Side-effect Management:

When medical illness emerges during treatment, with known or suspected relationship to treatment, this is ideally identified as an unwanted, treatment-related adverse event that may require intervention. Commonly encountered adverse events during antipsychotic therapy include sedation and extrapyramidal side-effects (EPS), most often addressed by dose reduction.

Medication-induced changes in weight and adiposity

Antipsychotic medications, including conventional antipsychotics available prior to the introduction of newer, atypical antipsychotic medications, can all cause and contribute to increases in weight and adiposity.(Allison, Mentore et al. 1999 Nov) Clinically significant weight gain was first observed during treatment with chlorpromazine, with low potency typical agents demonstrating more of an effect on weight than higher potency agents. A causal effect of antipsychotic treatment to induce weight gain has been established in double-blind, randomized, placebo-controlled clinical trials. Certain newer medications appear to have larger effects on weight gain than older agents, producing excessive weight gain in up to 50% of adult patients,(Baptista 1999 Jul) with children and adolescents apparently susceptible to still larger effects.(Kelly, Conley et al. 1998) Atypical antipsychotics such as clozapine and olanzapine, along with conventional low potency phenothiazines, can all cause clinically significant weight gain in some patients. High potency conventional antipsychotics like haloperidol, as well as atypical antipsychotics like aripiprazole, quetiapine, risperidone, and ziprasidone are associated with a lesser degree of weight gain. For example, haloperidol, aripiprazole, and ziprasidone produce a mean weight increase of only 1 kg over 1 year of treatment. The use of multiple psychiatric medications in the same patient (i.e., polypharmacy) has become a common part of psychiatric practice, despite limited research concerning the efficacy and possible increased weight gain liability associated with polypharmacy.

Learn more: Antipsychotic plus mood stabilizer-induced changes in weight and adiposity:

The use of multiple psychiatric medications in the same patient (i.e., polypharmacy) has become a common part of psychiatric practice, despite limited research concerning the efficacy and adverse events associated with this approach. Due to the prevalence and potential risks of polypharmacy, in the United States the National Association of State Mental Health Program Directors Research Institute has identified this area as a critical topic for research.(NASMHPD Medical Directors Council 2001 Sep) While polypharmacy is often motivated by the aim of improving efficacy or effectiveness in the treatment of severe chronic mental illness, this practice has public health implications with respect to possible increases in adverse events and costs.

Notably, clinicians have steadily increased their use of mood stabilizers in combination with antipsychotics in schizophrenia patients. One study observed that from 1994 to

1998, the percent of schizophrenia patients in the United States treated with mood stabilizers rose from 26.2% to 43.4%, with valproate accounting for 35% of those patients in 1998.(Citrome, Levine et al. 2000 May) Valproate is also among the top 10 most costly drugs to the Medicaid (government funding) program in most states within the United States. There are few studies looking at the combination of antipsychotics and mood stabilizers, and they offer discordant results with respect to efficacy.(Ko, Korpi et al. 1985 Feb; Dose, Hellweg et al. 1998 Jul; Hesslinger, Normann et al. 1999 Aug; Wassef, Hafiz et al. 2001 Feb) Abbott Laboratories sponsored a multicenter, randomized, prospective trial designed to study the effects of the addition of valproate to olanzapine or risperidone treatment in schizophrenia.(Casey, Daniel et al. 2003) Investigators have reported that valproate combination therapy resulted in significant PANSS total score reductions compared to antipsychotic monotherapy.(Casey, Daniel et al. 2003) However, the combination of valproate plus antipsychotics, including both olanzapine and risperidone, has also been associated with worsening of glucose and lipid metabolism and weight gain in comparison to antipsychotic treatment alone.(Meyer 2001 Apr 15; Casey, Daniel et al. 2003)

Weight gain is a common effect of both valproate and antipsychotics. Some evidence exists that valproate may cause additional weight gain when added to antipsychotics, with some indication that the size of this effect differs between antipsychotics.(Casey, Daniel et al. 2003) Casey et al observed mean increases in weight over 28 days of 7.7 lbs with olanzapine monotherapy and 8.3 lbs with the addition of valproate (p=NS). On the other hand, the addition of valproate to risperidone treatment showed an increase of 7.5 lbs, compared to 4.2 lbs during risperidone monotherapy (p=.039). Meyer et al observed similar increases in weight in patients treated with the combination of antipsychotics and valproate.(Meyer 2001 Apr 15)

Weight gain can lead to reduced quality of life for persons with schizophrenia(Allison, Mackell et al. 2003) as well as major adverse health consequences. In general, overweight and obesity are associated with increased risk of cardiovascular disease (i.e., coronary heart disease and cerebrovascular disease), type 2 diabetes mellitus, osteoarthritis, and increased risk of breast, prostate and colon cancers.(National Institutes of Health 1998) Increases in adiposity beyond the World Health Organization's threshold definition of overweight (i.e., 25 kg/m^2, or 23 kg/m^2 in Asians) are associated with progressive increases in mortality risk. The effects of adiposity on morbidity and mortality are mediated to a large extent through alterations in glucose and lipid metabolism.

