Research Article

Is a Glucocorticoid Antagonist a Potential Treatment Alternative for Antipsychotic-Induced Weight Gain?

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Abstract

Objective: To evaluate the efficacy and safety of mifepristone as a new treatment modality for antipsychotic-induced weight gain. **Methods:** We searched databases up to March 2021, for the published English-language literature including a Medical Subject Heading "Mifepristone," "Receptors, Glucocorticoid," "Weight gain," "Overweight," "Obesity," "Body Weight Change," "Antipsychotics Agents," "Glucocorticoid Receptor Blocker," "Glucocorticoid Receptor antagonist." We identified two clinical and four preclinical studies utilizing mifepristone as a treatment modality. **Results:** The results of the olanzapine clinical trial showed that mean increase in weight from baseline to day 14 was greater in the olanzapine with the placebo group (3.2 ± 0.9 kg) than the olanzapine with mifepristone group (2.0 ± 1.2 kg) and the mifepristone with placebo (2.0 ± 0.7 kg), and a similar effect was observed in the risperidone with mifepristone clinical trial. **Conclusions:** Mifepristone shows potential in the management of AIWG. Glucocorticoid antagonists can be a viable alternative to curb this side effect. Large-scale clinical studies are warranted to determine the medication's safety and efficacy based on this mechanism of action.

Keywords: Antipsychotics, obesity, olanzapine

Introduction

Obesity (body mass index [BMI] ≥30 kg/m^2) is a global pandemic.[1] Furthermore, obesity increases morbidity and mortality and is a significant risk for developing cardiovascular disease, metabolic syndrome, and diabetes.[2] About 32% of schizophrenia patients have metabolic syndrome and are overweight (BMI = 25–30 kg/m^2).[1,2] In addition, antipsychotic-induced weight gain (AIWG) stigmatizes antipsychotic medications, potentially leading to medication noncompliance.[2,3] AIWG can induce hypothalamic–pituitary–adrenal axis destabilization, histamine, serotonin, and dopamine receptor antagonism. Further, AIWG elevates glucocorticoid levels and decreases insulin receptor sensitivity.[2-4]

Antipsychotics adversely alter lipid and glucose metabolism.[5] Likewise, the antipsychotics upregulate the enzyme 11-β hydroxysteroid dehydrogenase-1. This enzyme converts inactive cortisone to active cortisol, causing obesity and insulin resistance.[5,6] Furthermore, the antipsychotic associated with a decrease in insulin sensitivity also leads to mitochondrial dysfunction, insulin resistance, and metabolic syndrome.[4]

Several pharmacological agents have shown promise to counter AIWG. These include psychostimulants, metformin, rosiglitazone, histamine antagonists, selective serotonin reuptake inhibitor, glucagon-like peptide-1 (GLP-1) analogs, sibutramine, amantadine, topiramate, phenylpropanolamine, modafinil, zonisamide, samidorphan, and α-lipoic acid.[2,8] Metformin and topiramate have the most supporting empirical evidence to address AIWG.[2,6-8]

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.jpp_33_21

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How to cite this article: Al Jumaili W, Trivedi C, Shah K, Adnan M, Mansuri Z, Jain S. Is a glucocorticoid antagonist a potential treatment alternative for antipsychotic-induced weight gain? J Pharmacol Pharmacother 2021;12:37-41.

Received: 11-03-2021 **Revised:** 20-04-2021
Accepted: 22-05-2021 **Web Publication:** 17-09-2021

Glucocorticoid receptor antagonists have shown evidence in mitigating AIWG.[6,7] Furthermore, mifepristone is the only US Food and Drug Administration (FDA)-approved antiglucocorticoid for type 2 diabetes glycemic control in Cushing's syndrome. Moreover, mifepristone is a synthetic progesterone receptor blocker and a glucocorticoid receptor antagonist hormone. It blunts weight gain in healthy nonobese patients on olanzapine or risperidone.[6,7] With mifepristone, AIWG benefit is rapid within 2 weeks of initiating the treatment.[3,5-7] In addition to that, mifepristone also has antiproliferative and antimetastatic effects on cancer cells.[4]

Mifepristone is the only FDA-approved antiglucocorticoid with potential insulin sensitizing properties.[4,7] Insulin receptor sensitivity is one of the primary underlying mechanisms of weight gain in metabolic syndrome, affecting different body organs and systems such as the brain, liver, pancreas, vascular endothelium, cardiovascular, skeletal muscle, and adipose tissue.[4] Beyond that, the regulation of oxidative phosphorylation improves mitochondrial dynamics. Mifepristone-induced activated protein kinase causes insulin sensitization. Such insulin sensitization ameliorates weight gain.[4] Recent evidence has shown the role of mitochondrial dysfunction in the development of obesity and metabolic syndrome.[4] Glucocorticoid receptor blockers (e.g., mifepristone) by increasing insulin sensitization and curbing glucocorticoid levels have shown efficacy in addressing AIWG. However, their exact action mechanism is yet to be determined.[4,6,7] The existing literature fails to summarize the safety and efficacy of glucocorticoid receptor blockers for the management of AIWG. This report aims to evaluate glucocorticoid receptor antagonists' role in reducing and preventing AIWG.

