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Priority Updates from the Research Literature from the Family Physicians Inquiries Network

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Can metformin undo weight gain induced by antipsychotics?

Convincing evidence shows that metformin alone and in combination with lifestyle changes is superior to lifestyle changes alone or placebo

Practice changer

Recommend metformin 250 mg 3 times a day, along with lifestyle modifications, to promote weight loss and decrease insulin resistance in patients who gain more than 10% of their pretreatment body weight on antipsychotic medications.

Strength of recommendation

B: Based on a single, well-designed, randomized controlled trial.

Wu R-R, Zhao J-P, Jin H, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA.* 2008;299:185-193.[1]

ILLUSTRATIVE CASE

Is there anything you can do for this patient? A 25-year-old man with newly diagnosed schizophrenia and a baseline weight of 175 pounds comes to see you because he has gained 18 pounds in the first 6 months after starting olanzapine.

Concerned because his mother has diabetes, he asks if you can help him lose weight safely. You make your usual recommendation that he increase his daily physical activity (including buying a pedometer, setting a daily step goal, and keeping a log)[2] and decrease his total caloric intake, but you know the chances of success are not great. What about a weight loss medication? Might that improve the odds?

Metformin might improve the odds. This study gives us an additional tool for treating antipsychotic-induced weight gain. This is useful information, because most second-generation (or atypical) antipsychotic medications cause weight gain. Weight gain can lead to decreased adherence to treatment and, therefore, increased risk of psychotic relapse in addition to the increased risk of diabetes and cardiovascular disease associated with weight gain.

Antipsychotics exhibit variability in the amount of weight gain and risk for diabetes they cause (**TABLE 1**). Olanzapine and clozapine definitely increase the risk for diabetes. The association of diabetes with risperidone and quetiapine is uncertain, and early experience with aripiprazole and ziprasidone does not indicate an increased risk of diabetes.[3,4]

The prevalence of obesity and diabetes among people with schizophrenia and affective disorders is 1.5 to 2 times higher than in the general population. This dif-

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Do you prescribe metformin for weight gain induced by second-generation antipsychotic medications?

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- ❑ No

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ference is likely due to a combination of sedentary behavior and the use of second-generation antipsychotics. Obesity and diabetes are risk factors for cardiovascular disease, and the relative risk of mortality from cardiovascular disease is significantly higher among people with psychiatric disorders than in the general population.[3] More than two thirds of patients with schizophrenia die of coronary heart disease, compared with about 50% of the general population.[4]

TABLE 1

Risk of weight gain and diabetes with atypical antipsychotic medications[3,4]

MEDICATION (TRADE NAME)	RISK OF SIGNIFICANT WEIGHT GAIN	RISK FOR DIABETES
Clozapine (Clozaril)	+++	+
Olanzapine (Zyprexa)	+++	+
Quetiapine (Seroquel)	++	? (discrepant results)
Risperidone (Risperdal)	++	?
Ziprasidone (Geodon)	+/–	–
Aripiprazole (Abilify)	+/–	–

Lack of evidence for weight loss drugs

The most recent guideline on this topic does not recommend any medication, citing a lack of evidence. In its 2003 consensus statement, a panel representing the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity[3] recommends:

- That patients taking second-generation antipsychotics have the following assessments at baseline and regular intervals: weight, height, waist circumference, blood pressure, fasting plasma glucose, and fasting lipids.
- Providing nutrition and exercise counseling to all patients who are overweight or obese at baseline.
- Initiating treatment with one of the second-generation antipsychotics with a lower risk of weight gain for patients at high risk of diabetes (ie, family history) and for patients who gain 5% or more of their initial weight or develop worsening hyperglycemia or dyslipidemia during treatment.

This guideline does not recommend metformin to reduce weight gain.

