National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes Mellitus Interagency Coordinating Committee

Psychoactive Drugs and Type 2 Diabetes

September 18, 2006
8:30 a.m.–3:30 p.m.
Bethesda Marriott Suites
Bethesda, Maryland

Summary Minutes

Welcome and Introductions

Judith E. Fradkin, M.D., Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, MD; and *Griffin P. Rodgers, M.D., M.A.C.P., Acting Director, NIDDK, NIH, Bethesda, MD*

Dr. Fradkin welcomed members to the meeting and expressed appreciation for the help DMICC members gave in developing the *Type 1 Diabetes Strategic Plan*. The Plan has been published in three versions: one for the scientific community, one for patients and their families, and the other with a summary and recommendations. These will be distributed to DMICC members.

She reported that the next DMICC meeting will occur on January 18, 2007, at the Natcher Conference Center on the NIH campus. Information regarding this meeting will be distributed as it is developed. The general topic will be unmet issues in clinical trials for diabetes; the meeting will be chaired by Dr. David Nathan.

Dr. Fradkin spoke of the recent tragic death of Dr. Wayne Fenton, Director of the Division of Adult Translational Research and Associate Director for Clinical Affairs at the National Institute of Mental Health (NIMH). Dr. Fenton was instrumental in helping to initiate this meeting and had been a tireless advocate for mental health services at the National and local levels. He remained a practicing psychiatrist even as he fulfilled administrative duties at NIMH. She asked that everyone keep Dr. Fenton and his family in their thoughts in the coming days.

Dr. Rodgers welcomed DMICC members and guests and provided an overview of the critical importance of this meeting in discerning the impact of psychotropic drugs as a risk factor for type 2 diabetes. He added that NIDDK is ready to work with NIMH on this issue and to do what is necessary to develop both a better understanding of the role of these agents regarding diabetes risk and strategies to address the problem.

SESSION I: OVERVIEW OF THE PROBLEM

Moderator

Mark Chavez, Ph.D., Chief of the Psychiatric Medication and Side Effects Program, and Chief of the Mood, Eating, and Sleep Disorders Program, NIMH, NIH, Rockville, MD

Disorders, Drugs, Metabolic Outcomes

John Newcomer, M.D., Professor of Psychiatry, Psychology, and Medicine, Washington University, St. Louis, MO

Dr. Newcomer provided an overview of data on the increased mortality associated with major mental disorders (slides 3–6). People with schizophrenia have a 20 percent shorter lifespan: there is approximately a 2-fold increase in mortality in people with bipolar disorders and approximately a 1.5-fold increase among those with unipolar disorders. In addition, in a study in Sweden, people with major mental disorders showed increased mortality from cardiovascular disease (2.7-fold), diabetes (2.3-fold), respiratory disease (3.2-fold), and infectious diseases (3.4-fold). State data from the United States also show that people with major mental disorders have a higher number of years lost to disease compared to the general population. The data are clear that there is a significant impact of mental disorders on lost years of life.

Dr. Newcomer reviewed data on the prevalence of modifiable risk factors for cardiovascular disease showing that there is a significantly higher prevalence of obesity, smoking, diabetes, and hypertension among those with major mental disorders (slide 7). Obesity also occurs at significantly higher rates among people with schizophrenia; these data are from 1989, which predates introduction of the second-generation antipsychotic (SGA) drugs (slides 8–11). He reviewed data on abdominal fat and mechanisms that may be responsible for increased insulin sensitivity as abdominal fat increases.

The metabolic syndrome is beginning to appear as an endpoint in some studies in psychiatric clinical trials (slides 12–20). Dr. Newcomer reviewed baseline data from the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) Study, which included patients with schizophrenia. Study findings indicate that this population has approximately a 2-fold prevalence of metabolic syndrome. Interestingly, almost all of the individual factors that are included in the metabolic syndrome also were present at a higher prevalence among study participants with schizophrenia. In addition, studies of drug-naïve people with schizophrenia at first episode indicate that increased metabolic risk probably is not independent of the use of antipsychotic drugs.

Dr. Newcomer reviewed extensive literature on antipsychotic and other psychotropic agents that contribute to weight gain (slides 21–23). In placebo trials comparing weight gain, SGA drugs are associated with approximately 2- to 5-fold increases in weight gain compared to placebo. This varies among SGAs. In addition, a recent meta-analysis of mean weight changes seen with antipsychotic agents indicated that the high-potency first-generation agents (FGAs) haloperidol and fluphenazine, and SGAs aripiprazole and ziprasidone, accounted for a mean weight increase of $\geq$ 1 kg in a 10-week study. At the higher end of the mean weight gain spectrum, the low-potency FGAs chlorpromazine and thioridazine, and SGAs olanzapine and clozapine, were associated with an approximately 3–4 kg mean weight gain over 10 weeks (slide 24). In a 4-week study of weight gain

with a co-prescription of risperidone and valproic acid or olanzapine and valproate, a weight gain of approximately 7 pounds was reported. Long-term use data show significant weight gain over 1 year (slide 26). In the CATIE study, for example, long-term use of olanzapine indicated approximately a 2-pound weight gain per month; for perphenazine and ziprasidone, there was a modest weight loss. In another study of the head-to-head use of aripiprazole and olanzapine, the group taking olanzapine had a 5.6-kg weight gain compared to a modest weight loss for the group taking aripiprazole (slide 28). Dr. Newcomer described studies of people who switch from one antipsychotic agent to another that also indicate significant weight loss (slides 29–30). This weight loss is greater than that seen with lifestyle changes in this population. Using metabolic endpoints in an ongoing NIMH study, after 3 months, people who received olanzapine had greater weight gain than those who received quetiapine, risperidone, or ziprasidone (slide 31). A summary of three studies on histamine type 1-receptor (H_1) affinity suggests that the H_1 receptor is associated strongly with the variance in how much of the weight gain potentially is the liability of SGAs (slide 32).

