Mechanisms of Antipsychotic-Induced Weight Gain

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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.

(J Clin Psychiatry 2001;62[suppl 23]:23–29)

Most American adults are overweight, with a body mass index (BMI) of more than 25 kg/m^2.[1] During the past 2 decades, there have been epidemic increases in the prevalence of obesity (BMI ≥ 30 kg/m^2), which is currently estimated at approximately 18%.[2]

Computed estimates of BMI among persons with schizophrenia and bipolar disorder exceed these general population estimates.[3,4] Of particular concern is the fact that the excess adipose tissue described in some psychiatric populations is often centrally distributed (i.e., this abdominal adipose tissue is reflected in the waist-to-hip ratio).[4] Central adipose tissue exhibits higher metabolic activity than peripheral tissue. These regional differences in metabolic activity promote elevated free fatty acid concentrations in the portal blood, which presage excess cardiac morbidity. The estimated waist-to-hip ratio in some psychiatric populations may be higher than in the general population. Importantly, these elevated estimates may be associated with exposure to antipsychotic drugs.[4–6]

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Presented at the symposium "Effects of Drugs on Body Weight and Glucose Regulation," which was held December 16, 2000, at the New York University School of Medicine, New York, and supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals, L.P.

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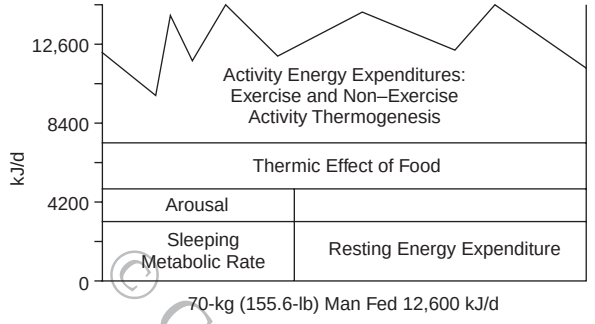
The standardized mortality ratio for persons with schizophrenia is significantly higher than in the general population.[7] The increased standardized mortality ratio reflects higher rates of both unnatural and natural death. Most persons with schizophrenia die of natural causes. Some of these natural causes are well-known obesity-related diseases (e.g., cardiovascular, respiratory, gastrointestinal, and genitourinary disorders).[7] The high prevalence of obesity, smoking, and alcohol abuse in persons with schizophrenia contributes to this increased risk.[7]

Weight gain induced by conventional antipsychotics was described soon after the introduction of these drugs.[8,9] Doss[10] retrospectively described differential weight gain liability in 78 randomly assigned patients after 36 weeks of treatment with conventional antipsychotics. The weight gain induced by conventional antipsychotics is comparable for oral and depot formulations.[11,12]

Several lines of evidence converge and suggest that some novel antipsychotics impart more substantial weight gain after short-term and long-term administration when compared with the older conventional medications.[3,13–15] For example, a weight gain liability is clearly established with treatment with clozapine.[15–18] Hummer and others[19] prospectively followed 81 ambulatory patients with refractory psychotic disorders who were treated with clozapine. After 1 year, 36% of patients had gained more than 10% of their initial body weight. The average weight gain for all clozapine-treated patients was 3.5 kg (7.8 lb).

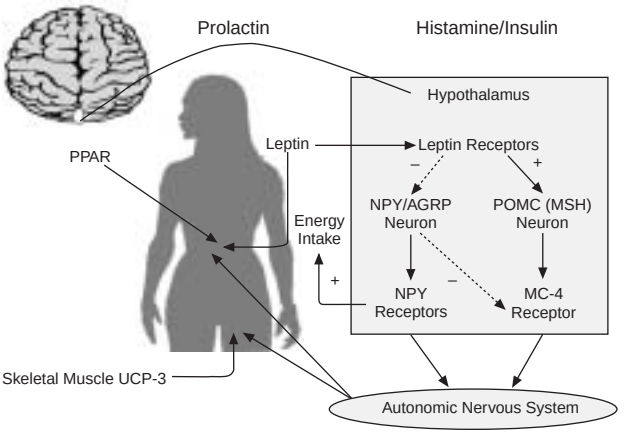
Allison and others[3] meta-analyzed 81 treatment trials (18 including comparison with placebo) that were at least 10 weeks in duration and compared mean weight gain among patients using conventional antipsychotics and

Figure 1. Daily Energy Expenditure[a]



[a]Reprinted, with permission, from Ravussin and Bogardus.[36]

