

TARGETED CARE PLANS FOR SCHIZOPHRENIA

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Case Presentation

Thomas was a 40-year-old, white male, with a 16-year history of schizoaffective disorder (Slide 1). He first became ill at 24 years of age and had an unstable course for ~10 years, characterized by frequent hospitalizations and partial adherence. Unfortunately, during episodes of psychosis, he was also extremely violent. During his first hospitalization, risperidone was initiated, which he used intermittently for ~10 years. There are no records documenting his weight and metabolic parameters at 24 years of age prior to receiving psychiatric medications. During his last psychiatric hospitalization at 34 years of age, olanzapine was prescribed and he stabilized. He entered a period of stable outpatient treatment and had not had a psychiatric hospitalization for 6 years.

When Thomas began taking olanzapine, his weight was 200 lbs, which, given his height, corresponds to a body mass index (BMI) of 28, putting him in the overweight category. However, he had no metabolic monitoring for 3 years. After 3 years of treatment with olanzapine, he had gained substantial weight, increasing to 258 lbs, which corresponds to a BMI of 36 and class 2 obesity.

At 37 years of age, he was switched to aripiprazole with the hope that it might be more weight neutral. Six months after the switch, his weight decreased slightly to 253 lbs, but his blood work indicated an improvement in cholesterol and triglycerides. His blood pressure was normal, he did not smoke, he had no family history of cardiac disease, and his high-density lipoprotein cholesterol was 45 mg/dL.

Currently, Thomas does not want a change in medication to avoid a psychotic relapse and is currently working with his primary care physician on diet modification and increasing his exercise. At 40 years of age (3 years after the switch from olanzapine to aripiprazole), he has remained psychiatrically stable. Unfortunately, his weight remained the same as before the medication switch at 256 lbs.

This case illustrates some of the issues that clinicians might want to consider. What went wrong in this patient who, under medical care, went from being overweight to class 2 obesity within a few years? Could this have been prevented? It is clear today that clinicians and patients can choose between a wide variety of available antipsychotics. However, it is also increasingly clear that the best choice takes into account not simply efficacy and short-term tolerability, but long-term medical risks, particularly cardiovascular risk because it is one driver of premature mortality in patients with schizophrenia.

SLIDE 1
Case Presentation: Thomas

40-year-old, white male with a 16-year history of schizoaffective disorder

Age 24 years–onset of illness and unstable period for ~10 years
- A decade of numerous hospitalizations; extreme violence when psychotic.
- First hospitalization (24 years of age): risperidone started
  - No BMI available
- Last hospitalization (34 years of age): olanzapine started
  - Weight 200 lbs (5'11") = BMI 28 (overweight)

Age 34 years–stable outpatient period begins
- No hospitalizations for 6 years
- Initially maintained on olanzapine
- No metabolic monitoring done for 3 years
- After 3 years on olanzapine
  - Weight: 258 lbs = BMI 36 (class 2 obesity)
  - Labs: glc 94 (HbA1c 5.2); Chol 230; LDL-C 141; TG 295

Age 37 years–switch to aripiprazole
- 6-month follow-up
  - Weight: 253 lbs = BMI 35
  - Labs: glc 97 (HbA1c 5.2), Chol 212; LDL-C 127; TG 267

Age 40 years
- 3-yr follow-up: Psychiatrically stable but
  - Weight: 266 lbs=BMI 37
  - Labs: glc 79 (HbA1c 5.4); Chol 220; LDL-C 134; TG 240
- Patient does not want to risk relapse and works with PCP on diet modification

BMI=body mass index; chol=cholesterol; glc=glucose; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride; PCP=primary care physician.

Heterogenity of Antipsychotic Efficacy and Tolerability

Clinicians commonly discuss first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs).[1-3] This two-class distinction is the result of convention and history, and one might wonder if it serves well as the basis for choosing an antipsychotic. Several recent reviews and meta-analyses have concluded that antipsychotics are too heterogeneous with regards to both efficacy and side effects. They should not be grouped into classes,[2] which will not come as a surprise to clinicians who use these drugs.

SGAs, or newer antipsychotics, were ushered in with great hopes for better efficacy compared with older or FGAs, such as haloperidol. Unfortunately, seminal trials during the last several years, such as the Clinical Antipsychotic

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Trials of Intervention Effectiveness (CATIE) or the European First Episode Schizophrenia Trial (EUFEST), have clearly shown that the hope for superior efficacy for newer drugs compared to the older ones, if appropriately dosed, did not materialize.[4,5]

However, this does not mean that there are no efficacy differences. In a meta-analysis of 150 randomized, controlled trials, Leucht and colleagues[2] found four antipsychotics (amisulpride, clozapine, olanzapine, and risperidone), to be better than FGAs for overall efficacy with small to medium effect sizes. In a second meta-analysis, Leucht and colleagues[3] compared only SGAs and again found small efficacy differences. For example, olanzapine was superior to aripiprazole, quetiapine, risperidone, and ziprasidone, and risperidone was more efficacious than quetiapine and ziprasidone. It is not clear in any given patient if this difference in efficacy is relevant.

