Physician’s Guide for Clinical Psychiatry Lecture Series

Pharmacological Management of Antipsychotics-induced Weight Gain

(2) Antipsychotics Induced Weight Gain: Metformin

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This chapter will be summarized in following sections:

1. Does metformin have role in prevention and treatment of antipsychotic induced weight gain?

2. Does metformin have role in treatment of antipsychotic induced dyslipidemia?

3. Does metformin have effect on weight gain associated with antipsychotics use in children and adolescents with autism spectrum disorders?


5. What dose of metformin is found effective in treatment of antipsychotic induced weight gain?

6. Precautions with metformin use: When to discontinue metformin treatment?

7. Contraindication for metformin use.

8. Laboratory monitoring with metformin use.

9. Common adverse events associated with metformin.
Does metformin have role in prevention and treatment of antipsychotic induced weight gain.

Systematic review and meta-analysis conducted by De Silva et al. will answer this question.

Reference: 1 (pdf)

All double blind placebo controlled trials assessing the efficacy of metformin in the treatment of antipsychotic induced weight gain were included (from January 2000-December 2015):

- Meta analysis of 12 published studies with a total of 743 patients.
- All were parallel group randomised controlled trials comparing treatment with metformin or placebo of patients on atypical antipsychotics.

Results:

(a) Meta-analysis of 12 studies found that that treatment with metformin resulted in:

- significantly more weight loss than placebo in patients treated with antipsychotics \[-3.27 \text{ kg} \ (95 \% \ CI \ -4.66 \text{ to } -1.89) \ (Z = 4.64, \ p < 0.001)\].
- significantly more reduction in BMI than placebo in patients treated with antipsychotics \[-1.13 \text{ kg/m2} \ (95 \% \ CI \ -1.61 \text{ to } -0.66) \] \ (Z = 4.65, \ p < 0.001).
(b) Meta-analysis of 9 studies found that that treatment with metformin resulted in:

- **significant reduction in Insulin resistance index** than placebo in patients treated with antipsychotics \([-1.49 \text{ (95\% CI } -2.40 \text{ to } -0.59) \text{ (} Z = 3.23, p < 0.001)]\).

(c) Meta-analysis of 10 studies found that that treatment with metformin:

- **did not** result in significant reduction in **fasting blood sugar** compared to placebo in patients treated with antipsychotics \([-2.48 \text{ mg/dl (95\% CI } -5.54 \text{ to } 0.57) \text{ (} Z = 1.59, p = 0.11)]\).

(d) Is this weight loss with metformin clinically meaningful?

Note that weight losses of 5% or more can result in clinically significant reduction of morbidity and mortality.

According to Wang et al. (2) following % of patients reduced their body weight by 7%:

- Metformin group: 40.6 %
- Placebo group: 7 %

(e) Metformin appears to be **more effective in preventing antipsychotic induced weight gain in first episode patients** than in chronic patients who have already gained weight.
(f) trials longer than 12 weeks showed that patients on metformin continued to lose weight with time.

- likely that continued metformin use is beneficial.

(g) metformin plus life style modification was superior to metformin treatment alone.

Conclusion:

This meta-analysis confirms that metformin is effective in treating antipsychotic induced weight gain in patients with schizophrenia or schizoaffective disorder.
(2) Does metformin have role in treatment of antipsychotic induced dyslipidemia?

Wu et al. published analysis of two randomized, placebo-controlled trials will answer this question. This is the first clinical trial that examines the effect of metformin treatment on antipsychotic-induced dyslipidemia in patients with first-episode schizophrenia.

Reference: 3 (pdf)

- 201 schizophrenia patients with dyslipidemia after being treated with an antipsychotic were assigned to take 1000 mg/day metformin (n=103) or placebo (n=98) for 24 weeks, with evaluation at baseline, week 12 and week 24.
- Primary outcome was: low-density lipoprotein cholesterol (LDL-C) levels.

Results:

(a) After metformin treatment, the mean difference in the LDL-C value between metformin treatment and placebo was:

- At baseline: 0.16 mmol/l
- End of week 24: –0.86 mmol/l : decreased by 1.02 mmol/l (P<0.0001)

(b) 25.3% of patients in the metformin group had LDL-C ≥3.37 mmol/l at week 24.
(c) Metformin treatment also have a significant effect on:

- reducing weight, body mass index
- reducing insulin, insulin resistance index
- reducing total cholesterol and triglyceride
- increasing high-density lipoprotein cholesterol.

