Schizophrenia Bulletin vol. 39 no. 3 pp. 481–482, 2013
doi:10.1093/schbul/sbt039
Advance Access publication March 13, 2013

EDITORIAL

SMRI Contributions to Drug Development for Schizophrenia and Bipolar Disorder

E. Fuller Torrey* and Jana C. Bowcut

Stanley Medical Research Institute, Chevy Chase, MD

*To whom correspondence should be addressed; Stanley Medical Research Institute, 8401 Connecticut Ave, Suite 200, Chevy Chase, MD 20815, US; tel: 301-571-2078, fax: 301-571-0775, e-mail: torreyf@stanleyresearch.org

Key words: schizophrenia/bipolar disorder/repurposed drugs/infectious agents/drug development

The development of better drugs for the treatment of schizophrenia and bipolar disorder has been the primary goal of the Stanley Medical Research Institute (SMRI) since its inception. The first SMRI treatment trial was funded in 1992, and since then, approximately 200 additional trials have been funded. The SMRI strategy has been to focus resources on approaches not being widely pursued by the National Institute of Mental Health (NIMH) or the pharmaceutical industry. Three main approaches have emerged: (1) repurposing drugs, (2) testing drugs targeting specific infectious agents that may be etiologically involved, and (3) using postmortem brain tissue to identify promising pathways for drug development. The total SMRI investment in these 3 approaches is now approximately $17 million per year.

1. *Repurposing drugs*: This strategy takes drugs approved for other diseases and tries them for psychiatric disorders, based on clinical observations or scientific theory. Given the fact that the antipsychotic chlorpromazine, the antidepressant iproniazid, and the antianxiety drug meprobamate were all initially discovered as repurposed drugs, this strategy for drug development has probably been underutilized. Thomas Insel, director of NIMH, recently noted that "it seems likely that progress in treatment development will come more from repurposing compounds than from developing new molecular entities." SMRI supports approximately 50 trials at any given time, mostly repurposed drugs used as add-ons to existing medications. All past and present trials are listed on the SMRI website www.stanleyresearch.org. Such trials have included a wide variety of over-the-counter preparations such as aspirin and vitamins; health food products such as curcumin and Chinese herbs; and drugs used to treat other conditions—eg, allopurinol for gout; hydroxychloroquine and artemether for malaria; ondansetron for nausea; and methotrexate for psoriasis and rheumatoid arthritis. SMRI has also supported a few nondrug trials such as those evaluating the effects of transcranial magnetic stimulation, magnetic seizure therapy, and probiotic supplements. We have supported relatively few trials of cognitive or behavioral therapy because this approach seems to have been adequately covered by NIMH.

Repurposed drugs for which SMRI has supported multiple trials and for which we have had some positive results include anti-inflammatories such as aspirin and cyclooxygenase (COX)-2 inhibitors; statins; estrogen and raloxifene; omega-3 fish oil; folate; pregnenolone; and valnoctamide.[1] The last drug is closely related to valproate and has been sold as an over-the-counter anxiety medication in Europe for many years. An initial SMRI study has reported it to be an effective mood stabilizer and subsequent animal studies have shown that it has a low risk of teratogenicity. We currently have a phase 2 study underway in hopes that valnactomide might be developed into an effective mood stabilizer for women with bipolar disorder, being less teratogenic than any mood stabilizers currently available. For selected drug trials, we have also recently begun collecting blood at the beginning and end of trials to see whether we can identify neurochemical, infectious, or immune predictors of drug response.

2. *Testing drugs targeting specific infectious agents that may be etiologically involved*: SMRI has had an ongoing research program on infectious agents interacting with predisposing genes as possible etiological agents for schizophrenia and bipolar disorder. It is thus of interest that some of the earliest drugs used in psychiatry were originally developed as drugs for infectious diseases, eg, chlorpromazine was originally developed as an antiprotozoal and anthelmintic, iproniazid as an antituberculosis drug, and meprobamate as an antibacterial agent.

