

PHYSICIANS DISCUSS THE
CONSENSUS STATEMENT ON
ANTIPSYCHOTIC MEDICATIONS
AND OBESITY AND DIABETES

In 2003, the U.S. Food and Drug Administration (FDA) asked all manufacturers of atypical antipsychotic medications to add a statement to their package inserts warning of an increased risk of hyperglycemia and diabetes in patients taking these medications.

In November 2003, a panel convened by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity heard presentations from experts in the fields of psychiatry, obesity, and diabetes, as well as from representatives from the FDA and the manufacturers of atypical antipsychotics: AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, and Pfizer. The consensus statement developed by this panel was originally published in the February 2004 issue of *Diabetes Care* and was reprinted in the February 2004 issue of *The Journal of Clinical Psychiatry*.

Recently, John M. Kane, M.D., a Founding Director of the CME Institute of Physicians Postgraduate Press, Inc., assembled a group of experts to discuss the consensus statement and the FDA's suggested changes in labeling in order to advise clinicians how these recommendations may affect their treatment of patients with antipsychotic medications. Their discussion appears here.

This special commentary is another in a series of independent projects undertaken by the CME Institute as a service to its members and the broader academic community.

Faculty affiliations and disclosures appear at the end of this Commentary.

Metabolic Effects of Treatment With Atypical Antipsychotics

John M. Kane, M.D.; Eugene J. Barrett, M.D., Ph.D.; Daniel E. Casey, M.D.; Christoph U. Correll, M.D.; Alan J. Gelenberg, M.D.; Samuel Klein, M.D.; and John W. Newcomer, M.D.

The metabolic effects of treatment with antipsychotic medications have been under considerable debate. The main purpose of this discussion is to allow readers to get a sense of the information that is available regarding metabolic effects and the studies that are underway to expand this information (Appendix 1). The knowledge base about metabolic effects is evolving, so some of the conclusions drawn in this discussion may be tentative. For a list of antipsychotic medications affected by the FDA's recent request for a labeling change, see Table 1.

The Prevalence of Obesity and Type 2 Diabetes in the Population of Patients Who Are Treated With Antipsychotic Medications

Dr. Kane: What is the prevalence of obesity and type 2 diabetes in the population of patients who are treated with antipsychotic medications?

Dr. Barrett: There is certainly an increased prevalence of obesity and very likely an increased prevalence of diabetes in patients taking antipsychotics compared with the general population, although there are no good databases that can provide information on age-matched individuals, especially not with a correction for family history or other confounding factors.

Dr. Correll: There actually seem to be 2 questions—first, whether individuals with schizophrenia or bipolar disorder are at greater risk for obesity and type 2 diabetes than the general population even without taking antipsychotic medications, and secondly, to what extent antipsychotic medications increase rates of obesity and type 2 diabetes.

Dr. Kane: The prevalence of obesity and type 2 diabetes in schizophrenia or bipolar disorder—even without the addition of antipsychotic medication—is unclear, and it is hard to draw conclusions as to whether obesity is more prevalent in these patients than in the general population.

Dr. Casey: I agree about the lack of precision in our existing knowledge on the epidemiology and population characteristics of diabetes in people taking antipsychotics; however, the evidence consistently shows that the diabetes rate is perhaps 50% to 100% higher in people taking these medicines, given the caveat that we do not have corrections for age, gender, body mass index, family history, and other factors.

Dr. Newcomer: I would emphasize that we can be more certain about the converse. There is very little to suggest that rates of obesity and of type 2 diabetes are lower in populations who need to take antipsychotic medications. We can debate the strength of the evidence about how much higher these rates are, and I agree the evidence is certainly stronger for a higher obesity rate than it is for an increased rate of type 2 diabetes, but I would say that we can be confident that there is no indication that these

Table 1. Atypical Antipsychotic Medications

Aripiprazole
Clozapine
Olanzapine
Quetiapine
Risperidone
Ziprasidone

populations are at lower risk. The logical conclusion is that psychiatric populations need to get the same level of public health concern and monitoring as the general population.

Dr. Correll: One small group that may have a lower risk at baseline is children and adolescents who are treated with antipsychotic medications for disruptive behavior disorders and aggression. Often, these patients have comorbid attention-deficit/hyperactivity disorder that is treated with stimulants and so may start antipsychotic treatment with lower body mass index (BMI) levels. However, in our ongoing prospective study of children and adolescents who start taking these agents, lower BMI or stimulant cotreatment did not protect them from weight gain while taking antipsychotic medications. Even though they start at a lower BMI, they are still at the same risk.

Dr. Casey: When addressing this topic, we must avoid the error of blaming the patients for gaining weight or developing type 2 diabetes. There is no evidence that the patients themselves or their psychiatric illnesses are the cause of these potential problems, although there may be an important patient-treatment interaction.

