UPDATE ON ATYPICALS

Preemptive tactics to

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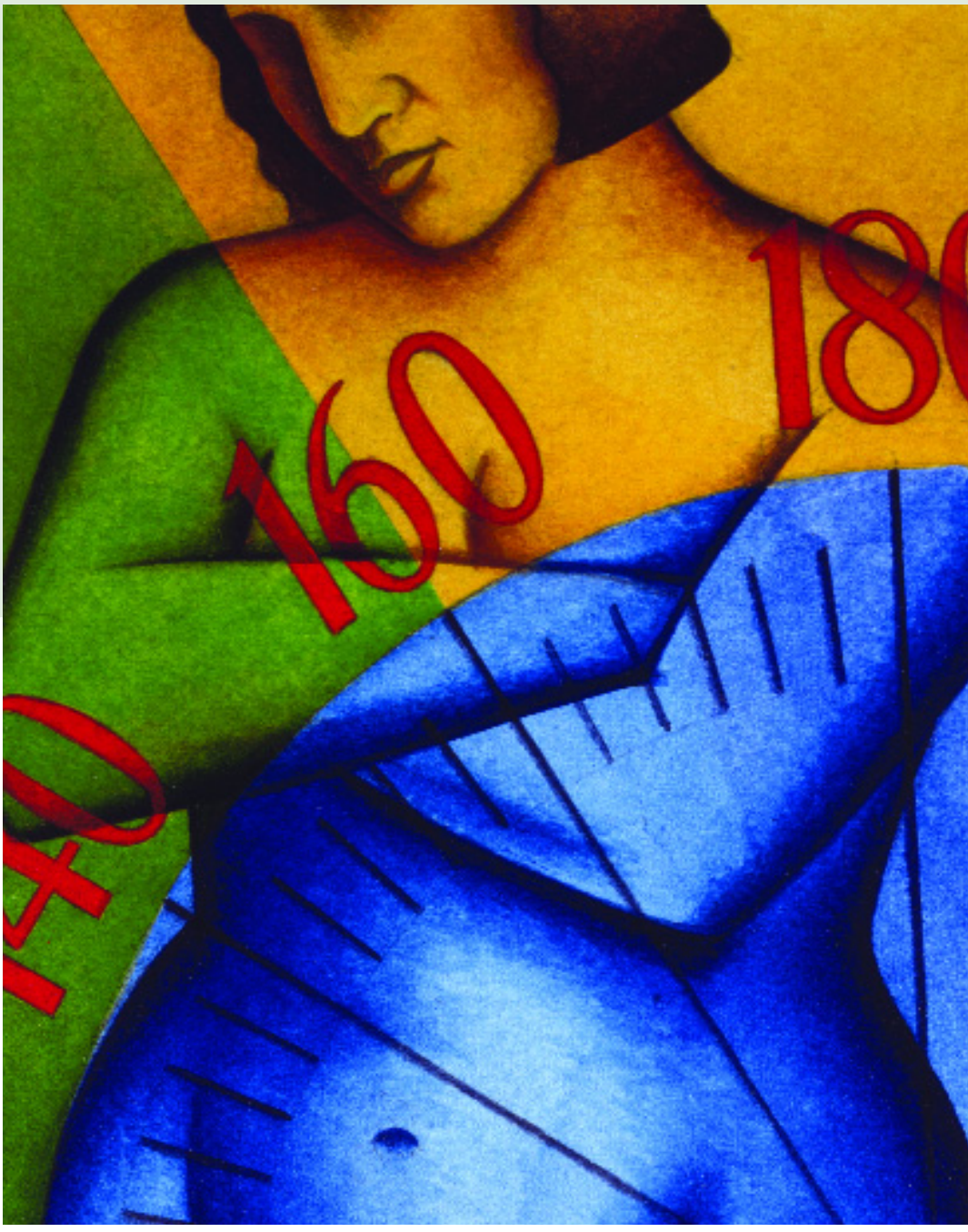

Current PSYCHIATRY

reduce weight gain

Teaching patients about appetite control before starting atypical antipsychotics can help keep excess pounds off.

Given the efficacy and safety profiles of atypical antipsychotics, their potential to cause weight gain represents not a barrier to access but a side effect to be managed. Behavioral and/or drug interventions can help protect patients from the medical risks and social consequences of weight gain during antipsychotic treatment.

Let's look at possible mechanisms of antipsychotic-induced weight gain and a rational strategy for controlling weight in patients taking these medications. This strategy applies to all atypical antipsychotics and psychiatric diagnoses.

