Mind and Metabolism in Harmony: Addressing the Metabolic Side Effects of Second-Generation Antipsychotics with Topamax, Metformin, and GLP-1 Agonists

Tiffany R. Pressley, DNP, APRN, PMHNP-BC, PMH-BC, CMSRN, CNE
School of Health Sciences, Francis Marion University

Nina M. Russell, DNP, MSN-Ed., APRN, FNP-C
School of Health Sciences, Francis Marion University

Abstract

This discussion paper addresses the significant metabolic burden associated with the use of second-generation antipsychotics (SGAs). These medications are effective in managing various psychiatric disorders. However, patients taking SGAs often experience common side effects, such as weight gain, insulin resistance, dyslipidemia, and an increased risk of metabolic syndrome (Speyer et al., 2021; Welge et al., 2023). These common adverse/side effects can severely impact the physical health and overall quality of life of patients, including mental health and self-esteem (Blasco et al., 2020). Over time, these effects may lead to long-term health complications, including cardiovascular disease and type 2 diabetes. Hence, while supporting psychiatric symptom management, these medications can simultaneously create a major challenge for both patients and healthcare providers (Welge et al., 2023).

The opportunity for improvement lies in recognizing and incorporating effective strategies to manage these side effects (Pearl et al., 2023; Wajid et al., 2023). Practitioners must ensure that psychiatric patients do not face additional health risks because of their psychiatric treatment. This discussion paper seeks to provide sensible solutions to lessen or alleviate the metabolic risks associated with SGAs through integration of adjunct therapies, such as Topamax (topiramate), metformin, and GLP-1 receptor agonists (Vanderah, 2024, Pearl et al., 2023; Wajid et al., 2023). The integration of this intervention could significantly improve patient outcomes by addressing the dual challenge of maintaining metabolic health while managing psychiatric symptoms, ultimately improving patient outcomes and quality of life.

Keywords:Second-Generation Antipsychotics, Metabolic Syndrome, GLP-1 Receptor Agonists, Topiramate, Psychiatric Treatment, Cardiometabolic Risk

Depression has no boundaries and, according to the World Health Organization (2023), impacts more 280 million adults, internationally. Between 2017 and 2023, U.S. adult depression rate increased almost 10%; among women, the incidence of depression increased by 10.5%, nearly twice the rate of men (Witters, 2023). Notably, women are 50% more likely to be diagnosed with major depressive disorder than males (World Health Organization, 2023). Still, women with unipolar depression are 1.3 times more likely to develop bipolar disorder over a 15 year period (Baryshnikov et al., 2020). Sadly, many who suffer from depression are either unable or unwilling to seek treatment leading to 700,000 suicides annually (World Health Organization, 2023). Early identification, diagnosis, and treatment are key to reducing current international suicide rates; as such, healthcare professionals are charged with screening all

patients for major depressive disorder (Parish et al., 2023; Simon et al., 2024).

Similarly, obesity among Americans continues to rise. In August 2024, the National Center for Health Statistics (NCHS) found 40.3% of U.S. adults, ages 20 and older, classified as obese; additionally, 9.4% classified as severely obese (Emmerich et al., 2024). This shows a statistically significant increase in severe obesity from previous NCHS reports. Moreover, the prevalence of 41.3% obesity among women continues to surpass the obesity rate of 39.2% among men (Emmerich et al., 2024). Despite the knowledge and resources to manage depression and obesity, the collective health of the U.S. continues to fall short as compared to other countries (World Health Organization, 2023).

