

Why NIMH Should Not Stop New Drug Trials for Schizophrenia

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Summary

Schizophrenia is one of the most important and expensive diseases in the United States. A primary responsibility for developing better drugs for this disease lies with the pharmaceutical industry and the National Institutes of Mental Health (NIMH). Using ClinicalTrials.gov, the online registration for drug and other clinical trials, we assessed trends in drug trials for schizophrenia from 2005 to 2017. During that period the pharmaceutical industry reduced drug trials for schizophrenia by 59 percent. NIMH reduced all schizophrenia related clinical trials by 45 percent but reduced drug trials by 88 percent. The reduction in clinical trials for schizophrenia sponsored by NIMH is apparently the result of a deliberate policy to phase out support of such trials, as confirmed by statements made by the director

of NIMH, Dr. Joshua Gordon. It is recommended that this policy be immediately reversed since better medications are essential to helping people with this devastating disease.

Introduction

The national failure to provide adequate treatment to those with schizophrenia is one of the most important healthcare issues in the United States today, extracting enormous tolls both socially and economically. Untreated and undertreated individuals with this disorder constitute the majority of the mentally ill homeless population as well as the mentally ill inmates filling county jails and state prisons. Individuals with severe mental illness such as schizophrenia comprise a disproportionate share of people with mental illness who are shot by police, as well as those who commit mass killings – people like Seung-Hui Cho at Virginia Tech, Jared Loughner in Tucson, James Holmes in Aurora and Aaron Alexis at the Washington Navy Yard. The most recent estimate of the annual cost of schizophrenia in the United States, based on 2013 data, was \$155.7 billion, including \$37.7 billion in excess direct health care costs; \$9.3 billion in non-health care costs (e.g. jail costs); and \$117.3 billion in indirect costs such as lost wages and caregiver costs.¹

Antipsychotic medications are the standard treatment for schizophrenia. At present, 20 different antipsychotics are available in the U.S. Clozapine is the one most recently approved – nearly twenty years ago. Although the majority of patients have improved symptoms using these drugs, approximately 15 percent respond minimally or not at all. The currently available antipsychotics can also have serious or unpleasant side effects for many people, including weight gain, increased blood sugar and lipids, and movement disorders. A major goal of the psychiatric research community has been to develop more effective drugs with fewer side effects.

