The Effectiveness Criterion: Balancing Efficacy Against the Risks of Weight Gain

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The decision to stay with a treatment or switch to a different one depends on the balance between overall effectiveness, efficacy, and tolerability. One of the challenges with antipsychotic medication treatment of serious mental illness is the risk of weight gain, which can be considerable for some patients. This article reviews the issue of weight gain associated with antipsychotics and places it within the context of metabolic issues in general. The concept of "number needed to treat" is introduced to interpret the results of the Clinical Antipsychotic Trials of Intervention Effectiveness for schizophrenia, particularly to examine the balance between overall effectiveness, efficacy, and tolerability of the different antipsychotic treatments tested. Predictors of weight gain for olanzapine are reviewed for schizophrenia and bipolar disorder, as is a monitoring plan applicable for all patients receiving antipsychotic therapy. *(J Clin Psychiatry 2007;68[suppl 12]:12–17)*

Treatment decisions involving antipsychotic medication require careful consideration of the individual patient's clinical needs and can give rise to significant therapeutic dilemmas. One adverse outcome that is the focus of recent attention is weight gain. This article will review weight gain and obesity within the context of the patient with schizophrenia. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study results[1–3] regarding weight gain will be examined, and the concept of "number needed to treat" (NNT) will be used to examine the balance between efficacy and safety.[4] The decision to "switch or stay" regarding antipsychotic medication treatment will be discussed within the context of known predictors of weight gain and the expectation of efficacy. Monitoring strategies appropriate for all patients receiving antipsychotics will be reviewed.

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OBESITY IN CONTEXT

Obesity is defined as having a high body mass index (BMI), calculated as the quotient of body weight (kg) divided by the square of height (m). The prevalence of obesity has increased across the United States, and it is estimated that 30% of the general population is obese (BMI greater than 30 kg/m^2).[5] Obesity is a major risk factor for type 2 diabetes mellitus and is an important component of the metabolic syndrome, and not surprisingly the prevalence of both diabetes[6] and metabolic syndrome[7] is also increasing among the general population.

Patients with schizophrenia have higher rates of obesity, type 2 diabetes mellitus, and metabolic syndrome than the general population. Among the patients participating in phase 1 of the CATIE study,[8] the mean BMI was 30 kg/m^2. Forty-six percent of patients met the metabolic syndrome criterion of abnormal waist circumference,[8] and 11% of patients had diagnosed diabetes mellitus at baseline.[1] Despite the relatively common occurrence of metabolic problems, the rate of treatment at baseline was surprisingly low; for example, only 12% of the patients with dyslipidemias were receiving treatment for this condition.[9]

Of concern is the relationship between obesity and mortality. In a now-classic long-term prospective study conducted by the American Cancer Society,[10] 750,000 men and women were followed between 1959 and 1972 for their incidence of mortality as it related to their weight. Individuals closest to an average weight and 10% to 20% below average weight had the lowest mortality. Mortality among men and women 30% to 40% heavier than the average weight was close to 50% greater. Among individuals more than 40% heavier than the average,

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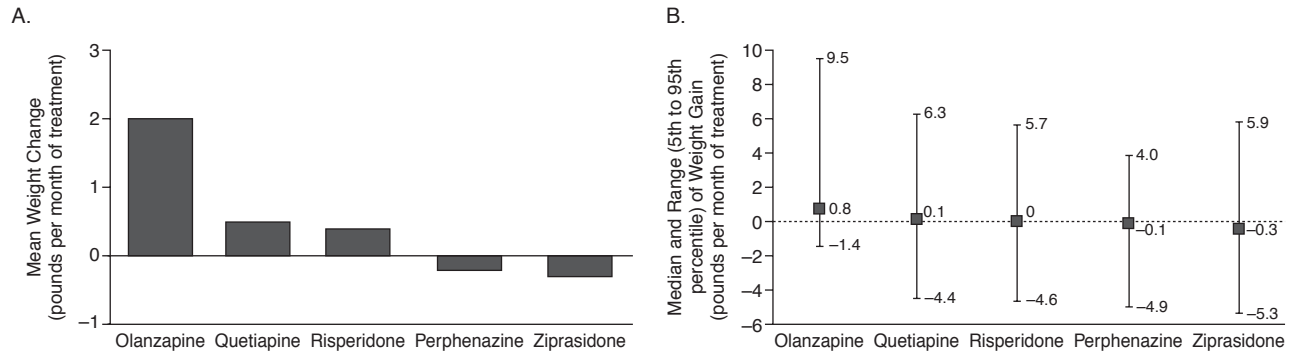
Figure 1. Weight Change per Month of Antipsychotic Treatment in Phase 1 of CATIE[a]



