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REVIEW

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Weight gain and glucose and lipid metabolism disturbances during antipsychotic medication

A review

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Abstract Antipsychotic medication is the mainstay of treatment for functional psychotic illnesses. However, for some patients weight gain and the disturbances in blood-lipid levels and glucose balance associated with their use are significant disadvantages, and pose health risks that may affect prognosis. A substantial body of evidence suggests that weight gain is at least partly related to the blocking effects of antipsychotic medication on serotonin- and histamine-mediated neurotransmission. The disadvantages associated with weight gain can be reduced by an appropriate choice of antipsychotic and avoidance of polypharmacy, by regular monitoring of the patient's weight, and, if necessary, by the patient's participation in a dieting programme.

Key words antipsychotic agents · hypercholesterolaemia · hyperglycaemia · hypertriglyceridaemia · weight

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Introduction

The choice of drug to treat a patient with psychosis is one of the most critical clinical decisions. The conventional antipsychotics, which have been used since the early 1950s, remain effective, especially for the treatment of delusions and hallucinations, and when used regularly, for the prevention of occurrence of new psychotic episodes. However, some 20–30 % of schizophrenia patients respond only partly, or not at all, to conventional antipsychotics [1]. In addition, their use is often associated with various neurological and other kinds of adverse effects, which may have negative effects on compliance, quality of life and prognosis.

Recent years have seen the development of new antipsychotic compounds with fewer neurological adverse effects and more extensive effects on various psychotic symptoms. These second-generation antipsychotic medicines (such as clozapine, olanzapine, quetiapine, risperidone, sertindole and ziprasidone) are a heterogeneous group of compounds that have proved more effective than conventional antipsychotics for the treatment of negative, affective and cognitive symptoms associated with psychoses [1]. Because they are better tolerated, their use has markedly increased over the last years.

Antipsychotic medication is often used for long periods, years or decades, which makes long-term tolerability particularly important. Weight gain and metabolic disorders are associated with psychoses independently [2] and also with antipsychotic therapy with conventional antipsychotic medicines and clozapine. Recently, attention is increasingly being paid to weight gain associated with the use of the new second-generation antipsychotic medicines [3]. Weight gain can affect patient compliance, impair quality of life and lead to withdrawal from social contact [4].

Long-term weight gain is the most important risk factor for adult onset diabetes. The metabolic syndrome associated with obesity also involves other significant

risk factors for cardiovascular disease (Table 1) [5]. Consequently, weight gain can have a negative effect on the prognosis in a patient on antipsychotic medication. The prognosis is often further adversely affected by other factors prejudicial to health, such as smoking and poor dietary habits [6, 7]. For instance, in patients with schizophrenia, significant excess mortality from cardiovascular disease has been observed [8]. Metabolic changes can also increase risks of neurological adverse effects, because diabetes has been found to be a risk factor for abnormal movements and tardive dyskinesia [9, 10].

Prevalence of weight gain

Weight gain in association with use of the conventional antipsychotics was noted as early as the 1950s in connection with the use of chlorpromazine [11]. At the time, greater attention was paid to neurological adverse effects of antipsychotics, although weight gain can be observed in up to 50 % of patients on long-term antipsychotic medication. Weight gain is common with conventional low-potency antipsychotics such as thioridazine and chlorpromazine (Table 2) [3, 11]. Weight gain caused by them has been found to be between 1.5 and 4 kg during the first month of treatment, ceasing usually within one to two years of starting drug treatment.

With the second-generation antipsychotics clozapine and olanzapine most weight gain occurs during the first four to five months of treatment, but it continues for up to a year with olanzapine, and even longer with clozapine [12, 13]. With risperidone there is weight gain for some two to three months after the start of treatment. There are differences between the second-generation antipsychotics, because for example, weight gain associated with use of olanzapine and risperidone has been reported to be more easily reversed than the weight gain associated with use of clozapine. The effects of quetiapine and ziprasidone to weight have been less prominent [14–16].

Table 1 Disorders associated with the metabolic syndrome

Adiposity
Increased blood pressure
Impaired glucose tolerance and adult onset diabetes
Increased risk of coronary artery disease
Increased serum triglyceride concentration
Decreased high-density lipoprotein cholesterol level
Coagulation system disorders
Increased serum uric acid concentration

Table 2 Weight gain associated with antipsychotics [18]

Drug	Average weight gain (kg)	Weight gain in 10 weeks (kg)
Perphenazine	5.77	–
Clozapine	5.67	3.99
Chlorpromazine	4.19	2.10
Olanzapine	4.17	3.51
Thioridazine	2.81	3.49
Quetiapine	2.49	–
Risperidone	1.67	2.00
Fluphenazine	1.13	0.43
Haloperidol	0.51	0.48
Ziprasidone	0.28	0.04

Risk factors of weight gain

The mechanism behind the weight gain associated with use of antipsychotics is not fully known, and many factors seem likely to be involved. Little is known about them, but a low body mass index (BMI) when treatment is begun may predict that weight gain is likely to be significant, but the results of studies are conflicting [14]. Weight gain has also been reported to be greater in younger patients, and in men. In addition, racial variation can occur, and weight gain and adverse changes in lipid levels are reported more often in African American individuals [17]. It has been suggested that weight gain is related to more beneficial result of treatment, but patients who are not responding well often have their medication discontinued, which may give a spurious correlation between weight and efficacy. So this finding may simply reflect a relationship with duration of drug treatment [18].