A 2007 Cochrane review of interventions to reduce weight gain in patients with schizophrenia included 23 randomized controlled trials of a variety of weight loss interventions, including cognitive/behavioral interventions and a variety of medications, including sibutramine, orlistat, fluoxetine, topiramate, and metformin. The authors highlighted the limited number of studies of short duration and with small sample sizes and concluded that the evidence was insufficient for the use of pharmacologic interventions to prevent or treat weight gain.[5]

STUDY SUMMARY

Lifestyle changes and metformin compared

This randomized controlled trial was conducted in China and included 128 adults aged 18 to 45 with a first psychotic episode of schizophrenia. All patients had to have gained more than 10% of their pretreatment body weight during the first year of treatment with an antipsychotic medication (clozapine, olanzapine, risperidone, or sulpiride [not approved for use in the United States]). All study participants had to be under the care of an adult caregiver who monitored and recorded food intake, exercise, and medication intake. Patients with diabetes, cardiovascular disease, liver or renal dysfunction, substance abuse, or psychiatric diagnoses other than schizophrenia were excluded.

Patients were randomized to 1 of 4 groups for the 12 weeks of the study:

- Metformin alone, 250 mg 3 times daily
- Placebo alone
- Lifestyle intervention plus metformin
- Lifestyle intervention plus placebo

CONTINUED

FAST TRACK

More than two thirds of patients with schizophrenia die of coronary heart disease

PURLs methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

TABLE 2

Mean difference between baseline and endpoint (week 12) of treatment outcomes

(95% confidence intervals)[1]

	LIFESTYLE + METFORMIN	METFORMIN	LIFESTYLE	PLACEBO
Weight, kg	-4.7 (-5.7 to -3.4)	-3.2 (-3.9 to -2.5)	-1.4 (-2.0 to -0.7)	3.1 (2.4 to 3.8)
BMI, kg/m²	-1.8 (-2.3 to -1.3)	-1.2 (-1.5 to -0.9)	-0.5 (-0.8 to -0.3)	1.2 (0.9 to 1.5)
Waist circumference, cm	-2.0 (-2.4 to -1.5)	-1.3 (-1.5 to -1.1)	0.1 (-0.5 to 0.7)	2.2 (1.7 to 2.8)
Fasting glucose, mg/dL	-7.2 (-10.8 to -5.4)	-10.8 (-16.2 to -7.2)	-7.2 (-9.0 to -3.6)	1.8 (-1.8 to 3.6)

The lifestyle intervention included 3 components: (1) education: monthly programs on nutrition and physical activity; (2) diet: the American Heart Association step 2 diet (<30% calories from fat, 55% carbohydrates, >15% protein, with at least 15 g fiber per 1000 kcal); and (3) exercise: 1 week of sessions with an exercise physiologist followed by an individualized home-based exercise program.

Primary outcomes included changes in weight, body mass index (BMI), waist circumference, and fasting glucose (**TABLE 2**). Ten of the 128 randomized patients either discontinued the study or were lost to follow up, but all 128 patients were included in the analysis.

Best result: Lifestyle changes plus metformin

Compared with baseline, weight decreased by 7.3% in the lifestyle plus metformin group, by 4.9% in the metformin-only group, and by 2.2% in the lifestyle-only group; in the placebo group, weight increased by 4.8%.

Participants in all 3 intervention groups also showed significant decreases in the mean fasting glucose, insulin levels, and insulin resistance index (IRI). The insulin levels and the IRI increased in the placebo group.

No significant differences in adverse effects were noted among the 4 treatment groups.[1]

FAST TRACK

Before adding metformin for weight loss, contact the psychiatrist and discuss other antipsychotic drug options

WHAT'S NEW

Convincing evidence

This is the first randomized controlled trial to show convincingly that metformin alone or in combination with lifestyle changes is superior to lifestyle changes alone or placebo for reducing weight gain and other adverse metabolic outcomes induced by second-generation antipsychotics.

Intensive lifestyle interventions

Prior studies found that intensive lifestyle interventions can help reduce antipsychotic-related weight gain. A 3-month randomized controlled trial compared an early behavioral intervention (dietary counseling, an exercise program, and behavior therapy) with routine care in 61 patients with first-episode psychosis who were taking risperidone, olanzapine, or haloperidol;[6] significantly fewer patients assigned to behavioral intervention had an increased initial body weight of more than 7%: 39% in the behavioral intervention group vs 79% in the routine care group (P<.002).