Dr. Kane: That is an important message, but there is still a lack of clarity as to whether or not the psychiatric disorders themselves, even when untreated, are associated with an increased risk of obesity or type 2 diabetes.

Dr. Newcomer: There has been confusion in prior discussions of obesity and type 2 diabetes in psychosis and bipolar disorder as to whether it is the disease state itself (i.e., the biology of the psychiatric disorder) that causes weight gain or diabetes, or the socioeconomic and behavioral correlates of the disease, like reduced access to medical care or poor food choices, in that if you do not have a lot of money, it may be cheaper to feed yourself with fast food than it is with healthy salads. These are the unanswered research questions. There may well be some increased risk prior to treatment, but what contributes to that?

Dr. Casey: Evidence from the National Health and Nutrition Examination Survey (NHANES) III [Allison DB, et al. *J Clin Psychiatry* 1999;60:215–220], which surveyed an outpatient psychiatric population in 1989, prior to the atypical antipsychotic era, showed that patients with schizophrenia were overrepresented in the higher BMI categories compared with the general popula-

Table 2. Atypical Antipsychotics and Metabolic Abnormalities^a

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

^aReprinted with permission from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care* 2004;27:597.

Symbols: + = increase effect; - = no effect; D = discrepant results.

*Newer drugs with limited long-term data.

tion and underrepresented in the lower, healthy BMI categories. There is no reason to think that has improved over the past 15 years and considerable reason to think it has worsened.

Dr. Newcomer: I agree with you, but we should point out that NHANES was a telephone survey and we do not have the other clinical pieces such as family history in that data set that would help us evaluate the data.

Antipsychotic Medications and an Increase in Rates of Obesity, Type 2 Diabetes, and Dyslipidemia

Dr. Kane: To what extent do antipsychotic medications increase rates of obesity, type 2 diabetes, and dyslipidemia?

Dr. Gelenberg: The first point to make is that, although the atypical antipsychotic medications may have much in common, they are pharmacologically more dissimilar than similar, and we should look to the distinctions that were pointed out by the consensus.

Dr. Klein: That said, Table 2 in the consensus document [reprinted here as Table 2] accurately reflects the data regarding risks for weight gain. Diabetes, however, is more complicated.

Dr. Barrett: Those on the consensus panel were impressed that obesity was more predictable than diabetes in the trials that were done with the atypicals, even in those conducted by pharmaceutical companies who might be championing a particular drug. It was clear that the frequency with which weight gain occurred varied with each drug. The rates of new onset of diabetes—although some will occasionally occur very promptly—are so small relative to the rates of significant weight gain that they are harder to track in their prospective trials. Therefore, an increase in diabetes has less statistical evidence and is more arguable than weight gain.

Dr. Klein: It is easy to measure weight, but diagnosing diabetes requires more specialized testing, which was not included in most studies of antipsychotic medications. An occasional blood glucose measurement may have been performed, but oral glucose tolerance tests were almost never done in most of these studies.

Dr. Correll: Also, weight is easier to use as an outcome measure because it is a continuous variable, whereas diabetes and dyslipidemia have categorical cutoffs. What studies may be missing is the movement towards diabetes, which is found by measuring insulin resistance or the increase in lipids. Mean values, which are often seen in medication trials, may not reflect that overall there is an increase in lipids. The risk for future cardiovascular events does not depend on a cut-off score; rather, there is a continuous increase in risk, similar to weight gain in that there is a higher risk for cardiovascular morbidity even if a patient's triglyceride levels do not reach the limit of 150 mg per dL. If patients' triglycerides increase by 40 mg per dL, their risk of cardiovascular events is much higher, even if their levels started low. Future studies should address that and parse more carefully what happens with triglycerides in patients who take antipsychotic medications.

Dr. Klein: The other limitation is that if obesity in patients is causing diabetes, which is one hypothesis, obesity comes first and then diabetes later. In shorter studies, the prevalence would be much lower for diabetes than for weight gain and therefore harder to pick up. The majority of published studies were not long-term studies, so they were potentially biased against picking up the development of diabetes.

Dr. Newcomer: Right. An individual who has an increase in abdominal adiposity and a decrease in insulin sensitivity can have a long lag before the development of new-onset type 2 diabetes. The beta cells are initially going to hypersecrete insulin in a compensatory fashion, and only after some period of time—perhaps 7 to 10 years in vulnerable individuals—would the beta cells suffer relative failure and start to undersecrete insulin. Then there would be an increase in plasma glucose levels, which might eventually trigger a diagnosis of type 2 diabetes.