Figure 2. Human Body Weight Regulation[a]



[a]Reprinted, with permission, from Yanovski and Yanovski.[1]
Abbreviations: AGRP = agouti-related peptide, MC-4 = melanocortin-4, MSH = α melanocyte-stimulating hormone, NPY = neuropeptide Y, POMC = pro-opiomelanocortin, PPAR = peroxisome proliferator-activated receptor, UCP-3 = uncoupling protein 3.

atypical antipsychotics approved for use or under investigation. Mean weight gain with several atypical antipsychotics was greater than that with conventional antipsychotics. Interestingly, the atypical antipsychotic molindone was associated with a 0.39-kg (0.87-lb) weight reduction. The weight-loss and anorexiant properties of molindone have been described previously.[20–22]

Wirshing and others[23] retrospectively assessed weight gain in 92 male patients with schizophrenia enrolled in 8 antipsychotic efficacy studies conducted during a period of 6 years. Treatment with olanzapine and clozapine imparted the most weight gain, risperidone imparted an intermediate amount of weight gain, and sertindole induced less weight gain than haloperidol. The investigators determined that the weight gain plateaued at 20 weeks with olanzapine and clozapine versus 10 weeks with risperidone and sertindole. An inverse relationship between baseline BMI and weight gain was not seen. These data on weight gain converge with results from short-term, parallel-group design studies in patients with schizophrenia and bipolar disorder.[24–27] It is hypothesized that the disparate receptor pharmacology of the available antipsychotics may bestow differential weight gain liability.[3,27]

Conventional antipsychotics and atypical antipsychotics exhibit differential weight gain liability. Clozapine appears to have the greatest weight gain potential, and ziprasidone appears to have the least.[3,27] The amount of weight gain associated with these agents may increase the risk for weight-related medical comorbidity.[28]

A diverse constellation of sociodemographic and clinical characteristics (e.g., age, duration of treatment, appetite stimulation, baseline BMI) has been associated with antipsychotic-induced weight gain.[13,29,30] Elucidating these variables may assist the clinician in identifying a priori those patients at higher risk for weight gain and may shed light on possible pathogenic mechanisms. Emerging data suggest that novel antipsychotic–induced weight gain may predispose and portend risk for glucose-insulin dysregulation and lipid milieu abnormalities.[23,31–34] Of further concern, persons receiving antipsychotic medications are only about 25% as likely to receive lipid-lowering treatments compared with the general population.[35]

MECHANISMS OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

Body weight is dependent on the balance between energy intake and energy expenditure. Energy expenditure is further partitioned into resting energy expenditure and activity-related expenditure (Figure 1). When a person is in positive energy balance, weight is gained. Heritability studies suggest that up to 70% of body weight is genetically mediated, although environmental factors also play critical roles.[1,2] Neurobiological mechanisms that regulate energy intake may mediate their effects centrally (e.g., through increased appetite) or peripherally (e.g., through taste aversion). Most of the existing data describing mechanisms of antipsychotic-induced weight gain have emphasized changes in putative neurocircuits hypothesized to participate in increased energy intake (e.g., increased appetite).

Monoamines

The lateral hypothalamus is a critical anatomical site for weight regulation (Figure 2). Monoamine activity at the level of the hypothalamus is the most studied paradigm in antipsychotic-induced weight gain. For example, infusion of catecholamines into the lateral hypothalamus will reduce rat feeding behavior, an effect that is reversed with the infusion of various conventional antipsychotics.[37] It is hypothesized that putative anorectic agents (e.g., sibutramine) reduce weight by increasing norepinephrine and serotonin availability at the level of the hypothalamus.[38]

Dopamine robustly decreases feeding behavior in animal models. Dopamine agonists may effectively reduce weight gain, and, in open-label studies, amantadine has been shown to counteract olanzapine-induced weight gain.[39]

Serotonin is a well-known satiety factor. Absolute or relative increases in serotonin at diverse serotonin receptors have been shown to decrease feeding behavior, while antagonism of serotonin stimulates increased energy intake.[40,41] It remains to be elucidated which serotonin receptors are critical for feeding behavior.