Dr. Newcomer presented data on drug effects on insulin resistance and glucose or lipid metabolism. Several studies exist that are uncontrolled, observation studies, which were useful when antipsychotic drugs first were available. Large, observational data sets now exist, but the main problem is that these studies do not include blood assays; instead, the endpoint for indicating diabetes in these studies typically is an ICD code for diabetes or a co-prescription for a diabetes drug. In addition, there are few controlled, experimental studies.

The early uncontrolled, observation studies offered clues to the increased risk of diabetes with the use of antipsychotic agents; approximately 20–25 percent of the diabetes cases were occurring in the absence of substantial weight gain or obesity, which raised the possibility of increased diabetes risk with agent use. In the analyses of the observational data sets, statistical noise and variability of studies make it difficult to draw valid conclusions. In the controlled trials, it is possible to determine effects mediated by drug effects on fat mass and effects mediated independent of drug effects on fat (slide 37). Results of these trials indicated that there are no strong associations between drug effects on fat mass (slides 38–42), but studies on effects mediated independent of drug effects on fat found that some SGAs did show metabolic changes indicative of glucose and triglycerides (slides 43–53).

A pilot study for an upcoming clinical trial investigating the effect of switching medications from risperidone or olanzapine to ziprasidone indicate a rapid, significant drop in cholesterol levels (as much as 75 mg/dL after 6 weeks; slides 54–56). In addition, an American Diabetes Association (ADA) consensus statement listed a significant risk of diabetes and dyslipidemia with the use of clozapine and olanzapine, but disparate results for quetiapine and risperidone. This is in conflict with the U.S. Food and Drug Administration (FDA) labeling requirement that the "class effect" of SGAs should include an increased risk of diabetes.

Dr. Newcomer presented data from the Veterans Health Administration (VHA) indicating that approximately 25 percent of persons with diabetes have a mental health condition. In a review of data on monitoring, there is a disparity among VHA patients with diabetes in the types of monitoring they receive relative to a person with diabetes who does not have a mental health problem. For example, the odds that a person with diabetes and a mental health problem will receive no Hb1ac test, no LDL test, no eye exam, and no test for diabetes monitoring are far greater than among those with diabetes and no mental health problem (slide 66). To alleviate this, VHA developed a form to

assist in the monitoring of these patients (slide 67). Dr. Newcomer also reviewed an Institute of Medicine (IOM) report, "*Improving Quality of Health Care of Mental and Substance-Use Conditions*" and health care provider strategies for improving the focus on diabetes care. These include the following:

- Anticipate comorbidity and perform routine screening.
- Collaborate with primary care and relevant specialties, including:
  - Formal agreements among mental, primary, and other health care providers
  - Case management of patient care
  - Colocation of services
  - Delivery of integrated practices of primary and mental health care providers
  - Adopting the model to best meet patient needs and allow for easiest transition from the current structure.

The full report may be found at http://www.nap.edu/books/0309100445/html/196.html.

Discussion

Dr. Gilman Grave commented that the people with anxiety and depression were getting adequate care. Dr. Newcomer said that people with these conditions tend to be heavier users of medical services, and are very different than people with schizophrenia or other major mental disorders. Dr. Grave asked if psychiatrists have drugs they feel more comfortable prescribing, based on their patients' responses to the medications. Dr. Newcomer responded that there is a "gold standard" among psychiatrists regarding a treatment for patients who are resistant to other medications, and this is clozapine, an SGA that has significant side effects. Among the other SGAs, the CATIE study suggests that olanzapine, one of the higher metabolic risk agents, may have advantages for clinical efficacy.

Dr. Leonard Pogach commented that the data in the VHA article were from 1999–2000 and that new data show there are fewer disparities in treating patients. The VHA is correcting some of the situations regarding disparities seen in the earlier setting. Dr. Fradkin asked if anyone has reviewed data from health maintenance organizations (HMOs) for cortisol data, especially prior to diagnosis. Dr. Newcomer responded that he does not know of anyone who is examining these data.

Dr. Pogach added that H_1 effects seem interesting, and he would like to hear more about them. Dr. Newcomer posited that hypothalamic nucleic factors that regulate satiety and hunger have many biogenic immune receptors, including H_1 receptors. The theory is that if the H_1 receptor is blocked, hunger increases. An off-label study among aggressive children has shown this to be true.

Discussant
Samuel Dagogo-Jack, M.D., F.R.C.P., Professor of Medicine and Endocrinology, University of Tennessee College of Medicine, Memphis, TN

Dr. Dagogo-Jack reviewed several discussion points (see below) and wondered if what is occurring between antipsychotic agents and diabetes is a sporadic or endemic process (slides 1–2). A scientifically sound clinical study could be designed to determine the answer to the main question

being raised: Do antipsychotic agents cause diabetes? Issues that can be addressed are the differences (or similarities) between type 1 and type 2 diabetes, and if there are immunological markers. Population studies have shown that approximately 10–15% of people of northern European ancestry diagnosed with type 2 diabetes actually have Latent Autoimmune Diabetes of Adults (LADA), a form of latent type 1 diabetes. Persons with LADA progress rapidly to insulin requirement and can be identified using immunological markers.

