# Reducing the Burden of Side Effects During Long-Term Antipsychotic Therapy: The Role of "Switching" Medications

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One of the great challenges of long-term treatment of schizophrenia and related disorders is minimizing the medical or psychological burden from persistent side effects. Because of the differences in side effect profiles between the newer and older antipsychotic medications, and distinct differences among the newer agents themselves, the spectrum of side effects associated with antipsychotic therapy has changed tremendously. The authors review changing from one antipsychotic to another ("switching") as a potential treatment strategy for reducing the overall side effect burden of antipsychotic therapy. This review identifies 6 steps to the evaluation of switching antipsychotics because of side effects: (1) Establish a causal attribution that the clinical problem is an adverse effect of the antipsychotic medication; (2) Understand the course of the side effect, especially regarding present and future risks for the individual patient receiving the antipsychotic treatment; (3) Understand the potential risks and benefits of other side effect interventions that do not require switching the antipsychotic; (4) Be aware of the side effect profiles of other possible antipsychotics, with an understanding of the potential effectiveness of changing (switching) to another antipsychotic for this side effect; (5) Calculate the side effect risks of switching antipsychotics; (6) Calculate the efficacy risks of switching antipsychotics. The authors explain how to evaluate the specific side effect in the context of the current medication and the overall management of the patient.

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This article discusses the evaluation and management of many of the persistent side effects associated with long-term antipsychotic treatment, with an emphasis on the role of changing ("switching") antipsychotic medication as a potential strategy to address these side effects. Our focus will be on those side effects associated with long-term antipsychotic therapy that are common causes of distress, noncompliance, neurologic morbidity (e.g., parkinsonian side effects, tardive dyskinesia), or medical morbidity (e.g., cardiovascular disease). The specific side effects covered in this review reflect a significant shift in the treatment options available and a greater awareness of the potential long-term problems that arise from a wide range of adverse events. Twenty years ago, the predominant focus with first-generation, "conventional" antipsychotics was the neurologic side effects known as extrapyramidal side effects (EPS). This is not to say that conventional antipsychotics did not cause other significant or distressing side effects, but the problem of EPS eclipsed all others. There is a change in approach to side effect management of antipsychotics because (1) the magnitude of the neurologic side effects, although still present, is much lower with the newer antipsychotics[1] and (2) some, but not all, of the newer medications have greater problems with other, nonneurologic side effects, especially sedation, weight gain, and dyslipidemia.[2]

The term *side effect* has been deliberately chosen instead of *adverse event* to reflect the real-life problem of correctly attributing a suspected side effect to a specific medication. The indications for switching are generally divided into switching for efficacy and switching for side effects.[3–5] Although this division seems logical in theory, in actual practice the situation is often more complex and frequently involves a combination of inadequate efficacy and problematic side effects.[6] This review on the role of switching antipsychotics as a possible intervention therefore covers both EPS- and non–EPS-related problems. Of note is that this is *not* a comprehensive review of *all* side effects of antipsychotics, and does not discuss imminently life-threatening side effects (e.g., neuroleptic malignant syndrome, ketoacidosis). It also is not meant to be an exhaustive review of *all* possible treatment interventions for the side effects that are covered here. Rather, the article discusses the relative advantages and disadvantages of

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switching and other approaches to these side effects, to help clinicians better understand the most important aspects of the overall treatment approach. Also, the article will generally consider the situation facing the patient and clinician for which the antipsychotic medication is being prescribed for long-term maintenance treatment of schizophrenia or related disorder such that ongoing antipsychotic medication is indicated in the foreseeable future.

When considering what to do about a clinical problem that seems to be from a side effect of the current antipsychotic, it may be helpful to reduce the overall evaluation into smaller components. Generally, the decision to use a switching strategy to address a persistent side effect requires a full evaluation of the side effect problem. When switching medications is one of the options, it can be helpful to consider 6 steps:

1. Establish a causal attribution that the clinical problem is an adverse effect of the antipsychotic medication
2. Understand the course of the side effect, especially regarding present and future risks for the individual patient receiving the antipsychotic treatment
3. Understand the potential risks and benefits of other side effect interventions that do not require switching the antipsychotic
4. Be aware of the side effect profiles of other possible antipsychotics, with an understanding of the potential effectiveness of changing (switching) to another antipsychotic for this side effect
5. Calculate the side effect risks of switching antipsychotics
6. Calculate the efficacy risks of switching antipsychotics

## ASSESSMENT AND ATTRIBUTION CHALLENGES FOR SUSPECTED SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATION

One of the challenges in considering the intervention for a possible adverse event is the likelihood that the problem is indeed attributable to the current antipsychotic treatment.[7] Changing antipsychotic medications will not work for problems that are unrelated to the current medication. The first step is to evaluate the likelihood that the "side effect" problem is indeed an adverse event caused by the antipsychotic. Listed below are several common problems encountered when trying to evaluate the causal relationship between the antipsychotic and the possible side effect.

1. For side effects that present with behavioral symptoms: the degree to which the potential side effect overlaps with primary psychiatric symptoms
2. For side effects that overlap with medical risk factors: the degree to which the medical issue—obesity or dyslipidemia—was present before exposure to the current antipsychotic
3. For patients taking multiple medications: the likelihood that one or more than one coprescribed medication is the actual cause of the side effect or is part of a pharmacokinetic or pharmacodynamic interaction that exacerbates the side effect.