Methods

We searched databases, up to March 2021, PubMed, Google Scholar, ClinicalTrials.gov, and Cochrane library databases included in the search for the published English-language literature. For this search, we used the key terms, including a Medical Subject Heading (MeSH), "Mifepristone," "Receptors, Glucocorticoid," "Weight gain," "Overweight," "Obesity," "Body Weight Change," "Antipsychotics Agents," "Glucocorticoid Receptor Blocker," "Glucocorticoid Receptor antagonist," "FGA," and "SGA," to maximize the search sensitivity in the title or abstract. We included randomized controlled trial study designed from peer-reviewed journal publications that involved all age groups and both genders. In addition, we excluded case reports, poster abstracts, editorial and unpublished theses, publications in nonpeer-reviewed journals, and articles published in languages other than English. Farther, preclinical studies were excluded from the results but used as a reference for discussion. Two studies included focused on mifepristone as glucocorticoid receptor blockers and potentially utilizing this modality in clinical practice.

We based the PICO search algorithm for this review (Population, Intervention, Comparison, Outcomes, and Study Design) framework. Participants ([Adult] and [Schizophrenia or Bipolar or Schizoaffective or Major Depression] and [Weight Gain or Overweight or Obesity]); Intervention (Mifepristone or Glucocorticoid Receptor Antagonist); Comparison (Placebos or Metformin or Topiramate); Outcomes (Weight Reduction or Weight Loss or BMI or Waist Circumference); Study design (Randomized Controlled Trial).

Results

Gross *et al*. conducted a three-arm double-blind, placebo-controlled study in an inpatient setting on healthy males (18–40 years), with BMI ≥18 and ≤23 kg/m^2. Patients with stable body weight for the last 6 months were eligible for the study. Participants were randomized to risperidone with placebo (Group R, n = 30) arm, risperidone with mifepristone (Group R + M, n = 30) arm, or mifepristone with placebo (Group M, n = 16) arm. Risperidone dose ranged from 0.5 mg to 4.0 mg daily, and the mifepristone dose was 600 mg daily. Bodyweight was recorded at screening, baseline, and daily during the treatment period through day 28. The study scheduled a safety visit on day 28 after the last dose. Waist circumference was measured at baseline, day 28, and the safety visit or early termination visit. At the study's endpoint, the risperidone arm (Group R) gained significantly more weight than the risperidone and mifepristone arms (Group R + M) ($P < 0.001$). The mean body weight difference was seen by day 6 ($P < 0.01$) and persisted throughout the treatment for Group R + M. At the end of the study, 50% of risperidone patients showed a ≥7% increase in baseline body weight than 7% of patients on risperidone with mifepristone ($P < 0.05$). The risperidone patients had a statistically significant increase in waist circumference compared to those receiving both mifepristone and risperidone (risperidone: +3.65 cm, risperidone, and mifepristone: +1.99 cm [$P < 0.05$]).[6]

In another study by Gross *et al*., the primary inclusion criteria were BMI of 18–25 kg/m^2. The study's primary efficacy end point was to evaluate the mean change in absolute body weight at the end of the trial. This study was also a three-arm, double-blind, randomized clinical trial in the inpatient setting, using a parallel group design. After 1 week of observation, eligible subjects were randomized to receive either olanzapine 7.5 mg with placebo (n = 22), olanzapine 7.5 mg with mifepristone 600 mg (n = 24), or mifepristone 600 mg with placebo (n = 11) daily for 2 weeks. Bodyweight was measured daily and waist circumference at baseline and on day 14. Changes in BMI, waist circumference, and food intake were secondary study end points. The increase in the mean weight from baseline to day 14 was significant in the olanzapine with the placebo group (3.2 ± 0.9 kg) in comparison with the olanzapine and mifepristone group (2.0 ± 1.2 kg; P = 0.002). Statistically significant differences in mean change from baseline body weight were apparent as early as

day 2 and maintained throughout the treatment ($P < 0.0001$). Mean waist circumference increased from baseline to day 14 in all treatment categories, with the most significant increase observed in the olanzapine and placebo group (3.7 ± 1.3 cm vs. 2.2 ± 1.9 cm olanzapine with mifepristone vs. 2.1 ± 1.8 cm mifepristone and placebo, $P = 0.006$). The increase in waist circumference was more in olanzapine with the placebo group than the combination group ($P = 0.004$) and mifepristone with the placebo group ($P = 0.011$).[7]

Discussion

To our knowledge and literature search, this is the first review that discusses the role of glucocorticoid antagonism in the management of AIWG. The AIWG is associated with histamine-1, dopamine, and 5HT2c receptor antagonism.[2] It also involves endocrine factors such as increased insulin resistance and elevations in glucocorticoids secondary to disturbance of the hypothalamus–pituitary–adrenal axis.[2]

The two discussed clinical trials' findings and preclinical studies indicate that mifepristone addition to antipsychotics has clinically significant weight-limiting effects and improves insulin sensitivity.[6,7,9-15] The exact underlying therapeutic effects, response onset, optimal doses, and possible side effects need further empirical evidence for specific psychiatric conditions.[3-5] Not only mifepristone has antiglucocorticoid efficacy, similar to Metformin in reducing insulin resistance, improving glycemic control, stimulating mitochondrial function, and improving the lipid profile.[2-4]

Compared with metformin and topiramate, clinical trials found that mifepristone possessed a rapid onset of action (within 4 weeks) for weight reduction when administered with olanzapine.[2,6,7] Table 1 summarizes the various clinical trial findings.