Given the approximately 175 million world-wide prescriptions for antipsychotic medications each year, it is essential to determine if these agents are inducing diabetes in some persons (slide 3). It is important to tease out whether diabetes is associated primarily with the psychotic disorder or is caused by the medications given for the disorder. National data presented show a higher prevalence of diabetes among people with schizophrenia (slide 4). For the clinical presentation of diabetes, there also are data to help understand the problem (slide 5).

Dr. Dagogo-Jack reviewed the following discussion points (slide 6):

- Mechanisms of direct drug effects on insulin sensitivity and insulin secretion, independent of effects on adiposity (e.g., drug effects on the glucose transporter function and insulin signaling pathways).
- Although most current data concern the adverse effects of antipsychotics, there is evidence of substantial effects of certain mood stabilizers and antidepressants on weight. What are the effects of these medications on metabolic endpoints?
- What is the extent of background diabetes risk in psychotic disorders?
- Management of antipsychotic-associated diabetes.

Other discussion points included the role of weight gain and body composition, the role of the hypothalamic-pituitary-adrenal axis, and effects on insulin sensitivity and beta-cell function (slide 7). Better controlled trials and longer term measures are needed to address these questions. A recent study investigated the predictors of weight gain during olanzapine and risperidone treatment (slide 8). The study results suggest important areas of research that are not being addressed. For example, the study showed a flattening of the weight curve, despite continued medication. There also are the questions of weight gain and clinical response, and whether efficacy is an important issue regardless of the weight gain.

Dr. Dagogo-Jack pointed out the importance of understanding the differences between typical and atypical antipsychotic agents and metabolic risk (slide 9), and of investigating whether there are differential metabolic effects among atypical antipsychotic agents. Another issue is the amount of marketing exposure given to agents, which tends to increase the use of some agents. He listed the published side effects for existing FGAs and SGAs and noted that several of the adverse effects overlap across FGAs and SGAs (slide 10). Dr. Dagogo-Jack concluded his presentation by listing unanswered questions that need to be addressed (slides 11–15).

Discussion

Dr. Grave commented that he appreciated the discussion of separating out the antipsychotic aspects of a drug from its diabetigenic aspects. He noted that the animal study described by Dr. Newcomer

showed that insulin sensitivity is more acute among clozapine and olazapine than with risperidone. The other studies also showed H_1 affinity with some drugs, such as clozapine and olanzapine, which gives clues to the insulin problems. Dr. Dagogo-Jack responded that these clues may be important for advancing the field. Dr. Newcomer added that there has been a failure to replicate the study investigating histamine (i.e., H_2-blocker). The administration of clozapine rapidly decreases plasma cortisol, so weight gain increases incrementally. Still, no data have suggested that histone deacetylase activation plays a role in drug-mediated risk.

Dr. Newcomer addressed predicting clinical response. The one study that showed an approximately 15-kg weight gain came from an open-label study. It is true that clinical response in the first few weeks predicts weight gain, but after that there is little relationship. This is where the H_2 hypothesis came from. The hypothesis suggests that drugs that are more sedating during the first few weeks of treatment are associated with weight gain.

Dr. Pogach commented on the question about onset. A study by Lambert et al. in the *Journal of Epidemiology* used VHA data sets and suggested that the number of new cases of diabetes in patients on all antipsychotic agents equals approximately 4 per 100 patient-years. This order of magnitude within a 1-year retrospective study probably is reasonable. Dr. Dagogo-Jack had seen the article.

Dr. Mary Parks asked about the presentation on switching among agents and if there has been consideration of the switch in terms of efficacy. Dr. Newcomer responded that a switch is never risk free, and the psychiatrist needs to consider the risks involved.

Dr. Peter Savage commented that there appear to be similarities between this debate and the debate that has been ongoing for 30 to 40 years about whether hydrochlorothiazide diuretics cause diabetes. Some patients have increased glucose levels at the beginning of use, but few long-term data exist. In treating hypertension, the benefit of reducing heart attack and stroke risks far outweighs the risk of diabetes, if that risk turns out to be real. This exemplifies the importance of collecting good data. He also noted that the data on agent switching show a decrease in weight soon after the switch; this suggests that a biochemical signal changes in these people. Dr. Dagogo-Jack agreed that this area could yield important information.

SESSION II: PSYCHOACTIVE DRUGS AND THEIR METABOLIC OUTCOMES

Moderator
Sanford Garfield, Ph.D., Senior Advisor, Biometrics and Behavioral Science, NIDDK, NIH, Bethesda, MD

Mechanisms and Pathogenesis
Marilyn Ader, Ph.D., Associate Professor, Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, CA

Dr. Ader summarized the effects of atypical antipsychotic agents and their association with metabolic complications, including cardiovascular disease, diabetes, dyslipidemia, fasting

hyperinsulinemia, weight gain, and diabetic ketoacidosis (slide 2). She listed the three key questions to be addressed in the presentation (slide 3):

- What is the current understanding of the pathogenesis of type 2 diabetes?
- What are the available methods for quantifying insulin sensitivity and secretion to assess the effects of antipsychotics on these processes?
- What have preclinical studies revealed about the mechanisms by which antipsychotics induce metabolic abnormalities?

