OLANZAPINE - FOCUS ON THE CARDIOMETABOLIC SIDE EFFECTS

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ABSTRACT

In this article, we review the recent findings concerning weight gain, diabetes mellitus (DM), hyperlipidemia, cardiovascular side effects in patients receiving olanzapine. It will consider the OLZ is associated with an increase in metabolic syndrome or cardiovascular events, and knowledge of these risks is crucial for further monitoring of patients with OLZ-treatment. Although it is one of the most commonly prescribed and effective AATPs, olanzapine causes the most weight gain and metabolic impairments in humans. As noted with glucose abnormalities and antipsychotics, olanzapine has the greatest propensity for causing proatherogenic hyperlipidemia. The mechanism of dyslipidemia with OLZ is poorly understood, but OLZ has been shown to increase lipogenesis, reduce lipolysis, and enhance the antilipolytic effects of insulin in adipocytes. Olanzapine can induce cardiomyopathy in selected patients.

Taken together, all mentioned data indicate that interventions aimed at the amelioration of obesity and cardiovascular illness need to be as multipronged and complex as the contributing psychosocial, behavioural, and biological factors that make obesity and cardiovascular illness more likely in patients with severe mental illness, including schizophrenia.

Keywords: *olanzapine, weight gain, dyslipidemia, cardiovascular disease*

SAŽETAK

U ovom članku, razmatramo nedavna saznanja u vezi dobijanja u težini, šećerne bolesti (DM), hiperlipidemije i kardiovaskularnih neželjenih efekata kod pacijenata koji su na terapiji olanzapinom. Uz pretpostavku da je olanzapin u vezi sa povećanim rizikom za nastanak metaboličkog sindroma i kardiovaskularnih događaja, od presudnog je značaja poznavanje potencijalnih rizika kako bi se sproveo monitoring ovih pacijenata. Iako olanzapin (OLZ) predstavlja jedan od najčešće propisivanijih i najefektnijih atipičnih antipsihotika, ipak nosi i najvišu stopu rizika za nastanak metaboličkih smetnji kod ljudi. Olanzapin uzrokuje poremećaj metabolizma glukoze, povećava lipogenezu, smanjuje lipolizu, povećava antilipolitičke efekte insulina u adipocitima što uzrokuje dislipidemiju i doprinosi visokom proaterogenom potencijalu olanazapina. Opisani su i slučajevi kardiomiopatije usled primene olanzapina.

Sumarno posmatrano, literaturni podaci ukazuju na neophodnost složenih preventivnih i terapijskih protokola kod pacijenata sa mentalnim poremećajima, uključujući i shizofreniju, a koji su na terapiji olanzapinom, usmerenih na smanjenje psiholoških i bioloških faktora rizika za kardiovaskularne bolesti.

Ključne reči: *olanzapin, povećanje telesne težine, dislipidemija, kardiovaskularna oboljenja*

INTRODUCTION

Antipsychotics were first introduced into clinical practice in the 1950s and approved in 1996 by the FDA.

Antipsychotics are now frequently used beyond their core indications of schizophrenia and bipolar disorder. Off-label use of antipsychotics is frequent in major depressive disorder and other mood disorders, anxiety disorders and dementia (1-4). In recent years, the atypical antipsychotics or second-generation antipsychotics have become the drugs of choice for acute psychoses. They are "atypical" as they are differentiated from "conventional" or first-gen-

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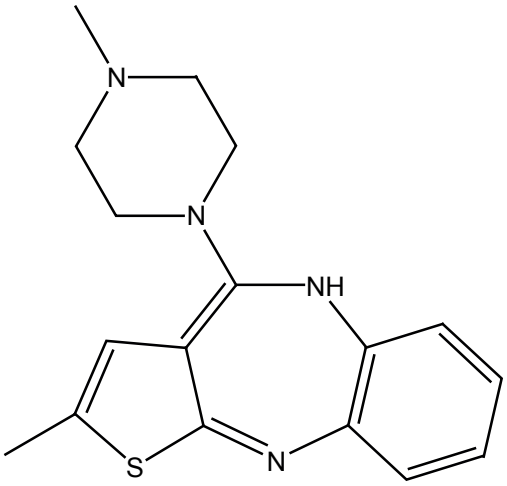

