

The Pharmacology of Weight Gain With Antipsychotics

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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. 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.

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Recent data strongly suggest that many antipsychotic drugs, particularly some newer or "atypical" antipsychotics, are associated with weight gain.¹ Since atypical antipsychotics have broad pharmacologic profiles, it is likely that multiple neurotransmitter systems and receptors affected by antipsychotics mediate weight gain, as well as have beneficial effects on mood, anxiety, and hostility.² This article aims to explore the disparity among different atypical antipsychotics to cause weight gain by looking at their individual effects on neurotransmitter systems and their specific receptor profiles. The possible impact of these receptor interactions on some of the factors currently known to influence weight regulation will also be explored. Other nonpharmacologic aspects of weight gain are discussed elsewhere in this supplement.

PHYSIOLOGY OF WEIGHT REGULATION

The regulation of body weight is a complex interplay between energy intake, energy expenditure, satiety

factors, and other controls of appetite.^{3,4} Other known or, as yet, unknown factors may also be involved. Hence, there are a number of axes along which it may be possible to interfere with the usual balance of these systems.

Extensive biochemical, pharmacologic, and endocrine research into the brain systems regulating food intake and energy homeostasis has identified a number of monoamines, neuropeptides, and hormones that may play a role in determining body weight (Figure 1). Several factors may be involved in altering their normal function, such as the presence of predisposing genes, endocrine abnormalities, or secondary effects of pharmacotherapy.

The hypothalamus is generally thought to be the structure most sensitive to neurohumoral manipulations that modulate eating. Hypothalamic amines, peptides, and circulating hormones participate in a complex network of systems that have distinct effects on patterns of eating behavior and metabolism of specific nutrients. For some systems, stimulation results in a net increase in energy intake and storage, while for others, stimulation results in a net decrease in energy intake and storage.³ It is likely that disturbances in monoamines, peptides, and their receptors in this region may underlie or modulate abnormal eating patterns, energy metabolism, and body weight changes.

NEUROTRANSMITTER SYSTEMS AND SPECIFIC RECEPTOR ACTIVITY IMPLICATED IN WEIGHT REGULATION

Serotonergic System

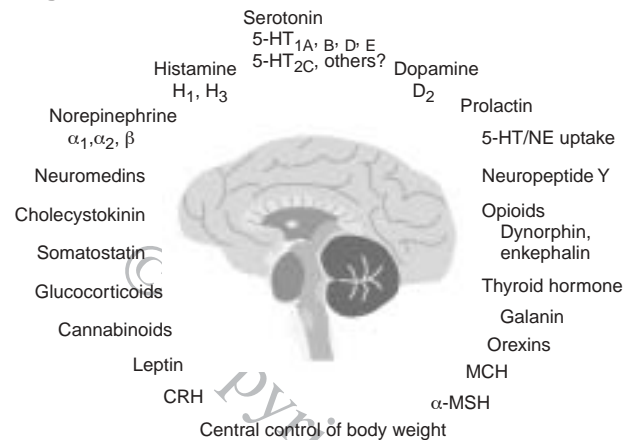
The serotonin (5-hydroxytryptamine, 5-HT) receptors now total at least 14 pharmacologically distinct subtypes assigned to 7 different families, located both pre- and postsynaptically throughout the mammalian central nervous

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Figure 1. Possible Endogenous Central Mediators of Body Weight^a



^aAbbreviations: CRH = corticotropin-releasing hormone, 5-HT = serotonin, MCH = melanin-concentrating hormone, α-MSH = alpha-melanocyte-stimulating hormone, NE = norepinephrine.

system (CNS).⁵ There are now many lines of evidence to suggest involvement of 5-HT neurotransmission and to implicate several specific 5-HT receptor subtypes in feeding behavior and body weight regulation. Additionally, data suggest that 5-HT has a role in the regulation of leptin (an adiposity signal) secretion.⁶

The antiobesity agent *D*-fenfluramine is believed to elicit its effect through release of 5-HT from nerve terminals and uptake blockade (activating both pre- and postsynaptic receptors). However, recent data suggest an association of chronic elevation of brain 5-HT turnover (as measured by internal jugular 5-HT metabolite overflow) with human obesity, implying tolerance to the usual response to 5-HT, i.e., a reduction in food intake.⁷