In response to the first question, Dr. Ader reviewed the current understanding of type 2 diabetes, including insulin resistance and its relationship to obesity and diabetes (slides 4–6). Studies have demonstrated that visceral fat induces insulin resistance, which confers a substantial risk of diabetes. Normally, insulin resistance—resulting from obesity, genetics, or environmental factors—will elicit a compensatory upregulation of pancreatic β-cell secretion of insulin; such individuals will exhibit fasting hyperinsulinemia but normal glucose tolerance (slides 7–8). If β-cell function is impaired due to genetic or acquired defects, however, secretory compensation for insulin resistance will be inadequate and glucose intolerance will occur; if β-cell defects are severe, type 2 diabetes may ensue.

The second question was addressed by a review of the quantitative approaches to assessing of insulin secretion and sensitivity. Dr. Ader provided an overview of methods to measure β-cell function (slides 10–14) and insulin sensitivity (slides 15–25). She focused on approaches that have been employed to measure the metabolic effects of antipsychotic agents, including homeostasis model assessment (HOMA), quantitative insulin sensitivity check index (QUICKI), and minimal model analysis of the frequently sampled intravenous glucose tolerance test (FSIGT). Fasting-based surrogate indices such as HOMA and QUICKI may be useful if β-cell function is normal or in clinical studies of subjects with minimal risk for diabetes. Dr. Ader also detailed model-based methods using the oral glucose tolerance test (OGTT), and discussed the limited utility of this method to distinguish changes in insulin sensitivity from other processes that can affect glucose and insulin dynamics during the OGTT—such as glucose absorption and insulin secretion (slide 25). Dr. Ader used the following table to summarize her presentation on the second question (slide 26):

- Glucose Clamp remains the "gold standard."
- Minimal model is accurate and provides a comprehensive metabolic profile (sensitivity, secretion, and β-cell compensation).
- "Surrogate measures" only reflect insulin resistance accurately with completely normal β-cells.
- OGTT methods remain to be proven accurate for insulin sensitivity *per se*.

The third question built on the review of the first two questions to see how they can be applied to the study of antipsychotic agents and type 2 diabetes. Dr. Ader reviewed the pathogenesis of type 2 diabetes (slide 28) to demonstrate the likely processes by which antipsychotics may increase diabetes risk. She discussed data that demonstrate that antipsychotics cause a differential effect to increase body weight (slides 29–30). Body weight does not always mirror body fat mass, however, especially visceral adiposity; she showed examples of this for both lean and obese individuals (slides 31–32).

Dr. Ader described a pre-clinical study to determine the metabolic effects of atypical antipsychotics in normal dogs. Animals were treated with either olanzapine, risperidone, or placebo for 6 weeks, and the treatment effects on body weight, adiposity, insulin sensitivity, and pancreatic β-cell function were assessed (slide 33). Body weight increased to a comparable degree with both olanzapine and placebo, but olanzapine induced a substantially greater increase in adiposity in both subcutaneous and visceral depots. Risperidone induced variable non-significant effects on body weight and a modest increase in adipose mass that did not differ from placebo. Hepatic insulin resistance was induced by olanzapine, but not by other treatments. Whereas increased adiposity may mediate olanzapine-induced insulin resistance, Dr. Ader presented studies in rats demonstrating antipsychotic-induced resistance within 30–45 minutes of a single injection of drug (slide 36), indicating that this effect can occur in the absence of changes in body weight or adiposity.

Assessment of insulin secretion and β-cell compensation indicated that olanzapine impaired the ability of pancreatic β-cells to compensate for insulin resistance. This was illustrated in slides 38 and 39, in which β-cell compensation during olanzapine treatment was compared with that observed in untreated dogs who developed comparable obesity and insulin resistance induced by a high-fat diet rather than by antipsychotic treatment. Animals with diet-induced resistance exhibited a healthy, robust compensatory upregulation of pancreatic insulin secretory function. In contrast, no such upregulation was observed in olanzapine-treated dogs. These data suggest a mechanism by which antipsychotics such as olanzapine may increase diabetes risk.

To explain whether the metabolic effects of antipsychotic agents are mediated by central or peripheral mechanisms, Dr. Ader discussed data generated in her laboratory studies using lean dogs and dogs made obese by a high-fat diet (slides 40–43). First, she demonstrated that the central nervous system is a potent regulator of lipolysis, as indicated by loss of pulsatile secretion of free fatty acids (FFA) during β_3-adrenergic blockade. Secondly, she has observed that animals made obese and insulin resistant exhibit dramatic increases in nocturnal FFA concentrations, suggesting a critical role of overnight FFA in the β-cell compensation for diet-induced resistance. These results may provide clues into the mechanisms by which olanzapine, which clearly acts centrally for its antipsychotic effects, may interfere with β-cell compensation during treatment. Further studies are needed to determine whether antipsychotics such as olanzapine induce direct impairment of pancreatic β-cells or whether the impaired compensation results from interference with signal(s) to the β-cells that results in secretory upregulation (slide 45).