[a]Data from Lieberman et al.[1]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

mortality was 90% higher. Coronary heart disease was attributed as the major factor in the mortality of persons who were overweight.

Treatment with antipsychotic medication may lead to an increase in patients' weight and may change their BMI from the normal range (18.5 to 24.9 kg/m^2) to the overweight (25–29.9 kg/m^2) or obese range (30 kg/m^2 or greater). BMI-related health risks are well established; the health risk associated with a BMI of 30 to 34.9 kg/m^2 is considered "high," the risk with a BMI of 35 to 39.9 kg/m^2 is considered "very high," and the risk with a BMI greater than 40 kg/m^2 is considered "extremely high."[11] The available antipsychotics have different propensities to cause weight gain. In an often-cited meta-analysis of weight change after 10 weeks of treatment at a standard dose,[12] mean increases in weight among the second-generation antipsychotics (SGAs) evaluated were 4.45 kg for clozapine, 4.15 kg for olanzapine, 2.10 kg for risperidone, and 0.04 kg for ziprasidone. Possible mechanisms for medication-associated weight gain include weight loss prior to drug treatment, food craving, alteration in resting metabolic rate, change in neurotransmitters (in general, α-adrenergic neurotransmission is thought to stimulate appetite, while β-adrenergic, histaminergic, dopaminergic, and serotonergic signal transduction confers satiety), and alteration of neuropeptides such as leptin and cytokines such as tumor necrosis factor.[13] The relative importance of these mechanisms may differ from medication to medication and from individual to individual.[14]

WHAT CAN WE LEARN FROM CATIE?

The primary objective of the CATIE study was to evaluate the effectiveness of antipsychotic medications in treating schizophrenia by assessing how long patients remain on their randomized medication. Time on medication can be viewed as a measure of effectiveness (how well a medication works in the real world with actual patients). Effectiveness is dependent on 3 components: efficacy (how well a drug reduces symptoms), safety and tolerability (how often the drug leads to adverse events), and adherence (whether the patient is actually taking the drug). Failure of any 1 or more of these 3 components will lead to an overall lack of effectiveness. In the CATIE study, time on medication was driven by this consideration of both efficacy and tolerability, and was dependent on input from both the clinician and the patient. Because CATIE was designed as a multiphase study, patients could discontinue their initial randomized medication and be re-randomized to another medication. Hence, the CATIE study resembles what can happen during regular clinical treatment—if one medication does not work for any reason, another medication is tried. CATIE is also unique in that it compared many different antipsychotics (5 in phase 1) among a large number of patients (1432 patients received medication in phase 1 of the study) for a relatively long amount of time (up to 18 months).

Of special interest for this discussion is the weight gain observed with the different antipsychotics being tested. In phase 1, weight gain greater than 7% from baseline to last observation occurred among 30% of the patients randomized to olanzapine, 16% for quetiapine, 14% for risperidone, 12% for perphenazine, and 7% for ziprasidone.[1] Mean weight change in pounds was 9.4, 1.1, 0.8, –2.0, and –1.6 for olanzapine, quetiapine, risperidone, perphenazine, and ziprasidone, respectively. However, patients randomized to olanzapine stayed on their randomized medication approximately twice as long as patients randomized to any of the others.[1] Thus, it would be more meaningful to examine weight change per month of treatment (see Figure 1A). However, these data do not inform the clinician of the variability of weight gain among a group of patients. We already know from the data for 7% weight gain from baseline that all antipsychotics are associated with weight gain for some patients, but how extreme are the 5th and