Diagnostic Considerations

To further complicate matters, obesity and depression potentiate one another. A 2020 study found a 55% greater risk for depression associated with obesity, and a 58% greater risk for obesity associated with depression (Blasco et al., 2020). Due to the cyclical relationship amid depression and obesity, successful management of one diagnosis is contingent upon the successful management of the other; thus, implementation of evidence-based guidelines are imperative to reducing the burden of these aforementioned prevalent conditions. Best practice requires providers to utilize appropriate screening tools, such as the Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7-Item (GAD-7), and Mood Disorder Questionnaire (MDQ) to screen for major depression, mood disorders, and suicidal risk. Furthermore, healthcare professionals must gather a complete family history, consider underlying, comorbid medical conditions (i.e., thyroid dysfunction, diabetes mellitus (DM), anemia, etc.), and evaluate for a pharmaceutical contribution (i.e., illegal substances, prescription drugs, alcohol, etc.). Providers should consider the following diagnostics: Urine drug screen, complete metabolic panel, complete blood count, glycosylated hemoglobin, and thyroid panel, to list a few (Parish et al., 2023; Simon et al., 2024).

Obesity and Lipogenesis

Obesity awakens the neuroendocrine system as a steady release of circulating ligands alter and even, destroys cellular and endothelial structures; insulin receptors (IRs) and cell size are key to understanding insulin resistance. Large adipocytes have large cellular membranes; consequently, the membrane expansion forces distance between each insulin receptor (IR) site. Bigger cells add even greater space among receptors; subsequently, obesity begets a prolonged rise in circulating insulin (Norris, 2024).

The relationship between diet and obesity has long been established. A diet rich in carbohydrates elevates serum glucose levels and stimulates physiologic processes. This series of events is interpreted by the cells as a personal attack that must be stopped. In an attempt to reduce circulating glucose levels, pancreatic beta cells increase production of insulin. The elevation in plasma glucose and corresponding serum insulin incite lipogenesis. For the obese or insulin resistant individual, this process begets an alternate pathway for energy. Lipogenesis involves the use of dietary energy sources, such as carbohydrates, to produce fatty acids (FAs) as an alternate source of energy. Lipogenesis occurs within the liver and adipose tissue; consequently; a rise in FA production results in high plasma triglyceride levels and ultimately, hepatosteatosis. Subsequently, this chain of events triggers the release of inflammatory agents, including leukotrienes, cytokines, and mast cells, which instigate and

worsen physiologic conditions (Norris, 2024).

As a defensive tactic, cells begin down regulation of IRs secondary to the barrage of circulatory ligands; adipose cells destroy existing IR sites; as an added measure, cells reduce IR synthesis. Obesity, hyperinsulinemia, and receptors site separation significantly reduce insulin-receptor binding and decrease cell's sensitivity to insulin; thus, contributing to insulin resistance. If left unchecked, these factors contribute to obesity, hyperlipidemia, hyperinsulinemia, DM, hypertension, or metabolic syndrome, and more (Norris, 2024).

Summary of the Evidence

Professional Practice Gap

Patients diagnosed with psychiatric conditions such as depression, anxiety, bipolar spectrum disorders, and schizophrenia spectrum and related disorders may experience improved symptom control with second-generation antipsychotics (SGAs); however, these medications are frequently linked to weight gain and adverse metabolic effects (Speyer et al., 2021; Welge et al., 2023). There is significant evidence supporting the need to address the metabolic burden associated the treatment of psychiatric illness with second-generation antipsychotics (SGAs). Key findings from research and trends in the literature include impact on cardiovascular and endocrine health (Libowitz & Nurmi, 2021), prevalence of metabolic side effects (Speyer et al., 2021), mechanisms of metabolic dysfunction (Iqbal et al., 2025), various clinical guidelines and warnings (Yan, 2008), adjunctive interventions (Patoulias et al., 2023), and increased healthcare costs and economic burden (Welge et al., 2023). However, despite these risks, SGAs are continuously prescribed without adjunctive treatment to address adverse/side effects.

Historically, the management of metabolic side effects in patient taking SGAs has been reactive rather than proactive. This method often fails to prevent complications such as weight gain, insulin resistance, and dyslipidemia. Key aspects of current practice include baseline and periodic metabolic monitoring of weight BMI, waist circumference, glucose level, and lipid profiles; medication selection based on metabolic risk; lifestyle and behavioral interventions; and pharmacological co-management.

