Balancing Therapeutic Safety and Efficacy to Improve Clinical and Economic Outcomes in Schizophrenia: Exploring the Treatment Landscape

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Abstract

Schizophrenia is a chronic, often debilitating illness that is associated with progressive cognitive and functional decline, and which requires lifelong pharmacologic and nonpharmacologic treatments for effective disease management. In an effort to provide the optimal overall care for patients with schizophrenia, careful consideration of the risks and benefits must be incorporated into treatment decisions. While much debate continues regarding whether newer second-generation (ie, "atypical") antipsychotics are superior to first-generation (ie, "typical") agents in the treatment of schizophrenia, it remains paramount that clinicians consider both the unique adverse effect profile of each medication and the clinical characteristics of individual patients that may influence the risk for specific adverse effects or treatment nonadherence. Perhaps the most important component of critical care for patients with schizophrenia is the monitoring for and management of cardiovascular and metabolic disorders, as they are key contributors to premature mortality in schizophrenia. Despite advances in nonpharmacologic treatments and ongoing drug development, antipsychotic medications remain the standard of care for the core symptoms of schizophrenia. There is a need for meticulous primary care in patients with schizophrenia, and optimal treatment of this complex disease should involve an integrative approach that combines psychosocial, educational, and pharmacologic management.

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When treating patients with schizophrenia, the overarching goals are to alleviate acute symptoms, maximize quality of life and functioning, and maintain recovery from acute illness.[1] Optimal treatment should involve an integrative approach that combines psychosocial, educational, and pharmacologic management. This article discusses the overall management of schizophrenia, including recommendations from practice guidelines, results of important clinical trials, factors involved in choosing an appropriate antipsychotic agent, and issues involved in managing drug side effects.

Pharmacologic Treatment

Antipsychotic medications are the mainstay of schizophrenia drug treatment. All of the antipsychotics are thought to work, at least in part, through actions on the dopamine type 2 (D_2) receptors, and these agents have traditionally been categorized into first-generation or second-generation groupings.[2] The first-generation antipsychotics (FGAs), previously referred to as "typical" antipsychotics, are thought to work almost exclusively through D_2 antagonism. It has been demonstrated that 65% to 70% occupancy at D_2 receptors is associated with an antipsychotic response, whereas 80% occupancy and higher is associated with extrapyramidal symptoms (EPSs), such as dystonia, psuedoparkinsonism, akathisia, and tardive dyskinesia.[2] Due to their strong affinity for the D_2 receptor, FGAs have a significant risk of side effects even at the lowest possible therapeutic dose. Haloperidol and fluphenazine are the FGAs with the most potent affinity for the D_2 receptor. The FGAs that are associated with somewhat lower rates of EPSs are those with less potency at the D_2 receptor and more anticholinergic receptor affinity, such as chlorpromazine and thioridazine (**Table 1**[3,4]). Although these differences in receptor affinities lower the risk of EPSs, they also increase the risk of sedation and secondary cognitive impairment.

The second-generation antipsychotics (SGAs), also termed "atypical" antipsychotics, have more potent antagonism at serotonin type-2A ($5\text{-}HT_{2A}$) receptors, and reduced binding affinity for D_2 receptors, which is thought to reduce (but not eliminate) the risk of EPSs and prolactin elevation.[2] However, many SGAs have turned out to have a high potential for metabolic adverse effects, such as weight gain, lipid abnormalities, glucose abnormalities, and even diabetes; although the exact metabolic risk profile varies from agent to agent (Table 2[3,5-7]).

Place of Antipsychotics in Schizophrenia Therapy

One of the major focuses of schizophrenia research over the past decade has been to examine the relative treatment benefits of each generation of antipsychotics. Results from several landmark clinical trials have been published during this time, the largest of which was funded by the National Institute of Mental Health. This trial, one of a series referred to as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), compared rates of all-cause discontinuation in 1432 patients treated with either an SGA (ie, olanzapine, quetiapine, risperidone, or ziprasidone) or the FGA perphenazine. Olanzapine showed a longer time to discontinuation for any reason compared with the other antipsychotics (9.2 months for olanzapine vs 3.5-5.6 months for the others); however, this difference was not significant when compared with perphenazine alone. Perphenazine showed effectiveness comparable to that of the other SGAs used in the study. Patients with schizophrenia treated with olanzapine experienced higher rates of clinically significant weight gain (≥7% of body weight) compared with the other antipsychotics (30% with olanzapine vs 7% with ziprasidone, 12% with perphenazine, 14% with risperidone, and 16% with quetiapine; P <.001) and had greater increases in glycated hemoglobin (A1C), total cholesterol, and triglycerides. Other adverse effects seen were generally consistent with those observed in clinical practice. Risperidone was associated with the greatest increase in prolactin (P <.001) and perphenazine had the highest rate of discontinuation due to EPSs (P = .002), although there were no significant differences in the rates of EPSs between the different treatment groups.[8] Another trial with a similar goal to CATIE was the European Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). This trial examined improvement in quality of life as measured by the Quality of Life Scale (QLS) in 185 patients who were treated over a period of 1 year with either an FGA or an SGA. No significant difference was observed in the primary outcome (QLS) in either treatment arm, nor in any of the secondary outcomes, including symptom improvement, treatment adherence, attitudes toward medication, or extrapyramidal side effects.[9]