(d) These effects occurred in a time-sequence manner:

- metformin treatment effects on weight gain and insulin resistance were significant at week 12, which is also the same for HDL-C.
- However, its effect on lipid profile such as LDL-C, total cholesterol and triglycerides did not appear until the end of trial at week 24.
- This is interesting, and suggests that metformin treatment effect on LDL-C, total cholesterol and triglycerides appear after the decrease in insulin resistance.

(e) They did not observe metformin treatment effect on fasting glucose (as discussed in above Systematic review and meta-analysis conducted by De Silva et al.

Conclusion:

this study has shown clearly that the addition of metformin to antipsychotics is a potential treatment to attenuate dyslipidemia in patients with schizophrenia.
Does metformin have effect on weight gain associated with antipsychotics use in children and adolescents with autism spectrum disorders?

16-week, double-blind, placebo-controlled, randomized clinical trial conducted by Anagnostou et al. will answer this question.

Reference: 4 (pdf)

Medication: Metformin or matching placebo titrated up to:

- 500 mg twice daily for children aged 6 to 9 years.
- 850 mg twice daily for those 10 to 17 years.

Results:

(a) Mean final dose:

- Age 6 to 9 years: both metformin and placebo (1000 mg/day).
- Age 10 to 17 years: metformin (1587 mg/day) and placebo (1674 mg/day).

(b) Metformin reduced BMI z scores from baseline to week 16 significantly more than placebo:
• Children receiving placebo continued to gain weight during the study, as expected for age (BMI z score increase negligible), whereas BMI z scores decreased in the metformin group.

• The benefits from treatment in this sample were not clear until after 8 weeks of treatment.

(c) Statistically significant improvements noted in secondary body composition measures (raw BMI, $-0.95$ [95% CI, $-1.46$ to $-0.45$] and raw weight, $-2.73$ [95% CI, $-4.04$ to $-1.43$])

(d) Statistically significant improvements noted in metabolic variables.

(e) Participants receiving metformin experienced nonsignificant increase in gastrointestinal adverse events during a significantly higher percentage of treatment days (25.1% vs 6.8%; $P = .005$).

• gastrointestinal adverse events were not responsible for any treatment discontinuation.

• they found no evidence that the benefit on BMI was due to gastrointestinal adverse events.

Conclusion:

metformin was well tolerated and effective at managing weight gain associated with atypical antipsychotic use in children and adolescents with ASD.
(4) How is metformin dosed: starting dose & titration.

METFORMIN DOSAGE INFORMATION:

Starting Dose:

- Glucophage: 500 mg twice a day or 850 mg once a day, given with meals.
- Glucophage XR: 500 mg once daily with the evening meal.
- Pediatrics: 500 mg twice a day, given with meals.

Dosage increases:

- Glucophage: made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses.
- Glucophage XR: made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal.
- Pediatrics: 500 mg weekly up to a maximum of 2000 mg per day, given in divided doses.

Doses above 2000 mg:

- may be better tolerated given 3 times a day with meals.
(5) What dose of metformin is found effective in treatment of antipsychotic induced weight gain?

This will be answered by summarizing positive randomized control trials on this topic with information on:

- Metformin dose
- Duration of treatment (trial)
- Antipsychotic dose and duration of treatment.

(a) Baptista et al. 2007 (pubmed)

- Metformin 850-2550 mg
- Duration 12 weeks
- Antipsychotic: Olanzapine (5-20 mg daily for more than 4 consecutive months)
- Metformin group lost 1.4+/−3.2 kg (p=0.01) and tended to decrease its leptin levels.
- Metformin did not improve the lipid profile and the Hb1c levels.

(b) Carrizo et al. 2009 (pubmed)

- Extended release metformin 500-1000 mg/day
- Duration 14 weeks
- Antipsychotic: Clozapine (196.8+/−132 mg daily, range: 25-500) for more than 3 consecutive months (86.5+/−40.6 months, range: 4-168)
• Metformin group lost -1.87 +/- 2.9 kg.

