

ATYPICAL ANTIPSYCHOTICS ISSUES MANAGEMENT

WEIGHT GAIN DATA

PUBLISHED LITERATURE / POSTERS REVIEW

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Preclinical

Potential Mechanisms Of Weight Gain

Mechanisms of Antipsychotic-Induced Weight Gain. *J Clin Psych* 2001;62 (23):23-29

McIntyre RS, Mancini DA, Basile VS

The estimated percentage of persons with schizophrenia who are overweight is higher than the percentage of persons in the general population who are overweight. The increased mortality rate for persons with schizophrenia is largely due to obesity-related diseases. The atypical antipsychotics offer an improved therapeutic index when compared with the conventional agents, but may impart serious adverse events such as weight gain. This brief review is intended to provide the practicing clinician with an update of disparate research paradigms under investigation in an attempt to delineate the biological mechanisms that presage weight gain. Research success in this area may invite novel prevention strategies and hint at potential mechanisms of antipsychotic drug action.

Genetic Dissection of Atypical Antipsychotic-Induced Weight Gain: Novel Preliminary Data on the Pharmacogenetic Puzzle. *J Clin Psych* 2001;62 (23):45-66

Basile VS, Masellis M, McIntyre RS, Meltzer HY, Lieberman JA, Kennedy JL

Atypical antipsychotics such as clozapine represent a significant improvement over typical antipsychotics in the treatment of schizophrenia, particularly regarding extrapyramidal symptoms. Despite their benefits, use is limited by the occurrence of adverse reactions such as sedation and weight gain. This article provides a comprehensive review and discussion of obesity-related pathways and integrates these with the known mechanisms of atypical antipsychotic action to identify candidate molecules that may be disrupted during antipsychotic treatment. Novel preliminary data are presented to genetically dissect these obesity pathways and elucidate the genetic contribution of these candidate molecules to clozapine-induced weight gain. There is considerable variability among individuals with respect to the ability of clozapine to induce weight gain. Genetic predisposition to clozapine-induced weight gain has been suggested. Therefore, genetic variation in these candidate molecules may predict patient susceptibility to clozapine-induced weight gain. This hypothesis was tested for 10 genetic polymorphisms across 9 candidate genes, including the serotonin 2C, 2A, and 1A receptor genes (HTR2C/2A/1A); the histamine H₁ and H₂ receptor genes (H1R/H2R); the cytochrome P450 1A2 gene (CYP1A2); the β 3 and α_{1a} -adrenergic receptor genes (ADRB3/ADRA1A); and tumor necrosis factor α (TNF- α). Prospective weight gain data

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were obtained for 80 patients with schizophrenia who completed a structured clozapine trial. Trends were observed for ADRB3, ADRA1A, TNF- α , and HTR2C; however, replication in larger, independent samples is required. Although in its infancy, psychiatric pharmacogenetics will in the future aid clinical practice in the prediction of response and side effects, such as antipsychotic-induced weight gain, and minimize the current “trial and error” approach to prescribing.

Mechanism of the Neuroleptic-Induced Obesity in Female Rats. *Prog. NeuroPsychopharmacol. & Biol. Psychiatr.* 1998(22):187-198

Baptista T, Contreras Q, Teneud L, Albornoz MA, Acosta A, Paez X, de Quijada M, Lacruz A, Hernandez L

1. Obesity is an undesirable side effect of neuroleptics which affects 50% approximately of patients under a program of chronic administration.
2. An animal model of neuroleptic-induced obesity and hyperphagia has been developed in female rats treated chronically with sulpiride (20 mg/Kg/ip. for 21 days). However, it is unknown whether or not the hyperphagia is essential for the development of this type of obesity.
3. Sulpiride or vehicle was administered in two experimental conditions: in the first one, food was available in an amount which was three times the previous individual daily food intake; in the second one, the daily food provision was maintained at the individual daily average before starting the treatments. This way hyperphagia was prevented in half of the groups. Besides the body weight gain measurement in all the groups, the serum levels of estradiol, prolactin, glucose and lipids were assessed in the groups with unrestricted food intake.
4. Food restriction prevented the sulpiride-induced weight gain, even though the rats displayed a permanent diestrus which suggests an hyperprolactinemia-induced impairment in the balance of the reproductive hormones that may promote weight gain. However, the basal levels of estradiol were not affected by sulpiride.
5. The high density cholesterol was significantly increased by sulpiride, and the serum glucose levels were significantly decreased, however, these changes were only detected during the first week of treatment.
6. The decrease in the serum glucose levels may be an early consequence of hyperinsulinemia.
7. Neuroleptic-induced obesity in rats appears to mimic energy intake, endocrine status and carbohydrate metabolism in humans under chronic neuroleptic administration. However, these rodents did not display the typical changes in blood lipids observed in human obesity.

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H1-Histamine Receptor Affinity Predicts Short-Term Weight Gain for Typical and Atypical Antipsychotic Drugs. *Neuropsychopharmacology* 2002:1-8

Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL

As a result of superior efficacy and overall tolerability, atypical antipsychotic drugs have become the treatment of choice for schizophrenia and related disorders, despite their side effects. Weight gain is a common and potentially serious complication of some antipsychotic drug therapy, and may be accompanied by hyperlipidemia, hypertension and hyperglycemia and, in some extreme cases, diabetic ketoacidosis. The molecular mechanism(s) responsible for antipsychotic drug-induced weight gain are unknown, but have been hypothesized to be because of interactions of antipsychotic drugs with several neurotransmitter receptors, including 5-HT_{2A} and 5-HT_{2C} serotonin receptors, H₁-histamine receptors, α_1 - and α_2 -adrenergic receptors, and m3-muscarinic receptors. To determine the receptor(s) likely to be responsible for antipsychotic-drug-induced weight gain, we screened 17 typical and atypical antipsychotic drugs for binding to 12 neurotransmitter receptors. H₁-histamine receptor affinities for this group of typical and atypical antipsychotic drugs were significantly correlated with weight gain (Spearman $p = -0.72$; $p < 0.01$), as were affinities for α_{1A} adrenergic ($p = -0.54$; $p < 0.05$), 5-HT_{2C} ($p = -0.49$; $p < 0.05$) and 5-HT₆ receptors ($p = -0.54$; $p < 0.05$), whereas eight other receptors' affinities were not. A principal components analysis showed that affinities at the H₁, α_{2A} , α_{2B} , 5-HT_{2A}, 5-HT_{2C}, and 5-HT₆ receptors were most highly correlated with the first principal component, and affinities for the D₂, 5-HT_{1A}, and 5-HT₇ receptors were most highly correlated with the second principal component. A discriminant functions analysis showed that affinities for the H₁ and α_{1A} receptors were most highly correlated with the discriminant function axis. The discriminant function analysis, as well as the affinity for the H₁-histamine receptor alone, correctly classified 15 of the 17 drugs into two groups; those that induce weight gain and those that do not. Because centrally acting H₁-histamine receptor antagonists are known to induce weight gain with chronic use, and because H₁-histamine receptor affinities are positively correlated with weight gain among typical and atypical antipsychotic drugs, it is recommended that the next generation of atypical antipsychotic drugs be screened to avoid H₁-histamine receptors.

Association of Antipsychotic Drug-Induced Weight Gain with a 5-HT_{2C} Receptor Gene Polymorphism. *Lancet* 2002 (359):2086-2087

Reynolds GP, Zhang, Z, Zhang X

A side-effect of treatment with antipsychotic drugs for schizophrenia is increased body fat, which leads to further morbidity and poor adherence to treatment. The 5-

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hydroxytryptamine 2C receptor (5-HT_{2C}) has been associated with this effect; we aimed to establish whether a genetic polymorphism of the promoter region of this receptor affects weight gain after drug treatment in first-episode patients with schizophrenia. We noted significantly less weight gain in patients with the -759T variant allele ($p=0.0003$) than in those without this allele, who were more likely to have substantial ($>7\%$) weight gain ($p=0.002$). We have identified a genetic factor that is associated with antipsychotic drug-induced weight gain.

Leptin Concentrations Are Increased in Subjects Treated With Clozapine or Conventional Antipsychotics. *J. Clin Psych* 2001(62):842-848

Hägg, S, Söderberg S, Ahrén B, Olsson T, Mjörndal T

Background: Overweight is a considerable clinical problem in patients treated with antipsychotic agents. Recent results suggest that insulin resistance with increased insulin levels is also associated with treatment with the atypical antipsychotic agent clozapine. Leptin is important for the control of body weight and has been proposed to be a link between obesity and the insulin resistance syndrome. This study examined if clozapine-treated subjects and subjects treated with conventional antipsychotics had increased leptin levels compared with the general population and whether there was a gender difference in this respect.

Method: Clozapine-treated patients ($N = 41$), patients treated with conventional antipsychotic drugs ($N = 62$), and healthy subjects from the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project ($N = 189$) were investigated with a cross-sectional study design. Weight, body mass index (BMI), and plasma leptin concentrations were measured, and all study subjects were investigated for the presence of diabetes mellitus. Drug treatment, health status, and smoking habits were registered.

Results: After adjustment for gender, BMI, smoking habits, age, and diabetes, hyperleptinemia was independently ($p < .001$) associated with clozapine treatment and with treatment with conventional antipsychotics ($p < .005$) within a multiple regression analysis. In separate multiple regression analyses, leptin levels were significantly associated with clozapine treatment in men ($p = .002$) and women ($p = .023$) and with conventional antipsychotic treatment in men ($p = .027$) but not in women.

Conclusion: Treatment with clozapine as well as with conventional antipsychotics is associated with increased levels of circulating leptin. Hyperleptinemia can be an important link in the development of overweight and the insulin resistance syndrome in subjects receiving antipsychotic drugs, especially atypical agents like clozapine.

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Preclinical study of the mechanisms underlying weight gain during olanzapine treatment. APA, 2001.

Heiman ML, Leander JD, Breier A.

Genetic Variant of the Histamine-1 Receptor (glu349asp) and Body Weight Change During Clozapine Treatment. *Psychiatric Genetics* 2002(12):169-171

Hong C-J, Lin C-H, Yu Y W-Y, Chang S-C, Wang S-Y, Tsai S-J

Clozapine treatment frequently causes body weight gain that may impair health and may affect patient compliance. While the histamine-1 (H₁) receptor may play a major role in the mechanism of the clozapine-induced body weight change, we tested the relationship between the genetic variant (Glu349Asp) of the H₁ receptor and the clozapine-induced body weight change. Eighty-eight schizophrenic patients treated with clozapine were included in this study. Analysis of body weight change after 4 months of clozapine treatment showed no relationship with the H₁ genotype. Further exploration of the other H₁ genotypes and the antipsychotic-induced body weight change may help in the understanding of the mechanisms of antipsychotic-induced body weight gain and in the choice of patient's antipsychotic regimens.

Brain Dopamine and Obesity. *The Lancet* 2001;357: 354-357

Wang, G, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS

Background: The cerebral mechanisms underlying the behaviours that lead to pathological overeating and obesity are poorly understood. Dopamine, a neurotransmitter that modulates rewarding properties of food, is likely to be involved. To test the hypothesis that obese individuals have abnormalities in brain dopamine activity we measured the availability of dopamine D₂ receptors in brain.

Methods: Brain dopamine D₂ receptor availability was measured with positron emission tomography (PET) and [C-11]raclopride (a radioligand for the dopamine D₂ receptor). Bmax/Kd (ratio of the distribution volumes in striatum to that in cerebellum minus 1) was used as a measure of dopamine D₂ receptor availability. Brain glucose metabolism was also assessed with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG).

Findings: Striatal dopamine D₂ receptor availability was significantly lower in the ten obese individuals (2-47 [SD 0-36]) than in controls (2-99 [0-41]; p ≤ 0.0075). In the obese individuals body mass index (BMI) correlated negatively with the measures of D₂ receptors (r=0-84; p ≤ 0.002); the individuals with the lowest D₂ values had the largest

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BMI. By contrast, neither whole brain nor striatal metabolism differed between obese individuals and controls, indicating that striatal reductions in D₂ receptors were not due to a systematic reduction in radiotracer delivery.

Interpretation: The availability of dopamine D₂ receptor was decreased in obese individuals in proportion to their BMI. Dopamine modulates motivation and reward circuits and hence dopamine deficiency in obese individuals may perpetuate pathological eating as a means to compensate for decreased activation of these circuits. Strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals.

Histamine Blockade

Olanzapine, weight gain and histamine: how are they related? April 24, 2001 (Internal document)

Leander JD.

Olanzapine is a relatively newly marketed psychotropic agent with demonstrated efficacy in the treatment of schizophrenia and related psychoses. In this respect, it is enjoying wide acceptance and is being increasingly used in the marketplace. With the growing level of acceptance of this new therapeutic, weight gain has been experienced by some of the patients as an undesirable side effect. It has been proposed that this weight gain, which is also produced by a number of other antipsychotics as well as olanzapine, is a result of these agents interacting with the histaminergic neurotransmitter system by blocking a subtype of histamine receptor, the H₁ subtype. The purpose of this paper is three-fold: 1) to review what is known about the histaminergic system in the brain; 2) to review what is known about histamine's role in the control of feeding and body weight; and then 3) to review the data suggesting that the weight gain with olanzapine is due to its interaction with the H₁ receptor subtype.

Weight Gain Interventions in Rats

Effects of clozapine, olanzapine and haloperidol on the microstructure of ingestive behaviour in the rat. Psychopharmacology. 2003;167:115-122

Hartfield AW, Moore NA, Clifton PG

Rationale: Antipsychotic drugs, particularly the newer atypical compounds, have been associated with rapid weight gain in a clinical setting. However, there are few reported animal models producing reliable hyperphagia correlating with the human weight gain liability of these drugs.

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Objective: To compare the effects of the classic neuroleptic haloperidol with the atypical antipsychotics clozapine and olanzapine on the microstructure of ingestive behaviour in rats.

Methods: Male hooded Lister rats drank a palatable high-calorie fat emulsion (10% Intralipid) during 30-min test sessions and microstructural analyses were made following administration of each drug over a range of doses.

Results: Clozapine (0.3 mg/kg) and olanzapine (0.1, 0.3, 1 mg/kg) significantly increased intake, whilst haloperidol (0.05, 0.1, 0.2 mg/kg) significantly decreased drinking. No significant changes in the latency to the first lick were observed following any of the drugs tested. Median interlick intervals showed small, dose-related increases after clozapine (3.0 mg/kg), olanzapine (0.3, 1.0 mg/kg) and haloperidol (0.1, 0.2 mg/kg). Olanzapine (1.0 mg/kg) significantly elevated the number of clusters of licking (bouts of licking separated by pauses greater than 500 ms), whilst clozapine and haloperidol did not. Mean cluster size (licks per cluster) was not affected by clozapine or olanzapine, but haloperidol (0.025, 0.05, 0.1, 0.2 mg/kg) produced marked, significant decreases in cluster size.

Conclusions: Clozapine and olanzapine increased fat intake whereas haloperidol did not, and this resembles the greater weight gain liability of atypical antipsychotics in humans. A delay or reduction of the post-ingestive satiety signal combined with preserved palatability appears to be the mechanism responsible for fat hyperphagia in rats treated with clozapine and olanzapine. Conversely, haloperidol leaves satiety unaffected but reduces the palatability of the fat emulsion resulting in reduced intake.

Weight Gain in the General Population

Obesity, the Metabolic Syndrome, and Cardiovascular Disease.
American Heart Journal. 2001;142(6):1108-1116

Vega, GL

This review provides an estimate of the relative risk for CHD that can be attributed to the “metabolic syndrome.” It also summarizes the guidelines recently released by the third Adult Treatment Panel (ATP) III 3 on detection and treatment of the syndrome.

Weight Change and Diabetes Incidence: Findings from a National Cohort of US Adults. *Am J Epidemiology* 1997;146(3):214-222

Ford ES, Williamson DF, Liu S

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Weight and DM

Metformin Reduces Weight, Centripetal Obesity, Insulin, Leptin, and Low-Density Lipoprotein Cholesterol in Nondiabetic, Morbidly Obese Subjects with Body Mass Index Greater Than 30. *Metabolism* 2001;50(7)856-861.