Dr. Ader also presented information on the mechanisms by which antipsychotic drugs alter body weight, adiposity, and body fat distribution (slides 46–48). Dogs treated with olanzapine and placebo consumed more calories over 6 weeks of treatment.(Note: All dogs, including in the placebo group, were fed *ad libitum* to permit possible treatment effects to increase intake.) This may explain the comparable body weight gain observed in these two groups. Animals that received risperidone consumed fewer calories compared to baseline, which suggests that any increases in body weight were due to drug-associated reductions in energy expenditure (slide 47). Changes in adiposity, however, could not be explained by caloric intake alone. Despite similar caloric intake, olanzapine-treated animals exhibited substantially greater adiposity, which suggests a preferential diversion of calories to fat deposition that may be mediated by upregulation of PPARγ gene expression (slide 48). Finally, Dr. Ader presented preliminary data indicating that the effects of olanzapine in impairing β-cell function were sustained over 24 weeks of treatment (slide 50). No

measurements were taken after treatment cessation to determine the reversibility of the observed metabolic effects of antipsychotics. Dr. Ader summarized the observed metabolic effects of antipsychotics (slide 51) and concluded by presenting OGTT data from olanzapine-treated dogs. These data indicated that the OGTT glucose pattern did not reveal underlying changes detected by more accurate experimental assessments (slide 52).

Discussion

Dr. Dagogo-Jack asked how it was possible for weight to stay the same while body fat increased. Dr. Ader said that in part, adipose tissue weighs less than other tissues (e.g., muscle). Dr. Dagogo-Jack followed up with a question about a study in humans using the same agents as used by Dr. Ader. This study also used a hyperglycemic clamp. Dr. Ader responded that this study's findings were similar to what her group found. The difference was that the human study did not measure insulin resistance. The prior study (published by Sowell and colleagues) also demonstrated similar insulin secretion after olanzapine treatment, but because insulin resistance was not measured, the authors concluded that drug treatment did not impair secretion. Subjects, however, did gain weight in the Sowell study, which suggests that resistance did occur. Thus, insulin secretion should have been elevated. Failure to detect such elevation is consistent with the observation that β-cell compensation was impaired by olanzapine.

Dr. Grave asked about the data on FFA and the frequency of the FFA pulses (slide 41). Dr. Ader said the pulses had a frequency of approximately 8 minutes. Dr. Fradkin wanted to know if what was seen in the studies was a function of the choice of drugs, and if there are implications for people who develop diabetes on these drugs. Dr. Ader responded that the animal studies provide strong evidence that drugs *per se*, in the absence of underlying psychiatric disease, can cause substantial metabolic effects. Little information currently is available on the other drugs in this class; more quantitative work must be undertaken in the clinical setting to determine drug effects in treated patients.

Discussant
Dr. Newcomer

Dr. Newcomer began the discussion by commenting on previous presentations; he listed the following general discussion questions:

- Are there effects of drugs to increase diabetes risk that are independent of drug effects on body weight and/or body fat?
- Are the metabolic effects of antipsychotics mediated by central or peripheral mechanisms?
- How can the DMICC facilitate the clinical research interaction between psychiatrists and basic researchers with expertise in diabetes pathogenesis and obesity?

There have been adiposity-dependent and adiposity-independent effects of antipsychotic agents on diabetes. Dr. Newcomer summarized the findings related to adiposity-dependent effects. There is some agreement that H_1-antagonism may account for some of the variance, although Lithium is a psychotropic medication that produces substantial weight gain over a year, but does not influence the H_1-receptor. Thus, other mechanisms should be investigated. The animal models also should be

validated. The dog model has done well in matching what is seen in humans; rodent models, however, have not been shown to match well to humans.

The weight gain described in previous presentations suggests that this could have clinical implications. If a group of agents causes extreme weight gain, and there is continual switching of agents, there appears to be an advantage to developing newer agents that do not cause weight gain. Studies of switching indicate that most patients have better psychiatric outcomes after switching, but the safety of those switches must be assessed. Another area of research need is that of pharmacologic and behavioral approaches to weight loss and the differences between people who take antipsychotic drugs and those who do not take these drugs. There also is interest in developing a better understanding of the mechanisms and genetic components of these issues.

Dr. Newcomer discussed the adiposity-independent mechanisms, such as the animal models seen in this research. He said that there is interest in and a need for the same types of understanding about new drugs that can be developed to block the negative effects of current pharmacologic agents. One approach is to study these drugs in people who do not have diabetes to see if the effects are the same as in people with diabetes. Determining phenotypic and genomic differences that cause hyperglycemia or triglyceride elevation, which do not occur in all people, could be an exciting field of study. On the positive side, it is known that some typical clinical indicators of diabetes offer clues to those patients who will have adverse effects with antipsychotropic drugs.

Dr. Dagogo-Jack asked Dr. Ader about the slide on OGTT (slide 52). He wondered if there could be another reason why the insulin secretion diminished and the insulin resistance worsened, but the glucose tolerance was unchanged after 6 months. Dr. Ader said it was a good question, and other mechanisms could account for this.

Dr. Newcomer interjected that what needs to be determined is whether animal models help show the incremental changes in diabetes risk. Dr. Dagogo-Jack said that people eat food that becomes glucose, rather than having it infused, and asked whether this changes the parameters. He said that it is important of understand downstream events associated with increases in body fat and how these data can be used to improve clinical care for people. Dr. Newcomer stated that the antipsychotic agents impact body fat and insulin sensitivity, and this can be studied for its impact on diabetes or cardiovascular disease. Dr. Ader added that what is being attempted is to study the effects of two drugs in a controlled environment; what is shocking is that any change could be detected in only 6 weeks.