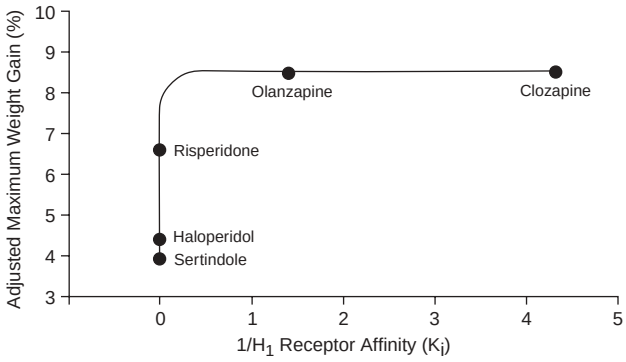
5-HT_{2C} is a candidate receptor for psychotropic-induced weight gain. Tecott et al.[42] bred a strain of mutant mice with functional 5-HT_{2C} receptors knocked out. These mice became obese later in life, developed laboratory evidence of the obesity syndrome (i.e., increased insulin and leptin), and had a propensity for seizures. Vickers et al.[43] compared the effects of a 14-day subcutaneous infusion of 5-HT_{2C} receptor agonists and the 5-HT releasing agent and reuptake inhibitor dexfenfluramine on food and water intake and weight gain in rats. *m*-Chlorophenylpiperazine (a metabolite of nefazodone) and fenfluramine are nonspecific agonists for the 5-HT_{2C} receptor. Interestingly, these experimental rats did not exhibit predictable decreased feeding behavior after administration of dexfenfluramine or *m*-chlorophenylpiperazine. Dexfenfluramine, the more active enantiomer of the serotonin release/reuptake blocker fenfluramine, has previously been demonstrated to reduce weight gain with depot conventional antipsychotics.[44]

5-HT_{2C} receptors are antagonized by various agents that produce weight gain (e.g., tricyclic antidepressants, novel antipsychotics) and are minimally affected by agents such as haloperidol that produce minimal weight gain. However, a recent analysis failed to correlate weight gain from clozapine, olanzapine, risperidone, haloperidol, and sertindole with 5-HT_{2C} affinity.[23] Another line of research evidence militating against this candidate receptor is the observation that ziprasidone (which imparts minimal weight gain) exhibits high in vivo affinity for the 5-HT_{2C} receptor.

Histamine

Histamine signaling in the hypothalamus may offer an antiobesity effect. Histamine-receptor populations (H_1, H_2, H_3) are involved in mediating drinking behavior in rats.[45] Agents with high affinity for histamine receptors (i.e., low-potency conventional antipsychotics, mirtazapine, and some over-the-counter drugs) have well-established effects of weight gain.[46] Wirshing et al.[23] found a robust correlation between novel antipsychotic affinity for the histamine receptor and antipsychotic-induced weight gain (Figure 3). It is postulated that histamine antagonism stimulates energy intake centrally by increasing appetite, with a resultant positive energy balance. Cimetidine, an H_2 antagonist, appears to reduce appetite and weight in overweight subjects[47] and to improve glucose control in patients with type 2 diabetes mellitus.

Figure 3. Weight Gain as a Function of H_1 Affinity[a]



[a]Reprinted, with permission, from Wirshing et al.[23]

Hormones

Weight dysregulation may disrupt both the reproductive and nonreproductive hormonal milieu. Polycystic ovarian disease, reported in female patients with epilepsy and bipolar disorder who are treated with valproic acid, is a metabolic and reproductive disorder in which excess weight is a common feature.[48,49]

Obesity is associated with elevated levels of androgen in females and decreased levels in males. These changes in hormonal levels may reduce the sensitivity of satiety neurons in the lateral hypothalamus. Elevated prolactin levels, associated with treatment with conventional antipsychotics and risperidone, may promote weight gain directly by decreasing insulin sensitivity or indirectly by further disrupting the androgen and estrogen ratios. This is currently under investigation.[50,51]

Other Neurotransmitters

Agents that positively modulate γ-aminobutyric acid (GABA) neurotransmission (e.g., divalproex sodium) have been reported to promote weight gain.[52–54] Agents that decrease glutamatergic function (e.g., lamotrigine, topiramate) impart minimal weight gain or induce weight loss.[13,48] For example, agonists at the glutamate *N*-methyl-D-aspartate (NMDA) receptor (e.g., glycine) have been noted to stimulate feeding behavior in rats when infused in the hypothalamus.[55] Some novel antipsychotics are hypothesized to enhance GABA function, which may alter the GABA-glutamate balance and thus foster weight gain.[51]

Neuropeptides and Cytokines

A disparate assortment of neuropeptides are noted to affect energy balance both centrally and peripherally.

