

Pharmacologic and Nonpharmacologic Strategies for Weight Gain and Metabolic Disturbance in Patients Treated With Antipsychotic Medications

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Objectives: To provide an overview of pharmacologic and nonpharmacologic strategies for antipsychotic-associated weight gain and metabolic disturbance, to identify important areas for future research, and to make practice recommendations based on current knowledge.

Methods: We undertook a selective review of interventions for weight gain and metabolic disturbance in the general population and in individuals treated with antipsychotic medications, focusing on randomized controlled trials in schizophrenia.

Results: Pharmacologic strategies include medication choice, medication dosage and formulation, choice of concomitant psychotropic medications, medication switching, medication addition to effect weight loss or prevent weight gain, and medications to increase insulin sensitivity. Medication choice and medication switching may have the most potent influence on weight and metabolic parameters. Modest short-term weight loss can occur with the addition of selective medications and (or) lifestyle interventions. However, more rigorous and longer-term studies are needed.

Conclusions: Although difficult, the prevention of weight gain and the promotion of weight loss are possible for individuals treated with antipsychotic medications. Further research, including diabetes prevention studies, is required. We suggest a pathway for the management of weight gain and emerging metabolic disturbance.

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Clinical Implications

- Psychiatrists have an important role to play in managing the weight gain and metabolic disturbance that can accompany antipsychotic treatment.
- Weight management and lifestyle advice should be offered to all patients.
- There is insufficient evidence to support the general use of pharmacologic interventions for weight management.

Limitations

- There are few rigorous RCTs, and most existing trials are short-term with small sample sizes.
- Trials have focused on weight loss or prevention as an outcome.

Key Words: schizophrenia, antipsychotic medication, weight management, metabolic disturbance, intervention, review

There is now consensus that antipsychotic medications are associated with various degrees of weight gain and metabolic disturbance (1). In addition to the need for systems of surveillance to identify metabolic disturbance (see the companion article in this issue, 2), there is clearly a pressing need for prevention and intervention strategies. However, there is little to guide clinicians other than personal experience and anecdotal reports. In this selective review, we provide an overview of pharmacologic and nonpharmacologic strategies for antipsychotic-associated weight gain and metabolic disturbance, focusing on published reports and RCTs in schizophrenia and borrowing from strategies used in the general population. We identify promising areas for research and make recommendations for clinical practice, based on current knowledge.

Pharmacologic Strategies

Medication Choice

Of all the pharmacologic strategies, choice of psychotropic medication may have the greatest influence on weight gain and associated metabolic disturbance. There is good evidence for a range of weight-gain liability among antipsychotic medications (1,3). However, weight gain varies considerably among individuals. Unfortunately, there are as yet no useful clinical (4) or genetic (5) predictors of individual weight-gain liability for specific medications—an important focus for future research.

Medication Dosage, Plasma Levels, and Route of Administration

There are few systematic studies exploring the effect of medication dosage and route of administration on weight gain. One study did report a threshold plasma concentration (but not dosage) of olanzapine associated with weight gain of 7% or more (6). However, unlike extrapyramidal side effects, antipsychotic weight gain does not appear to be heavily influenced by dosage within the usual therapeutic range. Clozapine may be somewhat of an exception, as reported in a recent study combining low-dose clozapine with fluvoxamine, which inhibits clozapine metabolism and raises clozapine plasma levels. In a 12-week RCT, inpatients with

treatment-resistant schizophrenia were assigned to high-dose clozapine (≥ 600 mg daily) or low-dose clozapine (≤ 250 mg daily) plus adjunctive fluvoxamine (50 mg). At study endpoint, only the high-dose clozapine group had elevations relative to baseline body weight, fasting glucose, and triglycerides (7).

In terms of medication formulation, a recent report of reduced weight gain with sublingual, compared with oral, olanzapine has gained some attention (8), but this has yet to be replicated in an RCT.

Concomitant Medication

Antidepressant and mood-stabilizing medications also cause weight gain (see Table 1; derived from 9,10), and these medications are commonly coprescribed with antipsychotics. Few studies have examined the weight and metabolic consequences of medication combinations. Haupt and coworkers reported that divalproex added to antipsychotic monotherapy resulted in increased adiposity and increased triglyceride levels after 6 weeks of treatment (11). It is unclear whether combining medications has an additive or synergistic effect on weight gain or whether there is a ceiling effect for a particular individual.

