

NEUROPSYCHIATRIC DISORDERS

Next-Generation Treatments for Mental Disorders

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There has been a steady retreat by the private sector away from developing medications for mental disorders. This retreat comes just as research is identifying new molecular targets, new clinical targets, and new uses of current treatments that may serve as the basis for the next generation of treatments for mental disorders.

INTRODUCTION

Although psychiatric medications have been among the most widely prescribed of all drugs in medicine for the past decade, the continuing high morbidity and mortality from mental disorders demonstrates the urgent need for better treatments. A number of recent reports detail the dire state of medication development for mental illnesses (1–4). The lack of new validated targets, the depleted pipeline of compounds, the absence of valid animal models, the increasing failure rate of clinical trials, and regulatory challenges have all been implicated as factors, with the end result being a retreat from investment by venture capital firms and a retreat from drug development by industry.

Notwithstanding the considerable challenges at a time when most investors are risk averse, exciting opportunities for drug discovery and development are emerging. Research findings have identified new molecular targets, new clinical targets, and new uses of current treatments, including strategic combinations of medical and psychosocial therapies, which can serve as the basis for the next generation of treatments for mental disorders. Progress will depend not only on translating this new biology to new treatments but also on creating a new culture for accelerating this translation based on standardization, integration, and sharing of data through new partnerships. Here, I discuss the steps needed to ensure that there will be a next generation of more effective interventions for mental illness. I will first suggest some long-term options, based on an emerging understanding of the molecular pathophysiology of mental disorders, and then will describe some shorter-term options, based on a new approach to the clinical syndromes.

THE UNMET NEED

The last five decades may appear, in retrospect, as a golden age of psychopharmacology. Beginning with the revolutionary discovery of the mood stabilizing effects of lithium, the antidepressant effects of the antituberculosis drug iproniazid, and the antipsychotic effects of the antiemetic drug chlorpromazine, more than 20 antipsychot-

ics and 30 antidepressants have been marketed, with combined sales of over \$25 billion in the United States in 2011 (5) (Fig. 1). Psychopharmacology has been through an unambiguous boom period. Against this picture of success, there are several inconvenient truths. In contrast to successes in other areas of medicine, these last few decades have not seen reductions in morbidity or mortality for people with serious mental illness, including relatively common disorders such as depression, bipolar disorder, and schizophrenia. In spite of increased medication use and the undeniable positive experience of some providers and some patients, epidemiological studies fail to show a significant reduction in morbidity as measured by prevalence (6) or mortality as measured by suicide (7). A recent report from Europe describes neuropsychiatric disorders as the largest contributor to the all cause burden of illness in the European Union (8). A separate study from the United Kingdom re-