Similar studies were completed in patients with schizophrenia who were experiencing their first episode of psychosis (FEP). The European First Episode Schizophrenia Trial (EUFEST) examined 498 such patients over 1 year of randomized treatment with haloperidol, amisulpride (an SGA not approved in the United States), olanzapine, quetiapine, or ziprasidone. More patients discontinued haloperidol for any reason than the other antipsychotics (72% vs 40% for amisulpride, 33% for olanzapine, 53% for quetiapine, and 45% for ziprasidone; P <.001). There were no differences in symptom improvement or rates of hospital admission between the treatment groups. Patients treated with haloperidol experienced the most EPSs, and patients treated with olanzapine experienced the most weight gain.[10] In the Comparison of Atypicals for First Episode Schizophrenia (CAFE) trial, patients treated with either olanzapine, quetiapine, or risperidone had similar all-cause discontinuation rates at 1 year, no differences in overall symptom severity measures, and side effects similar to those seen in other trials.[11]

Prior to these clinical trials, most practice guidelines unequivocally recommended the use of an SGA as a first-line agent for most patients with schizophrenia due to the lower risk of EPSs and the perceived enhanced efficacy.[12,13] Given the comparable effectiveness of FGAs seen in recent trials, and the concern about metabolic adverse effects with SGAs, current guidelines favor SGAs less enthusiastically, and encourage a careful risk/benefit analysis for each individual patient (Table 3).[1,4,14-18] Ideally, factors such as patient preference, prior treatment response, side effect profile, medical history and risk factors, and adherence history would be taken into consideration when selecting an appropriate antipsychotic.[1,4,17] In patients with schizophrenia experiencing their FEP, the SGAs are generally preferred for initial treatment.[1,14-16]

■ **Table 1.** Relative Potency and EPS Risk of FGAs[3,4]

Low	Medium	High
Chlorpromazine	Perphenazine	Haloperidol
Thioridazine	Loxapine	Fluphenazine
		Trifluoperazine
		Thiothixene

EPS indicates extrapyramidal symptom; FGA, first-generation antipsychotic.

■ **Table 2.** Relative Metabolic Risk of Antipsychotics[3,5-7,a]

	Weight Gain	Hyperglycemia	Dyslipidemia
Clozapine	High	High	High
Olanzapine	High	High	High
Quetiapine	Moderate	Moderate	High
Risperidone	Mild-moderate	Mild	MIld
Paliperidone	Moderate	Mild	Mild
Iloperidone	Moderate	Mild[b]	Mild[b]
Aripiprazole	Low	Low	Low
Ziprasidone	Low	Low	Low
Asenapine	Low	Low[b]	Low[b]
Lurasidone	Low	Low[b]	Low[b]
Haloperidol	Low-mild	Low-mild	Low
Perphenazine	Low-mild	Low-mild	Low
Chlorpromazine	High	High[b]	High[b]

[a]High > Moderate > Mild > Low.
[b]Limited data.

These patients are also particularly vulnerable to the adverse effects of antipsychotic medications, such as weight gain and EPSs, and are generally more responsive to lower doses than patients who have experienced multiple episodes. Therefore, the lowest possible dose, typically about half the dose used in patients with chronic schizophrenia, should generally be used in these patients, although dosing recommendations vary depending on the particular antipsychotic being used.[4,15]

