

DRUG BULLETIN

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Slim Pickings

The Evidence for Drug Treatment Options in Antipsychotic-Induced Weight Gain

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- ❖ Antipsychotic induced weight gain gives cause for concern in patients already at greater risk of morbidity and mortality than the general population.
- ❖ The four approved pharmacological treatments for obesity lack evidence of efficacy and safety in patients being treated with antipsychotics.
- ❖ Evidence for the efficacy and safety of other possible weight reducing medications in this population is not robust.
- ❖ Antipsychotic-induced weight gain is best managed by diet, exercise and behavioural intervention.

Introduction

Nearly all antipsychotics can induce weight gain, which in turn lowers self-esteem and causes increased morbidity and mortality¹⁻³. People with schizophrenia are at increased risk of morbidity and mortality, mainly from cardiovascular disease, compared with the general population⁴. Additionally patients with mental illness tend to have a higher body mass index (BMI) than the general population⁵. Obesity is one of the major risk factors for cardiovascular disease⁴. It is therefore very important to treat antipsychotic-induced weight gain.

Factors that contribute to obesity in schizophrenia include lifestyle factors, such as poor diet and lack of exercise, as well as weight gain induced by antipsychotics^{6,7}.

There are differing degrees of weight gain among patients treated with different antipsychotics⁷. Of the atypical antipsychotics those associated with the greatest weight gain are clozapine and olanzapine⁷. Chlorpromazine and thioridazine are

the typical antipsychotics reported to cause the most weight gain⁷.

Weight gain tends to occur within the first months of treatment and the pattern of weight gain has been found to vary with different agents¹. Thus, in long term studies clozapine has been associated with continuous weight gain, risperidone showed no weight gain initially then steadily increased without reaching a plateau, while olanzapine caused initial weight gain but reached a plateau after 40 weeks^{5,7}.

Some studies with aripiprazole have shown that patients with a low BMI gain weight, those with a moderate BMI show little weight change, and those with a high BMI lose weight^{4,7}. In studies with olanzapine, however, patients in all BMI groups gained weight⁴.

Mechanisms of Weight Gain

The specific mechanisms by which atypical antipsychotics cause weight gain are not fully understood⁸. However numerous central nervous

system (CNS), hormonal and metabolic mechanisms have been proposed¹.

Effects on serotonergic, dopaminergic, adrenergic, histaminergic, glutaminergic and anticholinergic receptors are all thought to promote weight gain^{9,10}. The balance between oestrogen and testosterone is also implicated⁹. Insulin sensitivity that can lead to insulin resistance is associated with physiological changes maintaining obesity^{1,9}. Leptin and neuropeptides are also involved in weight gain⁹. Weight gain depends on an interaction between biological, psychological and environmental factors¹. The factors inducing or reducing weight are finely balanced and weight gain can occur if this equilibrium is upset¹.

Drug Treatment Options

Generally pharmacotherapy for obesity should only be considered when non-pharmacological measures have failed¹¹. It is usually only used in patients with a BMI > 30, or a BMI > 27 with other risk factors¹¹. The aim of therapy is to lose 5-10% of baseline weight over 3-6 months and failure to meet this goal is usually an indication to stop treatment¹¹.

Approved Drugs

Currently there are only four drugs approved for weight loss in Australia¹². They are diethylpropion, phentermine, sibutramine and orlistat. Although all of these agents have been shown to produce effective weight loss, especially if used in combination with diet, exercise and behaviour modification^{13,14}, there are very few formal studies of their effectiveness in antipsychotic-induced weight gain.

Diethylpropion and Phentermine

Diethylpropion and phentermine are sympathomimetic amines, with CNS stimulatory effects, which are thought to lead to an increase in energy expenditure¹². They are dopaminergic agonists, which work by stimulating dopaminergic neurotransmitter pathways in the brain¹⁴. Both these drugs have been shown to produce effective weight loss, but are currently indicated only for short-term use¹⁴.

Their use is limited in patients taking psychotropic medication as they exacerbate psychosis and increase the risk of serotonin syndrome when taken with other serotonergic drugs^{12,13}.

There is no evidence specifically supporting their use in antipsychotic-induced weight gain^{2,3}.

Sibutramine

Sibutramine, which is a serotonin and noradrenaline reuptake inhibitor, induces a sensation of satiety¹². Some but not all studies have shown that sibutramine also increases energy expenditure¹⁴. Until recently there were no formal studies of the use of sibutramine in antipsychotic-induced weight gain⁸.

In a 12-week randomised, double-blind, placebo-controlled trial (RCT) of sibutramine, in 37 patients, with schizophrenia or schizoaffective disorder, taking olanzapine, the authors found that it may be an effective treatment for weight loss in the study population¹⁵.

Blood pressure and heart rate should be monitored in patients taking sibutramine and it should be used with caution in combination with other serotonergic medications^{1,11,15}.

Sibutramine has been reported to cause psychosis, panic and sleep disturbances and the product information cautions against its use in bipolar disorder^{2,3,12}.

Orlistat

By inhibiting gastro-intestinal lipases, orlistat prevents absorption of approximately 30% of dietary fat¹². It should be taken with a low calorie diet with <30% of the calories as fat¹². Because orlistat does not act centrally it may be a good choice for the treatment of antipsychotic-induced weight gain¹⁶. However the need for a fat restricted diet, to prevent unpleasant side effects, may limit its use¹.

In two case studies and a case series orlistat appeared to be a safe, well-tolerated and effective treatment for drug-induced weight gain^{17,18}. However there have been no formal studies of its use in antipsychotic-induced weight gain.

Other Possibilities

There are a number of other drugs, which have been reported, in a few case studies, case series

and small short RCTs, to promote weight loss in antipsychotic induced weight gain. However the evidence for their use is not robust and these medications are not approved for weight loss.

Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor, which is thought to have a potential for weight reduction mediated partly by its serotonin blocking effects^{1,20}.

Two small RCTs undertaken, in 31 and 30 patients, to show whether fluoxetine would prevent olanzapine-induced weight gain found no evidence of a weight reducing effect for fluoxetine in these patients^{8,20,21}.

Topiramate

Topiramate is a second-generation antiepileptic agent. It has a mixed profile of GABAergic and anti-glutamatergic action and has been associated with dose-related weight loss¹.

There are three case reports of weight loss observed in patients with olanzapine-induced weight gain treated with topiramate^{8,22,23,24}.

Another case study reported weight loss with topiramate and quetiapine in a paediatric patient²⁵. In one patient treated with clozapine, the addition of topiramate led to weight loss and no change in psychotic symptoms²⁶.

In an open uncontrolled study of 26 patients with bipolar disorder treated with olanzapine and topiramate over one year some benefits for controlling weight gain were noted²⁷.

A RCT of 43 women with olanzapine induced weight gain treated with topiramate led to a reduction in weight in these patients²⁸.

Although topiramate may be of some benefit in reducing weight its use may be limited by associated cognitive impairment and sedation¹.

Amantadine

Amantadine is an antiviral and an antiparkinsonian drug, which has been used to treat extrapyramidal side effects associated with antipsychotics²⁹.

In vivo studies have shown that amantadine increases dopamine, directly, by blocking dopamine uptake and indirectly, by blocking N-methyl-D-aspartate (NMDA) receptors²⁹. Since amantadine modifies dopamine and serotonin

neurotransmission it was hypothesised that it may also have weight-reducing effects²⁹.

A small case series and two open label studies found that amantadine limited weight gain or led to weight loss in patients treated with antipsychotics^{30,31,32}. In these three studies it was reported that there was either improvement, or no exacerbation, of psychotic symptoms in patients administered amantadine with their antipsychotic medication²⁹.

In a randomised, double-blind, parallel study of 125 patients taking olanzapine, who were treated for weight gain with amantadine, the authors found it to be an effective, safe and well-tolerated treatment²⁹.

In another open label trial, of 25 patients being treated with amantadine for olanzapine-induced weight gain, a weight reducing effect for amantadine was not demonstrated³³.

Amantadine can cause hallucinations, psychosis and depression^{2,12}.

Nizatidine, Famotidine and Cimetidine

Because there is a correlation between histamine affinity and weight gain, histamine-2 receptor antagonists have been considered in the treatment of antipsychotic-induced weight gain⁸. Histamine-2 receptor antagonists may induce weight loss by suppression of gastric acid secretion or by a direct effect on appetite^{16,34}.

Evidence for the efficacy of nizatidine in the treatment of weight gain in patients taking olanzapine consists of one case report³⁴, two small studies^{35,36} and two small RCTs^{37,38}. The authors in these studies concluded that nizatidine was an effective treatment for olanzapine-associated weight gain^{8,35,36,37,38}.

In a small RCT of 47 patients given nizatidine for quetiapine-induced weight gain the authors found some benefit in the nizatidine treated group³⁹.

A RCT of famotidine in 14 patients taking olanzapine for six weeks concluded that famotidine was not effective in preventing or attenuating weight gain in these patients⁴⁰.

Although cimetidine has been associated with weight loss in some trials no studies have been done of cimetidine in antipsychotic-induced weight gain¹⁶.

There were no significant adverse effects reported with the use of nizatidine or famotidine in any of these studies³⁶⁻⁴⁰.

Metformin

Metformin is an oral hypoglycaemic agent. It reduces hepatic glucose production and increases peripheral utilisation of glucose¹². It has been shown to improve insulin sensitivity and decrease body weight⁴¹.

One small paediatric study of 19 patients, evaluated the effect of metformin on weight gain associated with atypical antipsychotic therapy⁴². The authors concluded that metformin holds promise as a treatment for weight-gain in paediatric patients receiving antipsychotics⁴².

A small pilot RCT study of metformin in five obese women who had received antipsychotics for many years found that body weight loss was higher in the placebo group than in the metformin group⁴¹.

There is a risk of lactic acidosis with metformin¹².

Reboxetine

Reboxetine is a selective noradrenaline reuptake inhibitor and weakly inhibits serotonin reuptake¹². The adrenergic system may play a role in weight gain^{8,43}

A 6-week RCT was conducted in 26 patients to test the effect of reboxetine on the prevention or attenuation of weight gain associated with olanzapine⁴³. From this trial the authors concluded that reboxetine might reduce olanzapine-induced weight gain⁴³.

Naltrexone

Naltrexone, which is an opioid antagonist, has been shown to decrease weight by reversing hunger and craving¹¹.

However, although, two small pilot studies have been conducted with antidepressants and lithium, no trials have been reported in antipsychotic-induced weight gain¹¹.

Bupropion, Oestrogen and Quetiapine

Bupropion may be effective in obesity when combined with diet³.

Sixty-four patients on clozapine were switched to quetiapine plus clozapine in a 10-month retrospective open-label trial. The combination was found to reverse weight gain and improve glycaemic control^{1,44}.

Oestrogen is known to promote weight loss by various mechanisms so this could possibly be studied in relation to antipsychotic-induced weight gain^{2,9}.

However there is little evidence for the use of any of these agents in antipsychotic-induced weight gain^{2,3}.

Conclusion

From the evidence available there are no proven safe and effective pharmacological interventions for overweight patients taking antipsychotics¹.

Until these and other novel strategies have been properly tested and found to be effective antipsychotic-induced weight gain is best managed by diet, exercise and behavioural intervention¹.

References are available on request.

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