Mechanisms of weight gain

Even before conventional antipsychotics came into use, psychotic patients were often seen to lose weight during acute phases and gain weight during recovery phases, as appetite returned. The phases of psychosis are thus significant in terms of a patient's changes in weight. In schizophrenic patients negative psychotic symptoms, such as anhedonia and apathy may expose the patient to weight gain [4]. Lack of physical exercise due to fatigue caused by antipsychotics, and the consumption of high-calorie drinks because of anticholinergic effects (e. g. dry mouth) may also increase weight [19]. In addition, alcohol abuse is a common comorbid condition in schizophrenia [20] and may contribute to weight gain. Cognitive impairment, depression and deficient life control can also lead to unhealthy diet and poor health behaviour.

Despite efforts to target the effects of antipsychotics on limbic areas to reduce neurological adverse effects, they all have wide-ranging effects on various neural networks. Serotonin-mediated neurotransmission appears to be critical in relation to regulation of eating behaviour. In animal studies, 5-HT-$_{1A}$-, 5-HT-$_{1B}$- and 5-HT-$_{2C}$-receptor agonists reduce food intake and the corre-

sponding antagonists or a lack of 5-HT-$_{2C}$-receptors increase it. In rats, the activation of the 5-HT-$_{2C}$-receptor has also been reported to reduce eating [14]. Antipsychotic drug treatments may block all of the serotonin-binding sites mentioned above, and may therefore increase food intake. In some studies relationships between dosages of the antipsychotics and weight gains have been demonstrated when using chlorpromazine, olanzapine and risperidone, but no similar relationships have been reported with other antipsychotics [21].

The hypothalamus is one of the areas critically involved in weight regulation, and its histamine-mediated tract connections are involved in regulating energy balance and leptin-mediated food intake. Leptin is a peptide hormone produced by adipocytes, which conveys signals to the central nervous system about the mass of adipose tissue [22]. In animal studies the administration of leptin has been shown to reduce food intake, and in humans weight increase is related to increased leptin levels [23]. Patients suffering from anorexia nervosa have low levels of leptin secretion, which has been shown to increase as weight is gained [24]. Weight gain has been observed to be associated with increased leptin secretion at least when using clozapine, olanzapine, and also conventional neuroleptics [25]. With clozapine this starts by the end of the first week of treatment, but effects on weight and BMI can be seen only at the end of the third week of treatment. With olanzapine the corresponding changes occur about a week later [26]. Increased leptin secretion is, however, considered to be secondary to increased appetite and weight gain [11, 19]. It has also been suggested that treatment with antipsychotic drugs may reduce central nervous system sensitivity to the body weight-controlling leptin signal [26].

It has also been reported that the use of histamine-1-receptor inhibitors (some antipsychotics and antidepressants) may also be associated with weight gain. In addition, adrenergic and dopaminergic neural activities are considered to be significant in relation to appetite regulation, and stimulation of these neural networks reduces food intake [27].

Changes in glucose and lipid metabolism

Various mental disorders, e. g. depression, bipolar affective disorder and schizophrenia [2, 28] have been reported to be associated with increased risk of diabetes. This risk may be related to the disorders of eating behaviour often associated with these mental disorders.

Use of second-generation antipsychotics has been reported to be associated with deterioration of therapeutic equilibrium in diabetes and the occurrence of new cases of diabetes, especially when patients have been obese on starting treatment, or have gained weight significantly during the initial stages of treatment [12, 29]. It is difficult to estimate how commonly diabetes or impaired glucose tolerance occurs. The incidences have varied between 2.7 and even 36.6 %. However, the groups studied have been highly selected. In most cases the risk of worsening of diabetes or impairment of glucose tolerance was two to four times higher than it would have been in the population in general [12, 30, 31]. Weight gain is associated with increased insulin resistance and impairment of glucose control. Second-generation antipsychotics may also reduce insulin secretion while 5-HT-$_{1A}$ receptor blockade reduces the response of β-cells of the pancreas. Some second-generation antipsychotics may be associated with insulin resistance [32]. Although increases in patients' blood glucose levels have been fairly minor, e. g. 0.1–0.2 mmol/l with olanzapine and 0.7 mmol/l with clozapine, they have been greater than those caused by haloperidol, for example, and may increase the risk of cardiovascular disease in psychotic patients and contribute later to excess mortality in this vulnerable patient group.

