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Treatment-Refractory Schizophrenia: A Clinical Conundrum

edited by Peter F. Buckley and Fiona Gaughran. Springer, New York, NY, 2014, 230 pages, \$59.99 (hardcover).

Schizophrenia is arguably the most complex, heterogeneous, and disabling neuropsychiatric syndrome, with multiple symptom clusters. The 2 generations of pharmacologic agents used for the treatment of schizophrenia are called *antipsychotics* for a good reason, because all they treat are the *psychotic* symptoms such as delusions, hallucinations, and bizarre behavior. The subtype of patients whose psychotic symptoms fail to respond to these agents carries the label *treatment refractory*. However, what is often overlooked is the fact that cognitive deficits and negative symptoms, which are the real reasons for functional disability in schizophrenia, have no treatment and persist even after the psychotic symptoms are controlled. Thus, *all* patients with schizophrenia are *technically* treatment refractory, even those whose psychotic symptoms improve substantially.

This book is an excellent collection of chapters that collectively comprise the clinical and scientific knowledge base about refractory schizophrenia. They cover a comprehensive array of topics ranging across clinical assessment, biology, neurochemistry, medical and psychiatric comorbidities, the unique therapeutic role of clozapine, emerging neuromodulation therapies, psychosocial approaches, pharmacogenomics, family interventions, and the off-label approaches to the desperate subset of clozapine nonresponders.

For psychiatric practitioners, both prescribers and therapists, who manage schizophrenia on a daily basis, this book is a must-own reference because of the wealth of helpful information between the covers. After reading the book, I offer the following comments:

1. There is some overlap between some chapters (such as describing the many side effects of clozapine or the possible adjunctive therapies when clozapine fails). However, such issues are worth repeating.
2. The early use of clozapine in first-episode nonresponders deserves more mention.
3. Can the refractory subtype be identified much earlier in the illness instead of after multiple failed treatments and years of prolonged suffering?
4. The title of chapter 9 should have used the term *cognitive remediation* (which is a more widely used term than *cognitive therapies*).
5. A chapter about the refractory *primary* cognitive and negative symptoms and the various attempts to improve

them, also addressing the reversible *secondary* cognitive impairments and negative symptoms, would have been welcome.

6. I wish the term *client* was avoided, because schizophrenia is as devastating a medical illness as cancer or heart attacks. Does anyone refer to oncology and myocardial infarction patients as “clients”?
7. Cognitive-behavioral therapy and family interventions are rarely used for treating schizophrenia, so exposing clinicians to them is very useful.
8. A discussion of “spurious” refractoriness resulting from causes such as treatment nonadherence, ongoing substance use, pharmacokinetic factors such as cytochrome induction, or partial absorption due to the failure to take certain antipsychotics with food would have been valuable in helping clinicians avoid resorting prematurely to clozapine, with its serious metabolic and nonmetabolic complications.
9. Chapter 12 on pharmacotherapy is extremely valuable, especially the discussion of the emergence of biomarkers to predict outcomes such as response, the adequacy of a small dose, or the risk of diabetes.
10. Clozapine can be useful in several refractory disorders other than schizophrenia, such as bipolar disorder, borderline personality disorder, and tardive dyskinesia, and a brief review of those would have provided another dimension, in that refractoriness has a common response to the same drug (clozapine).
11. Finally, elaborating on the glutamatergic pathways as key in nondopaminergic, refractory schizophrenia and the glutamate modulatory effects of clozapine would have provided a nice update of future approaches in schizophrenia and a reminder of the diversity of etiologic pathophysiologies in the schizophrenia syndrome.

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