



12-12-2018

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A Review of Metformin to Reduce Weight in Patients Using Olanzapine

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Master of Science in Nursing, University of North Dakota, 2018

An Independent Study Submitted to the Graduate Faculty of the University of North Dakota

Grand Forks, North Dakota

December 2018

## PERMISSION

Title: A Review of Metformin to Reduce Weight in Patients Using Olanzapine

Department: Nursing

Degree: Master of Science in Nursing

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### **Abstract**

This review explores the case of a young Native American male who has been newly diagnosed with schizophrenia. The course of his mental illness is examined as it relates to his first psychotic episode. Furthermore, the adverse weight gain this patient experiences after beginning olanzapine therapy is examined. This clinical problem necessitates the need for providers to address this metabolic issue through prevention or early treatment. A literature review was conducted with the objective to explore efficacy of metformin therapy to reduce weight in adult patients (ages 18-64) diagnosed with schizophrenia using olanzapine. The general consensus of the literature recommended use of metformin to prevent weight gain or reduce weight in patients with schizophrenia using antipsychotics. Metformin was mostly well tolerated by patients with minimal side effects and patients demonstrated good adherence. Metformin initiated early into antipsychotic therapy was associated with less weight gain. Literature on use of metformin in patients on olanzapine is limited and more research is needed to guide practice.

## Background

Second generation antipsychotics (SGAs or atypical neuroleptics) are currently the preferred choice of antipsychotics for patients with schizophrenia. These medications are efficacious and have fewer side effects compared to first generation antipsychotics (FGAs or typical neuroleptics), which have high incidences of extrapyramidal symptoms and tardive dyskinesia (Berrahal et al., 2016). However, the incidence of metabolic syndrome is higher with SGAs than FGAs, which the patient or client often first recognizes by weight gain (De Silva et al., 2016). Metabolic syndrome is diagnosed when the patient has three or more of the following manifestations: increased abdominal girth, low high density lipoprotein, elevated fasting triglycerides, hypertension, and impaired fasting glucose (Meyer et al., 2005). Poorly managed metabolic syndrome leads to cardiovascular and cerebrovascular disease and subsequent decreased life span in patients with schizophrenia compared to the general population (Ongur, 2016). Evidence of development of metabolic syndrome was well established in the landmark National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. The findings of this study and numerous studies on antipsychotic associated weight gain (AAWG) that have followed raises the need for providers to monitor for the development of metabolic syndrome and limit morbidity that ensues in patients with schizophrenia.

Olanzapine (Zyprexa) is a SGA widely used in the management of schizophrenia, though is notable for significant weight gain (Baptista et al., 2007). In fact, olanzapine and clozapine (Clozaril) have the highest propensity for weight gain among all antipsychotics (Dayabandara et al., 2017). AAWG is a major cause of lack of adherence to treatment, which subsequently leads to increase in relapse, longer hospital stays, and functional impairment (Meyer et al., 2005).

According to Wu et al. (2008a), 70% of weight gain from olanzapine is observed in the first 12 weeks of therapy and plateaus around 39 weeks. Providers have the option of switching patients to a more weight neutral antipsychotic, however olanzapine is highly effective in the treatment of schizophrenia and has low rates of discontinuation compared to other antipsychotics. In addition, providers risk relapse with switching and increase the likelihood of discontinuation of antipsychotic therapy (Dayabandara et al, 2017). This poses a treatment challenge for providers managing these patients who may otherwise be experiencing good effect from olanzapine therapy.

Metformin is an oral anti-diabetic that is widely used in psychiatry in the management of AAWG for its safety, tolerability, high levels of adherence, and efficacy for metabolic control (Baptista et al., 2007). Metformin increases insulin sensitivity, suppresses appetite, and treats obesity (De Silva, 2016). Because it does not cause hypoglycemia or require monitoring, metformin is an easy addition to a patient's medication regimen. However, available research on AAWG is incongruent in their findings, which state metformin prevents weight gain, reverses weight gain, or has no effect at all (Hoffman, Case, & Jacobson, 2012).