Therefore, it is a good idea to consider these possible confounding and complicating factors when assessing the cause of the problem. *Because there is so much overlap between preexisting psychiatric and medical problems and subsequent side effects caused by antipsychotic exposure, the importance of having an adequate and well-documented mental status, history of risk factors (especially important for weight and metabolic disturbances), physical examination, and premedication laboratory values cannot be overemphasized.*

### Specificity Issues

There are some general principles regarding the type of side effect and specificity that can be useful to know. First, the more common the problem is in the patient population, the harder it is to disentangle medication side effects from other causes. For example, prolactin elevation can cause galactorrhea and amenorrhea in women and sexual dysfunction in men. Galactorrhea and, to a lesser extent, amenorrhea are not very common, and when either occurs in someone taking a medication known to raise prolactin, a causal relationship is likely. In contrast, sexual dysfunction is very common among the general population, let alone among patients with psychiatric difficulties. While undoubtedly antipsychotic-induced prolactin elevation will cause sexual dysfunction, it is more challenging to establish a causal relationship in an individual complaining of sexual dysfunction from medication than it is for galactorrhea and amenorrhea. One of the most important aspects of the clinical evaluation would be to have a reliable sexual history before the antipsychotic was started. Often this is not available or was not done, and therefore the clinician (and patient) may have a lot more guesswork involved in the assessment.

Regarding medical and neurologic problems, signs and symptoms of antipsychotic-induced parkinsonism are much more specific to antipsychotic exposure than obesity or dyslipidemia. Therefore, even without good medical records or an accurate history, it is generally easier to link the physical findings of cogwheel rigidity and shuffling gait to antipsychotic exposure for a person taking haloperidol for several years than it would be to link a body mass index of 35 in another patient with a similar length of treatment exposure to a second-generation antipsychotic known to be associated with weight gain. Table 1 illustrates the challenges in the evaluation and treatment of antipsychotic-induced obesity in comparison with antipsychotic-induced parkinsonism.

Table 1. Example of Extrapyramidal Side Effects (EPS) Versus Obesity

| Evidence | EPS | Obesity |
|---|---|---|
| Physical findings | Yes | Yes |
| Specificity to antipsychotic | High | Low |
| Prevalence in untreated population | Very uncommon | Very common |

## Time Course of Side Effect

Another important aspect when considering treatment options is understanding the time course of the side effect if left untreated—whether a side effect is related to transient changes in regimen and likely to be temporary or more likely to persist over time. Side effects that are likely to abate over time may not need permanent changes to the antipsychotic treatment regimen. Changing antipsychotic medication as an intervention is usually better reserved for persistent side effects that will not go away if "left alone."

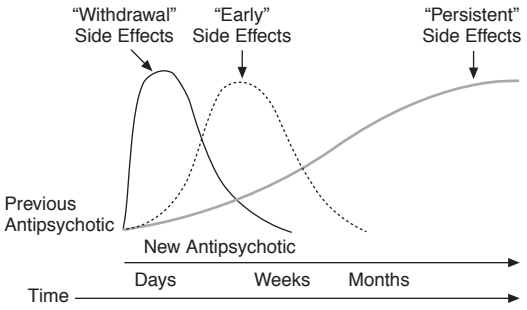
***Withdrawal problems as "side effects."*** As shown in Figure 1, withdrawal problems and "early" side effects are examples of types of "adverse effects" for which strategies other than switching should be considered. This consideration is especially important when evaluating new side effects that present shortly after one medication has been tapered or discontinued, or a new antipsychotic medication has been added.

In particular, it is important to be aware of the potential for withdrawal problems that can masquerade as side effects.[5,8] In general, anticholinergic withdrawal effects are very common when the adjunctive antiparkinsonian medication is lowered or discontinued.[9,10] In addition to malaise and gastrointestinal symptoms, anticholinergic rebound will also present as EPS or akathisia. Antihistaminic withdrawal from antipsychotics with $H_1$-antagonist properties (e.g., quetiapine or olanzapine) may present as insomnia and dysphoria.

***Early side effects that are transient and may abate over time.*** Some side effects may be transient and are associated with starting a medication or a dose increase. Disruptions in sleep-wake cycle are very common, with sedation seen when starting clozapine, quetiapine, or olanzapine, and less commonly with risperidone, ziprasidone, or aripiprazole.[6,11] Insomnia may occur in the reverse order, most common with aripiprazole, and to a lesser extent ziprasidone, and then the others.[12,13] However, although distressing and requiring attention, changes in sleep-wake cycle are often transient and will eventually go away in many cases. Therefore, the primary goal is to reduce distress and anxiety during this period and to "buy time" to complete the therapeutic trial of the change in dose or the change in medication.

