Agents to Consider for Prevention and Treatment of Antipsychotic Induced Metabolic Syndrome

Antipsychotic Induced Metabolic Syndrome (Background):

- Metabolic syndrome (MetS) is defined as a group of conditions that together raise the risk of coronary heart disease, diabetes, stroke, and other serious health conditions.
- The prevalence of MetS in patients with schizophrenia is 3-5X higher than in general population and twice as likely to die of cardio-vascular disease.
- In general, every kg ↑ in weight ↑ risk of CVD by 3.1%, ↑ of every 1 BMI ↑ risk of HF by 5-7% & risk of DM2 ↑ by 8.4%.
- Prevalence rate in antipsychotic-naïve patients ranges from 3.3% to as high as 26% and 32% to 68% with chronic treatment.
- Progressive Weight Gain.
- Class effects involving Histamine H1, Serotonin and Muscarinic Receptors.
- Marked differences exist between antipsychotics: Clozapine & Olanzapine have the highest liability to cause MetS & aripiprazole, brexpiprazole, Cariprazine, lurasidone and ziprasidone having lower liability.
- Increased baseline weight, being male and non-white are potential risk factors for antipsychotic induced MetS.

A. FDA Approved Medications:

Currently there are no FDA Approved Medications for prevention and treatment of antipsychotic induced metabolic syndrome.

B. Non-FDA Approved Medications:

1. Metformin, Metformin XR (Glucophage® or Glucophage XR®)
2. Topiramate, Topiramate ER, Topiramate Sprinkle Capsules (Topamax®, Topamax ER® Topamax Sprinkle Capsules®)
3. Olanzapine/Samidorphan (Lybalvi®)

Metformin/Metformin XR

The recommendations/guidelines below are based on the following publication.

Fitzgerald I, O'Connell J, Keating D, Hynes C, McWilliams S, Crowley EK. Metformin in the management of antipsychotic-induced weight gain in adults with psychosis: development of the first evidence-based guideline using GRADE methodology. *Evid Based Ment Health*. 2022;25(1):15-22. https://pubmed.ncbi.nlm.nih.gov/34588212/

I. Appropriateness of metformin:

1: There are two strategies:

A: Early intervention

B: Treatment of established weight gain

2: Early intervention is defined as **starting Metformin following a ≥7%** increase in baseline body weight, **within 1 month of antipsychotic treatment. *It should be noted that evidence supports improved efficacy of metformin in attenuating AIWG when initiated at earlier time points in antipsychotic treatment.**

3: Where lifestyle modifications are deemed appropriate and acceptable to the patient, they should be offered before metformin.

4: Use metformin as first-line for patients that lifestyle modifications are unacceptable or inappropriate.

5. If lifestyle modifications seem ineffective, metformin can be an alternative.

II. Baseline monitoring when initiating metformin:

A. Baseline renal function.
B. Dosage modification is required for eGFR<60 ml/min.
C. Metformin is contraindicated in those with an eGFR of <30 mL/min. (*good practice point*)

III. Metformin Dosing:

A. Starting dose: 500mg bid, increase in increments of 500mg every 1-2 weeks
B. Maximum dose of 2000mg/day

IV. Assessing response to treatment:

A. If used as an early intervention, treatment goal would be plateau of weight gain. Reversal of AIWG may also be a feasible goal.
B. When used to induce weight loss in those with established AIWG, treatment goal would be weight loss of at least 5% of baseline weight within 6 months.
C. Treatment goals should be individualized and agreed collaboratively with the patient.

VI. Ongoing monitoring:

A. Monitor renal function annually
B. Monitor renal function q3-6months in elderly and those with higher risk of renal impairment i.e., Chronic Renal Disease.
C. Intermittent monitoring of B12 specially when there is a risk of megaloblastic anemia.

VII. Management of side effects:

A. GI side effects are dose related and can be managed by dosage Reduction and/or slower dose titration.
B. Estimated risk of lactic acidosis is 4.3 per 100,000 person-years in metformin users. Renal dosing can mitigate the risk. Avoid metformin in certain groups including those with h/o Alcohol misuse, and in patients with interacting medications.

VIII. Deprescribing:

A. It's recommended to continue the metformin if treatment goals have been reached at 6 months. However, continuation needs to be part of the risk-benefit assessment.
B. The following is recommended if treatment goals have not been reached in 6 months:

1. Increase the dose to 2000mg/day where possible.
2. Discontinue If treatment has been optimized as much as possible.
3. Providers should check adherence and stop metformin if not mostly adherent.

The authors agreed not to endorse antipsychotic switching as a failed strategy prior to considering metformin, due to lack of supporting evidence of effective weight reversal and considerable associated risk. "Metformin offers a safe and similarly effective intervention to many lifestyle approaches, with superior efficacy to switching antipsychotics, but with much lesser associated risk".

