How to Appease the Appetite of Psychotropic Drugs

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Issue: *Psychotropic drugs affect many of the receptors that control appetite, feeding behavior, and energy expenditure.*

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

Obesity is reaching epidemic proportions in the United States, and psychotropic drugs may be important factors as both causes and treatments for it.[1–3] Beyond mere monitoring of weight, psychiatrists who understand the neuropharmacology of obesity may be able to exploit this information to create clever drug selections, switches, or combinations to mitigate or reverse psychotropic drug-induced weight gain. Here we will discuss some tips for applying the concepts of the psychopharmacologic mechanisms relevant to psychotropic drug-induced changes in body weight[1] to the selection of antidepressants and antipsychotics that can be risk factors for obesity.

Generally speaking, drugs that stimulate 5-HT_{2C}, D_2, or β_3-adrenergic receptors are more likely to be associated with either short-term weight loss or no weight gain.[1–4] On the other hand, drugs that block 5-HT_{2C}, H_1, and D_2 receptors are more likely to be associated with short-term weight gain.[1–5] Since long-term actions of psychotropic drugs are often the opposite of short-term actions,[5] one might expect these patterns to be reversed in long-term administration. What has more commonly been observed is that the short-term weight loss experienced by patients in acute treatment is not sustained when they are in maintenance treatment, and those who initially experience short-term weight gain have more profound weight gain with long-term treatment (see Table).

Drugs That Bind to "Thin" Receptors

The SSRIs indirectly activate the 5-HT_{2C} receptor by raising synaptic levels of serotonin,[1,2] resulting in many patients reporting short-term weight loss, but many reporting weight gain with longer-term treatment.[6] Fluoxetine and norfluoxetine also have direct agonist actions at 5-HT_{2C} receptors and often produce short-term weight loss but a long-term weight gain.[7] A metabolite of nefazodone, *m*-CPP, is also an agonist at 5-HT_{2C} receptors, possibly explaining why there are relatively few reports of weight gain with nefazodone.[2,6]

Bupropion has prodopaminergic and pronoradrenergic actions,[5] which could explain why there are few reports of weight gain with long-term treatment with this agent and numerous reports of short-term weight loss. Another drug with pronoradrenergic actions as well as proserotonergic actions is the most recently marketed appetite suppressant sibutramine.[8] As with all pronoradrenergic agents, weight loss could potentially occur via 2 mechanisms[1]: central, where activation of CNS adrenergic receptors reduces appetite, and peripheral, where activation of β_3-adrenergic receptors on adipose cells causes them to break

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Table. Possible Effects of Selected Psychotropic Drugs on Body Weight*

Drug/Potential Mechanisms	Short-Term	Long-Term
Antidepressants		
Bupropion/prodopaminergic and pronoradrenergic (β_3 stimulation)	– –	–
Nefazodone/*m*-CPP/5-HT_{2C} agonist	+–	+–
Venlafaxine/5-HT_{2C} agonist and pronoradrenergic (β_3 stimulation)	–	+–
SSRIs/5-HT_{2C} agonists	–	+
TCAs/H_1 blockade	+	++
Mirtazapine/H_1 blockade	+	++
Antipsychotics		
Typical (chlorpromazine, haloperidol)/ D_2 and H_1 antagonism	+	++
Atypical (clozapine, olanzapine, quetiapine, risperidone)/D_2, H_1, and 5-HT_{2C} blockade	+	++
Anorectic		
Sibutramine/proserotonergic and pronoradrenergic (5-HT_{2C} and β_3 stimulation)	– –	+–

*Symbols: + = minimal weight gain, ++ = moderate weight gain, – = minimal weight loss, – – = moderate weight loss, +– = weight gain or loss, depending on patient.

down fat and increase body metabolism.[1,3,6,8]

Nicotine is a drug of abuse that reduces appetite, causes weight loss, and is notorious for causing weight gain once an individual stops smoking. It produces nicotinic stimulation of receptors on dopamine neurons, causing release of central dopamine[5] and reduction of appetite.

Classical anorectics are all releasers of dopamine and indirect stimulators of D_2 receptors.[1,2,5] These include phentermine, diethylpropion, amphetamines, and others. Unfortunately, these agents are famous not only for inducing rapid tolerance to the appetite-suppressing actions, but also for causing abuse when administered long-term.[5]

Drugs That Bind to "Fat" Receptors

Several antidepressants and antipsychotics are associated with weight gain.[1,6] Tricyclic antidepressants and mirtazapine block H_1 receptors.[5] All antipsychotics block D_2 receptors to some degree,[5] many having an unfortunate triple effect that includes blockade of 3 receptors (D_2, H_1, and 5-HT_{2C}) at the same time[5]—a formula that can explain in part the all too common incidence of obesity and weight gain in patients taking not only conventional antipsychotics, but especially the newer atypical antipsychotics.

Fighting or Switching

To manage psychotropic drug–induced weight gain, one can either fight or switch. Switching to an agent that lacks interactions with receptors that lead to weight gain is perhaps most attractive, but not always feasible. All available intraclass alternates may share the same undesirable properties. In this case, however, empiric clinical observations suggest that some patients can nevertheless have very different responses to drugs that share the same mechanism, so a within-class switch may be worth a try. This may be particularly true for the typical antipsychotics loxapine and molindone, which seem to produce the least amount of weight gain among the neuroleptics. Sometimes weight gain in a patient receiving one of the atypical antipsychotics can be strikingly different from that associated with another atypical.

In other cases, the possibility of a clinical relapse is just too great a risk to justify discontinuation of the currently effective agent. In that case, clinical anecdotes and scientific rationale are the psychiatrist's best hope. Although essentially no controlled studies suggest that combining the offending drug with another agent with an opposing pharmacologic mechanism can be useful, some combinations may work, e.g., combining bupropion, SSRIs, venlafaxine, or stimulants with mirtazapine.[9] Since psychotic patients should not take stimulants, treatment with SSRIs, bupropion, venlafaxine, and, in some cases, low doses of direct-acting D_2 agonists such as cabergoline or bromocriptine might be helpful for patients with weight gain who are taking antipsychotics.

Hopefully, as the pharmacologic mechanisms of weight gain become better understood, well-designed studies geared toward the development of guidelines for managing weight gain by using combinations of psychotropic drugs will be forthcoming. ◆

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