Systemic administration and intraperitoneal injection of agonists at the 5-HT_{1A} receptor, such as 8-hydroxydipropylaminotetralin (8-OH-DPAT), tend to increase food intake in rats fed ad libitum, possibly due to decreased 5-HT release via presynaptic 5-HT_{1A} autoreceptors.^{8,9} However, in food-deprived rats, 5-HT_{1A} agonists decrease feeding.^{10,11} Studies also suggest that presynaptic mechanisms of 8-OH-DPAT-induced hyperphagia may require specific circulating levels of insulin and glucose, which are regulated via postsynaptic 5-HT_{1A} receptors.¹² However, there is no clinical evidence to suggest that agonists at 5-HT_{1A} receptors are associated with effects on appetite or body weight.¹³ It should be noted that the 5-HT_{1A} agonists used clinically (e.g., bupirone, gepirone) are full agonists at presynaptic receptors (where their activation decreases serotonin release), but during chronic administration, these receptors desensitize. At postsynaptic receptors, these agents are partial agonists, exhibiting antagonist properties when serotonin levels are high and agonist properties when they are low.¹³

Nonselective 5-HT_{1B/1A} agonists tend to reduce feeding in rats.¹⁴ Direct injection of 5-HT_{1B/1A} agonists into the rat paraventricular nucleus (PVN) has been shown to elicit hypophagia.¹⁵ Some nonselective 5-HT_{1B/1A} antagonists have been shown to inhibit *D*-fenfluramine-induced hypophagia,¹⁶ an effect not produced by selective 5-HT_{1A} antagonists. Other preliminary studies reveal no effect with more selective 5-HT_{1B} antagonists.¹⁷ However, knockout of the 5-HT_{1B} receptor in mice is reported to inhibit *D*-fenfluramine-induced hypophagia.¹⁸

The 5-HT_{2C} receptor in particular may play an important role in regulating feeding and is a promising target for antiobesity drug development.¹⁷ Nonselective 5-HT_{2C} agonists such as *m*-chlorophenylpiperazine (*m*-CPP) decrease feeding in rats.¹⁷ These compounds tend to be partial agonists that also block 5-HT_{2A} receptors.¹⁹ However, their effect is potently inhibited by selective 5-HT_{2C} antagonists such as SB242084.²⁰ Also, administration of some 5-HT_{2C}-selective antagonists alone can increase food intake and body weight in rats.²¹ Knockout mice lacking the 5-HT_{2C} receptor eat more, get heavier, have reduced response to *D*-fenfluramine, and show late-onset diabetes mellitus.²² In human subjects, *m*-CPP is associated with a decrease in appetite and food intake, and preliminary studies suggest moderate weight loss in subjects with obesity.²³

In addition to these 5-HT receptors, other subtypes may also be involved in regulating food intake. 5-HT_{2B} receptor activation has been reported to increase food intake in rats.²⁴ 5-HT_{2A} receptor activation has been reported to decrease food intake in rats via a peripheral effect²⁵ and also inhibit neuropeptide Y (NPY)-induced feeding via a central effect.²⁶

Histaminergic System

Hypothalamic histamine has been implicated in the control of energy homeostasis and may have a role in the modulation of leptin-induced feeding behavior via the H₁ receptor subtype.^{27,28} Glucoprivation induced peripherally by insulin leads to an increase in hypothalamic histamine turnover,²⁹ and activation of histamine neurons in the ventromedial hypothalamus (VMH) or PVN decreases volume of feeding in rats.³⁰ Specifically, food intake is suppressed by activation of postsynaptic H₁ receptors or inhibition of presynaptic H₃ receptors in the VMH or PVN in rats.²⁷ One possible mechanism of histamine (H₁)-induced suppression of feeding in rats is via inhibition of norepinephrine (NE) release in the PVN.³¹ H₂ receptor antagonism has also been implicated in weight gain in rats. Although traditional nonselective H₁ receptor antagonists such as cyproheptadine stimulate appetite and may be associated with body weight increase in humans,³² this property may be related to effects on other neurotransmitter systems (e.g., cyproheptadine is also a nonselective 5-HT receptor antagonist). Many psychotropic drugs with high affinities for H₁ receptors (and other receptors), such as the

antidepressants amitriptyline and mirtazapine,^{33,34} are also associated with weight gain.