Learn more:

Increased adiposity, particularly abdominal adiposity, is an established predictor of cardiovascular morbidity and mortality in men and women.(Manson, Colditz et al. 1990 Mar 29; Willett, Manson et al. 1995 Feb 8; Rimm, Stampfer et al. 1995 Jun 15) Underscoring the potential impact of this major medical condition, severe obesity (BMI >45) in a young adult (aged 20-30) is associated with a highly significant number of years of life lost, varying by gender and ethnicity with white males losing 13 years and black males losing 20 years of life.(Fontaine, Redden et al. 2003) In general, reported weight change over specific periods of time has tended to underestimate the extent of weight gain observed with any of the medications by using last-observation-carried-forward (LOCF) data, rather than "completer" analyses.(Zipursky, Gu et al. 2003) FDA-

approved weight loss agents are generally poorly tolerated in neuropsychiatric patients (e.g., due to events like activation, insomnia, and hallucinations), and initial efforts to identify tolerable augmentation strategies designed to attenuate the weight gain associated with atypical antipsychotics have been disappointing.(Poyurovsky, Pashinian et al. 2002 Jun)

Olanzapine induces clinically significant increases in short- and long-term weight gain. A comparative study of antipsychotic weight gain at 10 weeks of treatment showed a mean weight gain of 4.15 kg (9.15 lbs) with olanzapine, vs. 4.45 kg (9.81 lbs) with clozapine.(Blin 1999) Within the first three months of treatment, weight increases approximate a mean of 4 kg (8.8 lbs).(Allison, Mentore et al. 1999 Nov) Mean increases during 6-12 months of treatment with olanzapine or clozapine have been reported in the range of 14-26.4 lbs, with a mean of over 10 kg (22 lbs) at 12 months with olanzapine at 15mg/day, and individual patients experiencing 50-100 lb. increases. U.S. package insert data show that 29% of patients taking olanzapine for 6 weeks (vs. 3% of placebo controls), and 56% of patients taking olanzapine long-term, gain greater than 7% of their baseline weight.

Although risperidone can produce more weight gain than some high potency conventional agents and more than ziprasidone and aripiprazole, it produces relatively less short term weight gain than olanzapine and clozapine,(Penn, Martini et al. 1996 Jun) ranging from 3 to 5 lbs over the first 10 weeks of treatment.(Marder and Meibach 1994 Jun; Masand 1998; Ganguli 1999; Allison, Mentore et al. 1999 Nov) In a 6 month comparison, Tran et al reported that mean weight gain on risperidone was 5 lbs versus 9 lbs with olanzapine treatment.(Tran, Hamilton et al. 1997 Oct) However, longer treatment with risperidone has been associated with greater gains (9 lbs.) than those reported in the Tran study.(Wirshing, Wirshing et al. 1999 Jun) Interestingly, Ganguli et al. showed mean weight loss of 2 lbs with risperidone at a mean treatment duration of 125.3 days in unpublished data.(Ganguli 1999) It may be critical to consider and control for the previous treatment received, as switches from higher weight gain liability agents to lower liability agents can be associated with weight loss. Package insert data for risperidone indicate that 18% of patients gain 7% or more of their body weight over 6-8 weeks, vs. 9% of placebo controls.

Quetiapine treatment at 5-6 weeks is associated with approximately 2 kg (4.4 lbs) of weight increase.(Jones, Rak et al.; Arvanitis and Miller 1997) During long-term treatment, however, quetiapine treatment has been observed to produce additional weight gain. While one long term study indicated that average weight gain during quetiapine treatment was on the order of one kilogram (2.2 lbs),(Brecher, Rak et al. 2000) another analysis of 2,216 patients treated with quetiapine revealed an average weight gain of 6 lbs. after 9 to 12 months of treatment.(Jones, Rak et al.) One phase III trial of quetiapine suggests that weight gain in the short term (5-6 weeks) and long-term (9-12 months) tends to be roughly twice that of placebo.(Arvanitis and Miller 1997) Package insert data show that a significant 23% of patients (vs. 6% taking placebo) gained 7% body weight or more with 3 to 6 weeks of seroquel.

Ziprasidone appears to show comparatively little weight gain, with minimal weight gain recorded in studies of 4-week(Daniel, Zimbroff et al. 1999) and 28-week(Hirsch, Kissling et al. 2002) courses of treatment. Estimated weight in the Allision et al random effects model analysis cited above for clozapine and olanzapine was negligible.(Allison, Mentore et al. 1999 Nov) However, published data are somewhat limited for this

relatively new agent. Package insert data indicate weight gain of 7% or more in 10% of patients taking ziprasidone vs. 4% of placebo controls over 4 to 6 weeks of treatment.