Changing antipsychotic medications during this time to address "adverse events" that might represent withdrawal or early side effects would defeat the primary therapeutic purpose of the initial change. Of course, monitoring for withdrawal and early side effects is relevant whenever a switching strategy is used to address a persistent side effect. Depending on the reason for the switch, the withdrawal problem may even be perceived as "backfiring" by making the target side effect worse rather than better. An example here would be rebound EPS when an adjunctive anticholinergic is discontinued too early when switching from risperidone to quetiapine to improve persistent EPS. The importance of anticipating these potential effects (as well as possible) and explaining them to the patient is paramount here. Patients and their relatives can appreciate that a change in medication can result in a short-term "bumpy ride," and using phrases like "Let's see how your body adjusts to this new treatment" resonates with the experience of patients that a period of readjustment is anticipated.

Figure 1. Time Course of Side Effects: Withdrawal, Early, and Persistent




***Impact of a persistent side effect on outcome.*** Changing antipsychotic medication in response to side effects is more relevant for side effects that have been persistent or are likely to remain persistent. Therefore, one of the central aspects of the evaluation is to estimate the impact of the persistent side effect on various aspects of outcome. The assumption here is that the side effect in question has been correctly attributed to the medication and has been persistent. Because any pharmacologic intervention will have some risks and side effects, establishing the risks of *not* treating needs to be considered as well. On a practical level, one approach is to consider the impact of any side effect based on whether it causes distress and whether it causes physical or economic harm.

Distress and harm are both very important outcomes, but take different trajectories and require different approaches. Examples of side effects that are distressing but not dangerous might include sedation in someone who is not working, sexual dysfunction in someone without a sexual partner, amenorrhea that causes feelings of loss of femininity, feeling "like a zombie" because of persistent EPS, or feeling "fat and ugly" from a relatively minor weight gain. Examples of side effects that can be dangerous include a car collision partly caused by sedation in a patient who did not tell his doctor he worked as a taxi driver, amenorrhea that leads to a potentially risky work-

up for a pituitary tumor, suicide because of akathisia, or significant weight gain triggering diabetes mellitus in a vulnerable patient. The point here is that subjective distress and objective severity are not always the same, and the very same side effect can be a source of distress in some patients and quite dangerous in other patients. Furthermore, the "objective" severity of the side effect may not correlate with either distress *or* risk.

The aim of this discussion is to emphasize the need to proactively monitor present and future distress *and* future risk for *all* common adverse events. It is overly simplistic to think of one category of side effect as relatively "benign" and the other "serious." Depending on the individual and his or her situation, *all* side effects can be distressing and at times dangerous. Having said this, there may be some side effects that both clinicians and patients alike underestimate in terms of future risk, especially those pertaining to the change in risk factor status for heart disease.

One common approach to managing subjective distress from a side effect is to intervene when the distress is sufficiently severe that the patient is (or will become) noncompliant. The clinician will try to prevent the consequences of noncompliance, including relapse and rehospitalization. There are drawbacks to waiting until impending noncompliance before switching antipsychotics for distressing but not "harmful" side effects. First is that often the noncompliance will happen without forewarning; then the patient is much less likely to accept a medication switch. The other concern is that waiting to intervene until a patient wants to stop medication runs the risk of making noncompliance a primary means of communicating distress from side effects. Finally, it seems that distress in its own right should be relevant in a patient-centered decision-making approach to treatment as recommended by the President's New Freedom Commission on Mental Health.[14,15]

The other issue is that of harm, especially when there is a significant lag-time between medication exposure and adverse outcome. In the era of conventional antipsychotics, tardive dyskinesia was not acknowledged to be a serious side effect until the antipsychotic medications had been used for many years and longitudinal epidemiologic studies established the causal relationship between antipsychotic exposure and increased risk of dyskinesia. One of the barriers in treating tardive dyskinesia is that it is not painful and patients are often unaware of this side effect. Therefore, it was the clinician's responsibility to monitor for tardive dyskinesia, even in the absence of distress or complaints.[16] The growing awareness of the additional cardiovascular risk of weight gain and dyslipidemia caused by some, but not all, of the newer antipsychotics is strikingly similar to how awareness of the tardive dyskinesia problem evolved in the 1970s and 1980s. One difference is that tardive dyskinesia is now part of routine monitoring, whereas dyslipidemia does not seem to trigger any treatment response.[17,18] Another difference between tardive dyskinesia from conventional antipsychotics and obesity and dyslipidemia from the newer medications is that tardive dyskinesia is a class effect such that all of the conventional antipsychotics are believed to have approximately the same risk of tardive dyskinesia.[19] In contrast, there are large differences in likelihood of weight gain and dyslipidemia according to the specific individual antipsychotic agent. This difference is a theoretical basis for considering the possibility of switching antipsychotic medications as a strategy for reversing the weight gain or dyslipidemia when it is caused by the patient's maintenance antipsychotic medication, especially given the difficulty with effective interventions for dyslipidemia in this patient population.[20]

## COMPARING SWITCHING AND ALTERNATIVE STRATEGIES FOR SIDE EFFECTS

Since switching antipsychotics always involves commitment and effort for both the patient and physician, and may entail some efficacy risk for symptom control, it is important to consider other 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 more malignant course. An intervention decision may come later, upon receiving more information, which can be viewed as a kind of "tactical postponement." If the decision is that no pharmacologic or psychosocial intervention is warranted, then other strategies might be introduced in the hopes of reducing the side effect.