Unfortunately, compliance with guidelines is often poor in real-world practice (Welge et al., 2023). Many patients continue to receive high risk SGAs such as olanzapine and clozapine due to their superior efficacy and historical failed medication trials of other lower risk agents such as aripiprazole and lurasidone. While successful lifestyle and behavioral interventions are known to mitigate metabolic effects, consistent engagement in these intervention may be challenging due to lack of motivation, unmanaged psychiatric symptoms, and limited availability of resources (Speyer et al., 2021; Welge et al., 2023). The recommended change in practice has significant emerging success related to recent trials of GLP-1 receptor agonist, topiramate, and metformin that have been demonstrated to counteract weight gain and metabolic dysfunction (Richmond, 2025; Popoviciu, et al., 2023; Generali & Cada, 2014; Wu et al., 2012).

Pharmaceutical Management of Obesity

Adjunct medications for obesity, in combination with diet and exercise, may be instrumental in averting weight gain and other metabolic risks associated with second-generation antipsychotics, such as clozapine and olanzapine (Vanderah, 2024).

Biguanides

Glucophage (metformin), an antidiabetic biguanide, that reduces gluconeogenesis, enhances insulin sensitivity in peripheral tissue, and decreases circulating levels of glucose and insulin, as such moderating inflammation. Common side effects (SEs) of biguanides are largely gastrointestinal, including abdominal pain, gastroesophageal reflux, bloating, nausea, and diarrhea. Often, common SEs may be reduced or alleviated by prescribing the extended-release, rather than the immediate release form of Glucophage. Finally, a slower dose titration may allow the gastrointestinal tract to adjust with time (Vanderah, 2024). Glucophage is cost effective and often not associated with adverse effects, particularly when correctly prescribed (Vanderah, 2024).

Glucagon-like Peptide-1 Receptor Agonist

A novel drug popular following celebrity use and of course, social media. This class of drugs, known as glucagon-like peptide-1 receptor agonists (GLP-1RAs), are common household names, promising quick, easy results with little to no exercise. GLP-1RAs, such as Wegovy (semaglutide), suppresses hunger and promotes satiation. GLP-1RAs generate core, dietary modifications, including a decline in repetitive eating and portion control, each pivotal to weight loss and management. Nonetheless, this class of medications is not without side effects, for instance nausea, dyspepsia, gastroesophageal reflux, constipation, gallstones, to list a few. Additionally, providers must evaluate for contradictions related to personal and family of thyroid prior to prescribing this class of medication (Vanderah, 2024).

Antiseizure Medications

Topiramate (Topamax) has long been accepted for use as an antimigraine and as antiseizure medication; moreover, this medication may be used to increase satiety, reduce weight, or as an additive agent to offset the metabolic side effects of other treatments. The mechanism of action, ideal dose, and titration are poorly understood in relation to weight management as well as weight loss. Of significance, Topamax is associated with a few common side effects (SEs), consisting of difficulty concentrating, fatigue, dizziness, numbness or tingling to the extremities, nausea, dyspepsia, gastroesophageal reflux, or diarrhea, to list a few. These appear to be dose-dependent with higher dosages propagating greater and more severe SEs. Without fail, providers must routinely assess for medication SEs during follow-up visits to prevent severe, uncommon SEs (Pearl et al., 2023; Wajid et al., 2023).

Validation of the Evidence

Early pharmacological interventions, such as those involving metformin, topiramate, and GLP-1 receptor agonists, to reduce metabolic burden associated with the use of second-generation antipsychotics (SGAs), are supported by various studies. A double-blind, randomized study involving 84 women with first-episode schizophrenia demonstrated that metformin significantly ameliorated antipsychotic-induced amenorrhea, with 66.7% of participants experiencing resumed menstruation compared to 4.8% in the placebo group. The study also observed reductions in BMI and insulin resistance. These findings indicate metformin's efficacy in mitigating metabolic and hormonal adverse effects associated with antipsychotic treatment in women (Wu et al., 2012). A recently issued guideline advocates for the use of metformin in the management of weight gain associated with SGA-induced metabolic dysfunction, recommending early intervention rather than deferring until substantial weight loss has materialized (Richmond, 2025).