According to Ongur (2016), concern for the increased risk for suicide, homicide, and lethal accidents in patients with schizophrenia compared to the general population is given more attention than necessary because this only represents a small portion of the population. Instead, Ongur (2016) asserts that attention should be redirected to the increase risk for cardiovascular and cerebrovascular morbidity and mortality in patients with schizophrenia. This population lives an average of 20 years less than the general population, which is believed to be due to metabolic syndrome caused by antipsychotic therapy (Ongur, 2016). This investigation aims to explore the

efficacy of metformin therapy to reduce weight in adult patients diagnosed with schizophrenia using olanzapine therapy.

### **Case Report**

BD is a Native-American male who was first seen in office February 2017 at age 17 accompanied by his mother. On intake longstanding mental illness was evident based on patient and mother's report. Mother reports that patient was born at 36 weeks without complications and met his developmental milestones. BD has a history of physical abuse by his baby sitter at age nine and now experiences nightmares and flashbacks. At age ten BD's parents divorced, which introduced new stressors to his life, such as having to move often and seeing his dad infrequently. On intake BD reports he has one or two friends at school, eats lunch alone, chooses not to talk to others, and worries about scrutiny. He identifies as gay and struggles with his sexuality as he has not disclosed this to anyone until today. Depression was evidenced by low motivation, poor academic performance, self-injurious behaviors (cutting), and thoughts he would be better off dead. He admits to daily marijuana use and was encouraged to abstain due to negative influence on his mood. Furthermore, mother shares she notices BD has been more withdrawn. Initial diagnoses for BD were Major Depressive Disorder, moderate to severe, Unspecified Anxiety Disorder, and Cannabis Use Disorder. At this time patient was started on escitalopram (Lexapro) to target depressive and anxious symptoms.

After the initial consult BD and his mother struggle with making it to scheduled appointment and are not seen in office for three months. During this time BD attempted suicide in March 2017 for the first time by overdose on escitalopram (Lexapro). Suicide attempt is notable for occurring within a month of beginning escitalopram (Lexapro) therapy, which comes

with a Food and Drug Administration (FDA) Black Box warning for increasing suicidality in children adolescents, and young adults (Epocrates, 2018). BD had his first inpatient mental health hospitalization for medication adjustments and crisis intervention. He was discharged to a mental illness and chemical dependency (MICD) dual diagnosis day treatment program.

BD and his mother continue to struggle with follow up on mental health services and patient is not seen in office again for an extended period. During this time he had another inpatient mental health hospitalization after his first psychotic episode in August 2018 at age 19. BD was brought into the emergency department (ED) by an off duty officer after being noted to be walking barefoot at night and exhibiting bizarre behavior. While in the ED he was endorsing persecutory delusions of his parents trying to kill him. He was admitted to the inpatient mental health unit where his thought process continued to be grossly disoriented as evidenced by reports of persecutory delusions and visual hallucinations. During this hospitalization BD was MICD committed with a Jarvis through Hennepin County, provisionally discharged, and assigned a case manager.

Ascertaining a diagnosis is difficult for BD, which is further complicated by the fact he had infrequent contact with mental health services. It is unclear how long he was experiencing hallucinations, delusions, or other cardinal symptoms of schizophrenia. Substance induced psychotic disorder is also on the differential, however also cannot be diagnosed with certainty without knowing onset of his symptoms. Furthermore, schizoaffective disorder is also a possibility due to his history of depression. Due to these limitations, Unspecified Schizophrenia Spectrum Disorder is the most appropriate diagnosis.

BD returned to his outpatient psychiatrist for follow-up with his case manager in September 2018. During the hospitalization previously discussed, BD was stabilized on a high



dose of olanzapine at 40 mg daily and per his Jarvis order he was to continue to antipsychotic therapy. In office BD no longer endorsed delusions, paranoia, or hallucinations. Return to baseline functioning is evidenced by his ability to return to work his part time job. However, within three weeks BD gained 30 pounds, going from 153 pounds to 183 pounds. This rapid weight gain is alarming, because weight gain of more than 5% in the first month is a strong predictor of long-term weight gain (Dayabandara et al., 2017). In office, a goal was set with the patient to reduce this dose overtime or switch agents due to concern of rapid weight gain, development of metabolic syndrome, and subsequent morbidity.