During clozapine treatment an increase of serum cholesterol and triglyceride levels has been reported [12]. A statistically significant relationship has been found between the increase in cholesterol caused by the administration of olanzapine and weight gain [13, 33]. Changes in lipid levels can be attributed to weight gain associated with use of these compounds, because fat accumulating in the waist enhances release of free fatty acids in the liver, and accelerates liver triglyceride synthesis and very-low-density lipoprotein secretion. Increases in free fatty acid concentrations may also inhibit metabolism of glucose, especially in muscle tissue, resulting in impaired glucose tolerance and type-2 diabetes [5].

Weight gain and treatment

An appropriate choice of antipsychotics, avoidance of polypharmacy, diet therapy, regular monitoring of body weight, and, if necessary, participation in diet counselling can reduce problems resulting from weight gain and metabolic changes [18]. The aim of diet therapy is reduction of amounts of fat in the diet, and the object of physical exercise is to increase calorie consumption, even though the results of the latter have been only moderate. Monitoring of patients' body weight is particularly necessary during the first weeks and months of treatment [11]. Although there may be a relationship between the dose of antipsychotic agent and weight gain, dosage should not be reduced if weight gain occurs [17]. Changing the antipsychotic may be useful, but recommendations for change cannot be given until further comparisons of various molecules have been conducted.

So far there are no data about employment of anti-obesity medications in reduction of the weight gain associated to antipsychotics. In addition, some of these compounds affect dopamine and serotonin receptors, which are also the targets of antipsychotics. This is why the use of e. g. sibutramine has been considered to be contraindicated in psychotic patients because of risks of adverse effects, such as worsening of the psychosis or

onset of the serotonin syndrome, as a result of inhibition in dopamine, noradrenaline and serotonin re-uptake. Orlistat, which inhibits lipid absorption, has proved effective in weight reduction, but no study results are available of its use to prevent or alleviate weight gain associated with antipsychotics. There has been experimental use of fenfluramine, amantadine, nizatidine, metformin and tryptophan, resulting mostly from data from open trials and case studies [34, 35]. Increases in prolactin secretion caused by dopamine-receptor blockade may result in increases in androgen production, and changes in the oestrogen/androgen ratio may increase appetite and add to fat accumulation. Its antagonist, amantadine (a dopamine agonist) has been found to prevent weight gain associated with use of e. g. olanzapine, and to reduce patients' weights. However, with amantadine psychotic symptoms may aggravate. Use of tryptophan has been reported to be associated with eosinophilia and myalgia [11].

Psychotic patients with lipid metabolism disorders can receive not only diet therapy but can also be treated with e. g. statins. However, no clinical guidelines specific to psychotic patients can yet be given. Results of open trials show that triglyceride levels in patients who received gemfibrozil or pravastatin did not increase during treatment with olanzapine [33]. If statins are used, in addition to considering the costs of treatment, attention should be paid to the fact that some statins are metabolized via cytochrome 3A4. Caution is therefore needed in using any of them in conjunction with quetiapine and ziprasidone, which are metabolised via the same pathway [36]. Attempts can also be made to reduce the adverse effects of lipid metabolism disorders by means of low-dose aspirin.

Of the severe mental disorders, in particular schizophrenia results in incapacity for work, impairs quality of life, and is associated with a substantially high mortality rate from suicide even at a relatively young age [37]. Because the disorder is so severe and its treatment so difficult, adverse effects associated with its treatment have been considered more acceptable than those associated with treatment of some other disorders. As antipsychotics have improved, the attitude towards serious adverse effects has started to change, and the second-generation antipsychotics have in many respects significantly improved the drug treatment of severe mental disorders. They cause less neurological adverse effects than the conventional antipsychotics. Compliance is better than with the conventional early antipsychotics, and weight gain and metabolic problems do not detract from these advantages, and choice of an antipsychotic should continue to be based on assessment of the overall condition of the patient, not on assessment of individual adverse effects.

Data relating to the benefits of use of antipsychotics in the treatment of psychoses are convincing, but further information is needed about the significance of advantages and disadvantages during long-term treatment. Disadvantages associated with use of medication should be minimised by, for instance, appropriate monitoring and documenting in patient charts the effects of regular antipsychotic medication on patient's weight and metabolism (Table 3) [38]. Although there are no established follow-up guidelines, recommendations based on the more general guidelines suggested in Table 3 may be useful. In addition, actions in relation to other factors associated with risks to health (e. g. smoking, hypertension, diabetes) during treatment should also be carried out [7].

Table 3 Monitoring and therapeutic interventions in a patient at risk of weight gain or on second-generation antipsychotics

Weight and body mass index or waist circumference measurement: during every visit
Measurement of blood pressure: during every visit
Determination of blood glucose, triglyceride, cholesterol and prolactin levels once or twice a year, more often (e. g. every three months) in high-risk patients.
Patient should keep food record if weight gain has been more than 4 kg since the beginning of treatment
In case of weight increase over 7 % of the weight when starting treatment: consultation with a dietician or nutritionist, caloric restriction, more effective physical exercise

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