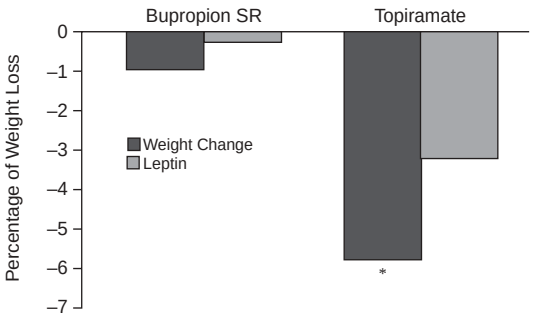
There has been a dearth of data describing the effects of novel antipsychotics on many of these proteins, which include insulin, neuropeptide Y, tumor necrosis factor α (TNF-α), pro-opiomelanocortin (and its cleavage products α melanocyte-stimulating hormone and adrenocorticotropic hormone), and agouti peptides.

Clozapine increases the levels of helical cytokines such as TNF-α, interleukin 2, and leptin.[56] The weight gain induced by this atypical antipsychotic may be related to these increases.

TNF-α is hypothesized to play a critical role in various metabolic, immune, and appetite behaviors[57] and affects glucose, protein, and lipid metabolism.[58–60] Circulating levels of TNF-α and its soluble receptors are increased in obese subjects compared with lean controls, and decrements in the levels are seen with weight loss.[61,62] Patients gaining weight with treatment with amitriptyline or nortriptyline exhibit elevations in the soluble TNF-α receptor patterns that preceded the increase in BMI.[18,59–65] Changes in receptor levels are hypothesized to be a sensitive marker for TNF-α activity, thus implicating TNF-α systems as critical to tricyclic antidepressant–induced weight gain. TNF-α has been shown to increase the release of leptin from adipocytes[60,64] and as such is a rational peptide to further investigate in subsequent antipsychotic-induced weight gain mechanistic studies. These studies are currently underway.[66]

Leptin, a product of the obesity gene, is one of several genes that participate in weight regulation. Inactivity mutations at the gene coding for the protein product leptin or its receptor have been shown to result in the obesity phenotype.[1] Exogenous administration of recombinant human leptin is under investigation as an adjunctive treatment for obesity.[1] The precise role of leptin requires further delineation; it is believed to act at the level of the hypothalamus and regulate energy expenditure, the neuroendocrine axis, and appetite. Leptin levels exhibit circadian variation and sexual dimorphism (levels are higher in females than in males at similar BMI) and correlate with adipose tissue and BMI levels.[13,31] Bromel et al.[63] described increased leptin levels in clozapine-treated persons (N = 12) with psychotic disorders. Significant increases in leptin levels were observed as early as week 2. This rapid increase and reversal after discontinuation of clozapine implicated direct or indirect effects of clozapine on leptin levels. Kraus et al.[67] noted increases in leptin levels commensurate with increases in body weight and BMI in a sample of inpatients with schizophrenia who were being treated with clozapine and olanzapine. The increased circulating plasma leptin levels would be predicted given the increase in adipose tissue with both olanzapine and clozapine; however, reduced feedback sensitivity of the central nervous system (CNS) to leptin cannot be ruled out. Others have speculated that weight gain with olanzapine may result from desensitization of the CNS to the peripheral leptin signal.[31]

Figure 4. Percentage Change in Weight After 8 Weeks of Treatment With Topiramate or Bupropion SR[a]



[a]Reprinted, with permission, from McIntyre et al.[71] Absolute weight loss was 1.2 kg (2.7 lb) for bupropion SR and 5.8 kg (12.9 lb) for topiramate. Abbreviation: SR = sustained release.
*p = .019.

Uncoupling Proteins

Uncoupling proteins (UCPs) regulate energy expenditure through peripheral mechanisms. There is tissue selectivity for UCP-1 through -3, with UCP-1 found in brown adipose tissue; UCP-2 ubiquitous in its distribution, with a preponderance in white adipose tissue; and UCP-3 found in skeletal muscle. UCPs reroute proteins, the products of oxidative phosphorylation, either to storage or to be dissipated as heat.[1] Although the effect of novel antipsychotics on UCPs has not been delineated, other neurotherapeutic molecules have been shown to affect UCP transcription.[68–70]