There is one thing that is clear: clozapine should be considered an antipsychotic in its own league. The recently updated Schizophrenia Patient Outcomes Research Team (PORT) guideline singles out clozapine as the treatment of choice for patients who not only do not respond sufficiently to other antipsychotics,[6] but also for patients with hostility and suicidality.

A similar picture of antipsychotic heterogeneity emerges with regards to side effects, including extrapyramidal side effects, weight gain, sedation, and prolactin elevation.[1]

Stage of illness is very important with regard to efficacy when treating a first-episode patient, a multiepisode (chronic) patient, or a refractory patient. With regard to first-episode patients, two randomized trials, Comparison of Atypicals for First Episode and EUFEST, have found comparable efficacy of antipsychotics for first-episode patients, although the EUFEST study did demonstrate differences in terms of all-cause discontinuation, a measure of effectiveness.[5,7] The influential National Institute for Clinical Excellence guidelines from Great Britain no longer prefer SGAs over FGAs for the treatment of first-episode schizophrenia, but suggest taking into account issues such as relative potential to cause EPS side effects, metabolic problems, or subjective tolerability.

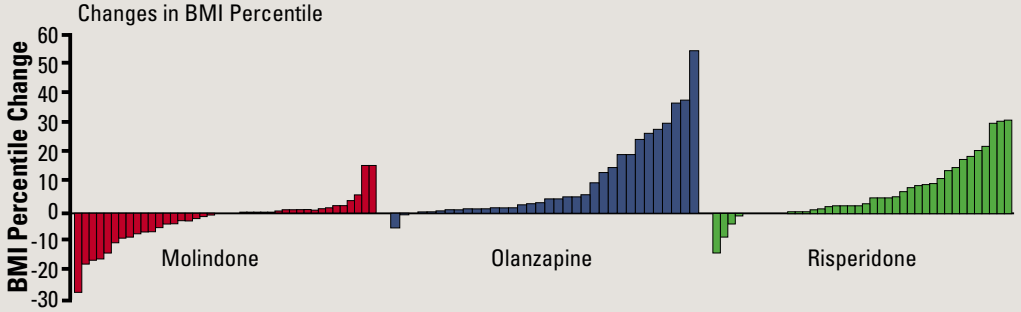
Antipsychotics are quite heterogeneous with regard to side effects (Slide 2).[2,8-10] Knowing this can help with the initial antipsychotic selection. For example, if a patient is very concerned about sedation, side-effect profiles should be examined and a medication should be chosen that has less of a risk for sedation. However, looking at how each individual patient responds to side effects is important. Slide 3 shows the distribution of weight gain for three drugs in patients who participated in The Treatment of Early Onset Schizophrenia Spectrum Disorders (TEOSS) trial.[11] TEOSS was a double-blind comparison of FGAs and SGAs in early onset schizophrenia. The distribution clearly illustrates that weight gain depends on individual vulnerability and the medication. Molindone appears to have a low risk for weight gain; hence, many patients seem to be losing weight in the TEOSS trial when they are switched to molindone.[11] On the other hand, a significant minority of patients on molindone gained weight in the trial. While on average molindone appears to be better than the distributions for olanzapine and risperidone, in any individual patient there is still the risk for weight gain, even with molindone. In Thomas' case, it should not come as a surprise that he gained a substantial amount of weight during the 3-year period he was treated

SLIDE 2
Antipsychotic Heterogeneity[2,8-10]

Medication	Efficacy*	EPS†	Weight Gain†	Sedation†	Prolactin Elevation†
Haloperidol	2	4	1	1	2
Clozapine	4	0	4	4	0
Aripiprazole	2	1	1	1	0
Olanzapine	3	1	4	3	0
Quetiapine	2	0	3	3	0
Risperidone	3	2	3	2	3
Ziprasidone	2	1	1	1	0

* 0=not effective; 4=most effective; † 0=not likely; 4=most likely

SLIDE 3
Weight Change with Antipsychotic Treatment Experienced in Subjects With Early-Onset Schizophrenia and Schizoaffective Disorder[11]



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with olanzapine. TEOSS nicely demonstrates the high risk for weight gain from olanzapine for the whole cohort.