Short-term clinical trial data from the aripiprazole package insert indicates that aripiprazole is associated with approximately 2 times the incidence of clinically significant (7% or more) weight gain compared to placebo. Pooled data from five short-term studies indicate that 4 weeks of aripiprazole treatment is associated with .71 kg (1.6 lbs) of weight gain.(Jody, Saha et al. 2002; Stock, Marder et al. 2002) Extrapolating this to 10 weeks for comparability with other agents, haloperidol is known to produce approximately 1 kg of weight increase over 10 weeks,(Allison, Mentore et al. 1999 Nov) which may crudely approximate expected gain over the same period for aripiprazole. In a 26-week double-blind study, aripiprazole was associated with a .87 kg (1.9 lbs) decrease in weight.(Carson, Pigott et al. 2002) Analysis of data from a 1 year double-blind study showed that aripiprazole was associated with 1.1 kg (2.4 lbs) of weight gain.(Jody, Saha et al. 2002) While published data are currently sparse for this relatively new agent, results suggest that aripiprazole compares favorably to other atypical antipsychotics associated with minimal weight gain.(Kane, Carson et al. 2002)

Medication-induced effects on insulin resistance, hyperglycemia, dyslipidemia and the metabolic syndrome

Treatment with antipsychotic medications can contribute to insulin resistance, hyperglycemia, dyslipidemia (e.g., hypertriglyceridemia), exacerbations of existing type 1 and 2 diabetes, new onset cases of type 2 diabetes, and cases of diabetic ketoacidosis or non-ketotic hyperosmolar, hyperglycemic states. There are presumed to be complex interactions between the effects of medications, disease, individual pharmacogenetics, and lifestyle. It has been observed that schizophrenia may be associated with insulin resistance in the form of impaired glucose regulation and elevated rates of diabetes mellitus, beginning prior to the introduction of antipsychotic medications (for review, see Haupt and Newcomer 2002).(Haupt and Newcomer 2002) However, antipsychotic treatment can cause and contribute to disturbances in glucose and lipid metabolism through treatment-induced increases in adiposity, and possibly through effects that are independent of adiposity

Learn more:
An established risk factor for insulin resistance, hyperglycemia, dyslipidemia, the metabolic syndrome and type 2 diabetes mellitus is weight gain in the form of increased adiposity, and antipsychotic medications can increase weight and adiposity (see above). Increased adiposity leads to decreased sensitivity to insulin actions, often referred to as insulin resistance. Insulin resistance can be associated with simple hyperglycemia or dyslipidemia, impaired glucose tolerance, or the full complement of changes called the metabolic syndrome, reflecting a continuum of disturbances leading up to frank type 2 diabetes mellitus. All of these conditions are characterized by decreased sensitivity to insulin actions on skeletal muscle (glucose disposal), liver (glucose production) and adipose tissue (lipolysis), with type 2 diabetes mellitus also characterized by progressive secondary disturbances in insulin secretion. Decreased insulin sensitivity in skeletal muscle tissue can lead to a decreased ability to increase glucose uptake after a meal, usually detectable early in the progression of insulin resistance as impaired glucose tolerance or post-prandial hyperglycemia. Decreased insulin sensitivity in liver tissue can

lead to an impaired ability to decrease glucose production, typically occurring later in the progression of insulin resistance and expressed clinically as impaired fasting glucose. Decreased insulin sensitivity at adipose tissue is characterized by an impaired ability to decrease lipolysis with corresponding increases in the release of free fatty acids (FFAs) into circulation.(Lebovitz 1999) Increased plasma FFA (triglyceride + glycerol) is detected clinically as an elevation in plasma triglyceride. The expression of decreased insulin sensitivity, therefore, can be seen not just through changes in glucose metabolism, but also through changes in lipid metabolism.

Of note, a recent report described impairments in insulin sensitivity in acutely psychotic, medication naïve schizophrenia patients.(Ryan, Collins et al. 2003) However, as confirmed by the observed elevations in cortisol levels, these patients were acutely stressed. Hypercortisolemia resulting from acute stress is commonly associated with insulin resistance, and may not be indicative of chronic insulin resistance. In contrast, effects on glucose metabolism in studies of stable patients have not been explained by disturbances in counter-regulatory hormones like glucagon and cortisol. Recent studies have indicated that agents like clozapine may have preferential capacity to increase circulating norepinephrine (NE) levels, but the relationship between increased NE and insulin sensitivity or secretion has not been delineated. In individuals with and without diabetes, NE can adversely affect glucoregulation.(Walters, Ward et al. 1997 Dec)