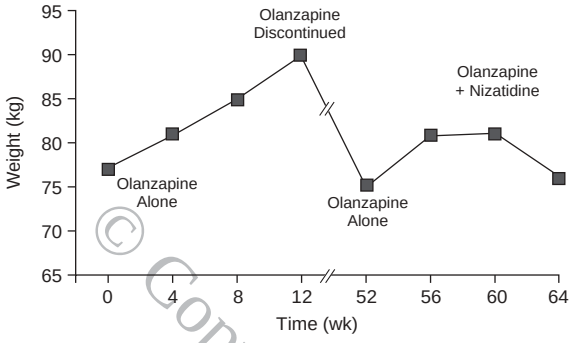
Peroxisome Proliferator-Activated Receptors

Energy storage in adipose tissue is in part mediated by receptors on preadipocytes that are called peroxisome proliferator-activated receptors (PPARs). These receptors promote the conversion of a non–lipid-storing preadipocyte to an adipocyte. Antipsychotic medication is associated with increased fat mass[4]; however, it is not known if novel antipsychotics affect these PPAR receptors.

COUNTERACTING ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

A variety of different techniques have been used to attempt to counteract antipsychotic-induced weight gain.[13] Dietary counseling and behavioral modification are integral components of any successful weight loss program.[1] Topiramate is an anticonvulsant agent synthesized from D-fructose. It also contains a sulfamate moiety essential for pharmacologic activity. It is approved for the treatment of seizure disorders and is under investigation in several therapeutic areas, including migraine, benign essential tremors, neuropathic pain, and bipolar disorder (Figure 4).[13,53,71]

Figure 5. Nizatidine, an H_2 Antagonist, May Control Olanzapine-Associated Weight Gain in Patients With Schizophrenia[a]



[a]Reprinted, with permission, from Sacchetti et al.[74]

Administration of topiramate has been shown to result in substantial weight loss in different patient populations.[72] This effect is likely mediated by several different mechanisms. For example, in rats, topiramate significantly reduces food intake and increases metabolic rate.[53,73] Centrally, topiramate reduces neuropeptide Y1 and Y5 receptors (receptors for the orexigenic neuropeptide Y). Peripherally, topiramate reduces leptin messenger RNA (mRNA) transcription in adipose tissue and significantly increases mRNA for UCP-2 in white adipose tissue. These central and peripheral effects are also noted with dexfenfluramine, and these molecular effects are hypothesized to result in increased thermogenesis and increased energy expenditure. It is not reliably known if novel antipsychotics negatively modulate the transcription of some of neuropeptide Y in predisposed individuals.

Histamine antagonists have also been utilized to minimize antipsychotic-induced weight gain. For example, nizatidine, an H_2 antagonist, has been demonstrated to attenuate overall olanzapine-induced weight gain (Figure 5).[74] We currently do not have an effective mechanistically based treatment for antipsychotic-induced weight gain. Some have observed improved therapeutic outcomes in persons who exhibit antipsychotic-induced weight gain.[13] Delineating the underlying mechanisms of antipsychotic-induced weight gain may promote novel approaches and further illuminate understandings of antipsychotic-induced weight gain and therapeutic activity.

CONCLUSION

This review of potential mechanisms of antipsychotic-induced weight gain is against a background of several other variables that may be associated with weight gain. These include a host of illness variables (e.g., inactivity, negative symptoms, poor access to exercise venues, and socioeconomic status) and increased exposure to obesity-promoting environments.[1]

The weight gain noted with many of the new atypical antipsychotics exceeds that imparted by the older conventional antipsychotics. Persons with schizophrenia appear to be more overweight than the general population. This excess weight may be overrepresented in the abdominal compartment and is associated with exposure to antipsychotic drugs. Novel antipsychotic–induced weight gain adds further risk for obesity-related morbidity in this already at-risk population.

The mechanisms of novel antipsychotic–induced weight gain clearly require further delineation. Weight gain in the general population is a multifactorial phenotype. Most data suggest that, by modulating central mechanisms, novel antipsychotics increase energy balance by increasing appetite. There is a paucity of data describing the peripheral (i.e., energy expenditure) mechanisms. Delineating the mechanisms of weight gain may further refine mechanistic models of antipsychotic action and guide future treatment approaches.

Drug names: amantadine (Symmetrel and others), amitriptyline (Elavil and others), bupropion (Wellbutrin), clozapine (Clozaril and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lamotrigine (Lamictal), mirtazapine (Remeron), molindone (Moban), nefazodone (Serzone), nizatidine (Axid), nortriptyline (Pamelor and others), olanzapine (Zyprexa), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax), valproic acid (Depakene and others), ziprasidone (Geodon).

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

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