Glueck CJ, Fontaine RN, Wang P, Subbiah MTR, Weber K, Illig E, Streicher P, Sieve-Smith L, Tracy TM, Lang JE, McCullough P

We studied 31 nondiabetic, habitually (≥ 5 years) morbidly obese subjects (mean \pm SD body mass index [BMI] 43 ± 8.7 , median 43). Our specific aim was to determine whether metformin (2.55 g/d for 28 weeks) would ameliorate morbid obesity and reduce centripetal obesity; lipid and lipoprotein cholesterol, insulin, and leptin levels; and plasminogen activator inhibitor activity (PAI-Fx), risk factors for coronary heart disease (CHD). The patients were instructed to continue their prestudy dietary and exercise regimens without change. After 2 baseline visits 1 week apart, the 27 women and 4 men began receiving metformin, 2.55 g/d, which was continued for 28 weeks with follow-up visits at study weeks, 5, 13, 21, and 29. Daily food intake was recorded by patients for 7 days before visits then reviewed with a dietitian. Kilocalories per day and per week were calculated. At each visit, fasting blood was obtained for measurement of lipid profile, insulin, leptin, and PAI-Fx. The mean \pm SD kilocalories consumed per day, $1,951 \pm 661$ at entry, fell by week 29 to $1,719 \pm 493$ ($P=.014$) but did not differ at weeks 5, 13, and 21 from that at week 29 ($P>.2$). Weight fell from 258 ± 62 pounds at entry to 245 ± 54 pounds at week 29 ($P=.0001$). Girth was reduced from 51.8 ± 6.2 to 49.2 ± 4.5 inches ($P=.0001$). Waist circumference fell from 44.0 ± 6.4 inches to 41.3 ± 5.9 ($P=.0001$). The waist/hip ratio fell from 0.85 ± 0.09 to 0.84 ± 0.09 ($P=.04$). Fasting serum insulin, 28 ± 15 μ U/mL at entry, fell to 21 ± 11 μ U/mL at week 29 ($P=.0001$), and leptin fell from 79 ± 33 ng/mL to 55 ± 27 ng/mL ($P=.0001$). On metformin, there were linear trends in decrements in weight, girth, waist circumference, waist/hip ratio, insulin, and leptin throughout the study period ($P<.007$). Low-density lipoprotein (LDL) cholesterol, 126 ± 34 mg/dL at study entry, fell to 112 ± 43 mg/dL at week 29 ($P=.001$), with a linear trend toward decreasing levels throughout ($P=.036$). By stepwise linear regression, the higher the entry weight, the larger the reduction in weight on metformin therapy ($R^2 = 31\%$, $P=.001$). The greater the reduction in kilocalories consumed per day, the greater the decrease in weight on metformin therapy (partial $R^2=15\%$, $P=.011$). The higher the waist/hip ratio at entry, the greater its reduction on metformin therapy (partial $R^2=11\%$, $P=.004$). The higher the entry serum leptin, the greater its reduction on metformin therapy (partial $R^2=29\%$, $P=.002$). The greater the reduction in insulin on metformin, the greater the reduction in leptin (partial $R^2=8\%$, $P=.03$). The higher the entry PAI-Fx, the greater the reduction in PAI-Fx on metformin (partial $R^2=43\%$, $P=.0001$). Metformin safely and effectively reduces CHD risk factors (weight, fasting insulin, leptin, LDL

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cholesterol, centripetal obesity) in morbidly obese, nondiabetic subjects with BMI>30, probably by virtue of its insulin-sensitizing action.

Rate of Weight Gain, Weight Fluctuation, and Incidence of NIDDM. *Diabetes* 1995;44:261-266

Hanson RL, Narayan KMV, McCance DR, Pettitt DJ, Jacobsson LTH, Bennett PH, Knowler WC

The relationships of rate of weight gain and weight fluctuation to incidence of non-insulin-dependent diabetes mellitus (NIDDM) were examined in Pima Indians. The 1,458 subjects were participants in a prospective study with examinations approximately every 2 years. Rate of weight gain was defined as the slope of the regression line of weight with time for two or more consecutive examinations —2 years apart and weight fluctuation as the root-mean-square departure from this line for four examinations. Among men, incidence of NIDDM was strongly and significantly related to rate of weight gain (e.g., age-adjusted incidence = 56.7/1,000 person-years in those with weight gain —3 kg/year and 16.9/1,000 person-years for those losing weight [$P_{\text{trend}} < 0.01$]). In women, weight gain was significantly related to diabetes incidence only in those who were not initially overweight (body mass index $< 27.3 \text{ kg/m}^2$). In contrast to the relationship with weight gain, weight fluctuation was not associated with incidence of diabetes in either sex. These findings suggest that weight control in overweight individuals may be a more effective strategy for prevention of NIDDM in men than in women, whereas prevention of obesity may prevent diabetes in both sexes. Concern about a diabetogenic effect of weight fluctuation should not deter weight control efforts.

Weight Gain in Patients with Mental Illness

Physical and Psychological Consequences of Weight Gain. *J Clin Psych.* 1999;60 (21):5-9

Kawachi I

Obesity and overweight are clearly associated with many serious conditions including type II diabetes, mellitus, hypertension, and coronary heart disease. Excess weight also increases the risk of death. Recent evidence suggests that weight gain itself, even if persons remain within the “normal” weight range, also increases the risk of medical illnesses and premature death. Persons who gain 5.0 to 7.9 kg (11 to 17.3 lb) as adults are 1.9 times more likely to develop type II diabetes mellitus and 1.25 times more likely to develop coronary heart disease than those who lose weight or maintain a stable weight after age 18 years. Gaining 11 to 20 kg (24.2 to 44 lb) or more in adulthood increases the risk of ischemic stroke 1.69 to 2.52 times. The relationship between weight gain and

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breast cancer has been difficult to study, primarily because postmenopausal hormone replacement therapy can mask the effect of weight gain on cancer risk. Accordingly, weight gain in adulthood has been associated with an increased risk of breast cancer only among women who have never used hormone replacement therapy. In addition to its adverse effects on disease outcomes, weight gain also impairs physical functioning, reduces quality of life, and is associated with poor mental health. These psychological and mental health consequences of weight gain can become an added burden for patients with schizophrenia and other mental disorders.

The Distribution of Body Mass Index Among Individuals With and Without Schizophrenia. *J Clin Psych.* 1999;60(4):215-220

Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, Weiden PJ, Cheskin LJ

Objective: The objective of this study was to estimate and compare the distributions of body mass index (BMI:kg/m²) among individuals with and without schizophrenia, and thereby, place the weight gain-inducing effects of antipsychotic drugs into context.

Method: Data sources were (1) the mental health supplement of the 1989 National Health Interview Survey (NHIS; N = 80,130 nonschizophrenic and 150 self-reported schizophrenic individuals), (2) baseline BMI data from a drug trial of the antipsychotic ziprasidone supplied by Pfizer Inc (420 noninstitutionalized individuals with chronic psychotic disorders [DSM-IV schizophrenia or schizoaffective disorder]) and (3) data from the National Health and Nutrition Examination Survey III (NHANES III; N = 17,689 nonschizophrenic individuals) to act as a control group for the ziprasidone trial data.

Results: After age-adjusting BMI in each data set, the NHIS data revealed that men with schizophrenia have mean BMIs similar to those of men without schizophrenia (26.14 vs. 25.63, respectively). In contrast, women with schizophrenia in the NHIS data set had a significantly (p<.001) higher mean BMI than did women without schizophrenia (27.36 vs. 24.50, respectively). Moreover, each decile was higher for women with schizophrenia than for women without schizophrenia. Analysis of the ziprasidone and NHANES III data sets revealed that, on average, men with schizophrenia have mean BMIs comparable to those of men without schizophrenia (26.79 vs. 26.52, respectively). In these 2 data sets, women with schizophrenia also had a mean BMI similar to those of women without schizophrenia (27.29 vs. 27.39, respectively).

Conclusion: Although there may be a small subpopulation of schizophrenic individuals who are underweight, individuals with schizophrenia were, on the whole, as obese as or more obese than individuals without schizophrenia, suggesting that weight gain induced by antipsychotic agents is an important concern for many individuals.

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Body Mass Index in Persons with Schizophrenia. *Can J Psychiatry*. 2001(46):549-555

Coodin S

Background: Schizophrenia has been associated with several health concerns and risks. Overall mortality among persons with schizophrenia has been shown to be about twice that of the general population. There is growing concern that persons with schizophrenia may also be at risk for being overweight or obese, compared with the general population. To examine this possibility, the author compared the distribution of body mass index values (BMI = kg/m²) in people with schizophrenia with that of the Canadian population as a whole.

Method: Weights and heights were obtained for 183 patients receiving treatment in a hospital-based program for persons with schizophrenia. These BMI values were compared with the results of Statistics Canada's 1996-1997 National Population Health Survey (NPHS), which provided average BMI values for the general population.

Results: The average BMI in the study sample was 29.02 with the average for men being 28.49 (range 15.55 to 49.22, SD 6.25) and the average for women, 30.02 (range 19.30 to 45.71, SD 6.45). This is compared with the NPHS average BMI of 26.3 for men and 24.3 for women. The prevalence of obesity (BMI>30) in the sample was 42.08%, 3.5 times that of the Canadian average of 12% and 2.8 times that of the 15% prevalence in Manitoba. In this sample, 26.78% had a BMI in the acceptable range, in contrast to the 48% of those in the NPHS who had a weight appropriate to their height.

Conclusions: This analysis provides evidence that the BMI distribution of the sample population is different from that of the national population as represented in the NPHS data. The data indicate that patients with schizophrenia are significantly heavier than the general population.

Obesity: What Mental Health Professionals Need to Know *Am J Psych* 2000;157(6):854-866

Devlin MJ, Yanovski SZ, Wilson GT

Objective: Obesity is a highly prevalent condition with significant health implications. This report summarizes recent clinically relevant findings concerning the pathogenesis and treatment of obesity and considers their implications for psychiatric diagnosis and management.

Method: The authors conducted selective reviews of the literature from the last 10 years. Topics included the biological and behavioral factors that contribute to the onset and maintenance of obesity, the relationship between obesity and psychiatric illness and treatment, and the questions of whether and how obesity should be treated.

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Results: Genetic effects, some mediated by eating behavior, contribute importantly to the potential for obesity, the expression of which is promoted by environmental factors that increase the availability of calorically dense foods and discourage activity. There appear to be behaviorally distinct subsets of obese persons who display particular patterns of disordered eating and elevated rates of psychopathology. Treatment with psychotropic medications may contribute to obesity in ways that are only partly understood. Although successful obesity treatment is associated with clear health benefits and available treatments offer benefit to some, relapse remains the rule.

Conclusions: Although the presence or development of obesity is a daunting problem, it should not be ignored by mental health professionals. Treatment should address not only obesity per se, but also its effects on self-esteem in a hostile cultural climate. Ongoing developments in basic and clinical research are likely to increase the range, efficacy, and acceptability of treatment options in the years ahead.

Increased Visceral Fat Distribution in Drug-Naïve and Drug-Free Patients with Schizophrenia. *International Journal of Obesity* 2002;26:137-141

Thakore JH, Mann JN, Vlahos I, Martin A, Reznick R

Objective: To investigate visceral fat distribution in patients with schizophrenia.

Design: Cross sectional study using CT scanning in patients with drug-naïve and drug-free schizophrenia.

Subjects: Fifteen (13 men and two women) subjects with schizophrenia (mean age 33.7y; mean body mass index (BMI)=26.7kg/m²), and 15 age- and sex-matched controls (mean age 30.5y; mean BMI=22.8kg/m²).

Measurements: Various fatness and fat distribution parameters (by CT scanning and anthropometry) and 16:00h plasma cortisol.

Results: In comparison to controls, patients with schizophrenia had central obesity and had significantly higher levels of plasma cortisol. Furthermore, previous neuroleptic exposure did not appear to influence these findings as both drug-naïve and drug-free patients had equally high levels of visceral fat deposition.

Conclusion: Central obesity is a well recognized risk factor in developing certain general medical conditions. This study shows that patients with schizophrenia have increased intra-abdominal fat which may provide one explanation for why they die prematurely.

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Determinants of Overweight and Obesity in Patients with Bipolar Disorder. *J Clin Psych* 2001;62(6) 486-791

Emslie JL, Mann JJ, Silverstone JT, Williams SM, Romans SE

Preclinical studies of weight gain during olanzapine treatment. *APA*, 2001.

Leander JD & Gleason SD.

The Impact of Weight Gain on Quality of Life Among Persons With Schizophrenia. *Psychiatric Services* 2003;54(4)565-567

Allison DB, Mackell JA, McDonnell DD

Weight gain has been associated with the use of antipsychotic medications, and research has linked obesity with reduced quality of life. This study sought to assess the impact of weight gain on persons with schizophrenia who are taking antipsychotic medications. The Psychological Well-Being Index, a measure of quality of life, was distributed to individuals with schizophrenia who belonged to mental health associations. Among 286 respondents, 56 percent gained no weight over a six-month period while taking antipsychotic medications, 19 percent gained one to ten pounds, 12 percent gained 11 to 20 pounds, and 14 percent gained more than 20 pounds. When gender and use of antipsychotics were controlled for, weight gain was related to poorer quality of life and reduced well-being and vitality. Clinicians should consider the effect of weight gain on quality of life when prescribing antipsychotics and should help patients adopt weight maintenance behaviors.

Awareness of Obesity and Weight Issues Among Chronically Mentally Ill Inpatients: A Pilot Study. *Annals of Clinical Psychiatry* 2002;14(1)39-45

Meyer, JM

Obesity in psychotic patients is a subject of increasing scrutiny, but there is a dearth of data regarding awareness about weight related issues among chronic inpatients. To assess this issue state hospital patients voluntarily completed an anonymous questionnaire concerning obesity, weight gain variables, concern about weight, and methods to control

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weight gain. Sex, age, weight, and height were collected with completed surveys. A total of 128 respondents completed the questionnaire of which 85% were male. Respondents' mean age was 39.8 years, mean BMI 30.84 kg/m² with 46.6% obese. There was a significant correlation between BMI and awareness of current weight status ($p=0.005$), but not between BMI and level of concern about weight among all respondents ($p=0.308$) or in the obese subgroup ($p=0.693$). Significantly fewer obese patients indicated no weight problem, or no need to control their weight compared to the nonobese ($p=0.004$), yet only 10% of obese patients requested to be placed on a mandatory monitored diet. Chronically mentally ill inpatients thus accurately perceive their obesity status, but level of concern does not correlate with BMI, and the obese are reluctant to choose mandatory dieting as a remedy. These findings have significant implications for programmatic measures to control weight gain among chronic inpatients, and for use of atypicals that have a greater propensity to cause weight gain.

Medical Management of Obesity Associated With Mental Disorders. *J. Clin Psychiatry* 2002;63(4)24-32

Malhotra S, McElroy SL

Obesity and mental disorders are major public health problems that co-occur to a significant degree. They also significantly overlap in phenomenology and response to medications. However, many psychotropic agents have adverse effects on appetite, binge eating, and weight. In this review, we aim to improve understanding of the relationship between obesity and mental illness and provide practical clinical guidelines for the management of obesity associated with mental disorders.

Overweight History in the United States

Weight Gain with Atypicals

Review of Atypical Antipsychotics and Weight Gain. *J. Clin Psych* 2001;62 (23): 5-12

Sussman, N

Prescribing an antipsychotic for a patient with schizophrenia requires a risk-benefit analysis. Weight gain has become an issue recently as a result of reports that 2 of the atypical antipsychotic agents, clozapine and olanzapine, are associated with a higher risk than other drugs of causing excessive weight gain. Some degree of weight gain may occur with any atypical antipsychotic agent, particularly early in treatment. A more

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important consideration is the long-term effects of the atypical antipsychotic on body weight, since many of the patients in this population require chronic therapy. This is important because weight gain is an adverse effect that is associated with noncompliance and medical problems. In this article, I review recent reports about the weight effects of different atypical antipsychotic drugs. To provide accurate understanding of the effects of atypical antipsychotic agents, data analyses should include both short-term and long-term findings, the relationship of changes in body weight to pretreatment body mass index (BMI), relationship to dose, both intent-to-treat and complete analyses, and presentation of both mean and median changes in weight. It is also important to know whether the studies have been done in an inpatient or outpatient setting, since patients who are institutionalized may be less likely to exhibit increases in body weight. Such complete information and multidimensional analysis would minimize obfuscation about the true nature of a drug's impact on body weight.

Antipsychotic-induced weight gain: A comprehensive research synthesis. *Am.J.Psychiatry* 1999;156(11):1686-1696.

D. B. Allison, J. L. Mentore, M. Heo, L. P. Chandler, J. C. Cappelleri, M. C. Infante, and P. J. Weiden.

Objective: The purpose of this study was to estimate and compare the effects of antipsychotics - both the newer ones and the conventional ones - on body weight.

Method: A comprehensive literature search identified 81 English- and non-English-language articles that included data on weight change in antipsychotic-treated patients. For each agent, a meta-analysis and random effects meta-regression estimated the weight change after 10 weeks of treatment at a standard dose. A comprehensive narrative review was also conducted on all articles that did not yield quantitative information but did yield important qualitative information.

Results: Placebo was associated with a mean weight reduction of 0.74 kg. Among conventional agents, mean weight change ranged from a reduction of 0.39 kg with molindone to an increase of 3.19 kg with thioridazine. Among newer antipsychotic agents, mean increases were as follows: clozapine, 4.45 kg; olanzapine, 4.15 kg; sertindole, 2.92 kg; risperidone, 2.10 kg; and ziprasidone, 0.04 kg. Insufficient data were available to evaluate quetiapine at 10 weeks.

Conclusions: Both conventional and newer antipsychotics are associated with weight gain. Among the newer agents, clozapine appears to have the greatest potential to induce weight gain, and ziprasidone the least. The differences among newer agents may affect compliance with medication and health risk.

Antipsychotic-Induced Weight Gain: A Review of the Literature. *J Clin Psych* 2001;62(7):22-31

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Allison DB, Casey DE

With the availability of the so-called novel antipsychotic agents, extrapyramidal symptoms are becoming decreasingly problematic for patients with schizophrenia, and simultaneously, a new symptom is emerging as a preeminent concern. This side effect is weight gain and its metabolic concomitants. This article reviews what is currently known about antipsychotic-induced weight gain, describes the magnitude of the problem, briefly touches on mechanisms of action, and addresses the correlation of interindividual variations in magnitude of weight gain. In addition, we address questions about the effects of weight gain on compliance and whether or not there is a correlation between weight gain and therapeutic efficacy. Finally, we address medical consequences of weight gain and review the literature supporting various treatment options for antipsychotic-induced weight gain. As will be seen, this is an area of research in its infancy, and much work remains to be done.

Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis. *Am J Psych* 1999(156):1686-1696

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ

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Antipsychotic-Associated Weight Gain and Clinical Outcome Parameters. *J. Clin Psych* 2001;62 (7):11-21

Blin O, Micallef J

Weight gain has been observed with many of the antipsychotics, including the atypical antipsychotics. The assessment of whether, and to what degree, a drug causes changes in body weight is not straightforward, since clinical studies performed during a drug development program are not designed to measure changes in body weight. Even when weight change data are obtained from adverse event data or from part of the vital signs measured during a study, assessment is not standardized. Nevertheless, evidence points to the fact that weight gain with the atypical antipsychotics is becoming an increasing problem. This review examines whether antipsychotic-associated weight gain, when it occurs, is associated with clinical outcome parameters.

Weight Gain Associated with Psychotropic Drugs. *Southern Medical Journal* 1989;82(5):611-617

Brady KT

The weight increase that is an often reported side effect of psychotropic drug use has implications for health risks as well as medication noncompliance. In this article I review the literature on the association between the use of several classes of psychotropic drugs and weight gain, discuss the possible mechanisms for this effect, and offer some practical approaches for reducing the risk of drug-induced weight gain, including the identification of a group of patients "at risk."

The Pharmacology of Weight Gain With Antipsychotics. *J Clin Psych* 2001;62(7):4-10

Casey DE, Zorn SH

In general, antipsychotic agents have diverse actions on a wide range of neurotransmitter systems. Data strongly suggest that a number of these systems may play a role in the regulation of body weight. In addition to having very distinct pharmacologic profiles, individual agents possess discrete weight gain liabilities. This article briefly reviews the evidence for the involvement of specific neurotransmitter systems in the control of body weight and describes the relevant pharmacologic characteristics of individual antipsychotic agents. By comparing the pharmacologic profiles of specific antipsychotic agents with their respective weight gain liabilities, this article attempts to gain an insight into the specific receptors underlying a drug's propensity to induce weight gain.

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However, there is still much to be learned concerning weight control mechanisms, and the role of many of the receptors at which antipsychotic agents are active remains unclear. In spite of this, an overview of current knowledge in the field may facilitate prediction of a potential novel antipsychotic agent's weight gain liability.

Antipsychotic-Induced Weight Gain and Therapeutic Response: A Differential Association. *J Clin Psych* 2002 (22):244-251

Czorbor P, Volavka J, Sheitman B, Lindenmayer J-P, Citrome L, McEvoy J, Cooper TB, Chakos M, Lieberman JA

This study investigated the association between antipsychotic-induced weight gain and therapeutic response to haloperidol and three commonly used atypical neuroleptic medications in schizophrenia and schizoaffective disorder. The subjects were 151 patients enrolled in a double-blind experiment with a duration of 14 weeks comparing the therapeutic efficacy of haloperidol (n = 36), clozapine (n = 38), olanzapine (n = 38), and risperidone (n = 39). Absolute and relative (%) gain in body weight and body mass index (BMI) was determined for the entire duration of the double-blind treatment period; therapeutic response was assessed by the total score and the individual subscales of the Positive and Negative Symptom Scale. Compared with the pretreatment baseline, results indicated that for olanzapine and clozapine, therapeutic response was closely related to an absolute and relative gain in weight and to a gain in BMI. No association between weight gain and therapeutic response was found for risperidone and haloperidol. These findings suggest that patients who are likely to have the maximal benefits of olanzapine or clozapine treatment for symptom alleviation are at the highest risk of a clinically significant increase in weight gain.

The Effect of Antipsychotic Drugs on Body Weight: A Retrospective Review. *J Clin Psych* 1979(40):528-530

Doss, FW

Weight gain in schizophrenic patients during chemotherapy was first reported with chlorpromazine. Since then other antipsychotic drugs have exhibited this effect, while some have reduced weight. A retrospective review of 78 schizophrenic patients revealed that thiothixene, fluphenazine, haloperidol, and thioridazine produced a mean weight gain and loxapine a mean weight loss after 12 and 36 weeks of treatment. The ability of an effective antipsychotic drug, such as loxapine, to prevent weight gain or to produce weight loss offers a clinical advantage in the treatment of those schizophrenic patients where weight gain would be a problem.

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Estimating the Consequences of Anti-Psychotic Induced Weight Gain on Health and Mortality Rate. *Psychiatry Research* 101 2001:277-288

Fontaine KR, Heo M, Harrigan EP, Shear CL, Lakshminarayanan M, Casey DE, Allison DB

Many anti-psychotic medications produce marked weight gain. In this study, we estimate the expected impact of degrees of antipsychotic-induced weight gain on selected mortality rate and incidence rates of impaired glucose tolerance (IGT) and hypertension (HTN) among US adults. Using raw data from 5209 respondents from the Framingham Heart Study's public use data set and national statistics on population demographics, we estimated the expected effect of weight gain on number of deaths and incident cases of IGT and HTN for a 10-year period commencing in 1999. Results indicated that the estimated deleterious effects of weight gain were greater for people with higher BMIs at baseline, for greater degrees of weight gain, for men than women, and for older than younger persons. Because there is a "U-shaped" relation between BMI and mortality rate, small to moderate weight gains among people with baseline BMIs less than 23 were predicted to decrease mortality rates, whereas weight gains among people with baseline BMIs above that level were expected to increase mortality rates. However, the relations of IGT and HTN with BMI are monotonically increasing. Thus, the anticipated effect of weight gain on IGT and HTN is deleterious regardless of baseline BMI. Because it is unclear whether the beneficial effects of the atypical agents on, for example, reducing suicide mortality, outweigh the putative increase in mortality due to weight gain, we estimate the beneficial effects due to decreased death from suicide with the potential deleterious effects due to a 10-kg weight gain. We found that 492 suicide deaths per 1000000 schizophrenic patients would be prevented over 10 years with the use of clozapine compared to 416 additional deaths due to antipsychotic induced weight gain. Although this estimate is rather crude and should be seen only as offering a sense of the likely situation, results suggest that the lives saved via clozapine may essentially be offset by the deaths due to weight gain. As we discuss, it is not possible to provide definitive estimates of the effect of antipsychotic-induced weight gain on health and mortality, but our findings suggest that the magnitude of weight gains induced by many antipsychotic agents is likely to have important deleterious effects on mortality and health.

Antipsychotic Metabolic Effects: Weight Gain, Diabetes Mellitus and Lipid Abnormalities. *Can J Psych* 2001 (46):273-281

McIntyre RS, McCann SM, Kennedy SH

Objective: To review published and nonpublished literature describing changes in weight, glucose homeostasis, and lipid milieu with antipsychotics.

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Methods: A Medline search was completed using the words weight gain, diabetes mellitus, cholesterol, triglycerides, risperidone, clozapine, olanzapine, quetiapine, ziprasidone, predictors, prolactin, obesity and conventional antipsychotics. Publications, including original articles, review articles, letters to the editor, abstracts or posters presented at professional meetings in the last 4 years, and references from published articles, were collected. Manufacturers, including Eli Lilly Canada Inc., Janssen-Ortho Inc, Pfizer Canada Inc, AstraZeneca Inc, and Novartis Pharmaceuticals, were contacted to retrieve additional medical information.

Results: The topic of antipsychotic-induced weight gain is understudied, and there are relatively few well-controlled studies. Weight gain as a side effect has been described with both conventional and atypical antipsychotics. Moreover, some atypical antipsychotics are associated with de novo diabetes mellitus and increased serum triglyceride levels. Predictors of weight gain may be age, baseline body mass index, appetite stimulation, previous antipsychotic exposure, and antipsychotic treatment duration.

Conclusion: Significant weight gain is reported with the existing atypical antipsychotics. The weight gain described is highly distressing to patients, may reduce treatment adherence, and may increase the relative risk for diabetes mellitus and hypertriglyceridemia. Physicians employing these agents should routinely monitor weight, fasting blood glucose, and lipid profiles.

A Review of the Effect of Atypical Antipsychotics on Weight. *Psychoneuroendocrinology* 2003 (28):83-96

Nasrallah H

Controlled research trials have shown that atypical antipsychotics have important advantages over standard antipsychotics, including a broader spectrum of efficacy and improved tolerability profile, particularly with regard to neurological adverse events such as extrapyramidal symptoms (EPS). Some atypical antipsychotics, however, tend to cause significant weight gain, which may lead to poor compliance and other adverse health effects. The mechanisms involved in antipsychotic drug-related weight gain are as yet uncertain, although serotonergic, histaminic, and adrenergic affinities have been implicated along with other metabolic mechanisms. The atypical antipsychotics vary in their propensity to cause weight change with long-term treatment. Follow-up studies show that the largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when constructing an algorithm for treatment due to the serious medical consequences of obesity.

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Weight gain over 4 months in schizophrenia patients: A comparison of olanzapine and risperidone. *Schizophrenia Research* 49(3):261-267, 2001.

R. Ganguli, J. S. Brar, and Z. Ayrton.

Weight gain frequently accompanies treatment with antipsychotics. In order to determine whether newer antipsychotic agents differ from each other with respect to weight gain, we compared two cohorts of patients with DSM-IV schizophrenia who had newly started treatment with either risperidone or olanzapine. After obtaining informed consent, data regarding body weight and height were culled from existing medical records of 100 patients (50 patients in each treatment group). Baseline body weight, close to the time of starting the new medication, and body mass index [BMI = weight (kg)/height (m) squared] were compared to the body weight and BMI following 4 months of treatment. There was no significant change in mean body weight or BMI in the group treated with risperidone (baseline weight = 83.1 kg (plus or minus) 20.5, follow-up = 82.8 kg (plus or minus) 19.9; matched pair $t = 0.66$, $P = \text{n.s.}$; baseline BMI = 29.6 (plus or minus) 9.4, follow-up = 29.5 (plus or minus) 9.1; matched pair $t = 0.79$, $P = \text{n.s.}$). However, in the group treated with olanzapine, there was a significant increase in both mean body weight and BMI (baseline weight = 84.9 kg (plus or minus) 25.0, follow-up = 87.1 kg (plus or minus) 25.1; matched pair $t = 4.62$, $P < 0.001$; baseline BMI = 29.5 (plus or minus) 7.4, follow-up = 30.3 (plus or minus) 7.5; matched pair $t = 4.43$, $P < 0.001$). In this naturalistic study, treatment with olanzapine was associated with a mean weight gain of about 2 kg from baseline, in patients with schizophrenia, while treatment with risperidone was associated with no mean weight change.

Effects of long-term treatment with antipsychotics on serum leptin levels. *Br.J.Psychiatry* 178(JULY):59-62, 2001.

Herran, M. T. Garcia-Unzueta, J. A. Amado, M. T. De La Maza, C. Alvarez, and J. L. Vazquez-Barquero.

Background: Abnormal regulation of the adipocyte-derived hormone leptin could play a role in body weight gain induced by antipsychotics.

Aims: To study the effects of long-term antipsychotic treatment on leptin levels in patients with schizophrenia.

Method: Serum leptin levels were determined in 59 out-patients with chronic schizophrenia and in the same number of healthy subjects controlled by gender, age and body mass index. **Results:** Leptin levels did not differ between patients and controls. Leptin levels in patients with schizophrenia correlated with weight gain, even after controlling for current weight, but did not show any association with clinical variables.

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Antipsychotic class tended to exert different effects over leptin levels (among atypicals, olanzapine induced a greater increase).

Conclusions: Elevation of leptin levels induced by chronic antipsychotic treatment can be attributed to weight gain, but other mechanisms could be involved. Declaration of interest: This study was supported by a grant from the Fundacion Marques de Valdecilla, 1996.

Antipsychotic metabolic effects: Weight gain, diabetes mellitus, and lipid abnormalities. *Canadian Journal of Psychiatry* 46(3):273-281, 2001.

R. S. McIntyre, S. M. McCann, and S. H. Kennedy.

Objective: To review published and nonpublished literature describing changes in weight, glucose homeostasis, and lipid milieu with antipsychotics.

Methods: A Medline search was completed using the words weight gain, diabetes mellitus, cholesterol, triglycerides, risperidone, clozapine, olanzapine, quetiapine, ziprasidone, predictors, prolactin, obesity, and conventional antipsychotics. Publications, including original articles, review articles, letters to the editor, abstracts or posters presented at professional meetings in the last 4 years, and references from published articles, were collected. Manufacturers, including Eli Lilly Canada Inc, Janssen-Ortho Inc, Pfizer Canada Inc, AstraZeneca Inc, and Novartis Pharmaceuticals, were contacted to retrieve additional medical information.

Results: The topic of antipsychotic-induced weight gain is understudied, and there are relatively few well-controlled studies. Weight gain as a side effect has been described with both conventional and atypical antipsychotics. Moreover, some atypical antipsychotics are associated with de novo diabetes mellitus and increased serum triglyceride levels. Predictors of weight gain may be age, baseline body mass index, appetite stimulation, previous antipsychotic exposure, and antipsychotic treatment duration.

Conclusion: Significant weight gain is reported with the existing atypical antipsychotics. The weight gain described is highly distressing to patients, may reduce treatment adherence, and may increase the relative risk for diabetes mellitus and hypertriglyceridemia. Physicians employing these agents should routinely monitor weight, fasting blood glucose, and lipid profiles.

How to Appease the Appetite of Psychotropic Drugs. *J Clin Psych* 1998;59(10):500-501

Stahl SM

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Take-Home Points

- Psychiatrists should consider weighing patients regularly because many patients experience weight change, especially weight gain, after administration of specific psychotropic drugs
- Consideration of the neuropharmacologic mechanisms of weight gain associated with certain psychotropic drugs can assist in the selection of specific drugs when obesity is an issue in the treatment of psychiatric disorders.

Weight Gain Associated with Use of Psychotropic Medications. *J Clin Psych* 1999;60 (21):16-19**Sachs GS, Guille C**

Weight gain is associated with the use of many psychotropic medications, including lithium, valproic acid, and several conventional and newer antipsychotics. Patients asked to select from among several comparable drugs often choose the one least likely to cause weight gain, even if the drug is less effective or has other troublesome adverse effects. For many patients, weight gain is so intolerable that they discontinue treatment. Patients who continue treatment are at risk for clinically significant weight gain that can progress to obesity. Even after patients stop taking the drug, weight gained during therapy may be difficult to lose. Thus, the best approach is to attempt to prevent weight gain when feasible, possibly through pretreatment dietary counseling and judicious drug selection, and to intervene as soon as weight gain becomes evident.

Weight Change and Atypical Antipsychotic Treatment in Patients With Schizophrenia. *J Clin Psych* 2001;62(2):41-44**Jones B, Basson BR, Walker DJ, Crawford AK, Kinon BJ**

Schizophrenic patients who have been prescribed atypical antipsychotics have a potential risk of gaining weight. The implications of weight gain for clinical care may differ depending on whether a patient is underweight or overweight at baseline. The exact mechanism for weight gain is not known, but several factors have been identified that can help predict which patients are at risk for gaining weight. These factors include better clinical outcome, increased appetite, and low baseline body mass index. In patients treated with olanzapine for up to 3 years, weight gain trended toward a plateau at approximately 36 weeks. Weight gain interventions, including behavioral modifications, show promise in controlling or reducing weight in patients treated with antipsychotics.

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Atypical Antipsychotics and Weight Gain: Incidence, Etiology and Treatment Modalities. *Acta Neuropsychiatrica* 2001(13):91-101

Huussen EM, Knegtering H, Slooff CJ, Kappert J

Introduction: Weight gain is a common side effect of atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine and sulpride). Overweight leads to several physical and psychosocial problems and increased mortality. These problems may also affect compliance in therapy and consecutively impair the treatment of psychotic disease.

Method: In this review article we present the data on prevalence and extent of weight gain in antipsychotic medication, found in Embase Psychiatry, leading to possible interventions.

Results: Several antipsychotics cause weight gain in a different extent and in several ways: by acting on the neurotransmitters systems modern antipsychotics may induce increased appetite, thirst and sedation with weight gain as result. Clozapine and olanzapine are associated with the most extensive weight gain. Multidisciplinary efforts are necessary to support patients to prevent and treat overweight induced by antipsychotics. In combination with dietary regime, behavioral therapy and patients' support groups, oral orlistat may prove to be a safe and suitable therapy in the future.

Effects of Atypical Antipsychotics on Weight and Serum Lipid Levels. *J Clin Psych* 2001;62(27):27-34

Meyer JM

Psychiatrists have become particularly concerned about health issues in patients with schizophrenia because of emerging data that link some of the newer atypical antipsychotics with both significant weight gain and increases in serum triglyceride levels. Excessive weight gain during antipsychotic therapy has an adverse effect on health and medication compliance, while hyperlipidemia presents an additional cardiovascular risk factor in patients with schizophrenia who typically smoke, are inactive, and possess poor dietary habits. An understanding of appropriate monitoring for metabolic adverse effects is important for those who prescribe atypical antipsychotics, as is a working knowledge of behavioral and pharmacologic treatments for weight gain and hyperlipidemia.

Bodyweight Gain Associated with Atypical Antipsychotics Epidemiology and Therapeutic Implications. *CNS Drugs* 2001;15(7):537-549

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Russell JM, Mackell JA

Atypical antipsychotic medications are associated with different adverse effects and efficacy profiles compared with conventional antipsychotics (i.e. less extrapyramidal symptoms, improved efficacy against negative symptoms and cognitive deficits, and most often a greater ability to improve patients' quality of life). However, the atypical antipsychotics may be associated with clinically significant bodyweight gain, increasing the risk of medical comorbidity, including diabetes mellitus, hypertension, cardiovascular disease and hyperlipidaemia.