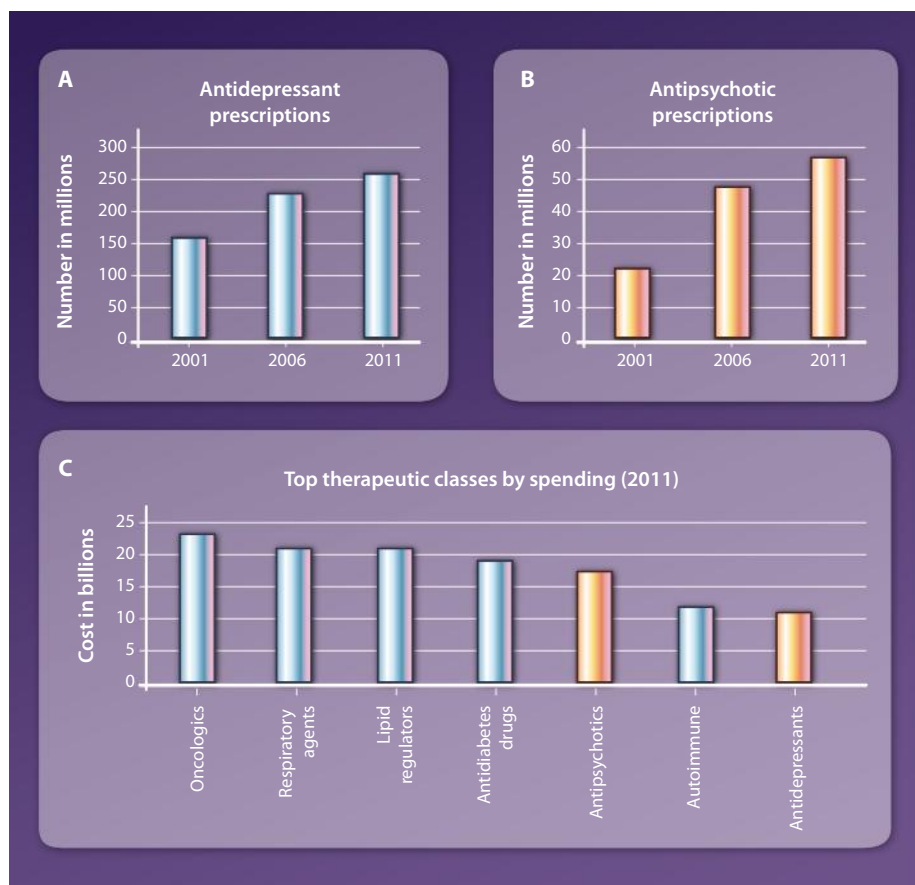


Fig. 1. The growth of psychiatric medications. Shown is the number of prescriptions (in millions) in 2001, 2006, and 2011 for (A) antidepressants and (B) antipsychotics in the United States. (C) Measured by expense (in billions), antipsychotics and antidepressants ranked fifth and seventh for all classes of medications prescribed in the United States, with a combined market of over \$25 billion in 2011. All data courtesy of (5).

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cently reported that for people under age 65, mental illnesses account for almost as much morbidity as all physical illnesses put together (9). Although this high rate of morbidity has been attributed to low rates of treatment in Europe, the results of some of the largest U.S. government-sponsored trials have been sobering, with low rates of remission following treatment with selective serotonin reuptake inhibitors (SSRIs) (10, 11) and high rates of discontinuation with antipsychotics (12). **And, perhaps most concerning, even when existing medications reduce symptoms, the effects are slow and incremental with little evidence for improved functioning or quality of life (13).** The conclusion from even a benevolent review of medications for serious mental illness is that existing medications help too few to get better and very few to get well.

People with mental illnesses need a new generation of treatments, but where will they come from?

NEW MOLECULAR TARGETS

The past decade has witnessed a revolution in genomics. In this period we have gone from fewer than 100 to more than 3,500 disease genes (<http://www.ncbi.nlm.nih.gov/Omim/mimstats.html>), from knowing nothing about common variants as risk factors to identifying more than 1400 alleles associated with 165 different diseases (14), and from searching for the first consensus genomic sequence to recognizing multiple forms of individual variation (15). For mental disorders, the genomic revolution remains incomplete. There are now several confirmed findings of common variants for schizophrenia and bipolar disorder, which in aggregate confer relatively small risk. **There is also the surprising discovery that rare structural variants, often de novo, are associated with several neurodevelopmental disorders such as autism conferring moderate to high risk (16–20).**

How do we get from genomic variants to new treatments? It is curious that many of the common variants associated with diabetes or heart disease identified by genome-wide association studies (GWAS) actually map to known drug targets (21). This, of course, raises the possibility that new alleles may also be targets. But there is a long and risky path from genomic variant or mutation to target.

It is worth considering what is meant by “target” in the drug development arena. In most areas of medicine, target means a protein integral to the pathophysiology of the

syndrome. In many areas of medicine, new targets are emerging from genomics. An example, from another disorder that emerges in childhood, may be helpful. Sickle cell anemia is caused by a mutation in adult hemoglobin that precludes oxygen-carrying capacity (22). This is not a problem in infancy because fetal hemoglobin is spared. Early in postnatal life, the increased expression of a transcription factor, BCL11A, represses the production of fetal hemoglobin, inducing the expression of adult hemoglobin. A common allele in the *BCL11A* gene that reduces expression of this transcription factor partially protects those with the sickle cell mutation. Accordingly, BCL11A is a target for drug development in sickle cell anemia—an antagonist of this transcription factor should derepress fetal hemoglobin and permit increased oxygen-carrying capacity.

This example is based on a mechanistic understanding of the disease in question and, importantly, a loss-of-function variant is protective. How does this compare to our findings in the genetics of mental illness? We still lack a fundamental understanding of pathophysiology for any of these illnesses. The one conspicuous observation from the genetics of mental disorders is that none of the scores of candidates from GWAS involve the usual psychopharmacologic suspects, monoamine transporters or receptors. The genetic signals identified thus far cover a broad span of biology but are enriched in neurodevelopmental or synaptic genes (23). Taken together, these results are beginning to point to new pathways involved in pathophysiology, suggesting an entirely new biology for mental disorders. **What we still lack from studies of the genetics of mental disorders are genes like *BCL11A* that confer protection.** These genes, as well as alleles associated with disease risk, may turn out to be important new targets. **In that respect, molecules that alter epigenetic modifications, protect against environmental stressors, or transcriptional regulators that shift developmental events may turn out to be the next generation of targets for mental illness.** And these may emerge not only from studies of probands but also from studies of unaffected twins or resilient populations. **For instance, the 70% of children with a chromosomal 22q11 deletion who do not develop psychosis may be more informative than the 30% who do.** We also need to consider that new targets may emerge not only from germline DNA variation but possibly from somatic mutations (24, 25). Somatic changes have