Adrenergic System

Direct injections of selective α_1 -adrenoceptor agonists into the PVN of rats result in reductions in food intake, whereas intra-PVN injections of selective α_2 -adrenoceptor agonists stimulate feeding.³⁵ In the same models, the effect of α_2 agonists is reversed by pretreatment with selective α_1 -antagonists such as prazosin, suggesting the presence of a mutually antagonistic equilibrium between α_1 - and α_2 -adrenoceptors. Prazosin also inhibits sibutramine-induced (see below) decreases in food intake in rats.³⁶ Clinically, there are no data to suggest effects on weight gain with any α -adrenoceptor antagonists. However, many psychotropic drugs with high affinities for α_1 - and/or α_2 -adrenoceptors (e.g., tricyclic antidepressants) are associated with weight gain, whereas those with low affinities for these receptors (e.g., selective serotonin reuptake inhibitors) are not.³³ A genetic polymorphism of the α_{2B} -adrenoceptor subtype may contribute to the pathogenesis of obesity in some populations.³⁷

Dopaminergic System

Local injections of dopamine into the lateral hypothalamus (LH) lead to decreased feeding in rats, probably via D_2 receptors. However, dopamine facilitates and reinforces feeding in mesolimbic areas. D_2 agonists inhibit feeding in both food-deprived rats and those fed ad libitum.³⁸ Nonselective D_1 agonists are also associated with reduced food intake and may act synergistically with D_2 agonists. The mixed D_2/D_3 antagonist sulpiride induces robust feeding and drinking when injected into the LH of rats. However, it is worth noting that the extent that this behavior is mediated via a specific interaction(s) with the dopaminergic or some other neurotransmitter systems is as yet unknown.

Monoamine Reuptake Sites

5-HT and NE reuptake sites are currently a prime target in the development of weight-reducing drugs.³⁹ Sibutramine, a mixed 5-HT/NE reuptake inhibitor, was recently approved as a treatment for obesity and purportedly exerts its effect by increasing NE at peripheral β_3 -adrenoceptors and NE and 5-HT at central receptors.⁴⁰

However, not all drugs that increase levels of norepinephrine and serotonin at the synapse induce weight loss. The novel antidepressant mirtazapine enhances NE and specifically 5-HT_{1A}-mediated serotonergic transmission via antagonism at α_2 -adrenoceptor and 5-HT₂ and 5-HT₃ receptors.³⁴ This drug possesses a propensity to induce weight gain. It has little affinity for α_1 -adrenoceptors, dopaminergic receptors, or muscarinic receptors, but is a potent antagonist at H₁ receptors. A weight gain liability of a drug with a broad pharmacologic profile is, therefore,

likely to be a complex derivative of multiple receptor interactions.

EFFECTS OF ANTIPSYCHOTICS ON BODY WEIGHT

The low-potency phenothiazines have long been associated with weight gain. For example, Amidson (1964)⁴¹ observed that patients taking chlorpromazine gained 9 lb (4.1 kg) on average over 12 weeks. Chlorpromazine was associated with greater increases than perphenazine and clopenthixol. The high-potency agents such as haloperidol are associated with a comparatively lower weight gain liability⁴² versus lower potency agents and newer generation drugs. Many other conventional antipsychotics from a range of drug classes are also associated with significant weight gain.¹ Exceptions to this are molindone and loxapine, which appear to be associated with weight loss.^{1,43}

Treatment with clozapine, the first atypical antipsychotic, is associated with clinically significant weight gain in a large proportion of patients. The effect appears to be more substantial than that observed with conventional agents.^{44,45} A 10-week study comparing the effects of clozapine and haloperidol on weight gain in outpatients who had been only partially responsive to treatment with traditional antipsychotics found that clozapine induced significantly more weight gain than haloperidol (mean = 11.7 lb vs. 1.5 lb [5.3 kg vs. 0.7 kg]).⁴⁵ Clozapine patients in this trial continued to gain weight during a 1-year follow-up.