Figure 1. Olanzapine ($C_{17}H_{20}N_4S$) structure

eration antipsychotics based on their clinical profile. They have fewer side effects regarding extrapyramidal symptoms when compared to typical antipsychotics. Schizophrenia is a devastating illness that affects up to 1% of the population; it is characterized by a combination of positive symptoms, negative symptoms, and cognitive impairment. The atypical antipsychotic (APs) drugs have become the most widely used agents to treat a variety of psychoses because of their superiority with regard to safety and tolerability profile compared to conventional/'typical' APs (1-4).

Olanzapine (Figure 1) (OLZ; $C_{17}H_{20}N_4S$; 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine) is an antipsychotic drug of the thienobenzodiazepine class that is effective in treating schizophrenia and acute manic episodes, and in preventing the recurrence of bipolar disorders (5). It is as has been shown to have some therapeutic advantages over other classic antipsychotics in terms of symptom reduction and its adverse event profile. It has a low propensity to cause extrapyramidal effects or sustained increases in prolactin levels (6, 7). Nevertheless, treatment with OLZ is associated with a higher risk of weight gain and, more extensively, metabolic syndrome than other typical and atypical antipsychotics (8).

Olanzapine is known as MARTA (multi-acting receptor targeted antipsychotics). Proposed mechanisms of action of atypical antipsychotics as well as olanazapine, is dopaminergic and serotonergic modulation and induction

Table 1. Potential clinical efficacy, benefits and possible effects related to the mechanisms of action of olanzapine. EPS, extrapyramidal symptoms

Mechanism of action	Clinical efficacy	Possible effects
D_2 antagonism	↓ positive symptoms	EPS ↓negative symptoms ↑ cognitive symptoms hyperprolactinaemia
D_2 partial agonism	↓ positive symptoms ↓ negative symptoms ↓ cognitive symptoms	little or no EPS behavioral activation
5-HT_2A antagonism	↓ negative symptoms	↓ EPS ↑ weight gain hyperphagia and obesity ↑metabolic syndrome
5-HT_1A partial agonism	↓ negative symptoms ↓ cognitive symptoms ↓ anxiety symptoms ↓ depressive symptoms	No adverse effects
Muscarinic antagonism	↓ EPS	↓ anticholinergic symptoms e.g. dry mouth, constipation, tachycardia
Muscarinic agonism	↓ psychotic symptoms ↓ cognitive symptoms	No adverse effects
Adrenergic α_1 and α_2 antagonism	No effects on negative and positive buhevior symptoms	↓adrenergic symptoms e.g. orthostatic hypotension and consequently induced tachycardia hyperphagia and obesity ↑metabolic syndrome
Histamine H_1 antagonism	↓ positive symptoms	↑ sedation ↑ weight gain hyperphagia and obesity ↑metabolic syndrome
Glutamate modulation	↓ positive symptoms ↓ negative symptoms ↓ cognitive symptoms ↓ illness progression	No adverse effects

of neuroplasticity. OLZ shares higher affinity to 5-HT_2A receptors than D_2 receptors (high 5-HT_2A/D_2 ratio). In comparison to the other atypicals, olanzapine presents high affinity for serotoninergic 5-HT_2A, 5-HT_2C, 5-HT_3, and 5-HT_6 receptors, medium affinity for dopaminergic D_1, D_2, D_3, D_4, D_5, and muscarinic M_1–M_5 receptors, low affinity for adrenergic α_1 and α_2 receptors, and the highest affinity for histamine H_1 receptors (olanzapine is the most potent histamine H_1 antagonist known) (*Table 1*) (9, 10).

Although the usual dose range for olanzapine is 5–15 mg/d, there are no standard reference values with respect to the expected concentrations of olanzapine after therapeutic administration. In clinical studies, steady state blood (plasma) concentrations of olanzapine are rarely over 150 ng/mL, but the potential for toxicity has been suggested at concentrations as low as 100 ng/mL (11).