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95th percentiles? Figure 1B displays the median and range for weight gain in pounds per month of treatment. Some patients randomized to olanzapine lost 1.4 lb per month, and some gained 9.5 lb per month. Patients randomized to medications that had an average (and median) weight loss, perphenazine and ziprasidone, still show variability in weight change, with some patients randomized to ziprasidone losing 5.3 lb per month and others gaining 5.9 lb per month.[1]

In order to evaluate the risk of weight gain and place it into clinical perspective regarding medication selection, other components of effectiveness need to be examined. Ultimately, there will need to be a favorable balance of benefit to risk. The CATIE study provided a myriad of different outcomes in addition to the primary outcome measure of time on medication. Comparing these can be difficult, but one method is to convert the outcomes to a common unit of measure. NNT is one such method in which 2 interventions can be directly compared on an outcome of interest. The NNT is the number of patients one would have to treat with one of the interventions instead of the other before expecting one additional occurrence of an outcome of interest. For example, an NNT of 10 would mean 10 patients would have to receive one of the interventions instead of the other to see 1 additional occurrence of an outcome of interest, be it response, remission, or weight gain beyond 7% of baseline. Thus, NNT can be used to gauge how different interventions really are.[15] Simply stated, the smaller the NNT, the larger the differences between the 2 interventions. "Number needed to harm" (NNH) is similar in concept to NNT, but traditionally refers to adverse outcomes that clinicians attempt to avoid. In general, a large NNT of 100 or more means that there is little difference between choosing one intervention versus another for the outcome measured. A small NNT of 2 would be a very important difference. However, some NNTs may be clinically important even if they are relatively large; for example, when the outcome is death and the intervention is an immunization. Some NNTs may be clinically unimportant, even if they are relatively small; for example, when the outcome is mild dry mouth.

NNT is easy to calculate; only 2 numbers are required, and they are generally available when studies are reported: percentage of patients who had the outcome for each of the 2 interventions being compared. These 2 percentages are subtracted to get the difference, and the reciprocal of this difference is the NNT. By convention, when not presenting fractions, we round the NNT up to the next *higher* whole number. Table 1 provides an example.

Effectiveness and safety outcome data were extracted from the 3 principal publications that documented the results of phases 1 and 2 of the CATIE schizophrenia study.[1–3] NNT and NNH were calculated from the categorical results.[4] During phase 1, 74% of patients discontinued their treatment before 18 months. However, this rate varied from drug to drug, with the lowest rate of all-cause discontinuation being observed for olanzapine (64%) and the highest rate being observed for quetiapine (82%).[1] The difference between olanzapine and quetiapine on this measure can be expressed as an NNT. The calculation is straightforward: NNT = 1/(0.82 – 0.64) = 1/0.18 = 5.6, rounded up to 6. This is interpreted as follows: for every 6 patients treated with olanzapine instead of with quetiapine, there was 1 additional person who completed the 18 months of phase 1 of CATIE. All-cause discontinuation integrates several components, including efficacy and tolerability, and examining the NNT for discontinuation related to these components can help assess their relative importance. Table 2 provides some NNT data for various outcomes observed in phase 1.

Table 1. Calculating Number Needed to Treat (NNT): Example

Both Drug A and Drug B are used to treat depression
Relapse rate at 1 year is 50% for Drug A and 30% for Drug B
How many patients do you need to treat with Drug B instead of Drug A to avoid 1 relapse?
NNT = 1/[0.50 – 0.30] = 1/0.20 = 5
By treating 5 patients with Drug B instead of Drug A, you avoid 1 relapse

In phase 1 of CATIE, overall effectiveness demonstrated an advantage for olanzapine with an NNT for all-cause discontinuation ranging from 6 for olanzapine versus quetiapine, to 11 for olanzapine versus risperidone.[4] This overall effectiveness incorporates an efficacy advantage seen in every 8 to 11 patients and a tolerability disadvantage seen in every 12 to 31 patients. The data show that weight gain or metabolic effects can be expected in every 12 to 18 patients in terms of discontinuation from treatment, or for every 4 to 7 patients in terms of weight gain over 7%.