Managing Cardiovascular Risks

Psychiatrically stable patients on maintenance antipsychotic treatment are at risk for developing metabolic syndrome. In routine clinical practice, clinicians likely encounter many patients with schizophrenia who already have cardiovascular risk factors or full metabolic syndrome similar to Thomas. Thomas did not present to his outpatient psychiatrists as an antipsychotic-naïve patient. Instead, he presented with a particular weight and metabolic situation, which, in part, was the result of years of treatment with antipsychotics. As seen in the CATIE study, 36% of male patients and 52% of female patients had metabolic syndrome at study entry.[12] In such patients, clinicians are faced with two choices to manage cardiovascular risk: trying to reverse the problem by switching antipsychotics, or staying on the antipsychotic while adding ameliorative medications or behavioral interventions.[13-19]

Switching Antipsychotics

Switching to an antipsychotic with low liability toward weight gain and metabolic problems, such as aripiprazole or ziprasidone, seems a reasonable strategy that is supported by the literature.[13,20] Clinicians seem to have adopted this approach as one that avoids the monitoring issue as suggested in a study by Morrato and colleagues.[14] Despite its support and intuitive allure, however, the strategy might not work clinically in all patients. In an open-label study, Kim and colleagues[21] reported on 15 patients with schizophrenia: 33% did not tolerate the switch, and there were no striking improvements in metabolic parameters in the remainder of the patients.

It is hoped that the completion of the large, randomized National Institute of Mental Health–sponsored Comparison of Antipsychotics to Metabolic Problems (CAMP) trial can further clarify the picture regarding safety and efficacy of switching antipsychotics for metabolic reasons in patients with schizophrenia and schizoaffective disorder.[15] In the CAMP trial, all patients received a behavioral intervention while they either stayed on their current antipsychotic, which in this trial was olanzapine, quetiapine, or risperidone, or were switched to aripiprazole. At this point, the PORT guidelines did not find sufficient evidence to recommend switching for metabolic reasons as a clinical strategy.

Thomas opted to change antipsychotics despite the risk for relapse, which was a concern because of his history of violence. Unfortunately, the switch has not made a meaningful difference in his weight, at least not in a 3-year, long-term follow-up. However, his metabolic parameters, with the exception of triglycerides, which are most likely directly related to his weight and not his medication, have improved overall and are satisfactory.

Treating Metabolic Issues

If Thomas did not switch medications and had stayed on olanzapine, several options are supported by clinical trials for treating metabolic issues. A statin, such as rosuvastatin[16] or metformin,[17] or a weight loss drug, such as sibutramine,[18] could have been added. In addition, clinicians should also recommend psychosocial weight loss interventions to overweight patients with schizophrenia as an evidence-based intervention that is endorsed by the PORT group.[19] Key elements of such interventions include psychoeducation, behavioral self-management, goal setting, regular weigh-ins, self-monitoring, and dietary and activity modification for ≤3 months. Thomas is currently managed with this strategy and trying to lose weight. Outside of such a program there may be little chance for him to succeed in the long run, and medication to help reduce his weight and improve his triglycerides could become necessary.

Prevention and Early Intervention of Weight Gain and Metabolic Problems

Primary prevention is always preferred over having to limit damage from the development of an iatrogenic complication, which is particularly important in children who seem to be at a higher risk than adults for side effects from antipsychotics. In a review of randomized trials conducted in early-onset schizophrenia spectrum disorders, Kumra and colleagues[22] found that children are more sensitive than adults to developing side effects, including EPS, sedation, prolactin elevation, and weight gain.

Focusing on cardiovascular risks, Corell and colleagues[10] measured changes in weight, lipids, and metabolic parameters in the observational Second-Generation Antipsychotic Treatment Indications, Effectiveness, and Tolerability in Youth study. This was a cohort study where 338 antipsychotic-naïve youth were started on an antipsychotic. Patients gained weight quickly, and after only 3 months of treatment their weight increased significantly on aripiprazole, risperidone, quetiapine, and olanzapine (Slide 4).[10] In contrast to weight gain with all antipsychotics, only aripiprazole had no significant effects on cholesterol and lipids; the other antipsychotics all increased cholesterol and lipid levels.

A naturalistic study was conducted where antipsychotic-naïve, first-episode patients were randomized to olanzapine, haloperidol, and risperidone. All patients gained weight after 3 months, olanzapine induced the most weight gain (19 lbs), haloperidol induced the least weight gain (8 lbs), and risperidone induced a 13-lb weight gain.[23] Interestingly, after 1 year of treatment, all three groups overlapped because the two arms that lagged behind initially, risperidone and haloperidol, had caught up with olanzapine. Weight gain is a very concerning side effect for patients experiencing a first episode of schizophrenia because they are typically naïve to antipsychotic exposure. Unfortunately, it now appears that weight gain is the rule and not the exception in first-episode patients once they start antipsychotics.

