Switching Antipsychotics as a Treatment Strategy for Antipsychotic-Induced Weight Gain and Dyslipidemia

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Patients taking antipsychotic medications for psychiatric disorders also have many risk factors for medical comorbidities and early death. While these risk factors were present before the arrival of the newer antipsychotic medications, the overall risk factor burden is exacerbated for those high-risk patients whose antipsychotic therapy causes or aggravates obesity or dyslipidemia. Therefore, there is an urgent need for effective interventions to address problems related to the additional iatrogenic burden from weight gain and dyslipidemias caused by antipsychotic medications. For patients with schizophrenia, complete discontinuation of antipsychotic therapy is not advisable and, therefore, pharmacologic options are narrowed to dose adjustments, adding adjunctive agents to induce weight loss, discontinuation of other adjunctive agents associated with weight gain, or changing the antipsychotic medication (“switching”). This article reviews the evidence showing that relative to other possible treatment options, switching to an antipsychotic with a lower propensity to induce weight gain or dyslipidemia can be effective for reversing the weight gain and dyslipidemia caused by previous antipsychotic treatment.

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As improved psychiatric outcomes are achieved due to increased antipsychotic efficacy, mental health providers need to expand their treatment focus to include nonpsychiatric factors that may impact the short- and long-term health of their patients.\(^1\) Among these factors are metabolic health parameters, such as obesity and dyslipidemia, that have been linked to an increased long-term risk for hypertension, type 2 diabetes, cardiovascular disease (CVD), and stroke.\(^2,3\) As discussed elsewhere in this supplement, marked differences exist with respect to the weight and metabolic profiles associated with the first-generation antipsychotics (FGAs) versus the second-generation antipsychotics (SGAs), and within the SGA class as well.\(^4,5\) Given the fact that antipsychotics differ in their metabolic impact and that so many antipsychotic agents are currently available, switching drugs may be an option for selected patients.\(^6,7\) Currently, switching antipsychotics for any reason (efficacy or safety) is much more common than ever before, with 1-year switch rates ranging from 25% to 50%.\(^7\) Of these switches, it has been estimated that approximately 30% were initiated to address undesired side effects, such as weight gain.\(^8,9\)

This report will review the growing evidence for the potential efficacy of switching antipsychotic medications to address the side effects related to metabolic issues, particularly weight gain and dyslipidemia. The discussion will focus not only on what to expect in terms of weight change and lipid effects from switching, but also on placing this treatment option in the context of other available clinical options.

WHY IS SWITCHING AN IMPORTANT STRATEGY?

Switching antipsychotics can be an effective intervention for some patients whose weight gain or dyslipidemia is caused or significantly exacerbated by their current treatment. Since switching antipsychotics always involves commitment and effort by both the patient and physician, and may entail some efficacy risk for symptom control, this discussion will start with a brief review of other psychosocial and pharmacologic options that do not require changing antipsychotic medication. The presence of a new side effect does not automatically require treatment. Other strategies include “watchful waiting,” with repeated observations to determine whether the side effect takes a more benign or malignant course. An intervention decision may come later, upon receiving more information, which can be viewed as a method of “tactical postponement.” If it is decided that no pharmacologic or psychosocial intervention is warranted, other strategies may be introduced in the hopes of reducing the side effect. In the case of weight gain and dyslipidemia, these strategies might include repeated assessments for noncompliance related to distress from weight gain or more careful monitoring for dyslipidemia. Psychosocial strategies, such as diet and exercise programs, are well known and certainly should be used as first-line therapy or in parallel with other strategies.

However, longitudinal follow-up studies\(^9,10\) of patients treated with some SGAs, most notably olanzapine and clozapine, indicate that these iatrogenic problems (i.e., weight gain and dyslipidemia) are likely to persist in the years ahead. Complete reversal to “baseline” status before either olanzapine or clozapine was started was unlikely to occur as long as that medication was continued.\(^10\) Therefore, the effectiveness of psychosocial and “watchful waiting” approaches can be assessed on an individual basis by evaluating the change(s) in risk factor parameters via a comparison of the difference between the preswitch baseline to the postswitch, post-intervention result. In other words, if a person gains 13.6 kg (30 lb) or 3 body mass index (BMI) units from changing from medication A to medication B, and then loses 4.5 kg (10 lb) or 1 BMI unit after a program of diet and exercise,
Switching Antipsychotics

