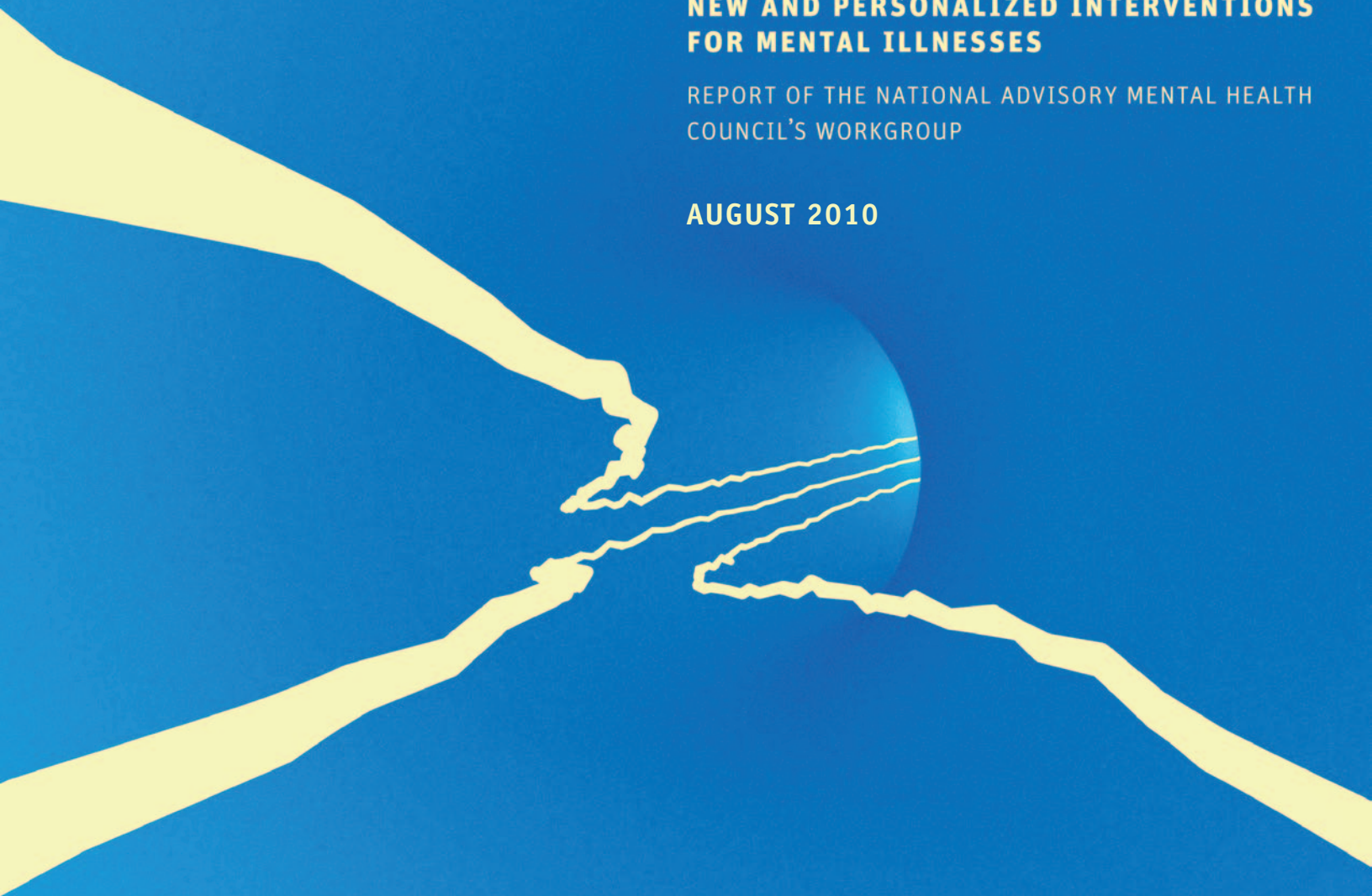


FROM DISCOVERY TO CURE

**ACCELERATING THE DEVELOPMENT OF
NEW AND PERSONALIZED INTERVENTIONS
FOR MENTAL ILLNESSES**

REPORT OF THE NATIONAL ADVISORY MENTAL HEALTH
COUNCIL'S WORKGROUP

AUGUST 2010



Executive Summary

Mental disorders are common both in the United States and internationally. An estimated 26.2 percent of Americans ages 18 years and older—about one in four adults (or 57.7 million people)—suffer from a diagnosable mental disorder in a given year. While mental disorders are widespread in the population, the main burden of these illnesses is concentrated in a much smaller proportion of the population; about 6 percent, or 1 in 17 people, suffer from a serious mental illness. Many of these Americans benefit from the substantial progress that has been made in identifying and testing efficacious psychotherapeutic and pharmacological interventions for various disorders among youth and adults. Nonetheless, these treatments are not cures and too many patients fail to respond or fail to achieve complete remission.

Recent breakthroughs in basic science and in the understanding of complex illnesses offer promising new opportunities for researchers to pursue and offer new hope for those living with mental illnesses. Now is an exciting, perhaps critical, time to take advantage of new breakthroughs and tools. But the paths for treatment discoveries are not clearly marked. Despite the tremendous advances in basic neuroscience and behavioral science that drive our understanding of the mechanisms underlying mental disorders, there is a dearth of new therapeutics in the discovery pipeline.

The purpose of this report is to provide guidance to the National Institute of Mental Health (NIMH) on promising research investments in the rapidly changing research environment. It is the product of a workgroup created by the National Advisory Mental Health Council (NAMHC) in response to the need for preemptive and personalized interventions in concert with Strategic Objective #3 in the [NIMH Strategic Plan](#)—to “develop new and better interventions that incorporate the diverse needs and circumstances of people with mental illnesses.” The charge to the workgroup was to lay the foundation for developing the next generation of interventions for mental disorders, especially those interventions that are tailored to the individual (i.e., personalized) and that prevent the damaging consequences of these illnesses (i.e., preemptive). This

charge was designed to complement two earlier reports, [Transformative Neurodevelopmental Research in Mental Illness](#), which looked at basic neurodevelopmental research for understanding mental illnesses and [The Road Ahead: Research Partnerships to Transform Services](#) which looked at services research, including the dissemination and uptake of current interventions.

In the course of its deliberations, the workgroup explored the opportunities and challenges in the following aspects of treatment development:

- Drug Development: From Target Identification to Clinical Trials
- Developing New Non-Pharmacological Treatments
- Optimizing Current Treatments
- Personalized Treatments for Mental Illnesses
- Shared Resources: Data and Talent

The workgroup’s subsequent recommendations are intended to be applicable to developing interventions in all modalities, but members recognize that much of the report is in the language of drug development. In that the workgroup heartily endorses the development of better non-pharmacological treatments, including behavioral approaches, devices, and the use of emerging technologies, it also encourages alternate and efficient models of development appropriate for these domains.

Ideally the workgroup’s recommendations will lead quickly to new interventions to stop the progression of mental illnesses before their devastating consequences ensue, ultimately leading to clear and profound improvements in outcomes for individuals with mental illnesses. Such a shift—from treating symptoms to preemption and personalization—will benefit those currently living with mental illnesses and provide future generations with the potential for prevention of illness or early diagnosis and cure. Basic and clinical science advances—such as elucidation of disease mechanisms and pathophysiological pathways, data sharing, and innovative trial designs—need to be harnessed in order to find cures for mental disorders.

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I. Introduction

Mental disorders are common both in the United States and internationally. An estimated 26.2 percent of Americans ages 18 and older—about one in four adults—suffer from a diagnosable mental disorder in a given year.¹ This figure translates to 57.7 million people with a diagnosable mental disorder in a year. In addition, an estimated four million American children and adolescents suffer from a severe mental illness.² While mental disorders are widespread in the population, the main burden of illness is concentrated in a much smaller proportion of the population; about 6 percent, or 1 in 17, people suffer from a serious mental illness. Mental disorders are the leading cause of disability in the United States and Canada for persons ages 15 to 44.³ Many people suffer from more than one mental disorder at a given time.⁴ Nearly half (45 percent) of those with any mental disorder meet criteria for two or more disorders, with severity strongly related to comorbidity.⁵

With half of all mentally ill adults reporting symptoms of mental illness by the age of 14 and three quarters by their mid 20s,⁶ it is increasingly clear that understanding the origins of mental illness requires studies that elucidate the mechanisms of developing brain architecture and chemistry. This is particularly important given that the onset of symptoms may not indicate the actual beginning of the illness; symptoms may appear long after the causal processes leading to mental illness have begun.⁷

Substantial progress has been made in identifying and testing efficacious psychotherapeutic, somatic, and pharmacological interventions for various disorders among youth and adults. Nonetheless, results to date suggest that with even our most effective current interventions, many patients fail to respond or fail to achieve complete remission. Further, there is little research to guide a patient and clinician in matching the best treatment strategy to the patient's genetic, physiological, or behavioral characteristics and affording *personalized* care.

Despite tremendous advances in basic neuroscience and behavioral science that drive our understanding of the neural circuitry and neurobiological mechanisms underlying mental disorders, there is a dearth of new therapeutics in the discovery pipeline.

As an example, consider the investments of the pharmaceutical and biotechnology industries in developing new small molecule drugs for mental disorders. The high cost of developing novel drugs, the high attrition rate of candidate therapeutics during development and clinical testing, and adverse effects contribute to the high rate of failure of new compounds in clinical trials.⁸ In 2009, the number of novel drugs approved by the U. S. Food and Drug Administration (FDA) for all disease areas continued to remain low, with only 19 new molecular entities approved (see Figure 1).⁹

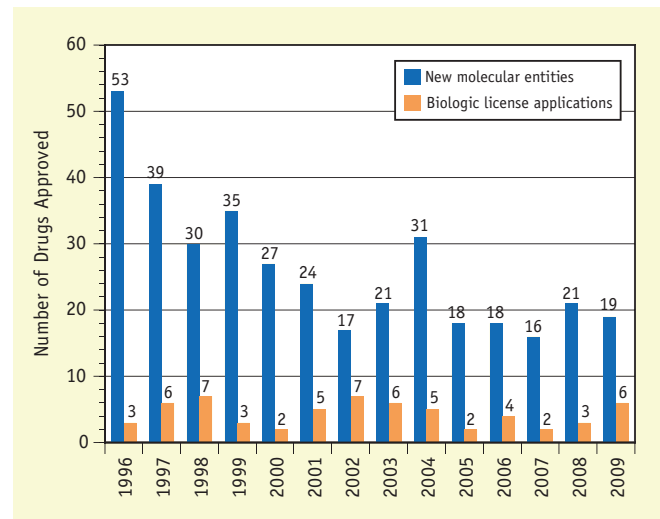


Figure 1. Novel drugs approved by the FDA in 2009.
Reprinted with permission.

