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EDITORIAL

The Field of Schizophrenia: Strengths, Weaknesses, Opportunities, and Threats

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At the same time that this issue commemorates the seminal contributions of Eugene Bleuler, we are also confronted with a climate in which the lay press finds occasion to call into question the very real progress that has been made in the understanding and treatment of mental illnesses. A recent example is provided by Marcia Angell's 2-part contribution to the New York Review of Books.[1,2] Perhaps, in this context, it is a fitting time to step back and conduct a so-called SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis of the schizophrenia field.

The strengths of the field can be highlighted by the enormous investment in and globalization of research to better understand and treat this illness. For example, a recent Schizophrenia International Research Society Satellite meeting in Sao Paulo, Brazil, brought together over 450 investigators and clinicians and underscored the important work that is being done across South America and around the world. There are 3 valuable journals that focus on schizophrenia, and the Schizophrenia Research Forum has provided a very welcome platform to facilitate dialogue among investigators in this area.

The efficacy of the treatments that are used to manage schizophrenia is impressive from many perspectives and rivals thosein general medicine. In the acute treatment, second-generation antipsychotics increase the percentage of responders from 24% with placebo to 41% (absolute risk difference [ARD]=18%, relative risk [RR]=70% weighted), translating into a number-needed-to-treat (NNT) of 6, which is considered a medium effect size.[3] Antipsychotic maintenance treatment reduces relapse rates from 54% to 20% within approximately 10 months (ARD = 37% relative risk reduction [RRR] = 66% weighted).[4] This translates in an NNT of 3, which is considered a large effect size. Robinson et al[5] have shown that among first-episode patients, relapse rates were 5 times higher in those who discontinued medication as opposed to those who continued.

Although medications can be very helpful for positive symptoms (and to some extent negative symptoms), the ability of these drugs to ameliorate problems in cognitive functioning, motivation, social interactions, etc, are limited (though these domains are a focus of ongoing drug development). At the same time, the introduction of antipsychotic medications into clinical practice has enabled many individuals to lead meaningful lives in the community without the continual burden of psychotic symptoms. Nonadherence in medication taking is an enormous problem throughout medicine, but we have made progress in establishing psychosocial,[6] pharmacologic,[7,8] and technological[9] approaches to monitoring and facilitating adherence.

A common misconception is that a biological basis for an illness and the effectiveness of a pharmacologic treatment obviate the need for or desirability of ''talk'' therapies. This is far from the case, just as an experiential or environmental cause of a psychological or behavioral problem does not preclude the potential value of medication.

Strategies for combining psychosocial and pharmacologic treatment have increasingly been studied and recommended as essential ingredients of state-of-the-art care.[10] The funding of the recovery after an initial schizophrenia episode (RAISE)[11] project by National Institute of Mental Health (NIMH) was a major recognition of the potential importance of demonstrating the effects of enhanced and systematic, integrated, and specialized care for early phase schizophrenia patients in ''real-world'' community settings across the United States All treatments, however, should be the focus of empirical investigation and be ''evidence based.''[12] The Schizophrenia Patient Outcomes Research Team recommendations represent an attempt to review and summarize the current evidence regarding treatments for schizophrenia.[13–15]

Neuroimaging studies have provided evidence that brain structural abnormalities are present early in the course of schizophrenia prior to antipsychotic treatment and that individuals at risk for developing psychosis

demonstrate brain alterations during the transition to psychosis.[16–18] In addition, "follow back" data[19] indicate that cognitive deficits are evident as early as the first grade in individuals who are destined to go on to develop schizophrenia. It should also be pointed out that many such individuals demonstrate motor and sensory abnormalities before exposure to antipsychotic medications.[20,21] In this context, early recognition and prevention efforts during the prepsychotic symptom manifestation phase have already been fruitful,[22] so that the inclusion of an attenuated psychosis syndrome into *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) is being considered.[23]

There are also inherent weaknesses in our work that should be acknowledged. We still do not understand the etiology and pathophysiology of schizophrenia although this remains true of many major illnesses in general medicine as well. The emphasis of the recent Research Domain Criteria (RDoC) initiative by the NIMH[24,25] on the need to develop a nosological system that better reflects basic disease mechanisms is a laudable and necessary goal. The apparent overlap among a variety of disorders in genetics, intermediate phenotypes, and response to pharmacologic agents underscores this need. At the same time, we should not lose sight of the fact that the DSM-IV diagnosis of schizophrenia has not only excellent reliability in the hands of trained clinicians but also ample validity on which to base many critical medical decisions. Although we have not identified, the specific "lesion" that is also true of many other diseases in medicine and does not preclude the application of a variety of other validating criteria, such as course and prognosis as well as genetic, neuropsychologic, neurophysiologic, neuroimaging, and neuropharmacologic studies. The same need remains for further identifying biological mechanisms and predictors of treatment response that would enable true personalization of care.