This literature review assesses the various bodyweight gain liabilities associated with atypical antipsychotics, as well as the effects of bodyweight gain on quality of life. The issue of prevention and management of this often neglected adverse effect is also examined.

Most studies reviewed indicate that clozapine and olanzapine are associated with more bodyweight gain than the other atypical antipsychotics. There are potential factors that place certain patients at a greater risk for bodyweight gain, including low pretreatment body mass index, young age and being of female gender. Furthermore, bodyweight gain associated with the use of atypical antipsychotics has been reported to be associated with clinical improvement, although this has not been substantiated widely. It is unclear whether increased medical comorbidity, including diabetes mellitus, coronary artery disease and/or elevated triglyceride levels, is secondary to the bodyweight gain associated with atypical antipsychotics, or the result of the agents themselves.

A patient's quality of life may be greatly affected by excessive bodyweight gain; either by increased comorbid medical illness, an increased relapse rate associated with noncompliance, or the social stigma associated with being obese. However, most studies reveal that treatment with atypical antipsychotic medications is associated with improved quality of life compared with that achieved with conventional antipsychotic medications. Because bodyweight is an important health risk associated with atypical antipsychotics, prevention and effective management of bodyweight are paramount in preventing comorbid medical illness, relapse and possible noncompliance.

Atypical Antipsychotics and Weight Gain – A Systematic Review. *Acta Psychiatrica Scand* 2000;101:416-432

Taylor DM, McAskil R

Objective: To review systematically data relating to weight changes with atypical antipsychotics.

Method: We conducted a Medline search on October 29 1999 and covered the period 1980-99. All recovered papers were examined for further relevant reports. In addition, we wrote to pharmaceutical manufacturers and 10 practising clinicians to ask them to provide other relevant reports known to them.

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Results: Eight reports mentioning change in body weight were retrieved. Data relating to weight changes were of variable quality. Weight changes were indicated by a variety of measures. The majority of reports related to short-term changes.

Conclusion: All atypical drugs, with the exception of ziprasidone, have been associated with weight increases. Clozapine seems to have the highest risk of weight gain, followed by olanzapine and quetiapine. There is probably a lower risk with risperidone, sertindole and zotepine and a still lower risk with amisulpride. Ziprasidone appears not to be associated with weight gain. In the absence of more compelling data, these rankings must be considered approximate and preliminary. Longer, more robust trials are needed.

Weight Gain: Side Effect of Atypical Neuroleptics? *J Clin Psych* 1999;19(4):316-321

Wetterling T, MuBigbrodt HE

During clinical experience with the “atypical” neuroleptic drugs clozapine, risperidone, and zotepine, some patients have shown a marked weight gain. To prove whether weight gain is a relevant side effect of atypical neuroleptics, the charts of all patients admitted with DSM-III-R diagnoses of schizophrenia, schizoaffective disorder, or delusional disorder in the years 1991 to 1995 were evaluated. A retrospective chart review was performed, which included all patients who were treated longer than 2 weeks with a single neuroleptic. The data analysis showed that weight gain must be considered as a common side effect of atypical neuroleptics (clozapine, risperidone, sulpiride, or zotepine). The mean weight gain (3.1, 1.5, 1.9, or 4.3 kg, respectively) was significantly higher than that of patients treated with “classic” neuroleptics (mean, 0.0-0.5 kg) (Kruskal-Wallis, $p=0.01$). Young and not obese patients show the highest weight increase. Because weight gain occurs in the first weeks of treatment, particularly in previously untreated subjects, this side effect has to be considered in view of compliance with long-term neuroleptic medication.

Bodyweight Gain with Atypical Antipsychotics A Comparative Review. *Drug Safety* 2001;24(1):59-73

Wetterling T

The atypical antipsychotics have been shown to have superior efficacy compared with typical antipsychotics such as haloperidol, particularly in the treatment of negative symptoms of schizophrenia. Furthermore, they induce less extrapyramidal effects. However, following clinical use, marked bodyweight gain has been frequently observed with some of the atypical antipsychotic drugs.

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In order to examine and compare the frequency, amount and conditions of bodyweight gain during treatment with atypical antipsychotics, studies concerning bodyweight gain with these agents were identified through a MEDLINE search from 1966 to March 2000. Although comparison is limited by the different designs and recruitment procedures of the reviewed studies, the available data support the notion that the frequency as well as the amount of bodyweight gain is high in patients treated with olanzapine (average bodyweight gain 2.3 kg/month), clozapine (1.7 kg/month), quetiapine (1.8 kg/month), and possibly also zotepine (2.3 kg/month). Moderate changes in bodyweight have been observed in the treatment with risperidone (average bodyweight gain 1.0 kg/month). Ziprasidone seems to induce only slight bodyweight changes (0.8 kg/month). Bodyweight gain most frequently occurs in the first 12 weeks of treatment. Patients who were underweight at the beginning of treatment are at highest risk of gaining bodyweight. The underlying pathomechanism still remains largely unclear. The relative receptor affinities of the atypical antipsychotics for histamine H₁ receptors as well as the ratio of their affinity for serotonin 5-HT₂ and dopamine D₂ receptors appear to be the most robust correlate of bodyweight gain. Furthermore, the induction of leptin secretion may have an important impact on bodyweight gain in patients treated with atypical antipsychotics. Although many questions concerning the pathogenesis of bodyweight gain remain unresolved, this adverse effect has to be taken into consideration when prescribing the atypical antipsychotics, particularly in view of its effect on compliance during long term treatment and the long term effects of obesity on mortality and morbidity.

Novel Antipsychotics: Comparison of Weight Gain Liabilities. *J. Clin Psych* 1999;60:6:358-363

Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J, Mintz J, Marder SR

Background: We performed a retrospective analysis of 122 clinical records of 92 male patients with DSM-III-R schizophrenia to examine the relative weight gain liabilities of clozapine, risperidone, olanzapine, and sertindole compared with haloperidol. We hypothesized that the unique pharmacodynamic profiles of these agents would contribute to different amounts and patterns of weight gain.

Method: Data were analyzed to determine differences in weight gain during treatment among patients receiving 5 different drug treatments (clozapine [N = 20], olanzapine [N = 13], risperidone [N = 38], haloperidol [N = 43], and sertindole [N = 8]). Measures of maximal weight gain, final weight, and duration to maximal weight gain were calculated.

Results: Repeated measures analyses of variance controlling for age, treatment duration, and initial weight revealed statistically significant differences between groups on all 3 measures. Clozapine and olanzapine had the greatest maximal weight gain liability (F = 4.13, df = 4,23; p = .01). Weight gain with clozapine, but not olanzapine or risperidone, appears to persist (as reflected by final weight) despite behavioral interventions (e.g., nutritional consultation, suggested exercise regimen; F = 5169, df = 4,23; p = .003).

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Clozapine- and olanzapine-treated subjects appeared to gain weight over a prolonged period of time, whereas risperidone- and sertindole-treated subjects had a more limited period of weight gain ($F = 2.95$, $df = 4,25$; $p = .04$).

Conclusion: Clozapine and olanzapine caused the most weight gain, risperidone was intermediate, and sertindole had less associated weight gain than haloperidol. The relative receptor affinities of the novel antipsychotics for histamine H_1 appear to be the most robust correlate of these clinical findings.

Weight Gain with Olanzapine

Long-term olanzapine treatment: Weight change and weight-related health factors in schizophrenia. *Journal of Clinical Psychiatry* 62(2):92-100, 2001.

B. J. Kinon, B. R. Basson, J. A. Gilmore, and G. D. Tollefson.

Background: Weight change and the weight-related health factors of nonfasting serum glucose, serum cholesterol, and diastolic blood pressure levels were analyzed in patients with DSM-III-R schizophrenia and related disorders who received treatment with olanzapine for up to 3 years, and comparisons were made to patients treated with haloperidol. Baseline body mass index (BBMI; kg/m^2) and dose (mg/day) were investigated as predictors of long-term weight change experienced during olanzapine treatment.

Method: This analysis retrospectively examined 573 patients receiving olanzapine and 103 patients receiving haloperidol for 39 weeks or more from a study of 1996 patients randomly assigned 2:1 to either olanzapine, 5 to 20 mg/day, or haloperidol, 5 to 20 mg/day. After 6 weeks of acute therapy, patients continued for 1 year or more with either double-blind or open-label olanzapine therapy or double-blind haloperidol therapy.

Results: Mean weight gain for olanzapine-treated patients observed for a median of 2.54 years trended toward a plateau after the first 39 weeks of treatment with a last-observation-carried-forward mean weight change of 6.26 kg (13.8 lb) and a median of 5.90 kg (13.0 lb). This was significantly higher than that for haloperidol-treated patients, whose mean weight gain was 0.69 kg (1.5 lb) after 1.15 years ($p < .001$). Patients with higher BBMI (> 27.6) gained significantly less weight during treatment with olanzapine than their lighter counterparts (BBMI < 27.6) ($p < .001$). The effect of olanzapine dose on weight was not significant (p (greater-than or equal to) 183). Median serum glucose at endpoint was not significantly associated ($p = .096$) with weight change for olanzapine. Median serum cholesterol and diastolic blood pressure for olanzapine-treated patients at endpoint showed a relationship with weight change that was statistically (p (less-than or equal to) .001) but not clinically significant. The difference in incidence of elevated serum glucose, cholesterol, or diastolic blood pressure between olanzapine and haloperidol therapy groups was not different ($p > .05$).

Conclusion: Mean weight gain during olanzapine treatment trended toward a plateau after the initial 39 weeks of treatment with no further significant gain out to 3 years.

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Higher BBMI was predictive of a lower long-term weight gain, while dose was not a significant predictor of greater longer term weight change. The relationship between weight change and glucose was not statistically significant. The association between weight change and changes in cholesterol as well as changes in diastolic blood pressure was statistically significant but not considered clinically relevant based on the ranges observed.

Continued improvement in quality of life despite weight change during olanzapine treatment. *Biol.Psychiatry* 49(8 SUPPL.):54S, 2001.

B. J. Kinon, D. R. Milton, and J. A. Gilmore.

Background: Change in quality of life was measured as a function of weight change in schizophrenic patients who received treatment with olanzapine (OLZ).

Methods: This analysis retrospectively examined 760 patients receiving OLZ treatment. Data were collected from a controlled, multi-center, double-blind, parallel clinical trial with patients (N = 1996) diagnosed with DSM-III-R schizophrenia, schizoaffective or schizophreniform disorders. The Heinrichs-Carpenter Quality of Life Scale (QLS) and the Medical Outcomes Study Short Form Health Survey (SF-36) were used to evaluate diverse aspects of quality of life. The QLS provided clinician-rated assessment of current patient functioning, richness of personal experience, quality of interpersonal relationships and productivity in occupational roles. The SF-36 scale provided patient-rated subjective evaluation of physical and mental health. Change in quality of life as a function of change in weight was measured up to 52 weeks for OLZ-treated patients (LOCF).

Results: Up to week 52, a significant positive association ($p=0.002$) was found between improvement in the QLS Total score and weight change during OLZ therapy. Similar associations were demonstrated between improvement in SF-36 rated subjective perceptions of functioning and OLZ-related weight change.

Conclusions: These findings suggest that weight change (gain) during long-term OLZ treatment generally does not detract from treatment-related improvements in key aspects of patients' quality of life.

Gilmore, and G. D. Tollefson. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. *Journal of Clinical Psychiatry* 62(4):231-238, 2001.

B. R. Basson, B. J. Kinon, C. C. Taylor, K. A. Szymanski, J. A.

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Objective: Clinical factors predicting weight change in patients with schizophrenia and related disorders during acute treatment with the antipsychotic drugs olanzapine, risperidone, and haloperidol were sought through retrospective analyses.

Method: Six-week body-weight data from 2 trials, study 1 comparing olanzapine and haloperidol (N = 1369) and study 2 olanzapine and risperidone (N = 268), were analyzed. Effects of 8 clinically relevant covariates - therapy, clinical outcome (Brief Psychiatric Rating Scale), baseline body mass index (BBMI), increased appetite, age, gender, race, and dose - on weight were compared.

Results: In study 1, olanzapine (vs. haloperidol) therapy, better clinical outcome, lower BBMI, and nonwhite race significantly affected weight gain. Effects of increased appetite and male gender on weight gain were significant for olanzapine but not for haloperidol. In study 2, better clinical outcome, lower BBMI, and younger age significantly affected weight gain. Increased appetite was more frequent during olanzapine treatment than during haloperidol, but not significantly different from risperidone. Significant differences in effect on weight change were found between olanzapine and haloperidol but not between olanzapine and risperidone. No evidence was found that lower antipsychotic drug doses were associated with lower weight gain.

Conclusion: This report identifies predictive factors of acute weight change in patients with schizophrenia. Similar factors across antipsychotic drugs in predicting greater weight gain included better clinical outcome, low BBMI, and nonwhite race. Factors differing between conventional (haloperidol) and atypical (olanzapine) agents included increased appetite and gender. Choice of atypical antipsychotic drug (olanzapine vs. risperidone) was of minor importance with regard to influence on acute weight gain.

Polymorphisms of CYP2D6 as a risk factor for weight gain with olanzapine. *Schizophrenia Research* 49(1-2):283-284, 2001.

V. L. Ellingrod, D. D. Miller, S. K. Schultz, S. Arndt, and H. J. Wehring.

Background: Weight gain has been seen with atypical antipsychotics (APPs). Risk factors for this are unknown. Previous work suggests CYP2D6 polymorphisms are related to medication morbidity.

Aims: Examine the relationship between CYP2D6 and AAP weight gain. **Methods:** Eleven subjects from the MH-CRC at Iowa were given olanzapine and genotyped for CYP2D6. Data was available for up to 47 months. Genomic DNA was analyzed for CYP2D6*1, *3, and *4 alleles using polymerase chain reaction. A linear regression used percent change in body mass index (BMI) as the dependent measure. CYP2D6 Genotype, dose and duration of olanzapine exposure were independent. The model, independent variables, and interactions were tested for significance.

Results: Six subjects were genotyped as *1/*1 and five were *1/*3 or *4. No group differences were found. The model was significant (F = 10.69, df = 1,9, p < 0.0097) for genotype. Subjects with a *1/*3 or *4 genotype experienced a larger percent change in BMI than those with a *1/*1 genotype.

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Conclusion: The *1/*3 or *4 genotype, potentially results in increased serum concentrations of olanzapine, leading to increased medication exposure for patients with this genotype. CYP polymorphisms resulting in increased AAP exposure may be a trigger for AAP weight gain.

Association of Olanzapine-Induced Weight Gain With an Increase in Body Fat. *Am J Psych* 2001(158):1719-1722

Eder U, Mangweth B, Ebenbichler C, Weiss E, Hofer A, Hummer M, Kemmler G, Lechleitner M, Fleischhacker WW

Objective: The goal of this study was to explore the pathophysiology of weight gain during treatment with olanzapine for schizophrenia.

Method: The authors used a prospective, controlled, open study comparing body weight, body mass index, and related biological measures in mentally and physically healthy volunteers and olanzapine-treated patients with schizophrenia. Weight, eating behavior, leptin serum levels, body mass index, and body composition were assessed over an 8-week observation period.

Results: A significant increase in body weight, leptin serum levels, and percentage of body fat was seen in patients treated with olanzapine, but the drug-free comparison group did not show any significant changes. The weight gain during antipsychotic treatment with olanzapine was mainly attributable to an increase in body fat; patients' lean body mass did not change.

Conclusions: In addition to the original finding that an increase in body fat is mainly responsible for olanzapine-induced weight gain, these findings confirm results obtained in other studies showing increases in body weight and serum leptin levels during treatment with second-generation antipsychotics.

Weight Gain Associated With Increased Food Intake and Low Habitual Activity Levels in Male Adolescent Schizophrenic Inpatients Treated With Olanzapine. *Am J Psych* 2002(159):1055-1057

Gothelf D, Falk B, Singer P, Kairi M, Phillip M, Zigel L, Poraz I, Frishman S, Constantini N, Zalsman G, Weizman A, Apter A

Objective: The authors studied weight gain mechanisms and energy balance in patients treated with olanzapine.

Method: The body mass index of male schizophrenic adolescent inpatients treated with olanzapine (N=10) and of 10 matched patients treated with haloperidol (N=10), were measured at baseline and after 4 weeks of treatment. For the patients treated with olanzapine, caloric intake, resting energy expenditure, and physical activity (determined

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through accelerometry and heart rate monitoring) were assessed at baseline and after 4 weeks of treatment.

Results: Body mass index significantly increased in those treated with olanzapine but not in those given haloperidol. The increase in body mass index was due to an increase in caloric intake without change in diet composition. Olanzapine had no significant effect on resting energy expenditure. Daily energy expenditure was very low before and after treatment.

Conclusions: Olanzapine-induced weight gain is associated with a general increase in caloric intake.

Olanzapine-Induced Weight Gain in Patients With First-Episode Schizophrenia: A Double-Blind, Placebo-Controlled Study of Fluoxetine Addition. *Am J Psych* 2002(159):1058-1060

Poyurovsky M, Pashinian A, Gil-Ad I, Maayan R, Schneidman M, Fuchs C, Weizman A

Objective: Since olanzapine-induced weight gain may be attributable to the antagonistic activity of olanzapine at the serotonin-2C receptor, the authors hypothesized that it might be attenuated by addition of the selective serotonin reuptake inhibitor fluoxetine.

