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ADJUNCTIVE USE OF METFORMIN IN THE TREATMENT OF ATYPICAL ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

ADJUVANTNA PRIMENA METFORMINA ZA TRETMAN POVEĆANJA TELESNE TEŽINE NASTAO ZBOG KORIŠĆENJA ATIPIČNIH ANTIPSIHOTIKA

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Summary

Introduction. Atypical antipsychotics are the gold standard in the treatment of psychotic and other mental disorders due to their efficacy and tolerability. However, the relatively frequent occurrence of antipsychotic-induced metabolic syndrome has encouraged research into possible solutions to this problem, including the adjunctive use of metformin. The aim of this review article is to present a concise, comprehensive and critical overview of the aforementioned issue based on the analysis of available experimental research. **Material and Methods.** PubMed and Google Scholar databases were searched for relevant literature published in a fifteen-year period between 2008 and 2022. The following terms were used in the search: atypical antipsychotics, metformin, and weight gain. Only double-blind, placebo-controlled, randomized, and cohort studies were taken into consideration. **Results.** A total of 145 papers were analyzed, of which 10 papers with 852 subjects met the inclusion criteria. All the reviewed studies concluded that the adjunctive administration of metformin at a daily dose of 500 mg to 2,000 mg has significantly reduced atypical antipsychotic-induced weight gain, with a favorable effect on other metabolic parameters that were examined in the analyzed papers. **Conclusion.** Taking into account the increased cardiovascular morbidity and the consequent mortality among those who have been using atypical antipsychotics in the long term, it is necessary to assess the risks and benefits of introducing adjunctive metformin in every patient who is at risk of developing metabolic syndrome. In order to recommend the routine use of metformin in such indications, studies that would include a larger sample and a longer period of treatment are needed.

Key words: Antipsychotic Agents; Schizophrenia; Metformin; Body Weight; Metabolic Syndrome; Metabolic Side Effects of Drugs and Substances; Olanzapine

Sažetak

Uvod. Atipični antipsihotici predstavljaju zlatni standard u lečenju psihotičnih i drugih mentalnih poremećaja zbog svoje efikasnosti i podnošljivosti. Međutim, relativno česta pojava metaboličkog sindroma indukovanog antipsihoticima je podstakla istraživanja o mogućim rešenjima ovog problema, uključujući i adjuvantnu primenu metformina. Cilj ovog preglednog članka je da predstavi koncizan, sveobuhvatan i kritički prikaz navedene problematike na osnovu analize dostupnih eksperimentalnih istraživanja. **Materijal i metode.** Za pretragu literature su korišćene *Pubmed* i *Google scholar* baze podataka za petnaestogodišnji period od 2008. do 2022. godine. Termini koji su korišćeni prilikom pretrage su: atipični antipsihotici, metformin i povećanje telesne težine. Razmatrane su isključivo dvostruko slepe, placebo kontrolisane, randomizovane i kohortne studije. **Rezultati.** Analizirano je ukupno 145 radova od kojih je 10 radova sa 852 ispitanika odgovaralo kriterijumima za uključivanje. Utvrđeno je da je adjuvantna primena metformina u dnevnoj dozi od 500 mg do 2.000 mg kod osoba kod kojih je zbog korišćenja atipičnih antipsihotika došlo do povećanja telesne mase u svim istraživanjima dovela do redukcije telesne mase, uz povoljan uticaj i na druge metaboličke parametre koji su ispitivani u pojedinim istraživanjima. **Zaključak.** Uzimajući u obzir povećan morbiditet od kardiovaskularnih oboljenja i konsekventni morbiditet u populaciji osoba koje dugoročno koriste atipične antipsihotike potrebno je kod svakog pacijenta koji je pod rizikom od pojave metaboličkog sindroma proceniti potrebu za uvođenjem adjuvantnog metformina. Za preporuku rutinske upotrebe metformina za navedenu indikaciju potrebne su studije koje bi obuhvatile veći uzorak i duži vremenski period lečenja.

