The NIMH Experimental Medicine Initiative

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Much has been written about the dire state of treatment development for mental disorders (1). While there has been progress in the development of devices and psychosocial treatments, psychopharmacology over the past decade appears to have stalled after four decades of exuberant growth (2).

There are several reasons for the lack of progress in medication development: preclinical studies appear neither predictive or reproducible, there are few novel targets for Phase I and Phase II studies, and several expensive recent Phase III studies have failed. Psychiatric drug development is now seen as high risk. Indeed, large pharmaceutical companies have reduced investment in central nervous system disorders from 267 projects in 2009 to 129 projects last year, with many of these projects focusing on neurological and not psychiatric disorders (3).

It is important to note that four decades of drug development resulting in over 20 antipsychotics and over 30 antidepressants have not demonstrably reduced the morbidity or mortality of mental disorders. While there may be many explanations for the unabated public health needs associated with mental illness, there can be little doubt that we need additional research and development to provide the preventive interventions and cures that will reduce morbidity and mortality. Current medications have an important role in the toolbox of interventions but, either alone or in combination with other treatments, they have not proven sufficient. The question is how to develop the next generation of interventions.

PREVIOUS CLINICAL TRIALS

The National Institute of Mental Health (NIMH) has tried to answer this question by focusing on each of the issues noted above: problematic preclinical studies, lack of novel targets, and failure of Phase III trials. Others have argued for the need to move rapidly into human trials due to the difficulty extrapolating from preclinical results (4,5). Here we describe changes in the clinical trials portfolio to search for novel targets and increase the likelihood of Phase III success. The approach has been called the shift to experimental medicine at NIMH. Although this term has been used to describe broadly the clinical study of mechanisms of disease, for NIMH, experimental medicine refers to an approach to clinical trials.

The first step before changing the clinical trials approach was a review of the portfolio in 2012. In the previous year, NIMH supported over 250 clinical trials at a cost of roughly $150M per year. More than half of these trials were for psychosocial interventions. Our initial review demonstrated a large number of under-powered trials that were slow to recruit and even slower to publish. Indeed, a 2012 review of trials across the National Institutes of Health (NIH) reported that fewer than half published results within 30 months of completion (6). Most trials were looking for an efficacy signal, but were designed not to rigorously test a hypothesis about how or for whom the intervention should work. Few trials included any test of mechanism of action. Trials rarely included measures of dose-response or tests of duration that could inform their adoption and reimbursement in the real world. Given the range of issues, NIMH announced in 2014 that it would no longer accept proposals for clinical trials unless they were responsive to a Request for Applications (RFA).

NEW CLINICAL TRIALS

In 2014, NIMH released three RFAs to solicit proposals for clinical trials (see http://grants.nih.gov/grants/guide/rfa-files/). In line with an experimental medicine approach, each of these RFAs refocused trials from simple tests of efficacy to studies of disease mechanism (7). The new approach required a measure of target engagement, where the target ideally was linked to some mechanism of disease but could also be a mechanism of action of the intervention. The prototype of a target might be a measure of receptor occupancy. A clinical trial of a drug thought to work as a dopamine receptor antagonist would need to demonstrate a dose for engagement or occupancy of the dopamine receptor and then test for efficacy at that dose.

This simple requirement has two important implications. First, it allows negative efficacy data to be informative. Second, it allows a test of the importance of the target. In five decades of treatment development, there have been essentially no mechanisms falsified in neuropharmacology, in part because target mechanisms are rarely tested in clinical trials.

Of course, receptor occupancy is a high bar for target engagement, unlikely to be feasible in most studies. For psychosocial studies, the target could be a shift in attentional bias or social cognition or family dynamics, as assessed by changes in objective measures included in the trial. For device studies, the target might be a change in EEG or evoked potentials or the blood-oxygen-level dependent (BOLD) signal. The choice of target is critical because the choice of intervention is almost always iterative. Each new intervention is a step along a path toward much more

effective treatments. To accelerate that path, NIMH believes that an understanding of the target will prove to be the critical insight, not a slight increase in effect size.

As a further test of this approach, NIMH sponsored a series of contract trials called Fast-Fail trials (FAST). These trials were based on an analysis of failed Phase III trials that suggested a need to insert go - no go decisions into earlier phases of the development process (5). By failing early and often, development could focus on the treatments most likely to succeed in Phase III. In addition to requiring measures of target engagement, the FAST studies had specific milestones built in for assessing progress. Since these trials were funded as contracts, project management was rigorous and funding was contingent on hitting these milestones. Current trials include assessing the kappa opiate receptor for anhedonia in depression and a GABA-A agonist for social cognition in autism, with measures of target engagement and specific efficacy outcomes built in.

ENHANCING IMPACT

The new experimental medicine approach asks applicants to answer two simple questions about their experimental design: Will negative results be informative? Will positive results have an impact? Target engagement addresses the question about negative results. The impact of positive results is more complicated. In spite of the considerable experimental evidence of efficacy for targeted psychotherapies such as cognitive behavioral therapy and dialectical behavior therapy, and considerable data about the most effective use of medications, our field faces a crisis of failed implementation.