Most of the new atypical antipsychotics appear to be associated with weight gain liabilities.^{1,46,47} The meta-analysis of Allison et al.¹ investigated 81 studies of weight gain after 10 weeks of treatment with a range of antipsychotic drugs (molindone, ziprasidone, fluphenazine, haloperidol, risperidone, chlorpromazine, sertindole, thioridazine, olanzapine, clozapine). All of the drugs investigated, with the exception of molindone and ziprasidone, were associated with weight gain. Among the conventional agents, weight change ranged from a reduction of 0.39 kg with molindone to an increase of 3.19 kg with thioridazine. Haloperidol was associated with an increase of 0.48 kg. With the atypical agents, the largest gain was found with clozapine (4.45 kg), followed by olanzapine (4.15 kg), sertindole (2.92 kg), and risperidone (2.10 kg). Ziprasidone was associated with a mean increase of only 0.04 kg. In the longer term, weight gain with either clozapine or olanzapine may be substantially higher.⁴⁸

Recent studies demonstrate that body weight increase with clozapine and olanzapine is associated with increased leptin levels, whereas with haloperidol it is not.⁴⁹ Whether this is a cause or effect of increased food intake is unclear.

ANTIPSYCHOTIC RECEPTOR PROFILES

It is generally accepted that antagonism at central dopaminergic D_2 receptors is a key factor in the treatment of

schizophrenia. Indeed, all antipsychotic agents possess this feature, and a positive correlation between the dose adequate to treat positive symptoms and the drug's D_2 receptor affinity has been repeatedly replicated in the literature.^{48,50} The atypical antipsychotic agents tend to be characterized by having combined antagonist activity at both D_2 and 5-HT_{2A} receptors and generally have higher affinities for the 5-HT_{2A} receptor.^{48,50} This property, in part, may confer additional antipsychotic efficacy and has been proposed to underlie their lower extrapyramidal side effect liability and negative symptom efficacy.⁵¹ However, both the conventional and atypical agents possess diverse pharmacologic profiles encompassing a variety of effects via interactions with a number of other neurotransmitter receptors. Their different activities at some of these receptor systems may underlie their different propensities to induce weight gain. In particular, many atypical agents are antagonists at H_1 -histaminergic, α_1 -adrenergic, and 5-HT_{2C} -serotonergic receptors. A summary of the relative receptor activities of various antipsychotic drugs is presented in Table 1 and more detailed nonhuman and human affinity constants have been reported elsewhere (references 52–54 and A. W. Schmidt, M.A.; L. A. Lebel, B.S.; H. R. Howard, Jr., M.S.; et al., manuscript submitted). The possible relationships of the various neurotransmitter receptor activities of antipsychotic drugs to weight gain and to other potential side effects are summarized in Table 2. These effects will vary depending on a drug's affinity for various neurotransmitter receptors and also by the combination of receptor affinities it exhibits. For example, a drug with high antagonist affinity at α_1 -adrenergic receptors (e.g., clozapine) would be predicted to more likely produce hypotension and sedation than a drug with more moderate or lower affinity for this receptor (e.g., ziprasidone).

It is widely known that thioridazine stands among the typical antipsychotics that possess the largest weight gain liability. This compound has higher affinity for α_1 -adrenoceptors and M_1 -muscarinic acetylcholine receptors than it does for the D_2 receptor.⁵⁵ Its affinities for H_1 -histaminergic receptors and 5-HT_{2A} receptors are similar to its affinity for the D_2 receptor.

The traditional high-potency antipsychotic haloperidol has a high affinity for D_2 receptors. It does not, however, possess similar or higher affinities at any of the other

Table 1. Comparative In Vitro Receptor Binding (human receptor affinity)^a

| Receptor | Ziprasidone | Risperidone | Olanzapine | Quetiapine | Clozapine | Haloperidol |
|---------------------------------|-------------|-------------|------------|------------|-----------|-------------|
| D_2 | ++++ | ++++ | ++ | + | + | ++++ |
| 5-HT_{1A} | ++++ | + | 0 | + | + | 0 |
| 5-HT_{1D} ^b | ++++ | + | + | 0 | 0 | 0 |
| 5-HT_{2A} | +++++ | +++++ | ++++ | + | ++++ | + |
| 5-HT_{2C} | +++++ | ++++ | ++++ | 0 | ++ | 0 |
| α_1 | ++ | ++++ | ++ | ++ | ++++ | ++++ |
| H_1 | ++ | ++ | ++++ | ++++ | ++++ | + |
| M_1 | 0 | 0 | ++++ | ++ | ++++ | 0 |
| 5-HT uptake | ++ | 0 | 0 | 0 | 0 | 0 |
| NE uptake | ++ | 0 | 0 | + | + | 0 |

^aAdapted from Schmidt et al.⁵⁴ and A. W. Schmidt, M. A.; L. A. Lebel, B. S.; H. R. Howard, Jr., M.S.; et al., manuscript submitted.