Approximately 85 % of an oral OLZ dose is absorbed but, as about 40 % is inactivated by first-pass hepatic metabolism, its oral bioavailability is about 60 %. OLZ has a mean half-life in healthy individuals of 33 hours (range 21-54 hours). Peak plasma concentrations are reached within six hours. The drug is approximately 93 % bound to plasma proteins, mainly albumin (90 %) and alpha 1-acid glycoprotein (77 %). Its distribution volume is 16.4 ± 5.1 L (X±SD). Mean apparent plasma clearance is 26 L/h (range 12-47 L/h). After the administration of [14C]-OLZ in a single load pharmacokinetic study, approximately 87 % of the radioactivity was excreted, with 30 % appearing in the faeces and 57 % in the urine (10-12).

Psychiatrists have gradually prescribed antipsychotic drugs in come to reduce psychiatric symptoms, and extrapyramidal symptoms and tardive dyskinesia occur less frequently with atypical agents. Beside that, these medications may present a different set of adverse effects (10-12).

In this article, we review the recent findings concerning weight gain, diabetes mellitus (DM), hyperlipidaemia, cardiovascular side effects in patients receiving olanzapine. Evident increase in cardio-metabolic side effects during olanzapine administration inevitably leads to a question of its effect on the cardiovascular system of diseased psychotic patients. Bearing in mind that the treatment of these diseases is most often lifelong, it is clear that the degree of exposure of treated patients with olanzapine is long lasting, and for these reasons, not only the positive therapeutic effects of the drug must be seriously analyzed, but also the degree of impact of its adverse effects on the general health of the diseased.

Atypical antipsychotics are responsible for increasing cardiovascular risk by more than 30% in schizoid patients (10). Similar results were also seen in the increased risk for the development of metabolic syndrome and the risk of diabetes. Given that these drugs have a significant place in consumption, their impact on the health budgets in the countries where they are used is high (10). The treatment of cardiovascular and metabolic complications caused by the use of atypical antipsychotics is inevitable and this cost represents additional pressure on health funds (11, 12).

It will consider the OLZ is associated with an increase in metabolic syndrome or cardiovascular events, and knowledge of these risks is crucial for further monitoring of patients with OLZ-treatment. Recognizing these complications in addition to the necessary monitoring, opens space for the development of new drugs or procedures that need to eliminate or at least significantly reduce the consequences of cardiometabolic complications caused by the application of atypical antipsychotics, in this case olanzapine.

WEIGHT GAIN

Weight gain and obesity are critical issues in patients with schizophrenia. The abnormal nutritional status and 'developmental' obesity in schizophrenia have been described more than half-century ago. To date, there are over 2600 papers indexed by Medline on the topic of weight gain and obesity in schizophrenia. Patients with schizophrenia consume unhealthy food (13-15). A recent meta-analysis of 31 studies about dietary patterns identified a high consumption of saturated fat and low intake of fruit and dietary fiber. Also, controlled investigation indicated that patients with schizophrenia had higher daily intake of calories and protein per kilogram of body weight, which was independent of BMI. Social isolation, low interest in social achievement, and unmarried and unemployed status are common in patients with schizophrenia and lead to decreased levels of participation in sports and other mainstream physical activities (14).

The importance of neurotransmitter and hormonal effects in the weight accrual of patients with schizophrenia has been studied for olanzapine. Leptin levels were similar in schizophrenia patients and healthy control subjects with comparable BMIs (15). An inverse association was observed for baseline weight and leptin levels with the extent of weight gained during 3–6 months of antipsychotic monotherapy (16). This study suggesting a drug--mediated disruption of the hypothalamic appetite control, as well as prevous animal study, also indicated that olanzapine increased the orexigenic NPY mRNA and decreased the anorexigenic POMC in the arcuate nucleus (17) and upregulated ghrelin and ghrelin signaling, leading to hyperphagia.

Histaminergic transmission is involved in energy homeostasis and also seems to be relevant to antipsychotic-related weight gain, as the extent of histamine H1 receptor (H1R) antagonism of antipsychotics was the best predictor of the degree of weight gain in clinical studies. 5-HT2c antagonism has been implicated in antipsychotic drug-related weight gain too, and most second-generation antipsychotics, especially for olanzapine, which is a potent 5-HT_2c antagonist. Synergistic effects between the blockade of D_2 receptors and 5-HT_2a or 5-HT_2c receptors might play a key role in triggering a cascade of events that lead to increased energy intake and weight gain (18-22).