Prescribing Highlights for Metformin and Metformin Extended-Release: for more details, please refer to the full prescribing information)

Brand Name	• Glucophage®, Glucophage XR
Class	• Biguanide
Mechanism of Action	• Metformin (1) decreases hepatic glucose production, (2) decreases intestinal absorption of glucose, and (3) improves insulin sensitivity by increasing peripheral glucose uptake and utilization
Dose	• **Immediate release:** initiate therapy with 250 mg or 500 mg twice daily then titrate (as tolerated) to maintenance dose of 750 mg to 2 g by mouth once daily in 2 to 3 divided doses • **Extended release:** initiate therapy with 500 mg once daily and titrate in 500 mg increments every 2 to 6 weeks based on tolerability to maintenance dose of 1 to 2 g by mouth once daily
Black-Box Warning	• Fatal lactic acidosis
Contraindications	• **eGFR < 30 mL/min/1.73 m2** • Known hypersensitivity to metformin • Acute or chronic metabolic acidosis
Warnings/ Precautions	• Risk factors for lactic acidosis include (1) renal impairment, (2) concomitant use of certain drugs (see below) (3) age ≥ 65 years, (4) having a radiological study with contrast,(5) surgery and other procedures, (6) hypoxic states, (7) excessive alcohol intake, and (8) hepatic impairment • Avoid initiation in eGFR 30-45 mL/min/1.73 m2 • Lactic acidosis • Vitamin B-12 deficiency with chronic use
Adverse Drug Reactions	• Diarrhea • Nausea • Vomiting • Flatulence • Dyspepsia • Abdominal pain
Drug-Drug Interactions	• Thiazides and other diuretics, phenothiazines corticosteroids increase blood glucose • Topiramate or other carbonic anhydrase inhibitors may increase the risk for lactic acidosis
Monitoring Parameters	• **Renal function**: prior to therapy initiation, and at least annually or at least every 3 to 6 months if eGFR is <60 mL/minute/1.73 m2 • Hgb, HCT- initially, then annually • Vitamin B12 serum concentrations every 1 to 2 years • HbA1C: twice yearly (at-goal) or quarterly (not-at goal)

	• **ALT at baseline and periodically thereafter**

Topiramate, Topiramate ER, and Topiramate Sprinkle Capsules:

For Antipsychotic Induced Weight Gain (AIWG): The typical **initial dose** is 50mg twice daily, if tolerated, the maximum dose is 100-200mg twice daily after 1 week.

Prescribing Highlights for Topiramate: (For more details, please see the full prescribing information and the Section N of the Medication Practice Guidelines related to the Mood Stabilizers Section.

Brand Name	• Topamax
Class	• Antiepileptic (mood stabilizer)
Mechanism of Action	• Thought to be related to decreasing appetite and increasing satiety but does not alter energy expenditure. It is also proposed to work via improvement in insulin sensitivity related to reduction in leptin concentrations and visceral fat.
Dose	• **For Weight Management:** The typical initial dose is 50mg twice daily, if tolerated, the maximum dose is 100-200mg twice daily after 1 week. One study cites up to 300mg total daily dose.
Black-Box Warning	• None
Contraindications	• None
Warnings/ Precautions	• Acute Myopia and Secondary Angle Closure Glaucoma • Oligohidrosis and Hyperthermia • Metabolic Acidosis • Suicidal Behavior and Ideation • Cognitive/Neuropsychiatric Adverse Reactions • Pediatric Patients • Fetal Toxicity • Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use) • Kidney Stones • Hypothermia with Concomitant Valproic Acid (VPA) Use • Paresthesia • Adjustment of Dose in Renal Failure • Decreased Hepatic Function • Monitoring: Laboratory Tests
Adverse Drug Reactions	Common (Partial list): • somnolence • cognitive dysfunction • weight loss, anorexia • nausea, diarrhea, abdominal pain, dyspepsia • nervousness • dizziness • fatigue • ataxia • insomnia • insomnia • mood disturbance, depression

Drug-Drug Interactions	• CYP3A4 substrate • CYP2C19 inhibitor, weak • CYP3A4 inducer, minor • antiepileptic agent • CNS depression • hyperthermia • hypokalemia • metabolic acidosis • urine alkalinizer
Monitoring Parameters	Cr at baseline; bicarbonate at baseline, then periodically; height, weight in peds if prolonged tx; s/sxs of depression, behavior changes, suicidality

Prescribing Highlights for Olanzapine plus Samidorphan: For more details, please see the full prescribing information.