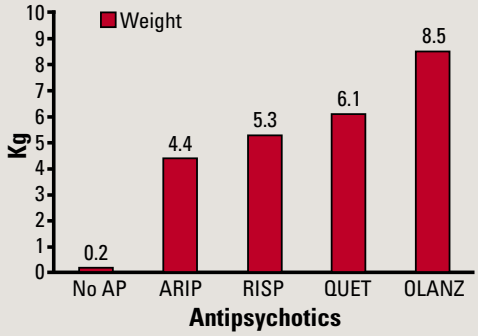
Prevention of Mortality and Morbidity

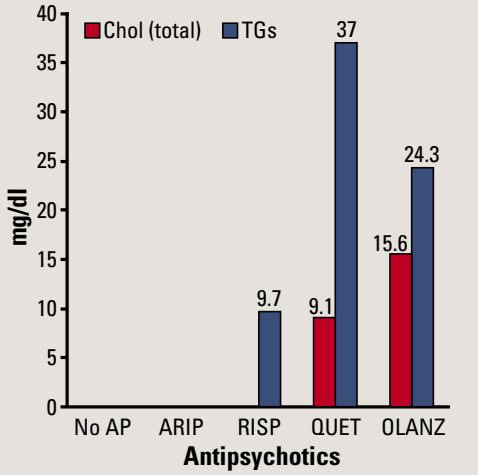
Following several randomized, first-episode treatment studies,[5,7] it is now generally accepted that olanzapine is associated with the most severe metabolic abnormalities, and the aforementioned influential PORT guidelines specifically recommend against using olanzapine or clozapine as a first-line treatment for first-episode patients with schizophrenia unless there are other overriding factors.[6] By contrast, data from the EUFEST trial that randomized ~500 first-episode patients to low-dose haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone, suggest that ziprasidone might be an effective, low-risk choice in avoiding weight gain. EUFEST patients randomized to ziprasidone for 1 year gained an average of 10 lbs compared to 16 lbs with haloperidol or 31 lbs with olanzapine. Weight gain of >7% at baseline was observed from a low of 37% of patients randomized to ziprasidone to a high of 86% of those randomized to olanzapine. Given comparable efficacy, side-effect profile and selecting a low-risk choice becomes an important consideration when choosing an initial antipsychotic for first-episode patients (Slide 5).[24-27]

For those patients who need to be treated with olan-

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SLIDE 4
SATIETY Cohort Study 12-Week Follow-up[10]





N=272; 13.9 years of age; 57% male

SATIETY=Second-Generation Antipsychotic Treatment Indications, Effectiveness, and Tolerability in Youth; AP=antipsychotic; ARIP=aripiprazole; RISP=risperidone; QUET=quetiapine; OLANZ=olanzapine; Chol=cholesterol; TGs=triglycerides.

SLIDE 5
Mortality and Morbidity Prevention[24-27]

Select
- Low-risk choice
- Patient factors
- Early ancillary treatments
  - Behavioral prevention[17,25]
  - Adjunctive metformin[17]

Monitor
- Follow guidelines (eg, ADA)[27]

Adjust
- Switch antipsychotics
- Add behavioral treatment[19]
- Treat medical morbidities

ADA=American Diabetes Association.

zapine or clozapine, attempting to stunt weight gain by adding metformin early in the course of treatment can be effective.[22] The addition of early behavioral intervention to counteract weight gain during treatment of first-episode psychosis has been shown to be effective in the short run.[24,25] Unfortunately, the benefit of a time-limited early behavioral intervention is lost as early as 6 months later.[26]

Conclusion

Regardless of the initial antipsychotic choice, frequently monitoring for iatrogenic side effects from medication is imperative. Thomas was not appropriately monitored, and time was lost during those 3 years where he went from being overweight to obese. As Churchill said, "However beautiful the strategy, you should occasionally look at the results." Several guidelines are available, including those from American Diabetes Association, the Mt. Sinai Consensus Conference, and the Massachusetts General Hospital Schizophrenia Program. With regard to altering or switching antipsychotics, adding behavioral treatment, or treating comorbidities, treatment should be adjusted in response to the identified problems. Thomas' cholesterol, in the absence of other cardiac risk factors, is acceptable based on the guidelines from the National Cholesterol Education Program. He does not have diabetes, and his low-density lipoprotein is acceptable. His triglycerides are concerning and are likely related to his obesity; therefore, he might need more aggressive treatment in the future.

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