In general, medication discontinuation is not a practical option, at least when there is a diagnosis of schizophrenia or schizoaffective disorder.[21] The tacit assumption is that regardless of whether or not the patient remains on this specific antipsychotic, ongoing antipsychotic treatment is needed. Therefore, the range of options does *not* include discontinuing antipsychotics altogether or changing to a different class of psychotropic medication. However, the patient or family will want to know whether stopping medications altogether is an option, and it is important to discuss and remind patients and families about the benefits of maintenance antipsychotic treatment.

Aside from switching medications, the other common active therapeutic interventions for adverse events include dosage lowering and adding an adjunctive medication to counteract the side effect. *Regarding dosage lowering, it is very important to be familiar with the sensitivity of the specific side effect to a lower dosage*. Persistent sedation, akathisia, and motor signs of parkinsonism often respond very well to dosage lowering, and this is a very appealing strategy for patients whose lowest effective antipsychotic dosage has not been established. If used, the dosage lowering should be small and gradual (e.g., 20% per month) and the

patient told that the goal is to *lower* the antipsychotic dosage, *not to stop it entirely.* Other side effects that may occasionally respond to dosage lowering include sexual dysfunction, galactorrhea, and amenorrhea. *The most important finding from studies of the relationship between antipsychotic dosage and the metabolic risk factors of weight gain and dyslipidemia is that, at least within the dosage ranges used to treat schizophrenia and bipolar disorder, these adverse events are unrelated or minimally related to the maintenance dose.*[22] *Therefore, dosage lowering as a routine strategy for reversing significant weight gain or dyslipidemia is not recommended.*

Adding adjunctive agents to counteract the side effect is the traditional method for dealing with EPS problems from the older conventional antipsychotics. Although effective for reducing the motor abnormalities of parkinsonian manifestations of EPS, adjunctive agents are less effective in treating the subjective and behavioral manifestations of EPS and also lead to problems of their own. Most notably, the addition of an anticholinergic agent such as benztropine significantly worsens cognitive functioning. Given that schizophrenia patients already have difficulty with cognition and one of the potential advantages of the newer medications is their relative benefits on cognitive functioning, there are significant drawbacks to relying on this strategy for residual EPS that develops during antipsychotic therapy. Adjunctive treatments are available for persistent sedation and hyperprolactinemia and are appropriate when dosage lowering or switching agents is not feasible. Finally, the issue of adding an adjunctive medication to induce weight loss is often considered for weight gain associated with olanzapine or clozapine. While it is beyond the scope of this review to cover this area in detail, these agents often have risks of their own (e.g., cognitive problems from topiramate), may be expensive (e.g., sibutramine), or may be difficult to implement (e.g., orlistat). Most of all, these adjunctive strategies do not completely reverse the weight gain that occurs with the clozapine or olanzapine, the most problematic antipsychotics in terms of weight liability.[22,23] The available literature on the impact of these adjunctive strategies is scant and, overall, the extent to which these add-on approaches can reverse adverse effects is not impressive. Additionally, it is not clear which agent one might choose.

In summary, there are adjunctive approaches to addressing persistent EPS, sedation, hyperprolactinemia, and weight gain associated with antipsychotic exposure. They all share the advantage of being able to provide pharmacologic assistance to the side effect without exposing the patient to potential efficacy risks inherent in switching antipsychotics. They have the disadvantage, relative to switching, of having limited effectiveness in fully reversing the underlying problem and also have the potential to create new problems of their own. Our understanding would be advanced by a new wave of studies comparing these adjunctive strategies to the option of switching medications. Additionally, our patients would benefit from information from studies as to when is the right time to intervene. For example, if a patient was gaining weight during the first 3 weeks of treatment, should a switch be considered then or should the situation be kept under review, with the option to switch later, if weight gain persists.

## EFFECTIVENESS OF SWITCHING FOR SIDE EFFECTS

With the widespread use of the newer antipsychotics, the relative burden of side effects has shifted away from EPS toward other problems such as weight gain, metabolic problems, sedation, and sexual dysfunction (Table 2). Nevertheless, fewer EPS is not the same as no EPS, and switching to alleviate EPS remains important.

### Reversing Antipsychotic-Induced Weight Gain

There are major differences among the atypical antipsychotics in their propensity to cause weight gain, in terms of both the proportion of patients who experience weight gain and the time course and average amount of weight gained after a switch. The overall pattern is that clozapine and olanzapine have the greatest propensity to induce weight gain, risperidone and quetiapine are intermediate, and ziprasidone and aripiprazole the least.[24]

The results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), adjusting for exposure length, found that the average weight gain for olanzapine was 2 lb/mo.[19] Risperidone patients and quetiapine patients also gained weight, but the magnitude of weight gain was much lower (0.5 lb/mo for quetiapine and 0.4 lb/mo for risperidone). In contrast, perphenazine and ziprasidone patients were more likely to lose weight, with a mean loss of 0.2 lb/mo for perphenazine and 0.3 lb/mo for ziprasidone ($p < .001$). Since most (approximately 80%) of the patients in the CATIE study had been taking another antipsychotic before switching to their CATIE study medication, these 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,[13,25] it appears that aripiprazole is similar to ziprasidone in its weight profile and does not seem to cause significant weight gain when compared with haloperidol, a prototypic low weight gain, conventional antipsychotic drug. In a 26-week, double-blind, randomized study[26] of patients with schizophrenia treated with olanzapine ($N = 161$) or aripiprazole ($N = 156$), patients had a mean weight increase of 4.23 kg with olanzapine and a mean weight loss of 1.37 kg with aripiprazole ($p < .001$) by week 26. Switching to ziprasidone or aripiprazole is the