yielded some of our best targets for oncology but have been entirely neglected as a mechanism for mental illness.

Psychiatric genetics may still be in its infancy, but we are seeing some interesting candidates emerge. The calcium channel CACNA1 (26, 27), the potassium channel KCNH2 (28), Vasoactive intestinal peptide receptor 2 (16), DISC1 (and other pathways leading to AKT-mTOR signaling) (29–31), and Ankyrin-3 (32) are a few of the many recent genetic findings that could serve as portals to explore druggable targets for schizophrenia or bipolar disorder. For autism, in addition to a series of synaptic protein genes, including Shank 3 (33), CNTNAP-2 (34), and Neurexin-1 (35), that have emerged from genetic studies, the mGlu5 receptor is being explored as a potential target. Importantly, we need a better biological understanding of these putative targets to know which protein is affected, whether the genetic variation confers gain or loss-of-function and, ultimately, how genetic variation links to disease pathophysiology (as in the example of BCL11A and sickle cell disease). Even in major depressive disorder, a disorder with low heritability in which genetics has not been informative, molecular targets are emerging either from postmortem studies of people who die with depression or from molecules associated with depression-like behavior in animals. A range of such proteins including fibroblast growth factor 2 (36), P11 (37, 38), macrophage migration inhibitory factor (39), and neuritin (40) or trophic factors involved in neurogenesis, such as brain-derived neurotrophic factor (BDNF), are garnering considerable interest as new targets for antidepressants (41, 42).

The pathway from molecular target to lead compound has increasingly used high-throughput screening followed by chemical optimization to develop a candidate medication. Although this process has traditionally been the domain of industry, over the past 7 years the National Institutes of Health (NIH) Molecular Library Screening Center Network (<http://mli.nih.gov/mli/mlp-overview>) has allowed academic investigators with a new target to create high-throughput assays and screening against a diverse small-molecule library. Academic scientists have been able to focus on phenotypic assays and rare and neglected diseases where industry may see little commercial interest. These resources provide new tools for interrogating molecular targets emerging

for mental illnesses or drugs to manipulate the epigenome or transcription factors. In a recent example, researchers screened 1000 compounds for pro-neurogenesis effects to identify potential new antidepressants (41).

Even if we identify targets, develop robust in vitro assays for screening, and create small-molecule leads for the targets, we face a considerable challenge. Increasingly, mental disorders are recognized as neurodevelopmental disorders with changes occurring in fetal or early postnatal life although behavioral symptoms may not be manifest for years or decades (43). This means that even if we could find an ideal molecular target involved in the pathophysiology of the disease, the ideal time to intervene may precede symptom onset by years. Clearly, we will need biomarkers to detect risk or prodromal stages of these disorders well before symptoms are manifest.

One new opportunity for identifying both biomarkers and pathophysiologic pathways of neurodevelopmental disorders is the use of induced pluripotent stem cells (iPSCs). Although techniques to derive and differentiate these cells are still being optimized, iPSCs from a small number of subjects with schizophrenia have been induced to differentiate into neurons (44). The value of iPSCs will likely become more evident by growing different populations of neurons from adults with rare highly penetrant mutations (e.g., deletions of 22q11 or duplications of 16p11) where abnormal developmental pathways may emerge. This approach has already been described for a form of syndromic autism called Timothy syndrome caused by a rare mutation in a calcium channel gene (45). When differentiating patient-derived iPSCs into different cell types, astrocytes and other non-neuronal cells should not be neglected, particularly given that astrocytes outnumber neurons in the adult brain and appear to be important for neuroplasticity (46).

NEW CLINICAL TARGETS

Most clinical researchers when they consider “new targets” are focused on clinical symptoms (e.g., the cognitive deficits in schizophrenia or the social deficits in autism). Because clinical targets generally identify an unmet clinical need, they are a critical consideration for treatment development. And because treatments that address clinical targets do not necessarily require an understanding of pathophysiology, they are arguably the low hanging fruit of treatment

development. Indeed, in psychiatry, virtually all current medications owe their origins to astute clinical observation rather than molecular target-based drug design.

