

It is illegal to post this copyrighted PDF on any website. NIMH Drug Trials for Schizophrenia

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Schizophrenia is one of the most important diseases in the United States both socially and economically; a study estimated its annual cost to be \$155.7 billion in 2013.¹ The major developers of new drugs for schizophrenia have been the pharmaceutical industry and the National Institute of Mental Health (NIMH). In recent years, the former have reduced their efforts to develop new schizophrenia drugs, in part because of the failure of genetic research to identify new targets for drug development.

To assess the number of treatment trials for schizophrenia for industry and NIMH, we examined all trials registered on ClinicalTrials.gov from 2005 to 2017.² The pharmaceutical industry funded 718 trials, with the number decreasing over time. In 2005–2007, they funded 218 trials, but in 2015–2017, only 90 trials, a decrease of 59%. During the same period, NIMH funded 166 trials, decreasing from 38 in 2005–2007 to 21 in 2015–2017, a reduction of 45%. However, when these 21 trials are examined, almost all utilized nonpharmacologic agents (eg, transcranial magnetic stimulation) or psychosocial interventions (eg, cognitive remediation). Thus, over the 3-year period 2015–2017, NIMH funded only 2 trials using a pharmacologic agent intended to improve the symptoms of schizophrenia.

The current NIMH policy for treatment trials requires the identification of specific biological targets for each trial. This policy was based on policies established by the previous Director of NIMH, Thomas Insel. At the 2017 International Conference on Schizophrenia Research, the current director, Joshua Gordon, indicated that individuals with schizophrenia and their families should not expect new drugs from NIMH. He acknowledged that neither genetic research nor the study of complex circuits was likely to produce new treatments anytime 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 make them available to more people.”³

We believe that restricting targets to genetics or neural circuits is too narrow a vision. Ironically, the

strongest genetic finding for schizophrenia to date, the major histocompatibility complex on chromosome 6, points to immunologic/inflammatory abnormalities. Neuropathological, clinical, and epidemiologic studies, as well as preliminary clinical trials, also point toward an altered immune system in schizophrenia.⁴ NIMH should undertake a major treatment initiative directed at the subset of individuals with evidence of immune activation, using as targets the normalization of the immune system. Since many potential immune-based schizophrenia treatments involve compounds that 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. Additional promising treatments for which targets are available include neurohormones such as estrogen and related selective estrogen receptor modulators⁵ and the use of probiotics and other agents to modulate the microbiome and the gut-brain axis.⁶ Some of these compounds also may be effective for bipolar disorder and major depression, especially for patients with psychotic features.⁷

Finding better drugs for schizophrenia has been a central goal for NIMH since it was created by Congress in 1946. There has been no significant pharmacologic advance for schizophrenia since clozapine was approved almost 30 years ago. Given the importance of this disease, it is unacceptable for NIMH to abandon efforts in this field, especially at this time when NIMH has received significant budget increases from Congress for each of the last 2 years.

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REFERENCES

1. Cloutier M, Aigbogun MS, Guerin A, et al. The economic burden of schizophrenia in the United States in 2013. *J Clin Psychiatry*. 2016;77(6):764–771.
2. Torrey EF, Yolken RH, Lamb HR, et al. Why NIMH should not stop drug trials for schizophrenia. Treatment Advocacy Center website. <http://www.treatmentadvocacycenter.org/storage/documents/why-nimh-should-not-stop-new-drug-trials-for-schizophrenia.pdf>. June 2018.
3. Heimer H. ICOSR 2017: The prospects for new drugs to treat schizophrenia. Schizophrenia Research Forum. <http://www.schizophreniaforum.org/news/icosr-2017-prospects-new-drugs-treat-schizophrenia>. April 5, 2017.
4. Müller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. *Schizophr Bull*. 2018;44(5):973–982.
5. Kulkarni J, Gavrilidis E, Wang W, et al. Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age. *Mol Psychiatry*. 2015;20(6):695–702.
6. Severance EG, Dickerson FB, Yolken RH. Autoimmune phenotypes in schizophrenia reveal novel treatment targets. *Pharmacol Ther*. 2018;189:184–198.
7. Dickerson F, Adamos M, Katsafanos E, et al. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: a randomized controlled trial. *Bipolar Disord*. 2018;20(7):614–621.

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