In a retrospective analysis of 1191 patients diagnosed with schizophrenia or schizoaffective disorder treated with olanzapine (23), approximately 15% of subjects had a rapid change of ≥7% body weight during the first 6 weeks of treatment, with a mean weight gain of 1.8–3.2 kg (about 4% of the baseline body weight) during the first 2 weeks. Increasing evidence indicates that antipsychotics have greater orexigenic weight gain potential in children and adolescents than in adults (24) and that young patients receiving antipsychotics are at increased risk of being or becoming overweight or obese. A recent comparison of pooled long-term studies (median followup = 201 days) of patients treated with olanzapine indicated a mean weight gain of 4.8 kg in adults, but 11.2 kg for adolescents (22-24). A debate is continuing with regard to the inverse relationship between baseline BMI and antipsychotic- induced weight gain. Pooled longitudinal data in patients treated with olanzapine (mean modal dose = 13.3 mg/day) indicated that the slowing in the rate of weight gain observed after 2–4 months of treatment was greatest for patients who were obese at baseline (25, 26).

METABOLIC SYNDROME

Also, atypical antipsychotics such as olanzapine often induce excessive weight gain and type 2 diabetes. In the past decade there have been numerous case reports, retrospective studies, and epidemiological investigations suggesting that certain OLZ may be associated with a great risk of DM. Although it is one of the most commonly prescribed and effective AATPs, olanzapine causes the most weight gain and metabolic impairments in humans. By World Health Organization criteria, 10.1% of patients developed diabetes mellitus (DM) after only 6 weeks of antipsychotic therapy (P =0.016) (27-28).

However, the mechanisms underlying these drug-induced metabolic perturbations remain poorly understood. Clinical studies have suggested the involvement of multiple genes, including those that encode the histamine, α-adrenergic, and serotonin (5-HT) receptors. Among them, *Htr2c* encodes the 5-HT 2C receptor, which acts in the brain to regulate food intake, body weight, and glucose metabolism (29, 30). Blockade of HTR2C signaling in mice leads to hyperphagia and obesity (31) that resemble AATP-induced metabolic symptoms in humans. Rates of metabolic syndrome are significantly higher in schizophrenia than in the general population. OLZ, as an atypical antipsychotic, has been associated with detrimental effects on metabolic risk factors. The pathomechanisms that underlie metabolic syndrome as a complication of antipsychotic treatment are not fully understood. Probably, the effects of OLZ on histamine H1, serotonin 5-HT2c and muscarinic M3 receptors are thought to play a central role. In addition, antipsychotics may have direct effects that cause leptin insensitivity as well as on appetite regulation (30-33).

Olanzapine, after clozapine, shows the strongest association with the risk for diabetes. Other studies have demonstrated significant changes in blood glucose levels with antipsychotic therapy despite not measuring other markers of glucose-insulin homeostasis. Lindenmayer and colleagues randomized 157 patients with schizophrenia to 14 weeks of therapy with clozapine, haloperidol, olanzapine, or risperidone. Fasting blood glucose was measured at baseline, at 8 weeks, and at end point (34, 35).

Olanzapine was associated with a significant increase in fasting glucose at end point (mean change from baseline 14 mg/dL, P < .02). Glycosylated hemoglobin (HbA1c) has been used as a surrogate marker for insulin resistance and glycemic control in the assessment of some antipsychotic medications. Olanzapine is associated with elevations in HbA1c levels. In some patients, a direct effect of olanzapine on pancreatic β-cell function may be present (36) but more commonly the accumulation of body weight with central adiposity, and the resultant increase in insulin resistance, would explain the development of diabetes mellitus over time.

Using the Food and Drug Administration (FDA) adverse events database, the risk of diabetes mellitus was increased for olanzapine, risperidone, clozapine and quetiapine, whereas a decreased risk was found for haloperidol, aripiprazole and ziprasidone (34, 36).