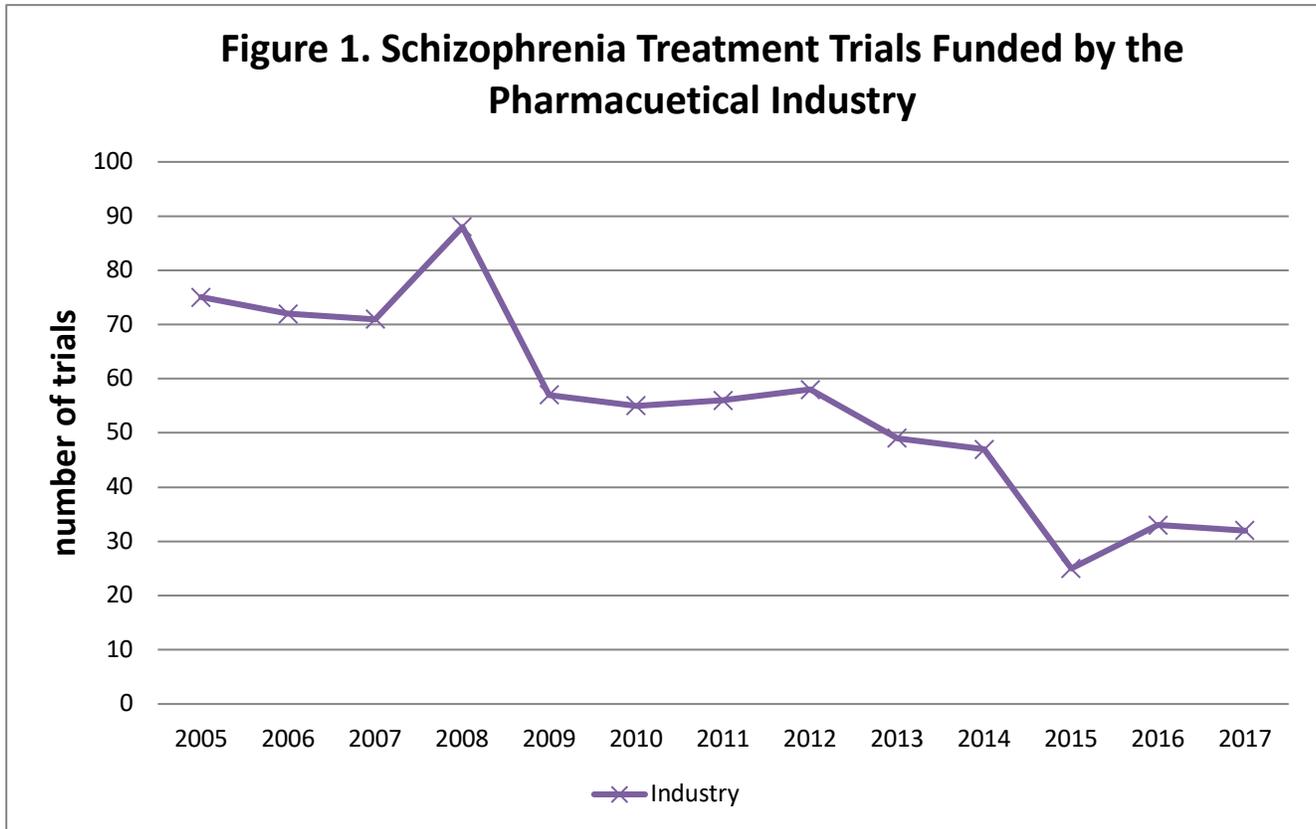
The major developers of new drugs for schizophrenia in the U.S. have been the pharmaceutical industry and the NIMH, with some contributions from non-profit foundations and universities. In recent years, major pharmaceutical companies, such as Pfizer, Lilly, and AstraZeneca, have reduced their efforts to develop new drugs for schizophrenia. A major reason for this has been the failure of genetic and other molecular biology research to identify new targets for drug development.^{2,3} Rather than step up to fill the void, NIMH has exacerbated the problem by reducing its support for clinical trials as well, apparently as a deliberate policy strategy. To quantify the overall scale of this reduction and to assess the reduced role of NIMH in schizophrenia drug development we undertook the following study.

Method

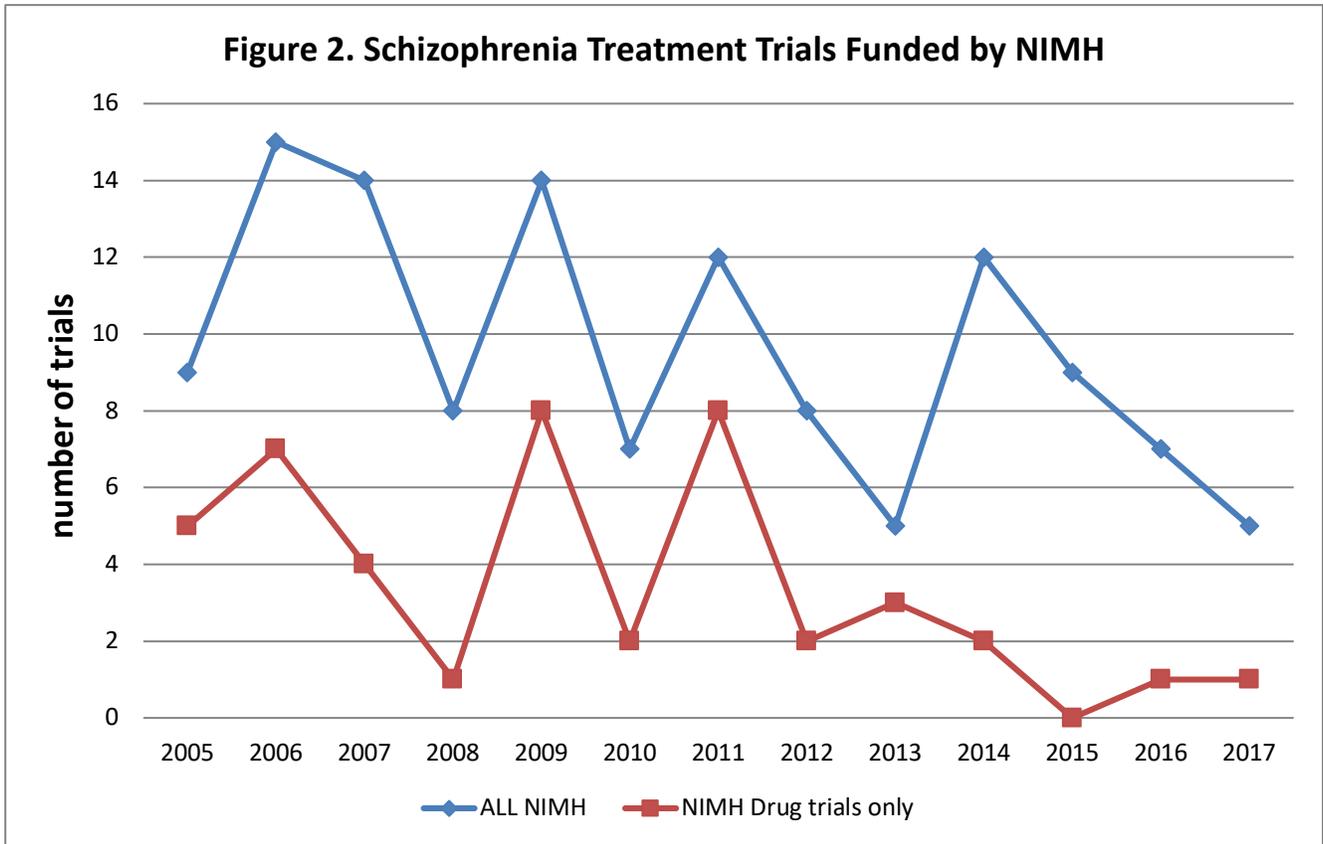
ClinicalTrials.gov is a website maintained by the National Library of Medicine for the registration of all clinical trials. Researchers are expected to register their trial at the time they begin. Trials can be sorted by year of registration, disease, and funding source, e.g. National Institutes of Health, pharmaceutical industry, other. NIMH is one part of the National Institutes of Health and has primary responsibility for schizophrenia research. We therefore examined all registered trials for schizophrenia sponsored by NIMH or the pharmaceutical industry for the years 2005 to 2017.