Method: First-episode hospitalized schizophrenia patients (N=30) were randomly assigned in an 8-week double-blind study of olanzapine, 10 mg/day, coadministered with either fluoxetine, 20 mg/day (N=15), or placebo (N=15).

Results: The group receiving olanzapine plus fluoxetine showed significantly less improvement in positive and disorganized symptom dimensions than the group receiving olanzapine plus placebo. The two groups demonstrated similar and substantial gradual weight gains.

Conclusions: These results suggest that fluoxetine coadministration is clinically ineffective and cannot attenuate olanzapine-induced weight gain.

Decrease of Energy Expenditure Causes Weight Increase in Olanzapine Treatment – A Case Study. *Pharmacopsychiatry* 2002(35):124-126

Virkkunen M, Wahlbeck K, Rissanen A, Naukkarinen H, Franssila-Kallunki A

The aim of this study was to evaluate the mechanisms underlying weight gain induced by the atypical antipsychotic, olanzapine. We performed euglycemic, hyperinsulinemic clamp combined with indirect calorimetry on a 48-year-old male with antisocial personality disorder, alcohol dependence and paranoid ideation before and after one month of olanzapine (10 – 15 mg/day) therapy. The patient gave his informed, written

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consent for this study. The results were a weight gain of 6 kg and a decrease in both basal (from 1673 to 1613 kcal/24h) and 3-hour (from 22.8 to 20.2 cal/kg fat free mass/min) energy expenditure. Serum thyroid hormone and high-density lipoprotein cholesterol levels decreased, and the triglyceride and low-density lipoprotein cholesterol levels increased. Insulin sensitivity did not change. We conclude that decreased basal energy expenditure may contribute to weight gain in olanzapine treatment.

Weight Gain with Clozapine

Clozapine: Diabetes Mellitus, Weight Gain, and Lipid Abnormalities.
J Clin Psych 2001;62 (23):39-44

Henderson DC

Clozapine remains the most effective agent for treatment-resistant patients with schizophrenia. Recently, treatment with clozapine has been linked to a number of metabolic disturbances, including weight gain, diabetes mellitus, and serum lipid abnormalities. Despite the potential risks of medical morbidities, clozapine continues to have a major role in the care of treatment-resistant patients with schizophrenia. This article discusses the diagnosis and significance of the above metabolic abnormalities and potential mechanisms for these abnormalities as well as recommendations for monitoring and treatment.

Effects of Long-Term Administration of Clozapine on Body Weight and Food Intake in Rats. *Pharmacology Biochemistry and Behavior* 1993(45):51-54

Baptista T, Mata A, Teneud L, De Quijada M, Han H-W, Hernandez L

Previous reports have shown that long-term administration of typical and atypical neuroleptics induced obesity in female but not in male rats. It has been suggested that impaired ovarian steroidogenesis related to neuroleptic-induced hyperprolactinemia is necessary to observe the body weight changes. This hypothesis was tested with clozapine, an atypical neuroleptic that produces in rats a shorter increase in serum prolactin levels than do other neuroleptics. The effects of clozapine on body weight and food intake were assessed in female and male rats under treatment with any of the following doses: 0.5, 1.25, 5, 10 and 20 mg/kg IP for 21 days. Vaginal cycle under clozapine treatment, as an indirect indicator of ovarian steroidogenesis, was also assessed. Obesity was not observed in any group. By contrast, clozapine at the doses of

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10 and 20 mg/kg significantly decreased body weight and feeding in male rats. Clozapine at the doses of 5 and 10 mg/kg IP induced permanent diestrus. The failure of clozapine to induce obesity in female rats, despite impaired vaginal cycle, can be considered indirect evidence that drug-induced hyperprolactinemia is not sufficient to observe neuroleptic-induced obesity in rats.

Differential Effect of Clozapine on Weight: A Controlled Study. *Am J Psych* 1996 (153):817-819

Bustillo JR, Buchanan RW, Irish D, Breier A

Objective: This study examined whether clozapine induces more weight gain than haloperidol and whether weight gain is related to clinical improvement.

Method: The weight and symptoms of 39 outpatients with schizophrenia who were randomly assigned to double-blind treatment with either clozapine or haloperidol were assessed. The weight and symptoms of 33 of the patients who chose to take clozapine during a 1-year follow-up after the study ended were also assessed.

Results: The patients treated with clozapine gained significantly more weight over baseline (7%) than the haloperidol-treated patients (1%). Weight gain was not significantly correlated with improvements in either positive or negative symptoms. Fifty-eight percent of the patients followed for 1 year gained at least 10% over their baseline weight.

Conclusions: Weight gain is an important side effect of clozapine and is unrelated to the drug's differential antipsychotic efficacy.

Serum Leptin Levels Increase Rapidly After Initiation of Clozapine Therapy. *Psychiatry* 1998(3):76-80

Bromel tT Blum WF, Ziegler A, Schultz E, Bender M, Fleischhaker C, Remschmidt H, Kneg J-C, Hebebrand J

Weight gain is a major side-effect of treatment with clozapine. In order to investigate the influence of the atypical neuroleptic clozapine on leptin secretion, serum leptin levels were measured in 12 patients at baseline and for a 10-week period after initiation of treatment. Serum clozapine levels and levels of its metabolites were simultaneously assessed. Alterations of body weight and body composition were determined. During the 10-week observation period leptin levels differed significantly from the levels determined at baseline ($P < 0.0001$). During the first 2 weeks of treatment serum leptin levels at least doubled in eight of the 12 patients. The maximal relative increase over baseline was 536%. Low doses of clozapine were sufficient to induce this effect. Within a 10-week period mean body weight, mean body mass index, mean fat mass and mean lean body mass all increased. Based on the results we suggest that in predisposed

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individuals clozapine induces an increased appetite; overeating and weight gain can ensue, which in turn underlie elevated leptin secretion.

Clozapine and Body Mass Change. *Society of Biological Psychiatry* 1998(43):520-524

Frankenburg, FR, Zanarini MC, Kando, J, Centorrino, F

Background: Patients treated with clozapine have been reported to gain weight. We hypothesized that patients would also experience an increase in body mass, which can be more directly related to cardiovascular morbidity.

Methods: Forty-two patients who had been treated with clozapine for at least 1 year were weighed and measured, and waist-hip ratios (WHR) and body mass index (BMI), measured as kg/m^2 , were calculated. Patients were also asked about a series of factors potentially related to change in body mass.

Results: Female patients gained both weight and body mass. Their WHR after 37 months of clozapine therapy was .83, with a significant increase in BMI from 23.2 to 29.1 kg/m^2 ($p = .001$). Male subjects also gained weight and body mass. Their WHR after 39 months of clozapine therapy was .93, with a significant increase in BMI from 26.4 to 29.7 kg/m^2 ($p < .001$). Stepwise multiple-regression analysis showed that factors related to final body mass were initial body mass, dose of clozapine, and decrease in smoking. Baseline BMI contributed most to the Δ BMI, but the addition of dose and decrease in smoking made significant contributions to the model.

Conclusions: Both female and male patients treated with clozapine gain body mass. This may place them at greater risk for cardiovascular morbidity.

Clozapine, Diabetes Mellitus, Weight Gain, and Lipid Abnormalities: A Five Year Naturalistic Study. *Am J. Psych* 2000(157):975-981

Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC

Objective: The goal of this 5-year naturalistic study of patients treated with clozapine was to examine the incidence of treatment-emergent diabetes mellitus in relation to other factors, including weight gain, lipid abnormalities, age, clozapine dose, and treatment with valproate.

Method: Data on age, gender, race, diagnosis, family history of diabetes, and age of clozapine initiation were collected from medical records of 82 outpatient with schizophrenia or schizoaffective disorder. Clozapine dose, data on use of valproate, and laboratory test results were recorded at 6-month intervals.

Results: The mean age at the time of clozapine initiation of the 82 patients was 36.4 years; 26.8% of the patients were women, and 95.5% were Caucasian. The mean

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baseline weight was 175.5 lb. and the mean body mass index was 26.9 kg/m². Thirty patients (36.6%) were diagnosed with diabetes during the 5-year follow-up. Weight gain, use of valproate, and total daily dose of clozapine were not significant risk factors for developing diabetes mellitus. Patients experienced significant weight gain that continued until approximately month 46 from initiation of clozapine. There was a nonsignificant increase in total serum cholesterol and a significant increase in serum triglycerides level. **Conclusions:** The results support the hypotheses that patients treated with clozapine experience significant weight gain and lipid abnormalities and appear to be at increased risk for developing diabetes.

Weight Gain Induced by Clozapine. *European Neuropsychopharmacology* 1995(5):437-440

Hummer M, Kemmler G, Kurz M, Kurzthaler I, Oberbauer H, Fleischhacker WW

Patients were investigated to gain more insight into the incidence and time course of clozapine induced weight gain (n = 81) and to compare weight gain in patients treated with clozapine (n = 31) with that of patients treated with standard antipsychotics (haloperidol, n = 11). 35.7% of the patients treated with clozapine gained weight according to our definition. If patients gained weight on clozapine this side effect was apparent within the first 12 weeks of treatment. Deviation from normal body weight at the beginning of treatment showed a significant influence on weight gain. Sex, severity of illness, comedication, mean clozapine dose and degree of improvement did not show an influence on this side effect. Weight increase was significantly higher in patients treated with clozapine than in patients treated with haloperidol.

Weight Gain Among Schizophrenic Patients Treated With Clozapine. *Am J Psychiatry* 1992(149):689-690

Lamberti JS, Bellnier T, Schwarzkopf SB

A retrospective chart review was used to assess weight changes in 36 chronic schizophrenic inpatients who were treated with clozapine after being treated with standard neuroleptics. The average weight gain during 6 months of clozapine treatment was 16.9 lb; 75.0% of the patients gained at least 10 lb. The results confirm previous findings of clozapine-associated weight gain.

Clozapine-Induced Weight Gain: Prevalence and Clinical Relevance. *Am J Psych* 1992(149):68-72

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Leadbetter R, Shutty M, Pavalonis D, Vieweg V, Higgins P, Downs M

Objective: The aim of this study was to determine the prevalence and clinical relevance of weight gain during clozapine treatment. Previous reports indicated clinically significant weight gain in 13% to 85% of patients and an average gain of 9.0 to 24.7 lb.

Method: Twenty-one state hospital patients with treatment-resistant schizophrenia or schizoaffective disorder were weighed weekly for 12 weeks before clozapine treatment and during the first 16 weeks of treatment. Psychiatric symptoms were rated with a modified version of the Brief Psychiatric Rating Scale (BPRS).

Results: The mean weight gain for the entire group was 13.9 lb, or 8.9% of body weight. During the 16 weeks of clozapine treatment, 38% of the patients experienced marked weight gains and 29% had moderate weight gains. The improvements in BPRS total score and composite negative symptom score were significantly greater for the eight patients with marked weight gains than for the other 13 patients.

Conclusions: Clozapine's propensity to induce weight gain may relate to the drug's efficacy and/or its unique neuropharmacologic effects. Increased attention to this phenomenon is important because of the morbidity associated with obesity.

Effect of Clozapine-Quetiapine Combination Therapy on Weight and Glycaemic Control. *Clin Drug Invest* 1999(2):99-104

Reinstein MJ, Sirotovskaya LA, Jones LE, Mohan S, Chasanov MA

Objective: The purpose of this open-label, non-randomised, 10-month, retrospective comparative study was to assess changes in weight and diabetes status for patients initially treated with clozapine who developed diabetes and who were then switched to clozapine-quetiapine combination therapy.

Methods: Sixty-five clinic charts were reviewed. All patients were from long-term care facilities. Bodyweight data were collected for this group of 65 randomly selected schizophrenic patients who were on clozapine initially (200 to 800 mg/day for 6 months) and then had quetiapine ('Seroquel') added to their therapy. Clozapine dosages were reduced as quetiapine was added proportionally: 25% of the clozapine dose was changed to quetiapine, using a ratio of exactly 1mg clozapine to 2mg of quetiapine. The quetiapine dosages ranged from 200 to 800 mg/day. This means that each patient received 6 months of clozapine therapy followed by 10 months of combination treatment with clozapine-quetiapine. Weights were recorded monthly, and diabetes status was also performed for patients who developed the condition during clozapine monotherapy.

Results: Changes in weight and the status of diabetes were determined in patients switched from a 6-month clozapine therapy to the 10-month combination clozapine-quetiapine treatment. All changes were statistically significant ($p < 0.001$). Use of this combination therapy in the management of weight gain and diabetes resulted in a 100% satisfactory response. All 65 patients showed weight loss ranging from 0.22 to 10.5kg (0.5 to 23lb) [mean 1.8kg (3.98lb)] after the first month of combination therapy, and the

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improvement continued through the study duration (10 months). Marked total weight loss ranged from 0.45 to 18.6kg (1 to 41lb), with a mean loss of 4.2kg (9.2lb) over the 10-month study period. 20% of patients (13 patients) who developed diabetes during the 6-month clozapine monotherapy showed significant improvement of disease status with addition of quetiapine. Compliance with medication was 100% and no significant adverse events were observed. The most common adverse event reported by patients was drowsiness. However, this did not contribute a valid reason for discontinuation of clozapine-quetiapine therapy and could be corrected by dosage adjustment at any time of the report of this adverse effect by patients.

Conclusion: An unexpected, yet welcome, clinical effect of quetiapine is its apparent propensity to induce weight loss and improve glycaemic control in patients who gain weight and develop diabetes on clozapine therapy. The results of this retrospective study support the safety and tolerability of clozapine-quetiapine combination therapy.

Clozapine and Weight Gain. J. Clin Psych 1994(55/9):157-160

Umbrecht DSG, Pollack S, Kane JM

Background: To investigate the association of clozapine treatment and weight gain, we studied short- and long-term weight gain, correlation of weight gain with treatment response, and risk factors for weight gain in 82 patients with chronic schizophrenia who received clozapine treatment for up to 90 months.

Method: Weight values were obtained through retrospective chart review. Clozapine was titrated over an average of 3 to 5 weeks up to a dose of 500 to 600 mg/day. Psychopathology was assessed with the Brief Psychiatric Rating Scale and Clinical Global Impressions scale.

Results: A clinically significant weight gain occurred mostly during the first 6 to 12 months, but continued well into the third year of treatment. Weight gain and treatment response were not correlated, and early weight gain was not a predictor of response. The cumulative incidence of patients becoming substantially overweight exceeded 50%. Being underweight at baseline correlated with maximum amount gained ($p = .000$), and being overweight at baseline correlated with percentage above ideal weight ($p = .006$).

Conclusion: Treatment with clozapine is associated with a high incidence of substantial weight gain, posing a potential long-term health risk. Studies are needed of the underlying mechanisms of weight gain, as well as the treatment for this side effect.

Weight Gain with Risperidone

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Weight Gain With Risperidone Among Patients With Mental Retardation: Effect of Calorie Restriction. *J Clin Psych* 2001(62):114-116

Cohen S, Glazewski R, Khan S, Khan A

Background: The atypical antipsychotics cause weight gain, which is poorly understood in terms of its mechanism and treatment. A usual recommendation for treatment of antipsychotic-induced weight gain includes calorie restriction and exercise. The authors describe their recent clinical experience with calorie restriction in adults with mental retardation treated with risperidone.

Method: A retrospective chart review was performed on the records of 50 adult patients with mental retardation treated with risperidone while residing at a habilitation center. We assessed dose and duration of risperidone treatment, weight, changes in calorie intake, and frequency of aggressive behavior.

Results: Of the 50 patients, 39 had adequate data for analysis. Thirty-seven of the 39 patients gained weight with a mean of 18.8 lb (8.3kg) over about 2 years. Twenty of the 37 patients were calorie restricted. Three of the 20 calorie-restricted patients lost weight at a rate of 0.2 lb (0.1kg) per month. The other 17 calorie-restricted patients and the 17 patients who were not calorie restricted continued to gain weight at a rate of 0.8 lb (0.4kg) per month over about another 2 years of treatment. The amount of weight gain was not dose related. Calorie restriction led to no deterioration in behavior.

Conclusion: The current investigation lends support to data that note weight gain with risperidone in adults with mental retardation. It suggests that calorie restriction does not lead to weight loss or behavioral deterioration and that weight gain is not dose related.

Weight Gain with Quetiapine

Effect of Clozapine-Quetiapine Combination Therapy on Weight and Glycaemic Control. *Clin Drug Invest* 1999(2):99-104

Reinstein MJ, Sirotovskaya LA, Jones LE, Mohan S, Chasanov MA

Objective: The purpose of this open-label, non-randomised, 10-month, retrospective comparative study was to assess changes in weight and diabetes status for patients initially treated with clozapine who developed diabetes and who were then switched to clozapine-quetiapine combination therapy.

Methods: Sixty-five clinic charts were reviewed. All patients were from long-term care facilities. Bodyweight data were collected for this group of 65 randomly selected schizophrenic patients who were on clozapine initially (200 to 800 mg/day for 6 months) and then had quetiapine ('Seroquel') added to their therapy. Clozapine dosages were reduced as quetiapine was added proportionally: 25% of the clozapine dose was changed

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to quetiapine, using a ratio of exactly 1mg clozapine to 2mg of quetiapine. The quetiapine dosages ranged from 200 to 800 mg/day. This means that each patient received 6 months of clozapine therapy followed by 10 months of combination treatment with clozapine-quetiapine. Weights were recorded monthly, and diabetes status was also performed for patients who developed the condition during clozapine monotherapy.