### **Literature Review**

This investigation aims to explore the efficacy of metformin therapy to reduce weight in adult patients (ages 18-64 years old) diagnosed with schizophrenia using olanzapine therapy. Electronic databases used for this investigation include PsychInfo, PubMed, Scopus, and CINAHL. Key terms searched include “olanzapine,” “metformin,” “weight gain,” and “antipsychotic associated weight gain.” Search results will be limited to adults diagnosed with schizophrenia and articles published in English. The literature reviewed will include participants with comorbidities (e.g. anxiety, depression, bipolar disorder). Participants with preexisting diabetes will be excluded from this review. It is anticipated the findings will indicate metformin is an effective intervention to reduce weight in non-diabetic patients with schizophrenia on olanzapine.

This review begins with the work of Dr. Trino Baptista, a physician and researcher from the University of the Andes in Venezuela, who has done extensive work on the relationship between antipsychotics and metabolic syndrome. Baptista et al. (2006) took interest in the issue of olanzapine associated weight gain (OAWG) and conducted a study of metformin use in

patients taking olanzapine. This is an important study that is referenced by many of the subsequent studies in this literature review. In a 14-week randomized control trial (RCT), 40 adult inpatients with schizophrenia or schizoaffective disorder on olanzapine were given metformin 850-1700 mg or placebo daily. Metformin was titrated according to clinical response. At the end of the study, the investigators did not find metformin to be effective for lowering body weight. However, the investigators acknowledge the limitations of not having a long enough intervention period or a large enough sample size.

Dr. Trino Baptista continued to develop this research in 2007 with a larger sample size. In this study Baptista et al. (2007) successfully found evidence of weight loss in patients on olanzapine with adjunctive metformin. In another double-blind RCT, 80 participants were randomly assigned to receive adjunctive metformin 850-2550 mg or placebo in combination with olanzapine daily for 12 weeks. Titration of metformin to high doses was well tolerated by participants. The median amount of weight loss in the treatment group was about three pounds. While a modest decrease in weight, the treatment group lost up to ten pounds at the end of the 12-week trial while the placebo group only maintained weight at the end of this period. While the length of study time was short, this study can be appreciated for its large sample size and the majority of the participants had schizophrenia (76 participants). However, this was achieved by including 60 inpatients and 20 outpatients with schizophrenia in the study, which limits control of the study.

Baptista et al. (2008) tested the efficacy of treating OAWG with combination therapy. However, their research found insignificant results with metformin combination therapy with sibutramine for treatment of OAWG. Originally developed as an antidepressant, sibutramine is a anorectic agent that decreased appetite and reduces calorie intake used in the treatment of obesity

(National Institute of Health [NIH], 2018). In this study, 30 inpatient adults with chronic schizophrenia converted from long-term use of FGAs to olanzapine monotherapy. After conversion was completed, participants received metformin plus sibutramine or placebo for 12 weeks. The dose of metformin plus sibutramine was gradually increased in the treatment group from 850 mg to 1700 mg and 10 mg to 20 mg respectively. Metformin and sibutramine was titrated according to clinical response. The results did not find efficacy in this combination for treatment of metabolic symptoms and weight loss observed in the treatment group compared to placebo group was statistically insignificant. Furthermore, it should be noted that since this time sibutramine has taken off the market due to adverse cardiovascular effects, including increased blood pressure, increased heart rate, myocardial infarction and stroke (NIH, 2018).

Hoffman, Case, and Jacobson (2012) also proposed use of combination therapy to prevent or treat OAWG. In a 22-week outpatient setting RCT, 199 participants were given olanzapine alone, olanzapine plus algorithm A, or olanzapine plus algorithm B. Algorithm A and B both utilized equivalent doses of amantadine, metformin, and zonisamide, but medications were scheduled differently. All three medications have had reports of promoting weight loss (Hoffman, Case, & Jacobson, 2012). Amantadine is primarily used to treat Parkinson's disease and extrapyramidal symptoms and zonisamide is primarily used as an anticonvulsant (Hoffman, Case, & Jacobson, 2012). In algorithm A, olanzapine was given with amantadine with a possible switch to metformin and then to zonisamide. In algorithm B, olanzapine was given with metformin with a possible switch to amantadine and then zonisamide. Switches in medications were made according to the algorithm and determined by rate of weight gain. Participants who received olanzapine plus algorithm B (where metformin was initiated first) had the least weight gain. The results of this study demonstrate the benefits for treating OAWG using combination

therapy based on clinical feedback. These findings support Baptista et al.'s (2008) proposition to treat OAWG with combination therapy and recommendation to tailor therapy based on clinical response.