Medication Switch

Switching from one antipsychotic medication to another can have significant effects on body weight and metabolic parameters. Data from the recently reported CATIE trials provide evidence of beneficial weight change with switching to an antipsychotic medication having a more neutral metabolic profile. Mean (SD) weight changes when patients were randomly assigned to a different antipsychotic were as follows: olanzapine, +0.9 kg (0.1 kg) monthly; quetiapine, +0.2 kg (0.1 kg) monthly; risperidone, +0.2 kg (0.1 kg) monthly; perphenazine, -0.1 kg (0.1 kg) monthly; and ziprasidone, -0.1 kg (0.1 kg) monthly (12).

A study of overweight or obese (that is, BMI > 26 kg/m²) olanzapine-treated patients switched to risperidone and followed for 20 weeks reported a 32% reduction in the rate of the metabolic syndrome at study endpoint, as well as significant reductions in body weight, BMI, waist circumference, and blood pressure (13). In another report, outpatients suffering predominantly from schizophrenia were switched from a previous antipsychotic (olanzapine, $n = 104$; risperidone $n = 58$; or conventional antipsychotic, $n = 108$) to ziprasidone (mean dosage 91 mg daily) and reevaluated after 6 weeks. Weight and metabolic benefit depended on which drug patients were switched from. Those switched from olanzapine experienced the greatest metabolic benefit, with significant reductions in body weight (1.76 kg), nonfasting total cholesterol, and triglycerides. Those switched from risperidone experienced less weight loss (0.86 kg) but similar reductions in nonfasting total

Abbreviations used in this article

BMI	body mass index
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBT	cognitive-behavioural therapy
CI	confidence interval
RCT	randomized controlled trial

Table 1 Weight gain with antidepressant and mood stabilizer medications ^a		
	Risk	Comment
Antidepressants		
Tricyclic or monoamine oxidase inhibitor	(+++)	Amitriptyline > imipramine
Selective serotonin reuptake inhibitor	(+) to (++)	Paroxetine > others
Novel	(-) to (+++)	Initial (6 to 8 kg) weight loss often followed by longer-term weight gain Bupropion (-) Nefazodone (0) Mirtazapine (+++)
Mood stabilizers		
Lithium	(+++)	Can range from 10 to 35 lbs in longer-term use
Valproic acid	(++)	Associated with polycystic ovarian syndrome and metabolic syndrome
Gabapentin	(+) to (++)	May be dose-related
Carbamazepine	(+)	Less than valproate or gabapentin
Lamotrigine	(0)	Minimal weight gain
Topiramate	(-)	Associated with weight loss or weight stability
^a Derived from Fava (9) and Aronne (10)		
+ = increased risk of weight gain; ++ = greater risk of weight gain; +++ = greatest risk of weight gain; - = weight loss or weight stabilization		

cholesterol and triglycerides. However, those switched from conventional antipsychotics had no change in weight or lipid measures (14). A companion paper from the same data set supports the view that stable but symptomatic patients can be safely switched from a previous antipsychotic according to various switching strategies (for example, abrupt discontinuation of previous antipsychotic or gradual cross-titration), often with benefit in terms of psychiatric symptomatology (15).

Discontinuing or switching antipsychotics may be particularly critical when the development of diabetes or diabetic ketoacidosis can be clearly linked to a new antipsychotic prescription, as resolution of diabetes can occur in this situation (16).

Medication to Effect Weight Loss or Prevent Weight Gain

In the general population, controlled clinical trials have established modest efficacy for obesity drugs in combination with lifestyle therapy (17). Orlistat (a lipase inhibitor) and sibutramine (a serotonin–dopamine–norepinephrine reuptake inhibitor) are the only drugs currently approved for long-term weight loss. Average weight loss in the general population (psychiatric patients were excluded) at 12 months was 2.7 kg (95%CI, 2.3 to 3.1) for orlistat and 4.3 kg (95%CI, 3.6 to 4.9) for sibutramine (18).

In the context of antipsychotic-induced weight gain, brief (6 to 16 weeks) RCTs have been conducted in schizophrenia patients for several compounds (summarized in Table 2). We

have focused on weight change to compare efficacy between studies identified with a systematic search and retrieval protocol (19).