The situation with drug development for mental disorders is worse than other areas of medicine (see Figure 2).¹⁰ Virtually all drugs approved for mental illness have been incremental changes of compounds available four decades ago. NIMH’s practical trials, such as [Clinical Antipsychotic Trials of Interventions Effectiveness \(CATIE\)](#) and [Sequenced Treatment Alternatives to Relieve Depression \(STAR*D\)](#), document the limited effectiveness of today’s medications and demonstrate the need for a new generation of medications for mental disorders. The recent announcements by several key pharmaceutical companies of their moves out of psychiatric drug development raise the question of who will develop this next generation of treatments.

To generate new interventions, the NIMH must actively pursue the pathways to cure and prevention. Now is an exciting, some say critical, time to make this shift. The [NIMH Strategic Plan](#) has laid out current opportunities. Neuroscience, like oncology and immunology, has seen recent breakthroughs in basic science and understanding of complex illnesses that not only offer exciting opportunities for researchers to pursue, but also instill hope for those living with mental illnesses. In addition, the climate of collaboration among the National Institutes of Health (NIH), FDA, academic health centers, and indus-

try has been refreshed, opening up new opportunities for identifying research gaps and finding ways to fill them.

But the path for discovery is not clearly marked. As with other illnesses in which the cause of disease and its mechanisms are unknown, if researchers are to approach intervention discovery productively, they must first illuminate the underlying pathophysiological processes. The hurdles are many. For instance, the initial pathogenesis underlying a mental illness may vastly predate the collection of behavioral data or tissue samples from the symptomatic individuals, complicating the identification of the relevant pathways.¹¹ As a result, it is especially critical to look early in the disease process, to think developmentally, and to emphasize the initial drivers of mental illness and the pathways that mediate their effects. Researchers in the basic sciences are now poised to do so and to have their findings translated into better interventions for mental illnesses.

The purpose of this report is to provide guidance to NIMH on promising research investments in the rapidly changing research environment. New therapeutic opportunities in mental illness—such as target identification, elucidation of disease mechanisms and pathophysiological pathways, data sharing, and innovative trial designs—need to be harnessed to find cures for mental disorders.

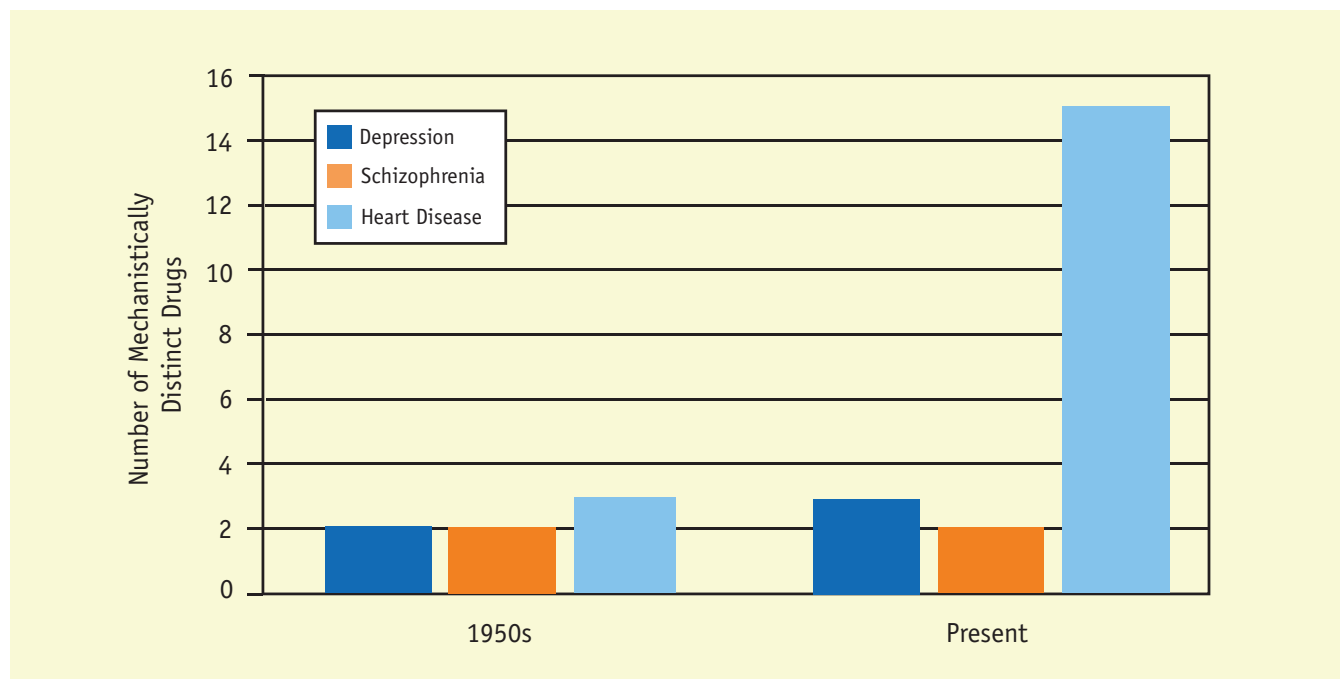


Figure 2. Drug development in the past 50 years.

II. Workgroup’s Background and Process

NIMH’s mission is to support research to “transform the treatment of mental illnesses ... paving the way for prevention, recovery, and cure.” To achieve this mission, NIMH supports a broad array of science. NIMH-supported basic research identifies possible targets for treatments, and NIMH-sponsored efficacy and effectiveness trials address the potential utility of existing preventive and therapeutic interventions. However, the Institute receives relatively few applications proposing to translate basic findings into the development of novel interventions. In addition, the Institute receives very few applications proposing to develop personalized or preemptive treatments.

“Personalized” means that there is something known about the individual that differentially predicts how he or she will respond to a given treatment. Evidence-based treatment algorithms are helpful, but too general, with little tailoring based on individual differences (e.g., genomic variations), and supported by very little actual evidence beyond acute treatment.

“Preemptive” means that a disease process is arrested before the illness occurs or early in its course, so that devastating and perhaps irreparable consequences do not occur. Here, along with prevention intervention programs outlined in the recent Institute of Medicine (IOM) report on preventing mental illness,¹² progress in discovery and translational developmental neuroscience will pave the way to innovative interventions heretofore unanticipated.

This workgroup was created by the NAMHC in response to the need for preemptive and personalized interventions, in concert with Strategic Objective #3 in the [NIMH Strategic Plan](#)—to “develop new and better interventions that incorporate the diverse needs and circumstances of people with mental illnesses.” The workgroup’s members are listed in Appendix A; their areas of expertise span molecular biology to services research, and they represent NIH, academic institutions, small and large private industry, and non-profit foundations.

More specifically, Strategic Objective #3 of the NIMH Strategic Plan has three goals relevant to this workgroup:

1. Further develop innovative interventions and designs for intervention studies.
2. Expand and deepen the focus to personalize intervention research.
3. Identify and systematically study elements of personalized mental health care.

Charge to the Workgroup

To lay the foundation for developing the next generation of interventions for mental disorders, especially those that are preemptive and personalized, the workgroup was asked to address the following questions:

1. Research Opportunities and Needs
 - a. How can novel treatment targets best be identified (molecules, cells, circuits, behaviors, domains of function, or clinical dimensions of psychopathology)?
 - b. How can target validation, assay development, lead generation, and lead optimization occur more efficiently to foster pharmacological strategies? What steps must be taken to advance devices, behavioral, and other approaches?
 - c. How can viable candidates from pre-clinical studies be more rapidly and safely developed through Phase I, II, and III trials in humans?
 - d. What new trial designs and analysis techniques can be used to identify moderators and mediators of treatment effects for personalized interventions? When should interventions be adapted for sub-groups?
 - e. How can biomarkers or biosignatures be used to individualize interventions, including preemptive interventions? How can developmental trajectories best be incorporated into this research?

2. Infrastructure Opportunities and Needs

- a. What programs from NIH (e.g., Molecular Libraries, Therapeutics for Rare and Neglected Diseases (TRND) Program), RAID, Biomedical Research, Development, and Growth to Spur the Acceleration of New Technologies (BRDG-SPAN) program, the Foundation for the National Institutes of Health (FNIH), academia, and industry can be leveraged?
- b. What new infrastructure would speed this translation? Does NIMH have an efficient model for supporting this research? Are there grant mechanisms or other funding streams that might be particularly useful for this area of research?
- c. What partnerships must be established or re-conceptualized?

Workgroup Process and Principles

The workgroup met twice in late 2009 for two-day meetings to discuss the issues before it, to hear from experts in programs and fields relevant to its charge (see Appendix B) and to receive briefings from NIMH and NIH program leaders on current initiatives across NIH (see Appendix C).

Early in its deliberations, the workgroup agreed on a set of overarching principles to guide NIMH efforts toward the development of novel interventions for mental illness:

- **Limited budgets mean that difficult decisions must be made and priorities set.** New research priorities must be quickly shared with the field to facilitate the search for novel and personalized treatments. But because science moves quickly, priorities designated in 2010 must be reassessed periodically with respect to the NIMH portfolio and their productivity. New priorities should be anticipated and initially promising, but ultimately unproductive leads should be dropped.
- **Novel pharmacological and non-pharmacological treatments are needed, requiring the best of basic science research.** To parlay basic molecular, cellular, systems, and behavioral science into translational science, new avenues of research in all these domains and their interaction are needed to elucidate the pathway to personalized and preemptive interventions.