Affinity represented as: +++++ (very high, $K_i < 1$ nM); ++++ (high, $K_i = 1\text{--}10$ nM); ++ (moderate, $K_i = 11\text{--}100$ nM); + (low, $K_i = 101\text{--}1000$ nM); 0 (negligible, $K_i > 1000$ nM).

^bBovine.

Table 2. Clinical Implications of Various Receptor Activities of Antipsychotic Drugs^a

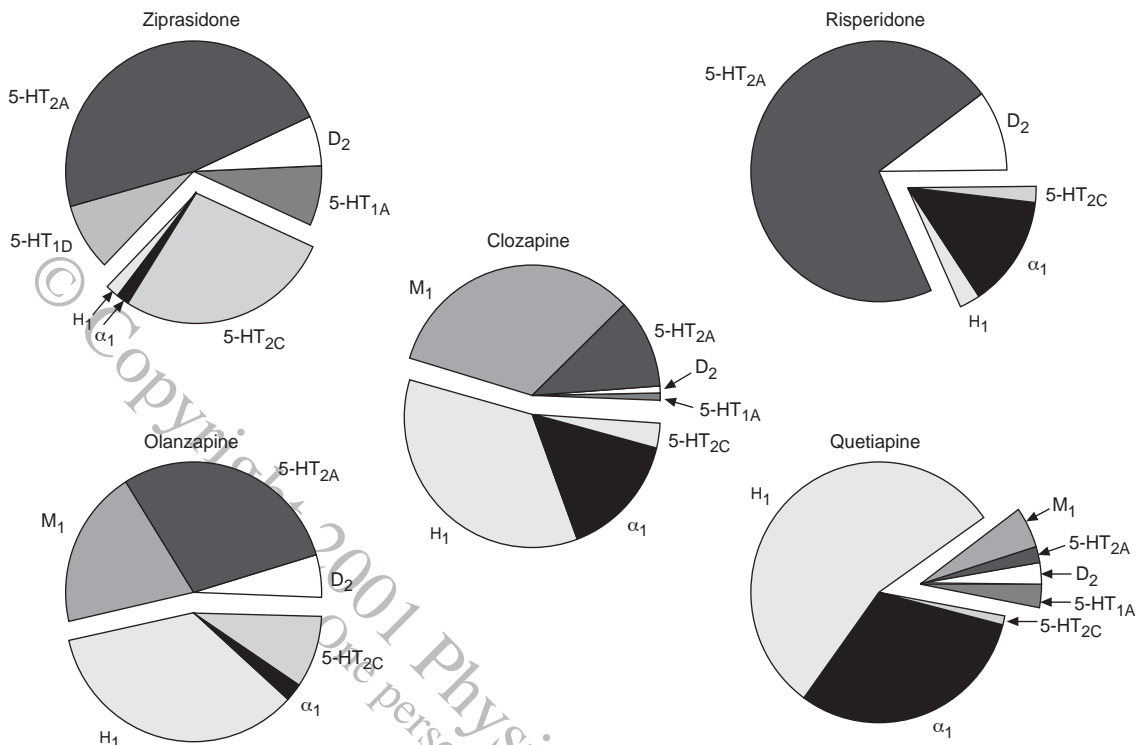
| Receptor Activity | Possible Clinical Effects |
|---|---|
| D_2 receptor antagonist | Antipsychotic activity vs positive symptoms, EPS, endocrine effects |
| 5-HT_{1A} receptor agonist | Antidepressant and anxiolytic activity, improved cognition, reduced EPS, increased or decreased body weight |
| 5-HT_{1D} receptor antagonist | Antidepressant activity |
| 5-HT_{2A} receptor antagonist | Antipsychotic activity vs negative symptoms, reduced EPS |
| 5-HT_{2C} receptor antagonist | Improved antipsychotic efficacy vs positive symptoms, body weight gain |
| α_1 -Adrenoceptor antagonist | Sedation and hypotension, effect on body weight gain |
| H_1 -histamine receptor antagonist | Sedation and body weight gain |
| M_1 -muscarinic receptor antagonist | Memory impairment, GI symptoms, dry mouth, blurry vision, improved EPS |
| High $5\text{-HT}_{2A}/D_2$ receptor binding affinity ratio | Improved antipsychotic activity and lower EPS than that expected from D_2 receptor antagonism alone |
| Mixed serotonin and norepinephrine neuronal reuptake inhibition | Antidepressant and anxiolytic activity, reduced body weight gain |