Both typical and atypical antipsychotics can cause significant increases in cholesterol, triglycerides and low-density lipoprotein cholesterol. The risk of hyperlipidaemia differs for individual antipsychotics. The risk of hyperlipidaemia appears higher for patients under treatment with clozapine and olanzapine (37) particularly for younger patients. *Simpson* and colleagues found that olanzapine, but not ziprasidone, significantly increased total cholesterol (median change from baseline to end point at 6 months, 13 mg/dL, P = .03) and low-density lipoprotein (LDL) cholesterol (median change from baseline to end point at 6 months, 17 mg/dL, P = .04) (37, 38).

In a further study, lipids were measured at multiple time points over 28 weeks, and olanzapine was associated with significant increases in total cholesterol. Olanzapine has been shown to be associated with unfavourable lipid derangements compared with aripiprazole. As noted with glucose abnormalities and antipsychotics, olanzapine has the greatest propensity for causing proatherogenic hyperlipidaemia. The mechanism of dyslipidaemia with OLZ is poorly understood, but OLZ has been shown to increase lipogenesis, reduce lipolysis, and enhance the antilipolytic effects of insulin in adipocytes (37-40).

CARDIAC DYSFUNCTION

Schizophrenia is associated with increased mortality and reduced life expectancy, with cardiovascular disease being the most frequent cause of death. Antipsychotics have detrimental effects on different risk factors for cardiovascular disease (41).

Patients with schizophrenia are at high risk of metabolic syndrome, a cluster of risk factors for cardiovascular disease. Prevous cohort study confirmed that 40% percent of 3470 French patients with schizophrenia (mean age at inclusion 39.3 years) died during an 11-year follow-up period. In the Olmstead County study, patients with schizophrenia had a significantly increased mortality, in particular from cardiovascular disease (42-44). Patients with schizophrenia frequently have multiple risk factors for cardiovascular disease. Firsty, excess prevalnce od obesity and increased BMI in patients with mental disorder in one of the major factor for develpment of cardiovascular disease (44). Monitoring glucose is crucial, and patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Beside abdominal obesity, dyslipidemia, hypertension and diabetes mellitus and have additive effects on an individual's risk of developing diabetes mellitus and cardiovascular disease. Rates of smoking are higher in schizophrenia patients than in the general population. Schizophrenic patients who smoke are at higher risk of death as well as death from cardiovascular disease than schizophrenic patients who do not smoke (45, 46).

Furthermore, typical and atypical antipsychotics are associated with a significant dose-related increase in the risk of sudden cardiac death. Some of the cases of sudden cardiac death have been associated with cardiac arrhythmia, in particular torsade de pointes, possibly secondary to a prolongation of the QT interval (45-47). But, OLZ was initially linked to potential QTc prolongation. Extensive studies have shown modest Qtc interval prolongations for these patients that are most likely not clinically relevant and with no evidence for increased mortality by disturbed Ot-changes by OLZ (48). But, study conducted by Morissette indicate that olanzapine possesses direct cardiac electrophysiological effects. They demonstrated that olanzapine can prolong cardiac repolarization in a reverse frequency- dependent manner by blocking time-dependent outward potassium current involved in cardiac repolarization. In fact, they shown that olanzapine 5.7 μM caused a significant prolongation of cardiac repolarization (13%) (49).

Adverse hemodynamic effects are possible with olanzapine, particularly orthostatic hypotension, bradycardia and tachycardia (50), which are most likely owing to adrenergic α1 blockade. Because of the antagonism of α1-receptors, OLZ is associated with orthostatic hypotension and consequently induced tachycardia, but in lowpotency. This risk of a OLZ-hypotension is not pronounced for olanzapine. Especially in eldery, OLZ is associated with increased risk of cardiovascular disease and also, this drug has also been associated with venous thromboembolism and pulmonary embolism. Again, OLZ seems to be associated with a low risk (51, 52).