Results: Changes in weight and the status of diabetes were determined in patients switched from a 6-month clozapine therapy to the 10-month combination clozapine-quetiapine treatment. All changes were statistically significant ($p < 0.001$). Use of this combination therapy in the management of weight gain and diabetes resulted in a 100% satisfactory response. All 65 patients showed weight loss ranging from 0.22 to 10.5kg (0.5 to 23lb) [mean 1.8kg (3.98lb)] after the first month of combination therapy, and the improvement continued through the study duration (10 months). Marked total weight loss ranged from 0.45 to 18.6kg (1 to 41lb), with a mean loss of 4.2kg (9.2lb) over the 10-month study period. 20% of patients (13 patients) who developed diabetes during the 6-month clozapine monotherapy showed significant improvement of disease status with addition of quetiapine. Compliance with medication was 100% and no significant adverse events were observed. The most common adverse event reported by patients was drowsiness. However, this did not contribute a valid reason for discontinuation of clozapine-quetiapine therapy and could be corrected by dosage adjustment at any time of the report of this adverse effect by patients.

Conclusion: An unexpected, yet welcome, clinical effect of quetiapine is its apparent propensity to induce weight loss and improve glycaemic control in patients who gain weight and develop diabetes on clozapine therapy. The results of this retrospective study support the safety and tolerability of clozapine-quetiapine combination therapy.

Effect of Quetiapine on Changes in Weight Treatment of Schizophrenia

Goldstein JM, Jones AM, Rak IW

Background: Atypical antipsychotic agents have shown to be effective treatments for schizophrenia. Although atypical antipsychotics have a better extrapyramidal symptom side-effect profile than conventional antipsychotics, some are associated with an increase in weight.

Objective: To determine the effect of long-term treatment with quetiapine on weight gain in patients with schizophrenia.

Methods: Patients (n=2216) from controlled, uncontrolled, and open-label extension (OLE) studies were evaluated for weight gain at specified time intervals over at least 52 weeks. Patients were grouped using a last observation carried forward approach, within specified time intervals. Patients only received quetiapine during the controlled and OLE studies.

Results: There was a small mean weight increase of 2.08 kg (± 0.15 ; n=778) over the first 5-6 weeks. Similar mean weight increases of 2.16 kg (± 0.46 ; n=171) at 9-10 weeks,

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1.85 kg (\pm 0.48; n=556) at 6-9 months, and 2.77 kg (\pm 0.56; n=360) at 9-12 months were observed. The average mean daily dose of quetiapine for the patients at 9-12 months was 428 mg/d. Only 1 patient from the 2216 cohort (0.05%) withdrew due to an adverse event of weight gain.

Conclusion: These results indicate that the weight gain associated with long-term treatment with quetiapine is modest, being slightly less than that reported for risperidone and considerably less than olanzapine and clozapine.

Risk of Adverse Events Associated with Canadian National Outcomes Measure

McIntyre R, Trakas K, Lin D, Balshaw R, Hwang P, Robinson K, Eggleston A, CNOMSS

Introduction: Weight gain, sedation and extrapyramidal symptoms (EPS) are common adverse events (AEs) of antipsychotic treatment. Development of AEs is an important risk factor for non-adherence to antipsychotic medication. Clinically significant weight gain in non-psychotic individuals increases the risk of hypertension, diabetes mellitus, coronary heart disease, stroke, and cancer.

Objective: To determine the relative risk of treatment-related adverse events in olanzapine, quetiapine, and risperidone-treated patients in the Canadian National Outcomes Measurement Study in Schizophrenia.

Conclusions: The results of this study add to the growing confluence of data suggesting that weight gain liability exists amongst the novel atypical antipsychotics under study. However, the evidence in this study may also suggest that a relative liability for weight gain needs to be further delineated.

Effects on Weight Change of Switching From Olanzapine to Quetiapine.

Masand PS, Gupta S, Virk S, Schwartz T, Hameed A, Frank BL, Lockwood K

The purpose of this study was to evaluate effects of switching from olanzapine to quetiapine on body weight in chronic, psychiatrically ill patients. Sixteen patients who were psychiatrically stable on olanzapine but had gained weight were gradually switched to quetiapine and followed for 10 weeks. Enrollment criteria included body mass index greater than 25 kg/m² and weight gain of at least 20% of body weight on olanzapine. Weight change as both a categorical and a continuous variable was examined using *t*-test for paired scores. Efficacy was measured using the Positive and Negative Syndrome Scale (PANSS), while the medication-related side effects were assessed using the Simpson-Angus Scale (SAS). Twelve patients completed the study. Weight decline after switching to quetiapine was statistically significant (mean change 103 to 101 kg; 2.25 kg

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per patient; $P=0.03$); effect size was small (Cohen's $d=0.12$). PANSS variables of Somatic Concern and Guilt Feelings declined after the switch ($t=2.88$; $P=0.13$ and $t=2.62$; $P=0.021$, respectively). There was no increase in psychiatric symptoms during the 10-week follow-up. There were no statistically significant differences in SAS variables. This pilot study suggests that switching to quetiapine may be a viable strategy for patients who experienced weight gain associated with olanzapine. The switch to quetiapine was well tolerated; patients lost weight while taking quetiapine without relapse of symptoms at the 10-week follow-up.

Weight Gain in Adolescents

A long term comparison of olanzapine and risperidone on weight gain as side effect in adolescents with recent-onset schizophrenia. Anonymous. Anonymous. *Schizophrenia Research* 49(1-2):290, 2001.

M. J. Van Bruggen, D. H. Linszen, P. M. Dingemans, and M. E. Lenior.

Weight gain is an important side effect of antipsychotic drugs, which can induce non-compliance, and therefore negatively influence the course of schizophrenia. Weight gain can also lead to obesity with negative consequences for the general health of patients. In this study we compared two novel antipsychotic drugs, olanzapine and risperidone, in their long-term effect on weight in adolescent patients with a first or second psychotic episode. Eighty-six adolescent and young adult patients had sufficient data to perform analysis over time on weight gain. Of these patients weight was assessed at 7 moments in time, from admission to our clinic till 8 months after discharge. Analyses over time were performed comparing olanzapine and risperidone in their effect on weight, controlling for baseline-weight. All patients gained weight significantly over time, but there was no difference in weight gain between olanzapine and risperidone. Most weight gain occurred in the first 8 months of the study, reaching a possible plateau-effect after the first 8 months. Weight gain was not significantly different between males and females.

Weight Gain Associated With Olanzapine and Risperidone in Adolescent Patients: A Comparative Prospective Study. *J. Am. Acad. Child Adolesc. Psych* 2002,41(3):337-343

Ratzoni G, Gothelf D, Brand-Gothelf A, Reidman J, Kikinzon L, Gal G, Phillip M, Apter A, Weizman R

Objective: To evaluate weight gain associated with olanzapine, risperidone, and haloperidol treatment and its clinical risk factors in adolescent patients.

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Method: The study was conducted at three adolescent psychiatric departments in two mental health centers in the Tel Aviv area. All patients were Jewish Israelis. Weight and body mass index (BMI) of hospitalized adolescents treated with olanzapine (n=21), risperidone (n=21), or haloperidol (n=8) were prospectively monitored on a weekly basis for the first 12 weeks of treatment. Various clinical risk factors were tested for association with weight gain.

Results: The olanzapine and risperidone groups experienced significant weight gain between baseline and endpoint ($p < .01$), whereas the average weight of the haloperidol group did not change. Average weight gain was significantly higher for the olanzapine group (7.2 ± 6.3 kg, $11.1\% \pm 7.8\%$) than for the risperidone (3.9 ± 4.8 kg, $6.6\% \pm 8.6\%$) and haloperidol (1.1 ± 3.3 kg, $1.5\% \pm 6.0\%$) groups. Extreme weight gain ($>7\%$) was recorded in 19 patients (90.5%), 9 patients (42.9%), and 1 (12.5%) patient, respectively. Gender (males), low concern about gaining weight (females), low baseline BMI, and paternal BMI were positively correlated with weight gain, whereas previous neuroleptic history, neuroleptic dosage, response to treatment, and illness duration were not.

Conclusions: Olanzapine and risperidone are associated with extreme weight gain in adolescents, much higher than that reported in adults. This side effect, should be taken into consideration before prescribing these medications, especially in patients at high risk.

Risperidone-Associated Weight Gain in Children and Adolescents: A Retrospective Chart Review. *Journal of Child and Adolescent Psychopharmacology* 2000(10):259-268

Martin A, Landau J, Leebens P, Ulizio K, Cicchetti D, Scahill L, Leckman JF

Objective: Risperidone use has been associated with substantial weight gain in children and adolescents. Reports available to date have consisted of small case series evaluated without standardized indices of developmentally normative weight increase. The purpose of this study was to evaluate age- and gender-adjusted weight changes linked to risperidone use in a juvenile psychiatric inpatient population.

Method: Thirty-seven child and adolescent inpatients treated with risperidone for 6 consecutive months were compared to a group of 33 psychiatric inpatients with no atypical neuroleptic exposure. Weight, height, and body mass index (BMI) were recorded on at least a monthly basis, and Tanner staging was completed on admission. Percent change from baseline weight, changes in standardized z scores of weight for age and gender, and proportion of subjects experiencing a $\geq 7\%$ weight increase from baseline were compared among groups.

Results: Subjects in both groups were comparable at baseline except for gender distribution (more males were in the risperidone group, $p < 0.05$). Risperidone-treated children and adolescents experienced significant weight gain between baseline and endpoint (paired t test, $p < 0.001$) that was first evident within 2 months of starting treatment, progressed steadily at an average rate of 1.2 kg/month and did not reach a clear

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plateau during 6 months of observation. Significant increases in standardized weight were noted at 3 and 6 months for risperidone-treated subjects. Risperidone use conferred a substantial risk of gaining over 7% from baseline weight (odds ratio = 3.5, 95% confidence interval = 1.8-6.6, $p < 0.001$).

Conclusions: Six-month exposure to risperidone was associated with clinically significant weight gain in 78% of treated children and adolescents (as opposed to 24% of those in the comparison group, $p < 0.001$). Risperidone dosage, concomitant medication use, and other demographic characteristics such as age, pubertal status, gender, and baseline weight and BMI were not associated with an increased risk of morbid weight gain. Standardized z scores offer advantages for the assessment of weight change among developing children and adolescents.

Weight Gain in the Elderly

Weight variance associated with atypical neuroleptics in nursing home dementia patients. *Journal of the American Medical Directors Association* 2(1):26-28, 2001.

R. J. Goldberg.

Objective: Atypical antipsychotics have been reported to cause significant weight gain. This study examined potential weight gain associated with the use of olanzapine or risperidone.

Design: A retrospective chart review. Setting: Three long-term care facilities. Participants: Dementia patients ($n = 50$) given olanzapine or risperidone for the management of noncognitive behavioral disturbances.

Measurements: Weight changes over a 4-month period. Results: Overall, patients in both groups lost weight over a 4-month period. Four (16%) of the risperidone patients and no olanzapine patients gained more than 5 pounds.

Conclusion: Weight change does not seem to be a significant clinical issue for older dementia patients taking low doses of atypical neuroleptics.

No Weight Gain Among Elderly Schizophrenia Patients After 1 Year of Risperidone Treatment. *J. Clin Psych* 2002(63):117-119

Barak Y

Objective: Weight gain has been reported in younger patients treated with most atypical neuroleptics. The goal of this study was to examine whether elderly schizophrenic patients gain weight while being treated with risperidone.

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Method: Data are from an international multicenter, open-label study of 180 elderly (69 men, 111 women), chronically ill, psychotic patients (meeting DSM-III-R criteria for schizophrenia or schizophreniform disorder; median age = 72 years [range, 54-89 years]), 97 of whom completed the 12-month study. At endpoint, the mean dose of risperidone was 3.7 mg/day. Patients were weighed at baseline and at endpoint.

Results: There was no significant weight gain in patients who completed the trial (N = 96) or in those who did not complete the entire trial (N = 31).

Conclusion: The results suggest that risperidone treatment is not associated with weight gain among elderly persons with chronic psychosis.

Non-Pharmacological Interventions

Novel antipsychotics: Comparison of weight gain liabilities. *Journal of Clinical Psychiatry* 60(6):358-363, 1999.

D. A. Wirshing, W. C. Wirshing, L. Kysar, M. A. Berisford, D. Goldstein, J. Pashdag, J. Mintz, and S. R. Marder.

Background: We performed a retrospective analysis of 122 clinical records of 92 male patients with DSM-III-R schizophrenia to examine the relative weight gain liabilities of clozapine, risperidone, olanzapine, and sertindole compared with haloperidol. We hypothesized that the unique pharmacodynamic profiles of these agents would contribute to different amounts and patterns of weight gain.

Method: Data were analyzed to determine differences in weight gain during treatment among patients receiving 5 different drug treatments (clozapine [N = 20], olanzapine [N = 13], risperidone [N = 38], haloperidol [N = 43], and sertindole [N = 8]). Measures of maximal weight gain, final weight, and duration to maximal weight gain were calculated.

Results: Repeated measures analyses of variance controlling for age, treatment duration, and initial weight revealed statistically significant differences between groups on all 3 measures. Clozapine and olanzapine had the greatest maximal weight gain liability (F = 4.13, df = 4,23; p = .01). Weight gain with clozapine, but not olanzapine or risperidone, appears to persist (as reflected by final weight) despite behavioral interventions (e.g. nutritional consultation, suggested exercise regimen; F = 5.69, df = 4,23; p = .003). Clozapine- and olanzapine-treated subjects appeared to gain weight over a prolonged period of time, whereas risperidone- and sertindole-treated subjects had a more limited period of weight gain (F = 2.95, df = 4,25; p = .04).

Conclusion: Clozapine and olanzapine caused the most weight gain, risperidone was intermediate, and sertindole had less associated weight gain than haloperidol. The relative receptor affinities of the novel antipsychotics for histamine H1 appear to be the most robust correlated of these clinical findings.

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A program for treating olanzapine-related weight gain. *Psychiatric Services* 52(7):967-969, 2001.

M. P. Ball, V. B. Coons, and R. W. Buchanan.

This study evaluated the effectiveness of a Weight Watchers program for patients with schizophrenia who had olanzapine-related weight gain and ascertained whether the severity of patients' psychiatric symptoms was correlated with the patients' success in losing weight. Seven men and four women who had been treated with olanzapine and who had gained at least 7 percent of their pretreatment body weight attended Weight Watchers meetings and were offered supervised exercise sessions. The patients' weight, body mass index, and psychiatric symptoms were assessed and were compared with those of a matched comparison group who did not attend the Weight Watchers program. Only the men experienced significant weight loss. No correlation was found between weight loss and exercise or change in psychiatric symptoms.

Weight gain in patients treated with olanzapine: a retrospective survey. *APA*, 2001.

Findlay LJ, Munoz-Carbone CE, Jackson WT, Logalbo AP, Husain N, Lyons P, May RS.

Objective: To study the side effect of weight gain associated with olanzapine treatment with consideration of variables of interest such as patient complaints of weight gain, comorbid medical conditions, concurrent medications, prescription adherence, and treatment response.

Method: Clinic charts of 145 psychiatric outpatients treated with olanzapine were retrospectively surveyed with attention to several variables of interest possibly related to the side effect of weight gain. The review divided patients into three groups: those with documented weight gain that complained of weight gain, those that gained weight but did not complain, and those that did not gain weight.

Results: There was evidence of weight gain in over one-third (36%) of all patients. Those who gained the most weight on olanzapine ($\underline{M} = 9.7$ kg, $\underline{SD} = 4.9$ kg) had a high proportion (87.5%) of stable or improved treatment ratings, 68.8% were rated as compliant with treatment, and 18.8% were taken off olanzapine. Of the patients who were treated with olanzapine only ($\underline{n} = 19$), 42.1% gained weight ($\underline{M} = 1.76$ kg, $\underline{SD} = 3.1$ kg) and 26% of them complained about it during their clinic visits, but they all remained on the medication. Of the patients on olanzapine only, 84% were rated as having a stable or improved treatment response. Only nine patients from the entire sample (6.2%) had their olanzapine treatment discontinued due to weight gain. They tended to have more comorbid medical problems and concurrent medications than other study participants. Of

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the patients on olanzapine who did not gain weight, 20.4% were rated as not compliant with medication, 18.3% were rated as intermittently compliant, and 59.1% were reported to be stable or improved.

Conclusions: The most compliant patients appeared to have the best treatment outcome and the highest risk to gain weight. Apart from the side effect of weight gain, patients appeared to tolerate olanzapine treatment quite well.

Educational interventions for the management of antipsychotic-related weight gain. APA, 2001.

Littrell KH, Petty RG, Hilligoss NM, Peabody CD, Johnson CG.

Background: Recent literature has focused on the weight gain liability associated with atypical antipsychotics. Recommendations are emerging which emphasize the importance of careful monitoring of weight in patients treated with these agents. Furthermore, preliminary data indicate that patients may benefit from interventions which include nutritional counseling and exercise programs to reduce the impact of antipsychotic-related weight gain.

Objective: To determine the effect of a modular educational program on weight gain among olanzapine treated patients.