SESSION III: PREVENTION AND TREATMENT

Moderator

Michael J. Sernyak, Professor of Psychiatry, Yale University School of Medicine, New Haven, CT, and Chief of Psychiatry and Mental Health Service Line Manager, VA Connecticut Healthcare System, West Haven, CT

Drugs and Lifestyle Intervention

Tony Cohn, M.B.Ch.B., M.Sc., Lecturer, Department of Psychiatry, University of Toronto, Ontario, Canada

Dr. Cohn presented slides on prevention and treatment of antipsychotic-associated metabolic disturbance using both pharmacological and lifestyle interventions (slides 1–2). He described the scope of the mental health problem (slide 3). He also reviewed monitoring for metabolic disturbances (slides 3–7). There are approximately six guidelines for monitoring, and they converge on the understanding that antipsychotic agents may lead to a higher risk of diabetes. Challenges in monitoring include the following (slide 8):

- Monitoring is not widely accepted or implemented;
- No reports of applying the various international guidelines in real-world settings and no studies of cost-effectiveness;
- Issue of responsibility—who is responsible—the psychiatrist/family physician/internist;
- Competing demands in mental health care and the de-medicalization of psychiatry, which implies that there is little medical knowledge or emphasis on medical needs in many mental health settings.

Dr. Cohn presented an overview of strategies for prevention and treatment, including strategies that have been effective and those that have been ineffective (slide 9). It is accepted in the clinic that patients experience weight gain with the use of most antipsychotics, mood elevators, or antidepressants (slides 10–13). Strategies involving the dosages administered, formulations, and route of administration have not been effective in ameliorating weight gain. Attention to medication choice and concomitant medications (slides 14–15) has been more helpful. In addition, as noted previously, studies of medication switching point to possible weight benefits from such switches (slides 16–18).

Lifestyle approaches to weight loss for people without mental disorders include diet, increasing physical exercise, and behavioral therapy (slides 19–20). Pharmacologic augmentation approaches include the medications orlistat and sibutramine, each of which has produced modest weight loss after 12 months (slide 21). Historically, there have been many weight loss drugs that have been used among people with mental illness (slides 22–23). Dr. Cohn described a Cochrane Review conducted on randomized controlled trials for weight gain in people with schizophrenia (slides 24–28). Results indicated that lifestyle modifications were successful in the two published prevention trials (slides 29–30). General results of the prevention studies that added pharmacologic agents were summarized and indicated that, compared to control groups, some pharmacologic agents were associated with less weight gain (topiramate and roboxetine) (slides 32–36). Studies in people with established weight gain and lifestyle and medication addition showed that there was a positive effect, although two of the three lifestyle studies had nonsignificant results (slides 37–39). Studies of medication addition for established weight gain showed variable results (slides 40–45).

Conclusions include the following (slide 46):

- Modest weight loss of ~ 2–4 kg (4.4–8.8 lb) in short-term studies of ~ 3-months-duration is possible in patients with schizophrenia.

- In the studies done to date, lifestyle interventions may be more effective in prevention than when there is established weight gain.
- Pharmacological agents that show some positive results include topiramate, roboxetine, amantadine, and fluvoxamine (with clozapine).
- Pharmacological agents that show negative results include fluoxetine, nizatadine, famotadine, and metformin.
- Pharmacological agents that show mixed results include nizatadine and sibutramine.
- Dropout rates among the psychiatric population may be similar to those of the general population.

Dr. Cohn described limitations in these studies (slide 47) and discussed new medications under development and new information about intervention sequencing (slides 48–50). He completed his presentation by providing conclusions (slide 51):

- In managing metabolic disturbances associated with psychotropic medications, the choice of medications, metabolic monitoring, ongoing assessment of risk and benefit, and careful switching of medications can be effective.
- The population with mental disorders should be recognized as high risk for type 2 diabetes. Specific screening and management protocols should be implemented and mandated.
- Weight control is possible with lifestyle interventions and selective medication additions.
- Further study is needed in this population, with larger samples and longer treatment durations. These studies also should include an evaluation of diabetes prevention initiatives.

Questions

Dr. Garfield commented on the interventions described that have been used in the general population. He asked what strategies were used in the mental health population to help make the interventions successful. Dr. Cohn responded that there are case-management models in mental health related to medications; these same models are an advantage in this population for lifestyle interventions because the patients are used to following medication directions. Dr. Newhouse added that there are extra strategies for patients in a mental health setting. Another issue is that mental health populations may not receive treatment for medical disorders. CATIE data showed that 89 percent and 65 percent of those with criterion-level dyslipidemia and hypertension, respectively, were not being treated.

Dr. Rohan Ganguli commented that it is difficult to improve compliance for chronic diseases, and it may be that compliance among mental health patients may not be different from the general population. Dr. Sernyak added that compliance with psychotropic medication perhaps is remarkable given that compliance often relates to side effects, and the side effects of antipsychotic drugs often are intolerable. Dr. Fradkin asked if intervention by lifestyle enhances compliance because it makes patients feel that the physician is more involved in their care. Dr. Newhouse agreed that this may be so.

Discussant
Dr. Sernyak

Dr. Sernyak presented questions for discussion:

- How should diabetes prevention and treatment strategies be applied to the psychiatric population? What are the specific challenges and opportunities? Are standard medication and behavioral approaches effective?
- How can lifestyle interventions be integrated into mental health care?
- Does use of expert guidelines for monitoring patients who take antipsychotic medications (e.g., Mt. Sinai recommendations, ADA/American Psychiatric Association recommendations) improve patient outcomes (e.g., diabetes prevention, prevention of weight gain)?
- What lifestyle interventions to prevent or reduce weight gain and prevent diabetes mellitus are practical, effective, and can be delivered in a variety of mental health consumer settings?

