstrate the power and pitfalls of what Kuhn (20) described as scientific paradigms that sustain the practice of “ordinary science” and that resist fundamental questioning.

**MIND, THE GAP**

In the period from 1993 to 2004, only 8% of central nervous system (CNS) drug candidates that reached the stage of initial human testing (phase 1) eventually achieved regulatory approval (21). Failures occurred occasionally because a significant toxicity emerged in late-stage clinical trials but more commonly because of an inability to
demonstrate efficacy. More recently, European regulators have begun to demand either improvement in efficacy over existing drugs or biomarkers that identify patient subgroups for whom a new drug would be advantageous. Perhaps understandably, many pharmaceutical companies have decided that the science to achieve these goals is lacking and that, for the time being, resources could be more productively spent on other disease areas.

The central problem is clear: Neither vast unmet medical need, nor large and growing markets, nor concerted sales campaigns that attempt to recast “me-too drugs” as innovative (22) can illuminate a path across very difficult scientific terrain. Compared with other areas of translational medicine, psychiatry finds itself with few, if any, validated molecular targets. Indeed, short of a proof-of-concept clinical trial, it is not easy to define criteria for molecular target validation for polygenic human brain disorders. As noted above, current animal-based assays have failed to identify efficacious drugs with new molecular mechanisms, and given scant understanding of the pathophysiology of common psychiatric disorders, it is difficult to develop better models. Furthermore, objective diagnostic tests and treatment-responsive biomarkers are lacking. Without the latter, clinical trials of psychiatric treatments are dependent on disease definitions grounded in the descriptive psychiatry of the 1960s and 1970s (23) as well as on subjective rating scales that are unsatisfactory for conditions in which symptoms wax and wane over time and change with context.

The best-recognized obstacles to effective clinical translation in psychiatry include the complexity of the brain and the associated challenge of connecting levels of analysis from molecules to cells, synapses, circuits, and thence to higher cognition, emotion regulation, and executive function. The relative uniqueness of the human brain creates high hurdles for development of animal models. Anatomically, much of the neural circuitry involved in psychiatric symptoms—for example, that of the prefrontal cerebral cortex—is new or vastly expanded in humans, and gene expression patterns in the human cerebral cortex also appear to be newly evolved, even compared with nonhuman primates (24). That said, for neural circuits that are conserved in evolution—those involved in basic emotions such as fear and reward as well as some basic cognitive functions—rodents and other organisms can potentially provide useful preclinical models (16, 25). Transgenic mice constructed with highly penetrant genetic variants that cause rare monogenic disorders have also proven informative (26), and in the case of fragile X syndrome they have predicted drug efficacy against a subset of symptoms (27). However, most psychiatric disorders are highly heterogeneous and polygenic (28), casting doubt about the utility of existing genetic mouse models. Overall, industry has come to the justifiable view that with few exceptions, valid disease models do not exist for psychiatric disorders.

Unfortunately, the need for models is greater in psychiatry than in other areas of medicine because the human brain is generally inaccessible to direct study. In other fields, diseased tissue is often removed by biopsy or resection and made available for study (for example, analysis of somatic mutations or transcriptomes) or for generation of cell lines. In contrast, removal of brain tissue is generally reserved for brain tumor and epilepsy surgeries and would not necessarily reveal mechanisms of psychiatric diseases that, far from being cell autonomous, reflect abnormal functioning of widely distributed circuits. Thus, most human brain studies are perforce limited to indirect methods such as electroencephalography and noninvasive neuroimaging. These are substantial challenges, but it is still important to ask whether useful lessons can be learned from recent research history and whether new tools, ideas, and forms of organization that are emerging in neuroscience, and in the life sciences more broadly, can help revitalize translational psychiatry.

REFOCUSING TRANSLATIONAL PSYCHIATRY

The exit of the pharmaceutical industry from psychiatry, even in the face of substantial markets, underscores the difficulty of brain research but, more importantly, draws attention to the limitations of translational paradigms of the past several decades. It is time to eschew models and tools that have progressively shown themselves to be unsuccessful. It is time to look beyond pathophysiological hypotheses derived from small, disconnected islands of data that we had the good fortune to acquire. Given the radical incompleteness of our knowledge of the molecular and cellular bases of psychiatric illness, large-scale, unbiased (hypothesis-free) approaches to data collection and analysis should prove to be critical platforms for new, effective hypothesis generation. For such approaches to achieve the scale and scope that will be necessary to understand heterogeneous, polygenic disorders of the human brain, they will require broad collaboration and sharing of tools, specimens, and data. Given the uniqueness of the human brain, such approaches must be complemented by tool building that will advance human experimental neurobiology.

Fortunately, this is a time in the life sciences—and in neuroscience more particularly—when new tools, new ideas, and new kinds of scientific organization (based on collaboration) can help revitalize translational psychiatry. For example, the cost of DNA sequencing has declined by ∼1 million-fold over the past decade, making it feasible to study the large number of subjects necessary to discover the genetic architecture of heterogeneous, polygenic disorders (28). Human neurons can be derived from readily obtainable skin fibroblasts or blood cells, and these systems are beginning to show promise as disease models that should prove amenable to high-throughput biological and chemical interrogation. At the level of basic neurobiology, optogenetics has given neuroscientists the ability to activate or inhibit single cell types and, thus, selected circuits with remarkable specificity and temporal control (29). This technology complements and will likely inform advances in human neurobiology, including various modalities of neuroimaging, and may also help explicate clinical responses to interventions such as deep brain stimulation (4). Studies of structural and functional connectivity may also complement genetics in facilitating diagnostic reform and the identification of biomarkers.