Table 2. Summary of Side Effects With Atypical Antipsychotics[a]

| Medication | Extrapyramidal Side Effects/ Tardive Dyskinesia | Prolactin Elevation | Weight Gain | Glucose Abnormalities | Lipid Abnormalities | Sedation | Hypotension | Anticholinergic Side Effects |
|---|---|---|---|---|---|---|---|---|
| Clozapine | 0 | 0 | +++ | +++ | +++ | +++ | +++ | +++ |
| Risperidone | + | +++ | ++ | ++ | ++ | + | + | 0 |
| Olanzapine | 0 | 0 | +++ | +++ | +++ | + | + | ++ |
| Quetiapine | 0 | 0 | ++ | ++ | ++ | ++ | ++ | 0 |
| Ziprasidone | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 |
| Aripiprazole | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 |

[a]From the American Psychiatric Association *Practice Guideline for the Treatment of Patients With Schizophrenia*.[2]
Symbols: 0 = no risk or rarely causes side effects at therapeutic dose, + = mild or occasionally causes side effects at therapeutic dose, ++ = sometimes causes side effects at therapeutic dose, +++ = frequently causes side effects at therapeutic dose.

most direct and effective way to reverse weight gain induced by other atypical antipsychotics.

Data from a ziprasidone switching study[12] showed that patients who had previously been receiving olanzapine lost an average of 3.9 lb (1.8 kg) over 6 weeks when switched to ziprasidone—a statistically significant change ($p < .0001$). Patients previously receiving risperidone also lost weight, with an average decrease of 1.9 lb (0.9 kg), whereas patients switched from high-potency conventional antipsychotics did not experience any significant weight change.[12] A comparable switching study found very similar results in the pattern of weight loss for switches to aripiprazole. In this study, 311 stable but symptomatic outpatients with schizophrenia who were switched from their prior antipsychotic to aripiprazole for up to 8 weeks showed a pattern of weight change at 8 weeks that was strikingly similar to the results in ziprasidone short-term switching studies.[13] Patients who were switched from olanzapine (N = 169) lost more than 2 kg ($p < .001$); those switched from risperidone (N = 106) lost 0.7 kg ($p = .07$), and those switched from haloperidol (N = 14) showed a 0.1-kg weight gain (not statistically significant).

It is important to appreciate that these switch studies are open-label and without a comparator drug (or a "continue on present treatment" comparator arm). They are also generally funded by the pharmaceutical company that markets the switch medication. Although the CATIE study was not designed to address all these methodological and "independence" issues, it is noteworthy that tolerability results relating to the weight profile were not as pronounced as in the open-label switch studies. More "definite" switch studies are needed.

### Reversing Antipsychotic-Induced Dyslipidemia

While differences in weight profiles among the antipsychotics are now well known, there also are striking differences in their effects on cholesterol and triglyceride levels. Some of the newer antipsychotics are also associated with increases in levels of cholesterol and triglycerides. Total cholesterol levels < 200 mg/dL are considered desirable; 200 to 239 mg/dL is borderline high, and ≥ 240 mg/dL is high. Triglyceride levels are considered normal at < 150 mg/dL, borderline high at 150 to 199 mg/dL, high at 200 to 499 mg/dL, and very high at ≥ 500 mg/dL; and elevated triglycerides are associated with an increased risk of coronary heart disease.[27] *It is very important to know that for individual patients, the adverse impact on lipids does not necessarily correspond to the weight changes*.[28,29] *In other words, for individual patients, the propensity for dyslipidemia does not match the weight gain, and these parameters need to be considered separately. Therefore, switching to reverse dyslipidemia is a distinct indication from switching to reverse weight gain.*

Olanzapine and quetiapine were associated with increased levels of total cholesterol (9.4 and 6.6 mg/dL, exposure-adjusted) and triglycerides (40.5 and 21.2 mg/dL) in the CATIE trial, whereas risperidone lowered cholesterol slightly (cholesterol, –1.3 mg/dL; triglycerides, –2.4 mg/dL), as did ziprasidone (cholesterol, –8.2 mg/dL; triglycerides, –16.5 mg/dL).[19] Previous studies have found that both olanzapine and clozapine are associated with significant increases in triglyceride levels from baseline and significantly higher triglyceride levels than haloperidol[30]; in a 26-week head-to-head trial, more patients given olanzapine developed abnormal plasma lipid levels than did patients given aripiprazole.[26] Extreme elevations in triglyceride levels have also been reported for olanzapine and quetiapine in a context of only modest weight gain (12.3 and 8.5 lb, respectively).[31]

