# Advantages and Limitations of Newer Antipsychotics: Evidence from Large Comparative Trials

For over fifty years, antipsychotic medications have represented a cornerstone of the therapeutic armamentarium for schizophrenia. Dopamine receptor antagonists can often reduce and sometimes eliminate the debilitating effects of hallucinations, delusions and disorganized thoughts and behavior, especially early in the course of schizophrenia. However, many patients relapse and begin to experience persistent psychotic symptoms despite optimized antipsychotic therapy. Additionally, patients are often burdened with treatment-related side effects that range from unpleasant to life-threatening. Large comparative trials across first-generation antipsychotics (FGAs)—relatively selective dopamine D2 receptor antagonists—and second-generation antipsychotics (SGAs)—mixed serotonin/dopamine receptor antagonists—have increasingly refuted the long-held suggestion that SGAs as a class hold an inherent efficacy advantage over FGAs. Furthermore, after twenty years on the U.S. market, clozapine still claims uncontested superiority in treatment-refractory schizophrenia despite intense efforts to develop new "clozapine-like" antipsychotics. And, while non-clozapine SGAs were widely touted as possessing more benign side-effect profiles than FGAs, comparative studies have demonstrated that, although SGAs generally produce fewer neurological side effects, they often produce considerable weight gain and dysregulation of glucose and lipid control. The accompanying three articles provide practical insights on the advantages and limitations of FDA-approved antipsychotic treatments in adults with schizophrenia, ranging from individuals with first-episode psychosis to chronic "treatment-responsive" illness to those with treatment-refractory schizophrenia.

*Taken together, these three articles highlight the valuable data emerging from recent clinical trials to help guide clinicians in the treatment of schizophrenia and related disorders.*

Drs. Freudenreich and McEvoy review the results of large, randomized treatment trials in first-episode schizophrenia. Although prescriptions of FGAs in first-episode schizophrenia have declined considerably in favor of SGAs, the authors highlight the absence of a clear-cut advantage in efficacy for SGAs over FGAs. While most FGA-to-SGA comparative studies have used haloperidol as the FGA comparator, the authors argue that mid-potency FGAs, when dosed judiciously, can limit both extrapyramidal side effects (EPS) and reduce the risk of cardiometabolic side effects often associated with SGAs. The EUFEST study in adults with first-episode schizophrenia highlights the risk of weight gain associated with FGAs and SGAs (1). The authors recommend a pragmatic treatment approach for first-episode patients, based on the premise that the best treatment for an individual patient can only be identified through open and honest sharing of information by both patient and clinician and that the process is necessarily exploratory and iterative. Long-acting injectable antipsychotics should be considered early in the course of treatment if nonadherence is identified (2). Likewise, clozapine should be considered early rather than late, given the importance of avoiding progressive functional deterioration and of optimizing long-term outcome.

Drs. Miyake, Miyamoto and Jarskog review the evidence for progress in antipsychotic drug development as new SGAs continue to come to market. Clozapine set a new bar for antipsychotic drug efficacy when it was introduced in 1990. Since then, eight additional antipsychotics have been approved, all following the same basic serotonin-dopamine antagonist model. That these agents are effective antipsychotics is not disputed, but more recent effectiveness studies such as CATIE (3) and CUtLASS (4) have generally provided sobering results, indicating that SGAs as a class do not have clear-cut benefits over judiciously dosed FGAs. In addition, larger, well-designed comparative trials of new agents generally lag their market introduction by many years. The authors consider aripiprazole, paliperidone, asenapine, iloperidone and lurasidone in this review of the pharmacological properties, efficacy and safety of the more recently introduced SGAs and how published data on these agents may be used to judge progress in antipsychotic drug development. With advances generally limited to aspects of

tolerability, this paper highlights: 1) the need for long-term trials with appropriate FGA and SGA comparators to establish the relative merits of the newer SGAs; and, 2) with the qualified exception of aripiprazole, the continued reiteration of the serotonin-dopamine antagonist mechanism in the newest antipsychotics sows doubt that meaningful benefit beyond that provided by more established therapies can or should be expected.

Dr. Meltzer provides a compelling case for why clozapine remains the antipsychotic of choice for many patients with treatment-refractory psychosis and also sheds light on why clozapine remains dramatically underused, especially in the U.S. Agranulocytosis and myocarditis represent the most serious and potentially life-threatening side effects of clozapine. Clozapine is also associated with a high rate of weight gain, hyperlipidemia, diabetes mellitus and an increased risk of seizures. The highest incidence of the most serious "non-metabolic" side effects is during the first 3–6 months of clozapine treatment and specific monitoring practices can help minimize these risks. The increased risk for metabolic dysregulation may persist indefinitely, but the adverse impact on health outcome can often be attenuated through regular monitoring of metabolic indices together with encouraging active and healthy lifestyles and consideration of potential adjunctive therapies such as metformin or topiramate for weight gain (5), as well as use of established treatments for emergent hypercholesterolemia, hypertriglyceridemia and diabetes mellitus. Importantly, beyond treatment-refractory psychosis, clozapine has also been found to reduce the risk of suicide and is often effective for reducing involuntary muscle movements in tardive dyskinesia.

Taken together, these articles highlight data that have emerged from recent clinical trials to help guide clinicians in the treatment of schizophrenia and related disorders. Large comparative trials have demonstrated comparable efficacy for FGAs and SGAs alike for positive symptoms and different, yet burdensome, side effects are associated with both classes. Importantly, comparative efficacy data are generally lacking for the more recently introduced SGAs and enthusiasm for their purported advantages should be tempered until such data become available. Negative symptoms and cognitive deficits represent major determinants of global functioning that remain inadequately treated by all available antipsychotics. Furthermore, no FGA or SGA can match the unique efficacy of clozapine in patients with treatment-refractory psychosis and its use should be encouraged. Until more effective treatments become available, psychiatrists will serve their patients with schizophrenia best by engaging them openly and honestly in the decision-making process regarding the risks and benefits of currently available treatments. It is also clear that more effective use of established medications and therapeutic approaches is both possible and desirable.

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## References


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