With the introduction of chlorpromazine, phenothiazine treatment was observed to contribute to abnormalities in glucose regulation, including reports of aggravation of existing diabetes and new onset type 2 diabetes mellitus.(Haupt and Newcomer 2001 Dec) Higher potency older antipsychotic agents like haloperidol are less consistently associated with diabetes mellitus, suggesting that medication effects on glucose regulation may vary in magnitude across individual agents in parallel with drug effects on weight gain. Hypertriglyceridemia, commonly observed in the setting of insulin resistance, is also reported during antipsychotic treatment. Early studies identified the association between phenothiazine treatment and increases in plasma lipids.(Clark, Dubowski et al. 1970 Nov-Dec)

Recent reports suggest that certain newer antipsychotic medications, perhaps even more than older agents, can contribute to the occurrence of clinically significant glucoregulatory abnormalities (e.g., new onset diabetes), dyslipidemia (e.g., increased plasma triglyceride) and increased weight and adiposity (for review see Haupt and Newcomer 2001).(Haupt and Newcomer 2001 Dec) Reports again indicate that the effect size of such adverse events, or the frequency, may vary across different medications.

Learn more:
Hyperglycemia, exacerbation of existing type 2 diabetes mellitus, new onset type 2 diabetes mellitus, and diabetic ketoacidosis have been associated with treatment using clozapine,(Koval, Rames et al. 1994 Oct; Kamran, Doraiswamy et al. 1994 Sep; Kostakoglu, Yazici et al. 1996 Mar; Peterson and Byrd 1996 May; Pierides 1997 Jul; Popli, Konicki et al. 1997 Mar; Yazici, Erbas et al. 1998; Ai, Roper et al. 1998 Aug; Hagg, Joelsson et al. 1998 Jun; Wirshing, Spellberg et al. 1998 Oct 15; Melson, Selke et al. 1999; Maule, Giannella et al. 1999 Apr; Mohan, Gordon et al. 1999 Feb; Smith, Kenney-Herbert et al. 1999 Feb; Colli, Cocciolo et al. 1999 Jan; McDonnell and Ruderman 1999 Nov; Selke, Newcomer et al. 2000; Wehring, Alexander et al. 2000 Jul; Henderson, Cagliero et al. 2000 Jun; Rigalleau, Gatta et al. 2000 Jun; Koller, Schneider

et al. 2001 Dec 15; Avram, Patel et al. 2001 Nov; Griffiths and Springuel 2001 Oct 2) and olanzapine.(Fertig, Brooks et al. 1998 Dec; Wirshing, Spellberg et al. 1998 Oct 15; Paizis, Cavaleri et al. 1999; Gatta, Rigalleau et al. 1999 Jun; Ober, Hudak et al. 1999 Jun; Lindenmayer and Patel 1999 Sep; Von Hayek, Huttl et al. 1999 Sep; Goldstein, Sporn et al. 1999 Sep-Oct; Selke, Newcomer et al. 2000; Bettinger, Mendelson et al. 2000 Jul-Aug; Rigalleau, Gatta et al. 2000 Jun; Van Meter, Seaburg et al. 2001 Dec; Muench and Carey 2001 Jul-Aug; Kropp, Emrich et al. 2001 Jun; Selva and Scott 2001 Jun; Bonanno, Davydov et al. 2001 May; Bechara and Goldman-Levine 2001 Nov; Seaburg, McLendon et al. 2001 Nov; Griffiths and Springuel 2001 Oct 2; Ananth, Gunatilake et al. 2001 Sep; Dervaux, Mascarenhas et al. 2001 Sep 22; Koller and Doraiswamy 2002; Johnson, Al-Taher et al. 2002 Jan 1) Fewer reports have been associated with quetiapine(Sobel, Jaggers et al. 1999 Aug; Bettinger, Mendelson et al. 2000 Jul-Aug; Procyshyn, Pande et al. 2000 Sep; Wilson, Hammond et al. 2001 Apr; Griffiths and Springuel 2001 Oct 2) risperidone,(Wirshing, Erhart et al. 2000; Croarkin, Jacobs et al. 2000 Jul-Aug; Wirshing, Pierre et al. 2001 Jul 15; Haupt and Newcomer 2001 Jun; Griffiths and Springuel 2001 Oct 2; Mallya, Chawla et al. 2002; Koller, Cross et al. 2003) and ziprasidone.(Yang and McNeely 2002) Deaths have been attributed to the induction of diabetic ketoacidosis or other hyperglycemia-related events during treatment with certain atypical antipsychotics.(Von Hayek, Huttl et al. 1999 Sep; Koller, Schneider et al. 2001 Dec 15; Koller and Doraiswamy 2002; Koller, Cross et al. 2003) Recent reports have also identified clinically significant increases in plasma triglycerides in patients treated with clozapine,(Ghaeli and Dufresne 1996 Sep 1; Spivak, Roitman et al. 1998 Jul-Aug; Gaulin, Markowitz et al. 1999 Aug) olanzapine,(Meyer 1999 Dec; Osser, Najarian et al. 1999 Nov; Lindenmayer and Patel 1999 Sep; Sheitman, Bird et al. 1999 Sep) and quetiapine.(Meyer 1999 Dec)