Switching to a medication with a more favorable lipid profile can improve these measures. Switching from olanzapine to aripiprazole resulted in statistically significant reductions ($p < .02$) in levels of total cholesterol (233.7 to 194.6 mg/dL) and low-density lipoprotein cholesterol (146.8 to 117.9 mg/dL) after 12 weeks of treatment.[32] One year of treatment with ziprasidone was also effective in reducing triglyceride levels in patients previously given olanzapine (–31 mg/dL; $p = .0001$) or risperidone (–17 mg/dL; $p < .05$).[33] Thus, switching to an antipsychotic with a low liability for adverse lipid effects is an effective means of lowering antipsychotic-associated elevations in cholesterol and triglycerides. Because patients respond differently to medications, there is always a possibility that a patient's psychotic symptoms will not respond as well to the new medication as to the old. Therefore, switching is indicated only when there is a clear relationship between

antipsychotic exposure and blood lipid changes, when the patient does not agree to dietary interventions or lipid-lowering agents, or when lipid levels remain elevated despite active dietary or statin treatment.

On the basis of a review of the literature, Newcomer[22] reported that clozapine and olanzapine cause sustained elevations in lipid levels, whereas there appears to be limited, if any, increased risk for treatment-induced dyslipidemia with risperidone or quetiapine treatment. Based on accumulating data from clinical trials, evidence to date suggests that ziprasidone and aripiprazole treatment are associated with a particularly low risk of dyslipidemia or other adverse effects on glucose or lipid metabolism. Findings from the CATIE study demonstrated that olanzapine was associated with greater increases in indexes of lipid metabolism than the other treatments examined, whereas ziprasidone was the only drug in the study that was associated with improvement in metabolic variables (note that aripiprazole was not included in CATIE). Open-label studies not withstanding (given the methodological caveats above) have found dramatic and very significant reductions in lipid and cholesterol levels when patients were switched from olanzapine and, to a lesser extent, from risperidone to ziprasidone.[33] A very similar pattern of lipid benefits has also been seen when switching from olanzapine to aripiprazole therapy.[32] Given that elevations in lipid levels are considered an independent risk factor for heart disease, clinicians should measure baseline fasting lipid and cholesterol levels before starting patients on antipsychotic therapy. At the present time, the extent of monitoring these adverse effects appears to be low and inconsistent in clinical practice.[34]

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. As previously noted, patients switched to ziprasidone from olanzapine and, to a lesser extent, to ziprasidone from risperidone had sustained reductions in serum cholesterol and triglyceride levels. The fact that switching from conventional antipsychotics did not change plasma triglyceride or cholesterol levels suggests that the benefits of ziprasidone and aripiprazole on dyslipidemia are related to the removal of a previous antipsychotic medication rather than any intrinsic weight loss or lipid-lowering benefits of the drug. The treatment implication for switching is that the potential usefulness of switching from an antipsychotic that causes dyslipidemia to one that does not would depend whether the dyslipidemia could be traced to the onset of exposure to the current antipsychotic. Switching would presumably not be effective for dyslipidemia unrelated to antipsychotic exposure.

### Switching for Persistent EPS

Although more severe forms of EPS are much less common with the first-line atypicals, patients still may experience EPS that are more subtle and harder to detect yet still debilitating. Patients may complain of being lethargic, tiring easily, or experiencing emotional numbing, without having the obvious motor signs of muscle rigidity, tremor, or shuffling gait. Clozapine and quetiapine are associated with EPS levels that are comparable to those found with placebo,[2] whereas dose-dependent EPS are found with risperidone, particularly at the upper end of the dose range.[35] Olanzapine and ziprasidone have a lower EPS liability than risperidone,[2] but some EPS may occur in vulnerable patients or when these agents are used at high doses. The EPS liability of aripiprazole seems to depend on the type of EPS in that it has little to no parkinsonian symptoms, but acute dystonia[36] and akathisia having been reported. Clinical trials of aripiprazole show no signal of motor parkinsonism (cogwheel or leadpipe rigidity, shuffling gait). Like quetiapine, aripiprazole does not demonstrate a dose-EPS relationship for parkinsonian signs of EPS in fixed-dose clinical trials.[37] However, unlike quetiapine, there may be a signal in clinical trials, as well as clinical practice, that akathisia does occur with aripiprazole. In an analysis of clinical trials, approximately 6% of olanzapine-treated patients, 10% to 12% of aripiprazole-treated patients, and 24% of haloperidol-treated patients experienced akathisia.[38]

### Switching to Reduce Anticholinergic Burden

When conventional agents were the only antipsychotics available, clinicians often considered the ongoing use of anticholinergic medications (e.g., benztropine) necessary to adequately control EPS in patients with schizophrenia being treated with antipsychotics. Nevertheless, routine use of anticholinergic agents was controversial even before the advent of the newer antipsychotics because of concern about the adverse consequences, such as delayed response to antipsychotic treatment and problems with memory and attention associated with anticholinergic agents.[39] However, potential benefits are lost if the patient continues to receive concomitant anticholinergic therapy.[40] If lowering the dosage of the antipsychotic is not feasible or does not reduce EPS so that the patient continues to need anticholinergics to manage EPS, a medication switch should be considered. A population-based pharmacoepidemiologic study showed that switching from a conventional to an atypical antipsychotic (except risperidone) led to subsequent reduction in anticholinergic use.[41] Given the known detrimental effects of anticholinergic agents on cognition, the single most important clinical consideration is to minimize the use of the anticholinergic medications that were so frequently coprescribed with the older conventional agents to control EPS.