We are currently conducting drug trials against 2 infectious agents of interest. Herpes simplex virus (HSV-1) has been shown in multiple studies to be associated with lower cognitive function in individuals

with schizophrenia and bipolar disorder as well as in individuals without a psychiatric diagnosis. Valacyclovir, an antiviral drug widely used for the suppression of HSV-1 and HSV-2, has been shown in a published report and another still-unpublished study to modestly improve cognitive function in individuals with schizophrenia and bipolar disorder and who have not been sick for many years and who have antibodies to HSV-1.[2] Two larger follow-up studies are in progress, assessing not only cognitive function but whether the improved cognitive function also improves the person's real life function.

Another infectious agent of interest is *Toxoplasma gondii,* a parasite that must complete its life cycle in felines. Antibody and epidemiological studies have suggested that exposure to this parasite may result in an increased risk of developing schizophrenia in some people. It is also of interest that some antipsychotics and mood stabilizers can inhibit the replication of this organism. Drugs currently available against *T. gondii* are relatively ineffective or toxic. Trials using relatively weak antitoxoplasmosis agents, such as trimethoprim–sulfamethoxazole and artemisinin derivatives, as adjunctive treatment have not demonstrated clinical efficacy in individuals with schizophrenia. SMRI has therefore contributed to the funding of the development of much more effective anti-*Toxoplasma* drugs, one of which has shown much promise in animal models and is being further developed for possible trials in humans. It appears to be the first drug that is effective against the cyst stage of *T. gondii*, and it is this stage that the organism commonly uses when it resides in brain tissue.

3. *Using postmortem brain tissue to identify promising pathways for drug development*: The SMRI postmortem brain collection has been widely used by researchers on schizophrenia and bipolar disorder. During the past 15 years, it has supplied tissue to 283 laboratories in 21 countries. Most of this tissue came from 2 matched cohorts: a Consortium Collection of 60 brains (15 each with schizophrenia, bipolar disorder, major depression, and normal controls) and an Array Collection of 105 brains (35 each with schizophrenia, bipolar disorder, and normal controls). As a condition for using this tissue, researchers must agree to send us their data, which are then added to a cumulative online database. For the Consortium Collection, this database now includes 2636 neuropathological and neurochemical markers from 12 different brain regions. Genetic data related to these same brains have been added, including 17 gene expression microarray data sets as well as genome-wide and individually genotyped data on single-nucleotide polymorphisms (SNPs). Next-generation sequencing (RNA–seq) is in process and will be available soon.

This collection of neuropathological, neurochemical, and genetic data for the same brains allows researchers to ascertain how genetic factors may interact with neuropathological and neurochemical factors to cause disease, thus identifying promising pathways that could be used for drug development. It is called the Stanley Neuropathology Consortium Integrative Database and its description has been published.[3] It is available online to everyone without charge at www.stanleyresearch.org. It is currently being used by almost 600 researchers, including many working with pharmaceutical and biotechnology companies.

In summary, the development of better drugs for treating schizophrenia and bipolar disorder should be a high priority for psychiatric research. These diseases not only have high morbidity and mortality, but they are also very-expensive-to-treat diseases. SMRI has contributed to these efforts for 20 years by supporting trials of repurposed drugs, focusing on infectious agents, and developing a neuropathology–gene database to identify pathways for drug development.

References

1. Torrey EF, Davis JM. Adjunct treatment for schizophrenia and bipolar disorder: what to try when you are out of ideas. *Clin Schizophr Relat Psychoses*. 2012;5:208–216.
2. Prasad KM, Eack SM, Keshavan MS, et al. Antiherpes virus-specific treatment and cognition in schizophrenia: a test-of-concept randomized double-blind placebo-controlled trial [published online ahead of print April 6, 2012]. *Schizophr Bull*. doi: 10.1093/schbul/sbs046.
3. Kim S, Webster MJ. The Stanley Neuropathology Consortium Integrative Database: a novel, web-based tool for exploring neuropathological markers in psychiatric disorders and the biological processes associated with abnormalities of those markers. *Neuropsychopharmacology*. 2010; 35:473–482.