Mechanisms of weight gain

Neuroleptic antipsychotics may act on the hypothalamic feeding center and directly stimulate appetite, a dynamic that was suggested 20 years ago.[1] More recent evidence suggests that antagonism of serotonin (5-HT2C) or histamine (H1) receptors may play a role in antipsychotic-related weight gain. Other neurotransmitters and receptors may also be involved.

Serotonin receptor antagonism. Agents that stimulate 5-HT2C receptors—such as fenfluramine and M-chlorophenylpiperazine[2]—have been associated with weight loss. Conversely, agents that antagonize these receptors have been hypothesized to increase appetite and cause weight gain.[3]

For example, a strain of mice craved carbohydrates and became obese after the genes for 5-HT2C receptors were removed.[4] Atypical antipsychotics also antagonize 5-HT2C receptors more than the older neuroleptics do, which may explain the atypicals' greater associated risk for weight gain.

Histamine receptor antagonism. Other researchers have suggested that antipsychotic-induced weight gain is associated less with serotonin receptors than with histamine receptor antagonism:

- Astemizole—a potent H1 receptor antagonist used to treat allergic rhinitis—was the first medication associated with weight gain by this mechanism.[5]
- Wirshing et al[6] recently reported an exponential relationship between antipsychotics' H1 receptor affinities and maximum weight gain.

Clozapine and olanzapine have very strong binding affinity to both 5-HT2C and H1 receptors. This characteristic may explain why patients often experience increased appetite and weight gain while taking these antipsychotics.

Other neurotransmitters. Atypical antipsychotics have diverse pharmacologic profiles, and their interactions with dopamine and other neurotransmitter receptors produce a variety of effects (*Table 1*). These neurotransmitter systems and receptor subtypes appear to help regulate food intake and energy homeostasis and may play a role in weight gain associated with antipsychotic use.[7] For example:

- Clozapine and olanzapine have a higher affinity for serotonin receptor subtypes 5-HT2A and 5-HT2C and for H1 and muscarinic (M1) receptors than they do for D2 receptors. This preferential antagonism of 5-HT2A versus D2 receptors is a defining characteristic of novel antipsychotics and explains why they offer broader efficacy and fewer side effects than the older neuroleptics. However, 5-HT2C receptor antagonism has been implicated as a cause of increased appetite.[4]

Table 1

RECEPTOR BINDING AFFINITIES OF ATYPICAL ANTIPSYCHOTICS

Drug	Dopamine	Serotonin		∂1 adrenergic	Histamine	Muscarinic
	D2	5HT2A	5HT2C		H1	M1
Clozapine	+	++++	+++	+++	++	
Olanzapine	++	++++	++++	–	++	–
Quetiapine	+	+	+	+++	++	–
Risperidone	++++	+++++	++	+	+++	–
Ziprasidone	++++	+++++	+	0	++	–

- Clozapine, but not olanzapine, also has a higher affinity for adrenergic (∂1) receptors than for D2 receptors. Clozapine is associated with greater mean weight gain than olanzapine, risperidone, or ziprasidone.[8]
- Risperidone—with a lower weight gain potential than most atypicals—displays high affinity for 5-HT2A and ∂1 receptors and a lower affinity for 5-HT2C receptors than for D2 receptors.[8]
- Ziprasidone's weight gain potential is even less than risperidone's, and the exact mechanism is unknown.[8] Some animal studies suggest that ziprasidone's effects on the noradrenergic system may explain its low weight gain potential.[9]
- Aripiprazole's long-term weight gain potential is not yet known.

A strategy for managing weight gain

Four predictors of weight gain have been identified in patients with schizophrenia:

- better clinical outcome
- low baseline body mass index
- younger age
- increase in appetite during treatment.[10]

When appetite increases, patients are at risk of overeating to satisfy their hunger. An average increase of 500 calories per day will cause an average weight gain of 1 lb per week. Therefore, minimizing an increase in caloric intake may minimize weight gain.

One can lose weight by reducing caloric intake or increasing caloric output, such as with exercise. Thus, behavioral interventions focusing on both nutritional education and exercise are showing benefit in minimizing antipsychotic-related weight gain. The "wellness clinic" described by Wirshing et al achieved weight loss in patients taking antipsychotics through rigorous interventions, including education, exercise classes, and group support.[6]

A strain of mice craved carbohydrates and became obese after the genes for 5-HT2C receptors were removed

A rational approach for minimizing weight gain in patients taking antipsychotics is summarized in *Table 2*. This strategy combines nutritional and exercise education and drug therapy, when indicated.