Ključne reči: antipsihotički agensi; šizofrenija; metformin; telesna težina; metabolički sindrom; metabolički poremećaji izazvani lekovima; olanzapin

Introduction

Atypical antipsychotics are medications primarily used in the treatment of psychotic disorders, but they are also widely used in other indications, such as bipolar disorder, depression, anxiety disorders, sleep disorders, personality disorders, Parkinson's and Alzheimer's disease, in line with the demands

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Abbreviations

BWG – body weight gain
BMI – body mass index
HOMA-IR – homeostasis model assessment of insulin resistance
HbA1c – hemoglobin A1c

and safety concerns of the modern emergency psychiatry [1, 2]. One of the most common side-effects of these medications is metabolic syndrome, which includes: body weight gain (BWG), insulin resistance, high blood lipids, as well as the consequently increased risk of type 2 diabetes and cardiovascular diseases [3]. This is also confirmed by the data indicating that the prevalence of type 2 diabetes in younger patients with schizophrenia is higher than in the general population [4] and that a myocardial infarction is the leading cause of death among patients suffering from major mental disorders [5]. Clozapine and olanzapine are two atypical antipsychotics with the greatest potential for cardiometabolic side-effects, risperidone and quetiapine pose a moderate risk, while ziprasidone, aripiprazole, brexpiprazole, cariprazine and lurasidone carry the lowest risk [6, 7]. The BWG rate is the highest during the first six months of treatment, and remains high even later [8]. Apart from health risks, obesity induced by psychiatric drugs also has a great impact on the patient's self-confidence [9], as well as negative effect on their compliance. A precise mechanism of body weight increase caused by the use of atypical antipsychotics has not been completely described yet, but it is believed that an important role is played by the central histamine H1 antagonism and increased appetite [10]. An important reason for the necessary intervention regarding this problem is the fact that polypharmacy, which leads to even more pronounced side-effects, is widespread in psychiatric practice [11, 12]. Potential therapeutic interventions directed towards the prevention of the antipsychotic-induced metabolic syndrome include a change of drug, which carries a risk of relapse, and a change of lifestyle, including a controlled diet and physical activities, which is a great challenge in this population. Professional literature offers some considerations on the adjuvant use of medications such as topimarate, sibutramine, aripiprazole, and reboxetine in the context of having potentially favorable effects on the reduction of cardiometabolic risk induced by atypical antipsychotics [13]. However, apart from the aforementioned interventions, the literature has recently been mentioning adjuvant use of metformin, as a highly effective method of controlling body weight increase induced by antipsychotic therapy. This medication is a derivative of biguanide and it is used in treating diabetes mellitus type 2. It reduces hepatic gluconeogenesis and impacts insulin resistance by boosting peripheral glucose utilisation, while reducing resorption of glucose from the gastrointestinal tract [14]. Recommendations for the use of metformin for this indication are also present in clinical practice guidelines, so the Clinical Practice Guidelines of the Canadian Medical Association for adult obesity also recommend the use of metformin for treating obesity induced by antipsychotics [15]. Furthermore, the Practice Guidelines of the American Psychiatric Association for the treatment of patients with schizophrenia claim that the use of metformin is justified in patients receiving atypical antipsychotics who have not been diagnosed with hyperglycemia. It is concluded that its use is safe, while the desired effects on body weight and other metabolic abnormalities are easily achieved [16].

The objective of this research is to analyze the available literature data on the use of metformin in the treatment of atypical antipsychotics side-effects, primarily increased body weight.

Material and Methods

PubMed and Google Scholar databases were searched for relevant literature published in a fifteen-year period, between 2008 and 2022. The following terms were used in the search: atypical antipsychotics, metformin, and weight gain. A total of 145 papers matched previously mentioned criteria, but only double-blind, placebo-controlled, randomised and cohort studies were analyzed. Systematic reviews, literature searches, meta-analyses and research including children and animals were excluded. It was determined that only 10 papers met inclusion criteria. We examined the titles, abstracts, and full texts of relevant papers. The collected data were then summarized and presented.