To date, the most advanced large-scale, unbiased investigations of psychiatric disorders lie in genetics. Given the heterogeneity of psychiatric illnesses and the very large number of genetic variants that confer risk—common and rare, single-nucleotide variants (SNVs) and larger copy number variants (CNVs), inherited variation, and de novo mutation—success depends on diverse (and still evolving) study designs that compare very large numbers of affected and unaffected human subjects. There is no shortage of skepticism about the ability of genetics to inform the biology of polygenic disorders, but that bias is often based on mistaken expectations. The value of genome-scale genetic analyses for psychiatry, as for much of medicine, lies in the iden-
tification of biochemical pathways involved in disease pathogenesis because these pathways offer clues about what functions to target for therapeutics discovery. This research is still in its early stages and thus has not yet defined clear disease-related biochemical pathways. Nonetheless, emerging results from genome-scale genetics studies of schizophrenia and of both monogenic and complex forms of autism appear not to pinpoint random loci in the genome but, rather, to suggest certain areas of neuronal function—for example, synaptic transmission—as possible sources of disease risk (30, 31). In addition to genetics, large-scale studies of gene function, epigenetics, transcriptomics, and proteomics should all contribute to a new understanding of pathogenesis as they have in other fields of medicine. However, given the inaccessibility of the living human brain and the limitations of postmortem tissue for functional analyses, all of these follow-on studies to genetics will require the identification of appropriate living systems in which to conduct experiments.

Without biologically appropriate living systems (cells or organisms) that permit robust and high-throughput interrogation of the functions of disease-risk alleles compared with neutral or protective alleles, recent genetic findings will yield only a fraction of their informational potential. Without appropriate living systems it will not be possible to study epigenetic modifications of risk versus protective genes, changing transcription profiles, or biochemical mechanisms relevant to psychiatric disease. I would argue that in developing or selecting relevant test systems, it is more important to be able to accurately model molecular mechanisms of disease than behavioral outputs.

As described, animal behavior can, in the right circumstances, be both informative and useful in treatment development (13, 25–27); however, excessive reliance on what is called face validity—behavior that plausibly models human symptoms—has often led into blind alleys (11). Reliance on symptomlike behavior rather than on molecular mechanism is akin to classifying all winged animals together rather than classifying by evolutionary relationships. Although a stretch, the issue may be akin to cancer, in which the mutations within cancer cells (that is, molecular mechanisms) are proving to be more important to therapy than cell of origin. Although rodent models will remain useful for some translational investigations and, of course, for basic studies in neuroscience, they lack many molecular (24) and circuit-based characteristics needed for molecular studies of psychiatric disease. In addition, the construction of transgenic mice is simply too slow and too costly to interrogate all of the allelic variants of interest or even functions of the genes in which they reside. Nonhuman primates may prove to be useful models in some cases but are likely to be used only rarely because of cost, less well developed technology (such as production of transgenic lines), and ethical hurdles. For initial high-throughput molecular investigations of the functions of the hundreds of risk alleles emerging from genetic studies, perhaps invertebrate models or zebrafish will prove useful, albeit at the price of evolutionary distance.

An important set of tools for the study of molecular mechanisms comes from the ability to generate neurons in vitro from human embryonic stem cells (hESCs) or induced pluripotent stem cells (iPSCs) derived from human skin fibroblasts or the ability to derive neurons directly from human fibroblasts in vitro. Although still in the early stages, this technology is being used to compare neurons from patients with neurons derived from control subjects (32). Given the cell-type specificity of such important properties as gene expression, synaptic connectivity, and neurotransmitter and receptor utilization, the next stage of progress will require the engineering of neurons that approximate real, mature neural cell types relevant to pathogenesis. Although cultured neurons will never be identical to those embedded in circuits in a brain, they are likely to prove informative and permit high-throughput approaches. For example, genetic engineering of cultured human neurons using elements that encode functional protein domains—such as transcription activator–like effector nucleases (TALENs) (33), zinc finger nucleases, or zinc finger transcription factors—should facilitate mechanism-based biological analyses and high-throughput chemical biology screens aimed at the development of compounds to be used as research tools and therapeutics. These cultured designer neurons might also be used to engineer small, reproducible circuits in vitro to study synaptic protein networks already implicated by genetic results in autism, schizophrenia, and bipolar disorder; such circuits can then be used in chemical biology screens.

Should it be possible to reproduce disease mechanisms in culture and to rescue disease phenotypes with candidate drugs, companies and regulators would then need to muster the courage to proceed from cell-based models with compelling molecular mechanisms into early human trials without requiring the intermediate step of possibly misleading animal behavioral models.

REFERENCES AND NOTES


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