The introduction of chlorpromazine in one setting increased the prevalence of diabetes from 4.2% to 17.2%, an increase similar to that noted in some recent reports concerning the introduction of newer antipsychotic medications.(Thonnard-Neumann 1968 Jan) These and other reports prompted the National Diabetes Data Group in the late 1970s to add phenothiazines to the list of medications that can disturb whole-body glucose metabolism.(National Diabetes Data Group 1979 Dec) While low potency phenothiazines have most frequently been associated with abnormalities in glucose regulation, this association is not consistently observed for all older antipsychotics.(Schwarz and Munoz 1968 Aug; Keskiner, el-Toumi et al. 1973 May-Jun) The increased use of older high potency antipsychotics, versus low potency phenothiazines, in the years prior to the introduction of newer antipsychotic medications may have contributed to the reduction in the number of reports concerning antipsychotic-related hyperglycemia over that same period. In general, these early studies of medication effects on glucose and lipid metabolism, like earlier studies of glucose metabolism in unmedicated schizophrenia patients, suffered from a lack of controls and limited assessment of confounding variables (e.g., adiposity). The current evidence for antipsychotic-associated hyperglycemia spans case reports and case series, FDA MedWatch data, case-control comparisons, prospective observational studies and one small prospective randomized trial.(Henderson, Cagliero et al. 2000 May; Haupt and Newcomer 2001 Dec; Koller, Schneider et al. 2001 Dec 15; Glick, Fryburg et al. 2001 May; Koller and Doraiswamy 2002; Newcomer, Haupt et al. 2002; Koller, Cross et al. 2003) Random plasma glucose data from Pfizer's clinical trial dataset suggest that ziprasidone may be similar to risperidone and haloperidol in the rate of associated hyperglycemia.(Pfizer) Aripiprazole, relatively new to the market, has not been associated with published reports of impaired glucose metabolism to date. During brief

> randomized treatment with several newer and older antipsychotic agents, with groups ranging in size from 27 to 34 subjects, fasting plasma triglycerides increased during olanzapine, quetiapine and thioridazine treatment with modest to non-significant decreases observed during ziprasidone, risperidone and haloperidol treatment.(Pfizer)

Insulin resistance in the form of impaired fasting glucose, impaired glucose tolerance, dyslipidemia, the metabolic syndrome or frank type 2 diabetes mellitus can all contribute to functional disability, suffering, and increased health care costs through morbidity related to microvascular (i.e., retinopathy, neuropathy, nephropathy) and macrovascular (i.e., peripheral vascular, coronary heart, cerebrovascular) disease.(Ratner 1998) Exemplifying high impact morbidity, impaired glucose control and type 2 diabetes mellitus are the major cause in the United States for non-traumatic amputations, blindness and end-stage renal disease. In addition, NCEP recognizes the metabolic syndrome as a major risk factor and type 2 diabetes mellitus as a risk equivalent for cardiovascular disease, the combination of coronary heart and cerebrovascular disease (e.g., stroke and myocardial infarction).(National Cholesterol Education Program 2001) Considerable recent evidence indicates that even early manifestations of insulin resistance, such as isolated postprandial hyperglycemia (2-hour postprandial glucose >140mg/dl) in the setting of normal fasting plasma glucose and normal glycated hemoglobin (<6.1%), are associated with elevated cardiovascular mortality (2-fold increased risk).(Gerich 2003) These reports indicate that treatment-induced hyperglycemia can have important clinical significance even when glucose levels do not reach "impaired" or diabetic thresholds. This is one of the reasons behind the growing public health interest in the role of insulin resistance in the metabolic syndrome. The metabolic syndrome includes a combination of increased abdominal adiposity, insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, hypercoagulability, endothelial dysfunction and other features, sometimes alternatively defined under the terms insulin resistance syndrome or syndrome X. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines provide the United States definition of the metabolic syndrome: ≥ 3 of the following criteria: 1) increased abdominal adiposity (waist circumference >102cm in men, >88cm in women); 2) high triglyceride (≥150mg/dL [≥1.69mmol/L]) or use of a lipid lowering drug; 3) low HDL cholesterol (<40mg/dL [<1.03mmol/L] in men and <50mg/dL [<1.29mmol/L] in women); 4) high BP (systolic ≥130mm Hg or diastolic ≥85mm Hg) or use of an antihypertensive; 5) high fasting glucose (>110mg/dL).(National Cholesterol Education Program 2001) Using these criteria it is estimated that over 20% of the United States population, and approximately 60% of the obese United States population, has the metabolic syndrome.(National Cholesterol Education Program 2001; Park, Zhu et al. 2003) Established risk factors include older age, sedentary lifestyle, postmenopausal status, and high carbohydrate diet. Lifestyle changes associated with schizophrenia as well as the effects of antipsychotic medications may contribute to insulin resistance and other elements of the metabolic syndrome. Based on high rates of obesity in individuals with schizophrenia, and estimates that 60% of obese individuals have the metabolic syndrome, substantial number of patients may be affected by this condition. Public health (e.g., ATP III) recommendations to screen for the metabolic syndrome suggest that clinicians would be wise to incorporate screening for increased adiposity and indicators

of insulin resistance in individuals with schizophrenia who are treated with medications known to increase body weight and plasma glucose and lipids.