Results

This research systematically presents data obtained from ten experimental studies including 852 subjects related to adjunctive use of metformin in the treatment of atypical antipsychotic-induced metabolic syndrome.

The research conducted by De Silva et al. [17] is a double-blind, placebo-controlled, randomised study which lasted 24 weeks and evaluated the effects of metformin in patients with antipsychotic-induced weight gain. The study included 66 patients older than 18 years who met the diagnostic criteria for schizophrenia or schizoaffective disorder and whose body weight had increased by more than 10% in comparison to the period before the introduction of atypical antipsychotics. The subjects were treated with olanzapine, clozapine, risperidone, aripiprazole and amisulpride, while the patients receiving other psychotropic medications which are associated with BWG (lithium, carbamazepine, valproate and antidepressants) were excluded from the research. Metformin was given at a dose of 500 mg twice a day, while the control group received placebo. The patients with poorer tolerance to metformin received 500 mg a day. The subjects were advised to include high-fibre foods, fruits and vegetables in their diet, to reduce the intake of simple sugars and products with high concentration of fats, and to introduce 30 minutes of moderate exercise a day; however, these parameters were not monitored. The change in the group that was using metformin was -1.56 kg, while in the placebo group the change of weight was +1.0

kg, which was interpreted as a statistically significant difference (p = .03). No statistically significant difference was noted regarding the waist/hip ratio or the sugar blood level between the two groups.

Wang et al. [18] examined the efficacy of metformin in patients with the first episode of schizophrenia whose body weight had increased by more than 7% in comparison to the period before they started receiving antipsychotic therapy. This randomized, placebo-controlled 12-week study included 72 patients, 66 of whom managed to complete the study. Metformin was given at a dose of 1,000 mg/day, while the primary outcome was related to the changes in body weight, and the secondary related to the changes in the body mass index (BMI), fasting glucose and insulin, as well as in the insulin resistance index. In the group treated with metformin a decrease in body weight by 5.1% was observed, while an increase of weight by 3.9% was observed in the placebo group. The BMI decreased by 1.3 in the group treated with metformin, while it increased by 0.9 in the placebo group. The values of insulin and insulin resistance index (HOMA-IR) showed statistically significant decreases in the study group after 4, 8 and 12 weeks of the study, while they increased in the placebo group. More patients in the study group (N = 13; 40.6%) lost weight by more than 7% in comparison to the placebo group (N = 3; 8.8%), which was noted as statistically significant (p = .003).

Chen et al. [19] published a randomized, double-blind, placebo-controlled, 24-week study, in which they studied the effects of metformin on the metabolic syndrome in patients with schizophrenia who were using clozapine for more than three months. Out of 55 subjects, 28 were receiving 1,500 mg of metformin a day, while 27 were receiving placebo. The metabolic parameters were monitored during weeks 2, 4, 8, 16 and 24 and body weight was measured each time. After 24 weeks, body weight (p < .0001), BMI (p < .0001), fasting glucose (p < .0001), high-density lipoprotein cholesterol (p = .03), insulin level (p0.01) and HOMA-IR (p = .02) showed significant changes in the group treated with metformin. At the end of the metformin therapy, 8 patients lost more than 7% of weight, but they regained the weight after they stopped using metformin. Based on this research, the authors concluded that adjuvant use of metformin is efficient in treating metabolic syndrome.

Agarwal et al. [20] conducted a double-blind, randomised clinical trial to examine the effects of metformin on early comorbid glucose dysregulation in people with the schizophrenic spectrum disorders. In this study, 30 subjects who were overweight or obese (BMI > 25) under the age of 40 with a diagnosis of schizophrenia spectrum and prediabetes/diabetes were divided into two groups. The first group (N = 21) received metformin (1,500 mg/day), while the other (N = 9) was using placebo for 4 months. A total of 22 patients finished the trial (n = 14 metformin and N = 8 placebo), and the group that used metformin showed a significant decrease of the HOMA-IR index (p = .043) and fasting glucose levels (p = .007) in comparison with the placebo group, while no differences were noted between the groups in relation to the hemoglobin A1c (HbA1c) level. The weight loss in the metformin group was in significant correlation with the decrease in subcutaneous, but not in visceral or hepatic fatty tissue. The results of this trial indicate that metformin had positive effects on dysglycemia and insulin sensitivity, regardless of the weight loss in younger population with diagnosed psychotic disorder and prediabetes/diabetes.