Dr. Ren-Rong Wu, a psychiatrist from China, is another influential investigator who has led several studies on metabolic syndrome with antipsychotic use. Wu et al. (2008a) tested the efficacy of metformin on OAWG in 40 antipsychotic-naïve adults. These participants were newly diagnosed with schizophrenia, starting olanzapine after their first psychotic episode, and were all in the same stage of their disease. In this 12-week double-blind RCT, olanzapine plus placebo or olanzapine plus metformin was administered in a highly controlled setting. All patients ate the same diet, participated in the same exercise regimen, and were not on any other medications prior to this study for at least three months. Weight gain in the olanzapine plus placebo group was clinically significant, or 7% of their bodyweight. The effects of metformin in the treatment group were not robust and suggest prophylactic use of metformin to prevent OAWG rather than treat obesity that has already developed. Fewer patients on olanzapine plus metformin gained weight compared to patients who received olanzapine plus placebo, but weight loss was not observed. The results of this study has strong reliability due to the controls applied to this inpatient sample. However, generalizability is limited because these controls create an artificial environment for interpreting the results and limit the ability to apply them to patients in the community. Nevertheless, these findings have important implications for clinical practice. Because the study was conducted in young patients who were antipsychotic naïve, we can assess the effects of olanzapine on metabolic syndrome. Not only did these findings substantiate the utility of metformin to prevent weight gain, it also demonstrated significant weight gain early in olanzapine therapy.

Despite the lack of literature on metformin therapy in patients on olanzapine, there is good studies that supports the use of metformin in patients with schizophrenia on SGAs, such as olanzapine. In a larger RCT, Wu et al. (2008b) compared four interventions in 128 adult inpatients with schizophrenia. Interventions included metformin 750 mg daily alone, placebo daily, lifestyle interventions alone, or lifestyle interventions plus metformin 750 mg daily for 12 weeks. These patients had gain more than 10% of their predrug weight within the first year of starting clozapine, olanzapine, risperidone, or sulpiride. Wu et al. (2008b) found that lifestyle interventions plus metformin 750 mg daily yield the greatest amount of weight loss. However, the metformin treatment alone led to greater weight loss than lifestyle interventions alone.

Metformin use with AAWG in patients with schizophrenia after their first psychotic episode was investigated again by Wu et al. (2012) in a longer study. In this double-blind RCT, 84 female outpatients who experienced amenorrhea and AAWG from antipsychotics were randomly assigned to received metformin 1000 mg or placebo daily for 24 weeks. At the end of the study 67% of participants in the metformin group both resumed their menstrual cycle and lost an average of 4.1% of their bodyweight. This was not observed in the placebo group, where only 4.8% of participants resumed their menstrual cycle and gained on average 3.7% of their bodyweight. Participants in this study were on one of the four following medications: clozapine, olanzapine, risperidone, or sulpiride. However, the authors do not identify how many participants were on olanzapine or how they responded to metformin or placebo. Nevertheless, the findings of this study suggest metformin is effective in promoting weight loss in patients with schizophrenia and on SGAs, such as olanzapine.

These findings were later reinforced in Wu et al.'s 2016 research that continued to focus on first-episode patients beginning antipsychotic therapy. The primary investigation of this study

was to evaluate the efficacy of metformin to treat antipsychotic-induced dyslipidemia in adult patients with schizophrenia after their first psychotic episode. The authors also measured bodyweight response to metformin therapy as a secondary outcome measurement. In this study 201 adult patients with schizophrenia were randomly assigned to receive metformin 1000 mg or placebo daily in a 24-week RCT. Similar to the previous study discussed, participants were on one of the four following medications: clozapine, olanzapine, risperidone, or sulpiride. 47.8% of these participants were on olanzapine, however the exact response to metformin or placebo is not identified. The authors state that significant weight loss was seen in the metformin group, but they do not define what is significant or say how much weight lost was measured. The findings of this study showed weight loss effects were not seen until 12 weeks of treatment and continued up until the end of the study. The results from this study reiterates the efficacy of metformin to reduce weight in patients on antipsychotics and supports the need for long term treatment to see therapeutic effects in patients using SGAs.