- **Mental disorders are developmental disorders at every level of analysis.** This workgroup endorses the recommendations made by the [NAMHC Workgroup on Neurodevelopment](#) and referred to its report frequently during its deliberations, while careful not to duplicate its efforts.
- **Investments should be efficient and therefore preference should be given to efforts that maximize broad access rather than sole-use infrastructure initiatives.** Investing once in obtaining data or resources for all to use is efficient, allows new basic researchers to quickly engage in mental health research, and fosters collaboration as well as the ability to validate findings across sites.
- **Individuals living with mental illness, their family members, and clinicians must be informed about basic and clinical research.** This knowledge base is essential for enabling these key stakeholders to contribute to the research enterprise as participants and through public priority setting. These efforts pave the way for the adoption of personalized care in the community when it becomes available.

These principles shaped each of the workgroup's topical discussions presented in Section III. These same principles guided the development of, and priorities for, the tactical recommendations presented in Section IV. They provided direction and recurring themes throughout this report, but, to avoid redundancy, are not repeated in each applicable topic and recommendation. The workgroup recognized that new interventions must include innovative psychosocial treatments as well as medications, and that new biomedical treatments will be most successful in the context of treating the whole patient, even though the workgroup focused mostly on medication discovery and development. The principles and recommendations presented in this report may prove helpful in developing new psychosocial interventions, but nonpharmacological interventions may have additional or alternate options for fostering efficient discovery, development, and validation.

III. Opportunities and Needs: Assessment of Changing Paradigms and Evolving Science

Several shifts in thinking and practice must occur to forge new interventions. Novel conceptual frameworks need to be explored; new research tools and techniques deployed; and existing and future resources more productively and effectively marshaled. This section reflects the workgroup’s discussions in response to its charge—to identify research opportunities and challenges, and when possible, identify infrastructure and resources needed to overcome those challenges and respond to those opportunities. Each section summarizes the need for new perspectives or approaches in the search for novel pharmacological and non-pharmacological interventions. There are two basic approaches: (a) development of novel, more effective treatments and (b) tailoring current treatments to increase effectiveness. The specific recommendations cascading from these discussions appear in the subsequent section of this report.

The canonical drug discovery and drug development pathway is shown in Figure 3. Traditionally NIH has supported the earliest phases of this pathway and the late phases,

especially Phase III clinical trials. By contrast, industry has invested in this entire spectrum of activities, with a nearly unique competence in the middle phases, such as high-throughput screening, optimization of a probe to a lead compound, and the transition from preclinical studies to clinical trials. The recent announcements of decreasing industry investments in psychiatric drug discovery and development beg the question of who will support continued progress for new medications for mental illness. In fact, as detailed below and in Figure 3, NIH is already embarking on many of the stages in this pipeline, including some that have traditionally been exclusively industry’s domain. But before recommending a full-fledged drug development effort at NIMH, it is worth noting that the average cost of bringing one drug to market has been estimated at \$1 billion, which is nearly the entire yearly extramural NIMH budget.¹³ Thus, the question is not whether NIMH should participate in drug development, but rather where along this pipeline can NIMH best catalyze new treatment development.

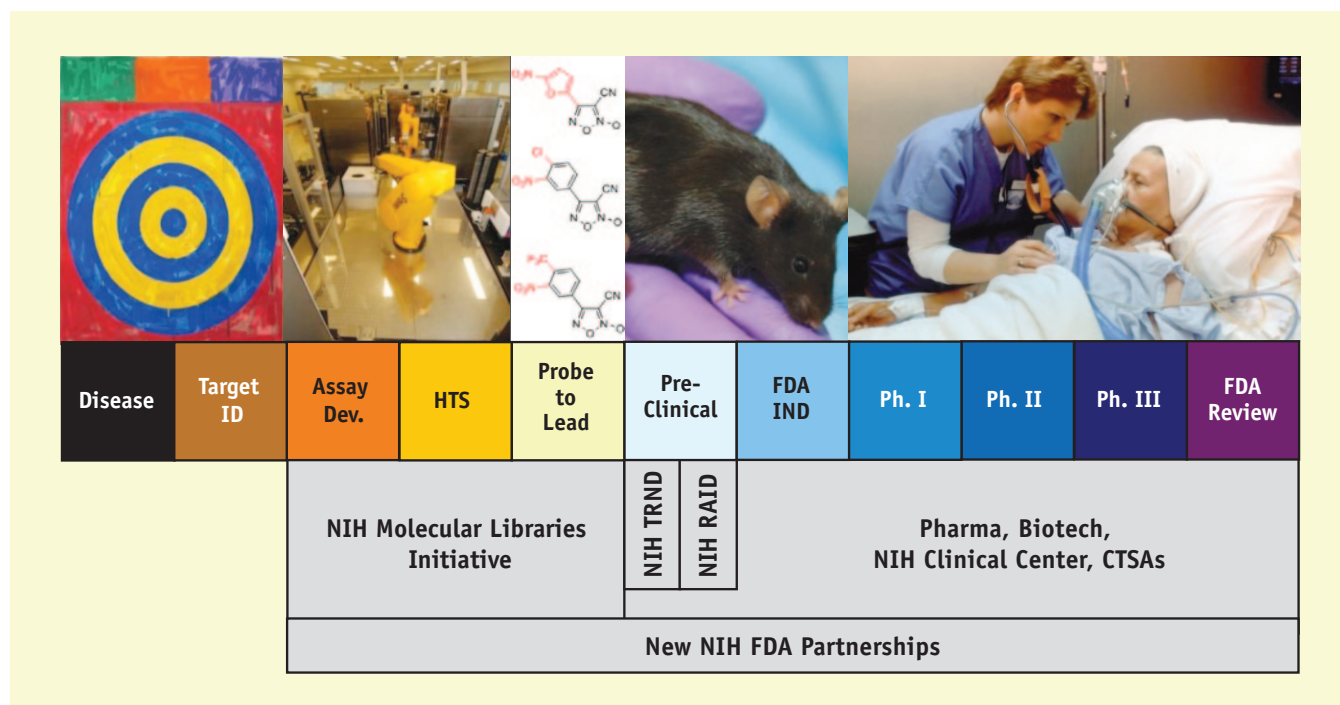


Figure 3. Overview of NIH efforts in intervention development.

Drug Development in Mental Illnesses: From Target Identification to Clinical Trials

Chart 1 from Insel & Scolnick (2006) compares the traditional model for drug development for mental disorders with modern drug discovery. Psychiatric medications have been largely based on drugs discovered four decades ago by serendipity. Repurposing medications used for other indications remains a very real opportunity in 2010, but the continued development of medications that resemble currently available monoamine uptake inhibitors or receptor blockers will be unlikely to yield new compounds with much greater efficacy. The model used in most other areas of medicine begins with an understanding of molecular pathophysiology to generate novel targets followed by development of screens for small molecules against these targets. This approach has been successful for developing novel, effective compounds in oncology and cardiology. It should be equally effective for mental illnesses.

But psychiatric drug discovery presents unique challenges. Psychiatric genetics has not yet yielded a validated target for any mental disorder. The dependence on clinical observation for diagnosis of psychiatric disorders is a huge barrier to treatment discovery. Mental disorders are increasingly considered developmental brain disorders. By the time a diagnosis can be made, the causal factors in the disease process may no longer be evident, and it is even possible only the biological after-effects of the disease remain. Thus current diagnostic categories likely do not distinguish among causal factors or provide homogeneous endophenotypes. The process is further hampered because in psychiatry, unlike oncology or immunology, the diseased tissue cannot be removed for *in vitro* analysis and treatment development.

Treatment development in mental disorders has been dependent upon animal behavior, but the homologies between behavioral phenotypes in animals and humans are rarely compelling and the degree of shared circuitry underlying behaviors is variable and in many cases unknown. Animal studies are limited by differences in how behavior is measured and by species and strain differences. This problem has contributed to the limited ability of existing preclinical models to predict the efficacy of drugs in human clinical populations. Consequently, drugs that appear promising in preclinical studies have lacked efficacy in patients. These are costly errors in terms of time and money. There are further issues with the tests developed using model animals. For instance, by defining new drug validation as a response similar to that of existing drugs, the field has perpetuated the development of “me-too” compounds, rather than discovering new mechanisms of action. The inclusion of clinically relevant, phylogenetically conserved behavioral measures that assess disease-related domains of function (e.g., fear, social avoidance, and memory loss) may still provide initial proof-of-concept of new therapeutics and allow testing of proposed therapeutic mechanisms. However, it is essential that the predictive validity of specific behavioral measures be carefully evaluated to determine their utility in therapeutic development.

Target Identification

Epigenetic changes, brain circuit activation, intracellular signaling pathway modification, structural brain changes, neuroplasticity, changes in RNA expression, proteomic or metabolomic markers all hold great promise for understanding early disease processes and, by extension, may reveal novel treatment targets. If a given manipulation of a proposed disease pathway produces similar biological outcomes across different model systems (*in vitro* and *in vivo*), it enhances the attractiveness of the model as a tool for exploring mechanisms of pathology and pursuing targets within that cascade. Thus, NIMH-supported research should focus on model systems that incorporate factors that are thought to be etiological in, or capture the pathophysiological basis for, human syndromes or symptoms of disorders so that the range of measures explored is more likely to be predictive of treatment efficacy. This is the process of drug development currently pursued in many other areas of medicine (Chart 1).

For instance, determining the capacity for and mechanisms underlying cellular, circuit and behavioral plasticity in systems relevant to mental disorders would provide powerful and novel targets for interventions (behavioral,

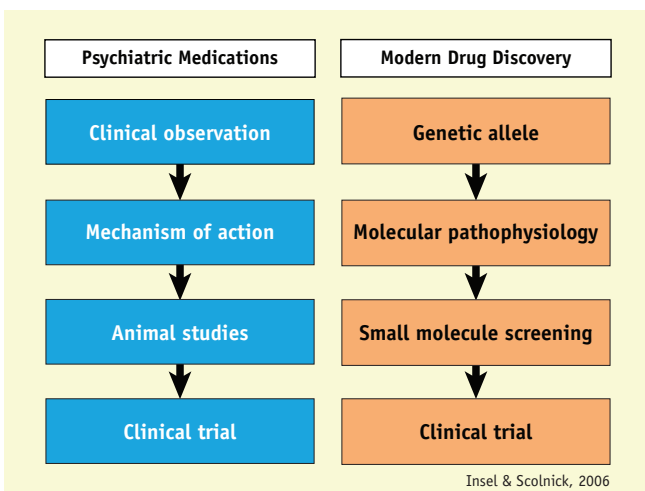


Chart 1. Pathways in drug development.

pharmacological, electrophysiological) that could improve the function of these systems. Interventions designed to enhance or modify target circuits could provide a mechanism to reverse or circumvent the functional deficits associated with circuit abnormalities or, when used in combination with other therapeutic approaches, enhance the capacity of the system to respond to other forms of treatment. When used in the context of trials, interventions designed to enhance plasticity in critical circuits could uncover the mechanisms underlying treatment response and provide a way to predict individual treatment responses. Particular attention should be devoted to discovering the sensitive and critical periods when neuroplasticity in specific circuits is greatest and maximally responsive to intervention, and across the lifespan in populations at risk for developing specific mental disorders.