Method: Twelve patients (6 M, 6F) with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder entered this 4-month study. All patients began olanzapine treatment at study entry. The patients were then randomized into an intervention group (3 M, 3 F) and a standard care group (3 M, 3 F). The intervention group participated in a one-hour, weekly class which used a modular educational program on nutrition and exercise. The patient's weights and BMI's were recorded monthly. Results: The mean change in weight of the intervention group was +1 lb (range -10.5. to 7.5 lbs), while the mean change in the standard of care group was +6.4 lbs (range -13 to +26 lbs). The mean change in BMI's of the intervention group and standard of care group was +0.3 (range -1.4 to +0.9) and =0.9 (range -2.6 to +3.5), respectively. Although there was not a statistically significant difference in BMIs (baseline to endpoint) in either group, subjective reports of personal comfort and self-image were notably different. Gender differences were noted in both the intervention group and the standard care group. At endpoint, males gained more weight than females in the intervention group (M=+8 lbs; F=-0.7 lbs) and the standard of care group (M=+13.7 lbs; F=-2.5 lbs).

Conclusions: This small, preliminary study suggests that an educational intervention may positively influence antipsychotic-induced weight gain as well as influence feelings of self-image. Larger, extended, controlled trials are needed to more fully understand the impact which educational interventions may have on preventing or limiting antipsychotic-induced weight gain.

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Healthy living: a novel weight control program for overweight and obese seriously and persistently mentally ill (SPMI) adults on atypical antipsychotics. APA, 2001.

Vreeland B, Menza M, Minsky S, Radler DR, Roemheld-Hamm B, Stern R, Touger-Decker R.

Background: Atypical antipsychotic agents have revolutionized treatment for individuals with serious mental illness. However, weight gain secondary to medication, and the complications associated with weight gain, have been receiving critical attention. There is little known about how to manage this problem.

Method: Thirty-one subjects on atypical antipsychotic medication for a minimum of 3 months, from two partial care programs participated in an intensive 12 week, multi-modal, weight control program that incorporated nutrition counseling, exercise, and behavioral interventions. Measures of BMI, weight, hunger level, exercise level, and knowledge of nutrition and exercise were compared from baseline to the end of the the study. Additionally, weight and BMI changes from 15 patients in a comparison, non-intervention, "treatment as usual" group were compared with pilot findings. All patient weight records from the partial care programs where the subjects attended were reviewed. If weight records were available during the same time frame as the study period, they underwent a retrospective chart analysis. In all, 15 patients were matched for weight collection time frame, age, BMI, diagnosis, and atypical medication. These 15 patients were included in the comparison group.

Results: Twenty-seven of the thirty-one subjects completed the intensive twelve-week weight control pilot study. Weight and BMI measures were significantly reduced. There was a mean weight loss of 5.9 pounds and a mean reduction in BMI of 0.96. Significant improvements in hunger level, exercise level, and knowledge of nutrition were also observed. The 15 patients in the non-intervention group had a mean weight gain of 6.4 pounds and a mean BMI increase of 1.2.

Conclusion: Individuals with schizophrenia and schizoaffective disorder are able to attend and benefit from an intensive weight control program. The Healthy Living program was able to affect exercise habits, hunger level, and knowledge of nutrition and exercise, which resulted in a significant reduction in weight and BMI. However, patients who do not receive weight intervention continue to gain weight. Professionals treating individuals who are on atypical antipsychotic medication should educate and encourage patients to engage in weight control activities.

Wirshing et al. J Clin Psych 1999;66(6):358-363

Pharmacologic Interventions

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Options for pharmacological management of obesity in patients treated with atypical antipsychotics. *Intl Clinical Psyc* 2002; 17(4):145-160

Werneke U, Taylor D, Sanders TAB

Obesity is associated with considerable morbidity and decreased life expectancy. Weight gain is a commonly encountered problem associated with antipsychotic treatment. We reviewed the literature regarding the mechanisms of weight gain in response to these agents and eight substances implicated as potential obesity prevention or treatment: orlistat, sibutramine, fluoxetine, topiramate, amantadine, nizatidine and cimetidine, and metformin. Weight gain in response to antipsychotic treatment may be mediated through serotonergic, dopaminergic, adrenergic, cholinergic, histaminergic and glutaminergic receptors. Sex hormone dysregulation and altered insulin sensitivity have also been implicated. Two compounds, orlistat and sibutramine, have been shown to help prevent weight gain following a hypocaloric diet, but orlistat requires compliance with a fat-reduced diet, and sibutramine is unsuitable for patients taking serotonergic agents. The weight reducing effect of fluoxetine, even in conjunction with a hypocaloric diet, is only transient. Topiramate, amantadine and metformin may have adverse side-effects potentially outweighing the weight reducing potential. The effectiveness of cimetidine and nizatidine remains unclear. The hazards of these agents in psychiatric population are discussed. It is concluded that the current evidence does not support the general use of pharmacological interventions for overweight patients treated with antipsychotic medication, although individually selected patients may benefit.

Nonpharmacologic and Pharmacologic Management of Weight Gain. *J Clin Psych* 1999;60 (21):31-36

Greenberg I, Chan S, Blackburn GL

Obesity increases the risk of several serious health problems, including heart disease, type II diabetes mellitus, hypertension and osteoarthritis. Patients taking certain psychotropic medications may gain a significant amount of weight (as much as a 5% increase in body weight within 1 to 2 months), placing them at risk for obesity. Body weight monitoring and prudent drug selection are the best approaches to preventing weight gain in patients taking psychotropic drugs. When weight gain (>5% of initial body weight) is unavoidable, intervention counseling should begin. Nonpharmacologic measures for managing weight gain include a balanced deficit diet of 1000 calories and higher, depending on the patient's weight; 30 to 60 minutes of physical activity daily; and behavioral training to restrain excess caloric intake. Each of these measures requires a considerable commitment on the part of the patient and works best with support from the physician and weight-loss support groups. Drug therapy for weight loss is available (at

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present, sibutramine is the only approved appetite suppressant in the United States); however, for most patients already being treated with a psychotropic agent, the risks (such as drug interactions, adverse events, compliance problems) of adding an antiobesity agent probably outweigh the benefits. Surgical intervention for obesity should be reserved for morbidly obese patients whose disease is intractable to medical therapy

Reboxetine

Attenuation of Olanzapine-Induced Weight Gain with Reboxetine in Patients with Schizophrenia: A Double-Blind, Placebo-Controlled Study. *Am J Psyc* 2003; 160:2:297-302

Poyurovsky M, Isaacs I, Fuchs C, Schneidman M, Faragian S, Weizman R, Weizman A

Objective: Since increased norepinephrine availability may account for the weight-reducing effect of appetite suppressants, the authors hypothesized that the addition of the selective norepinephrine reuptake inhibitor reboxetine may prevent or attenuate olanzapine-induced weight gain.

Method: Twenty-six patients hospitalized for first-episode DSM-IV schizophrenic disorder participated in the study. In addition to 6 weeks of treatment with olanzapine, 10 mg/day, patients were randomly allocated in a double-blind design to receive either reboxetine, 4mg/day, (N=13) or placebo (N=13).

Results: Ten patients in each group completed the 6-week trial. Patients given olanzapine and reboxetine demonstrated a significantly lower increase in body weight (mean=2.5 kg, SD=2.7) than those given olanzapine and placebo (mean=5.5 kg, SD=3.1). Significantly fewer patients in the olanzapine/reboxetine group (N=2 of 10) than in the olanzapine/placebo group (N=7 of 10) gained at least 7% of their initial weight, the cutoff for clinically significant weight gain. The addition of reboxetine to olanzapine treatment was safe and well tolerated by the patients. A between-group difference in the reduction of Hamilton depression scale scores was seen that favored the olanzapine/reboxetine group (mean difference=-31, SD=1.25).

Conclusions: The selective norepinephrine reuptake inhibitor reboxetine may reduce olanzapine-induced weight gain in schizophrenia patients, and activation of the adrenergic system may attenuate weight gain induced by atypical antipsychotic agents.

H2 Antagonists

Breier et al.

Amantadine

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Amantadine Treatment of Psychotropic-Induced Weight Gain in Children and Adolescents: Case Series *J Child and Adolescent Psychopharmacology*. 2002;12(3):249-257.

Gracious BL, Krysiak TE, Youngstrom EA

Gracious and colleagues have a publication describing eight boys and one girl ages 9-16 years old who were treated with an open trial of amantadine 100 mg po bid or tid for weight gain associated with antipsychotics, lithium, &/or sodium valproate. Side effects and body mass index (BMI) were determined at baseline and during amantadine treatment. A mean weight gain of 10.5 kg (19.9% mean increase in body weight) occurred from baseline to the beginning of amantadine treatment. Paired samples 2-tailed t-tests showed significant increases in group weight and BMI from baseline to the start of amantadine at the $p = 0.001$ level. Amantadine trial length averaged 14.5 weeks (range 4-33). A planned comparison using repeated measures (within-subjects) ANOVA for three separate time points demonstrated strong support for a "slowing weight gain" mechanism, $p = 0.001$ for weight gain and body. On average, there was no significant decrease between the beginning and end of the amantadine regimen in terms of weight: $F(1,8) = 0.31$, $p = .591$, or BMI: $F(1,8) = 1.20$, $p = 0.305$. There was no significant increase in weight during the amantadine trial according to paired t-tests. However, weight change was strongly correlated with the length of amantadine treatment, $r = -.63$, $p < 0.05$. Scatterplots (Figure 2) clearly revealed that one subject on clozapine was an outlier in the direction of continued significant weight gain (7.1 kg). The association between length of time taking amantadine and weight loss became even stronger when clozapine is excluded from the analysis: $r = .93$, $p < 0.001$. Weight loss was strongly correlated with length of amantadine treatment ($p = <0.05$). Weight loss of more than two kilograms was observed in 44% (4/9) of patients without reported side effects. One child experienced orthostasis and tachycardia with concomitant stimulant medication (relatively high dose Adderall). No other side effects or exacerbation of psychiatric symptoms were reported.

Of the patients who lost weight, average BMI decreased by 3.4 kg/m² over the mean course of 22.5 weeks. In addition to these objective results, several patients and their parents reported noticeable decreases in appetite as well as the frequency of eating and amount of food consumed while taking amantadine. One parent described the anorectic effect as short-lasting; if the child missed or took the second dose late in the day, an increase in appetite similar to that at baseline was experienced. No negative effects were noted on growth for any subjects.

Effect of Amantadine on Weight Gain During Olanzapine Treatment. *European Neuropsychopharmacology* 2001:000-000

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Floris M, Lejeune J, Deberdt W

Patients treated with olanzapine may gain weight, especially in the first months of therapy. Amantadine (100-300 mg/day) was started in 12 patients having a mean weight gain of 7.3 kg during olanzapine treatment. The patients' weight stabilised and over 3-6 months they lost an average of 3.5 kg. No clinical deterioration occurred and no adverse effects were reported. These observations merit confirmation in randomized, controlled trials.

Sibutramine

Long-Term Weight Loss with Sibutramine A Randomized Controlled Trial. *JAMA* 2001; 286(11): 1331-1339

Wirth A, Krause J

Context: Treatment of obesity requires long-term therapy, which can be hampered by difficulties in achieving patient compliance. The effectiveness of sibutramine hydrochloride in treating obesity has been shown in randomized controlled trials.

Objective: To compare the effectiveness of 2 distinct sibutramine regimens with each other and with placebo for weight reduction among obese persons.

Design: Randomized, double-blind, parallel-group placebo-controlled trial from April 1997 to September 1998.

Setting: One hundred eight private practices and 3 outpatient departments of university hospitals in Germany.

Patients: A total of 1102 obese adults (body mass index, 30-40kg/m²) entered the 4-week open-label run-in period with 15 mg/d of sibutramine, 1001 of whom had weight loss of at least 2% or 2 kg were randomized into the 44-week randomized treatment period.

Interventions: Patients were randomly assigned to receive 15 mg/d of sibutramine continuously throughout weeks 1-48 (n = 405); 15 mg/d of sibutramine intermittently during weeks 1-12, 19-30, and 37-48, with placebo during all other weeks (n = 395); or placebo for weeks 5-48 (n = 201).

Main Outcome Measure: Weight loss during the randomized treatment period, compared among all 3 groups.

Results: Mean weight loss in the intention-to-treat population during the 44-week randomized treatment period was 3.8 kg (4.0%) in patients receiving continuous therapy (95% confidence interval [CI], -4.42 to -3.20 kg) and was 3.3 kg (3.5%) in patients receiving intermittent therapy (95% CI, -3.96 to -2.66 kg), vs a mean weight gain of 0.2 kg (0.2%) (95% CI, -0.60 to 0.94 kg) in patients receiving placebo. Therapeutic equivalence of the 2 active treatments could be shown. Although there was a greater weight loss in the continuous than in the intermittent group, this difference was nonsignificant (P=.28) and the 95% CIs were within the predefined range of therapeutic equivalence-0 ± 1.5 kg (-1.37 to 0.28 for the intent-to-treat population). Overall weight loss during the 48-week period 7.9 kg and 7.8 kg in the continuous and intermittent

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groups, respectively, but was 3.8 kg in the sibutramine run-in placebo group. Waist circumference reduction, triglyceride levels, and high-density lipoprotein cholesterol concentrations were also positively influenced by sibutramine treatment. Systolic and diastolic blood pressures were stable across all 3 groups. Overall, adverse events occurred at similar frequencies across all treatment groups, but the proportion was lowest in the group receiving intermittent therapy.

Conclusions: Sibutramine, administered for 48 weeks to a typically obese population, results in clinically relevant weight loss compared with placebo. Regarding effectiveness, continuous and intermittent sibutramine therapies are equivalent and the safety profiles for both treatments are comparable.

Topiramate

Topiramate Produced Weight Loss Following Olanzapine-Induced Weight Gain in Schizophrenia. *J. Clin Psych* 2002;63(11)1045

Levy E, Margolese HC, Chouinard G,
Letters to the Editor – Case Report

Weight Loss with Toprimate. *Ann Pharmacotherapy*. 2001;35:1141-1142

Littrell KH
Letter to the Editor – Case Report

Metformin

Metformin for Weight Loss in Pediatric Patients Taking Psychotropic Drugs. *Am J Psyc* 2002;159 655-657

Morrison JA, Cottingham EM, Barton BA

Objective: Metformin was assessed as a treatment for weight gain in children taking olanzapine, risperidone, quetiapine, or valproate.

Method: The subjects were 19 patients aged 10-18 years; 15 were white and four were black, and there were 12 boys and seven girls. In a 12-week open-label study, each patient received metformin, 500 mg t.i.d. Changes in weight and body mass index were evaluated by using repeated measures analysis of variance.

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Results: Of the 19 patients, 15 lost weight, three gained 1.6 kg or less, and one had no change. The mean changes in weight and body mass index at 12 weeks were highly significant.

Conclusions: Metformin merits further study as a treatment for weight gain in patients taking psychotropic medications.

Adderall, the atypicals, and weight gain [4]. *J.Am.Acad.Child Adolesc.Psychiatry* 40(6):620, 2001

J. P. Horrigan, L. J. Barnhill, and R. R. Kohli.

Treatment of weight-gain with fluoxetine in olanzapine-treated schizophrenic outpatients. *Schizophrenia Research* 49(1-2):236, 2001.

Fluoxetine

J. Lauriello, J. Bustillo, R. Hammond, M. Bogenschutz, and S. J. Keith.

Olanzapine (OLZ) has become a first line treatment for schizophrenia. Although its side-effect profile is quite favorable it can induce significantly more weight-gain than many other anti-psychotics. Fluoxetine (FLX), a serotonin reuptake inhibitor, is an effective anorectic agent during the first few months of its use. Since OLZ-induced weight-gain may be mediated by its serotonergic blockade; FLX may be an effective anorectic agent in OLZ-treated patients. As the maximum weight-gain with OLZ and weight-loss with FLX occur between 8 and 12 weeks with both treatments, early addition of FLX may prevent OLZ-induced weight gain. The primary goal of this study evaluated the efficacy of high-dose FLX (60mg) as a weight reducing agent for patients with early weight-pain with OLZ. Persons with schizophrenia (N = 53) initiated open-label OLZ and weighed weekly. N = 31 met predetermined criteria of sustained 3% weight-gain during the initial 1-2 mos of OLZ treatment and were randomized to double-blind FLX or placebo for 4 mos. N = 10 did not gain the weight and N = 12 terminated prior to randomization. Outcome measures to be presented are weight, appetite and body-fat composition. We also explore the effects of OLZ treatment and addition of FLX on cigarette smoking parameters

Phenylpropanolamine

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Phenylpropanolamine Appears Not to Promote Weight Loss in Patients with Schizophrenia Who Have Gained Weight During Clozapine Treatment. *J Clin Psych* 2002;63(4):345-347

Borovicka MC, Fuller MA, Konicki PE, White JC, Steele VM, Jaskiw GE

Ongoing Clinical Trials

Amantadine (HGJN)

Primary Objective

The primary objective of this study is to assess the effect of sixteen weeks of olanzapine plus amantadine compared with olanzapine plus placebo in treating olanzapine-associated weight gain as measured by the difference between groups in mean change from baseline to endpoint in total body weight.