^aAbbreviations: D = dopamine, EPS = extrapyramidal motor symptoms, 5-HT = serotonin, GI = gastrointestinal, H = histamine, M = muscarinic.

receptors previously mentioned (see Table 1).^{52,53} At 5-HT_{2A} receptors, α_1 -adrenoceptors, and H_1 receptors, the traditional antipsychotic molindone has a low affinity relative to D_2 receptors.⁵⁵ This agent is unusual in that its use can be associated with modest weight loss.

Clozapine has the highest propensity to cause weight gain of all the antipsychotic drugs. In receptor binding studies, clozapine demonstrates higher affinity for 5-HT_{2A} , 5-HT_{2C} , H_1 -histaminergic, α_1 -adrenergic, and M_1 -muscarinic receptors than it does for dopaminergic D_2 receptors (see Table 1).^{52,53} Its affinity for 5-HT_{1A} receptors, where it appears to be a partial agonist, is similar to that for the D_2 receptor (Figure 2).

Olanzapine is another atypical antipsychotic agent with a high propensity to cause weight gain (second only to clozapine). Like clozapine, it also has higher affinities for 5-HT_{2A} , 5-HT_{2C} , H_1 -histaminergic, and M_1 -muscarinic

Figure 2. Relative Affinities of Atypical Antipsychotics for Different Receptor Subtypes^a

^aData from Schmidt et al.⁵⁴ and A. W. Schmidt, M. A.; L. A. Lebel, B. S.; H. R. Howard, Jr., M.S.; et al., manuscript submitted. The subtypes potentially relevant to weight gain (5-HT_{2C}, α_1 , and H₁) have been offset for emphasis.

receptors compared with its affinity for the D₂ receptor (see Table 1).^{52,53} However, unlike clozapine, it has lower affinity for the α_1 -adrenoceptor than it does for the D₂ receptor (see Figure 2).

Another new atypical agent, quetiapine, has higher affinity for H₁-histaminergic receptors and α_1 -adrenoceptors and approximately similar activity at the M₁-muscarinic, 5-HT_{1A} (partial agonist), and 5-HT_{2A} receptors compared with its affinity for the D₂ site (see Table 1).^{52,53}

Risperidone, which has a slightly lower weight gain liability than most atypical agents, displays higher affinity for 5-HT_{2A} receptors and α_1 -adrenoceptors and lower affinity for 5-HT_{2C} receptors compared with its affinity for the D₂ receptor.

Ziprasidone, the newest atypical antipsychotic,^{52,56} has a neurotransmitter receptor-binding profile distinct from that of the other atypical antipsychotics. Like risperidone, it has a high affinity for D₂ receptors and an even higher affinity for 5-HT_{2A} receptors. However, unlike all the other antipsychotic drugs, ziprasidone has a greater degree of serotonergic and a lesser degree of adrenergic, histaminergic, and muscarinic receptor properties (see Table 1) (references 52 and 53 and A.W. Schmidt, M.A.; L.A. Lebel, B.S.; H.R. Howard, Jr., M.S.; et al., manuscript submitted). Ziprasidone possesses high affinity for 5-HT_{1A} receptors, where it is a full agonist,⁵² and higher affinity for

5-HT_{2C} and 5-HT_{1D} receptors compared with its affinity at the D₂ receptor. Unlike olanzapine, clozapine, and quetiapine, ziprasidone does not interact with M₁-muscarinic receptors. In addition, ziprasidone possesses only modest affinity at both the H₁-histaminergic receptor and at the α_1 -adrenoceptor. Another unique feature of ziprasidone is that, unlike all the other antipsychotic drugs, this drug possesses moderate affinity as an inhibitor of rat and human 5-HT and NE reuptake.^{52,57} Its affinity at these neurotransmitter uptake sites is comparable with that of the antidepressants amitriptyline and imipramine.⁵²