The study conducted by Wu et al. [21] was a double-blind study assessing the efficacy of metformin in treating olanzapine-induced BWG. A total of 40 subjects diagnosed with schizophrenia were using olanzapine (15 mg/day) along with metformin (750 mg/day) (N = 20) or olanzapine (15 mg/day) with placebo (N = 20). During the trial, the parameters such as body weight, BMI, waist circumference, waist/hips ratio showed a smaller increase in the group that was receiving metformin. Furthermore, it was noticed that the values of insulin significantly increased in the eighth and twelfth week in the placebo group, while they remained unchanged in the metformin group. Less patients from the metformin group (N = 3, 16.7%) than in the placebo group (N = 12, 63.16%) presented with BWG in regard to their baseline weight by more than 7%, which was statistically significant p < .001.

Rado J. et al. [22] published a 24-week placebo-controlled pilot study during which they examined the efficacy, tolerability and safety of adjuvant metformin therapy in the treatment of olanzapine-induced BWG in adults diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, or depression with psychotic symptoms. The research included 25 patients using olanzapine, while other antipsychotics were not allowed. Metformin was administered in the study group at doses up to 2,000 mg/day. Olanzapine-metformin group showed the average weight gain of 2.5 kg, which was less than in the placebo group, where the average weight gain was 5.8 kg (p < .05). The average BMI increase in the study group was 0.85, while the control group showed an increase of 2.02 (p < .045).

A double-blind study conducted by Jarskog et al. [23] monitored the effects of metformin on weight reduction of obese patients diagnosed with schizophrenia or schizoaffective disorder. A total of 148 clinically stable, obese patients participated in this 16-week study. The study group included 58 patients who were receiving their regular psychiatric therapy along with 2,000 mg metformine a day. The results showed a significant weight reduction in the study group of - 3.0 kg, while weight reduction in the control group was - 1.0 kg. Metformin group also showed significant changes in BMI (p = .006), triglyceride levels (p = .037) and HbA1c (p = .04). The tolerance of metformin was satisfactory.

Tang C. et al. [24] published a randomized, double-blind, placebo-controlled study aiming to estimate the effects of metformin on the antipsychotic-induced weight gain, its safety and tolerability. The study lasted

24 weeks and included 17 patients between the age of 16 and 40, diagnosed with the first psychotic episode. The inclusion criterion was a weight increase of more than 5% in comparison to the period before atypical antipsychotics were introduced. The study group included 8 patients and the average dose of metformin was 1,200 mg/day, while the tolerability was good. In the metformin group, five patients completed the study, four of them lost weight (average - 1.9 kg), while one patient gained weight (1.0 kg). In the placebo group, out of eight patients who completed the study, seven gained weight (average + 3.8 kg), while only one lost weight (- 1.9 kg). During the phase of discontinuation, between 24 and 36 weeks, three out of five patients from the metformin group gained weight (average + 3.4kg) and two lost weight (average - 1.8 kg), while seven out of eight patients from the placebo group gained weight (average 1.8 kg) and in one patient the weight remained the same. The results showed that patients in the metformin group gained less weight that those in the placebo group, but there was no statistically significant difference between the two groups during the phase of discontinuation.