Nizatidine. Nizatidine, a histamine H₂ receptor antagonist, was studied in Turkey in two 8-week trials. Atmaca and colleagues investigated nizatidine (150 mg twice daily) in olanzapine-induced weight gain (20) and quetiapine-induced weight gain (21). Nizatidine was well tolerated, and there were no dropouts. Both studies showed weight loss relative to placebo (see Table 2), but interpretation is limited by the small sample size and short study duration.

In a larger study, Cavazonni evaluated the efficacy of 2 fixed dosages of nizatidine (150 mg twice daily, *n* = 113; and 300 mg twice daily, *n* = 112) for preventing weight gain with olanzapine (22). There was an early transient effect for the higher dosage only, in that there was less weight gain relative to placebo observed after 3 and 4 weeks. However, there was no difference at the end of the trial. These studies suggest that, although nizatidine may have an early transient effect on weight, this may not be sustained.

Famotidine. Famotidine is another H₂ antagonist. Poyurovsky examined the effect of famotidine on preventing olanzapine-associated weight gain in first-episode individuals (23). Famotidine addition was ineffective in attenuating weight gain, adding further evidence for the limited utility of H₂ antagonists in weight control.

Table 2 RCTs of pharmacologic interventions for weight gain in schizophrenia

Agent	Author, Antipsychotic, Trial Duration	Agent dosage; intervention group, <i>n</i> ; outcome, weight change relative to placebo (95%CI)
Nizatidine Histamine H ₂ receptor antagonist	Atmaca (20), olanzapine, 8 weeks	150 mg twice daily; <i>n</i> = 18; -6.8 kg (-7.9 to -5.7 kg)
	Cavazzoni (22), olanzapine, 16 weeks	300 mg twice daily; <i>n</i> = 58; less weight gain at 3 and 4 weeks, effect lost at 16 weeks. 150 mg twice daily; <i>n</i> = 57; no effect
	Atmaca (21), quetiapine, 8 weeks	150 mg twice daily; <i>n</i> = 14; -2.2 kg (-2.9 to -1.5 kg)
Fluoxetine Selective serotonin reuptake inhibitor	Poyurovski (24), olanzapine, 8 weeks	20 mg daily; <i>n</i> = 15; no effect
	Bustillo (25), olanzapine, 16 weeks	60 mg daily; <i>n</i> = 15; no effect
D-Fenfluramine Removed from market	Goodall (55), typical depots, 12 weeks	30 mg daily; <i>n</i> = 9; -2.6 kg (-5.5 to -0.1 kg)
Phenylpropinolamine Removed from market	Boravicka (56), clozapine, 12 weeks	75 mg; <i>n</i> = 8; no effect
Roboxetine Serotonin norepinephrine reuptake inhibitor	Poyurovski (26), olanzapine, 6 weeks	4 mg daily; <i>n</i> = 13; -3.0 kg (-5.6 to -0.5 kg)
Famotidine Histamine H ₂ receptor antagonist	Poyurovski (23), olanzapine, 6 weeks	40 mg daily; <i>n</i> = 7; no effect
Amantadine Antiparkinsonian	Deberdt (27), olanzapine, 16 weeks	100-300 mg; <i>n</i> = 35; -1.7 kg (-3.9 to 0.5 kg)
Sibutramine Serotonin norepinephrine-dopamine reuptake inhibitor	Henderson (28), olanzapine, 12 weeks	15 mg; <i>n</i> = 19; -4.6 kg (-5.2 to -4.0 kg)
	Weiden (29), mixed atypical and typical antipsychotics, 16 weeks	15 mg; no effect
Topiramate Anticonvulsant	Ko (30), atypical antipsychotic, 12 weeks	200 mg daily; <i>n</i> = 17; -5.1 kg (-7.4 to -2.7 kg)
		100 mg daily; <i>n</i> = 16; -1.4 kg (-4.2 to 1.5 kg)

Fluoxetine. Two RCTs have examined the efficacy of fluoxetine (a selective serotonin reuptake inhibitor)—one in preventing, and the other in treating, olanzapine-associated weight gain. Both had negative results. Poyurovsky examined whether the coadministration of fluoxetine (20 mg daily) might prevent or attenuate olanzapine-induced weight gain over 8 weeks in individuals with first-episode schizophrenia (24). Both treatment and placebo groups demonstrated similar and substantial weight gains. Bustillo examined higher dosages of fluoxetine (60 mg daily) for treating patients who had gained more than 3% of their baseline weight in the first 8 weeks of olanzapine treatment and found no evidence of a weight-reducing effect (25).