Wang et al. (2012) also investigated the effects of metformin on AAWG in adult patients with schizophrenia after their first episode of psychosis. These participants had already gained a clinically significant amount of weight, which the authors define as at least 7% of their body weight, upon entering the study. In this double-blind RCT, 72 adult patients received metformin 1000 mg or placebo daily as an adjunct to a SGA for 12 weeks. Weight loss in the metformin group was clinically significant. The placebo group continued to gain weight on top of the 7% clinically significant AAWG. Unlike the previously study, Wang et al.'s (2012) research included participants on other atypical antipsychotics and only 15 participants were on olanzapine. However, the findings of this study are significant in this review for a several reasons. First, it is notable that this study examined the effects of metformin in patients who had

already gained a clinically significant amount of weight. This is an issue providers often encounter, because they inherited a patient with metabolic syndrome or preventive measures were not initiated in a timely manner. In addition, even though not all participants were on olanzapine, atypical antipsychotics have similar side effect profiles. Therefore providers can use the findings of this study to make informed decisions for patients afflicted with AAWG or OAWG.

Similar to Dr. Ren-Rong Wu's work, Rado & von Ammon Cavanaugh (2016) also found evidence of treatment-over-time effects observed later into metformin therapy in the treatment of OAWG. In this double blind RCT of community-dwelling adult patients, 25 adult participants beginning olanzapine therapy were randomly assigned to receive either adjunctive metformin or placebo for 24 weeks. In addition to its long study period, control for the influence of other antipsychotics is also a strength of this study. Patients on antidepressants and mood stabilizers were included in this study, though use of other antipsychotics within 3 months of the study was not allowed in this study to fully appreciate the metabolic effects of olanzapine. Metformin extended release formulation was titrated up to 2000 mg daily or as clinically indicated and was well tolerated. The results of this study did not demonstrate efficacy of metformin to reduce weight in patients on olanzapine therapy, but it did show evidence of the ability to prevent weight gain. At the end of the 24-week trial, the treatment group gained an average of 5.5 pounds versus 12.8 pounds gained by the placebo group (increases of 3% and 7% of body weight respectively). The generalizability of this study is limited by its small sample size of 25 participants. Furthermore, it should be noted that patients with schizophrenia, schizoaffective disorder, bipolar disorder, and major depression with psychotic features were all included in this study.

De Silva et al.'s (2015) study on metformin therapy in adult patients with schizophrenia or schizoaffective disorder also suggested treatment over longer periods of time. These participants had already been afflicted with AAWG and had gained more than 10% of their bodyweight from SGAs. In an outpatient, double blind RCT, 66 South Asian patients received metformin 500 mg or placebo twice a day for 24 weeks. While not robust, the findings of this study indicate metformin can be used to reduce bodyweight in patients with schizophrenia or schizoaffective disorder and on a SGA. At the end of the study, the metformin group on average lost 1.84% of their bodyweight whereas the placebo group gain 1.4% of their bodyweight. However, only 18 participants of this study were on olanzapine and only ten participants were in the metformin group. In addition, several articles in this review indicate a 7% change in bodyweight is clinically significant and none of the participants of this study lost more than 5% of their bodyweight. Furthermore, the authors acknowledge that weight loss could be influenced by the East Asian ethnicity of participants. Nevertheless, this study is remarkable for its long study period which showed evidence of a significant time-by-treatment interaction with metformin use. Significant weight loss was not seen until 2-3 months after treatment was initiated, which suggest that some of the studies in this review may not have been long enough to fully appreciate the effects of metformin.

Jarkskog et al. (2013) also found evidence of a time-by-treatment effect with metformin use. Jarkskog et al. (2013) investigated the efficacy of metformin to promote weight loss in overweight adult patients with schizophrenia. Overweight was defined as a body mass index (BMI)  $\geq 27$ . In this double blind RCT, 148 outpatients received metformin or placebo for 16 weeks. At the end of the study, participants in the treatment group lost a mean average of 2.8% of their bodyweight compared to 1% loss in the placebo group. Unfortunately the authors do not



specify what medications the patients are on and only state the patients were receiving one or a combination of two FDA-approved antipsychotics. In addition, confounding factors of this study include weekly diet and exercise counselling that likely promoted the observed weight loss. However, this study does offer evidence that there is utility in use of metformin to reduce weight in overweight patients with schizophrenia on antipsychotics.