RAPID-ACTING ANTIDEPRESSANTS

The 30 antidepressants available today show modest efficacy after 6 weeks of treatment in randomized clinical trials. For a disorder that has the single greatest burden of disease and a high mortality, waiting 6 weeks for evidence of response seems a low bar indeed. Recent studies with intravenous ketamine appear to confer remission from severe depression, even treatment-resistant depression, within 3 hours (47). Although this remission is not permanent and there remain questions about the adequacy of the placebo comparison, these results move the goalposts, suggesting that a new clinical target for antidepressant response could and should be efficacy within 3 hours. Ketamine is not the answer (because of potential abuse), but ketamine has provided the proof-of-principle that safe, effective 3-hour antidepressants should be achievable. The recent demonstration of cellular changes in hippocampal neurons within 3 hours of ketamine administration to rats suggests a potential cellular correlate for these rapid antidepressant effects, yielding a potential phenotype for screening relevant compounds (48, 49).

COGNITIVE AGENTS FOR SCHIZOPHRENIA

One reason suggested for the lack of better public health outcomes for those with schizophrenia has been that the disabling cognitive deficits of the disorder are not treated by current antipsychotic medications (13). Problems with working memory, executive function, and attention are often severe enough to preclude employment or academic success even in someone no longer experiencing hallucinations or delusions. Medications that could treat these cognitive deficits could improve the chances of full recovery for some of the 60 million people with schizophrenia worldwide. A number of compounds with new mechanisms of action are in clinical development, based on results from preclinical studies or sometimes clinical observations (Table 1).

PROSOCIAL COMPOUNDS

One other example of an emerging clinical target deserves special mention. The prevalence of autism has increased from 1 in 1500

to 1 in 88 over the past two decades (50). Many of those with an autism diagnosis have no language and remain severely disabled by this neurodevelopmental disorder, but there are no medications for the core symptoms (social deficits, language disorder, and stereotypic behavior). In contrast to the motor and cognitive deficits of many other neurodevelopmental syndromes, the core deficits of autism often respond well to intensive behavioral interventions, demonstrating that they are indeed malleable. Prosocial compounds, which increase social engagement, are certainly a possibility based on research with animals and healthy human volunteers, but this clinical target is just beginning to be developed as a resource for people with autism (Table 1). Certain neuropeptides, such as oxytocin and vasopressin, may increase social motivation and social cognition (51). The recreational drug MDMA has been proposed as a prosocial compound (52). Most impressive are recent results with arbaclofen (a GABA_B agonist) (53, 54) and an mGluR5 antagonist (55), two new treatments for fragile X syndrome, a neurodevelopmental disorder frequently associated with autism. Although the effects of these two drugs are modest, they seem to improve social engagement. Again, the important aspect of these results is the proof-of-concept—increasing social engagement is now a feasible clinical target with implications for autism, schizophrenia, and potentially other syndromes.

NEUROPLASTICITY

Mental disorders are increasingly understood as disorders of brain circuits. While there remain major questions about the boundaries and specificity of these circuits, neuroimaging has already begun to map out areas of increased or decreased activity that appear to be associated with the symptoms of psychosis, mood, and anxiety disorders (56). Treatments based on neuroplasticity, now often called neuromodulation, will require careful targeting of specific circuits. In animal studies, optogenetics (which uses light to alter neuronal firing in awake, behaving animals) has provided a powerful, precise tool for manipulating circuits (57). We lack noninvasive means for manipulating circuits this precisely in humans, but regional transcranial magnetic stimulation (rTMS) has been shown to alter cortical activity and modestly reduce depressive symptoms (58). Invasive approaches, such as deep brain stimulation (DBS), target ar-

Table 1. R & D pipeline in three new areas for psychiatric medications.