Switching Antipsychotic-Induced Weight Gain

In general, patients with schizophrenia appear more prone to weight gain, perhaps due to poor eating habits and lack of physical activity. This problem is compounded by the fact that many FGAs and some SGAs can cause weight gain. There are major differences among the SGAs in their propensity to cause weight gain, both in terms of the proportion of patients who experience weight gain and the time course and average amount of weight gained after a switch. The greatest weight gain liability is associated with clozapine and olanzapine, followed by risperidone and quetiapine.13,14 Ziprasidone generally causes little or no weight gain (average weight gain about 0.5 kg [1.1 lb] in short-term trials16), which compares very favorably with the average weight gains of 2.3 to 6.8 kg (5 to 15 lb) seen in short-term clinical trials16 with the other SGAs.15

The results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study,17 funded by the National Institute of Mental Health, confirmed these findings.17 CATIE compared treatment with perphenazine (an intermediate-potency FGA), olanzapine, quetiapine, risperidone, and ziprasidone for up to 18 months of treatment in 1432 patients and found that olanzapine was associated with the greatest weight gain. Adjusting for exposure length, the average weight gain for olanzapine was 0.9 kg/mo (2 lb/mo). Patients treated with risperidone or quetiapine also gained weight, but at a smaller magnitude (0.22 kg/mo [0.5 lb/mo] for quetiapine and 0.18 kg/mo [0.4 lb/mo] for risperidone).17 In contrast, perphenazine- and ziprasidone-treated patients were more likely to lose weight, with a mean loss of –0.9 kg/mo (–2.0 lb/mo) for perphenazine and –0.13 kg/mo (–0.3 lb/mo) for ziprasidone (p < .001).17 Since most (about 80%) of the patients in the CATIE study had been taking another antipsychotic prior to switching to their CATIE study medication, these weight change findings are consistent with the hypothesis that weight change is a predictable switching outcome and can be based on the weight profile of the preswitch and postswitch antipsychotics.

Because aripiprazole was not yet available, it was not included in the CATIE study. However, based on other switching studies,18-21 it appears that aripiprazole is similar to ziprasidone in terms of its weight-neutral profile and does not cause significant weight gain compared with haloperidol, a prototypic low–weight gain FGA.18-21 In a 26-week, double-blind, randomized study22 of patients with schizophrenia treated with olanzapine (N = 161) or aripiprazole (N = 156), a greater proportion of patients treated with olanzapine compared with aripiprazole exhibited clinically significant weight gain (i.e., ≥2% increase in body weight) at 26 weeks (37% vs. 14%, p < .001, respectively). Patients had a mean weight increase of 4.23 kg (9.40 lb) with olanzapine and a mean weight loss of 1.37 kg (3.04 lb) with aripiprazole (p < .001) by week 26. When this study was extended to 52 weeks,23 clinically significant weight gain was still experienced by 24% of patients receiving olanzapine and only 10% of those receiving aripiprazole (p = .008, last observation carried forward [LOCF]).
Switching to reverse antipsychotic-induced dyslipidemia

The potential for metabolic side effects (e.g., elevated lipid levels, hyperglycemia) with SGAs has alerted psychiatrists and other mental health clinicians to focus on the physical, as well as the mental, health of their patients. The baseline prevalence of the metabolic syndrome in patients in the schizophrenia CATIE study was recently compared with a matched sample from the Third National Health and Nutrition Examination Survey (NHANES III). 26 Of 689 patients enrolled in the CATIE study for whom sufficient metabolic data were available, 51.6% of the females and 36% of the males met the more inclusive criteria (fasting glucose threshold of 100 mg/dL) of the American Heart Association. Even when differences in BMI were controlled for, the schizophrenia cohorts entering the CATIE study were already twice as likely to meet criteria for metabolic syndrome than the general population reflected in the NHANES sample. Findings from the CATIE study 27 demonstrated that olanzapine was associated with greater increases in indexes of glucose and lipid metabolism than the other treatments examined in the study, while ziprasidone had been the drug in the study that was associated with an improvement in metabolic variables (note that aripiprazole was not yet available for inclusion in the CATIE study).