Spokes et al. [25] published a retrospective cohort study on the effects of metformin in patients receiving clozapine. The digital medical records of patients with

Table 1. A short presentation of the analyzed studies
Tabela 1. *Sažete karakteristike razmatranih istraživanja*

	Authors *Autori*	Type of study *Vrsta istraživanja*	Study duration (weeks) *Trajanje istraživanja (nedelje)*	Number of subjects *Broj ispitanika*	Antipsychotics *Antipsihotici*	Dose of metformin (mg/day)/*Doza metformina (mg/dan)*	Outcome measures *Mere ishoda*
1.	De Silva et al. *De Silva et al.*	Randomized double-blind, placebo-controlled/*Randomizovano duplo-slepo, placebo kontrolisano*	24	66	Several different atypical *Više različitih atipičnih*	1,000	Body weight *Telesna težina*
2.	Wang et al. *Wang et al.*	Randomized placebo-controlled/*Randomizovano placebo kontrolisano*	12	72	Several different atypical *Više različitih atipičnih*	1,000	Body weight, Insulin, HOMA-IR *Telesna težina, Insulin, HOMA-IR*
3.	Chen et al. *Chen et al.*	Randomized double-blind placebo-controlled/*Randomizovano duplo-slepo, placebo kontrolisano*	24	55	Clozapine *Klozapin*	1,500	Body weight, BMI, glucose, lipids, insulin, HOMA-IR/*Telesna težina, BMI, glukoza, lipidi, insulin, HOMA-IR*
4.	Agarwal et al. *Agarwal et al.*	Randomized double-blind/*Randomizovano duplo-slepo*	17	30	Several different atypical/*Više različitih atipičnih*	1,500	Glucose, HOMA-IR *Glukoza, HOMA-IR*
5.	Spokes et al. *Spokes et al.*	Retrospective cohort/*Retrospektivno kohortno*	108	90	Clozapine *Klozapin*	1,000 - 2,000	Body weight *Telesna težina*
6.	Wu et al. *Wu et al.*	Double-blind, placebo-controlled/*Duplo-slepo, placebo kontrolisano*	12	40	Olanzapine *Olanzapin*	750	Body weight *Telesna težina*
7.	Rado et al. *Rado et al.*	Randomized placebo-controlled *Randomizovano, placebo kontrolisano*	24	25	Olanzapine *Olanzapin*	2,000	Body weight, BMI *Telesna težina, BMI*
8.	Frederic et al. *Frederic et al.*	Double-blind *Duplo-slepo*	16	148	Several different atypical/*Više različitih atipičnih*	2,000	Body weight, BMI, lipids, HbA1c/*Telesna težina, BMI, lipidi, HbA1c*
9.	Tang et al. *Tang et al.*	Randomized double-blind placebo-controlled/*Randomizovano duplo-slepo, placebo kontrolisano*	24	17	Several different atypical/*Više različitih atipičnih*	1,200	Body weight *Telesna težina*
10.	Hakami et al. *Hakami et al.*	Retrospective cohort/*Retrospektivno kohortno*	273	309	Several different atypical/*Više različitih atipičnih*	1,000	Body weight *Telesna težina*

Legenda: BMI – indeks telesne mase, HOMA-IR – indeks insulinske rezistencije, HbA1c – glikolizirani hemoglobin

therapy-resistant schizophrenia who received clozapine in the period between 2017 and 2019 were analyzed retrospectively. In 90 of the analyzed subjects, the use of metformin was related to the overall weight gain (1.32% vs. 5.95%, p = .031), as well as a weight gain by more than 7% (37.8% vs. 63.0%, p = .025) in comparison to the placebo group.

The latest study, conducted by Hakami et al. [26] in 2022, examined the effects of antipsychotics on body weight and the effects of adjuvant use of metformin on the antipsychotic-induced weight gain. A total of 395 patients participated in the study, with 309 of them in the placebo group and 86 in the group treated with adjunctive metformin. In the placebo group, only 67 patients (21.68%) lost weight, 43 (13.92%) showed no change in body weight and 199 (64.4%) gained weight. In the metformin group, 35 (40.7%) lost weight, 18 (20.93%) showed no change in body weight and 33 (38.37%) gained weight. The first group presented a significant change in body weight of + 2.5 kg, while in the metformin group the weight change was - 0.04, p < .0001. The statistical analysis showed that a simultaneous use of metformin and antipsychotics was associated with a decrease in the trend of weight gain, while the use of antipsychotics alone was associated with an increase in body weight.