Medications that have powerful effects are likely to have clinically significant side effects. Antipsychotic medications were initially associated with a variety of movement disorders, some acute, some chronic, and some at times irreversible but all troublesome. Although the risk of these adverse effects has been reduced substantially[26] (and some patients with schizophrenia as well as unaffected family members have been found to have movement disorders prior to receiving medication[27–29]), we have now confronted another challenge in that some of the medications, which are most benign in terms of motor side effects are now associated with metabolic adverse effects, which can increase long-term health risks.[30] In addition, given the effects of antipsychotic drugs on nerve cells and neurotransmission in the brain, concern has been raised as to their long-term effects on brain morphology. Although some studies have linked changes in brain morphology with chronic treatment,[31] others have demonstrated that such changes occur to a greater extent, the longer someone remains psychotic.[32] Research also suggests that among chronic patients, a progression in gray matter loss appears to be related to an increased number of psychotic episodes, with atypical antipsychotic drugs attenuating these changes.[33]

There is no doubt that antipsychotic drugs have been widely and increasingly used in a variety of disorders other than schizophrenia. Some of this use is no doubt inappropriate or shortsighted, yet a good deal of it is likely thoughtful and well intentioned. Where inappropriate marketing has contributed to misuse, this should be curtailed, but we also must rely on physician education to facilitate the most judicious use of medications, even in situations of considerable uncertainty. And most importantly, the relative/comparative effectiveness of different treatment approaches should be the focus of carefully controlled research for which additional funding needs to be made available.

There are incredible opportunities that lie ahead of us, and as is always the case in the history of science, to some extent these are unimaginable. The developments in unrelated disciples including physics, chemistry, and microbiology or communication, computation, and nanotechnology will have a profound effect on our ability to make progress in understanding the extraordinary organ that we call the brain and the things that influence its functioning as well as developing new treatments and new delivery methods. The only thing that will hold us back is inadequate capital, both human and economic, or insufficient determination.

When we turn to threats, we face some of the most daunting challenges. Despite the efforts and progress referred to previously, psychiatry in general remains the focus of considerable controversy, misunderstanding, and even attack. The validity of psychiatric diagnosis and the DSM process is the focus of criticism because we have not identified the lesions, the diagnostic process depends upon "soft" subjective phenomena, and our diseases lack clear-cut boundaries and are often very heterogeneous in onset, course, treatment response, and outcome. Clearly, enormous efforts are under way to improve this situation, but at the same time, we should not lose sight of the fact that these concerns are evident in many other diseases across medicine. In addition, the brain is by far the most complex organ and is not directly accessible for biopsy, while animal models are difficult to develop for complex and interactive emotional, behavioral, and cognitive processes.

Some critics go so far as to say that psychiatric illnesses are myths (an argument that we have heard before) and are at least partially the creation of the psychiatric community looking for additional patients and the pharmaceutical industry seeking to sell more medications.[1,2] We need to remind our critics of the relative consistency in the prevalence of schizophrenia worldwide, from the developing to the highly developed countries, where the presence of psychiatrists and pharmaceutical company

"marketing" varies enormously. Even more importantly is the high heritability of illnesses like schizophrenia and many other psychiatric disorders. Though the genetic findings are complex and raise additional questions, they make it very difficult to dismiss the validity of such diagnoses. And, of course, in the final analysis, it is the tremendous personal suffering, family burden, and loss of human potential that is so striking and so palpable to anyone who knows, loves, or works with any individual afflicted with such an illness.

There is no doubt that there have been missteps, overreaches, conflicts of interest, missed opportunities, inappropriate marketing, shoddy diagnoses, sociopolitical conflicts, and every imaginable type of human frailty. But what is required is honest and well-meaning debate, reflection, collaboration, and most importantly, more research done by well-trained investigators all over the world, whether in academia, in the pharmaceutical and biotech industries, or in federal and state agencies and foundations.

Ironically, one of the greatest current threats to schizophrenia research and the development of new treatments is the withdrawal of a number of major pharmaceutical companies from a broad-based commitment to central nervous system research. Though considerable progress has been made through worldwide grass roots, political and educational efforts to increase public awareness and understanding, reduce stigma, and increase funding and services for people with chronic and severe mental illness, much remains to be done. Articles such as that published in the New York Review[1,2] by a distinguished academic medical scholar force us to acknowledge how deep the misunderstanding can be when we see a statement such as "whereas conditions such as schizophrenia and depression were once mainly self-limited or episodic, with each episode usually lasting no more than 6 months and interspersed with long periods of normalcy, the conditions are now chronic and lifelong." To give emphasis to the false proposition that schizophrenia involves mostly periods of normalcy except for the iatrogenic induction of chronicity is inconsistent with scientific evidence in the post-antipsychotic drug era and incompatible with all of the descriptive longitudinal studies in the pre-antipsychotic medication era. This underscores how much remains to be done to educate not just the lay public but also our colleagues in other branches of medicine.

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