Reboxetine. Reboxetine is a selective norepinephrine reuptake inhibitor. Poyurovsky examined its addition for preventing weight gain in schizophrenia patients during olanzapine treatment (26). Reboxetine was well tolerated. There was less weight gain in the treatment group, compared with those receiving placebo. Between-group differences

emerged at Week 4 of the trial. The study is weakened by the short trial duration.

Amantadine. Amantadine is an antiparkinsonian drug. Deberdt examined the adjunctive efficacy of amantadine in individuals who had experienced weight gain of 5% or more during the first 9 months of olanzapine treatment (27). Amantadine was well tolerated, and there was greater weight loss at Weeks 8, 12, and 16, compared with placebo.

Sibutramine. Sibutramine is a weight-loss drug that inhibits reuptake of serotonin, norepinephrine, and to a lesser extent, dopamine; it is approved for long-term treatment of obesity. Its effectiveness for patients with schizophrenia has been explored in 2 RCTs, with different results. Henderson (28) conducted a trial of sibutramine addition in olanzapine-treated patients who had a BMI of 30 or more or BMI of 27 or more and at least one cardiovascular risk factor (that is, hypertension, lipid abnormality, or diabetes) (28). All patients participated in weekly group support consisting of weight education and behaviour modification. The sibutramine

group had more weight loss than the placebo group. There was also a relative decrease of hemoglobin A1c and a mean (SD) increase in blood pressure of 2.1 (8.5) mm Hg in the sibutramine group. Sibutramine did not worsen psychotic symptoms.

In an unpublished study, Weiden conducted a trial of sibutramine addition in schizophrenia outpatients with a BMI greater than 27 who were treated with various antipsychotic medications (29). All received dietary counselling. There was no difference in weight loss between the sibutramine group and the placebo group. In a post hoc analysis, weight loss in patients assigned to sibutramine who were on a typical antipsychotic (haloperidol) was greater than in the patients assigned to atypical antipsychotics. Sibutramine was generally well tolerated, with no significant exacerbation of symptomatology; one patient developed new-onset asymptomatic hypertension at 4 weeks and discontinued the medication without further problems.

Topiramate. Topiramate is an anticonvulsant medication that has been used for various other conditions, including bipolar affective disorder, and has also been found to have weight-loss properties. In a trial conducted in Korea, Ko added topiramate titrated to 2 dosage endpoints (100 mg or 200 mg daily) in a group of hospitalized inpatients treated with atypical antipsychotics for schizophrenia and having a BMI 25 or more (30). Compared with placebo, topiramate 200 mg, but not topiramate 100 mg, was effective in inducing weight loss. Parasthesia was a frequent side effect, occurring in 58.8 % of the patients taking topiramate 200 mg, compared with its occurrence in 25% taking topiramate 100 mg and in 10% receiving placebo. There was no occurrence of the serious side effects, such as metabolic acidosis, narrow-angle glaucoma, or nephrolithiasis, that have been reported with topiramate, nor was there reported worsening of psychotic symptoms or cognitive impairment at either dosage, although formal neuropsychological testing was not conducted.

In summary, these RCTs are variable in outcome. Interpretation is limited by the short study durations and variability of the interventions themselves. Of drugs currently on the market, there were negative results for histamine H₂ antagonists (specifically, nizatidine and famotidine) and fluoxetine, mixed results for sibutramine, and positive results for topiramate (200 mg), roboxetine, and amantadine. Currently, there is interest in the use of the antidiabetic agent metformin in antipsychotic-treated patients, for both weight and metabolic benefit, following a promising open-label study of its use in a pediatric sample (31). However, metformin addition was not effective in preventing weight gain in an adult sample of more chronic patients with schizophrenia who were switched to olanzapine (32). Additional studies of metformin are underway in psychiatric populations. In general, further

study is needed with longer treatment duration and larger study samples to investigate the effectiveness and safety of drug additions for weight and metabolic benefit.

Weight-Loss Drugs in Development

Of the weight-loss drugs currently in development, rimonabant, a selective cannabinoid CB1 receptor antagonist submitted to the Food and Drug Administration for approval, may have special applicability in the psychiatric population. Rimonabant has shown promising Phase 3 results in weight loss, in smoking cessation, and in improving the metabolic profiles of patients with the metabolic syndrome (33). These conditions are all highly prevalent among individuals with serious mental illness.

