Wyoming Drug Utilization Review

Antipsychotic Agents and Metabolic Disorders

Written by Alex Allen PharmD, 2024

Antipsychotic agents, especially second-generation antipsychotics (SGAs), are used to treat patients with serious mental illnesses (SMIs) such as schizophrenia or bipolar disorder. However, these agents are not benign; association has been made between SGAs and metabolic side effects such as obesity, diabetes, metabolic syndrome, and other concerning sequelae (1). A review of the literature is in order, as well as an investigation into the best practices surrounding mitigating these side effects.

Recently, there has been some research into the mechanisms behind antipsychotic induced weight gain. It has been proposed that antipsychotics disrupt metabolic regulation by activating hunger centers, disrupting food reward circuitry, and inhibiting satiety sensation (2). There may also be a direct effect on metabolism through increasing glucose output, decreasing glucose uptake, and increasing adipogenesis and lipogenesis. Though these mechanisms are not exactly clear, they indicate that metabolic disturbances are a multifaceted problem spawned by antipsychotic use (2).

	Receptor Binding Profiles					Risk		
	D	H	5-HT	M	α	Weight Gain	Glucose Abn	Lipid Abn
Aripiprazole	+/+++	0/++	++	0	++	++	+	+
Asenapine	+++/++++	+++	+++	0	+++	++	+	+
Cariprazine	0/++++	0/++	+/+++	0	0/+	+ (*)	+ (*)	+ (*)
Paliperidone	+++	+/++	+/++	0	+++	+++	+/++	+/++
Lurasidone	0/+	0	+/++	0	++	+	+	+
Olanzapine	++	++	++	++	++	++++	++	++
Quetiapine	+	0/+++	+/++	+	+/++	+++	+/++	++
Risperidone	++	+	++	0	++/+++	+++	+/++	+/++
Ziprasidone	++	0/++	+++	0	++	+	+	+
Clozapine	+/++	++	+/++	+++	++	++++	++	++

A table showing the different binding affinities of the first- and second-generation antipsychotics, and their propensity for weight gain, glucose abnormalities, and lipid abnormalities. (*) represents limited data. Table adapted from Siafis et al.

Many studies and meta-analyses have been conducted to establish which side effects are a concern with SGAs, how much of a concern they are, and which SGAs are (relatively) safer than others. Every antipsychotic has a risk for metabolic side effects. Aripiprazole, lurasidone, and ziprasidone have relatively lower risk compared to olanzapine and clozapine (1). Olanzapine and clozapine appear repeatedly in the literature as agents whose metabolic disturbances are notoriously frequent, and whose effects are difficult to counter. Olanzapine and clozapine are also cited as diabetogenic (3), which makes them even more important to be aware of.

WY-DUR
University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Ave
Laramie, WY 82071
307-766-6750
www.uwyo.edu/DUR

Edited by
Aimee Lewis, PharmD, MBA
Karly Bentz

Olanzapine and clozapine are often on the list of SGAs that can be attributed to increased weight, increased LDL, and increased triglyceride levels (1,3). Both of these agents have strong levels of antagonism at serotonergic 5-HT2C receptors and histaminergic H1 receptors, which contributes to their effect on weight (1,3). However, their diabetogenic effect cannot be attributed solely to weight gain; rather, there is a direct effect on the pancreas, liver, and skeletal muscles by olanzapine and clozapine which is likely the cause of insulin dysregulation and development of diabetes (3).

Adding samidorphan to olanzapine has unclear benefits for reducing weight gain and metabolic syndromes (4). Olanzapine with samidorphan (OLZ/SAM) sold under the brand name of Lybalvi, is shown to reduce the probability of weight gain and reduces total cholesterol (5). However, the evidence is low-quality, and per a meta-analysis of OLZ/SAM's effect on short-term weight gain and cardiometabolic changes, there may even be an increased risk of weight gain (4). Additionally, there is no observable effect from OLZ/SAM on LDL, HDL, triglycerides, glucose, or insulin compared to regular olanzapine. It is worth noting that samidorphan is well tolerated among patients receiving olanzapine. However, samidorphan is a potent mu-opioid antagonist, meaning that patients who take OLZ/SAM may be at risk of opioid withdrawal if they take concurrent opioids. Despite this, OLZ/SAM is likely not harmful to patients overall (4).

Metformin has shown some short-term benefits for preventing excessive weight gain and glucose dysregulation in patients who are starting an SGA. In a meta-analysis, metformin was shown superior to placebo for metabolic parameters including insulin regulation, cellular glucose uptake, fasting glucose, and weight changes (6). Metformin was also shown beneficial for weight loss – in one study contained in the meta-analysis, 40.6% of patients in the metformin group reduced their body weight by 7%. This is significant, as losses greater than 5% result in clinically significant reductions in morbidity and mortality outcomes. Metformin appeared to be more effective at prevention than at reduction; first episode patients who started metformin alongside an antipsychotic showed mean weight loss of 5.94 kg, while metformin started in patients who were on antipsychotics chronically showed mean weight loss of 2.06 kg. The authors speculate that this is due to the rapid metabolic changes occurring in patients who have just started taking antipsychotics. The authors then state that early intervention is key to mitigating the impact of metabolic disorders on patients taking an antipsychotic, and advocate that in all patients showing signs of metabolic disturbance, metformin should be considered (6).

More research is needed into mitigation of SGA-associated weight gain and metabolic disturbances. Opting for relatively safer SGAs such as aripiprazole or ziprasidone where possible may be a more viable strategy for patients who are not already stabilized on another agent. Metformin appears promising in conjunction with SGAs to prevent weight gain and mitigate diabetogenic effects. Samidorphan is another option for preventing weight gain caused by olanzapine specifically, but its long-term effects are unclear, and evidence for its use is low-quality. Metformin would still be a better choice for any other SGA, and because the evidence is conflicting and low-quality, samidorphan should not be first-line at this time. Ultimately, weight gain and metabolic disturbances in conjunction with SGA use appears to be a multifaceted problem, and there is not one easy solution to make these agents safer or mitigate their metabolic effects.

References

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6. Asanka de Silva V, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systemic review and meta-analysis. BMC Psychiatry. 2016;16(1):341.

The P&T Committee met for its quarterly business meeting on November 14, 2024.

Highlights of this meeting include:

The systemic agents for atopic dermatitis will no longer require a step through pimecrolimus or tacrolimus. They will now become step two after the topical steroids.

Dupixent is approved for treatment of COPD. The medication will be limited to patients who have been diagnosed with COPD for at least one year, has been on triple inhaled therapy for at least three months and at a stable dose for at least one month, have eosinophil levels greater than 300 and have had two moderate or one severe exacerbation in the last year.

Piasky, Livdelzi, Ebglyss, and Cobenfy were reviewed with no evidence of a difference in safety or efficacy versus the current products in their respective class. All were limited to indication and referred to the Department of Health for cost analysis and PDL placement.

Nemluvio, Yorvipath, Miplyffa, Aqneursa and Vyalev were all limited to indication. Additionally, Yorvipath will be approved for patients who are at least three months post-surgery.

Tryvio will be limited to patients who have been on at least three antihypertensives from different pharmacological classes for at least one year with continued uncontrolled hypertension.

All prior authorization criteria are open for public comment. Comments should be sent by email to alewis13@uwyo.edu by January 15, 2025. The draft Preferred Drug List will be posted for public comment at www.uwyo.edu/DUR. Any comments should be sent via email prior to December 15, 2024.

The next P&T Committee meeting will be held February 13, 2025 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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School of Pharmacy
Dept. 3375
1000 E. University Avenue
Laramie, WY 82071

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