Results

From 2005 to 2017 the pharmaceutical industry funded a total of 718 treatment trials for schizophrenia. As can be seen in figure 1, there was a gradual decrease in such trials over time. When the number of trials in 2005-2007 (n=218) is compared to the number of trials in 2015-2017 (n=90), the decrease in schizophrenia-related trials is 59 percent.



From 2005-2017 the National Institutes of Health funded a total of 166 treatment trials for schizophrenia. Of the 166 trials, 124 were funded by NIMH and 42 by other institutes. The largest number of the non-NIMH trials (n=25) were studies on smoking and street drug use by individuals with schizophrenia, funded by the National Institute on Drug Abuse. As can be seen in figure 2, there was also a decrease in NIMH trials over time but less so than the decrease in industry-funded trials. When the number of NIMH trials for 2005-2007 (n=38) is compared with the number for 2015-2017 (n=21), the decrease in schizophrenia-related trials is 45 percent.



Further examination of the individual trials, however, produces a different picture. As would be expected, almost all of the industry-supported trials involved pharmacological agents intended to improve the symptoms of schizophrenia. NIMH-funded trials, by contrast, included some pharmacological agents intended to improve symptoms of the disease but also non-pharmacological agents (e.g. transcranial magnetic stimulation, electroconvulsive therapy); various forms of psychotherapy and cognitive remediation; social skills training; and other non-pharmacologic interventions designed to improve the quality of life for persons with this disease. We therefore compared the individual NIMH-funded treatment trials for 2005-2007 with those for 2015-2017.

Among the 38 NIMH-sponsored treatment trials for 2005-2007, 16 (42 percent) used pharmacological agents intended to improve the symptoms of the disease. Two others used non-pharmacological agents and the remainder were attempts to ameliorate side effects of the antipsychotics,

improve social function, etc. Among the 21 NIMH-sponsored treatment trials for 2015-2017, only two trials (10 percent) used a pharmacological agent intended to improve the symptoms of the disease (figure 2). This represents an 88 percent reduction in schizophrenia-related treatment trials compared to a decade earlier. Two other trials used non-pharmacological agents and others targeted side effects, and various forms of non-pharmacological therapy such as cognitive remediation.