It appears that an efficacy advantage for olanzapine drove the overall lower all-cause discontinuation rate for olanzapine, and thus the advantageous NNT observed for olanzapine compared with the other antipsychotics in terms of all-cause discontinuation. The NNT (or NNH) for discontinuation because of weight gain or metabolic effects for olanzapine, although statistically significant, did not reach the same level of magnitude as the NNT for efficacy.[4]

Patients who discontinued phase 1 prior to completion were offered participation in phase 2. Phase 2 of CATIE consisted of 2 pathways: a "clozapine pathway," in which patients were re-randomized to receive either open-label clozapine or double-blind olanzapine, risperidone, or quetiapine,[2] and a "ziprasidone pathway," in which patients were re-randomized to receive double-blind ziprasidone, olanzapine, risperidone, or quetiapine.[3] For either pathway, patients could not be randomized to the same

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Table 2. Number Needed to Treat in Phase 1 of CATIE[a]

Outcome	Olanzapine vs Risperidone	Olanzapine vs Quetiapine	Olanzapine vs Ziprasidone	Olanzapine vs Perphenazine
Discontinuation due to all causes	11[b]	6[b]	7[b]	9[b]
Discontinuation due to efficacy loss	8[b]	8[b]	11[b]	10[b]
Discontinuation due to intolerability	–12[b]	–26	–29	–31
Discontinuation due to patient decision	15	11[b]	10[b]	16
Hospitalization	28	12[b]	16[b]	23
Discontinuation due to weight gain or metabolic side effects	–14[b]	–18[b]	–17[b]	–13[b]
Prescription of antidiabetic	–82	–67	–71	–61
Prescription of statin	–81	–323	–30[b]	–57

[a]Data from Citrome and Stroup.[4] The smaller the number needed to treat, the larger the differences between the 2 drugs. Negative numbers indicate advantage for the non-olanzapine comparator.
[b]Statistically significant (95% CI did not cross from + to –).
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Table 3. Number Needed to Treat: Weight Gain and Weight Loss in Phase 2 of CATIE ("ziprasidone pathway")[a]

Outcome	Ziprasidone vs Olanzapine	Ziprasidone vs Risperidone	Ziprasidone vs Quetiapine
Discontinuation due to all causes[b]	–10	–8	15
Discontinuation due to weight gain or metabolic side effects[b]	12[c]	21[c]	11[c]
Weight gain > 7%[b]	6[c]	16	14
Weight loss > 7% in patients with weight gain > 7% in phase 1[d]	3	5	3

[a]The smaller the number needed to treat, the larger the differences between the 2 drugs. Negative numbers indicate advantage for the non-ziprasidone comparator.
[b]Data from Citrome and Stroup.[4]
[c]Statistically significant (95% CI did not cross from + to –).
[d]Data from Stroup et al.[3] Of 61 patients who gained over 7% of their body weight in phase 1, 42% of ziprasidone-treated patients, 20% of risperidone-treated patients, 7% of quetiapine-treated patients, and 0% of olanzapine-treated patients lost over 7% of their body weight during phase 2.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

medication they were receiving in phase 1. Of the 74% of subjects who discontinued phase 1, approximately half entered phase 2.[2,3] Choice of pathway was made by the clinician. Although the clozapine pathway was intended for patients who discontinued phase 1 because of lack of efficacy, many of these patients were enrolled in the ziprasidone pathway instead. About half of those in the ziprasidone pathway had discontinued phase 1 because of inefficacy.

The clozapine pathway results demonstrated superiority of clozapine to both risperidone and quetiapine in all-cause discontinuation.[2,3] The ziprasidone pathway failed to demonstrate the superiority of ziprasidone in all-cause discontinuation. Of interest is the occurrence of weight gain and weight loss. The patterns of weight change mirrored what was observed in phase 1, with ziprasidone presenting the most favorable weight and metabolic profile. Table 3 displays NNT for all-cause discontinuation, showing a statistically significant advantage for ziprasidone in terms of discontinuation because of weight or metabolic effects with NNTs of 12, 21, and 11 when comparing it with olanzapine, risperidone, and quetiapine, respectively.

Thus, NNT (or NNH) can help place the wide array of CATIE results into clinical context and permits quantification of the differences observed between the antipsychotics that were tested.