Importantly, many of these challenges are being surmounted. Studies of human genetics suggest that disease genes have structural variants that are rare and common variants that are not very penetrant. There is an opportunity to use model organisms to explore the impact of genetic variants on brain development and neuronal function. Although genetic studies of mental disorders are in the early stages, model systems could be created based on these genetic variants to identify biosignatures of early effects and to develop treatments that reverse and prevent pathology (see, for instance, Niwi *et al.*, *Neuron*, 2010). Novel approaches that address the complex interplay of genetic and environmental factors within a neurodevelopmental context are also needed. Finally, in some cases, the best “preclinical” models may be typical humans engaging in tasks that are disrupted by disorders. Alternately, *in vitro* models such as iPS cells, which contain the full genetic complement of an individual with a particular disorder, may provide unique opportunities for therapeutic targeting and testing. That is, the iPS cells recapitulate the alleles and mutations of each individual—allowing for “personalized” cell biology. In his Nobel Lecture, Sydney Brenner, Ph.D. argued that modern genetics makes humans our best animal model.¹⁴ These human model systems are relatively new concepts with the potential to provide early and more predictive tests of novel treatments.

Assay Development and High-Throughput Screening

Once a target is identified as relevant to a biological process or disease state, the central scientific challenge is identifying small molecules that are effective at modulating that target.¹⁵ This requires an assay for high-throughput screening and a library of compounds to be

screened. In the past decade, small molecules have proven to be exceedingly important in exploring function at the molecular, cellular, and *in vivo* levels. Small molecules also have proven valuable for treating diseases, and most medicines marketed today are from this class. Screening molecular libraries for molecules that are potent and selective for a given target has traditionally been the exclusive domain of industry. The [Molecular Libraries \(ML\) Probe Production Centers Network](#), funded through the NIH Roadmap, offers scientists in academia support for assay development, access to large-scale screening capacity, a large diverse chemical library, and the medicinal chemistry and informatics necessary to identify chemical probes to study the functions of genes, cells, and biochemical pathways.¹⁶ The ML program includes a network of centers: the NIH Chemical Genomics Center, an intramural component, and several extramural centers. NIH anticipates that these projects also will facilitate the development of new drugs by providing early-stage chemical compounds that will enable researchers in the public and private sectors to validate new drug targets, which could then move into the drug development pipeline. While this program has successfully identified over 120 probes using 300,000 compounds since 2005, only 2.8 percent of the assays, 6 percent of the screening efforts, and 10 percent of the probes were relevant to mental disorders. Thus, NIH has produced the capacity for assay development and high-throughput screening, but too few mental health researchers appear to be using this new resource.

Probe to Lead Optimization

It is recognized that high-throughput screening alone will seldom yield the chemical probes that have the properties needed to fully advance our understanding of novel targets and mechanisms. Thus, it is critical to invest in chemical optimization of initial hits to achieve small molecule reagents that possess the selectivity and pharmacokinetic profiles required for *in vitro* and *in vivo* studies in model systems. This is especially true for diseases of interest to NIMH, because studies of effects of novel small molecule reagents *in vivo* require optimization of pharmacokinetic properties and central nervous system (CNS) availability. In addition to medicinal chemistry, this requires focused efforts of drug disposition scientists who are working closely with chemists, molecular pharmacologists, and *in vivo* neuropharmacologists to study and optimize the pharmacokinetic properties of novel probes. This is critical for both the basic science studies required to advance understanding of novel mechanisms and to pave the way for selection of potential drug leads that can

be further optimized as clinical development candidates in the context of programs such as the [TRND Program](#), the [NIMH Small Business Research Program](#), and the [National Cooperative Drug Discovery and Development Program \(NCDDDG\)](#).

NIH created TRND in May 2009. The goal of TRND is to “de-risk” rare and neglected diseases for industry investment (although costs are not necessarily decreased). The program also focuses on neglected targets. The program extends NIH’s efforts to accelerate the probe to lead to candidate phases, progression into pharmacokinetic and pharmacodynamic studies (PK/PD), and the development of public/private partnerships based on compounds that are ready to be tested in people. As with the Molecular Libraries effort, it is clear that there are many compounds from immunology, oncology, and infectious disease that are ready to advance to optimization. NIMH has had a few similar efforts, such as the development of non-peptide analogues for CRF and NK-1 receptors, but optimization is still not a robust effort. Fortunately, an effort parallel to TRND is being launched specifically dedicated to CNS diseases, both rare and common, via the Neuroscience Blueprint in 2010. The NIH Blueprint (BP) Neurotherapeutics Grand Challenge initiative will provide a bridge between the ML program and first-in-human studies. It is anticipated that the ML, TRND, and BP Neurotherapeutics programs will be critical resources for future research on identifying targets and developing drugs for mental illnesses.

The Gap between Basic and Clinical Research

The broad accessibility of high-throughput screening approaches such as ML is a crucial innovation in closing the gap between fundamental discoveries and their therapeutic application. Once a hit is found, there is some capacity for probe development with the goal of drug discovery for neuroscience disorders. Where the science is supportive, medicinal chemistry has progressed to the point that moving directly to the synthesis and development of new chemical entities suitable for therapeutic use may be appropriate (i.e., synthesizing small molecules, RNA, or protein aptamers). Lead optimization activities focus on medicinal chemistry, potency, sensitivity, pharmacokinetic, toxicity, scale-up synthesis, and formulation. The NCDDDG supports many components of the therapeutic discovery process including medicinal chemistry, novel target, model, assay, imaging tool discovery and validation, Phase I safety and tolerability studies, biomarkers and pharmacokinetic studies, and early Phase II proof

of concept studies in patients. Through the NCDDDG and other NIH programs such as the ML, SBIR, TRND, and RAID programs, NIMH-supported investigators can pursue lead optimization and candidate selection with the goal of initiating Phase I studies and proceeding through Phase II proof-of-principle and/or proof-of-concept studies. However, there are gaps along this continuum, in particular with regard to target discovery, rapid screening and validation for novel targets, availability of disease-relevant models and screens, access to medicinal chemistry, and resources for Phase I and II studies. As a result, efforts are still needed to fill these gaps, including the need to expand innovative screening approaches such as exploratory studies of iPS cells, and biosignature discovery.

NIMH and industry need to reduce the time it takes to develop and move drugs to market so that patients will benefit sooner. To compress the development timeline, a more systematic way of moving into early-phase drug development is required. Once a method for assessing outcomes is in place, it would be useful to accelerate and improve the development of a Phase I/Phase II proof-of-concept capabilities in the field, which requires enhanced clinical trial infrastructure and a commitment to efficient designs, like seamless adaptive designs. For example, performing early trials in clinical research units capable of noninvasively monitoring pharmacologic engagement of the target receptor or circuit(s) (e.g., expertise in neuroimaging, automated behavioral measures or other evoked responses) could inform dose selection for proof of concept trials assessing behavioral or functional endpoints. However, from the NIMH perspective, the goal should be to put in place a smooth and efficient process for intervention discovery, from Phase I safety and dose finding studies in typical humans through proof-of-concept Phase II studies, and the establishment of clinical efficacy.

Phase III Trials

NIMH has long invested in randomized clinical trials, providing the public with information about treatment efficacy from non-industry supported trials. A review of these trials reveals at least three areas of continuing need. First, there are few innovative treatments in the NIMH portfolio. Second, many of the trials are slow to recruit and slow to publish (relative to the urgent need for better treatments) and some are conducted long after treatments reach the marketplace. And finally, in recent years these trials have tended to grow larger to have sufficient power to identify smaller effects, meaning that during this period of flat budgets the Institute has been investing more dollars in studies with less public health impact.

Against this overall trend, the workgroup heard about bright spots in recent trials where innovative approaches could transform current treatments. A new focus on glutamate receptors as a target for antidepressant action has yielded early evidence for rapidly acting antidepressants

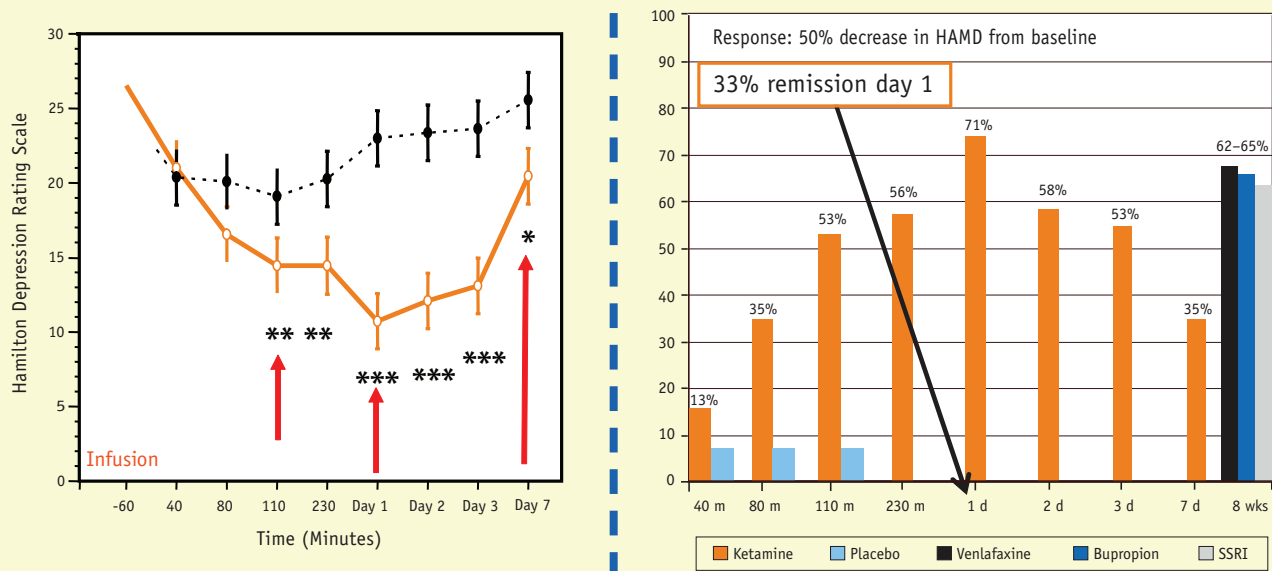
with effects evident in hours rather than weeks (see Sidebar 1). Trials underway for Fragile X syndrome with metabotropic glutamate receptor 5 (mGluR5) antagonists hold promise for new therapeutics for intellectual deficits (see Sidebar 2).