Dr. Sernyak said he is impressed by the fact that mental health patients have a life expectancy of as much as two decades less than the general population due to their illness. They are a vulnerable population that needs help from the scientific community in solving this problem. He expressed concern that there has been a de-medicalization of the psychiatric profession in past decades; most psychiatric patients with severe mental illness are seen and prescribed medications by physicians with little or no recent medical training. In the VHA, when a patient commits suicide, there is an extensive review to determine how it could have been prevented. When a 40-year-old psychiatric patient dies of a myocardial infarction, however, there is not nearly the same level of scrutiny. The point of this example is that, to date, there is little recognition that concomitant medical illnesses associated with psychiatric illness demand the same level of attention.

Dr. Sernyak stated that there is a need to develop best practices for mental health treatment and to increase funding for issues related to finding solutions for treating those with mental health and concomitant conditions, such as cardiovascular disease and diabetes. The average body mass index (BMI) in his VHA clinic is 30.2, and he has few strategies to address this. Practicing in the VHA has several advantages in addressing medical and psychiatric comorbidities:

- There is an easily accessed, complete medical record. The electronic medical record allows a physician treating a person with mental illness to know if a fasting glucose has been taken on the patient.
- Mental health care and medical care are, to some degree, integrated. Integration with primary care is a critical issue. Having primary care physicians as part of the case team for psychiatric patients allows a focus on each of the physical needs of the patient.
- Data available through the record allow for examination of monitoring strategies.

Dr. Sernyak addressed the issue of monitoring and optimal screening sets. The population of interest should be all patients with mental illness. It is important to show that monitoring is effective and that the information is useful and will affect decisionmaking. Important questions remain regarding monitoring, such as what are the goals of weight monitoring, who is responsible for monitoring and initiating medical tests, and who maintains treatment? Few answers to these questions exist.

Dr. Sernyak described the clinical trials that are needed to inform the field. Large trials are needed to examine critical issues, including:

- What is the most cost-effective way to screen for diabetes?
- What is the most effective way to intervene in this population to prevent "pre-diabetes" from progressing to diabetes mellitus?
- What are effective interventions for weight loss?
- Can diabetes, hyperlipidemia, and hypertension be treated as intensively in this population as in the general population?
- What are the roles of non-pharmacological interventions?

Discussion

Dr. Garfield commented on the number of areas in which research needs to be conducted. He asked who is responsible for this special and vulnerable population (i.e., patients with diabetes and mental illness). Dr. Sernyak stated that subpopulations, such as children and adolescents, are an issue of concern. Dr. Garfield asked if anything is known about this. Dr. Newcomer said that weight gain may be worse in children and adolescents, but it is not known if this is because they are still growing or if the drugs have greater negative effects. Data in this area are lacking. A recent publication indicated that the number of prescriptions in this population is growing exponentially, with most being written by nonpsychiatric physicians. Another issue is the shortage of child psychiatrists, which results in primary care physicians handling many of the mental health issues for children and adolescents. Most of these patients take more than one drug.

Dr. Pogach noted that the goal of any treatment is to improve longevity. It seems that strategies for disease prevention, such as smoking-cessation programs, would be best for those with mental illness. If there are significant numbers of psychiatric patients with multiple risk factors for diseases for which there are proven strategies within the general population, those interventions should be tried with psychiatric patients. It seems advantageous to identify risks, prioritize those that reduce longevity, and treat them until the money runs out.

Key points and recommendations suggested during the rest of the discussion included the following:

- Treatment should be as aggressive in the mental health population as in the general population.
- Access to care always is an issue, and is more important in this population.
- Overall indications are that care for this population is improving, although there is room for additional improvement.

Dr. Fradkin commented that an intriguing recent publication showed that the prevalence of schizophrenia was increased 2-fold among children born during times of famine (i.e., the Dutch famine). This also has been shown for children with diabetes. Dr. Sernyak responded that interesting data exist on seasonal births and infectious diseases, but he did not know if these data can be confirmed.

Dr. Dagogo-Jack noted that there is no blood test for schizophrenia as for some other diseases. He also asked if there is a progression to schizophrenia that could provide a clue to eventual overt disease. Dr. Sernyak posited that there is no way at this time to predict schizophrenia, but it would

be worth pursuing. An increasing amount of attention is being paid to presyndromal schizophrenia, and we are learning more about the abnormal experiences that patients report before receiving a formal diagnosis of schizophrenia.

SESSION IV: PANEL DISCUSSION: KEY UNANSWERED QUESTIONS AND COMPELLING RESEARCH OPPORTUNITIES

Moderator
Dr. Fradkin

Dr. Fradkin introduced the panel members and asked that they discuss what they had heard today and their impression of the research needed to advance knowledge in the area of antipsychotic drugs and diabetes. She noted that Dr. Sernyak, a member of the panel, was unable to participate. The panel included:

> *Rohan Ganguli, M.D., Professor of Psychiatry, Pathology, and Health & Community Systems, Western Psychiatric Institute & Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA*
>
> *Gail Daumit, M.D., M.H.S., Assistant Professor of Medicine, Epidemiology, and Health Policy and Management, Johns Hopkins Medical Institutions, Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, MD*
>
> *Richard Kahn, M.D., Chief Scientific and Medical Officer, ADA, Alexandria, VA*
>
> *Mary Parks, Director, Division of Metabolic and Endocrine Drug Products, FDA, Silver Spring, MD*

Dr. Ganguli began the panel discussion by describing his psychiatric practice, and said that he has seen patients who are dying at earlier ages from diseases, just as had been described during the day's presentations. Many of his patients are overweight or obese and have concomitant diseases. The issue is how to treat these patients effectively. Integrated care is needed for patients who do not have access to the best programs in the country, and improved access is needed for all patients before they can get the care they need to address these diseases. Dr. Ganguli added that he would like to try lifestyle interventions and intensive monitoring in his practice if he could determine how to implement them. He suggested that there be more studies on practical interventions.