The relative importance of these differences among the SGAs will vary from patient to patient, but by examining the magnitudes of NNT (or NNH), the clinician can begin to make risk-benefit decisions specific to the individual patient's needs and/or preferences.

SWITCH OR STAY?

The need for individualized treatment decisions and the criteria that influence these decisions are illustrated by the following 2 fictional patients.

Deciding whether to continue treatment with a particular antipsychotic or switch the patient to another can pose substantial dilemmas for the clinician. Take, for example, the following fictional case: Mr. A, a 40-year-old white man with schizophrenia, has been hospitalized about 5 times in the past 15 years. He responds reasonably well to olanzapine or risperidone, but not to haloperidol, and he objects to extrapyramidal side effects, particularly akathisia. Both of Mr. A's parents have type 2 diabetes mellitus. Mr. A's BMI is 27.5 kg/m^2, and he eats high-fat foods and does not exercise. He smokes 2 packs of cigarettes per day. He has been placed on treatment with risperidone 4 mg/day, but after 1 month he complains of feeling restless.

Mr. A presents with a number of conflicting issues that make medication choice difficult, which emphasizes that

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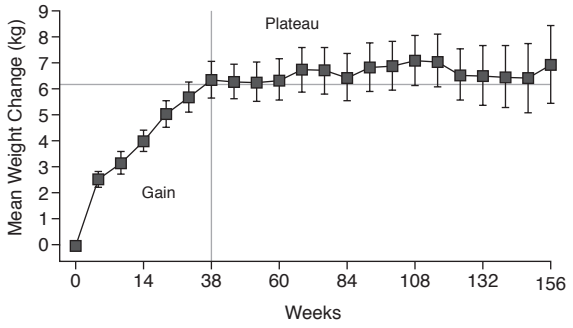
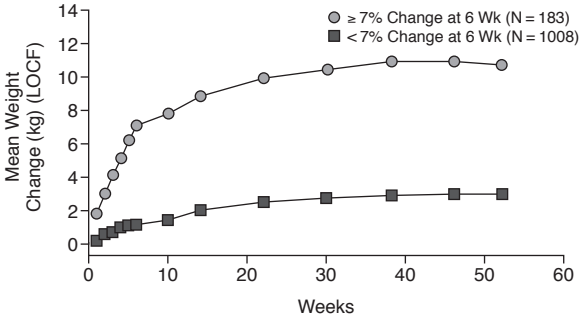
Figure 2. Weight Change in Patients Treated With Olanzapine During a 3-Year Observation Period[a]



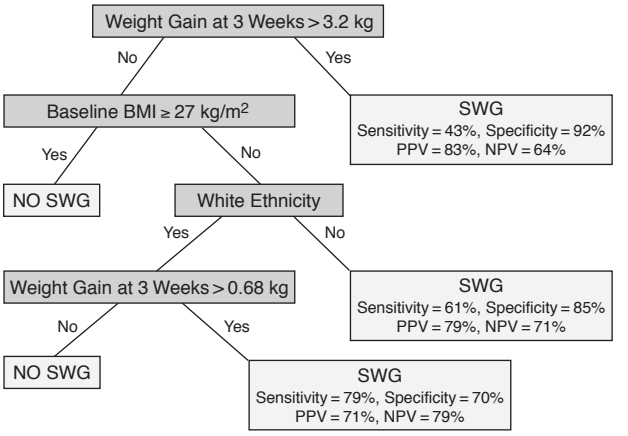
[a]Reprinted with permission from Kinon et al.[16] Total study N = 573; figure presents data for 147 patients who completed the 3-year observation period. No formalized weight-moderating interventions were included in the study. Study design included both open-label and double-blind treatment.

Figure 3. Weight Change in Patients Treated With Olanzapine During a 1-Year Period, According to Percentage of Weight Change at 6 Weeks[a]



[a]Reprinted with permission from Kinon et al.[17]
Abbreviation: LOCF = last observation carried forward.