Learn more:
Hypertriglyceridemia, commonly associated with insulin resistance, is also a strong predictor of cardiovascular events,(Austin 1991 Jan-Feb; Despres and Marette 1994 Aug; Semenkovich 1995) and the combination of hyperglycemia, dyslipidemia and abdominal adiposity is strongly predictive of increased cardiovascular morbidity.(Kaplan 1989 Jul; Austin 1991 Jan-Feb; Despres and Marette 1994 Aug; Semenkovich 1995) One of the most established effects of adiposity on cardiovascular risk occurs via perturbations of lipid metabolism. Increased adiposity, especially increased visceral abdominal adiposity, is associated with increased small, dense low-density lipoprotein (LDL) particles and decreased high-density lipoprotein (HDL) cholesterol.(Albrink, Krauss et al. 1980; Terry, Wood et al. 1989; Reaven, Chen et al. 1993) Since LDL cholesterol comprises 60-70% of the total cholesterol level, total cholesterol has been used as a marker for increased LDL level in population studies. The National Health and Nutrition Examination Study III (NHANES III) provided prevalence data indicating that hypercholesterolemia (total cholesterol $\geq$240) increased with increasing BMI in men.(Brown, Higgins et al. 2000) A similar relationship was observed in women, although BMIs greater than 27 kg/m^2 were not associated with further increases in cholesterol levels. These increases in cholesterol are strongly associated with increased cardiovascular risk.(Assmann and Schulte 1992; Lamarche, Lemieux et al. 1999) Recent meta-analyses have reported that hypertriglyceridemia is an independent risk factor for cardiovascular disease.(Assmann, Schulte et al. 1998; Austin 1999) Some early studies failed to identify a relationship between plasma triglycerides and cardiovascular disease, probably due to the fact that hypertriglyceridemia can be a result of other cardiovascular risk factors such as obesity, sedentary lifestyle, diabetes, and cigarette smoking. Emphasizing concern about the role of triglycerides in cardiovascular disease, current ATP III recommendations state that greater emphasis needs to be placed on therapeutic lifestyle changes in people with hypertriglyceridemia.(Eidelman, Lamas et al. 2002) Applying this information to the treatment of patients with schizophrenia, clinicians should carefully consider the clinical relevance of medication effects on plasma glucose and lipids.

Metabolic disturbance without weight gain during antipsychotic treatment:

Weight gain producing increased visceral adiposity can increase insulin resistance and contribute to hyperglycemia.(Banerji, Lebowitz et al. 1997 Aug) Treatment-related changes in glucose regulation are expected secondary to changes in adiposity. However, approximately 20-25% of cases of new onset type 2 diabetes mellitus in schizophrenia patients may occur in the absence of weight gain, suggesting potential direct effects on insulin secretion or action in a smaller subset of patients.(Haupt and Newcomer 2001 Dec) The results of a study by Newcomer and colleagues using fasting and post-load plasma measures from modified frequently sampled oral glucose tolerance tests indicated that newer antipsychotic treatments, particularly clozapine and olanzapine, could be associated with disturbances in glucose regulation independent of differences in adiposity.(Newcomer, Haupt et al. 2002) Insulin resistance varied across medication groups in this initial study, even with groups matched for adiposity and age and balanced for ethnicity. Henderson and colleagues have observed similar results with a frequently sampled intravenous glucose tolerance test in subject groups similarly matched for

adiposity, age and race.(Henderson, Cagliero et al. 2000 May) In their study, the authors reported higher post-load plasma glucose values and lower insulin sensitivity in clozapine- and olanzapine-treated subjects, as compared to risperidone-treated subjects. Taken together, available data and case reports suggest that most patients treated with antipsychotics who develop insulin resistance do so as a direct result of antipsychotic-associated weight gain. However, less consistent changes in insulin sensitivity or secretion independent of adiposity may occur in some individuals. Reports of sporadic cases of deaths associated with diabetic ketoacidosis underscore that large defects in insulin action at adipose tissue, potentially related to decreases in insulin secretion may occur in some patients.