Effect of behavioral interventions

Many patients who have followed behavioral interventions that emphasize nutrition and exercise have lost at least some of the weight they gained during antipsychotic treatment:

- In a study by O'Keefe, nearly 80% of patients who gained >20 lbs while taking antipsychotics then lost at least 10 lbs while in behavioral intervention programs.[11]
- Patients with schizophrenia or schizoaffective disorder who experienced olanzapine-related weight gain lost weight while attending a 10-week Weight Watchers program.[12]
- Patients who gained weight while taking antipsychotics lost weight with a step-wise behavioral approach that included increasingly intensive interventions (self-

weighing, food diaries, nutrition consultation, and attendance at a "wellness clinic").[6]

- 70% of 74 psychiatric inpatients lost weight across 6 to 34 months with a reduced-calorie diet, group therapy, and behavior modification.[13]

The effectiveness of weight management programs associated with antipsychotics may depend on the target population. In a retrospective chart review, Cohen et al found that calorie restriction did not lead to weight loss among 50 adult inpatients with mental retardation who were being treated with risperidone.[14]

Timing is important. During olanzapine treatment, mean weight gain has been reported to plateau after approximately 39 weeks, with the most rapid gains in the first 12 weeks.[6] Thus, early weight control efforts likely would be most effective. Two small, prospective studies suggest that starting behavioral interventions before you start olanzapine therapy may be the most effective strategy to minimize weight gain.

Provide specific nutritional education; discourage eating junk food and encourage drinking water and eating fruits and vegetables

In the first study—a randomized trial of 12 patients with schizophrenia—those who received an educational intervention prior to starting olanzapine treatment gained a mean 1 lb in 4 weeks, compared with 6.4 lbs in a standard-care group.[15] The behavioral intervention included a weekly 1-hour class using educational materials on nutrition and exercise.

In the second study, our group offered 22 psychiatric outpatients a nutrition course before starting olanzapine treatment.[16] We included 17 patients with psychotic disorders and 5 with nonpsychotic diagnoses—including major depressive disorder, bipolar disorder, and stuttering—to compare antipsychotic-related weight gain between psychotic and nonpsychotic populations.

We began by talking with each patient for 5 minutes about the following nutritional concepts:

- Weight gain is associated with increased appetite.
- The more you eat, the more weight you gain.
- To reduce hunger, it is better to snack on fruits, carrots, broccoli, or low-fat crackers than on high-calorie "junk food" such as potato chips, ice cream, candy, and cake.
- Drink water or diet sodas instead of sugary soft drinks.

At follow-up visits, we spent 2 minutes reinforcing the educational messages by:

- asking if patients' appetite had increased
- re-emphasizing that they should eat low-fat snacks to reduce hunger and drink water or diet sodas instead of sugary soft drinks.

After about 7 months, the mean weight gain from olanzapine therapy was 5.27 lbs, which is 40 to 60% less than that seen in studies of olanzapine without structured interventions.[6,8,17] Mean weight gain was 5 lbs for the psychotic patients and 6.2 lbs for the nonpsychotic group, which suggested that

Table 2

STRATEGY FOR MANAGING WEIGHT IN PATIENTS TAKING ANTIPSYCHOTICS

- **Begin nutritional and exercise education** before starting antipsychotic treatment.
- **Monitor weight weekly** in the first 4 to 6 weeks of antipsychotic therapy, when the risk for weight gain is highest. Ask if the patient's appetite has increased.
- **If a patient gains >10 lbs** during the first 4 to 6 weeks, consider adding nizatidine, 300 mg bid; topiramate, 100 to 200 mg/d; or amantadine, 100 mg bid, to the antipsychotic regimen.
- **Continue adjunctive therapy** until appetite has decreased and weight gain has stabilized, then taper off the medication and continue to monitor weight. Emphasize the importance of proper food choices.
- **Review the patient's diet at every visit.** Provide very specific nutritional education. Discourage eating "junk food" such as chocolate, potato chips, cake, cookies, and soft drinks, and encourage drinking water and eating fruits and vegetables.

Related resources

- Wirshing DA, Wirshing WC, Ksyar L, et al. Novel antipsychotics: a comparison of weight gain liabilities. *J Clin Psychiatry* 1999;60:358-63.
- Casey DE, Zorn S. The pharmacology of weight gain with antipsychotics. *J Clin Psychiatry* 2001;62 (suppl 7):4-10.

DRUG BRAND NAMES

Amantadine • Symmetrel
Aripiprazole • Abilify
Clozapine • Clozaril
Nizatidine • Axid
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Topiramate • Topamax
Ziprasidone • Geodon

DISCLOSURE

Dr. Nguyen is a speaker for Eli Lilly and Co. and GlaxoSmithKline; receives research support from Eli Lilly and Co., GlaxoSmithKline, and Forest Laboratories; and is a consultant to Eli Lilly and Co., Organon, and GlaxoSmithKline.