Treatment-Resistant Schizophrenia and the Role of Clozapine

For patients who have failed treatment with adequately dosed trials (generally 4-6 weeks) of more than 1 antipsychotic medication, the most evidence-based treatment strategy is to initiate clozapine.[1,4,14-16] Clozapine may be instituted earlier in the treatment of patients with schizophrenia who have persistent suicidality, aggression, or hostility, as these patient populations in particular seem to benefit from clozapine (as in 1 meta-analysis which demonstrated a 3-fold reduction in suicidal behaviors compared with other antipsychotics).[1,4,19] The high risk of weight gain and other metabolic effects, and the risk for agranulocytosis, myocarditis, orthostatic hypotension, seizures, and other adverse effects limit the use of clozapine, but many experts agree that the agent is likely underutilized.[15,20] For patients who do not respond to at least 8 weeks of clozapine treatment with plasma levels greater than 350

mcg/L, there are limited data to support the use of clozapine augmentation with other antipsychotics.[21] Data collected from a meta-analysis of 5 randomized placebo-controlled trials also suggest that, in comparison with placebo, augmentation with lamotrigine improved outcomes in patients with schizophrenia treated with clozapine.[22]

Long-Acting Injectable Antipsychotics

A considerable challenge in the treatment of schizophrenia is medication nonadherence. Approximately 40% to 60% of patients with schizophrenia are nonadherent or only partially adherent to their antipsychotic medication.[23] One strategy for dealing with adherence issues is the use of long-acting injectable (LAI) antipsychotics. First-generation LAIs have been available since the 1960s, but the repertoire of options has expanded recently to include the SGAs, such as risperidone, paliperidone, olanzapine, and aripiprazole.

Traditionally, LAIs were used predominantly in patients with a history of nonadherence to medication and/or relapse of illness related to nonadherence. More recently, some authors have recommended considering an LAI in any patient for whom long-term treatment is needed.[24] The potential benefits of using an LAI over an oral antipsychotic medication include the potentially earlier detection of relapse (because the patient is coming in for regularly scheduled injections), a reduced risk of accidental overdose or missing doses of medication, and the ability to differentiate between symptom relapse due to lack of efficacy versus poor treatment adherence.[23] Pharmacoepidemiologic and naturalistic studies have demonstrated that the use of LAIs may aid in relapse prevention, although randomized controlled trials have failed to show a difference in relapse rates when comparing an LAI, such as risperidone or olanzapine, with oral antipsychotic medications, such as olanzapine, fluphenazine, or risperidone.[25]

Managing Metabolic Adverse Effects

A key issue in the successful treatment of patients with schizophrenia is the management of adverse drug reactions such as EPS, hyperprolactinemia, and, in particular, metabolic syndrome, which is a focus of this article. Metabolic adverse effects are not a new phenomenon in antipsychotic drug treatment. De Hert et al recently compared a historic cohort of patients with schizophrenia experiencing their FEP treated with FGAs with an

■ **Table 3.** Antipsychotic Recommendations From Schizophrenia Guidelines/Algorithms[1,4,14,15,17,18]

	APA	TMAP	IPAP	PORT	WFSBP	NICE
FEP	SGA	SGA	SGA[a]	SGA[b] or FGA	SGA or FGA	SGA or FGA
Second and subsequent episodes	SGA, FGA, clozapine	SGA or FGA	SGA[a]	SGA[c] or FGA	SGA or FGA	SGA or FGA
Treatment resistance[d]	Clozapine	Clozapine	Clozapine	Clozapine	Clozapine	Clozapine

APA indicates American Psychiatric Association; FEP, first episode of psychosis; FGA, first-generation antipsychotic; IPAP, International Psychopharmacology Algorithm Project; NICE, National Institute for Health and Care Excellence; PORT, Patient Outcomes Research Team; SGA, second-generation antipsychotic; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.
[a]FGA if SGA not available.
[b]Other than clozapine or olanzapine.
[c]Other than clozapine.
[d]Persistent symptoms despite adequate trials of 2 antipsychotics.

age- and sex-matched cohort of those treated with SGAs. They found no differences in the incidence of metabolic syndrome at baseline in the 2 treatment cohorts, and both had an increase in the rate of metabolic syndrome over time. However, after an average of 3 years of drug treatment, the patients treated with SGAs had a 3 times higher rate of metabolic syndrome (odds ratio, 3.6; 95% CI, 1.7-7.5) and, on average, twice the amount of weight gain and body mass index (BMI) increase, as those treated with FGAs.[26] Another study estimated that antipsychotics account for 3.1% of diabetes cases over and above the 10% base rate of diabetes seen in patients with schizophrenia.[27]