Based on a literature review, Newcomer 11 reported that clozapine and olanzapine caused sustained elevations in lipid levels, while there appeared to be limited if any increased risk for treatment-induced dyslipidemia with risperidone orquetiapine treatment. Using accumulated data from clinical trials, 11 no evidence to date has suggested that aripiprazole and ziprasidone treatment are associated with an increased risk of dyslipidemia or other adverse effects on glucose or lipid metabolism. Data were recently presented from a case-control study 28 of patients with schizophrenia or affective psychosis in the California Medicaid system who were receiving antipsychotic monotherapy. The study 27 compared 5316 incident cases of hyperlipidemia with 31,338 matched controls and found that patients treated with aripiprazole or ziprasidone had a risk of developing hyperlipidemia comparable to those treated with FGAs. In contrast, patients treated with clozapine, quetiapine, risperidone, and olanzapine had a significantly elevated risk of hyperlipidemia compared to those receiving FGAs.

Studies 3, 5, 6, 24 have noted dramatic significant reductions in lipid and cholesterol levels when patients were switched from olanzapine and, to a lesser extent, from risperidone, to ziprasidone. A very similar pattern of lipid benefits also has been seen with aripiprazole therapy. 12, 23 In the same long-term (52-week) open-label trial 25 evaluating the effects of aripiprazole compared with olanzapine on mean changes in weight discussed...

Switching to aripiprazole or ziprasidone is the most direct and effective way to reverse weight gain induced by other SGAs. Data from a ziprasidone switching study 7, 16 showed that patients who had previously been receiving olanzapine lost an average of 1.8 kg (3.9 lb) over 6 weeks when switched to ziprasidone (p < .0001). Patients previously receiving risperidone also lost weight, with an average decrease of 0.9 kg (1.9 lb) (Figure 1A). A follow-up study 24 demonstrated that patients who remained on ziprasidone for the following year continued to lose weight. After 58 weeks of ziprasidone therapy, patients who previously been receiving olanzapine lost a mean of 10 kg (22 lb), while those switched from risperidone lost a mean of 6.8 kg (15 lb), and those switched from FGAs had not done...
earlier, serum triglyceride levels were also evaluated. Baseline values were similar for both aripiprazole and olanzapine treatment groups (137 and 128 mg/dL, respectively). Patients treated with olanzapine had higher mean changes in fasting serum triglycerides compared with those treated with aripiprazole at week 52 (29.87 and 0.60 mg/dL, respectively) and at endpoint (24.78 and 4.91 mg/dL, respectively).

Given that elevations in lipid levels are considered to be an independent risk factor for heart disease, clinicians should measure baseline fasting lipid and cholesterol levels before starting patients on an antipsychotic, especially clozapine and olanzapine, that is associated with elevated lipid levels. When sustained elevations in lipid or cholesterol levels occur in association with an antipsychotic medication, switching can be a very effective way to reduce or even normalize these metabolic risk factors.

**WHO IS A CANDIDATE FOR SWITCHING?**

When an unwanted side effect, such as obesity, appears during treatment with antipsychotic medication, the clinician’s options include (1) psychosocial interventions (conservative approaches such as diet and exercise); (2) re-evaluation of the risks/benefits of any adjuvant medications (such as certain mood stabilizers) that may be exacerbating the weight problem; (3) adding a medication to induce weight loss (not advised due to lack of evidence); and (4) assessing the risks and benefits of switching to a different antipsychotic.1,25,30 When a patient shows clinically significant obesity and has previously responded to an antipsychotic other than clozapine, in general, Expert Consensus Guidelines1 recommend the combination of psychosocial interventions plus a trial switch to an antipsychotic with less weight gain liability.

Given that switching antipsychotics can be an effective strategy to reverse weight gain or dyslipidemia, in which target patient population would such a switch be indicated? Clinicians should consider switching antipsychotics when there is a clear relationship between antipsychotic exposure and change in health-risk category (i.e., obesity, diabetes, sleep apnea), the patient is about to stop or has stopped antipsychotic use because of weight gain, the patient has bulimia, or the patient is abusing weight loss drugs due to newly developed weight gain on antipsychotic treatment. Current evidence6 indicates that switching is an effective strategy primarily in patients whose weight gain is attributable to preswitch antipsychotic and in whom long-term monotherapy with a weight-neutral agent can be maintained. In this population, the effectiveness of switching appears to be related to a reversal of the weight-increasing effects of a prior antipsychotic medication.6

Switching antipsychotics is not effective in patients whose obesity or dyslipidemia is unrelated to their current antipsychotic. Therefore, given the high rates of obesity and dyslipidemia that are unrelated to antipsychotic exposure, the importance of recording accurate baseline preswitch weight and fasting metabolic parameters cannot be overstated. Switching would also not be effective for patients who are obese or have a dyslipidemia on an existing relatively “weight-neutral” agent, nor for individuals who develop obesity as a result of a side effect of another agent (i.e., marijuana).