Sidebar 1. Clues for Faster-Acting Antidepressants

Antidepressants that are currently available on the market provide relief for some individuals, but often take several weeks to show therapeutic effects. While most of the current drugs are classified as monoamine uptake inhibitors, the blockade of monoamine uptake occurs within minutes to hours, which is weeks before observable therapeutic effects. Studies of the delayed neurochemical effects of antidepressants point to changes in glutamate receptors, especially a reduction in the NMDA family of receptors. Could an NMDA antagonist leapfrog several weeks of neurochemical adaptation to have a more immediate antidepressant effect? Data reported by Carlos Zarate, M.D. and colleagues suggest that ketamine, which targets NMDA receptors, provides relief of depressive symptoms in hours rather than weeks. Following intravenous administration of a sub-anesthetic dose of ketamine, patients with treatment-refractory depression report remission of a broad range of depressive symptoms within 6 hours. One of the most profound changes is a rapid reduction in suicidal ideation. However, ketamine is unlikely to serve as a useful clinical tool. The effects are short-lived, generally wearing off within 7 days. More important, ketamine is a dissociative anesthetic which has been abused as a recreational drug and is associated with a number of significant adverse effects.

Nevertheless, the evidence for the ability to treat depression in hours rather than weeks resets expectations for drug development in this area. This proof-of-principle study with ketamine suggests the need for more selective, safer, oral NMDA antagonists. These findings, if replicated widely, pave the way for a next generation of antidepressants. They also reveal an opportunity for studying the biology of antidepressant response. Previous studies comparing neuroimaging or physiology at baseline and after 6 weeks of antidepressant treatment have been handicapped by non-specific changes over the long time period for antidepressant response. Compressing response into a period of hours rather than weeks allows more precise study of changes associated with the lifting of mood. NIMH researchers have been using a noninvasive imaging technique called magnetoencephalography (MEG) to capture the brain's split-second responses to rapidly flashing stimulus pictures of fearful faces as a potential biomarker for antidepressant response. While healthy participants' regional activity decreased quickly as they habituated to the faces, patients' activity showed an opposite trend, and actually increased over time. The more robust this increase, the more symptoms improved just four hours after a patient received a single infusion of ketamine. The lag in neural activity could be a window into the dysfunctional workings of the glutamate-related circuitry targeted by the medication, an important lead to developing new and fast treatments.

Robust, rapid, and relatively sustained antidepressant effect of low dose ketamine, and response rates to ketamine in a double-blind placebo crossover trial in patients with treatment-resistant major depression.



Zarate et al. Arch Gen Psychiatry, 2006

Sidebar 2. Clinical Tests Begin on Medications to Correct Fragile X Defect

Fragile X syndrome is the most common inherited cause of intellectual disability, affecting 1 in 4,000 males and 1 in 6,000 females; however, to date there have been no medications that could alter the disorder's neurologic abnormalities. In addition to those affected by Fragile X syndrome directly, the implications of this research into autism could be very far reaching. Currently there are no medications for the core symptoms of autism, which affects 1 in 110 children in the U.S.

The potential therapeutic described below is the outcome of basic research that traced how an error in the Fragile X mental retardation gene (FMR1), in effect, turns off the gene. Research in recent years by Mark Bear, Ph.D. and colleagues has identified the molecular consequences of this silencing of FMR1. In typical brains, metabotropic glutamate receptors (mGluRs), a class of receptors on brain cells, stimulate the synthesis of proteins at synapses. The FMR1 gene is necessary to help dampen this synthesis. If FMR1 protein does not provide this "brake," synaptic protein synthesis is excessive and connections do not develop typically. These synaptic changes, in turn, appear to be the mechanism for the learning deficits associated with Fragile X syndrome. If FMR1 is the brake, the mGluR5 receptor appears to be one of the accelerators for protein synthesis in the synapse. In studies of mice without a functional FMR1 gene, blocking the mGluR5 receptor reduces protein synthesis and restores normal function in mice. This "cure" of Fragile X syndrome in mice has raised great hopes for a new treatment of Fragile X syndrome and other forms of intellectual deficit in humans.

Several companies are developing and testing mGluR5 antagonists as therapeutics. NIH-supported scientists at Seaside Therapeutics in Cambridge, MA, are beginning a clinical trial to evaluate safety, tolerability, and optimal dosage of a novel compound, STX107, a selective and potent antagonist for mGluR5. The initial Phase I study involves healthy volunteers. If results suggest that the medication is safe and tolerable, the study will progress to a Phase II test of dosage and efficacy in adults with Fragile X syndrome. If STX107 shows promise in adults, the compound will be assessed for pediatric safety prior to initiating clinical trials in children. The genetic underpinnings of the syndrome mean that it is present from birth, so the potential for targeting the underlying mechanisms of the disorder early in life when the brain is still developing could have broad therapeutic implications in this and other populations. Curiously, the effects in mice have been observed even with treatment during adulthood. The treatment of developmental disabilities opens a new therapeutic area and reminds us that genetic disorders may respond to non-genetic treatments.

Developing New Non-pharmacological Treatments

Just as with research in drug treatments, the past decades of research in behavioral interventions have brought relief to many with mental illnesses. The initial success of intervention development in early behavior therapy was based upon a single guiding principle: use behavior to understand psychopathology and to create therapies based on the current understanding of principles governing behavior change. This principle was devoted to strengthening processes that were adaptive and opposite to identified pathological processes. Unfortunately these treatments can be difficult to find in the community and, like pharmacological treatments, they are not always curative and do not work for all. The workgroup discussions focused on finding the mechanisms of action to aid in understanding how and why a new behavioral treatment may work. But new findings from behavior, cognition, emotion, psychophysiology, and human development must also be brought to bear on testing the underlying mechanisms of pathology and identifying new treatments. For instance, can the work in cognitive bias modification, temperament, or other areas be extended into new treatments for severe mental illnesses? Studies of cognitive remediation (see Sidebar 3) promise a new approach to the prodrome of schizophrenia based on principles of neuroplasticity.

Personalized treatments have been central to early behavior therapy. Such an approach can be made even more effective as we identify and validate additional mechanisms that are involved in pathology and assess for their presence in the individual patient. Thus, as called for in NIMH's new Research Domain Criteria (see [RDoC](#)), future research should assess the presence and degree of processes that are common to the disorder or class of disorders and are functionally involved in their maintenance. These might include both psychological mechanisms (e.g., attentional bias, interpretive bias, worry, and interpersonal problems) and related biological mechanisms (e.g., extent of fear circuit activation, and hypothalamic-pituitary-adrenal (HPA) axis activity). Studies could then identify whether targeting each process contributes to clinical improvement. In addition, the new categories can be thought of as intermediate endophenotypes, serving the needs of treatment development work and genetics.

Sidebar 3. Cognitive Retraining: Minimizing Schizophrenia's Wake

The cognitive deficits that characterize patients with established schizophrenia also affect “ultra high risk” or “prodromal” adolescents, and predict conversion to full-blown psychosis (35% within 2 years). Moreover, the severity of these deficits predicts outcome several years later. These data strongly indicate that cognitive dysfunction represents both a significant risk factor for psychosis and a poor prognostic factor, and should be a primary target for aggressive early intervention in young populations.

Dr. Sophia Vinogradov and her associates have begun to apply intensive neuroplasticity-based computerized cognitive training exercises to ultra high risk adolescents and to recent onset youth with the goal of improving cognitive functioning and enhancing long-term outcome. The recent onset youth are showing significant benefits of laptop-based cognitive training compared to the computer games control group.¹⁷ Their work with adult patients suggests that this cognitive intervention restores functioning and aspects of impaired neural circuit functioning. These initial findings indicate a promising, low-risk avenue for investigation in preventing the cognitive disabilities associated with schizophrenia.



Trial by Design: Explanatory or Pragmatic Intention

In medicine as a whole, randomized trials are routinely categorized as either having a pragmatic or explanatory aim. Pragmatic clinical trials seek to answer the question: “does this intervention work under usual conditions?” whereas, explanatory trials are focused on the question: “can this intervention work under ideal conditions?” Trials with an explanatory aim can be defined as clinical trials in which the hypothesis and study design are developed specifically to evaluate the efficacy of an intervention (maximizing signal detection) and by a desire to understand the mechanism by which the intervention is associated with benefits or harms. In practice, explanatory trials focus on translating laboratory findings to clinical practice, and are usually labeled as T1 translation. Conversely, trials with a pragmatic aim (frequently called effectiveness trials in psychiatry) can be defined as clinical trials in which the hypothesis and study design are developed specifically to answer a question faced by decision makers at one or more levels of the health care system, from patients and doctors

to public policy makers. The second area of translation, to the community and back, is frequently called T2 translation and requires that clinical trials be moved from the research clinic into the community. It is critical that explanatory and pragmatic aims be kept clear and distinct as the experimental designs differ in many respects.¹⁸

Personalized Trials for Mental Illnesses

(Section revised December 2010)

For nearly every mental disorder, we have interventions of proven efficacy in randomized clinical trials. Nonetheless, results to date indicate that often times interventions have only relatively modest effectiveness, and many individuals do not derive sufficient benefit. While existing studies answer important questions about potentially best overall treatments, these studies do not typically address important practical questions about who is most likely to respond to a given intervention. Especially for medications, clinicians are left to using trial and error, often subjecting patients to weeks of ineffective treatment or aversive side effects before finding an effective treatment regimen. Medications are neither specific for current diagnostic categories (e.g., SSRIs are used in both mood and anxiety disorders) nor are they consistent for patients with the same diagnosis. Biomarkers may facilitate the identification of subgroups with specific response to medications or psychosocial treatments (see Sidebar 4 and Sidebar 5).