Dr. Daumit reiterated that an important research question is, if the current expert guidelines are used to monitor patients who take antipsychotic drugs, will this improve patient outcomes, prevent diabetes, or decrease weight gain? These are consensus guidelines rather than evidence-based guidelines, so it is not known if they can be expected to address the issues discussed here. The next issue would be to identify effective health care models for coordination between mental health and medical care systems to implement the guidelines. It also will be important to know who is responsible and to test these models.

Dr. Daumit commented on earlier discussions about weighing the risks and benefits of psychiatric versus medical treatment. Additional research is needed on the mechanisms of these treatments, and decisionmaking analyses and tools should be developed in both areas to help weigh the benefits and risks. In addition, it is important to bring patients and their families into these discussions.

Dr. Daumit described an NIMH-funded pilot study on lifestyle interventions to adapt interventions developed for the general population to the psychiatric population. It has been shown that interventions generally contain a "teachable moment," when researchers are able to have more influence than at other times; identifying the moment in studies of people with mental illness could help improve the success of the interventions.

Dr. Kahn said that the most compelling research question is whether schizophrenia—or the drugs used to treat it—are risk factors for diabetes. It is important to know the biology of schizophrenia regarding metabolism. Focusing on the drugs, what can they tell us about glucose regulation? This is a new approach to the problem, and more research should be conducted on the relationship between the brain and metabolism. Researching the metabolism of the drugs may provide a new understanding of pathways in the brain. Using these drugs as models, it is important to know how they influence body weight.

Dr. Kahn commented on the conflict between taking drugs that may have side effects—such as weight gain or diabetes—but that offer management of a life-threatening disease. Priorities should be realistic and efficient. One strategy would be to switch drugs to eliminate the secondary conditions.

Dr. Kahn offered his impression that lifestyle interventions should be viewed as a way of life, rather than a medical intervention. Lifestyle interventions are not medical treatments and should not be offered as such.

Dr. Parks recognized that this issue is not new to the FDA. A letter was sent in 2003 to manufacturers of the atypical antipsychotics asking that they label their drugs with a warning regarding hyperglycemia and diabetes associated with their use. At that time, there was not enough information about individual drugs in this class, so a general class-labeling warning was issued. This will be reviewed if strong evidence is found to change or alter the warning.

Dr. Parks commented that the risk of metabolic complications and cardiovascular disease from these drugs needs further study. More collaboration is needed between the FDA and external investigators, academic investigators, and manufacturers in studying the risks. Understanding the mechanisms involved also is important and could provide clues to the types of clinical studies needed to answer some of these questions. Perhaps some newer diabetes drugs in the approval process could be assessed for increasing the risk of diabetes or hyperglycemia.

The FDA could help to determine the types of monitoring needed to identify problems with patients and with using the drugs. In addition, answering some of these questions may enable the development of guidelines for treatment that can be applied in a clinical setting.

Closing Remarks and Adjournment

Dr. Fradkin

Dr. Fradkin thanked participants and said that she expects NIDDK to work with NIMH to address some of the issues raised in this meeting. She noted that some initiatives already underway could be used in this regard. For example, an NIDDK funding mechanism known as the Diabetes Prevention and Control Projects (R18 for full studies and R34 for planning grants) focuses on developing disseminatable, cost-effective strategies to deliver proven interventions, such as preventing or reversing weight gain in people at risk for diabetes. She suggested that studies funded under this mechanism might address this challenge in people with mental illnesses. Community health centers and other facilities in which those with mental illness receive care are a potential venue where strategies that are developed, proven, and validated can be translated and disseminated. This type of prevention effort should go forward.

Dr. Fradkin also stressed the importance of pathophysiology studies, and of bringing diabetologists and obesity experts together with people with access to patient populations to jointly study the pathophysiology. Little was said about genetics in the meeting, but it may be worthwhile to include genetics components in studies of people on antipsychotic drugs to better understand those who are susceptible to becoming obese and to developing diabetes. A large clinical study in a schizophrenic cohort could be useful. In general, efforts should be made to foster conditions that allow collaboration between those with schizophrenia expertise and those with metabolic expertise.

Dr. Garfield thanked everyone and said that having the FDA work with NIDDK and NIMH in this area will be explored.

Dr. Chavez thanked participants and raised a few final questions. He asked Dr. Ader to identify issues of pathophysiology that should be addressed. Dr. Ader responded that the data suggest that dietary intake alone in this population does not account for the increase in diabetes. It is a fundamental question in diabetes and obesity research, not just in populations taking these drugs. She said that where these drugs are acting is very basic, but there must be more metabolic research to determine what is happening in these interactions. There must be a funding mechanism to bring together metabolism researchers, endocrinologists, psychiatrists, and general practitioners to address these questions. No single type of researcher seems to have the basic knowledge to answer all of the research questions.

Dr. Grave commented on Dr. Dagogo-Jack's statement regarding the need for research on the ability to identify early metabolic changes that predict schizophrenia. This may be a worthwhile area of study.

Dr. Fradkin concluded that she would raise some of these issues with participants representing the Diabetes Centers at an upcoming meeting.

The meeting adjourned at 3:15 p.m.