So, there is a mismatch between the time required for the development of weight gain, particularly truncal adiposity, and the length of many of the studies looking at changes in plasma glucose or a threshold diagnosis of type 2 diabetes. This time lag has contributed substantially to the confusion about whether or not there is a correlation between weight gain and the incidence of type 2 diabetes in many of the published studies. People point to the fact that many studies that have looked at this have failed to find such a correlation, but that does not take into account that there may be a large mismatch between when the weight gain is being measured and when the beta cell failure is sufficient to manifest hyperglycemia. There has been little standardization in the studies in this area about whether they are looking at young, lean subjects at baseline who can be presumed to have fresh, intact beta cells, or whether they are studying people who have already had 10 years of beta cell stress with substantial abdominal adiposity at baseline.

Dr. Klein: It may be worth mentioning what the experience is with weight gain in the general population. Data from large epidemiological studies [*Colditz GA, et al. Ann Intern Med 1995;122:481-486*] found a 5-kg gain in body weight after age 18–20 years doubled the risk of type 2 diabetes. A 15-kg weight gain increases the risk 6-fold. The weight gain in patients taking these antipsychotics ranges from 0.5 to 5 kg at 10 weeks. That amount of weight gain is a significant risk factor for diabetes.

Dr. Casey: The same amount of weight gain has a very different impact on different patients' overall risk of diabetes. If a person starts at a BMI of 20 and gains 5 body mass units, the risk of type 2 diabetes increases approximately 5-fold. If a person starts with a 25 BMI and the same amount is gained, the risk increases up to 30 times, and adding 5 units from 30 to 35 BMI increases the risk approximately 90-fold. The starting point is very important.

Dr. Barrett: The table category (see Table 2) was carefully labeled "weight gain" as opposed to "obesity," because obesity is also a categorical endpoint, and depending on where people started they may not have become obese, but they may have gained considerable weight. We have to be careful about using the term "obesity" and instead say "weight gain of a significant amount."

One of the striking things in reviewing these data is how some individuals gained substantial weight rather abruptly after beginning treatment, not uncommonly 5 to 15 kg gained in 12 to 16 weeks, while some people gained virtually none.

Dr. Klein: Yes, and weight gain can lead to diabetes in anyone, unless schizophrenia somehow protects people from getting diabetes, which is unlikely.

Dr. Gelenberg: A number of patient groups who are treated with antipsychotic medications, notably people with bipolar disorder, are often treated concomitantly with a drug from another class that perhaps through a different mechanism also will cause an additive weight gain. They get multiple pharmacologic provocations for weight gain at once.

Dr. Correll: Particularly valproate, which has been associated with diabetes and weight gain by itself, may have this additive effect. The additive effect has not yet been seen as strongly for lithium [*Keck PE, et al. J Clin Psychiatry 2003;64:1426-1435*].

Dr. Casey: To turn the discussion to dyslipidemia, there is clear evidence of both a drug component and a generalized lipid component. As one's weight increases, so do one's lipids. But it has been shown that with some of the atypicals, cholesterol can increase 10% or 15% within a month, long before weight gain would be expected to have contributed to that degree of total and LDL cholesterol elevation and triglyceride elevation [*Lindenmayer J-P, et al. Am J Psychiatry 2003;160:290-296*].

Dr. Newcomer: Cases of severe hyperglycemia or metabolic decompensations like diabetic ketoacidosis have been reported in the absence of weight gain or very early in the course of treatment when there has not yet been an opportunity to have gained substantial fat mass. Cases that occur in the absence of obesity or substantial weight gain are in the minority but are noteworthy.

Dr. Barrett: One of the pieces that the consensus group felt poorly equipped to deal with was the question of whether there is a separate effect of one or more of these agents on the secretory capacity of insulin. One would expect that if an individual presents with either severe hyperglycemia or ketoacidosis—particularly in the absence of a major gain in weight—the beta cells would have been somehow targeted. Little work has been done on this beyond case reports. A canine study compared olanzapine and risperidone [Ader M, et al. *In: Program and Abstracts of the 63rd Scientific Sessions of the American Diabetes Association. June 6–17, 2003; New Orleans, La; Abstract 2331–P*]. Olanzapine, more than risperidone, impaired the increase in insulin secretion that typically occurs when animals, like people, gain weight. Despite few data, there is certainly a suspicion of a particular insulin sensitivity. Even in the absence of obesity, a number of people develop type 1 diabetes in their 30s and 40s and 50s, what we call late-onset, autoimmune diabetes in adults. If an additional stressor occurs, their pancreases cannot keep up, and they present with diabetes. However, this has not been well studied, nor has antibody formation in individuals who have presented with ketoacidosis.

Dr. Newcomer: In the few case reports where researchers have looked for the antibodies, they have not found them. Insulin secretion may go up during treatment as a consequence of increasing fat mass, but it may not go up as much as it should [Henderson D. *Presented at the 40th annual meeting of the New Clinical Drug Evaluation Unit. May 30–June 2, 2004; Phoenix, Ariz*]. There should be a full compensatory response to keep glucose levels under control.