### Reversing Prolactin-Related Side Effects

Elevations in prolactin levels are clinically silent, and yet the clinical effects of hyperprolactinemia can be disruptive and distressing. Clinicians should measure serum

prolactin levels and counsel their patients about the potential consequences of hyperprolactinemia. In women, the common presentations of elevated prolactin levels are amenorrhea and galactorrhea, which can cause significant distress and can lead to unnecessary examinations for prolactin secreting tumors. In men, the most common consequence of elevated prolactin levels is sexual dysfunction. Most of the atypical antipsychotics are associated with less prolactin elevation than the conventional antipsychotics.[42,43] However, risperidone is the notable exception. Prolactin changes associated with risperidone are even greater than those seen with conventional antipsychotics.[19] Aripiprazole appears to be the least likely of the newer atypicals to raise prolactin levels,[44] as demonstrated in an aripiprazole switching study in which serum prolactin levels fell for all groups following a switch from olanzapine, risperidone, or haloperidol to aripiprazole.

### Reducing the Burden of Persistent Sedation

Although sedation can be therapeutically desirable in the short-term, persistent long-term sedation is usually a problem because it interferes with cognition and social and vocational functioning. It can be very frustrating for patients to achieve a fuller range of symptom control from a newer medication only to have their activities curtailed because of persistent sedation. Sedation is a dose-related side effect; it may also appear temporarily during the first weeks or months of taking a new medication. When sedation persists beyond the early treatment period and cannot be managed by dose reduction, it is an appropriate target for switching. In general, in maintenance treatment, aripiprazole and ziprasidone often seem to be less sedating than the other atypical antipsychotics,[6,11] and either would be a good choice for addressing sedation. Although addition of adjunctive modafinil has been reported to be helpful,[45] this approach would seem most appropriate when sedation is a transient or "early" problem.

## RISK OF OTHER SIDE EFFECTS

Figure 2 summarizes the expected side effect benefits when changing antipsychotic medications. The side effect risks are therefore also shown in the table by reversing the arrows. The magnitude and direction of side effect changes is predictable in both directions. In other words, any side effect that will improve from switching from medication A to B can be expected to worsen to the same degree when switching from medication B to A. Of course, because individual patients do not have the exact same vulnerabilities, this table can be used as a general guide to estimate the general likelihood of a side effect occurring when someone starts a new medication.

It should be noted that with the availability of ziprasidone and aripiprazole, there are 2 antipsychotics that share all of the following potential benefits: low propensity for weight and metabolic disturbances and low EPS liability. Therefore, it is possible for an antipsychotic to have the low weight-gain liability associated with the high-potency conventional antipsychotics and the low EPS liability associated with the newer atypical antipsychotics. On the other hand (see also below), whether these agents will prove as efficacious as their predecessors is a consideration. Moreover, the dosing profile (and equivalence) of these drugs is unclear, and this further complicates the switching considerations. These counterbalances are exemplified well in the overall results of the CATIE study[19] wherein olanzapine was associated with the greatest adverse effect burden, yet proved manifestly superior in terms of overall symptom response and the duration that patients stayed on this medication.

The extent to which a given medication will yield a consistent response to symptoms remains the major consideration in selecting antipsychotic medications. Tolerability and adverse effect profile, albeit of critical importance, are not (yet) the primary drivers of choice of medications. Of course, the relative weight of each consideration will be individualized in each patient. These risk-benefit analyses are complex and should be informed and individualized. Much progress has been made already, and newer medications will further permit refinement of medication selection to minimize side effect burden.

### Efficacy Risk of Switching Antipsychotics

The major risk in switching antipsychotics for side effects is that the variability in individual response to medication will mean that, in practice, there is no assurance that the new medication being introduced to alleviate the persistent side effect will have the same efficacy as the current antipsychotic medication. Therefore, a patient who has achieved excellent efficacy with his or her current antipsychotic medication and is considering a switch for side effects is taking a chance that the new, postswitch medication will not work as well. One of the most vexing situations involves a person who has had an excellent efficacy response to clozapine but has developed severe metabolic side effects.

In such cases, often there is no easy answer. However, there are a few principles that might provide some guidance in difficult situations:

- In general, the differential efficacy characteristics of the antipsychotic medications are most problematic for patients who have achieved excellent efficacy on their current medication. The differential efficacy is less of a problem when the current medication is not completely effective and a change in medication is being contemplated for efficacy reasons as well as tolerability reasons.
- When switching a patient from an agent that has excellent efficacy but has side effects, educate the