• Leptin levels also tended to decrease after metformin.

• Insulin & triglyceride-HDL-C ratio significantly decreased (p<0.05, effect size 0.59 and 1.99 respectively) and HDL-C significantly increased (p=0.001, effect size 0.95) after metformin.

(c) Chen et al. (pubmed)

• Metformin 1500 mg/day

• Duration 24 weeks

• Antipsychotic: Clozapine (dose not known; on clozapine for > 3 months)

• After the 24-week intervention, body weight (P < .0001), body mass index (P < .0001), fasting plasma glucose (P < .0001), high-density lipoprotein cholesterol (P = .03), insulin level (P = .01), and homeostasis model assessment index (P = .02) had significant changes in the metformin group.

• At the end of the intervention, 8 patients (28.57%) lost more than 7% of their body weight in the metformin group.

• This beneficial effects of metformin on body weight disappeared after discontinuing this medication.

(d) De Silva et al. 2015 (pubmed)

• 500 mg twice daily

• Duration 24 weeks

• patients treated with atypical antipsychotics (details not known)
• Mean change in body weight in the metformin group was -1.56 kg (95% CI=-3.06 to -0.05) and 1.0 kg (95% CI=0.03-1.97) in the placebo group. Between-group difference was 2.56 kg.

• At 24 weeks the between-group difference showed significant time-by-treatment interaction (F=3.23, p=0.004). Between-group difference in BMI showed significant time-by-treatment interaction (F=3.41 p=0.03).

(e) Jarskog et al. 2013 (pdf)

• Metformin 500 mg twice daily increased to maximum of 2000 mg/day

• Duration 16 weeks

• patients were receiving one or a combination of two FDA-approved antipsychotics with no change in antipsychotic agents for 2 months and no change in dosage for 1 month prior to study entry.

• Mean change in body weight was -3.0 kg (95% CI=-4.0 to -2.0) for the metformin group and -1.0 kg (95% CI=-2.0 to 0.0) for the placebo group, with a between-group difference of -2.0 kg (95% CI=-3.4 to -0.6).

• Metformin also demonstrated a significant between-group advantage for BMI (-0.7; 95% CI=-1.1 to -0.2), triglyceride level (-20.2 mg/dL; 95% CI=-39.2 to -1.3), and hemoglobin A1c level (-0.07%; 95% CI=-0.14 to -0.004).

(f) Klein et al. (pubmed)

• Metformin 850 mg twice daily

• Duration 16 weeks

• Ages 10-17

• patients whose weight had increased by more than 10% during less than 1 year of olanzapine, risperidone, or quetiapine treatment.
• Weight was stabilized in subjects receiving metformin, while those receiving placebo continued to gain weight (0.31 kg/week).

(g) Wang et al. 2012 (pubmed)

• Metformin **500 mg twice daily**

• **Duration 12 weeks**

• The body weight, body mass index, fasting insulin and insulin resistance index decreased significantly in the metformin group, but increased in the placebo group during the 12-week follow-up period.

• Significantly more patients in the metformin group lost their baseline weight by more than 7%, which was the cutoff for clinically meaningful weight loss.

(h) Wu et al. 2012 (pubmed)

• Metformin **1000 mg/day**

• **Duration 24 weeks**

• Among patients treated with metformin, BMI decreased by a mean of 0.93 and the insulin resistance index by 2.04.

(i) Wu et al. 2008 (1) (pubmed)

• Metformin **750 mg daily**

• **Duration 12 weeks**

• Lifestyle-plus-metformin group had mean decreases in body mass index (BMI) of 1.8 (95% confidence interval [CI], 1.3-2.3), insulin resistance index of 3.6 (95% CI, 2.7-4.5), and waist circumference of 2.0 cm (95% CI, 1.5-2.4 cm).
• metformin-alone group had mean decreases in BMI of 1.2 (95% CI, 0.9-1.5), insulin resistance index of 3.5 (95% CI, 2.7-4.4), and waist circumference of 1.3 cm (95% CI, 1.1-1.5 cm).

• The lifestyle-plus-placebo group had mean decreases in BMI of 0.5 (95% CI, 0.3-0.8) and insulin resistance index of 1.0 (95% CI, 0.5-1.5).