New strategies	Discovery targets	Treatment targets in development	Clinical trials
Rapid-acting antidepressants	Trophic factors: (BDNF, FGF2) Neuritin P11 MIF	NR2B antagonist: (AZD6765), phase 2 Ketamine, phase 2 Muscarinic receptor antagonist: (scopolamine), phase 2	NCT01482221 NCT01627782, NCT01558063, NCT00768430 NCT01613820, NCT00369915
Prosocial drugs (Autism, fragile X syndrome)	Synaptic proteins: (Shank3, CNTNAP2, Neuroligin 2,3, Neurexin 1)	GABA _B agonists: (STX207), phase 3 mGluR5 antagonists: (AFQ056), phase 2 (RO4917523), phase 2 (RO5028442), phase 1 (STX107), phase 1 Oxytocin receptor agonist: (Carbetocin), phase 2a Vasopressin V1A rec. antagonist: (RG7314), phase 1	NCT01282268 http://clinicaltrials.gov/ct2/results?term=AFQ056+fragile+x NCT01517698 NCT01474278 NCT00965432 http://kyalinbio.com/products.html http://www.roche.com/research_and_development/pipeline/roche_pharma_pipeline.htm?ta=%25&Phase=%25&submit=Show+pipeline
Cognitive enhancers (Schizophrenia)	Ion channels: (KCNH2, CACNA1C) NRG1-ErbB4/DISC ligands: (PI3 Kinase, mTOR inhibitors) Epigenetic modifiers: (HDAC2 siRNA) miR-137	GlyT1 inhibitor: (AMG747), phase 2 (RO4917838), phase 3 α 7 nicotinic agonists: (ABT126), phase 2 (AQW051), phase 2 (DMXB-A), phase 2 (EVP6124), phase 1 (TC5619), phase 2 H3 antagonists: (CEP26401), phase 1 AMPA Positive Allosteric Modulators: (PF4958242), phase 1	NCT01568229, NCT01568216 NCT01192906, NCT01192880, NCT01192867, NCT01235559, NCT01235520, NCT01235585 NCT01655680 NCT01163227 NCT00100165 NCT00968851 NCT01488929 http://www.ncbi.nlm.nih.gov/pubmed/21634396 NCT01511510, NCT01365338

eas identified by neuroimaging and show more substantial effects (59). Although neither of these approaches will likely be disseminated widely for mild to moderate depression, they offer real promise for severe, disabling depression that is refractory to other treatments.

Recently, several reports of clinical improvement with computer-based cognitive training have suggested that repetitive activation of specific circuits may be an effective, noninvasive form of neuroplasticity. Cognitive enhancement may be the future of psychiatric treatment, whether driven by a video game, a device, or a small molecule or, more likely, some combination. The evidence is mounting that intensive computer-based training in executive function tasks can improve symptoms in schizophrenia (60), attention bias training can mitigate anxiety symptoms in adults and children with anxiety disorders (61), and computer-based cognitive behavioral therapy can rival the results observed with a therapist (62). The duration of these effects needs to

be demonstrated. Relapses observed with DBS or rTMS suggest that changes in cognitive function, even when correlated with altered circuit activity observed with neuroimaging, may or may not be targeting the core pathophysiology. Nevertheless, cognitive training offers broad dissemination, individualized schedules of use, and presumably low rates of toxicity.

NEW APPROACHES FOR BETTER TREATMENTS

Transforming diagnosis. A major obstacle to progress has been the current diagnostic system based on consensus of the clinical symptoms rather than underlying biology. Indeed, recent data from genomics, neuroimaging, and longitudinal observational studies suggest that many of the current diagnostic categories (e.g., depression, schizophrenia, and autism) are heterogeneous, with subgroups that may respond differently to current treatments. Yet the drugs, especially the antidepressant and antipsychotic drug classes, perpetuate

the myth that these are singular disorders with singular treatments. This may be a case where our language has become a barrier to progress. An analogy with cancer may be apt. Oncology has shifted from diagnosis based on clinical symptoms, tissue of origin, and gross pathology to diagnosis based on molecular signature. This shift, described as “precision medicine”, has linked patients to more targeted treatments resulting in improved outcomes (63).

What would precision medicine look like for mental disorders? Biomarkers and cognitive tests promise to stratify patients with mental disorders, identifying subgroups with better responses to even currently available treatments. A recently completed trial of infliximab (Remicade), an antibody against TNF- α , in depressed patients with elevated cytokines exemplifies this approach (clinical trial NCT00463580) (64). Several current trials are searching for biomarkers or cognitive patterns that predict response to specific antidepressants or cognitive behavioral therapy (<http://embarc>.

utsouthwestern.edu) (65–67). But, equally important, a new effort at diagnosis based on biological features as well as the psychological symptoms may define new targets for treatment. The Research Domain Criteria (RDoC) project (<http://www.nimh.nih.gov/research-funding/rdoc/index.shtml>) has already begun to identify clinical targets, such as anhedonia (the inability to experience pleasure) and working memory, which may be closer to the core pathophysiology of mental disorders and, if properly treated, could have greater efficacy than the broad agents currently in use (68, 69).