Summary of Study Design

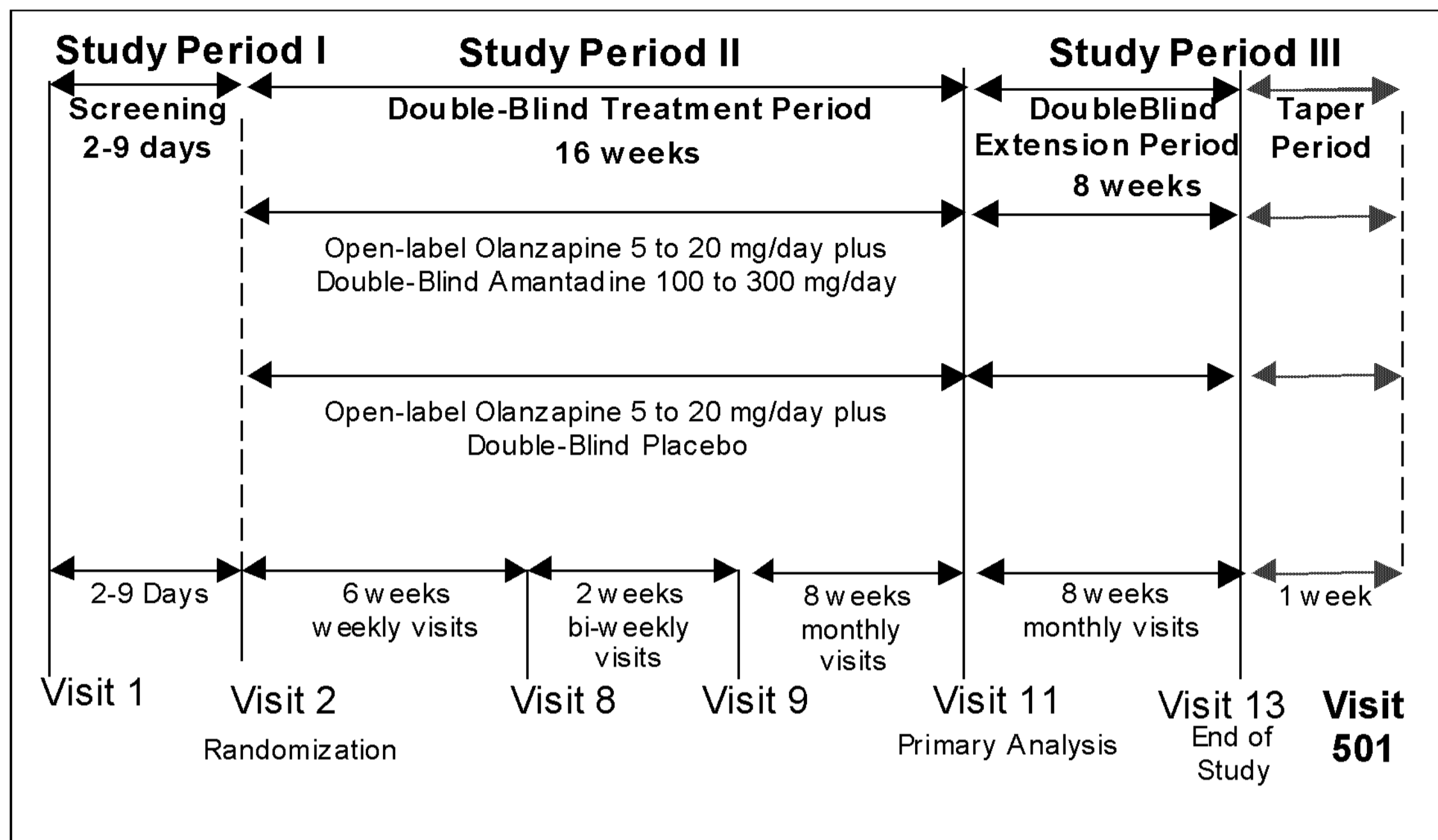
This is a randomized, double-blind, parallel study of both inpatients and outpatients meeting diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and who are currently being treated with olanzapine in a dose range between 5 to 20 mg/day. Approximately 145 subjects will be entered in order to randomize approximately 130 subjects to study medication (approximately 65 subjects to amantadine 100 to 300 mg/day, and 65 subjects to placebo).

After the screening phase of Study Period I, subjects who meet enrollment criteria will be randomized to Study Period II. Randomization will be in a 1:1 ratio into two treatment groups: olanzapine 5 to 20 mg/day in combination with amantadine 100 to 300 mg/day or olanzapine 5 to 20 mg/day and placebo. At all visits except Visit 1, all subjects will receive standardized nutritional counseling. Specific guidelines for nutritional counseling will be provided by the sponsor at the time of study start-up and training.

The study design is illustrated below:

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Sibutramine (HGJJ)

Primary Objective

The primary objective of this study is to assess the efficacy of 16 weeks of olanzapine plus sibutramine compared with olanzapine plus placebo in the treatment of olanzapine-associated weight gain as measured by the difference between groups in total body weight.

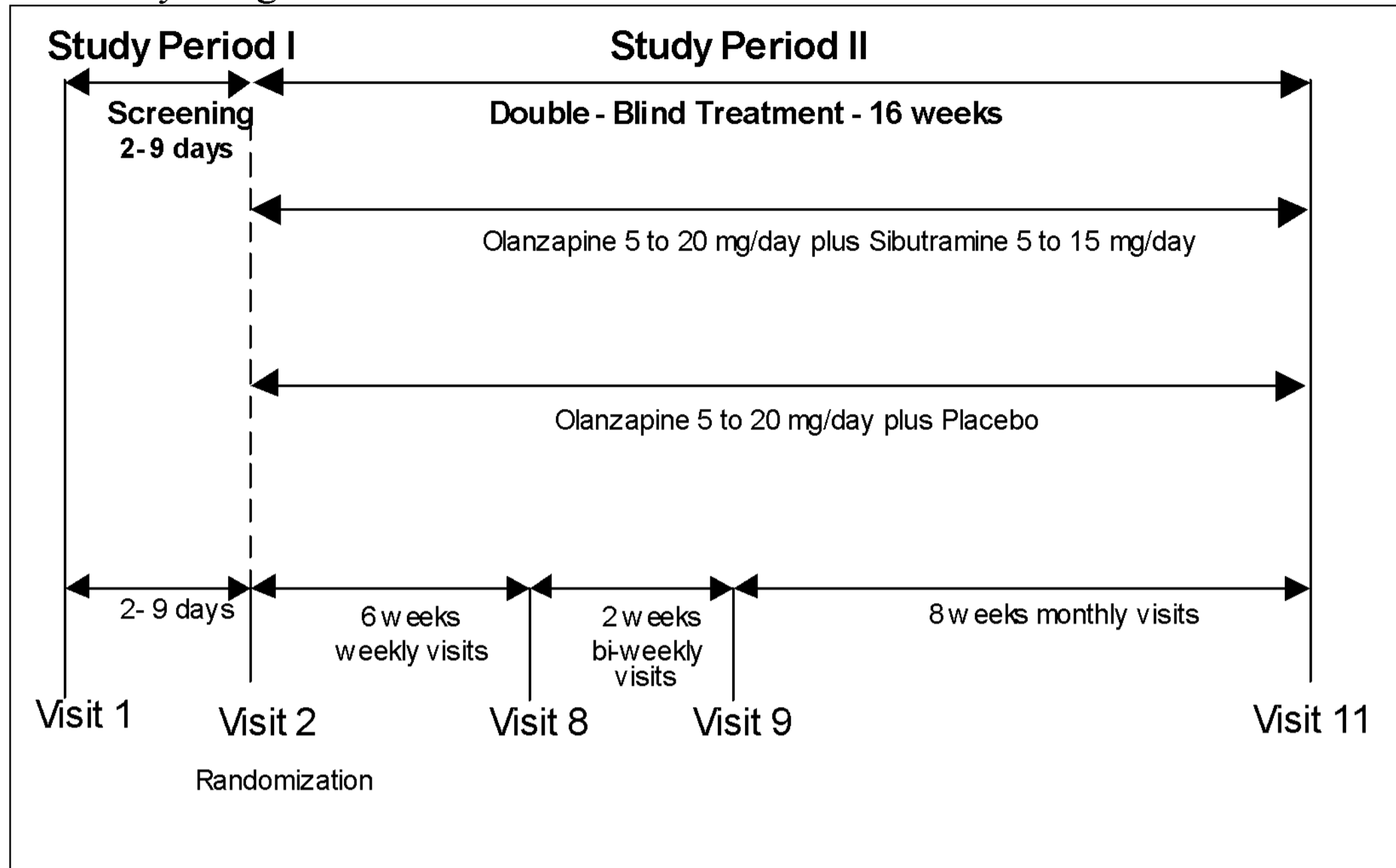
Summary of Study Design

This is a randomized, double-blind, parallel study of both inpatients and outpatients meeting diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Approximately 170 subjects will be entered in order to randomize approximately 150 subjects to study medication (approximately 75 subjects to sibutramine 5 to 15 mg/day, and 75 subjects to placebo). After the screening phase of Study Period I, subjects who meet enrollment criteria will be randomized to Study Period II. Randomization will be in a 1:1 ratio into two treatment groups: olanzapine 5 to 20 mg/day in combination with sibutramine 5 to 15 mg/day or olanzapine 5 to 20 mg/day and placebo. At all visits except Visit 1, all subjects will receive standardized nutritional counseling. Specific guidelines for nutritional counseling will be provided by the sponsor at the time of study start-up and training. Subjects in both therapy groups should be strongly encouraged to maintain their usual level of physical activity. Subjects should be discouraged from significantly changing their level of activity during the study.

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The study design is illustrated below:



Topiramate (Stanley Funded Trial: Conducted at the Pediatric Psychopharmacology Unit at Massachusetts General Hospital)

Primary Objective:

The primary objective of this study is to assess weight as the main outcome measure in youth treated with olanzapine plus topiramate.

Study Design:

This is open-label prospective study in patients meeting diagnostic criteria for manic, hypomanic or mixed episode associated with bipolar I or II disorder as defined by the DSM-IV and based on clinical assessment confirmed by structured diagnostic interview using the KSADS. Approximately 25 children & adolescents between the ages of 5 to 18 will be enrolled.

There will be two main groups. Subjects already on olanzapine therapy will be coadministered topiramate. Subjects who have not received treatment with olanzapine will be administered both olanzapine plus topiramate.

DNA Banking Study for Weight Gain (HGJL)

Primary Objective

The primary objective of this study is to collect DNA samples from individuals that have been diagnosed with schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorders not otherwise specified. The DNA samples will be stored for future research to identify genetic polymorphisms (also known as allelic variants or

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genetic markers) that are associated with schizophrenia and/or with patients' response to olanzapine. This future research will be used to delineate vulnerability markers for schizophrenia, enhance the understanding of olanzapine response and side effects, and develop new targets for future antipsychotic drug development

Summary of Study Design

Subjects with a DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective disorder, or psychotic disorders not otherwise specified, who have been treated with olanzapine for at least six months are eligible to participate in this study. This study is designed to collect DNA and hemoglobin A_{1c} samples from patients for future genetic research.

A Cross Sectional Comparison of Fasting Triglyceride Levels in Patients with Schizophrenic Disorders Treated Chronically with Olanzapine, Risperidone or Haloperidol (HGJX)

Primary Objective

The primary objective of this study is to determine whether there is a detectable difference in mean fasting triglyceride levels between outpatients with schizophrenia or schizoaffective disorder taking olanzapine or risperidone for >1 year.

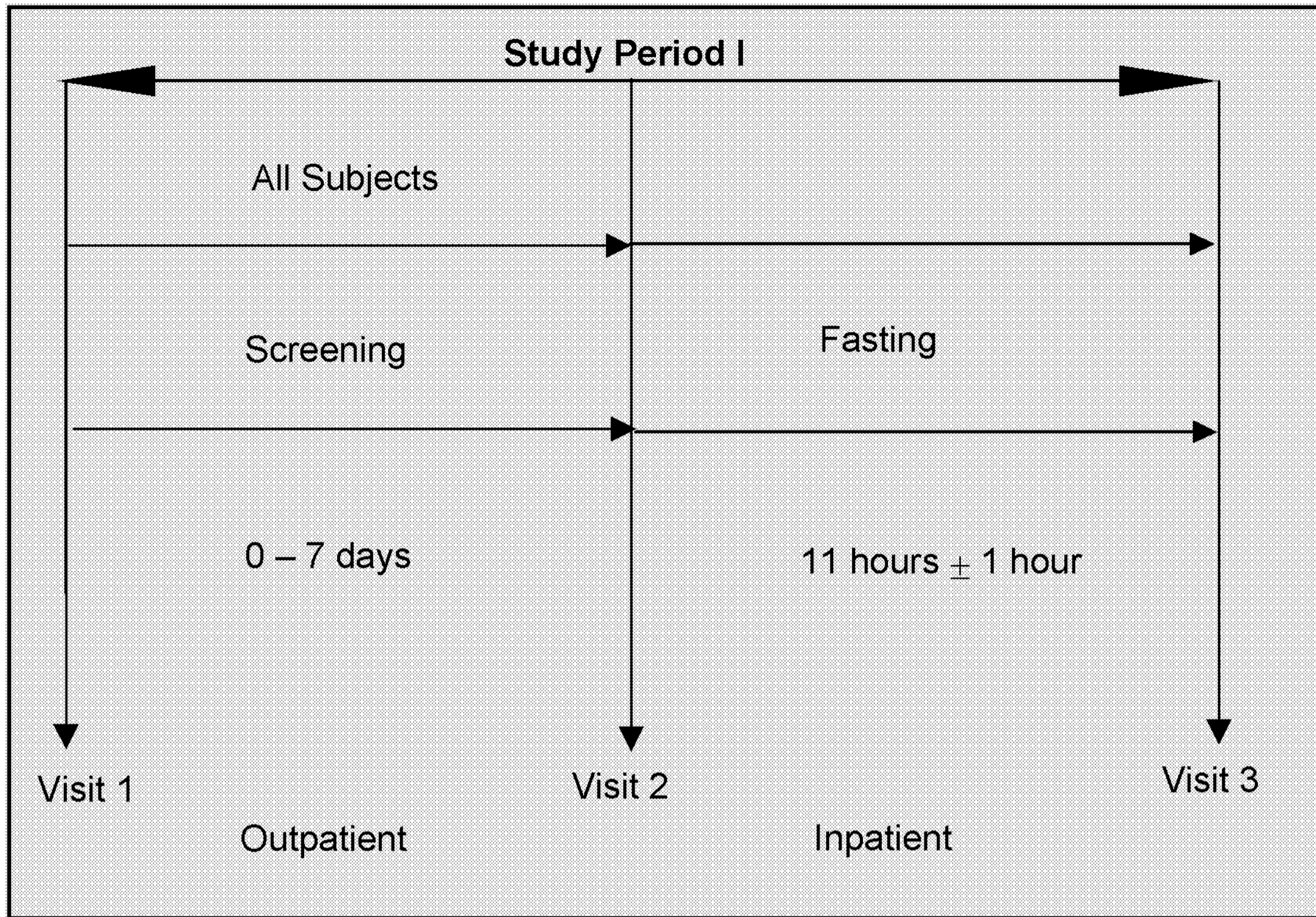
Summary of Study Design

This study compares a cohort of outpatients meeting diagnostic criteria for schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Subjects must be treated with olanzapine, risperidone, or typical antipsychotics as their only antipsychotic therapy at study entry. Approximately 240 subjects will be enrolled, with 80 subjects in the olanzapine and risperidone treatment groups and 60 subjects in the typical antipsychotics treatment group. Within each treatment group, subjects will be divided equally by gender. Subsequent stratification will be by BMI. Within each gender group, subjects will be allocated in approximately equal proportions among three BMI ranges, 21.0 – 26.0 kg/m², 26.1– 30.0 kg/m², and 30.1 – 35.0 kg/m².

The study design is illustrated in below:

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This is Mike Ackermann with a message to the field sales organization. I look forward to meeting with you all in Atlanta next week.

As we prepare for the upcoming centralized district meetings next week, there is new information happening in our marketplace that we wanted to share with you. We really have three things to feel great about:

1. redacted
2. We are very hopeful as an organization that we will hear about an approval for Zyprexa's use in Bipolar Maintenance any minute.
3. We are communicating with our customers proactively around medical data that impact patient safety because patient safety and improved quality of life is extremely important to Lilly.

redacted

Beginning this Thursday, January 15th, we will share data with clinicians regarding mortality data elderly patients with dementia to ensure they have the information they need to treat this fragile elderly patient population. The risk factors that predisposed these patients to increased mortality include age greater than 80 years old, sedation, concomitant benzodiazepine use, and the presence of pulmonary conditions. It is important to note that Zyprexa is not approved for use in this elderly patient population.

Now, this information was based on the same clinical trials that produced that data regarding cerebrovascular adverse event warning. The FDA has been made aware of this data but has not acted on it as of now. Although this information is not in our label, we feel it important to communicate this information to our customers **right away** in the best interest of the safety of patients.

Today, January 14th, you will receive 2 pieces of information pertaining to mortality in elderly patients with dementia:

1. A KM document that provides background information and clarity on how we are going to talk about this with customers between now and next week.
2. A health care practitioner letter will be provided to you regarding CVAE and mortality. Please print off copies and provide it to customers who have questions pertaining to either CVAE or mortality in elderly patients with dementia, per the instructions on KM that will be posted today.

We will discuss this information in greater detail and provide additional direction during the centralized district meetings next week in Atlanta.

As always, thank you for all that you do!

DRAFT FOR BUSINESS PLANNING PURPOSES ONLY!!!!

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