• placebo group had mean increases in BMI of 1.2 (95% CI, 0.9-1.5), insulin resistance index of 0.4 (95% CI, 0.1-0.7), and waist circumference of 2.2 cm (95% CI, 1.7-2.8 cm).

(j) Wu et al. 2008 (pubmed)

• Metformin **250 mg thrice daily**.

• Duration **12 weeks**

• Antipsychotic: **Olanzapine 15 mg/day**.

• The weight, body mass index, waist circumference, and waist-to-hip ratio levels increased less in the olanzapine plus metformin group relative to the olanzapine plus placebo group.

• The insulin and insulin resistance index values of the olanzapine plus placebo group increased significantly at weeks 8 and 12.

• Significantly fewer patients in the olanzapine plus metformin group relative to patients in the olanzapine plus placebo group increased their baseline weight by more than 7%.
(6) Precautions for metformin use: When to discontinue metformin treatment?

(A) RENAL IMPAIRMENT

Before initiating metformin: obtain an estimated glomerular filtration rate (eGFR):

- eGFR < 30 mL/min/1.73 m²: Contraindicated
- eGFR between 30-45 mL/min/1.73 m²: Initiation of metformin is not recommended
- If eGFR falls below 45 mL/min/1.73 m² during metformin treatment: assess the benefit and risk of continuing therapy.
- If eGFR falls below 30 mL/min/1.73 m² during metformin treatment: Discontinue metformin.

(B) LACTIC ACIDOSIS

There is risk of metformin associated lactic acidosis.

Nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence.
Metformin-associated lactic acidosis is characterized by:

- elevated blood lactate concentrations (>5 mmol/L)
- anion gap acidosis (without evidence of ketonuria or ketonemia)
- increased lactate:pyruvate ratio; metformin plasma levels were generally >5 mcg/mL.

If metformin-associated lactic acidosis is suspected:

- general supportive measures should be instituted promptly in a hospital setting, along with
- immediate discontinuation of metformin.

In metformin treated patients with a diagnosis or strong suspicion of lactic acidosis:

- prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin.

(C) AGE > 65

- The risk of metformin-associated lactic acidosis increases with the patient’s age.
(D) RADIOLOGIC STUDIES WITH CONTRAST:
Stop metformin at the time of, or prior to, an iodinated contrast imaging procedure in patients with:

- eGFR between 30 and 60 mL/min/1.73 m2
- patients with a history of hepatic impairment, alcoholism or heart failure
- patients who will be administered intra-arterial iodinated contrast

- Re-evaluate eGFR 48 hours after the imaging procedure, and restart metformin if renal function is stable.

(E) CARDIOPULMONARY DISORDER:
- acute congestive heart failure, cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia.
- When such an event occurs, discontinue metformin.

(F) HEPATIC IMPAIRMENT:
- increases risk of lactic acidosis.
(7) **Contraindication for metformin use.**

1. Severe renal impairment (eGFR below 30 mL/min/1.73 m²)
2. Known hypersensitivity to metformin hydrochloride.
3. Acute or chronic metabolic acidosis (including diabetic ketoacidosis, with or without coma): Diabetic ketoacidosis should be treated with insulin.

**NOT RECOMMENDED IN:**

- pregnancy.
- Patients below the age of 10 years.
- Metformin XR: below the age of 17 years.
(8) Laboratory Test with Metformin

(a) Renal function: estimated glomerular filtration rate (eGFR) and creatinine.
   • obtain before initiating metformin.
   • at least annually after initiation.
   • In patients at risk for the development of renal impairment (e.g., the elderly): renal function should be assessed more frequently.

(b) Hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices)
   • obtain before initiating metformin.
   • at least annually after initiation.

(c) Vitamin B12 levels:
   • when megaloblastic anemia is suspected.

(d) Fasting blood glucose and Glycosylated hemoglobin levels.

(e) Hepatic function test:
   • obtain before initiating metformin.
(9) Common adverse events associated with metformin use:

• Diarrhea
• Nausea/Vomiting
• Flatulence
• Asthenia
• Indigestion
• Abdominal Discomfort
• Headache
REFERENCES:

5. Metformin package insert. (pdf)
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