Prospective, randomized studies have been done and others are currently underway. Pharmaceutical companies have conducted studies with endpoint fasting glucose, fasting lipids, and BMI measures. Ongoing efforts are pursuing more sensitive measures such as fat mass and insulin-tissue-specific insensitivity, some coming from pharmaceutical companies and some from the National Institute of Mental Health. There is also a large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that should release results in the future, but there is some question about the sensitivity of the measures that were incorporated into that study at baseline.

Dr. Casey: The lipid area is significantly understudied in the population of patients who take antipsychotic medi-

cations. Lipids may be more important than diabetes because dyslipidemia appears to occur at a higher prevalence in this patient population. Patients taking antipsychotic medications die of cardiovascular disease at 2 to 3 times the rate of the general population [Casey DE, et al. *J Clin Psychiatry 2004;65(suppl 7):4–18*], but there are effective treatment interventions for cardiovascular disease through behavior and medicines. Lipid levels are a significant problem because physicians are seeing isolated hypertriglyceridemias and necrotizing pancreatitis.

Not all drugs that increase weight increase lipids, although most of them do. An example is the addition of divalproex sodium to either olanzapine or risperidone, which appears to confer significant protection against elevated cholesterol induced by the atypical antipsychotics and lower cholesterol in patients with migraines and bipolar and seizure disorders [Casey DE, et al. *Neuropsychopharmacology 2003;28:182–192*].

Dr. Newcomer: This is another area where researchers should be doing more work. There would be tremendous interest in a psychotropic drug that lowered lipid levels, but divalproex sodium has not consistently been found to have a cholesterol-lowering effect. In order to assert that a physician could see weight gain in a patient and not anticipate adverse metabolic effects in glucose metabolism and lipid metabolism, considerable data would be needed.

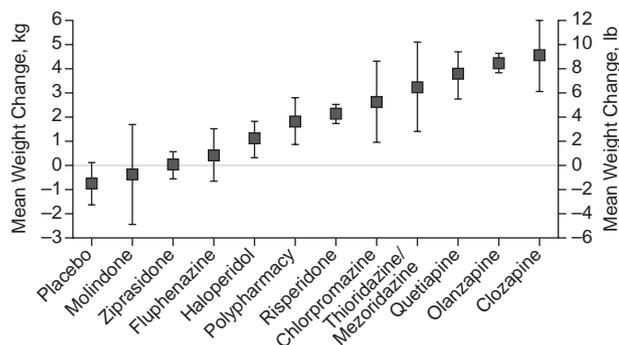
Dr. Correll: In my data on 250 adolescents—130 to 150 antipsychotic-naïve—who have completed an open-label, nonrandomized trial, divalproex sodium had no protective effect for HDL, LDL, cholesterol, or triglycerides. Since divalproex sodium causes weight gain, it would be very difficult to understand how it would protect against metabolic effects, particularly triglyceride elevation. Cholesterol may be more independent of weight gain, but I would be hard-pressed to come up with a mechanism for that.

Dr. Newcomer: One thing that is certain is that there appears to be some increase in the prevalence of obesity and cardiovascular disease in psychiatric populations. That is very important, because the best-developed story in medicine is the primary and secondary prevention of cardiovascular disease. Knowing what we know about what causes and contributes to cardiovascular disease, we are obligated to play detective and figure out why psychiatric patients are dying sooner and more often of cardiovascular disease than the general population. We should carefully study obesity, dyslipidemia, and hyperglycemia in these patients.

Evaluation of Differences in Risk Among Atypical Antipsychotics

Dr. Kane: Does everyone agree with Table 2 of the American Diabetes Association (ADA) consensus statement regarding the differences between the compounds?

Figure 1. Antipsychotics and Mean Weight Change During Short-Term (10-week) Treatment^a



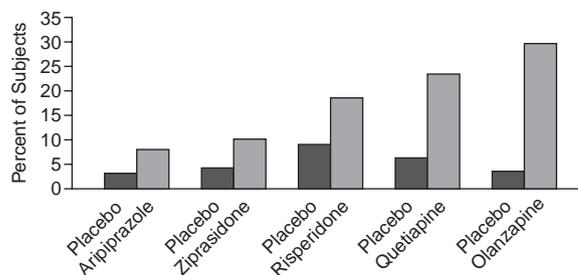
^aReprinted with permission from Allison et al. *Am J Psychiatry* 1999;156:1686–1696.