Personalized intervention strategies might also be pursued using adaptive designs that use post-baseline information (e.g., a biomarker or information about patient response collected during prior therapy) to determine the best next step for treatment. In this manner, adaptive designs can be used to examine algorithms for sequencing treatments, whereby patients who do not respond to initial therapies can be subsequently re-randomized to other treatment options.^{19,20,21} Notable examples of studies employing sequential randomization include the STAR*D study for treatment of major depressive disorder^{22,23} and the CATIE trial for treatment of schizophrenia.²⁴

Adaptive design principles can also be used to speed the process of drug development. A useful example is FNIH's coordination of the Investigation of Serial Studies to Predict Your Therapeutic Response (I-SPY) studies,²⁵ a multi-center clinical trial designed to evaluate the impact of chemotherapy before surgery on patients with locally advanced breast cancer. The research employs a groundbreaking clinical trial model that uses biomarkers from individual patients' tumors to screen promising new treatments and to identify which treatments are more

likely to be effective in specific types of patients. An I-SPY type trial for post-traumatic stress disorder (PTSD) could seek to examine how a range of markers could be used to construct a profile for stratifying patients to assess the prediction of treatment response. The exercise could be very informative in a number of ways and could also set the stage for an adaptive trial, in which both novel pharmacological mechanisms and novel behavioral interventions could be tested.

In a different context, the term “adaptive design clinical study” is used to refer to studies in which there is a prospectively planned opportunity to modify the study

design or hypotheses, usually based on interim analysis of accumulated data (see FDA distributed [draft guidance](#) (PDF) for comment in 2009). Interim modifications to the study design are made in an effort to identify best (optimal) clinical benefit in a timely and efficient manner. Modifications made to expedite conclusions regarding benefit or harm typically involve adjustments to the total sample size (e.g., early termination of enrollment), modifications to the random treatment allocation scheme (e.g., “play the winner” strategies), or elimination of selected treatment arms, based on cumulative accrued response.

Sidebar 4. Identifying and Validating Biomarkers and Biosignatures

As defined by IOM, biomarkers are “quantitative measurements that offer researchers and clinicians valuable insight into diagnosis, treatment, and prognosis for many disorders and diseases.”²⁶ Biosignatures are collections of biomarkers that when combined have increased predictive validity. One key to success in drug discovery is the ability to relate the function of underlying biochemical pathways to the pathophysiology of the disease. Conversely, the greatest source of failure is having to *guess* at the underlying biology. Hence, the identification of biomarkers and/or biosignatures can be seen as key to developing a robust set of personalized interventions for mentally ill patients. In addition to neuroimaging, biomarker identification and validation usually refers to one of the “-omics” platforms: genomics, transcriptomics (RNA expression), proteomics, and metabolomics. Physicians in other areas of medicine routinely use biomarkers to guide treatment; for example, the serum biomarker hemoglobin A1c for diabetes management, or cardiac enzymes for myocardial infarction. However, intervention biomarkers are largely absent for mental disorders (apart from substance abuse). It is now time to apply biomarker approaches to mental illnesses, such as ASD, schizophrenia, and bipolar illness, or to relevant functional dimensions, such as emotion regulation or cognitive control.

To personalize interventions in mental illnesses, it will be necessary to identify biomarkers and biosignatures that 1) provide new methods for identifying which treatment is or is not appropriate for a given individual either before treatment starts or early in treatment, or 2) establish surrogate endpoints that are validated reflections of clinical outcomes and thus facilitate more rapid intervention development and testing. In this context, collecting biospecimens for analysis (according to current hypotheses) and reanalysis (in light of new hypotheses), where appropriate, must be a priority in today’s early- and late-phase interventions research.

Sidebar 5. Treatment Development in Lung Cancer: From Basic Research to Targeted Treatment

One of the transformative insights in oncology over the past decade is that many common forms of cancer involve multiple subtypes of disease, with different responses to treatment. Biomarkers for these different subtypes have altered our approach to diagnosis and treatment. A case in point is [non-small cell lung cancer](#) (NSCLC). Gefitinib, which antagonizes EGFR-tyrosine kinase, was predicted to be a potent treatment for this form of lung cancer.²⁷ However, when gefitinib tested as a treatment for [locally advanced](#) or [metastatic](#) NSCLC, the response rate was low. Studies showed a survival benefit (though it does not reach statistical significance) in patients treated with gefitinib over those who were treated with placebo; however, this benefit appeared to be in only certain subgroups of patients. For instance, researchers noticed that women, patients who have never smoked, patients with adenocarcinoma, and East Asians responded well to treatment. Because the drug has some serious side effects, the ability to predict and selectively treat only patients who are likely to respond would be helpful in determining a patient’s course of treatment.

In order to determine what factors contributed to this exceptional response to gefitinib, researchers began performing screens at the gene and protein levels of lung adenocarcinoma tissue from those who did and did not respond to gefitinib treatment. A genome-wide screen identified implicated genes, which provided a basis for extensive expression studies at the protein level finally leading to the identification of nine proteins that distinguish responders from non-responders. A key predictor was the EGFR-tyrosine kinase itself. By using information about this gene, clinicians can now detect which patients are more likely to respond to gefitinib treatment, or whether another treatment route would be preferable. Gefitinib is now approved by the FDA for use in patients that have not improved after treatment with other chemotherapy.

Setting Priorities for Clinical Research and Clinical Trials

NIMH and the public should recognize the success of more than 20 years of high-quality intervention research in documenting the efficacy of current generation cognitive-behavioral, somatic, and pharmacological treatments. These evidence-based treatments should be adopted as is and established treatment algorithms followed. With these successes, there still remain unresolved questions about how best to optimize these treatments and why these treatments work for some and not others. As a result, there remains a steady interest among researchers to test the generalizability of these treatments as well as to tailor the treatment in some way in hopes of improving the treatment for all or some. Such studies can be seen as paths to personalized treatments, but among this large group there are some with greater promise for personalized care than others. Because of the considerable expense of planning and conducting any trials, NIMH will need to make choices in this time of limited budgets. Importantly, in an era of flat budgets, NIMH must make difficult decisions among trials offering to adapt current, modestly useful, treatments. What priorities should the Institute consider for investing in an adaptation of a current treatment?

As a general approach, NIMH should focus on public health importance and on scientific advancement in understanding an established treatment's balance of benefits and harms. In this context, further research to adapt these effective treatments is a priority when:

1. New research generates predictors of benefits that require validation that cannot be accomplished using existing data.
2. New research generates predictors of adverse events that require validation that cannot be accomplished through existing data.
3. The study tests a revised intervention that is based on remediating the documented mechanism of non-response.
4. The study tests the efficacy of an evidence-based treatment in one disorder or domain of function and adapts it for use in another (e.g., a successful intervention targeting cognition in schizophrenia is revised and tested to target cognition in ASD).
5. Only through adaptation will the treatment be accessible to a subgroup (e.g., taking an adult treatment and making it developmentally appropriate for, and/or testing safety and tolerability in, a young child).

In terms of costs and planning, NIMH will need to ensure support for trials testing promising new interventions and critical adaptations that will have great potential to improve public health. With limited budgets and increasing costs of clinical trials, the Institute will need to find a better balance between its support of such intervention trials and those adaptations that can offer patients and providers only modest improvement in care or uptake. The peer review process, with its scientific and public members, will be invaluable in making these essential assessments of public health and scientific impact.

Shared Resources: Data and Talent

Many improvements can be made in the conduct of clinical trials including the establishment of collaborations that foster the standardization of measures, and the sharing of resources (tools, clinical samples) and data. NIMH could leverage its investment in clinical trials by requiring standard collection of clinical, cognitive, and laboratory data that can be integrated across diagnostic groups, across sites, and across trials. Data collected in trials funded by NIH or industry are a rich resource but currently are not sufficiently shared. Enhanced sharing of data, including negative results of trials, would improve efficiency, decrease the cost of therapeutic development, and facilitate the establishment of a biologically-based discovery process. Sidebar 6 provides a description of an exciting effort in data sharing in the field of ASD, the National Database for Autism Research (NDAR).

NDAR exemplifies not only data sharing, but the value of collaboration. Collaboration is also a guiding principle for [FNIH](#), an important partner working with the government, academia, industry, and not-for-profit groups to share data and collaborate on projects. NIMH should be constantly seeking such avenues for collaboration. NIMH should actively engage industry and FNIH in partnerships to help close the gap between basic and translational research and clinical trials. With the closing of certain CNS activities across the pharmaceutical industry, NIMH and other NIH Institutes and Centers may want to think about incentives to attract both large and small business to CNS research. In addition, collaboration through NIMH's intramural research program could support early-phase clinical trials within a public-private partnership context. Another opportunity is the newly proposed NIH's Cures Acceleration Network (CAN), a bold new feature of the Patient Protection and Affordable Care Act of 2010 (H.R. 3590). CAN's goal is to dramatically advance development of new treatments and cures for debilitating and

life-threatening diseases by reducing barriers between laboratory discoveries and clinical trials.

When discussing data and resource sharing, there is always the question of incentive and the balance with intellectual property (IP) rights. These considerations are further complicated by financial conflict of interest issues that protect the objectivity of the data, be it funded by a Federal grant or through industry. Procedurally, can there be a new model of sharing that can deal realistically with these intertwined issues that affect both pharmaceutical and device development? For instance, can there be some Federal investment early in the process that would provide sufficient benefit to industry and allow the IP rights not to attach until a later time?

Those living with mental illness and their families and clinicians are key stakeholders in the research enterprise.