**HOW TO SWITCH: SPECIAL CONSIDERATIONS**

When the decision has been made to initiate an antipsychotic switch, the choice should be guided by each medication’s specific metabolic side effect profile as delineated by evidence in the medical literature. Based on the literature, either aripiprazole or ziprasidone is a reasonable first choice as a “switch” antipsychotic when a patient’s antipsychotic regimen is being changed due to weight concerns.6 For example, in a 2003 study by Casey’s group involving 311 patients, the switch to aripiprazole from either an FGA or an SGA produced a mean weight loss that ranged from 1.3 to 1.7 kg (2.8 to 3.7 lb) in a brief 8-week treatment period. Compared to weight-neutral agents (i.e., aripiprazole or ziprasidone), quetiapine and risperidone might have some utility as switch drugs for weight problems; however they would probably be lower in the hierarchy of options.6

In addition to careful patient selection, the issue of differential antipsychotic efficacy is another important consideration when switching antipsychotics to ameliorate weight gain. Differential efficacy can be a major problem when the patient has demonstrated a good therapeutic response to the current antipsychotic. In patients with schizophrenia, the most difficult symptoms to control are those of psychosis, and there is simply no guarantee that the switch medication will be as effective as the patient’s current treatment, even though the new drug’s propensity to induce weight gain may be lower.3,18 An additional consideration in switching involves the switch medication’s potential to maintain long-term efficacy and tolerance in the specific patient for whom the switch is being contemplated. Hence, prior to initiating a switch, the clinician must carefully assess the sum of evidence supporting the following: (1) that this specific patient can be successfully maintained on long-term monotherapy with this specific weight-neutral medication and (2) that switching for weight (or metabolic problems) realistically fits within this patient’s overall treatment plan.

Perhaps the earliest comprehensive source of available data with respect to the comparative impact of antipsychotic therapy on lipid profiles was assembled in 2000 in anticipation of the approval of ziprasidone. These data, which were drawn from an open-label, parallel-group study31 by the manufacturer, measured the fasting lipid profiles of 178 patients with schizophrenia after being treated with ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, or haloperidol for 15 to 25 days. Duration of treatment varied between the 6 antipsychotics due to differences in tolerability, pharmacokinetics, and the time required to reach steady-state. The study31 showed that median triglyceride levels in the quetiapine and olanzapine groups increased from baseline by 25.0 and 43.0 mg/dL, respectively (p < .001), while levels decreased by 17.0 mg/dL in the risperidone group and 37.0 mg/dL in the ziprasidone group. Triglyceride response was mixed among the older agents, with thioridazine increasing the median triglyceride level by 9.0 mg/dL, while haloperidol showed a decrease of 18.0 mg/dL.

Unfortunately, this manufacturer’s study offered information regarding differential antipsychotic impact on lipid trends only in the short term (6 weeks). Thus, trials that assess lipid levels over months or years are required for a more accurate assessment of long-term CVD risk. One such trial,22 a 52-week, open-label extension to a 26-week randomized, double-blind, placebo-controlled trial32 in stabilized patients (N = 310) with chronic schizophrenia, demonstrated that aripiprazole-treated patients showed statistically significant lower mean increases in cholesterol at all time points, as compared to those treated with olanzapine. At the 52-week time point, mean increase in cholesterol
was approximately 15 mg/dL for the olanzapine group, as opposed to an increase of <5 mg/dL for patients who received aripiprazole. In addition, patients treated with olanzapine showed a significant increase in weight and had higher fasting blood glucose levels than patients treated with aripiprazole.22,23