Although it did not meet the criteria for inclusion in our study, for the sake of scientific fairness, we would like to mention one research with negative results that was published in 2006. In this research, Baptista et al. [27] studied whether metformin prevents BWG and metabolic dysfunction in patients with schizophrenia who were treated with olanzapine during a 14-week double-blind study. Forty patients taking olanzapine (10 mg daily) were randomly allocated to metformin (n = 20; 850 to 1,700 mg daily) or placebo (n = 20). At week 14, BWG (kg) was similar in the metformin group (5.5 kg) and the placebo group (6.3 kg), p = .4. There were no differences in BMI, waist size, glucose, insulin, HOMA-IR, and plasma lipid levels in the study group and the placebo group. The authors concluded that metformin did not prevent olanzapine-induced BWG.

A short presentation of the analyzed studies is shown in **Table 1**.

Discussion

This review article included 10 experimental clinical trials with 852 patients in whom effects of adjuvant use of metformin on reduction of atypical antipsychotic-induced weight gain and other disturbed metabolic parameters were analyzed. All reviewed studies showed statistically significant favourable effects of metformin on increased body weight in comparison with placebo. The administered doses of metformin ranged from 500 to 2,000 mg/day and its tolerability was satisfactory. In general, in the groups receiving metformin only, mild side-effects such as nausea and vomiting were observed, which was not statistically relevant in comparison with the placebo group, while more serious side-effects such as lactic acidosis were extremely rare. Apart from body weight, the presented studies analyzed other parameters of metabolic syndrome as well. Even though De Silva et al. found statistically significant effects of metformin on body weight, no statistically significant difference related to the waist/hip ratio and fasting blood sugar level between the two groups was established [17]. However, Wang et al, Chen et al. and Agarwal et al. concluded that the levels of insulin and HOMA-IR decreased significantly in the metformin group [18–20]. Furthermore, the study conducted by Jarski et al, apart from effects on body weight and BMI, showed positive effects of metformin on the levels of triglycerides and HbA1c [23]. It is particularly important to mention the study conducted by Chen et al., which proved that the use of metformin is efficient, but the benefits disappear once the therapy is discontinued [19]. Although all studies included in this review showed statistically significant effects of metformin in regulation of body weight, it is necessary to mention that there is a research with negative results, such as the one conducted by Baptista et al. [27], which failed to prove positive effects of metformin on the olanzapine-induced weight gain. This result could perhaps be explained by the hypothesis that olanzapine-induced weight gain is mainly associated with direct appetite stimulation, a mechanism that is not primarily influenced by metformin, as pointed out by the authors [28].

The limitations of this study are a very small sample of participants who used metformin (fewer than 400), the relatively short period of monitoring, and the fact that the groups included mainly patients diagnosed with schizophrenia, even though it is known that atypical antipsychotics are also used for many other indications in psychiatry. Another limitation of this research is that metformin in the reviewed studies was not used to treat diabetes, but to reduce weight gain and other parameters of the metabolic syndrome.

Our results indicate a need to consider the introduction of adjuvant metformin in the early phase of treatment of every patient prone to weight gain using atypical antipsychotics in order to prevent morbidity caused by cardiovascular diseases and subsequent mortality, which is confirmed by the published data [29–31]. The goal of this study is consistent with one of the principal precepts of bioethics: “first, do no harm” and points to the fact that the patient, not the disease, must remain the focus of medical science [32].

Conclusion

Even though the use of metformin in treating atypical antipsychotic-induced weight gain and other metabolic abnormalities is still sporadic in our region, the available data confirm its efficiency and safety. This leads to a conclusion that it is justified to use metformin in order to prevent and reduce atypical antipsychotic-induced cardiometabolic side-effects. We believe that further research is needed in order to determine long-term efficiency and tolerability of metformin for this particular indication.

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