These individuals want to know that their gifts of time or samples will be used to their fullest extent to find cures. They see how such contributions resulted in great strides in childhood leukemias and Hodgkin's disease, as did the important role patients and providers played as collaborators in the research enterprise. The spirit was to learn something from every patient, yielding high rates of participation in trials. This process permitted the rapid assessment of the utility of a given treatment regimen and the rational and paradigmatic adjustment of the protocol for subsequent treatment trials. This is the spirit of collaboration that should be developed in psychiatric research. Venues such as the NIH's [Clinical and Translational Science Award](#) sites should be developed for just this integrative effort.

Sidebar 6. Working Together: National Database for Autism Research

NIMH investments in clinical trials can be optimized by standardized measurements (including potential biomarkers), integrated approaches across disease groups, and accessible databases. Increasingly, NIH-funded researchers are being encouraged to share their data—not just report their research findings in journals. To facilitate this, data sharing infrastructure is being created in certain fast-developing fields. For example, to optimize use of burgeoning knowledge about autism spectrum disorder (ASD), NIMH is leading a multi-Institute effort to develop a National Database for Autism Research (NDAR), a secure bioinformatics platform for scientific collaboration around ASD. Its objectives are to: 1) facilitate data sharing and scientific collaboration; 2) provide bioinformatics solutions to address community-wide needs; and 3) enable the effective communication of detailed research data, tools, and information.

Through this web resource, the broad ASD research community will exchange data, tools, and other research-related information. Later in 2010, NDAR will make available the data from more than 10,000 participants enrolled in ASD research studies. Investigators will be able to perform a single query in the NDAR portal to view results across multiple datasets.



IV. Tactical Recommendations

Ideally, new interventions will stop the progression of mental illnesses before their devastating consequences ensue, with clear and large effects in patients. Such a shift in focus—to preemption and personalization across the developmental course of illness—will benefit those currently living with mental illness and provide future generations with the potential and hope for early diagnosis and effective treatment and ultimately cure. The following recommendations were developed in considering all of the opportunities and challenges described above and represent the workgroup’s recommendations across four broad goals:

1. Discover and develop novel, effective interventions that prevent and cure mental illnesses.
2. Optimize NIMH’s clinical trials portfolio toward achieving personalized and preemptive interventions.
3. Use existing resources effectively.
4. Create partnerships to accelerate the above goals.

Goal 1: Discover and develop novel, effective interventions that prevent and cure mental illnesses

Barrier 1.1

Methods are needed to identify and engage neural circuits that can be manipulated in model systems and translated to human studies to test if these interventions can restore function in patients.

Recommendation 1.1

Develop methods that identify and engage neural circuits that impact function in patients.

- a. Develop a deeper understanding of network oscillatory patterns that emerge from particular neural circuits, their developmental trajectory, their function and dysfunction in mental illness, and their response to pharmacological and behavioral interventions.

- b. Apply novel approaches to probe the integrity of basic plasticity systems in disease states, and determine how to augment plasticity within the circuits that are disrupted in mental disorders.
- c. Identify and develop drugs, biologics, or devices that enhance plasticity and combine them with behaviorally based training that engages specific circuits.
 1. Couple the appropriate somatic treatment with the appropriate behavioral treatment program to alter and/or strengthen circuits. Look at combinations of different pharmacologic interventions with and without behavioral interventions.
 2. Take advantage of a neuroplasticity approach to behavior change. This would include research on the integration of brain-targeted approaches (such as pharmacotherapy and stimulation) and behavioral approaches (such as cognitive training and psychosocial rehabilitation) to improve outcome.
 3. Encourage the development of brain-computer interface devices that train specific information processes that are off-trajectory in mental illness in a way that is personalized to the individual rather than to a group average standard. These devices may also facilitate pharmaceutical development by serving as a sensitive and objective measure of enhanced learning and plasticity and/or to inform dose selection.

Barrier 1.2

The pipeline of novel interventions is restricted due to the paucity of identified and validated molecular targets that reside in or alter the affected neural circuits. The gap areas for therapeutics development include the identification of validated targets that are amenable to pharmacologic interventions and more efficient chemical approaches for hit-to-lead optimization. There needs to be a greater focus on applying basic research (typically supported by NIMH) to drug development (until recently, supported by industry).

Recommendation 1.2.1

Develop novel interventions (pharmacological, behavioral, or devices) based on pathophysiology.

- a. Hypothesize and test the developmental pathways of mental illness, from genes to biology, recognizing complex models of gene/environmental interaction.
 1. Focus on empirically defining impaired functions or symptoms via their underlying neurobiology rather than current diagnostic categories.
 2. Focus research on model systems research to examine and validate factors contributing to the onset of mental illness. Priority should be given to:
 - i. Validated model systems that accurately predict the ability of therapeutic strategies to reverse and prevent mental illnesses.
 - ii. Early-phase drug development that extends from target identification through lead optimization.
 - iii. Early phase studies to assess target engagement such as central nervous system penetration and bioavailability; and acute and chronic dosing, metabolism, safety, and toxicity.
 - iv. Proof-of-concept studies for novel behavioral or cognitive approaches to alter neural circuits underlying symptoms of mental illness.
 3. Priority should be given in the near term to clinical targets with observable, objective outcomes and a theory of, or data on, the mechanism of action (e.g., rapid antidepressants, prosocial agents that improve social behavior or function in ASD, and cognitive remediation in schizophrenia). In the coming years, priority should be given to new clinical targets that show meaningful changes in biological markers (biomarkers) found to be relevant to disease in animal models or human pharmacodynamic studies.
- b. Specific new directions should:
 1. Develop standardized methods for indexing brain function that reflect the physiological processes of key neural circuits and signaling pathways that are linked to the specific deficits observed in mental disorders.
 2. Use human iPSC cells or other cell-based models that can be derived from individuals with mental

illnesses to identify disease modifying neurobiological processes, genetic mediators, and developmental pathways, and to identify new targets for therapeutic development.

3. Expand the diversity of pharmacological target types under investigation (e.g., allosteric modulators, small molecule activators of transcription factors, drugs that affect functionally selective G-protein signaling pathways and histone deacetylase inhibitors).
4. Augment single-gene studies with models that take into account complex molecular genetic interactions (e.g., epistasis).

Recommendation 1.2.2

Create funding mechanisms that encourage and support early stage studies of pharmacokinetic properties and target engagement within the CNS of novel molecular probes and optimization of these properties to allow validation of novel therapeutic approaches.

Ultimately, validation of new targets and small molecule-based therapeutic approaches for CNS disorders requires highly optimized molecular probes that have appropriate pharmacokinetic properties and CNS exposure to allow hypothesis testing. Also, many *in vivo* studies with existing or commercially available molecules are performed in a setting where there is no understanding of the disposition of these compounds in preclinical models. Finally, a key step in advancing a molecular series from probe to drug lead status is demonstrating that the pharmacokinetic properties of the compound are amenable to optimization as a drug candidate. Drug disposition science has advanced to a highly sophisticated discipline in the pharmaceutical industry, but has not been implemented in NIH-supported institutions where novel targets and rare and neglected diseases will receive focused effort. It will be critical to invest in CNS drug disposition science, particularly in the wake of the de-prioritization of drug development for psychiatric disorders within some areas of the pharmaceutical industry. These efforts should include:

- a. Optimization of CNS exposure and pharmacokinetic properties of novel probes to allow *in vivo* studies of effects on brain circuits.
- b. Integration of *in vivo* bioavailability for small molecular probes (drug disposition science) into current NIH Roadmap discovery initiatives.

- c. Studies of basic principles of drug disposition, especially as it relates to blood-brain barrier penetration and CNS exposure.
- d. Development of novel approaches to increase delivery of small molecules and biological reagents to the CNS.
- e. Support for studies of disposition and target engagement and developmental effects of existing probes used by the neuroscience research community that will inform interpretation of future neuroscience studies.

Barrier 1.3

Mental illnesses require preventive medications, vaccines, or cognitive protective approaches as well as validated biomarkers for early detection and targets for early intervention.

Recommendation 1.3

Speed the identification of new validated targets (e.g., biological, behavioral, and clinical) as biomarkers and for development as new therapeutic interventions (e.g., developmentally based, pharmacological, behavioral, and medical devices).

- a. Search for biomarkers for early detection of the risk for mental disorders such as schizophrenia, PTSD, bipolar illness, and ASD, including behavioral and cognitive markers.
- b. Identify biomarkers predictive of treatment response and adverse treatment effects in patients. Incorporate markers in clinical treatment studies to increase efficiency (see 2.1 also).
- c. Define developmental trajectories (in humans and relevant model systems) of neural circuits and signaling pathways using the biomarkers and imaging approaches that distinguish individuals with mental disorders; plot the divergence from these trajectories in patients at risk; and develop interventions that are disease modifying, (e.g., that return patients to typical developmental trajectories of functioning in these critical neural circuits).

Barrier 1.4

The ability to rapidly test new therapeutic targets and candidates has been stymied.

Recommendation 1.4

Accelerate the transition into early-phase trials for new molecular entities relevant to mental illnesses.

- a. Develop new (preclinical/*in silico*) models to predict safety, efficacy, and adverse effects of novel treatments.
- b. Support, along with NIH: small molecule screening; bioavailability and toxicology studies required for FDA approval for testing in human studies; first-in-human Phase I studies of target engagement; bioavailability, safety and tolerability, and exploratory biomarkers; and proof of concept efficacy studies beyond currently known therapeutic receptor targets.
- c. Optimize pharmacokinetic profiles and CNS exposure across species to allow accurate predictions of disposition of new molecules in humans.
- d. Use small Phase I clinical studies to identify optimal parameters to rapidly assess target engagement, pharmacokinetics/pharmacodynamics optimal dose, exploratory biomarkers, and biomarker response in typical human subjects and in patients of interest.
- e. Use Phase I studies to test whether novel mechanism of action treatments engage the same preclinical circuit/pathway/biological mechanisms and translate to humans before a larger investment in early phase trials.
- f. Select subjects best suited to test the hypothesis that an intervention targets a specific mechanism. That is, ensure that the individuals in a proof-of-concept trial actually have the abnormality in the pathway being studied (e.g., a genetic abnormality/deficit in gating or cognitive processes) in order to rigorously test the biological hypothesis (pharmacologic and biological/disease mechanism).
- g. Foster collaborations between and among the NIMH, FDA, industry, and academic health centers for innovative science, sustainable infrastructure, and facilitated regulatory path(s) to registration of a novel drug or device.