This issue is critical for improving outcomes. Current treatment development assumes that all patients with the same label share the same pathophysiology and therefore should manifest comparable responses to a given treatment. There is no evidence to support this assumption. The RDoC approach moves in the direction of precision medicine for mental disorders by identifying deficits in circuit-based functions and targeting treatments to those patients with demonstrable dysfunction in the target of interest.

Combination therapies. Whereas most other complex diseases, from hypertension to cancer, are addressed with combined therapies, there is a curious expectation that singular treatments will suffice for mental disorders. In fact, most psychiatric patients receiving medication are on multiple drugs, but there is little scientific evidence to guide the use of combination therapies in most conditions and there are substantial problems with adherence to either combined or single medications. Effective psychosocial treatments, such as cognitive behavioral therapy, are often provided as an alternative rather than combined with medication, even though the evidence is increasing that both behavioral and medical treatments have effects on neuroplasticity. An emerging opportunity is the development of medications that enhance cognitive behavioral therapy. For instance, patients with specific phobias who receive D-cycloserine improve after two sessions of cognitive behavioral therapy rather than requiring 8 to 10 sessions, with evidence of sustained gains (70).

Preemptive treatments. Finally, mental disorders are increasingly viewed as neurodevelopmental syndromes. Just as myocardial infarction is a late manifestation of ischemic heart disease, psychosis may be a late manifestation of changes that begin much earlier in development. Defining the prodrome or ultra-high risk state of schizophrenia or bi-

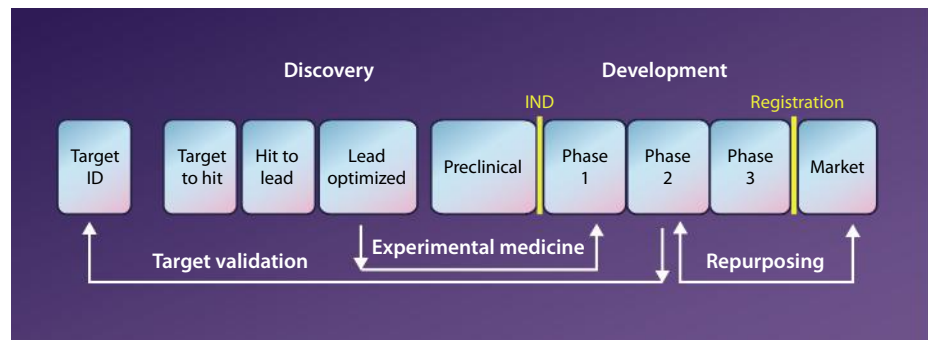


Fig. 2. Pipeline of medication development. The canonical pipeline for medication development is not working for mental disorders. A new strategy focusing on target validation, experimental medicine, and repurposing is required. Target validation tests whether a compound engages the presumed target and if that mechanism of action is involved in the disease. The experimental medicine approach leads quickly into patients to determine if a lead compound target is effective. In this new construct for drug development, the drug is a probe, the focus is on the target, and success can be defined by “fast fail.” Drug repurposing is an even faster way forward by identifying new beneficial effects of approved medications.

polar disorder is a high priority for research. There is not yet the equivalent of a risk calculator for psychosis as we have for myocardial infarction, but as many as 30% of adolescents on the path to psychosis can be identified with current diagnostic tools, largely focused on the cognitive changes that precede psychosis (71). What will be the intervention to preempt conversion to psychosis? Early trials of antipsychotic medications have been disappointing (72). But neurotechnologies, such as targeted cognitive training, that sharpen executive functions (e.g., working memory and verbal recall) may prove more acceptable and more effective than medications for the prodrome of schizophrenia (72) and have already proven useful for preempting depression (73). Neuroplasticity and neurotechnology approaches, based on current models of recruiting plasticity in development, may become a dominant strategy for preempting psychosis in an era when we understand that treatment is an effective form of prevention.

A NEW CULTURE FOR DISCOVERY

Success in the future will require not only a change in what we do, but how we do research. As pharmaceutical companies retreat from psychiatric drug development, it's clear that the past few decades of developing “me-too” compounds based on existing compounds no longer works. Paul and colleagues (74) have described the need for a new paradigm for drug development based on “fast fail” that is, focusing on proof-of-concept prior to proceeding to expensive phase 3 trials. The essence of this approach is validating a target in humans and demonstrating how

a new compound engages this target before launching a large-scale clinical trial (Fig. 2).