DISCUSSION

Antipsychotic agents, particularly the newer atypical agents, possess broad pharmacologic profiles with activity at a number of receptor sites at therapeutic doses.⁵⁸ Many of these neurotransmitter systems and specific receptor subtypes are implicated in the regulation of food intake and energy homeostasis and are likely to play a role in weight gain associated with antipsychotic use. Potential targets for interfering with normal body weight regulation may be either central or peripheral and may occur at any number of stages in a complex cascade of mediators. This plethora of neurotransmitter and neurohumoral systems and receptors involved in body weight regulation make the

weight gain liability of a potential novel agent difficult to predict. However, insight may be gained by comparing differences in the receptor-binding profiles of those antipsychotic drugs that cause the most weight gain with those that produce the least, and it may be possible to relate a drug's propensity to induce weight gain to its activity at particular receptors.

This analysis suggests that compounds that antagonize several specific receptors, in affinity ranges equal to or greater than their affinities at the D₂ receptor, may be linked with a high weight gain liability, perhaps higher than those with activity at a single receptor alone. This may be especially true for drugs that possess relatively high affinities (compared with D₂) for combinations of interactions with 2 or more of 5-HT_{2C}, α_1 -adrenergic, and/or H₁-histaminergic receptors. For example, some of the atypical agents, such as clozapine, olanzapine, and quetiapine, possess relative high affinity (defined relative to their own affinities for D₂ receptors) activity at H₁/ α_1 /5-HT_{2C}, 5-HT_{2C}/H₁, or H₁/ α_1 receptor combinations, respectively. Therefore, it is plausible that the clinically significant weight gain observed with administration of these drugs could, at least in part, be explained by these combinations of activity (see Figure 2). In contrast, risperidone's lower propensity to cause weight gain relative to these drugs may be explained by its relatively high affinity for α_1 -adrenoceptors together with only modest H₁ and 5-HT_{2C} antagonist properties.

Unlike findings for these other drugs, the meta-analysis from Allison et al.¹ revealed that among the antipsychotic drugs studied, ziprasidone is unusual in that it is considered "weight neutral," producing little if any weight gain after 10 weeks of administration clinically. Although it is not yet clear how ziprasidone differs from antipsychotic drugs that produce weight gain, several suggestions can be derived from consideration of ziprasidone's different pharmacologic profile. One interesting note is that among the compounds studied, ziprasidone possesses the highest affinity for 5-HT_{2C} receptors (as an antagonist) and is second only to clozapine in terms of its higher affinity for this receptor relative to D₂ receptors. So, having a very high affinity for 5-HT_{2C} receptors does not necessarily confer on a drug the propensity to induce weight gain. Thus, since 5-HT_{2C} antagonists are known to produce weight gain, one possibility is that ziprasidone's other pharmacologic properties could counteract the weight enhancing effect of its being a potent 5-HT_{2C} antagonist. The 2 unique features of ziprasidone that are candidates for this action are potent agonism at 5-HT_{1A} receptors (ziprasidone is a full agonist) and general activation of 5-HT and adrenoceptors (like that of sibutramine, an approved antiobesity drug) via combined 5-HT and NE uptake inhibition. Ziprasidone's relatively lower affinity, compared with risperidone, at both α_1 and H₁ receptors may also contribute to its lack of weight regulation in patients. Other pharmacologic prop-

erties may also contribute to ziprasidone's weight-neutral profile. For example, ziprasidone also differs from the other atypical antipsychotic drugs by having a relatively higher affinity for the 5-HT_{1D} versus the D₂ receptor. However, the role of the 5-HT_{1D} receptor in weight regulation is unknown at present.

There are a number of receptors at which antipsychotic drugs have high affinity whose role in weight regulation is still unclear. Similarly there are a number of neurotransmitter, hormone, and peptide receptors implicated in the control of food intake and weight regulation for which there are as yet no pharmacologic data available for antipsychotic drugs. Weight gain associated with antipsychotic treatment may have serious long-term consequences for patient health and compliance. The pharmacologic mechanisms underlying weight gain are presently poorly understood, and there is a need for further understanding of these systems and how antipsychotic agents interact with them. This may facilitate selection of appropriate antipsychotic treatment and improve the management of cases in which avoiding significant weight gain is of prime importance.

Drug names: amitriptyline (Elavil and others), buspirone (BuSpar), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), cyproheptadine (Periactin), haloperidol (Haldol and others), loxapine (Loxitane and others), mirtazapine (Remeron), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), prazosin (Minipress and others), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia).

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