All literature in this review was Level II evidenced based on Melnyk and Fineout-Overholt's rating system for the hierarchy of evidence. The strengths and limitations throughout the literature varied, but all of the RCTs of this review were well-designed. The investigators established clinical relevance of their investigation well and posed their hypothesis clearly. All studies were placebo controlled. All but two studies used double blinding. Four studies cited using an independent party to sort and distribute medications to ensure concealment. Methods of randomization were well executed and all but two studies employed random allocation via computer based generator.

The literature consistently stated metformin had clinical utility for OAWG or AAWG. All articles in this review stated that metformin either prevented OAWG or AAWG or reduced body weight in patients using SGAs. Length of the studies in this review ranged from 12 weeks to 24 weeks. Three of the studies suggested metformin therapy becomes more efficacious over time. This review studied patients at different stages of schizophrenia. Four of the studies showed evidence of preventing onset of OAWG or AAWG in patients after their first psychotic episodes and newly beginning antipsychotic therapy. The two studies that did not find efficacy in reducing body weight with metformin are notable for having patients who had been on long-term antipsychotic therapy. This further supports the idea that metformin is useful for prevention of weight gain, rather than treating weight gain that has already manifested. Research design could

not eliminate the influence confounding factors, such as genetics or lifestyle choices, which inherently compromise with results in these studies. Furthermore, it was consistent throughout the literature that metformin was safe to use, mostly well tolerated, and patients had high levels of adherence to treatment. Participant drop out was often cited to be due to gastrointestinal side effects. Many of these side effects could be alleviated by dose adjustment or resolved after discontinuation of metformin.

### **Implications**

Stakeholders of this clinical challenge include adult patients with schizophrenia on olanzapine, primary care providers (PCP), and psychiatric-mental health (PMH) providers. The PMH provider's objective in managing care for these patients should be remission of symptoms with minimal adverse effects. It is imperative for PCPs and PMH providers to take an active role in preventing and treating metabolic syndrome in this population. The high incidence of metabolic syndrome in patients taking olanzapine presents a learning opportunity for PCPs and PMH providers. Based on the this literature review, metformin should be used adjunctively in all patients with schizophrenia using SGAs, such as olanzapine. In addition, providers should be educated on evidence of weight gain early into olanzapine therapy, which should influence providers to initiate metformin therapy as a preventative measure. Education on adjunctive metformin use with olanzapine should also include education about metabolic monitoring for these patients. This should include monitoring bodyweight, waist circumference, BMI, blood pressure, fasting glucose, and a fasting lipid panel throughout the course of SGA therapy. Furthermore, providers managing olanzapine should be considering the need to refer the patient to a specialist should metabolic syndrome advance. This education can be implemented in the work place as a part of mandatory education that offers continue education units (CEUs) to

providers. Tip sheets that concisely outlines monitoring parameters can also be distributed throughout hospitals or clinics where patients on olanzapine are being managed.

This review also raises the need for further education in patients with schizophrenia on olanzapine and their support systems (e.g. families, caregivers, community-based mental health facility staff). These parties should be informed of weight gain trends early in treatment and how to monitor for its possible development. This information should include how to accurately monitor weight, abdominal girth, and the importance of regular physicals to evaluate overall metabolic condition. Patient education on weight management, dietary considerations, exercise, and lifestyle modifications to promote a healthy weight should also be provided and reinforced at every encounter with the PMH provider and the PCP. Providers should identify and address barriers to implementing these interventions and problem solve with the patient to work around these barriers. In addition, providers should educate these parties on the benefits and limitations of adjunctive metformin on OAWG and the prospect of improved outcomes if combined with lifestyle modifications. Furthermore, education should address side effects of metformin and the ability to manage them with dose adjustments to encourage adherence.

Literature on use of metformin in patients on olanzapine is limited and more research is needed to guide practice. For this reason, this review includes literature greater than 10 years. Expanding the scope of this investigation to include studies on SGAs provides greater insight on the influence of metformin to treat weight gain. There is a need for replication studies to validate these findings and incorporate them into practice. These replication studies need to be longer term, need to be conducted in larger sample sizes, and participants should be more homogenous (e.g. all first-episode, all long-term olanzapine users, patients within a certain BMI range, narrower range of age). The findings of the literature is summarized in Table 1.