Brand Name	• LYBALVI®		
Class	• Combination: Atypical antipsychotic/ Opioid antagonist		
Mechanism of Action	• The mechanism of action of olanzapine is unclear; however, its efficacy in the treatment of schizophrenia or bipolar I disorder is thought to be associated with the dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of Samidorphan is thought to be mediated through opioid receptor antagonism.		
	Indication	**Recommended Starting Dose**	**Recommended Maintenance Dose**
	Schizophrenia	• 5 mg/10 mg or • 10 mg/10 mg	• 10 mg/10 mg • 15 mg/10 mg • 20 mg/10 mg
	Bipolar I disorder (manic or mixed episodes)	• 10 mg/10 mg or • 15 mg/10 mg	• 5 mg/10 mg • 10 mg/10 mg • 15 mg/10 mg • 20 mg/10 mg
	Bipolar I disorder adjunct to lithium or valproate	• 10 mg/10 mg	• 10 mg/10 mg • 15 mg/10 mg • 20 mg/10 mg
Black-Box Warning	• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.		
Contraindications	• **Patients using opioids** • **Patients undergoing acute opioid withdrawal** • **If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate refer to the lithium or valproate Prescribing Information for the contraindications for those products**		
Warnings/ Precautions	• Cerebrovascular adverse reactions in elderly patients with dementia-related psychosis • Orthostatic hypotension and syncope • Leukopenia, Neutropenia, and		

	• Precipitation of opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids to avoid precipitation of opioid withdrawal. • Risk of opioid overdose & risk of resuming opioids in patients with prior opioid use • Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Agranulocytosis • **Increased risk of seizures.** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. • **Potential for cognitive and motor impairment** • Anticholinergic effects • Hyperprolactinemia • Neuroleptic Malignant Syndrome
Adverse Drug Reactions	• Schizophrenia (LYBALVI): weight increased, somnolence, dry mouth, and headache • Bipolar I Disorder, Manic or Mixed Episodes (olanzapine): asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor • Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine): dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia
Drug-Drug Interactions	• Strong CYP3A4 Inducers: Not recommended (e.g., **Carbamazepine**, Phenytoin, etc.) • Strong CYP1A2 Inhibitors: Consider dosage reduction of olanzapine component of LYBALVI **(e.g., Fluvoxamine)** • CYP1A2 Inducer: Consider dosage increase of the olanzapine component of LYBALVI **(Carbamazepine, smoking, etc.)** • CNS Acting Drugs: May potentiate orthostatic hypotension (7.1) • Anticholinergic Drugs: Can increase risk for severe gastrointestinal adverse reactions • Antihypertensive Agents: Monitor blood pressure • Levodopa and Dopamine Agonists: Not recommended
Monitoring Parameters	• Blood chemistries (electrolytes, renal function, liver function, TSH): annually • CBC: as clinically indicated • Extrapyramidal symptoms every visit: 4 weeks after initiation and dose change; annually. • Fasting plasma glucose/A1C: 12 weeks after initiation and dose change; annually • Lipid panel: 12 weeks after initiation and dose change; annually • Metabolic syndrome history: annually • Prolactin: Ask about symptoms at every visit until dose is stable. Check prolactin level if symptoms are reported • Tardive dyskinesia: Every visit; annually • Vital signs: Every visit (at least weekly during first 3 to 4 weeks of treatment);

	4 weeks after dose change • Weight/Height/BMI: 8 and 12 weeks after initiation and dose change; quarterly

- **Extended release:** initiate therapy with 500 mg once daily **with food** and titrate in 500 mg increments every 2 to 6 weeks based on tolerability to maintenance dose of 1 to 2 g by mouth once daily. Max. dose 2,000 mg

Topiramate and Topiramate ER:

For Weight Management: The typical initial dose is 50mg twice daily, if tolerated, the maximum dose is 100-200mg twice daily after 1 week.

C. Duration (Documentation Required)

1. Outpatient: Document rationale when making any medication change.
2. Inpatient: Document rationale when making more than 3 changes in any 7-day period.

D. Polypharmacy:

There are no studies supporting polypharmacy with the above three agents in context of prevention or treatment of antipsychotic induced metabolic syndrome. Therefore, concomitant use of more than one of the above agents should be avoided due to the lack of supporting evidence, possible increased risk of adverse effects, drug-drug and drug-disease interactions. Consider referring the patients with suboptimal response to the primary care provider for consideration of other drug classes i.e. glucagon-like peptide-1 (GLP-1) medications.

E. Standard Laboratory and Examination Requirements

1. For Inpatient: Basic laboratory studies on admission
2. For Outpatient: In accordance with the 2020 APA Guidelines, other relevant sections of the Medication Practice Guidelines and the FDA approved Prescribing Information for various agents.

F. Black Box Warning: Per the FDA approved Prescribing Information for various agents.

G. Warning & Precautions:

Documentation Required (In accordance to all the relevant sections of the Medication Practice Guidelines and the FDA approved Prescribing Information for various agents.

H. Drug-Drug Interactions, Pharmacology:

As mentioned in this and other relevant sections of the Medication Practice Guidelines, and www.epocrates.com Drug Interaction Check.

I. Pregnancy or breast-feeding:

Refer to other relevant sections of the Medication Practice Guidelines and the FDA approved Prescribing Information for various agents.

J. Serious adverse effects:

As mentioned in this and other sections of the Medication Practice Guidelines as well as the FDA approved Prescribing Information for various agents. (Documentation Required).

K. Common adverse effects:

As mentioned in this and other sections of the Medication Practice Guidelines as well as the FDA approved Prescribing Information for various agents. (Documentation Required)

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