Figure 4. Decision Tree for Predicting Which Patients Would Develop Substantial Weight Gain (SWG) During Olanzapine Treatment Using Weight Change at Week 3 in Addition to Baseline Predictors[a]



[a]Reprinted with permission from Lipkovich et al.[18] This tree was developed using a classification tree method based on an algorithm for recursive partitioning. The terminal nodes labeled "SWG" designate subgroups of subjects who were predicted to gain substantial weight based on the corresponding condition of the decision rule. The sensitivity, specificity, and negative and positive predictive values listed at each SWG node are the cumulative operational characteristics of the prediction rule achieved at that level.
Abbreviations: BMI = body mass index, NPV = negative predictive value, PPV = positive predictive value.

the choice to "switch or stay" is a highly individualized decision. Evidence-based medicine philosophy states that relevant clinical trials can inform the clinician in making thoughtful individualized treatment decisions. While NNT and NNH can help predict how often events can occur, there are no guarantees of weight gain or loss or drug efficacy. The patient's history is the best predictor of treatment success or failure. Regarding the prediction of weight gain, we can turn to studies that have examined the pattern of weight gain over time. In a retrospective analysis of 573 patients given olanzapine and 103 patients given haloperidol over a period of 39 weeks or longer, mean weight gain plateaued after the initial 39 weeks[16] (Figure 2). In addition, patients with a higher BMI at baseline had a lower long-term weight gain. In this study, dosage of olanzapine did not seem to affect weight.

In another report, patients with schizophrenia who were receiving olanzapine were examined regarding the impact of the rapidity of weight gain.[17] Patients who gained more than 7% of their body weight during the first 6 weeks of treatment with olanzapine were most at risk for significant weight gain in the future (Figure 3). Thus, by measuring the weight gain of patients during the first few weeks of olanzapine treatment, as well as assessing changes in appetite, patients at risk for substantial weight gain can be identified.

Another fictional case example can illustrate the challenges in treating patients with bipolar disorder who are at risk for weight gain. Ms. B is a 30-year-old white woman with bipolar disorder who was hospitalized once at age 25 after a suicide attempt. Her symptoms are under excellent control, but whenever she stops taking her medication (lithium), she becomes severely depressed and somewhat agitated, with marked insomnia and anorexia. Ms. B wants to become pregnant and is worried about postponing having a child.

Focusing on the risk of weight gain, what are the data regarding predictability of weight change with olanzapine? This question was investigated by pooling data from 4 long-term, randomized, multicenter studies in patients with bipolar mania or mixed mania.[18] Substantial weight gain (SWG) was defined as gaining 5 kg (or 7% of initial weight) within 30 ± 2 weeks. The baseline characteristics that were significantly related to SWG included younger

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Table 4. Monitoring Protocol for Patients Treated With Second-Generation Antipsychotics[a]

Parameter	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal/family history	✓					✓	
Weight (body mass index)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

[a]Copyright © 2004 American Diabetes Association. Reprinted with permission from the American Diabetes Association.[19]

age, nonwhite ethnicity, lower BMI, non-rapid cycling, and psychotic features. A weight gain of approximately 3 or more kg in the first 3 weeks of therapy predicted SWG by 30 weeks. A classification system with thresholds for early weight gain, baseline BMI, and ethnicity further improved predictions of SWG (Figure 4).

For both case examples, monitoring for weight and metabolic parameters is mandatory. The report from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes Consensus Panel contains valuable advice for the appropriate and prudent monitoring of patients who are at risk for type 2 diabetes mellitus.[19] Table 4 outlines their monitoring recommendations, but note that the most frequently assessed parameter is weight. Monitoring weight at each patient visit will allow the clinician to catch a problem early, before substantial weight gain has set in. It also underscores to both the patient and the clinician the importance of physical fitness.

CONCLUSIONS

The prevalence of obesity among patients with schizophrenia is higher than in the general population. Antipsychotics have been associated with weight gain, but this differs among both medications and individuals. NNT analysis can help us understand clinical trial results in terms of overall effectiveness, efficacy, and tolerability, and help predict how commonly we will see differences between agents. For individuals on treatment with SGAs, monitoring is mandatory. The monitoring of a patient's weight is relatively easy to do and can serve as an early-warning indicator that a "switch or stay" decision needs to be made.

Drug names: clozapine (FazaClo, Clozaril, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), 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. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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