> **Learn more: Combined effects of antipsychotic treatment and valproate on glucose and lipid metabolism:**
>
> Elevations in plasma glucose levels during combined treatment with antipsychotics and valproate have been reported.(Meyer 2001 Apr 15; Casey, Daniel et al. 2003) A few reports have described insulin resistance and elevated plasma insulin levels associated with valproate monotherapy.(Isojarvi, Rattya et al. 1998 Apr; Luef, Abraham et al. 2002 Jan) Contradictory data exist regarding the effects of valproate on lipid metabolism. Valproate treatment has been associated with decreases(Luef, Abraham et al. 2002 Jan; Casey, Daniel et al. 2003) and increases in total cholesterol.(Calandre, Rodriquez-Lopez et al. 1991 Apr; Isojarvi, Rattya et al. 1998 Apr; Stephen, Kwan et al. 2001 Aug)

Diabetes mellitus and acute diabetic complications, including diabetic ketoacidosis and non-ketotic hyperosmolar hyperglycemic states

While many patients treated with antipsychotic medications can experience an increase in adiposity and insulin resistance with related changes in the long-term risk for developing diabetes mellitus and cardiovascular disease, a much smaller number of patients can develop acute complications of severe hyperglycemia or hyperlipidemia including diabetic ketoacidosis. A search of the literature and unpublished post-marketing data up to Sept 2002, including recent analyses of the U.S. Food and Drug Administration MedWatch events database, found that of recently reported hyperglycemia-related deaths, 25 deaths were associated with clozapine treatment, 23 deaths with olanzapine treatment, 9 deaths with quetiapine treatment, and 4 deaths with risperidone treatment, principally in the context of diabetic ketoacidosis or related nonketotic hyperosmolar events.(Koller, Schneider et al. 2001 Dec 15; Koller and Doraiswamy 2002; Koller, Cross et al. 2003) Any attempt to interpret these case report numbers must take into consideration the denominator or number of prescriptions that underlie the adverse events (e.g., olanzapine has achieved fewer total prescriptions than risperidone, but olanzapine has a larger number of adverse event reports). In general, case reports have limited interpretability due to problems of under-reporting and reporting bias.

> **Learn more:**
> Diabetic ketoacidosis is an acute to subacute onset, potentially fatal, severe metabolic disturbance characterized by hyperglycemia (glucose usually > 300 mg/dL), hyperketonemia (total serum ketones > 3 mM), and metabolic acidosis (blood pH < 7.3 or $HCO3 \leq 15$ meq/L). diabetic ketoacidosis requires a lack of insulin secretion or activity at adipose tissue with failure to inhibit lipolysis, resulting in conversion of

liberated free fatty acids to ketone bodies in the liver. Symptoms of diabetic ketoacidosis include nausea, vomiting, anorexia, lethargy, and altered mental status. Until recently, it had been widely accepted that diabetic ketoacidosis was rare in type 2 diabetes, and usually associated with severe physiologic stressors. However, high rates of diabetic ketoacidosis in type 2 diabetes mellitus have been reported in various ethnic groups.(Umpierrez, Kelly et al. 1997 Mar 24) More recently, it has been recognized that not only is diabetic ketoacidosis common in type 2 diabetes, but this complication may not be restricted to higher risk groups. In a multiethnic population, Balasubramanyam et al observed that nearly 40% of cases of diabetic ketoacidosis were associated with type 2 diabetes mellitus, and that almost half of the patients with type 2 diabetes mellitus who presented with diabetic ketoacidosis had not been previously diagnosed with type 2 diabetes mellitus. Approximately half of these individuals had no identifiable stressor associated with the onset of diabetic ketoacidosis.(Balasubramanyam, Zern et al. 1999 Oct 25) Mortality rates from diabetic ketoacidosis range from 2% up to 20% or higher.(Malone, Gennis et al. 1992 Nov) Key factors that influence the outcome of diabetic ketoacidosis include the patient's age and general health, along with the time elapsed between symptom onset and diagnosis, and initiation of insulin treatment. Clinicians can reasonably be concerned that patients taking antipsychotic medications may tend to take longer than the non-psychiatric populations to identify signs and symptoms of diabetic ketoacidosis and then to work with care providers to initiate treatment. While monitoring can detect type 2 diabetes mellitus, diabetic ketoacidosis has a sudden and precipitous onset, making monitoring for this complication difficult or impossible. Clinicians, other caregivers and patients must be educated to recognize the signs and symptoms of this infrequent but serious complication.

Recommendations:

The recently published American Diabetes Association Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes statement (ADA, 2004) offered recommendations to clinicians. The Consensus Position noted the evidence for elevated rates of obesity and type 2 diabetes in populations treated with SGAs, but cited the limitations in available data that preclude judgement about whether this is a function of the illness itself versus its treatment. It was observed that high rates of smoking and physical inactivity increase risk for cardiovascular disease in this patient population, increasing the importance of any further increase in the risk for obesity and type 2 diabetes. On the key question of the relationship between the use of these agents and the incidence of obesity or diabetes, and despite shortcomings in many relevant studies, the committee found compelling evidence for an association between both clozapine and olanzapine therapy and treatment-induced weight gain as well as treatment-related diabetes and dyslipidemia,