Interestingly, some of previous clinical study, reported about the effects of olanzapine on inducing of specific cardiac disorders, such as myocarditis and cardiomyopathy. These rare but potentially fatal complications of antipsychotic treatment, myocarditis and cardiomyopathy are associated with antipsychotics are most frequently seen under treatment with clozapine, but can also occur with olanzapine treatment (53). Malays reported about 28-year-old male patient with bipolar disorder who taking olanzapine and lorazepam for almost 10 years and presented with weight gain, diabetes, and anasarca. Evaluation of the patient revealed he was in heart failure. The reason for his heart failure was ambiguous and an investigation into it revealed negative results. Literature search conducted showed a few reported cases of putative olanzapine induced cardiomyopathy and this is one of them. Well, cardiomyopathy is a less known side effect of OLZ (54). The main proposed mechanism for cardiomyopathy is myocarditis and myopericarditis by direct toxicity or allergic reaction. In animal studies, three months of olanzapine treatment was shown to induce ventricular hypertrophy of the heart. Cardiac lesions induced by neuroleptic drugs in the rabbit (55).

In practice, olanzapine induced cardiac disorder should be considered in a patient who develops dyspnoea or other signs of the heart failure (56). Olanzapine should be withdrawn in those cases and treatment of heart failure should be done on a routine basis. Olanzapine can induce cardiomyopathy in selected patients. Early recognition and cessation of the drug is required to prevent irreversible myocardial damage. Cardiac functional assessment is periodically required for the patients taking antipsychotics. Cautious use is required in patients with known heart disease.

CARDIOMETABOLIC MONITORING OF PATIENTS WITH OLZ-TREATMENT

Patients with severe psychiatric disorders and with antipsyhotic therapy are at increased risk of cardiovascular disease, although some of this risk may be conferred by the psychiatric disease or lifestyle. Weight gain, obesity, metabolic and cardiovascular disorders in patients with schizophrenia and other mental disorders are associated with a host of adverse physical and psychiatric outcomes, as well as with OLZ treatment (*Table 1*). Therefore, body weight and related metabolic indices need to be monitored routinely and targeted as part of a comprehensive and integrated care programme in patients with OLZ-treatment (33, 35, 57, 58).

Ideally, a treatment algorithm should start with healthy lifestyle education/instruction and with lower cardiometabolic risk antipsychotic than OLZ. It is reccomendation that only consider higher risk agents, such as olanzapine, when it has become clear that the physically safer medication is not sufficiently effective or tolerated. Psychiatric care providers should aim for balancing acute

and long-term efficacy as well as tolerability, and engage other medical specialists as needed to improve the overall well-being of patients with schizophrenia. American Diabetes Association and American Psychiatric Association suggested that optimal management of patients with schizophrenia should include baseline assessment on their weight, waist circumference, blood pressure, blood glucose level and lipidogram and family history on obesity, diabetes, dyslipidemia, hypertension and cardiovascular illness (33, 35). During the first three months, weight gain should be monitored on monthly basis, while biochemical analysis should be performed after the first three months, and then once a year. In patients with significant weight gain, increase of blood glucose level or dyslipidemia, the first intervention should be switch to another antipsychotic. If necessary, a patient should be referred to an endocrinologist and advised on changing their life style (57).

Suggested algorithm for cardiometabolic monitoring of patients treated with OLZ is precisely described by *Manu* and coworkers. Suggested algorithm for managing antipsychotic-related weight gain is power tool for prevention of cardiovascular disease and for decreasing of mortality in patients with psychotic disorders. Nevertheless, it is also important to consider that antipsychotics are currently the only medication class with evidence for effective treatment of psychosis (58-60).

CONCLUSION

Taken together, all mentioned data indicate that interventions aimed at the amelioration of obesity and cardiovascular illness need to be as multipronged and complex as the contributing psychosocial, behavioural, and biological factors that make obesity and cardiovascular illness more likely in patients with severe mental illness, including schizophrenia. The use of olanzapine in the treatment of psychosis, especially schizophrenia, has revolutionized the treatment of these diseases, but has led to the opening of a question and price that we have to pay in terms of the development of cardio-metabolic complications and their impact on the quality of life of the diseased. By clearly recognizing the complications and mechanism of their emergence, we are given the opportunity to better implement new therapeutic procedures, by introducing drugs of similar therapeutic potential, but with a significantly lower impact on the development of cardiometabolic complications by applying adequate hygienic dietary regimes and changing lifestyle habits.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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