Medications to Increase Insulin Sensitivity and Prevent Progression to Type 2 Diabetes

Type 2 diabetes is known to develop gradually over several years, and insulin resistance, or reduced biological effectiveness of insulin, precedes the diagnosis of type 2 diabetes (see 2). In the general population, medication strategies to improve insulin sensitivity have proven effective in preventing or delaying the development of type 2 diabetes in those at risk. In the Diabetes Prevention Program (34), conversion to type 2 diabetes was reduced by 31% at 2.8 years with metformin administration (although lifestyle intervention was more effective). Orlistat and acarbose (an alpha glucosidase inhibitor) have also proven effective in diabetes prevention (35,36). There are currently no published studies of diabetes prevention in the psychiatric population.

Nonpharmacologic Strategies

General Population

Lifestyle strategies incorporating changes in diet and physical activity are critical to improving or preventing components of metabolic disturbance such as diabetes (for example, 37). In particular, weight-loss strategies using dietary, physical activity, or behavioural interventions produce significant improvements in weight among persons with prediabetes and a significant decrease in diabetes incidence (38).

In terms of preventing type 2 diabetes, a metaanalysis reported a 50% reduction (relative risk 0.55; 95%CI, 0.44 to 0.69) in the 1-year incidence of diabetes in the lifestyle education group, compared with the control group (39). One study included in this metaanalysis is worth highlighting. The US Diabetes Prevention Program Research Group (34) studied the effects of an intensive program of diet and exercise, metformin, or placebo in individuals with impaired glucose tolerance. The lifestyle-modification group received intensive education and support and were advised to make a 7% reduction in body weight by adopting a low-fat, low-calorie diet and by engaging in moderate physical activity such as

Table 3 Key components for the management of overweight and obesity (adapted from ACSM, 42)

Component	Requirement
Diet	Energy intake restriction of 500–1000 kcal daily Dietary fat reduced to 30% of energy intake Optimal dosage of carbohydrate and protein not established
Exercise	Significant health benefits with 150 minutes of moderate (55%–69% of maximum heart rate) exercise weekly Overweight and obese individuals should increase to 200–300 minutes weekly
Behavioural therapy	Associated with improved long-term outcomes Training should be given in behavioural concepts (for example, problem solving, goal setting, social support) Encouragement should be given to individuals to self-monitor exercise and eating habits

brisk walking for 150 minutes weekly. The lifestyle changes in diet and physical activity were found to be more effective in reducing the incidence of type 2 diabetes than was treatment with metformin (a 58%, compared with a 31%, reduction in risk).

Similarly, in the management of obesity and overweight, a recent consensus concluded that the best way to lose weight was through a combination of physical activity and diet (40), although this should ideally be complemented with CBT. In a Cochrane review, Shaw (41) found that CBT, when combined with a diet–physical activity intervention, increased weight loss in obese people by 4.9 kg (95%CI, –7.3 to –2.4), compared with diet and exercise alone. Behavioural therapy alone was found to result in significantly greater weight loss (–2.5 kg) than placebo when assessed as a stand-alone weight-loss strategy (95%CI, –1.7 to –3.3). Overall, existing evidence suggests that effective treatments for adult obesity produce modest weight loss (about 2 to 5 kg) over 12 months, compared with no treatment or usual care (for example, 17). The key components for the nonpharmacologic management of overweight and obesity are identified in Table 3 (adapted from 42).

Schizophrenia

In the context of antipsychotic-related weight gain and metabolic disturbance, nonpharmacologic interventions have mostly involved individuals with schizophrenia. There are at least 3 systematic reviews examining behavioural interventions in this population (43–45) with a primary focus on weight reduction as an outcome. In the most recent and detailed review with no exclusion criteria based on methodological design, Loh and colleagues identified 23 studies, of which 19 reported weight loss (45). They concluded that, while much of the literature was methodologically flawed, behavioural interventions may be useful for the prevention of weight gain in schizophrenia. A systematic search and

retrieval protocol (19) identified 4 published RCTs of lifestyle interventions, which we now describe (see Table 4).