**Table-1**

<b>Author</b>	<b>Design</b>	<b>Study sample</b>	<b>Intervention</b>	<b>Strengths</b>	<b>Limitations</b>	<b>Findings</b>
Baptista et al. (2006)	Double-blind RCT	n=40 Adult outpatients and inpatients with schizophrenia or schizoaffective disorder on olanzapine	Received metformin 850-1700 mg or placebo daily for 14 weeks	<ul style="list-style-type: none"> <li>• Double blinding</li> <li>• Randomization</li> <li>• Only evaluated olanzapine</li> </ul>	<ul style="list-style-type: none"> <li>• Short study time</li> <li>• Small sample size</li> <li>• Outpatient and inpatient sample</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin did not prevent weight gain in patients using olanzapine</li> </ul>
Baptista et al. (2007)	Double-blind RCT	n=80 Adult inpatients with schizophrenia or bipolar on olanzapine	Received metformin 850-2550 mg daily or placebo for 12 weeks	<ul style="list-style-type: none"> <li>• Double blinding</li> <li>• Randomization</li> <li>• Only evaluated olanzapine</li> </ul>	<ul style="list-style-type: none"> <li>• Includes patients with bipolar disorder</li> <li>• Short study time</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin group lost weight and placebo group maintained weight</li> <li>• Metformin is safe, well tolerated, and can be used to reduce weight</li> </ul>
Baptista et al. (2008)	Clinical trial	n=30 Adult inpatients with chronic schizophrenia who switch from long-term conventional antipsychotics to olanzapine	Received metformin (850-1700 mg) plus sibutramine (10-20 mg) or placebo twice a day for 12 weeks	<ul style="list-style-type: none"> <li>• On olanzapine monotherapy for at least 4 months before start</li> <li>• Randomization</li> <li>• Only included patients with schizophrenia</li> </ul>	<ul style="list-style-type: none"> <li>• Short study time</li> <li>• Small sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Weight loss observed with intervention, but not clinically significant</li> <li>• Weight loss with metformin plus sibutramine not superior to metformin alone</li> <li>• GI upset noted from metformin plus sibutramine</li> </ul>
De Silva (2015)	Double-blind RCT	n=66 Adult South Asian outpatients with chronic	Received metformin 500 mg or placebo twice a day for	<ul style="list-style-type: none"> <li>• Double blinding</li> <li>• Randomization</li> <li>• Long study</li> </ul>	<ul style="list-style-type: none"> <li>• Only 15 of 66 participants on olanzapine</li> <li>• Participants</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin effective for reducing weight</li> <li>• Significant time-by-treatment effect (lag time)</li> </ul>

		schizophrenia or schizoaffective disorder afflicted with AAWG	24 weeks	time	could be on one or more antipsychotics	of 2-3 months)
Hoffman, Case, & Jacobson (2012)	RCT	n=199 Adult outpatients with schizophrenia or schizoaffective disorder	Received olanzapine alone, olanzapine plus algorithm A, or olanzapine plus algorithm B for 22 weeks. See literature review for details	<ul style="list-style-type: none"> <li>• Long study time</li> <li>• Randomization</li> <li>• Only evaluated olanzapine</li> </ul>	<ul style="list-style-type: none"> <li>• Included use of other medications not of interest in this review (amantadine and zonisamide)</li> </ul>	<ul style="list-style-type: none"> <li>• Participants who received metformin earlier in treatment had less weight gain</li> <li>• Suggest combined therapy and algorithm is more effective than monotherapy and standard treatment for weight loss</li> </ul>
Jarskog et al. (2013)	Double-blind RCT	n=148 Adult overweight outpatients with chronic schizophrenia or schizoaffective disorder	Received metformin 500 mg or placebo twice a day for 16 weeks	<ul style="list-style-type: none"> <li>• Double blinding</li> <li>• Randomization</li> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Does not tell what antipsychotics patients are on</li> <li>• Patients could be on any one or two antipsychotics to participate</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin was modestly effective in reducing weight</li> <li>• Significant time-by-treatment effect</li> <li>• Metformin was mostly well tolerated and side effects were minimal</li> </ul>
Rado & Von Ammon Cavanaugh (2016)	Double-blind RCT	n=25 Adult outpatients with schizophrenia, schizoaffective disorder, bipolar disorder, or major depression with psychotic features	Received olanzapine plus metformin or olanzapine plus placebo for 24 weeks	<ul style="list-style-type: none"> <li>• Naturalistic sample in a community setting</li> <li>• Long study time</li> <li>• Double blinding</li> <li>• Randomization</li> <li>• Only evaluated olanzapine</li> </ul>	<ul style="list-style-type: none"> <li>• Included other diagnoses that are not of interest in this review</li> <li>• Small sample size</li> <li>• Length of study</li> </ul>	<ul style="list-style-type: none"> <li>• Weight loss observed with metformin was no robust</li> <li>• Metformin is good for prevention of weight gain</li> <li>• Metformin is well tolerated</li> </ul>