Dr. Newcomer: Using pluses and minuses, with risperidone and quetiapine in the intermediate position, may not reflect the actual numbers. The writing committee's effort was focused largely on short-term, 10-week weight gain data (Figure 1), which there are more of than long-term data [Allison DB, et al. *Am J Psychiatry* 1999;156:1686–1696]. Drugs that are not as effective in stimulating appetite or curbing satiety tend to stop causing weight gain sooner than those drugs that tend to stimulate appetite or curb satiety more, so a 52-week trial may show even larger separation across the drugs. In long-term data sets, ziprasidone and aripiprazole show mean increases in weight of about 1 kg over the first year of treatment. Mean first year increases in weight for risperidone and quetiapine were between 2.0 and 3.5 kg, and for olanzapine at usual doses (12.5 to 17.5 mg/day) the mean weight gain was above 10 kg [Casey DE, et al. *J Clin Psychiatry* 2004;65(suppl 7):4–18]. Doctors need to keep their eyes on the real numbers because the working hypothesis is that a substantial portion of the risk of the metabolic syndrome is driven by how much weight is gained.

Dr. Correll: The minuses for aripiprazole and ziprasidone may also be caused by the fact that those agents came on the market later and are frequently given to patients who have already gained weight on previous medications and therefore may not continue to gain more weight on the new drugs. What physicians need to see before deciding that those agents have a low risk of weight gain are data showing little weight gain in antipsychotic-naïve patients. The pharmaceutical industry tells us that aripiprazole and ziprasidone may be weight-neutral, but that may not really be the case in patients who have not already gained 30% or 40% of their weight gain potential taking previous antipsychotic medications.

Dr. Barrett: Just to clarify the thought that went into the plus-minus rating, there are two ways of looking at these data: how much weight was gained and how

Figure 2. Percent of Subjects Reported to Gain $\geq 7\%$ of Baseline Weight During Short-Term Studies^a



^aReprinted with permission from Casey et al. *J Clin Psychiatry* 2004;65(suppl 7):9. Clinically significant weight gain defined by U.S. Food and Drug Administration as $\geq 7\%$ of baseline weight.

many patients had clinically significant weight gain. When the committee looked at the population of patients taking antipsychotic medications to see how many gained weight, the impression was that fewer people experienced clinically significant weight gain while taking ziprasidone and aripiprazole (Figure 2). That was why they wound up on the bottom of the list of weight-gain-causing antipsychotics. Some individuals gain 6 and 7 kg and others gain nothing or lose 1 or 2 kg in the course of time. Part of the reason for including a plus for ziprasidone and aripiprazole was not because of the mean gain of 1 kg in the course of a year but because there are individuals who will gain 5 kg in the course of the first 16 weeks of treatment. Those are the individuals who need attention in order to avoid weight gain.

Dr. Newcomer: It is important that the data presented to physicians not only include mean and median outcomes but also the baseline data. The baseline condition is important in estimating the patients' starting and ending risk.

Dr. Casey: I would like to add the caveat that the quetiapine data are probably significantly confounded by dose. The vast majority of the data on quetiapine in the literature is for doses that average approximately 300 mg/day, which is ineffective for most people with psychotic symptoms. Effective doses of 600 to 800 mg/day may show a very different profile.

Dr. Kane: Is there a consensus that there is a relationship between dose and effects across compounds, or do we not know enough to comment on that?

Dr. Casey: If you start at zero and go to maximum dose, you could show a change in weight gain for these drugs, but for the clinically relevant dose ranges for treating psychosis, it is much more debatable. For example, with olanzapine and clozapine, a clinically relevant dose-related increase in weight has not been seen.

Dr. Newcomer: One analysis of olanzapine [Nemeroff CB. *J Clin Psychiatry* 1997;58(suppl 10):45–49] found a

clinically significant difference in weight gain potential across the dose range from 1 to 17.5 mg. But we do not have an option to treat somebody who is responding to 17.5 mg/day of olanzapine with 1 mg/day.

Dr. Kane: Maybe what is necessary for research in this area is to identify the people who are vulnerable to weight gain and look at the dose relationship within that cohort, because it can be very difficult to identify dose relationship in a heterogeneous population.

Dr. Correll: Dose is not the best variable to study because people metabolize the medication differently. Blood drug levels may be more informative.

Other Factors That Contribute to an Increased Risk of Metabolic Syndrome Among Psychiatric Patients Receiving Atypical Antipsychotics

Dr. Kane: What factors contribute to increased risk of metabolic syndrome among psychiatric patients receiving atypical antipsychotic medications? What about genetic factors?

Dr. Correll: There are several risk factors that have not been studied enough. However, the genetic results in Chinese patients by Reynolds on 5-HT_{2C} promotor site polymorphism have been replicated in a Spanish-Caucasian population [Reynolds GP, et al. In: *New Research Abstracts of the 157th Annual Meeting of the American Psychiatric Association; May 4, 2004; New York, NY; Abstract NR 329:121–122*]. In those studies, any negative results were seen only in pretreated individuals taking clozapine for several years, so the effect of genetic risk may not have been seen because of the order effect. Researchers need to study the histamine response curve for any histamine polymorphism because there seems to be a strong relationship between antihistaminic effects and weight gain.