Small samples, small effect sizes

Past studies of metformin for antipsychotic-associated weight gain have generally shown a small benefit, though small sample sizes and small effect sizes prohibited definitive conclusions. Unlike the study by Wu and colleagues,[1] none of these past studies were designed to compare the combination of metformin and lifestyle intervention with metfor-

min alone, lifestyle intervention alone, or placebo alone.

Klein et al conducted a randomized placebo-controlled trial of metformin in 39 children ages 10 to 17 whose weight had increased more than 10% on atypical antipsychotic therapy.[7] The children treated with placebo gained a mean of 4 kg and increased their mean BMI by 1.12 kg/m^2 during 16 weeks of treatment, while those in the metformin group did not gain weight and decreased their mean BMI by 0.43 kg/m^2.

Baptista et al randomized 40 inpatients with schizophrenia, who were being switched from conventional antipsychotics to olanzapine, to either metformin (850-1750 mg/d) or placebo. Both groups gained a similar amount of weight after the 14-week study (5.5 vs 6.3 kg, metformin vs placebo). Three patients who started with high fasting glucose had decreases while taking metformin, and 3 patients given placebo developed elevated fasting glucose during the study.[8]

In another randomized controlled trial of metformin vs placebo in 80 patients who had been taking olanzapine for at least 4 months, Baptista et al found only a small, insignificant difference in weight loss after 12 weeks of treatment (metformin group lost 1.4 kg, placebo group lost 0.18 kg, *P*=.09). They reported that both groups were highly motivated to lose weight and were compliant with the healthy lifestyle recommendations.[9]

An adequately powered study

The trial[1] highlighted in this PURL had an adequate sample size to compare metformin plus a lifestyle intervention with either treatment alone or placebo. It showed a clinically important effect of metformin both by itself and in conjunction with the lifestyle intervention.

CAVEATS

Consider switching drugs

Before adding metformin to help with weight loss, primary care clinicians should contact the patient's psychiatrist to discuss the option of switching antipsychotic medications. Switching from a medication with a higher risk for weight gain, such as olanzapine, to one with a lower risk, such as aripiprazole or ziprasidone, can lead to significant weight loss.[10]

Not an option for some

However, some patients, especially those taking clozapine, may have already tried multiple antipsychotic agents without success, and switching is not an option for them.

Prescribing metformin

Contraindications

Metformin should not be prescribed to patients with serum creatinine concentrations of more than 1.5 mg/dL or those with unstable heart failure, due to the risk of lactic acidosis.

Dosing

The dose of metformin used in this study was 250 mg 3 times daily. The other studies cited used higher doses, ranging from 850 to 2550 mg daily. We recommend starting with a lower dose and increasing the dose as needed to achieve a therapeutic effect.

Duration of treatment

This trial was only 12 weeks in duration and does not give us evidence on long-term maintenance, so the decision about continuation will need to be individualized based on clinical judgment. If the patient loses weight, we think that either continuing the metformin or giving the patient a trial off of it (and restarting if the patient regains weight), would both be reasonable strategies.

Is this study applicable in the US?

This study was conducted in China, which raises the question of generalizability. We can think of no biological reason why these results may not apply to US patient populations.

FAST TRACK

Advise patients that possible GI side effects of metformin tend to lessen or disappear with time

CONTINUED

CHALLENGES TO IMPLEMENTATION

Adherence

These study participants were under the care of an adult caregiver who monitored and recorded food and medication intake and exercise level. The lifestyle intervention was thorough and structured and this kind of program is often not available to us for our patients. As a consequence, we may not obtain the same results as in this study. However, even the metformin-alone group showed improvements, and if our patients can reliably take their second-generation antipsychotic, they should also be able to take metformin reliably.

Patient resistance

Some patients may resist taking an additional medication to treat the side effects of their antipsychotic medication. Taking the time to educate them about the increased risk of diabetes and cardiovascular disease related to weight gain may help convince them to do so. Warn them about possible gastrointestinal adverse effects of metformin, which tend to lessen or disappear with time. ■

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FAST TRACK

If patients can reliably take their antipsychotics, they should be able to take metformin reliably

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