EXPERIMENTAL MEDICINE

For academic research, the focus on proof-of-concept can be developed in “experimental medicine” trials. This approach calls for small, deep trials to demonstrate target engagement, safety, and early signs of efficacy. Experimental medicine moves into human studies quickly with biomarkers, including imaging and physiological measures, to demonstrate biological effects and target engagement. Absent such markers, one cannot determine effective dose, that is, a negative result could reflect insufficient target engagement and a positive result may reflect off-target effects. Academic scientists can serve a critical role with these kinds of studies, derisking a new compound for further clinical development or demonstrating a fast fail for a new target in that disease population. There is an important, if subtle, change in perspective required. Academic progress is generally measured by positive findings resulting in publications. With 80% of compounds failing in phase 2 (2) and 70% of preclinical target validation claims appearing nonreplicable (75) the field needs more rigor, with progress defined by informative negative data as well as findings that promise a new therapeutic breakthrough.

REPURPOSING

Of course, past progress in therapeutic development has relied on keen clinical insights recognizing, for example, that an antihistamine or antitubercular drug conferred “off-

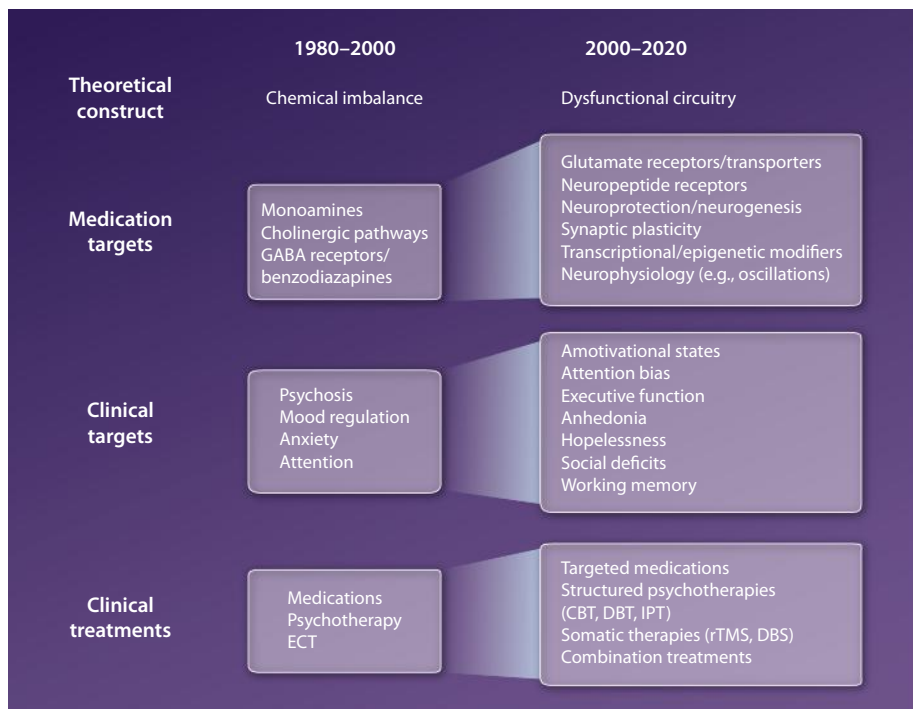


Fig. 3. New opportunities for treatment development. The enormous expansion of the medication portfolio for mental disorders between 1980 and 2000 was limited to a relatively narrow space of biology. Over the past decade, a new focus on the genetics and neurobiology of these disorders has generated a range of new targets for next-generation treatments. In addition, the broad categories of symptoms (analogous to fever or pain) are giving way to more targeted clinical symptoms that cut across current diagnostic bins (e.g., anhedonia and social deficits). And the limited options for treatments is expanding to include targeted behavioral interventions disseminated via new media, innovative somatic treatments based on identified circuit dysfunction, and strategic combinations (such as cognitive enhancers to improve the impact of cognitive behavior therapy). ECT, electroconvulsive therapy; CBT, cognitive behavioral therapy; DBT, dialectical behavior therapy; IPT, interpersonal behavior therapy; rTMS, transcranial magnetic stimulation; DBS, deep brain stimulation.