- h. Work with industry partners to validate new molecular targets, de-risk individual candidates for subsequent investment, and repurpose agents for new indications, especially for clinical development.
- i. Use NIMH's Division of Intramural Research Programs as an incubator for these efforts.

Goal 2: Optimize current treatments and NIMH's treatment research

Barrier 2.1

There are no sensitive and specific predictors of treatment response.

Recommendation 2.1

Find significant predictors or moderators of safety, benefits, and harms that will be useful for tailoring current treatments, setting up new research, and where possible, shedding light on underlying biology. Develop the principles of standardization, integration, and sharing in NIMH funded clinical research.

- a. Support exploratory trials to identify predictors and potent modifiers or mediators of response (e.g., multi-plex gene assays for responsiveness to SSRIs).
- b. Support the addition of a targeted, standardized set of biological samples or measures (e.g., imaging, collection of blood for future genomics, epigenomics, proteomics, etc.) to adequately powered treatment trials, to identify and validate novel biomarkers/biosignatures and their mechanisms.
- c. Support integration of findings from multiple studies via the deposition of data in a common format so that it can be shared/mined by the research community. Continue to provide NIMH research support to mine existing data sets, such as treatment data from NIMH-supported trials, including meta-analyses that combine data from multiple trials in order to identify predictor and moderator variables.
- d. Establish a mechanism to store and provide access to biospecimens (e.g., blood, brain, and peripheral tissues) from NIMH-funded trials and adequately powered research studies.

- e. Work with the FDA and industry to find a method for secondary analysis of academic and industry trials. Pursue strategies for mining pharmaceutical company data that protect intellectual property rights and preserve the confidentiality of personal health information.

Barrier 2.2

Design issues in current trials may be suboptimal, thus contributing to the rising number of "failed" trials of proven treatments.

Recommendation 2.2

Clarify design and operational issues to enhance signal detection and match the experimental design to the hypothesis being tested.

- a. Applicants should define the project as having explanatory or pragmatic intent.
- b. Encourage use of tools to inform scaling experimental design and operational considerations on the explanatory-to-pragmatic continuum.
- c. Identify and address systemic design problems contributing to reduced signal detection (e.g., site differences, subject selection criteria, poorly defined clinical hypotheses, and inflation in the placebo response).
- d. Where there is a compelling rationale for an NIMH-funded trial to contribute data that affects a product label, coordinate with FDA at the trial design stage and ensure that the conduct of the trial conforms to Good Clinical Practice regulatory standards.

Barrier 2.3

NIMH receives too few applications aiming to personalize treatment.

Recommendation 2.3

To facilitate and advance research toward personalized treatments, NIMH should:

- a. Encourage identification and validation of baseline and early-response biomarkers/biosignatures, and also surrogate endpoints, taking advantage of emerging technologies from the academic and private sectors.

- b. Systematically test the effects and limits of specific somatic and behavioral therapies, separately and in combinations, to understand their mechanisms of action.
- c. Identify a standard set of core data or specimens (e.g., genetic, epigenetic, transcriptomic, proteomic, hormonal, neural network, neurochemical domains, as well as functional and neuropsychiatric assessments) to be collected in appropriate clinical trials for mental illnesses. Standardized datasets and tissue repositories will allow for subsequent pooling of data and reanalysis.
- d. Utilize adaptive trial designs to facilitate iterative evaluation of treatment effects and to incorporate identified biomarkers and known risk factors to predict treatment response.
- e. Encourage personalization by accounting for patient preference.
- f. Develop trial designs, at least in non-pharmacologic studies, that personalize treatment on the basis of behavioral and psychosocial variables as well as biological variables (e.g., level of insight and motivation, presence or absence of family support, and substance abuse).
- c. Evidence to suggest that the adapted intervention will result in a substantial improvement in response rate, speed of response, an aspect of care, or uptake in community/practice settings when compared to existing intervention approaches.

Recommendation 2.4.2

NIMH should maximize its investment in pragmatic trials by encouraging trialists to consider the intervention's utility for service settings and/or for embedding features that can inform treatment development.

Although a list of exemplary features will change with time and can only be illustrative, consideration should be given to trials that can embed one or more of the following priority features:

- a. Ability to focus on identifying (and later validating) biomarker/biosignatures and other tailoring variables.
- b. Ability to be conducted on an electronic medical record platform in practice settings where results are intended to be generalized.
- c. Involvement of private partners, if appropriate and feasible, in addition to other governmental and nonprofit partners.
- d. Ability to be evaluated for the potential to change FDA labeling language and to be designed and conducted in a fashion that will allow use of data by regulatory agencies.
- e. Inclusion of a diverse sample of respondents (e.g., gender, race/ethnicity, income, in-take sources) in order to increase generalizability and facilitate implementation.
- f. Involvement of patient and family groups in the development and design of the trial, as well as patient and family group support during implementation and dissemination phases.
- g. Prompt and robust sharing of data and resources.
- h. Appropriate NIMH staff involvement in the development and design of the trial.

Barrier 2.4

Research trials are expensive and clear priorities are required to guide NIMH's future investments in interventions research.

Recommendation 2.4.1

NIMH should establish clear decision rules for deciding whether to invest in adapting or extending an effective treatment or preventive intervention. The need for an adapted or extended intervention should be justified in terms of:

- a. Theoretical and empirical support for the adaptation target (e.g., the adaptation changes a factor that has been associated with non-response, partial response, patient non-engagement, or relapse).
- b. Clear explication of the mechanism by which that moderator variable functions to disadvantage or advantage a subgroup (ideally, with behavioral and/or biological data that support the mechanism hypothesis).

Goal 3: Use existing resources effectively

Barrier 3.1

Efficient use of NIH and NIMH resources requires stronger data and resource sharing policies and appropriate infrastructure.

Recommendation 3.1.1

While working on strengthened NIH policies, NIMH should use current NIH guidance to establish data sharing expectations in the terms and conditions of more awarded grants and contracts.

- a. Ensure that data from trials of any design, size, dollar amount, or outcome (especially the null outcomes) are made available for secondary analysis.
- b. Explore mechanisms for continuing to share data and biospecimens collected in a clinical trial beyond the funding period for the project.
- c. Monitor data sharing behavior stringently, including discussions with grantee institutions regarding failures to meet the sharing terms and conditions of a specific award.

Recommendation 3.1.2

NIMH should create standards or models to facilitate sharing and create a rich, integrated resource that will allow data mining and will attract researchers from allied fields (academics and private industry) to address research questions of high priority to NIMH as follows:

- a. Data and Materials
 1. The NIMH genetics repository can be generalized for broader use to prospectively gather, assay, and to bank biological, neural network, and neural signature data.
 2. Start with expanding the [National Database for Autism Research](#) and the [Biomedical Informatics Research Network](#) and consider if other models might provide ideas for efficiencies (e.g., [Alzheimer's Disease Neuroimaging Initiative](#)).

- b. Within the framework of the NIH Common Fund, support efforts to standardize approaches seeking approval from Institutional Review Boards, Data Safety Monitoring Boards, and the FDA for Investigational New Drug or Investigational Device Exception or registration.
- c. Develop model experimental designs for:
 1. Preclinical toxicology and safety in juvenile animals, reproductive toxicology, and maternal/perinatal toxicology.
 2. Proof-of-concept designs.
 3. Adaptive treatment designs.
 4. Adaptive approaches to randomization.
 5. Patient preference designs.

Goal 4: Create partnerships

Barrier 4.1

A vibrant biotechnology community is needed to invest in promising new treatments. In recent years, this sector of private investment has faced severe financial constraints in light of the current economic downturn.

Recommendation 4.1.1

Support biotechnology and pharmaceutical companies by engaging them in public private partnerships to identify and validate specific markers and disease-relevant pathways in live subjects and patient samples.

Recommendation 4.1.2

NIMH should support collaborations that provide access to shared technology platforms for investigators in academic and small business settings. Such arrangements can be with industry partners, academic health centers, or in blended private/public collaborations.

Barrier 4.2

The role of patients and their families as collaborators in the research enterprise is not currently maximized to the fullest.

Recommendation 4.2

The NIMH should explore collaborative models such as those developed in the childhood leukemias and Hodgkin's disease for the systematic and informed engagement of patients, families, and clinicians in treatment protocols.

Barrier 4.3

Difficulty in balancing intellectual property needs, regulatory demands, and conflict of interest rules can stifle research and investment.

Recommendation 4.3

NIMH needs to join the discussions between NIH and FDA to explore the emerging domain of regulatory science. The task will be to preserve incentives for discovery and development via intellectual property while encouraging broad data sharing, reduce regulatory burden while ensuring safety, and facilitating partnerships between industry, academia, and government without injuring public trust.

V. Conclusions

The charge to this workgroup was both difficult to address and significant with respect to its impact on research and those living with mental illnesses. The workgroup members hope that the efforts recommended in this report draw mental health research closer to the spirit and hope of Sir Osler’s vision and ambitions.

As laid out in this report, it is time to speed the identification of new targets for new interventions that include small molecules, biologics, devices, and behavioral interventions. The workgroup proposes an early-phase research agenda that is preclinical through Phase I and proof-of-concept studies, with an eye toward the future, when it will be important to promote and accelerate the transition from first-in-human studies into proof-of-concept trials into Phase III studies. It will be crucial to identify and validate variables for developing adaptive personalized designs and preemptive clinical trials. Such a shift will benefit those living with mental illnesses. The shift also will enable the NIMH portfolio to move from studies searching for small treatment effects among existing modalities, to identifying and testing new robust treatments. Finally, existing

To wrest from nature the secrets which have perplexed philosophers in all ages, to track their sources the cause of disease, to correlate the vast stores of knowledge, that they may be quickly available for prevention and cure of disease—these are our ambitions.

— Sir William Osler

resources must be used more effectively, and the process for prioritizing and selecting clinical trials for funding deserves renewed consideration.

New tools and approaches provide NIMH with a historic opportunity to dramatically change the lives of those with mental illness. The challenges to developing new interventions for mental illnesses are great, but so are the scientific opportunities and public health ambitions before us.

Appendix A

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