Patients with schizophrenia who are early in the course of their treatment seem to be at higher risk for weight gain and other metabolic adverse effects with antipsychotic medications. In EUFEST, 86% of patients treated with olanzapine experienced clinically significant weight gain. Even 37% of the patients treated with ziprasidone, which is less likely to cause metabolic disturbances relative to other agents, experienced substantial weight gain, which was not significantly different from other antipsychotic treatments in the trial (P = .054).[10] Similarly, in the CAFE trial, 80% of patients with their FEP treated with olanzapine for 1 year gained a significant amount of weight, as did 50% of the patients treated with quetiapine and 58% of the patients treated with risperidone (P <.05 vs olanzapine).[11] For this reason, particular attention should be given to the metabolic risk profile when choosing an antipsychotic treatment for patients with their FEP. For example, some treatment guidelines recommend against the use of olanzapine as a first-line choice for such patients.[4] Children and adolescents are also particularly vulnerable to the risk of weight gain and other metabolic effects associated with SGAs.[28,29] Other risk factors for experiencing increased metabolic effects from antipsy-

chotics include lower initial BMI, personal or family history of obesity, tendency to eat when stressed, cannabis usage, and non-Caucasian race.[5,29-30]

In response to the recognition of the adverse metabolic effects linked to SGAs, the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity developed a joint consensus statement with recommendations for metabolic monitoring of all patients taking SGAs (**Table 4**).[5,6,29,31] Since then, others have proposed similar and perhaps even more rigorous monitoring guidelines (Table 4).[3,5,31] Despite these recommendations, however, metabolic monitoring is often inadequate. A recent meta-analysis of 39 studies conducted between 2000 and 2011 in the United States, United Kingdom, Canada, and Australia estimated that the rate of routine monitoring in patients being treated with antipsychotics was approximately 70% for blood pressure, 60% for triglycerides, 48% for weight, 44% for glucose, and 42% for cholesterol. Further, complete lipid panels and A1C were collected in only 22% and 16% of patients, respectively.[32]

Interventions for metabolic conditions in patients with schizophrenia are often less than ideal. In the CATIE trial, for example, only about 70% of patients identified as having diabetes at baseline were receiving hypoglycemic medications, 37% of patients with hypertension were being treated with antihypertensives, and only 12% of patients with dyslipidemia were receiving lipid-lowering medications.[33] Several other trials have demonstrated unmet health needs, limitations in access to care, and poorer quality of care that have been associated with poor medical outcomes in patients with schizophrenia.[29,32] This should be a concern for all clinicians, as the trend of premature death due to cardiovascular

■ **Table 4.** Recommendations for Metabolic Monitoring With Antipsychotics[5,6,29,31]

	Personal and Family History of Metabolic and/or CVD	Weight/BMI	Waist Circumference	Fasting Blood Glucose	Fasting Blood Lipids	Blood Pressure
Baseline	EU, SW, US, H	EU, SW, US, H	EU, SW, US, H	EU, SW, US, H	EU, SW, US, H	EU, SW, US, H
Weekly		EU (initially)				
4 weeks		SW, US				
6 weeks		EU	EU	EU	EU	EU
8 weeks		SW, US				
12 weeks		EU, SW, US	EU, SW	EU, SW, US	EU, SW, US, H	EU, SW, US
6 months					H	
Monthly		H (for first 6 months)				
Quarterly		SW, US, H		H (for first year)		
Annually	EU, SW, US	EU	EU, SW, US	EU, SW[a], US, H	EU, SW[a], H	EU, SW, US
Every 5 years					US	

BMI indicates body mass index; CVD, cardiovascular disease; EU, European; H, Hasnain et al; SW, Swedish; US, American Diabetes Association/American Psychiatric Association.
[a]Twice yearly in young patients.

disease (CVD) in patients with schizophrenia continues to rise, despite the declining risk of cardiovascular death in the general population.[29,34] Recognizing this problem, the National Committee for Quality Assurance implemented 4 new physician Healthcare Effectiveness Data and Information Set measures in 2013 related to the monitoring of patients with schizophrenia. These measures include diabetes screening for people with schizophrenia or bipolar disorder who are using antipsychotic medications, diabetes monitoring for people with diabetes and schizophrenia, cardiovascular monitoring for people with CVD and schizophrenia, and adherence to antipsychotic medications for all individuals with schizophrenia.[35]