target” effects for people with mental illness. These kinds of clinical insights may continue to lead to breakthroughs in the future, especially as we see new molecular entities emerging for cancer and infectious disease. In fact, in the near term, it seems likely that **progress in treatment development will come more from repurposing compounds than from developing new molecular entities**. This is especially attractive now because some of the molecular targets emerging for the pathophysiology of mental illness have currently available compounds developed for other indications. For instance, statins with effects on the mTOR pathway and drugs with effects on inflammatory pathways may have unexpected value for mental illness. The recent report of anti-inflammatory compounds attenuating the antidepressant actions of SSRIs in mice and humans is both counterintuitive and provocative, suggesting that cytokines in the brain, in contrast to the periphery, may be

increased by antidepressant treatment (76). And with several companies abandoning their lead compounds for mental illnesses, there is a potential unique opportunity for academic scientists to repurpose agents that have already surpassed the early hurdles of drug development. This is an ideal time to create a “medicine cabinet” for compounds that have shown considerable promise but will not be developed further by industry, as recently announced by NIH’s newest institute the National Center for Advancing Translational Sciences (<http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html>) (77, 78).

The public health burden of mental illness mandates that we develop better treatments. On the research side, this will require a fundamental change in how we approach treatment discovery, whether the treatment is a new molecule or a new technology (e.g., cognitive behavioral treatment or a device).

Standardization, integration, and sharing of data will be essential as we move forward. Several efforts are already underway to provide standard measures for clinical assessments and databases for integration of the relevant data from multiple studies (<http://www.cdsc.org>). Data sharing will be important not only for accelerating discovery but for facilitating replication. Recent reports suggest that many of the results from academic laboratories cannot be replicated by industry scientists (79, 80). Although there are many reasons why results may not replicate in an independent laboratory, sharing standardized data and reagents should increase the rigor and reproducibility of both preclinical and clinical studies.

Partnerships that foster precompetitive sharing of compounds as well as data among academia, foundations, industry, and government will likely serve both public and private interests, as we have seen in the semi-conductor industry. New models, such as Arch2POCM (81), the Foundation for NIH Biomarkers Consortium (<http://www.biomarkersconsortium.org>) (82), and the Innovative Medicines Initiative (83) could become the vanguard for a new culture that is based on accelerating therapeutics discovery for the public good. Importantly, as efforts like Arch2POCM focus on target validation rather than medication development, they can expand the precompetitive space of discovery with benefits for all participants, especially patients (83).

CONCLUSIONS

In spite of the perceived dire state of discovery in psychiatry, there are abundant opportunities for new treatment development, **breaking from a legacy of pharmacological incrementalism bolstered by exuberant marketing**. How ironic that just as the science has expanded so dramatically from the narrow biological space of 1980–2000 to this new biology of the current decade (Fig. 3), the private sector seems infected with a misguided sense of doom and gloom for research and development.

Genomics is delivering potential new molecular targets almost monthly, epigenomics is proving a new frontier for drug development, and **iPSC technologies are yielding the tools needed for studying neurodevelopmental disorders**. In the past couple of years, rapid-acting antidepressants, cognitive enhancers, and prosocial compounds have emerged as entirely new classes of treatments. New clinical targets, such as **anhedonia**, and new

biomarkers, such as cytokines and functional imaging, permit stratification of patient populations for better clinical response. And repurposing and rescuing of existing compounds, so useful in the past for mental disorders, is undergoing a rebirth.

Progress will require increased public-private cooperation. As industry shifts from psychiatry to areas perceived as lower risk, **government and academic scientists will need to catalyze discovery of molecular and clinical targets.** The shift from monoamines to new biology will be disorienting for some, but history will likely identify the current transition as a new, overdue chapter for academic psychopharmacology. Industry can also play a critical role, by sharing compounds and data that have been shelved, allowing the academic community to restore value and offering those with mental illness new hope.

It is important to realize that new treatments, even effective new treatments, may not alter morbidity or mortality unless there is access, financial support, and integration with overall health care. **In the United States, people with serious mental illness (psychotic disorders and disabling mood and anxiety disorders) die 8 years earlier than the rest of the population (84). Whereas suicide is more frequent in those with serious mental illness, most die of cardiovascular disease or the consequences of diabetes, which are not treated adequately.** Although people with serious mental illness have double the rate of smoking and a 50% increase in obesity (85), few receive adequate medical care outside of their psychiatric care. Indeed, measured by overall morbidity and premature mortality, this 7% of the nation (6) may suffer the greatest health disparities of any minority group. An important opportunity and an urgent need for treatment development is better integration of medical and psychosocial treatments with general health care for those with serious mental illness. This approach, which can improve adherence to treatments for the mental disorder as well as better health care for the frequent chronic medical illnesses, will be an important step to reduce not only morbidity and mortality but also the costs of mental illness.

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