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Metformin for Antipsychotic Drug (APD)-Associated Weight Gain

General considerations for weight interventions:

- Initiate discussion with patient about their weight. Are they aware of their weight gain/overweight/obesity? Are they motivated to lose weight? Are they concerned about potential weight gain with a new medication? Educate regarding risks of obesity and weight gain on long-term health.
- Assess extent of regular physical activity and overall diet. Patients should be encouraged to improve their lifestyles prior to pharmacotherapy for weight loss. Encourage consultation with dietician, if available.
- Has an APD switch already been tried or considered? If the current APD is working well for psychosis then the risks associated with switching APD must be considered carefully. If the current APD is not working well, then obesity represents another reason to consider switching to an APD with lower risk for weight gain.

When to consider Metformin for weight:

- If behavioral interventions have not been adequate and if change to an APD with lower liability for weight-gain is not indicated, then metformin augmentation is reasonable, using the following guidelines:
  1. BMI $\geq$ 27 kg/m^2
  2. In a patient with normal or elevated BMI who has experienced $\geq$5% weight gain within 1 month of starting a new APD (see below for rationale).
  3. In a patient for whom prevention of weight gain is a priority, metformin can be started in advance of starting a new APD.

Evidence to support Metformin for weight control:

- In the landmark Diabetes Prevention Program (DPP) – people with prediabetes had mean 2.1 kg weight loss with metformin compared to placebo over the 2-year double-blind phase (Knowler et al., NEJM, 2002; 346:393-403).
- In antipsychotic-associated weight change studies, meta-analysis demonstrates mean 3 kg weight loss with metformin compared to placebo in studies ranging from 12-24 weeks (Mizuno et al., Schizophr Bull, 2014; 40:1385-1404). Weight loss with metformin may be greater in first-episode psychosis (Wu et al, JAMA 2008; 299: 185-193), compared to chronic schizophrenia (Jarskog et al, AJP 2013; 170: 1032-1040).
- Metformin is effective for short-term prevention of weight gain in patients starting an antipsychotic with a high risk of causing weight gain, e.g. olanzapine (see Wu et al, AJP 2008; 165: 352-358). Note, evidence to support metformin for weight prevention is more limited compared to data supporting metformin for weight loss in already overweight individuals.
- Highlighting the risk for ongoing weight gain after starting a new APD, $\geq$5% weight gain within 1 month predicts $\geq$15% weight gain after 3 months (Vandenberghe et al., J Clin Psychiatry, 2015; 76(11):e1417-e1423).

Potential added benefits of metformin:

- Improve fasting glucose levels in patients with pre-diabetes
- Improve lipid profile
- Improve APD-associated hyperprolactinemia
- Restore menstruation for APD-associated amenorrhea

Metformin Side Effects:

Common and usually transient:

- Diarrhea
- Nausea/vomiting
- Abdominal discomfort

Infrequent:

- VitB12 deficiency

Rare:

- Hypoglycemia
  - In settings of serious malnutrition or alcohol abuse
- Lactic acidosis
  - Remains extremely rare, incidence ~3 in 100,000 patient-yrs, and risk is probably even lower in people without heart, kidney or hepatic disease.
  - 30-50% mortality
  - Non-specific but severe sxs (weakness, myalgia, somnolence, gastric pain, hypotension, bradycardia, hypothermia)

(Relative) Contraindications to Metformin:

- Congestive heart failure or other serious cardiac disease
- Serious hepatic or kidney disease
- eGFR < 45 mL/min/1.73 m^2 (Note: patients with diabetes with eGFR between 30 – 45 may take metformin with caution, but would discourage use in this eGFR range for weight control given increased risk of lactic acidosis)
- Metabolic acidosis (CO_2<20)
- Current alcohol abuse or dependence
- Recent iodinated contrast material
- Pregnancy (Category B)
- For a patient with diabetes mellitus who is not already taking metformin, consult with the diabetes provider regarding addition of metformin

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Pre-Metformin workup

- Review list of relative contraindications to metformin
- Obtain CMP
    - **Most important: eGFR > 45 mL/min/1.73 m^2**
    - If AST or ALT > 2x upper limit of normal, consider checking with PCP regarding etiology and advisability of metformin
- In patient with anemia or peripheral neuropathy, obtain VitB12 level. Supplement as needed.
- Assess alcohol use (general rule of thumb, no more than 5 twelve ounce beers per day or equivalent).

Initiating Metformin:

- Begin metformin 500 mg qdaily for 1-2 weeks
- Increase by 500 mg every 1-2 weeks, up to 1,000 mg BID, as tolerated.
- If GI tolerability problems emerge, adjust to highest tolerated dose. Consider switch to metformin ER
- Most people tolerate 1,000 mg BID without difficulty.
- Communicate with PCP to inform and educate as needed so as to avoid any misunderstanding.

Ongoing Monitoring

- Check eGFR at least annually, or q6 months if eGFR is <60 mL/min/1.73^2
- LFTs annually
- Assess alcohol use regularly
- Consider annual VitB12, especially in patients with anemia or peripheral neuropathy