Many factors may contribute to increased risk of metabolic syndrome, such as family history of obesity, eating behaviors, exercise patterns, and lifestyle, all of which may also guide treatment. These factors have been poorly studied because self-report data, like food or exercise logs, are very unreliable. Better studies would use accelerometers or other devices.

Dr. Barrett: Ethnic relationships may be important in studying the metabolic syndrome because Asian populations and South Indian populations seem to be at a higher risk even with a more modest weight gain. Characterizing how different populations respond to these agents would be very useful and more readily done than a pharmacogenomics study.

Dr. Newcomer: Researchers could begin with the risk factors that they are already aware of in the general population—such as ethnicity and cigarette smoking—and look at them in psychiatric populations with a working hypothesis that psychiatric patients are subject

to the same effects that have been seen in other human populations.

Strategies to Prevent or Minimize Metabolic Effects

Dr. Kane: What strategies can be employed to prevent or minimize metabolic effects?

Dr. Newcomer: The big debate is about the effectiveness of diet interventions.

Dr. Klein: A multidisciplinary, supervised behavioral therapy approach to dieting can help patients achieve about a 6% or 7% weight loss, and in the best of circumstances, a 10% weight loss at 1 year with regain of weight thereafter. Less aggressive means produce even less weight loss.

Dr. Newcomer: The people who lose up to 10% short-term, they gain about 5% back?

Dr. Klein: People often lose weight during the first 6 months and then begin to regain weight. By the end of a year they may regain about a third of the weight they lost. In the very best programs, with aggressive behavioral modification, patients may lose 8% or 10% at the end of 1 year. Weight loss in general is quite modest, perhaps 2% to 3% with diet therapy alone, if behavior modification is not part of the program.

Dr. Newcomer: Can I ask why the ADA guidelines gave a gain of 5% of initial weight as the point at which clinicians should consider switching patients' medications?

Dr. Klein: That was based on information that a 5% weight gain can increase the risk of developing diabetes. In addition, it is probably more difficult to get patients to lose weight than to prevent weight gain, so early intervention is better.

Dr. Barrett: Also, outcome data suggest that a 5% weight reduction will decrease the progression to diabetes [Klein S, et al. *Am J Clin Nutr* 2004;80:257–263]. Several individuals have to be involved with a patient to achieve significant weight loss, and that can be difficult to assemble. A fairly large number of people are being treated with antipsychotic medications who are considered to have a psychiatric illness but no medical illnesses. They are not seeing an internist or a pediatrician, and it falls to the psychiatrist to make medical interventions. Should an individual who starts an atypical antipsychotic be referred for ongoing care by a pediatrician or a family practitioner to monitor weight, lipids, and glucose and to make nutritional interventions? If all aspects of weight management are going to be handled by the psychiatrist, patients are not going to have much luck losing weight.

Dr. Klein: There are not many clinicians with expertise in obesity management.

Dr. Kane: Also, there are reimbursement issues because weight-management programs are not necessarily covered by insurance. And, weight-management pro-

Table 3. Monitoring Protocol for Patients Taking Atypical Antipsychotics**

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

*Reprinted with permission from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care* 2004;27:599.

**More frequent assessments may be warranted based on clinical status.

grams similar to the ones we discussed earlier were in nonpsychiatric populations. We do not have much faith in the efforts in weight loss that have been made to date, and we need to be more aggressive and develop new treatment paradigms.

Dr. Klein: Yes, considering that patients who enroll in obesity treatment clinical trials show modest benefits, providing weight management therapy in patients who have not even asked for their weight to be managed and who have psychiatric illness would probably have worse results.

Dr. Barrett: The question might be a little bit different if we are talking about preventing weight gain as opposed to getting people to lose weight. Has there been a circumstance where people starting on agents known to cause weight gain have been studied preemptively to see if there is greater success preventing weight gain than treating obesity that has already occurred?

Dr. Klein: Few data exist in that area, and the data that have been collected were in people who had volunteered to prevent weight regain after smoking cessation.

Dr. Barrett: That is certainly worth recommending for future research.

Dr. Casey: Clinicians should select medicines that have the least likelihood of imposing this problem in the first place, particularly since there is evidence that patients taking antipsychotic medications are at high risk for the morbid and fatal complications of weight gain.

Dr. Klein: But a medication that is chosen on the basis of effectiveness for psychiatric illness might cause a lot of weight gain but be in the patient's best psychiatric interest.

Dr. Casey: I would agree, although I would add that in head-to-head trials, most atypical antipsychotic medications show equal efficacy in the antipsychotic domains.