**Figure 2. Potential Side Effect Benefits When Switching Between Antipsychotic Medications[a,b]**

| Preswitch Antipsychotic | Postswitch Antipsychotic: Aripiprazole | Olanzapine | Quetiapine | Risperidone | Ziprasidone |
|---|---|---|---|---|---|
| Haloperidol | ↓↓ EPS<br>↓↓ Prolactin<br>↓ Akathisia<br>↓ Sedation | ↓↓ Akathisia<br>↓↓ EPS<br>↓↓ Prolactin | ↓↓↓ Akathisia<br>↓↓↓ EPS<br>↓↓ Prolactin | ↓ Akathisia<br>↓ EPS | ↓↓ EPS<br>↓↓ Prolactin<br>↓ Akathisia<br>↓ Sedation |
| Aripiprazole | | ↓ Akathisia<br>↓ Insomnia | ↓↓ Akathisia<br>↓ EPS<br>↓ Insomnia | ↓ Insomnia | ↓ Akathisia<br>↓ Insomnia |
| Olanzapine | ↓↓↓ Dyslipidemia<br>↓↓↓ Weight<br>↓↓ Sedation<br>↓ Prolactin | | ↓ Akathisia<br>↓ Dyslipidemia<br>↓ EPS<br>↓ Prolactin<br>↓ Weight | ↓ Dyslipidemia<br>↓ Sedation<br>↓ Weight | ↓↓↓ Dyslipidemia<br>↓↓↓ Weight<br>↓↓ Sedation |
| Quetiapine | ↓↓ Sedation<br>↓ Dyslipidemia<br>↓ Orthostatic Hypotension<br>↓ Weight | ↓ Orthostatic Hypotension | | ↓ Sedation | ↓↓ Sedation<br>↓ Dyslipidemia<br>↓ Orthostatic Hypotension<br>↓ Weight |
| Risperidone | ↓↓↓ Prolactin<br>↓ Dyslipidemia<br>↓ EPS<br>↓ Orthostatic Hypotension<br>↓ Sedation<br>↓ Weight | ↓↓ Akathisia<br>↓↓ EPS<br>↓↓ Prolactin<br>↓ Orthostatic Hypotension | ↓↓↓ Akathisia<br>↓↓↓ EPS<br>↓↓↓ Prolactin | | ↓↓ EPS<br>↓↓ Prolactin<br>↓↓ Weight<br>↓ Dyslipidemia<br>↓ Orthostatic Hypotension<br>↓ Sedation |
| Ziprasidone | ↓ Prolactin<br>↓ Sedation | ↓ Akathisia<br>↓ Insomnia | ↓ Akathisia<br>↓ EPS<br>↓ Insomnia | ↓ Insomnia | |

[a]Reprinted with permission from Weiden.[6]

[b]This table assumes that the problem in question has been established to be a result of the prior antipsychotic and is not caused by an unrelated process or exposure to another medication with a similar side effect problem. EPS refers to parkinsonism, including tremor, rigidity, and akinesia (bradykinesia), and does not refer to tardive dyskinesia or akathisia. Prolactin elevation is evident as amenorrhea and galactorrhea in women and should be considered in the differential diagnosis of sexual dysfunction in men. Dyslipidemia refers to elevated fasting triglyceride and cholesterol levels; the findings shown in this table have been documented to occur within 6 to 8 weeks of switching medications without other pharmacologic or dietary interventions.

Abbreviation: EPS = extrapyramidal symptoms. Symbols: ↓ = benefit may be of clinical significance but does not represent the best switch choice for that specific side effect, ↓↓ = significant benefit that will effectively reverse side effect for the majority of cases, ↓↓↓ = reserved for situations in which the preswitch antipsychotic is most associated with the side effect in question and the postswitch antipsychotic is likely to have the greatest magnitude of difference after a successful change in antipsychotic medication (i.e., "top choice" for switching if that is the primary reason for making the switch).

patient about the additional risk and consider doing a slow cross-taper with overlapping of both medications, and then a slow reduction of the first medication. While this may delay the benefits of reversing the side effects, it may also mitigate any possible symptom exacerbation from loss of efficacy from the first agent.

- Any medication selected primarily for side effect indications and used in patients who experience excellent efficacy with their current antipsychotic will seem like it does not work as well because of the artifact of differential efficacy and ordering of medications. One way around this issue is to start with the antipsychotic initially that is least likely to lead to future side effect switches.
- There is a natural human tendency to discount future risk relative to present risk (e.g., credit card problems, cigarette smoking). Therefore, we need to appreciate the potential seriousness of long-term side effects relative to the current risk of changing antipsychotic medications.

## CONCLUSION

Medication switches are the result of a calculated bet that a new medication will be better than the old. In the case of switches motivated by side effects, the good news is that there are more antipsychotics than before with markedly different side effect profiles. The risk, especially for patients who have achieved good to excellent efficacy on their current medication, is that efficacy of the new medication is unknown. When sedation, weight gain, elevated blood glucose levels, dyslipidemia, hyperprolactinemia, and EPS are long-term threats to safety and well-being, a medication switch may be indicated even when the current antipsychotic medication is adequately or successfully controlling the patient's primary symptoms. These side effects can seriously threaten the patient's physical health if ignored and may prompt medication nonadherence, which will eventually adversely affect the patient's mental health, as well. In many cases, the switch will not immediately alleviate the side effect problem, and often the patient will experience

increases in other side effects during the transition from one medication to another. Therefore, patient and clinician education and motivation are key to a successful switch.[46]

*Drug names:* aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), modafinil (Provigil), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax and others), ziprasidone (Geodon).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, topiramate is not approved by the U.S. Food and Drug Administration for weight loss and modafinil is not approved for the treatment of medication-induced sedation.

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