

Bridging the Efficacy-Effectiveness Gap in the Antipsychotic Treatment of Schizophrenia: Back to the Basics

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The primary objectives in the treatment of schizophrenia are to reduce the frequency and severity of psychotic exacerbations, ameliorate a broad range of symptoms, and improve functional capacity. Antipsychotic medications are the cornerstone of the pharmacologic treatment of schizophrenia. Despite the use of these agents for 60 years, however, schizophrenia continues to significantly limit the quality of life of a majority of affected individuals. Although this partially reflects the limitations of existing agents,^{1,2} our failure to maximize the benefits of the agents we have and optimally individualize treatment contributes significantly to the poor outcomes of many of our patients.³ An adequate knowledge of the following 3 basic sets of facts and their diligent application to treatment decisions for each patient with schizophrenia can enable optimal use of antipsychotic medications to help individuals lead maximally productive and meaningful lives:

1. What are the pathophysiology and clinical nature of schizophrenia? Exactly what are the targets of treatment?
2. What do antipsychotics do? How do different antipsychotics compare in terms of efficacy, adverse effects, and ease of use?
3. Given the above sets of facts, what are the keys to optimizing antipsychotic treatment in individual patients with schizophrenia?

Nature of Schizophrenia

Schizophrenia is a chronic remitting and relapsing psychotic disorder with significant impairments in social and vocational functioning, multiple psychiatric and medical comorbidities, and increased mortality.⁴ Relapses are associated with adverse short- and long-term sequelae, and remissions are generally incomplete. Schizophrenia is characterized by positive symptoms, disorganization, negative symptoms, cognitive deficits, and mood and motor symptoms, with the types and severity of symptoms differing among patients and over the course of the illness.⁵ The pathophysiology of the illness is still poorly understood, necessitating empirical treatments.⁶ Goals of treatment thus include treatment of acute psychotic exacerbations,

relapse prevention, and amelioration of a broad range of symptoms, including positive, negative, cognitive, and mood symptoms.

What We Know About Antipsychotics in the Treatment of Schizophrenia

There are 65 antipsychotic medications utilized across the world (18 are available in the United States). They are classified into 2 groups: first-generation antipsychotics (FGAs), of which there are 51, and second-generation antipsychotics (SGAs), of which there are 14 (8 FGAs and 10 SGAs are available in the United States).⁷ While all 65 agents are available in an oral formulation, 13 are available as short-acting injectable preparations, and 11 are available as long-acting injectable preparations. Antipsychotics are effective in both treating the acute psychotic episode and preventing relapses.⁸ Both FGAs and SGAs are effective in reducing positive and disorganization symptoms but are only minimally effective for negative and cognitive symptoms, which contribute significantly to the disability associated with schizophrenia.⁹ There are no consistent differences in efficacy among antipsychotic agents, except for the superior efficacy of clozapine in treating positive symptoms and disorganization in otherwise antipsychotic-refractory schizophrenia patients.^{10,11} Although SGAs were all initially believed to be more efficacious and tolerable than FGAs, results of large-scale studies (such as the Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE]) indicate that the SGAs are no more effective than FGAs.^{12,13}

In contrast to their efficacy in treating disorganization and positive symptoms, antipsychotics are less effective in reducing negative, cognitive, and mood symptoms. Much of their beneficial effect on these symptoms is associated with reduction in positive symptoms. While antipsychotics ameliorate these symptoms linked with improvement in positive symptoms, they worsen these symptoms in association with extrapyramidal symptoms (EPS; parkinsonian negative symptoms, "neuroleptic dysphoria," bradyphrenia). The net effect of an antipsychotic on these (negative, cognitive, and depressive) symptoms is therefore determined by the extent to which it reduces the symptoms associated with positive symptoms versus triggering the symptoms related to EPS. Therefore, avoiding EPS without the use of anticholinergic agents while achieving a robust antipsychotic effect is the goal of antipsychotic therapy in schizophrenia. Since medication nonadherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates.¹⁴

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Antipsychotic medications cause a range of neurologic, metabolic, cardiovascular, gastrointestinal, hematologic, genitourinary, musculoskeletal, endocrine, and other side effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their adverse effect profiles. Compared with FGAs, the SGAs were believed to have a lower risk of EPS but a higher risk of metabolic adverse effects. However, due to differences in pharmacologic profiles, there is substantial variation *within* the FGA and SGA classes in their propensity to cause EPS and metabolic adverse effects. Thus, no categorical distinction can be made between so-called FGAs and SGAs even with regard to these risks.^{15,16} Antipsychotic medications also differ in their propensity to cause other side effects, such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and related sexual dysfunction, and anticholinergic effects. There is substantial variation within both the FGA and SGA classes for each of these effects, with no definitive categorical separation between the 2 classes. The side effects with different agents also depend on the patients with schizophrenia, who vary in their vulnerability to develop various adverse effects. Therefore, the likelihood that a patient will develop a particular side effect depends on the agent selected, how that agent is used (eg, dose, titration method, the other agents used in combination with the antipsychotics), and the patient's vulnerability.

Optimizing Individual Outcomes

Given the significant variability in drug pharmacokinetics and treatment response in individual patients, it should be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in individual patients. It is not currently possible to predict which antipsychotic may be optimal for a given patient. There is no single best agent or best dose for all patients, although dose ranges for optimal effectiveness do appear to exist. Decisions about antipsychotic therapy therefore often entail a trial-and-error process involving careful monitoring of response and adverse effects, an ongoing risk-benefit assessment, and judicious switching if necessary. Measuring the full impact (benefit-to-risk ratio) of individual treatments in each patient by the practice of measurement-based care in conjunction with a protocol-based approach to such measurement is essential. A number of simple scales exist to facilitate such measurement.^{17,18} Additionally, the clinician-patient dyad should engage in collaborative and informed decision-making on an ongoing basis, evaluating needs and preferences, measured effects of current treatments, and available treatment options at each stage.

To achieve optimal therapy for schizophrenia, clinicians must balance efficacy, risks, and benefits of treatments in a way that is customized for the needs and vulnerabilities of the individual patient. Thoughtful, measurement-based care can reduce the significant gap between what we know about

best practices and the therapy that is actually provided for patients with schizophrenia.¹⁹ Collectively, we can do much to better utilize existing treatments to optimize individual outcomes and reduce the considerable morbidity and mortality associated with the illness.

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