Dr. Barrett: This is tremendously important because if there are substantial differences in efficacy for the primary use of the drug, selection should not be based on the incidence of side effects. If medications are equivalent, then the side effect question becomes a more important one. In the group of psychiatrists participating in the consensus conference, there was uncertainty about the equivalence, particularly with the newer antipsychotics

such as aripiprazole and ziprasidone because people did not have as much experience with them as with the others.

Dr. Klein: Are there situations where you would pick olanzapine as your first choice?

Dr. Kane: In a survey that was done recently [*Kane JM, et al. J Clin Psychiatry* 2003;64(suppl 12):1-100], psychiatrists were more likely to suggest risperidone as their first choice. There is still debate about the relative efficacy of atypical antipsychotic medications, but the only one that has consistently demonstrated superiority is clozapine, which is also associated with a considerable amount of risk. Clozapine tends to be used as a last resort—once patients get to it they have failed other drug trials. It is difficult to find a substitute.

Dr. Klein: Are most patients who have psychiatric illnesses and are treated with atypical antipsychotic medications living at home and cared for by their family members or are they independent, free-living, and working in society?

Dr. Kane: It is usually the former. Most have caregivers or are living in adult homes or supportive housing, but very few are functioning normally and independently in the community.

Dr. Klein: This suggests the family should become more involved than a primary care physician in the nutritional care of the patient and in watching for weight gain.

Monitoring of Metabolic Effects in Patients Taking Antipsychotic Medications

Dr. Kane: Do people generally agree that the monitoring protocol proposed in Table 3 of the ADA consensus report is appropriate (reprinted here as Table 3), or are there those who feel that it is inadequate?

Dr. Newcomer: The asterisk that indicates that more intensive monitoring may be required is very important to note. If someone experiences a rapid increase in waist circumference, or if they start out with a high level of baseline risk, physicians should not wait 3 months to measure weight, blood pressure, glucose, and lipids.

The only criticism that I have is that I am not sure the repeat lipid screen at 5 years is sufficient, especially given the high baseline risk in this population.

Dr. Correll: I agree entirely. The lipids should be monitored much more frequently, and given the fact that these agents may have intrinsic activity that goes beyond just the effect of weight gain on the lipids, that should be discussed and maybe even modified.

Dr. Barrett: The idea, particularly in terms of cardiovascular risks, was that the schizophrenic population is often composed of young people for whom lipids could be checked less frequently. But there are a number of individuals who, possibly for indications other than schizophrenia, are starting antipsychotic medications at 45 or 50 years old. Every 5 years is probably not optimal for these patients.

Dr. Kane: The best advice to give is to tailor your monitoring and treatment to your individual patients' needs and age-appropriate recommendations.

Dr. Correll: Clinicians will need direct guidance. When the ADA conference paper was being written, people from the diabetes side felt that it would be too complicated to give cutoff values to psychiatrists, and they would rather patients be referred to specialists. But not all clinicians know that lipid screenings should be performed more frequently after patients reach 60 years of age or a certain BMI. If the recommendations are left too vague, many patients will not be monitored appropriately. More clear guidance is needed as to when clinicians should do lipid screenings sooner than 3 months. To just say "perform screenings if there is a lot of weight gain" leaves too much room for error.

Dr. Newcomer: Handicapping the psychiatrists or assuming that psychiatric patients are deserving of some lesser standard of care should stop. All clinicians should try to follow the National Cholesterol Education Program Adult Treatment Panel III guidelines [*Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA 2001;285:2486–2497*].

Changing Patients' Medication Because of Adverse Metabolic Effects

Dr. Kane: When should clinicians consider changing medication based on apparent metabolic adverse effects?

Dr. Newcomer: Several pharmaceutical companies now have begun to do switch studies comparing the metabolic change that happens when patients switch medications with the metabolic change that happens with dietary interventions, which, as we have discussed, produce drops in weight of 10% under optimal circumstances, and likely less in a psychiatric population. Some of the study data that have been released about switching from a high-weight-gain treatment regimen to a low-weight-gain treatment regimen show a weight loss that may potentially exceed loss with dietary interventions over the long-term follow-up. A poster at the American Psychiatric Association meeting [*Weiden PJ, et al. In: New Research*

Abstracts of the 157th Annual Meeting of the American Psychiatric Association; May 4, 2004; New York, NY. Abstract NR 391:145–146] projected a mean drop in weight of 21.6 lb over 58 weeks in patients switching from olanzapine to ziprasidone. That exceeds 5% of their average baseline body weight, which begs the question about whether it is better to focus on intensive dietary programs or on switching medications.

Dr. Kane: Or—as someone suggested earlier—avoiding those risks up front, in terms of prevention.

Dr. Barrett: Having head-to-head trial data with clinically effective doses for treating psychosis will be helpful in showing weight gain and lipid changes that occur when switching medications. Then we would be on surer ground for making a recommendation.

