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Commentary

NIMH-Funded Pragmatic Trials: Moving On

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In 2007, NIMH completed a series of landmark practical clinical trials that assessed the effectiveness of currently available psychotropic medications. These trials—including the Clinical Antipsychotic Trials of Intervention Effectiveness study for schizophrenia, the Sequenced Treatment Alternatives to Relieve Depression study, the Treatment of Adolescent Depression Study, and the Systematic Treatment Enhancement Program for Bipolar Disorder study—involved approximately 10 000 patients at nearly 200 sites. Designed more than a decade ago at the beginning of the doubling of the NIH budget, these trials were a new venture for NIMH which had previously been more committed to efficacy rather than effectiveness research. It is timely to look back at this effort in 2010, not only with nostalgia for a period of robust budget growth but also with an eye to lessons learned. In this issue, March *et al* have developed a useful set of considerations for future pragmatic clinical trials to enhance their internal and external validity as well as efficiency.

Although none of these trials was perfect, taken together they reveal a sober message: the pharmacological treatments available today, even when optimized in a research study, help some patients get better, but too few completely recover. One might have surmized as much from the lack of improvement over recent decades in the morbidity and mortality from mental disorders despite a dramatic increase in the use of psychotropic medications. This is not to say that current medications cannot improve outcomes for people with mental illness if delivered as part of a package of evidence-based care. Rather, if we are honest with ourselves and our patients, we need to admit that today's medications may be good but they are not good enough. Even for the fraction of patients who ultimately respond, clinicians often must resort to trial and error before finding a regimen that works, subjecting patients to potentially life-threatening delays, ineffective treatment, or adverse side effects.

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In response to the sobering evidence from these effectiveness trials, we asked our National Mental Health Advisory Council this past year to help us consider how we could support research to develop substantially better interventions. A workgroup of the Council met through the winter to discuss opportunities and challenges in treatment development. Among their many suggestions was (a) a call to develop the next generation of highly effective therapeutic, preemptive, and preventive interventions, based on a better understanding of mental disorders and (b) a call to optimize the use of current treatments based on a better understanding of individual differences in response.

How will the workgroup's call for a new generation of truly robust and personalized interventions be met? First, truly novel compounds with far greater efficacy will require rational development based on understanding disease mechanisms, identifying targets that alter these mechanisms, and building a pipeline to create innovative treatments. Although research elucidating the genetic associations to autism, schizophrenia, and mood disorders has provided many new clues (Akil *et al*, 2010), there is a long trail from transcripts to targets. Neither common nor rare risk alleles will generate druggable targets without considerable investment in understanding the complex biology of disease. And identifying a molecular target is still only the first step toward a new medication. We might take some comfort knowing that the pathway from disease mechanisms to targets to novel therapeutics has been worked out in cancer and immunology. But thus far, this approach has not been successfully applied to develop novel treatments for mental disorders. Why? The workgroup stressed the need for a much deeper understanding of molecular pathophysiology to be able to identify druggable targets. The workgroup also reminded us of the power of astute clinical observation and the short-term potential of 'repurposing' drugs from other areas of medicine. In addition, a growing understanding of the neurodevelopmental bases of many mental disorders may soon permit earlier intervention than is currently possible, thereby mitigating, forestalling, or even completely preventing mental disorders. Finally, the Council workgroup reminded us that existing treatments can be personalized by shifting from clinical trials of group differences to ones in which

predictive biomarkers are identified and patients are stratified based on them.

Although scientific opportunities for progress have never been better, a critically important question is: who will develop this new generation of treatments for people with mental illness? Traditionally drug development has been mostly the role of industry. NIH has supported research to identify treatment targets, but subsequent stages including early and later phase clinical trials have been funded predominantly by industry. This traditional model appears to be in trouble. Some biotech and major pharmaceutical companies have moved away from developing treatments for CNS targets, in part, owing to the many generics on the market, recent failure of some novel agents such as those targeting receptors for neuropeptides, absence of predictive animal or cellular models, and the sheer expense and time-frames needed for developing CNS drugs (Paul *et al*, 2010).

This paradoxical situation of industry exodus in the face of scientific opportunities and enormous public health burdens from mental disorders compels NIMH to act: we cannot condemn millions of people with mental illness to a future without better treatments. But what can and should NIMH's role be in this process? Should NIMH become a drug discovery and development agency using public funds to create the next generation of treatments? Should NIMH focus more on its traditional core competence of basic neurobiology and target identification? How much should NIMH invest in more practical trials to identify the best use of current medications? As we wrestle with these questions, it may be useful to note some initiatives are already underway. NIMH coleads the Molecular Libraries Program, an NIH-wide Common Fund effort to enable academic researchers to screen for molecules that could become lead compounds for drug development. NIH has also developed programs for medicinal chemistry, toxicology, pharmaco-kinetics, and pharmacodynamics, to move lead compounds into early phase clinical trials. And the recently signed Patient Protection and Affordable Care Act (health care reform law) includes the Cures Acceleration Network which authorizes NIH to increase efforts to bring better treatments to the public. Note that the same Act also calls for NIH to fund more comparative effectiveness research, similar to the NIMH practical trials of this past decade.

Of course, drug development is costly and usually unsuccessful, requiring nearly $1.8 billion across 25 separate projects to successfully launch a single drug (3). With an annual budget of less than $1.5 billion, NIMH will clearly not be able to replace industry. But a few key discoveries from NIMH-supported science might catalyze what is currently a stalled process, helping to re-incentivize industry to invest in CNS drug innovation. NIMH-supported efforts are already using such an approach to develop new medication classes for fragile X syndrome and depression, and this model could be extended to build a pipeline for desperately needed treatments that provide rapid relief from depression, cognitive deficits in schizophrenia, or social deficits in autism.

Clearly, if industry continues to abandon development of treatments for mental illness, NIMH, either alone or in a partnership, will need to fill the gap. With a new NIH-wide priority on accelerating cures, NIMH hopes to be able to support more preclinical discovery and early phase clinical trials. And conducting clinical research more efficiently, including through some of the suggestions made by March and colleagues, may free up some of the resources required to make new investments. But limits in NIMH's funding dictate that, as we set priorities, hard choices will need to be made between investing in new treatments and attempting to optimize the use of existing ones or simply adapting them for use in another sub-population. Our mission—'transforming the understanding and treatment of mental illness'—requires that a new balance be struck to ensure that patients and families burdened by mental disorders get desperately needed, truly transformative treatments.

DISCLOSURE

The authors declare no conflict of interest.

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