A meta-analysis of controlled trials assessed pharmacological interventions for weight gain linked to mood stabilizers or antipsychotics. Topiramate demonstrated efficacy in addressing antipsychotic-induced weight gain, with the review of four randomized, double-blind, placebo-controlled trials revealing an average weight loss of 3.95 kg relative to placebo (Generali & Cada, 2014). GLP-1RAs have demonstrated substantial efficacy in enhancing metabolic wellness among individuals with obesity related to antipsychotic treatment. A meta-analysis of four randomized controlled trial confirmed that GLP-1RAs result in notable improvements in lipid profiles and glycemic control as well as considerable decreases in body weight and BMI (Popoviciu et al., 2023).

Consideration of Alternative Pharmacologic Weight-Management Agents

While multiple pharmacologic agents are approved for weight loss and weight management, this review focuses on topiramate, metformin, and GLP-1 receptor agonists due to their relatively robust evidence base in patients treated with second-generation antipsychotics. Other agents—including bupropion–naltrexone, phentermine, and phentermine–topiramate—have demonstrated efficacy in the general population but remain understudied in individuals with serious mental illness or antipsychotic-induced metabolic dysregulation.

Bupropion–naltrexone (Contrave) presents theoretical appeal given bupropion's favorable metabolic profile; however, data evaluating its safety and efficacy in patients receiving SGAs are limited. Additionally, bupropion's activating properties may pose risks for individuals with underlying anxiety, psychosis, or bipolar spectrum disorders, potentially limiting its clinical utility in this population (Lui et al., 2024).

Sympathomimetic agents such as phentermine, either alone or in combination with topiramate (Qsymia), are associated with appetite suppression and weight loss but raise concerns related to cardiovascular risk, insomnia, anxiety, and potential exacerbation of psychotic or manic symptoms. These risks are particularly salient for patients with serious mental illness, who already experience elevated cardiometabolic burden and psychiatric vulnerability. To date, controlled trials examining these agents specifically for antipsychotic-associated weight gain are lacking.

In contrast, metformin, topiramate, and GLP-1 receptor agonists have been evaluated in randomized controlled trials and meta-analyses involving patients treated with SGAs, demonstrating clinically meaningful improvements in weight, insulin sensitivity, and other metabolic parameters. As such, these agents currently represent the most evidence-supported pharmacologic options for addressing antipsychotic-induced metabolic side effects. Future research should explore the safety, tolerability, and efficacy of other weight-management medications in this population to expand the range of evidence-based interventions (Iannone et al., 2023).

Collaborative Decision-Making

Collaboration, between healthcare providers and patients, is key and ensures the treatment pathway is tailored to meet the needs of each individual. What's more, patients must actively participate in their healthcare decisions; this can only occur when patients are provided adequate education regarding the benefits and risks (Ayre et al., 2024). Another vital aspect is patient self-care, including adherence to medication, timely diagnostics, lifestyle modification, and observance of

appointments, etc. The nexus between practice guidelines and holistic practice, is a collaborative partnership (Ayre et al., 2024; Kappelin et al., 2023). After careful scrutiny of the evidence and prior to implementation of a treatment plan, clinicians must consider and appraise the patient's condition, associated risks and benefits, cost, concerns regarding treatment, and ultimately, their desired outcome (Ayre et al., 2024; Kappelin et al., 2023). While practice guidelines are derived from rigorous research studies, such guidelines often omit critical elements (i.e., patient beliefs, values, choice, economics, etc.). Therefore, the decision to implement treatment should culminate from a collaborative partnership (Ayre et al., 2024; Kappelin et al., 2023).

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