Dr. Yu is a speaker for Cephalon Inc., Eli Lilly and Co., Novartis Pharmaceuticals Corp., and Pfizer Inc.; receives research/grant support from Cephalon, Inc. and Eli Lilly and Co.; and is a consultant to Eli Lilly and Co.

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patients with schizophrenia or schizoaffective disorders may benefit from nutritional education.

Medications for weight control

Three medications—nizatidine, topiramate, and amantadine—have shown some effect in controlling weight gain when taken concomitantly with atypical antipsychotics. These medications affect different receptors, and how they affect weight gain is not entirely understood.

Nizatidine—a selective histamine (H2) receptor antagonist—was shown to be significantly more effective than placebo in reducing olanzapine-related weight gain when given to 132 patients at 300 mg bid.[18]

Topiramate is believed to stimulate 5-HT2C receptors, thus suppressing the increased appetite caused by 5-HT2C antagonism. Among 13 bipolar patients with significant weight gain associated with olanzapine treatment, 73% lost weight with topiramate at 90.4 +/- 48.4 mg/d.[18]

Amantadine has also been shown to minimize weight gain without worsening psychotic symptoms. A case series reported a weight gain of 15.8 lbs in patients taking olanzapine alone, compared with 7.7 lbs in patients taking olanzapine plus amantadine.[19]

Bottom Line

Behavioral and/or pharmacologic interventions can help minimize weight gain during antipsychotic treatment. Early intervention, close monitoring, and patient education are the keys to successful weight management.

References

1. Rockwell WJ, Ellinwood EH, Trader DW. Psychotropic drugs promoting weight gain: health risk and treatment implications. *South Med J* 1983;76:1407-12.
2. Walsh AE, Smith KA, Oldman AD, et al. m-Chlorophenylpiperazine decreases food intake in a test meal. *Psychopharmacology (Berl)* 1994;116:120-2.
3. Garattini S, Mennini T, Samain R. Reduction of food intake by manipulation of central serotonin: current experimental results. *Br J Psychiatry* 1989;155(suppl 8): 41-51.
4. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2C receptors. *Nature* 1995;374:542-6.
5. Howarth PH, Emanuel MB, Holgate ST. Astemizole, a potent histamine H1 receptor antagonist: effect on allergic rhinoconjunctivitis, on antigen and histamine-induced skin response and relationship to serum levels. *Br J Clin Pharmacol* 1984;18:1-8.
6. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: a comparison of weight gain liabilities. *J Clin Psychiatry* 1999;60:358-63.
7. Casey DE, Zorn S. The pharmacology of weight gain with antipsychotics. *J Clin Psychiatry* 2001;62 (suppl 7):4-10.
8. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999;156:1686-96.
9. Leibowitz SF. **Neurochemical system of the hypothalamus control of eating and drinking and behavior and water-electrolyte excretion.** In: Morgan P, Panksepp J (eds). *Handbook of the hypothalamus (vol, 3)*. New York: Marcel Dekker, Inc., 1980:299-438.
10. Basson BR, Kinon BJ, Taylor CC, et al. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. *J Clin Psychiatry* 2001;62(4):231-8.
11. O'Keefe C, et al. Reversal of weight gain associated with antipsychotic treatment (paper presentation). New Orleans: American Psychiatric Association annual meeting, 2001.
12. Ball MP, Coons VB, Buchanan RW. A program for treating olanzapine-related weight gain. *Psychiatr Serv* 2001;52(7):967-9.
13. Knox JM. A study of weight reducing diets in psychiatric in-patients. *Br J Psychiatry* 1980;136:287-9.
14. Cohen S, Glazewski R, Khan S, Khan A. Weight gain with risperidone among patients with mental retardation: effect of calorie restriction. *J Clin Psychiatry* 2001;62(2):114-16.
15. Littrell KH, et al. Educational interventions for the management of antipsychotic-related weight gain (paper presentation). New Orleans: American Psychiatric Association annual meeting, 2001.
16. Nguyen CT, Ortiz T, Franklin D, Yu B, Maguire GA. Nutritional education in minimizing weight gain associated with antipsychotic therapy. New Orleans: American Psychiatric Association annual meeting, 2001.
17. Kinon BJ, Basson BR, Gilmore JA, Tollefson GD. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. *J Clin Psychiatry* 2001;62(2):92-100.
18. Ketter TA et al. *Int J Neuropsychopharmacol* 2000;3(suppl l):S344.
19. Floris M, Lejeune J, Deberdt W. Effect of amantadine on weight gain during olanzapine treatment. *Eur Neuropsychopharmacol* 2001;11(2):181-2.