Included among these 2015-2017 NIMH funded treatment trials were several of questionable relevance to the treatment of schizophrenia. A study on “PET Imaging Study of Amish and Mennonite Patients with CNTNAP2 Mutations” appears to be a non-therapeutic genetic study. A study of “Reducing Stigma among Healthcare Providers to Improve Mental Health Services” is a study of stigma among healthcare workers in Nepal; given the vast cultural and resource differences, it is difficult to imagine how a study in Nepal will be helpful for the treatment of schizophrenia in the U.S.

Discussion

Given the fact that NIMH funded just two drug-related treatment trials to improve the symptoms of schizophrenia in the three-year period from 2015-2017, it would appear that the institute is abandoning the search for better drugs. The goal of finding better treatments for schizophrenia has been central to NIMH since it was created in the 1940s. Abandoning this goal represents a major departure. It also comes at a time when the pharmaceutical industry has markedly reduced research efforts to find better drugs for schizophrenia. One might have expected NIMH to have increased their efforts to offset the industry’s withdrawal, not to withdraw themselves.

The policy of phasing out new drug trials for schizophrenia is consistent with statements made by Dr. Joshua Gordon, the NIMH Director. The reason for this policy, according to Dr. Gordon, is the apparent failure of genetic research to identify any targets for drug development, as noted above.

Gordon also acknowledged that “neither genetic research nor the study of complex circuits was likely to produce new treatments any time soon... The path forward to better treatments in the short term,” according to Gordon, “is to use the treatments we have in a more efficacious way and to make them available to more people.”⁴

Dr. Gordon has been a strong supporter of genetic research, on which NIMH spent \$108 million in 2016, the most recent year for which data are available⁵. Such studies have shown the remarkable genetic diversity of schizophrenia, identifying more than 140 genes which increase risk for schizophrenia, mostly with small effect size. Such research has produced no practical targets for drug development for schizophrenia and, given the complexity of the genetic architecture of schizophrenia, is unlikely to do so in the foreseeable future. Thus to restrict schizophrenia drug development to genetic research means that no new drugs will be developed for an extended period of time.

Focusing exclusively on genetic research to identify new drugs for schizophrenia is a mistake. There are several alternative non-genetic targets for schizophrenia drug development, including the repurposing of promising drugs directed at immune pathways altered in schizophrenia.⁶⁻¹⁰ The role of these pathways in the pathogenesis of schizophrenia is supported by a range of genetic, neuropathologic, immunological and proteomic analyses, as well as recent studies documenting the importance of the immune system in brain functioning and development. Since many potential immune-based schizophrenia treatments involve compounds which are off-patent, and thus already available in relatively inexpensive generic versions, pharmaceutical companies will not undertake such drug development since it would not be profitable.

Studies supported by non-profit organizations have led to promising results in terms of symptom improvement in some individuals.¹¹ However, larger scale studies are necessary to define efficacy and to

identify individuals who would most benefit from this type of treatment. Such studies would also spur development of newer immune modulatory agents which might provide higher levels of efficacy, as has recently been the case for autoimmune disorders such as multiple sclerosis and systemic lupus.

Conclusion

The reality is that if NIMH will not support such research, it is unlikely to take place. Given the devastating toll that schizophrenia wreaks, such an abdication of responsibility is unconscionable. Those with schizophrenia, their families and the public at large are clamoring for breakthroughs to better treat this debilitating disorder. Psychiatric journals presently carry articles proclaiming “Anti-Inflammatories Offer Promise in Schizophrenia,”¹² but such promise is belied by NIMH’s failure to support such drug development.

Given the importance of schizophrenia and the need for new medications, it is unacceptable for NIMH to abandon efforts in this field. It is especially inexcusable at this time when NIMH has just received a large increase in its budget from Congress.

Moreover, with the pharmaceutical industry withdrawing from schizophrenia drug development, NIMH bears the responsibility for making this research area a major priority. Without new drugs deriving from studies of genetics and neuro-circuitry, drugs based on other pathways, such as those defining the immune system, needs to be pursued as the basis for clinical trials by the agency.

We urge Dr. Joshua Gordon to implement these policy recommendations immediately so that people with schizophrenia and their families can maintain hope that better medications essential to their treatment are being developed. Certainly, this critical objective – and millions of affected families – should not be neglected by the federal agency that, [according to its own website](#), is explicitly charged

with transforming “the understanding and treatment of mental illnesses through basic and clinical research” and “paving the way for prevention, recovery, and cure.”¹³

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