There are at least three issues affecting implementation. First, in most communities, in both the developed and the developing world, there are too few clinicians with supervised training in either psychopharmacology or those psychotherapies with the most evidence for efficacy. Second, for psychosocial treatments, the research establishing evidence rarely demonstrates the requisite dose or duration of treatment. And finally there has been little adherence to standards for fidelity, especially for psychotherapies. Without the regulatory framework that exists for medications and devices, neither patients nor payers know how to judge what a therapist actually delivers. Experimental medicine may not solve all of these issues, but properly designed experiments can at least establish dose and duration, with the potential for creating measures of fidelity as well.

BEYOND EXPERIMENTAL DESIGN

The aforementioned portfolio analysis revealed serious problems with several key measures of performance. While not ubiquitous, there were many trials that had failed to register in ClinicalTrials.gov, some with prolonged delays in enrolling the first subjects, and many failing to meet recruitment milestones. As noted above, many NIH trials were also slow to publish following completion of the study, with as many as 30% failing to publish any results (6). NIMH has also altered its expectations for clinical trials beyond experimental design. All trials funded by NIMH must be registered in ClinicalTrials.gov. To expedite enrollment, all multi-site trials are expected to have a centralized institutional review board (IRB). Recruitment will now be tracked in all studies, with funding terminated for studies that persistently fail to meet recruitment goals.

NIMH-funded clinical trials are now required to submit individual level data on a quarterly basis to the National Database for Clinical Trials Related to Mental Illness (http://ndct.nimh.nih.gov). The importance of sharing individual-level data became apparent in a recent reanalysis of 37 published clinical trials (8). In 35% of the trials, the reanalysis led to a different interpretation than reported in the original paper, with implications for the types and numbers of patients who should be treated.

Two other issues deserve note. Clinical trials of mental disorders have been impaired by the heterogeneity of our diagnostic classifications. It is not hyperbole to suggest that a study of a new drug for major depressive disorder is analogous to giving a new antibiotic to everyone with fever. No one should be surprised that 30% of patients respond to placebo and 50% fail to respond to the new treatment. We need precision medicine for mental disorders. The Research Domain Criteria (RDoC) project seeks to go beyond symptom-level classification to identify more precise categories that could be used to stratify patients for clinical trials (9). This approach may also yield new clinical targets, such as anhedonia, fear reactivity, or aspects of executive function, that take us beyond the current focus on antidepressants, antipsychotics, and anxiolytics.

Finally, it is a curious paradox that nearly all clinical trials study a single intervention and yet in the real world of practice nearly all patients receive multiple interventions. While research demands the purity of single variables, we must find a way for science to align more closely with the practical needs of patients. Is it realistic to expect conditions as complex as psychotic, mood, or anxiety disorders to respond to a singular intervention? The treatment of diabetes now involves a package of psychosocial, medical, and device based interventions. Surely the time has come to recognize that there is not a magic bullet for most people with mental disorders, that the best treatment will involve access to multiple interventions tailored to the needs of an individual patient and selected by an informed patient working with an informed provider. The NIMH supported Recovery After Initial Schizophrenia Episode (RAISE) study is an example of this approach that could serve as a model for future trials (see http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml).

The shift to deployment focused intervention studies, which take "real world" issues into account, may ostensibly appear to be a challenge to an experimental medicine approach.

In fact, it is essential for understanding both targets and impact.

CONCLUSIONS

We need a next generation of treatments for mental disorders. As one step towards this goal, NIMH has introduced a new set of requirements for clinical trials. The design of these trials follows an experimental medicine approach, with a focus on target engagement. Beyond design, these trials will require new levels of transparency and efficiency.

Public health success will ultimately depend on more precise stratification of patients for trials and the development of combinations of treatments that can optimize outcomes.

References

1. Hyman SE. Revolution stalled. Sci Transl Med 2012;4:155cm111.
2. Miller G. Is pharma running out of brainy ideas? Science 2010; 329:502-4.
3. Pankevich DE, Altevogt BM, Dunlop J et al. Improving and accelerating drug development for nervous system disorders. Neuron 2014;84:546-53.
4. Perrin S. Preclinical research: make mouse studies work. Nature 2014;507:423-5.
5. Paul SM, Mytelka DS, Dunwiddie CT et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 2010;9:203-14.
6. Ross JS, Tse T, Zarin DA et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. BMJ 2012; 344:d7292.
7. Insel TR, Gogtay N. National Institute of Mental Health clinical trials: new opportunities, new expectations. JAMA Psychiatry 2014;71:745-6.
8. Ebrahim S, Sohani ZN, Montoya L et al. Reanalyses of randomized clinical trial data. JAMA 2014;312:1024-32.
9. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. Am J Psychiatry 2014;171: 395-7.

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