The first step in treating metabolic complications with antipsychotics is prevention. Careful selection of an antipsychotic based on the individual patient's risk profile is crucial. Ideally, efforts to avoid antipsychotics with high metabolic liability should be made for all patients.[5] Promotion of a healthy lifestyle and education for the patient and their caregivers about metabolic risk is also important at the start of antipsychotic drug therapy.[3] Behavioral interventions to encourage smoking cessation, adopting a healthy diet, and exercising regularly can also be effective in these patients.[3,5] A recent meta-analysis of 10 trials investigating the use of nonpharmacologic interventions for antipsychotic-induced weight gain demonstrated a significant reduc-

tion in body weight for patients in the intervention groups compared with those in the treatment-as-usual group. Average weight loss was 2.56 kg ($P <.001$) and average decrease in BMI was $0.91 kg/m^2$ ($P <.001$).[36] Monitoring of weight, waist circumference, blood pressure, blood glucose, and lipids should be performed at baseline and regularly thereafter for patients on any antipsychotic. Monitoring these parameters only if a patient shows significant weight gain is inadequate, as antipsychotic-induced glucose and lipid abnormalities can occur even without significant weight gain.[3,5,37] If patients do gain 7% or more of their baseline body weight or develop other adverse metabolic effects, switching to an antipsychotic with less metabolic risk or adding medications such as statins, antihypertensives, or antidiabetic agents in collaboration with a primary care physician or specialist may be indicated.[3,5,6,29] The European Psychiatric Association, in conjunction with the European Association for the Study of Diabetes and European Society of Cardiology, has published a position statement with specific recommendations for cardiovascular risk management in patients with severe mental illness.[29] Specifically, various statins, fenofibrate, and omega-3 fatty acids have been shown to be effective for SGA-induced hyperlipidemia. Valsartan and telmisartan have been shown to be effective for hypertension in patients taking antipsychotic medications, and metformin has been widely studied for

antipsychotic-induced weight gain and glucose dys-regulation.[3,5,38] However, the long-term efficacy of both pharmacologic and nonpharmacologic treatments for antipsychotic-induced metabolic effects needs further investigation.

Nonpharmacologic Treatment

Despite the use of antipsychotic medications, many patients with schizophrenia continue to experience persistent symptoms and relapses, necessitating the use of multimodal care, including psychosocial therapies. Psychosocial treatments that have proved effective for the treatment of schizophrenia include cognitive behavioral therapy (CBT), social skills training (SST), family psychoeducation, assertive community treatment (ACT), and supported employment.[16,39] CBT focuses on identifying target problems or symptoms, such as persistent psychosis, and developing specific cognitive and behavioral strategies to cope with these symptoms, whereas SST uses role modeling, rehearsal, and positive feedback to teach interpersonal skills and other skills important for independent living.[39] Family psychoeducation engages patients and their close family members and caregivers to provide illness education, emotional support, and training on how to cope with symptoms and manage crises.[39] ACT involves a multidisciplinary treatment team providing outreach to patients in the community at a high rate of frequency, and has been found to significantly reduce hospital-izations and homelessness in patients who are at risk for repeated hospitalizations.[39] Supported employment consists of aiding in job searches, focusing on cli-ent preferences, providing ongoing job support, and integrating employment and mental health services.[39] Other psychosocial interventions, such as peer support services, cognitive remediation, and motivational inter-viewing to improve medication adherence have some preliminary evidence suggesting efficacy, but need to be examined further to establish their roles in treating patients with schizophrenia.[16,17,39]

Interventional procedures that have some evidence for use in schizophrenia include transcranial magnetic stimulation (TMS), transcranial direct current stimula-tion (tDCS), and electroconvulsive therapy (ECT).[40] TMS utilizes wire coils placed near the scalp to noninvasively induce electrical currents within the brain through the use of pulsating magnetic fields. It has been studied in the treatment of both the positive and negative symptoms of schizophrenia.[41] tDCS is a newer form of neurostimula-tion that has been shown in preliminary trials to reduce the severity of auditory verbal hallucinations in patients with schizophrenia.[42] ECT appears to be particularly use-ful in patients with treatment-resistant schizophrenia or catatonic features.[43]

Drugs in Development

Another focus of ongoing medical research for schizo-phrenia has been the identification of new drug targets to better and more comprehensively treat this complex illness. Many of the drugs currently in development for schizophrenia involve the glutamate pathway, including glycine agonists and reuptake inhibitors, metabotropic type 2/3 receptor agonists, metabotropic type 5 recep-tor agonists, and alpha7 nicotinic agonists.[40] The D_2 and dopamine type 3 receptor partial agonist, cariprazine, is also currently being evaluated.[44]

Conclusion

Antipsychotic medications are the standard of care for the treatment of schizophrenia. Although advances have been made over the past several decades, gaps in treatment for the psychiatric disease remain. Great care should be taken to choose the most appropriate treat-ment for each patient and to monitor for the effective-ness and adverse effects of such treatment. Managing the overall health of patients with schizophrenia should be a priority for all clinicians involved.

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