In the 4 studies, there were a total of 208 participants (98 men and 110 women) with an average age of 36.14 years and an average weight of 87.99 kg at the start of the study (as well as average BMI of 29.09 kg/m², reported in 3 studies). Participants were primarily outpatients and taking olanzapine in 3 studies (46–48). The length of the intervention ranged from 14 weeks (47) through 16 weeks (46,49) to 3 months (48). Three studies involved cognitive-behavioral group interventions incorporating education and discussion regarding diet and physical activity, and one study used one-on-one dietary counselling (48). Sessions included individual and group work, written exercises, tests, and discussions (46); development and rehearsal of self-monitoring skills (for example, modifying urges to overeat and changing snacking habits) (47); and the setting of regularly reviewed healthy-eating lifestyle goals (48).

Of note is a modification of the study reported by the US Diabetes Prevention Program Research Group (34). Weber and Wyne conducted a randomized, placebo-controlled pilot study of 17 outpatients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and having a BMI greater or equal to 25 kg/m² (49). Participants were randomized to a 16-week cognitive-behavioral group intervention or to treatment as usual. The intervention group received once weekly 1-hour group sessions developing cognitive-behavioral strategies to promote risk reduction and demonstrated to be successful in the Diabetes Prevention Program. These included role-playing, goal setting, problem solving, risk–benefit comparisons, and barrier discussions; as well, each participant kept a food and activity diary.

Table 4 RCTs of nonpharmacologic interventions for weight gain in schizophrenia

Author	Intervention	Outcome at final assessment: weight change (kg) / compliance and attrition
Littrell and others (46)	Weekly 1-hour group sessions for 16 weeks of diet and exercise education, compared with usual care; 2-month follow-up	Intervention = -0.27 kg, SD 4.28 kg; usual care = +4.34 kg, SD 5.89 kg; compliance rate, 92%; no dropout reported
Brar and others (47)	Two sessions weekly for 6 weeks, then one session weekly for 8 weeks of diet and exercise education compared with usual care (encouraged to lose weight)	Intervention = -2.00 kg, SD 3.79 kg; usual care = -1.10 kg, SD 3.11 kg (not significant); 15/28 patients attended all 20 sessions; 21% dropout in the treatment group
Evans and others (48)	Six 1-hour individual nutrition education sessions over 3 months (every 2 weeks) compared with usual care (plus passive nutrition information).	Intervention = +2 kg, usual care = +9.9 kg; compliance not reported; 21% dropout in the treatment group
Weber and Wyne (49)	Weekly 1-hour group sessions for 16 weeks of diet and exercise education compared with usual care	Intervention = -2.45 kg, usual care = -0.59 kg (not significant); compliance not reported; no dropout in treatment group

Implications

On the basis of their more rigorous design, these 4 studies confirm that modest weight-gain prevention or weight loss is possible in the short term, although there was not statistical significance in 2 studies (see Table 4; 47,49). Dropout was not high, as reported in a recent review (45), and we suspect that, with thorough attention given to the development of retention strategies, dropout can be minimized for individuals motivated to lose weight. At this stage, conclusions cannot be made regarding the necessary intensity of the intervention or effects on outcomes other than BMI or weight. There is clearly a need for further RCTs with larger samples and long-term follow-up to determine how best to package behavioural interventions (for example, group, compared with individual, modular, or stepwise interventions), to identify patient characteristics associated with adherence and successful outcome, and to examine how sustainable any outcomes are. Outcomes should also include measures of adiposity and metabolic syndrome other than just weight or BMI. Despite the low number of studies reported, the role of physical inactivity and poor diet as independent risk factors for cardiovascular disease, which is the primary cause of excess premature mortality among individuals with schizophrenia (50), infers the need for nonpharmacologic or lifestyle intervention regardless of weight loss per se.