Dr. Correll: Coming back to the ADA guidelines, a 5% body weight increase is the time point when clinicians should consider switching patients' medications, particularly if there is early weight gain, because the available data suggest that early weight gain predicts later weight gain. If a patient gains a lot of weight quickly, that agent is not a good fit for that patient.

Dr. Gelenberg: The ADA consensus emphasized this. Physicians need to work toward an overall balance. There may be times when the cardiovascular and metabolic risks are outweighed by the fact that a certain agent may be the main thing that keeps the patient alive, functioning, and free of psychosis. In that case, in a logical algorithm with appropriate consent, then the decision has to be for the lesser evil.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclor, and others), divalproex sodium (Depakote), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), molindone (Moban), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproate (Depacon and others), ziprasidone (Geodon).

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

Affiliations: From the Department of Psychiatry (Dr. Kane) and the Department of Psychiatry Research (Dr. Correll), The Zucker Hillside Hospital, Glen Oaks, N.Y.; the Department of Internal Medicine and Endocrinology, the University of Virginia, Charlottesville (Dr. Barrett); the Department of Psychiatry, Oregon Health and Science University, Portland (Dr. Casey); the Department of Psychiatry, Arizona Health Science Center, Tucson (Dr. Gelenberg); and the Department of Internal Medicine, Nutritional Science Section (Dr. Klein) and the Department of Psychiatry (Dr. Newcomer), Washington University School of Medicine, St. Louis, Mo.

Financial disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Kane is a consultant for Abbott, Pfizer, Johnson & Johnson, Eli Lilly, and Janssen and is a member of the speakers/advisory board for Bristol-Myers Squibb,

AstraZeneca, Lundbeck, Novartis, and Janssen. Dr. Barrett is a consultant for Pfizer, Bristol-Myers Squibb, and GlaxoSmithKline. Dr. Casey is a consultant for Abbott, AstraZeneca, Aventis, Bristol-Myers Squibb, Janssen, Eli Lilly, Novartis, Pfizer, and Sumitomo; and is a member of the speakers/advisory board for Abbott, Bristol-Myers Squibb, Janssen, Eli Lilly, Ortho-McNeil, and Pfizer. Dr. Correll is a member of the speakers/advisory board for Janssen, AstraZeneca, and Bristol-Myers Squibb. Dr. Gelenberg is a consultant for Eli Lilly, Pfizer, Vela Pharmaceuticals, Best Practice, Bristol-Myers Squibb, AstraZeneca, Wyeth, GlaxoSmithKline, Cyberonics, Roche, ZARS, Express Scripts, and

Janssen; has received grant/research support from Pfizer and Wyeth; and is a member of the speakers' bureau for Wyeth, Cyberonics, and Pfizer. Dr. Klein has received grant/research support from Transneuronix; has received honoraria from Merck; and is a member of the advisory board for Roche and Enteromedics. Dr. Newcomer is a consultant for Janssen, Eli Lilly, Pfizer, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Wyeth; has received grant/research support from Janssen, Eli Lilly, Pfizer, AstraZeneca, and Bristol-Myers Squibb; and has received speaking honoraria from Janssen, Pfizer, AstraZeneca, Bristol-Myers Squibb, and Sanofi-Synthelabo.

Appendix 1. Key Points on Metabolic Effects of Treatment With Atypical Antipsychotics

Prevalence

Evidence tends to indicate that the rate of diabetes is higher in individuals taking atypical antipsychotic medications than in the general population. It is unclear whether individuals with schizophrenia who are not treated with antipsychotic medications have a higher rate of diabetes compared with the general population.

Risk factors

Several atypical antipsychotics can produce weight gain in patients.

The rate of diabetes in patients given atypical antipsychotics is undetermined; however, weight gain leads to diabetes in the general population, and atypical antipsychotics can lead to weight gain.

Patients with a higher baseline body mass index have an increased risk of diabetes after weight gain compared with patients who have a lower body mass index with the same amount of weight gain.

Prevention and intervention

If possible, clinicians should try to choose medications that have a lower risk of causing weight gain.

Diet interventions with behavior modification may help patients gain less weight or even lose weight when taking an atypical antipsychotic.

Physicians should monitor patients' weight, body mass index, waist circumference, blood pressure, and fasting blood glucose every 3 months and lipid profile every 6 months—or more frequently if the patient has a rapid increase in waist circumference or a high level of baseline risk factors.

Physicians should consider switching patients' medication to one with a lower risk of weight gain if the patient gains 5% of his or her body weight.

Physicians should consider referring patients with class II and III obesity (body mass index > 35 kg/m²), diabetes, dyslipidemia and hypertension to medical specialists.

For the CME Posttest for this Commentary, see pages 1582–1584.

To hear audio excerpts from this discussion, go to www.psychiatrist.com/issues.