Given that the current evidence3 points to a differential effect on serum lipids across the various antipsychotics, expert consensus opinion supports switching to a relatively low lipid-impact antipsychotic, such as aripiprazole or ziprasidone, when signs of worsening dyslipidemia develop. To date, only Weiden’s group has tracked the results of a ziprasidone switch on lipid levels in 2 switch studies published in 20037 and 2004.31 In their initial 2003 study,7 which involved a brief 6-week assessment period, these researchers found that a switch from an FGA to ziprasidone produced no significant change in lipids. However, a switch from olanzapine to ziprasidone resulted in a median decrease of 50 mg/dL in triglycerides, with median total cholesterol decrease of 17 mg/dL. A risperidone-to-ziprasidone switch produced similar results, with a –29 mg/dL decrease in triglycerides and a 12 mg/dL decrease in total cholesterol at 6 weeks after the medication change.7,16 For a better assessment of long-term lipid trends after a switch, Weiden’s group33 extended the postswitch observation period to 58 weeks in their 2004 study, again assessing the utility of ziprasidone as a switch drug. At the end of 58 weeks, they observed that a switch from olanzapine to ziprasidone resulted in the largest mean decrease in cholesterol, approximately 20 mg/dL, while a switch from risperidone to ziprasidone produced a 13 mg/dL decrease, and an FGA-to-ziprasidone switch lowered cholesterol by approximately 10 mg/dL.33 Hence, as these 6-week and 58-week studies7,33 indicate, favorable decreases in lipid levels occur rather quickly following a switch to ziprasidone and are, in fact, sustained over the long term.

Although, as noted above, clinical trials only now are beginning to address the impact of switching antipsychotics to ameliorate dyslipidemia, nevertheless, the responsibility remains with the treating physician to be aware of future developments in this area. As with switching to improve weight issues, caution should be exercised whenever switching antipsychotics because of lipid elevation, since differential efficacy can be a major problem when the patient has experienced a good clinical response to the current antipsychotic.18 In addition, it must be remembered that switching medications is not a substitute for diet and exercise.29

Although antipsychotic medications may not be the root cause of all of a patient’s excess CVD risk factors, switching can be a very effective treatment option when a patient who is already at high risk for CVD has his or her problems exacerbated by medication. When dyslipidemia is a problem, possible indications for switching include (1) a clear relationship between the patient’s antipsychotic exposure and a change in health-risk category; (2) the patient’s opposition to dietary interventions or treatment with lipid-lowering agents; and (3) the persistence of elevated lipid levels despite active dietary or statin treatment.

CONCLUSION

When contemplating an antipsychotic switch to reverse weight gain or dyslipidemia, the physician should take into consideration the following factors: (1) the side effect’s relationship to the patient’s exposure to their current antipsychotic, (2) the patient’s BMI (obesity) status, (3) the patient’s overall medical health and risk factor status; and (4) any behavioral issues related to weight gain or obesity.5,29,30 In light of these factors, relative indications for an antipsychotic switch might include a history of significant weight gain or dyslipidemia associated with antipsychotic exposure; a BMI in the “obese” category (BMI > 30); preexisting diabetes, obstructive sleep apnea, or a history of heart disease; the presence of other risk factors for CVD (i.e., smoking, hypertension); the threat of noncompliance due to severe distress over weight gain; the onset of bulimia; and the abuse of diet pills or laxatives.30

Will switching antipsychotics in order to improve the lipid profile or weight status succeed in improving a patient’s long-term health? Given that many patients with schizophrenia have multiple risk factors for CVD, will the modification of only weight or just dyslipidemia significantly contribute to longevity or quality of life? In fact, as Wilson’s 1998 study24 has shown, it is precisely those patients who have multiple risk factors who stand to benefit the most when even 1 factor is corrected or improved. For clinicians who treat patients with antipsychotic medications, the need to address patients’ CVD risk factors may be viewed as a new and unfamiliar responsibility. Hence, change comes slowly. Remarkably, although the years 2004 and 2005 saw the publication of at least 3 major monitoring guidelines dealing with antipsychotics and metabolic side effects,3,15,38 as of July 2006,2 there had been no published reports of applying the various international guidelines in real-world settings.

In the overall treatment plan for patients with schizophrenia, the presence of medical/metabolic risk factors must be taken seriously by the treating physician,29 even when these risk factors are preexisting problems that have not been exacerbated by antipsychotic medication. Addressing these risk factors invariably communicates a hopeful message that the patient’s longevity and overall “wellness” are important.1 It also reinforces that fact that patients with serious mental disorders should routinely expect, and are definitely entitled to receive, the same level of attention to their physical health as nonschizophrenic patients.3,37

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax and others), valproate (Depacon and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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