Challenges in Working With the Seriously Mentally Ill and Practice Implications

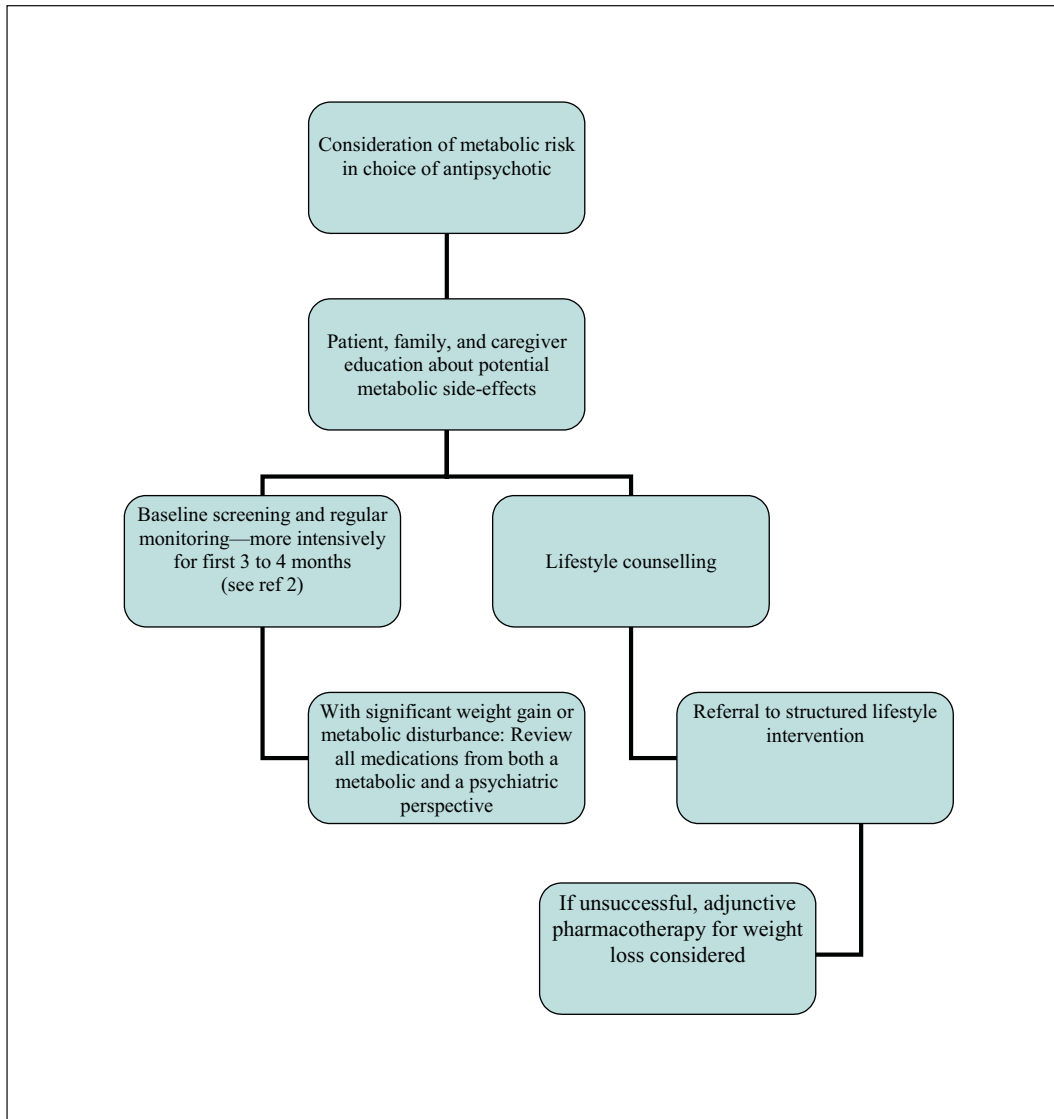
The development and delivery of effective, evidence-based interventions for the management of weight gain and obesity in this population is clearly in its infancy. Interventions will probably need to have realistic goals, be highly structured, provide early and intensive support initially, and offer reduced but continued support over time, if not indefinitely. Dealing with amotivation, poor insight, and the reduced

cognitive and social functioning often inherent to schizophrenia and related illnesses will remain as significant challenges to clinicians. However, we caution against the adoption of a nihilistic stance that perceives change as too difficult to warrant intervention (51). As this and other reviews have demonstrated, although weight loss, for example, may be difficult to achieve, it is evidently not impossible (43).

Psychiatrists will make choices concerning the prescription of psychotropic medications and will consider the possibility of medication additions. There is merit to incorporating lifestyle interventions within the skill set of the case management system, as opposed to referring individuals to a primary care physician or other health care provider for management of cardiovascular disease risk factors (52). Individuals with serious mental illness have frequent contact with their mental health service providers. Changing health behaviours can be difficult, and frequent reinforcement may play a critical role in successful long-term adoption of regular physical activity and diet modification. Additionally, there are mental health-specific barriers to physical activity and dietary change that can be more appropriately addressed by individuals trained to be sensitive and supportive in regard to these issues. This will require some investment in terms of training and resources. As well as a case management or “coaching” approach, structured programs, such as the research interventions described above, are needed to ensure the intensity in lifestyle change required to achieve metabolic benefit.

