Targeting Schizophrenia Research to Patient Outcomes

Mental disorders represent four of the top 10 categories of disease disability worldwide. In schizophrenia this disability is clearly evident in employment. In this issue of the *Journal,* Rosenheck and colleagues report analyses of data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, which involved more than 1,400 patient participants and gathered clinical, neuropsychological, quality of life, sociodemographic, psychosocial services, and employment information. The finding that barriers to employment range from clinical to social gives emphasis to the breadth of factors required in a medical model purporting to account for effects of illness and treatment on patients' lives.

"The biopsychosocial medical model . . . points to the importance of understanding cognitive pathology at all levels of the human system."

For example, CATIE results are a discouraging reminder that race plays a substantial role in so many aspects of our society; in this instance, being black compounds the negative effect of schizophrenia on competitive employment. Receipt of disability payments also has a negative effect on competitive employment, challenging social policy experts to devise a system that protects the provision of financial support for disabled individuals while avoiding disincentives for work accomplishment. The finding that the availability of psychosocial rehabilitation services increases the probability that an individual will find work is another call for policy action on the organization and delivery of mental health services. The effectiveness of supported employment and other vocational services has been documented (1), but most people with schizophrenia are treated in settings that do not offer these services. It is a shame that psychiatry has not been more aggressive in implementing these services and more successful in winning resources to support this vital element of care.

Other findings from the Rosenheck et al. study have direct implications for clinical care. Level of education is a predictor of work success. The early manifestations of a psychotic illness often occur during school years, but clinical intervention usually occurs months to years later. Earlier detection and intervention may facilitate educational achievement and provide a stronger base for patients' future accomplishment. Severity of symptoms and cognitive impairments is associated with vocational outcome. This finding calls for optimal symptom management, integrating psychosocial and pharmacologic treatments with documented effectiveness. Finding the drug and dose that minimize adverse effects on cognition, drive, motivation, affect, and movement is critical. With first-generation antipsychotic drugs, optimal risk-benefit ratios are usually found at doses substantially lower than those used in practice. Second-generation drugs tend to be more benign for these adverse effects, but serious metabolic effects should limit the use of some of these newer drugs. Adherence is a major problem with all the drugs, and relapse prevention is important for sustaining employment. Long-acting depot administration is underused in the United States and should not be stigmatized by reserving this treatment for the most difficult cases.

Rosenheck et al. also found that primary negative symptoms, as reflected in the intrapsychic functions assessed with the Quality of Life Scale, relate to work function, giving emphasis to this pathologic domain as an unmet treatment need in schizophrenia.

Cognitive capacity, measured by performance on neuropsychological tests, is related

to many aspects of function in everyday life. Most individuals with schizophrenia have impaired cognition, often moderate and sometimes severe. The relationship between neuropsychological capacity and functional outcome in schizophrenia is robust (2). We know less, however, about how this effect is mediated. Bowie et al., in another article in this issue of the *Journal,* replicate the observation of impaired neuropsychological performance and its modest relationship to negative symptoms and negligible relationship to positive symptoms and depression. The relationship of cognition to laboratory measures of functioning skills is robust, but the critical issue is how cognition affects real-life work, activities, and interpersonal functioning. Bowie et al. found that the effect of cognition on work and interpersonal function is indirect, mediated through an effect on functional skills. This is also the case with social activities, but here a direct effect is also observed. Some time ago (3), we reported that positive symptoms did not predict work and social function but that negative symptoms were more closely related to these outcomes. In the Bowie et al. study, a more precise result is reported. Positive symptoms did not have a significant direct effect on the three real-life functions, but negative symptoms did have a fairly robust effect on interpersonal function, and depression had a modest direct effect on all three functions.

The work of Bowie et al. has implications for improving functional outcomes. Identifying and treating depression and secondary negative symptoms is important. The field needs to discover efficacious treatment for primary negative symptoms. Regarding impaired cognition, functional skills as measured in the laboratory are closer to real-life outcomes and may be inviting targets for therapeutic intervention. This may involve restorative as well as compensatory treatments, although Bellack (4) has argued that the latter is likely to be more effective. Bowie et al. note the indirect effect of cognition on real-life function and caution that therapeutic advances that affect cognition per se may have limited effects on functional outcomes. This is a special concern in schizophrenia, where the impairments are long-term traits influencing development and adaptation years before psychosis is manifest. Nonetheless, a leading challenge in brain research is the discovery of treatments efficacious for cognition. First-generation antipsychotic medications, especially when used in substantial doses, impair cognition. Second-generation antipsychotic drugs have a reduced liability in this regard. But the field is still challenged to discover treatments with procognitive efficacy. The National Institute of Mental Health (NIMH) MATRICS process has made this a top priority, bringing together industry, the U.S. Food and Drug Administration (FDA), academic scientists, and NIMH with impressive progress. The FDA appears ready to grant an indication for a drug with cognition efficacy but will require evidence that the change in neuropsychological test performance results in a meaningful improvement for the person. Laboratory measures of function will be informative in this regard, but it has not yet been determined if a change in laboratory function will predict a change in real-life functioning. This issue of a clinical co-primary endpoint is addressed in an article by Keefe and colleagues in this issue of the *Journal.*

Clinical and research discussions often confound impairments assessed by means of neuropsychological tests with clinical observations of problems in attention, concentration, disorganized thought, and the like. For example, clinically observed problems in attention may have little to do with the ability to recognize degraded stimuli in a continuous performance task. Physicians can observe changes in memory function as a patient moves from normal to mild cognitive impairment to severe memory loss in dementia. But "normal" in this case is defined by the individual's life-long "usual" state. With cognitive deficits arising early in development and remaining stable, it is difficult to distinguish impaired cognition from the individual's natural capacity. Keefe and colleagues have taken a major first step in developing a clinical assessment approach for impaired cognition applicable in nondementing disorders. This is critical for two reasons. First, this domain of psychopathology has little to no correlation with most symptom domains

and only a modest relationship with negative symptoms; symptom assessment, therefore, is not a proxy for cognition. Second, if we use a treatment for impaired cognition, clinicians need to assess its effectiveness in individual cases. Clinical observation would be a valuable addition to neuropsychological testing and might substitute for formal testing in determining whether a treatment is effective. The FDA will be appropriately concerned with approving a drug without a sure method for the physician to determine the effect in each patient. Keefe et al. propose a method that captures real-life functioning in the assessment. As such, this may be the approach to the co-primary endpoint in clinical trials that is critical to winning a cognition indication.

This editorial highlights reports of three schizophrenia studies in this month's *Journal,* all of which grapple with the issue of improving real-world functional outcome for people who have schizophrenia. The lessons are also meaningful in other disorders where impaired cognition causes poor functional outcomes. The data from these studies are drawn from several levels of the human system and cannot be adequately addressed in a narrow disease model. The biopsychosocial medical model (5) is well suited for the integration of these data and points to the importance of understanding cognitive pathology at all levels of the human system. Cameron Carter addresses reports that examine cognition at the interface of neural systems and clinical manifestations in an accompanying editorial.

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