The Consensus Position emphasized the need for appropriate baseline and follow-up monitoring over the duration of SGA treatment, in order to detect the development of significant weight gain, dyslipidemia, and diabetes. Given the established role of weight gain in increasing risk for diabetes, dyslipidemia and other conditions such as cardiovascular disease, clinicians were particularly advised to track and record weight, body mass index (BMI) and waist circumference, and to encourage patients to monitor and record their own weight. The panel recommended baseline evaluation of personal and family history of obesity, diabetes, dyslipidemia, hypertension and cardiovascular

disease, along with baseline measures of weight and height, waist circumference, blood pressure, fasting plasma glucose and a fasting lipid profile. Identification of patients at baseline who are overweight (BMI 25.0-29.9) or obese (BMI $\geq$ 30), prediabetic (fasting glucose 100-125 mg/dl) or diabetic (fasting glucose $\geq$ 126 mg/dl), hypertensive (blood pressure > 140/90 mmHG), or dyslipidemic (http://www.clevelandclinic.org/heartcenter/pub/news/archive/2004/NCEPLDL7_13.asp) should result in appropriate treatment. Appropriate referrals to other health care providers were encouraged, including nutrition and physical activity counseling for all patients who are overweight or obese. Health professionals, patients and their families and caregivers were encouraged to be aware of the signs and symptoms of diabetes and acute complications such as diabetic ketoacidosis, and to know that treatment with some SGAs may be associated with significant weight gain, and an increased risk of diabetes and dyslipidemia.

The panel recommended that follow-up monitoring of weight take place at 4, 8 and 12 weeks and then quarterly after a start or change in SGA treatment, with more frequently monitoring indicated in individuals with increased risk (Table). It was proposed that patients gaining 5% or more of their baseline weight at any time during therapy initiate nutritional and exercise interventions and consider switching to a lower weight gain SGA. Fasting plasma glucose, lipid profiles and blood pressure were recommended for follow-up at 3 months and then annually for individuals with normal values and low baseline risk. Individuals with higher baseline risk for diabetes, dyslipidemia or hypertension, or those who develop increases in relevant parameters should consider more frequent assessments. The panel recommended that worsening glycemia or dyslipidemia during treatment lead to a consideration of switching to an SGA that has not been associated with significant weight gain or diabetes. It was recommended that patients developing diabetes be directed to an ADA-recognized diabetes self-management program, that they receive a referral to a clinician experienced in the care of diabetes, carry diabetes identification and pursue the same goals of therapy with respect to blood pressure, lipids, and glycemic control as persons without a psychiatric disorder.

Table*

	Start	4 wks	8 wks	12 wks	3 mos.	12 mos.	5 yrs.
Personal/family Hx	X					X	
Weight (BMI)	X	X	X	X	X		

Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

The Consensus Position emphasized the need for careful risk-benefit assessment in choosing among the SGAs for an individual patient, recognizing the potential advantages of even higher risk medications. However, the panel made clear that the risks of obesity, diabetes and dyslipidemia are important health considerations that should also influence drug choice.

Another recent development in this area began when the US Food and Drug Administration (FDA) requested information on hyperglycemia in patients treated with atypical antipsychotics. The FDA subsequently requested that all of the SGAs include in their package insert some additional warning language related to the risk of hyperglycemia during treatment with SGAs, with minor differences across individual agents. This so-called "class labeling" has generated controversy due to discrepancies with ADA Consensus Position Statement, including the FDA warning's lack of notation of increased risk with olanzapine and the absence of any mention of weight gain in relation to risk of hyperglycemia. Part of the FDA's response to criticism has been to argue that weight gain during antipsychotic treatment has not been proven in whole or in part to be related to incident hyperglycemia during antipsychotic treatment. The hypothesis that weight gain is only a risk factor in the general population, but not related to the risk of diabetes during antipsychotic treatment, (Boehm, Racoosin et al, 2004) would seem to depend on unknown protective factors to block the adverse effects of adiposity that have been well-established in a variety of human populations. Given the evidence for higher, rather than lower, prevalence of diabetes in psychiatric populations in most datasets examined to date, it seems unlikely that such protective factors are operating in individuals with psychiatric illness. Therefore, it would seem prudent to assume that antipsychotic-induced weight gain, just like any other increase in total fat mass, may be associated with a variety of adverse physiological effects.

Subsequent published consensus efforts have also addressed recommendations for screening weight, glucose, lipids, and blood pressure, with substantial overlap in recommendations. Unresolved discrepancies concern the use of screening tools like glycated

hemoglobin, which the American Diabetes Association does not recommend for screening the general population, and screening lipids at 5 years in the ADA criteria, which is not consistent with ATP-III criteria. Also under debate is the issue of whether well-developed guidelines for screening the general population should be applied less stringently to vulnerable psychiatric populations, based on perceived complexities in the application of screening procedures in the mentally ill. However, the authors are unaware of any previous examples of special populations that are at increased risk for disease receiving recommendations for lower levels of screening.

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