The reviewed lifestyle interventions focus on individual change. We suggest that the adoption of a broader ecologic framework (for example, see 53) is required to underpin research and practice in modifying patients’ obesogenic environment. This requires the acknowledgement of multiple influences on health behaviour, including social and physical

Figure 1 Pathway for the management of weight gain and metabolic disturbances in patients treated with antipsychotic medications



environmental influences. Hospitals, psychiatric facilities, and structured living settings that house individuals with schizophrenia and other forms of severe and persistent mental illness are challenged to provide environments that promote healthy living. All too often, such environments contribute to the problem of physical inactivity (for example, with confined living areas and limited opportunities for exercise) and unhealthy diets (through cost-based mass or institutional feeding, no control over portion size, lack of fresh fruits and vegetables, and open access to unhealthy snack foods). The reality that service users will spend much of their lives living in such “behaviour settings” underscores the importance of developing creative ways of modifying diet and physical

activity in these environments and evaluating whether these modifications can affect obesity and metabolic disturbance.

Summary of Evidence and Proposed Sequencing of Interventions

Overall, there is currently limited information in terms of RCTs to evaluate the effectiveness and safety of interventions to moderate antipsychotic-associated weight gain and metabolic disturbance. Existing data suggest that short-term, modest weight loss is possible with nonpharmacologic and selective pharmacologic interventions. At this time, there is insufficient evidence to support the general use of pharmacologic interventions for weight management.

The first strategy (see Figure 1) in preventing or alleviating weight gain or metabolic disturbance is to appraise metabolic risk when prescribing antipsychotic and other psychotropic medications, although priority should be given to achieving good control of the mental illness (54). Patients, family, and caregivers should be educated about metabolic risks and receive lifestyle advice regarding diet and physical activity (see Table 3). Baseline screening and a monitoring plan (2) must be initiated on commencement of antipsychotic treatment. During monitoring, if diabetes develops in close temporal relation to the new antipsychotic prescription, serious consideration must be given to discontinuing or switching the medication. With significant weight gain or emerging metabolic effects (for example, impaired fasting glucose or dyslipidemia), the risk and benefit of antipsychotic choice and concomitant medications should be reevaluated from both a psychiatric and a metabolic perspective, and at this stage, patients should be referred to a more structured and supervised lifestyle intervention. Patients should be referred to a primary care physician for management of diabetes, dyslipidemia, or hypertension. Adjunctive pharmacotherapy for weight loss should be reserved for patients who do not respond adequately to lifestyle interventions alone.

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Résumé : Stratégies pharmacologiques et non pharmacologiques pour la prise de poids et la perturbation métabolique chez les patients traités aux antipsychotiques

Objectifs : Fournir un aperçu des stratégies pharmacologiques et non pharmacologiques pour la prise de poids et la perturbation métabolique associées aux antipsychotiques, afin de discerner d'importants domaines de la future recherche, et de faire des recommandations de pratique, d'après les connaissances actuelles.

Méthodes : Nous avons entrepris un examen sélectif des interventions pour la prise de poids et la perturbation métabolique dans la population générale et chez les personnes traitées aux antipsychotiques, en mettant l'accent sur les essais contrôlés randomisés de la schizophrénie.

Résultats : Les stratégies pharmacologiques comprennent le choix de médicament, la posologie et la préparation du médicament, le choix de médicaments psychotropes concomitants, le changement de médicament, l'ajout d'un médicament pour agir sur la perte de poids ou prévenir la prise de poids, et les médicaments pour accroître l'insulinosensibilité. Le choix de médicament et le changement de médicament peuvent avoir la plus grande influence sur les paramètres du poids et du métabolisme. Une modeste perte de poids à court terme peut se produire avec l'ajout de médicaments choisis et/ou les interventions de mode de vie. Cependant, il faut des études à long terme plus rigoureuses.

Conclusions : Bien que difficile, la prévention de la prise de poids et la promotion de la perte de poids sont possibles pour les personnes traitées aux antipsychotiques. Il faut plus de recherche, y compris des études de prévention du diabète. Nous suggérons une piste pour le contrôle de la prise de poids et de la perturbation métabolique naissante.