Wang et al. (2012)	Double-blind RCT	n= 72 First episode schizophrenia who gain more than 7% of their predrug weight	Received metformin 1000 mg daily or placebo for 12 weeks	<ul style="list-style-type: none"> <li>• Randomization</li> <li>• Large sample size</li> <li>• Only included patients with schizophrenia</li> </ul>	<ul style="list-style-type: none"> <li>• Short study time</li> <li>• Does not describe randomization process</li> <li>• Included patients on medication not of interest in this review (clozapine, risperidone, sulpiride)</li> </ul>	<ul style="list-style-type: none"> <li>• Weight loss observed in the metformin group was clinically significant</li> <li>• Metformin was mostly well tolerated and has good adherence</li> <li>• Decrease in weight noted at 8 weeks and continued through the end of the study</li> </ul>
Wu et al. (2008a)	Double-blind RCT	n=40 Adult inpatients with schizophrenia after first-episode psychosis who were antipsychotic naïve and already gained more than 7% of their predrug weight	Receive olanzapine plus metformin 750 mg daily or olanzapine plus placebo for 12 weeks	<ul style="list-style-type: none"> <li>• Double blinding</li> <li>• Randomization</li> <li>• Only evaluated olanzapine</li> <li>• Only included patients with schizophrenia</li> </ul>	<ul style="list-style-type: none"> <li>• Small sample size</li> <li>• Short study time</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin effective for weight loss for OAWG or as a preventive measure</li> <li>• Metformin was well tolerated and had good adherence</li> </ul>
Wu et al. (2008b)	RCT	n=128 Adult inpatients with schizophrenia who gained more than 10% of their predrug weight	Receive one of four treatments: metformin 750 mg daily, lifestyle intervention, placebo, or lifestyle intervention plus	<ul style="list-style-type: none"> <li>• Randomization</li> <li>• Large same size</li> </ul>	<ul style="list-style-type: none"> <li>• Included patients on medication not of interest in this review (clozapine, risperidone, sulpiride)</li> </ul>	<ul style="list-style-type: none"> <li>• Lifestyle interventions plus metformin showed the most weight loss in AAWG. However, metformin alone was superior to lifestyle intervention alone for reducing body weight.</li> </ul>

			metformin for 12 weeks			
Wu et al. (2012)	Double-blind RCT	n=84 Adult outpatient Chinese women diagnosed with schizophrenia after their first psychotic episode who were afflicted with amenorrhea	Received metformin 1000 mg or placebo daily for 24 weeks	<ul style="list-style-type: none"> <li>• Double blinding</li> <li>• Randomization</li> <li>• Long study time</li> </ul>	<ul style="list-style-type: none"> <li>• Included patients on medication not of interest in this review (clozapine, risperidone, sulpiride)</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin promoted weight loss, but weight loss observed was not clinically significant</li> <li>• Metformin restored menstrual cycle</li> </ul>
Wu et al. (2016)	Double-blind RCT	n=201 Adults with schizophrenia diagnosed with antipsychotic-induced dyslipidemia	Received metformin 1000 mg or placebo daily for 24 weeks	<ul style="list-style-type: none"> <li>• Double blinding</li> <li>• Randomization</li> <li>• Long study time</li> </ul>	<ul style="list-style-type: none"> <li>• Included patients on medication not of interest in this review (clozapine, risperidone, sulpiride)</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin led to clinically significant weight loss</li> <li>• Time-by treatment effect observed</li> </ul>

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