However, compared with mifepristone and metformin, adding topiramate to olanzapine leads to a maximum weight loss of 4.4 kg after 10 weeks of AIWG treatment.[2] Further, mifepristone co-administered with risperidone showed similar results. Mifepristone treatment group gained 2.32 kg compared to 4.23 kg weight gain in the placebo group.[6] A meta-analysis of 12 studies observed an average weight reduction of 3.27 kg in participants taking metformin compared to placebo.[2] In another clinical trial referred to the results, mifepristone was found to help attenuate the effect of weight gain associated with olanzapine treatment during 2–4 weeks of the treatment period (mean difference: 1.2 kg).[7]

Although Orlistat has FDA approval for obesity and weight maintenance, there is limited evidence that it is effective in AIWG treatment.[2] Liraglutide, an FDA-approved obesity medication, is a GLP-1 receptor agonist. Liraglutide significantly reduces prediabetic obese patients' weight on antipsychotics, and this treatment modality is considered a hopeful new trending. We excluded this medication from this review, given that the only available data are from prediabetic patients and not from obese patients without prediabetes.[16] Further along, the FDA approved a combination of medications for obesity such as naltrexone/bupropion, bupropion/zonisamide, and phentermine/topiramate, which explained the multifactorial pathophysiological etiology of obesity.[17] However, there are not enough data regarding their efficacy or safety for AIWG.[17] Currently, there are no guidelines for AIWG treatment.[2,6,7]

The common adverse effects with mifepristone include mild gastrointestinal symptoms, reversible disturbance in TSH levels, and skin rash reported with mifepristone in a dose equal to 400 mg/day.[3] Mifepristone in higher doses for a prolonged duration might lead to endometrial hyperplasia and vaginal bleeding in postmenopausal women due to its antiprogesterone

Table 1: Overview of the clinical trial findings

	Clinical trials[6,7]	
	Study 1[7]	**Study 2[6]**
Publication year	2009	2010
Author name	Gross *et al*.	Gross *et al*.
Tittle of the article	Mifepristone treatment of olanzapine-induced weight gain in healthy men	Mifepristone reduces weight gain and improves metabolic abnormalities associated with risperidone treatment in normal men
Study type	Randomized controlled trial (2:2:1 randomization in three separate arms)	Randomized controlled trial (2:2:1 randomization in three separate arms)
Age of study population (years)	19-38	18-40
Study duration (days)	28	28
Number of patients in the treatment group	Mifepristone + olanzapine (n=24)	Risperidone + mifepristone (n=30)
Number of patients in the placebo	Olanzapine + placebo (n=22) Mifepristone + placebo (n=11)	Risperidone + placebo (n=30) Mifepristone + placebo (n=16)
Dose of the medication	Olanzapine dose 5-7.5 mg	Risperidone dose 0.5-4.0 mg
Findings	Mean increase in weight from baseline to day 14 was greater in the olanzapine + placebo group (3.2±0.9 kg) than the olanzapine + mifepristone group (2.0±1.2 kg) and the mifepristone + placebo (2.0±0.7 kg)	Average weight gain for risperidone + placebo is 4.23 kg, risperidone + mifepristone is 2.32 kg, and mifepristone + placebo is >2.87 kg

Table 2: Comparison between the mifepristone, metformin, and topiramate in terms of weight reduction effects, dose, treatment duration, and adverse effects

Name of the medication	Mifepristone[3,6,7,19]	Metformin[2,17,18,20,21]	Topiramate[2,20,22]
Dose range given	600/day	7501,500 mg/day	100-200 mg/day
Duration of treatment (weeks)	2-4	12-16	10
Weight reduction (kg)	3.2	3.27	4.4
Antipsychotic used	Olanzapine	Olanzapine	Olanzapine
Onset of action	Rapid onset	Slow onset	Slow onset
Neuropsychiatric effects	Antidepressant properties	No	Sedation, irritabilities, psychomotor agitation, cognitive impairment
Severity of the adverse effects	Rarely in small dose well tolerated	Observed initially well tolerated	Frequently reported not well tolerated
FDA recall	No	Recall for high NDMA in ER form	No

FDA=Food and Drug Administration, NDMA=Nitrosodimethylamine

hormonal effects. It is rarely associated with high blood pressure with hypokalemia because of high cortisol levels and mineralocorticoid receptor overactivation. There are no reports of neuropsychiatric symptoms or worsening of underlying psychiatric condition with mifepristone treatment.[3,19]

Metformin is commonly associated with mild initial transient gastrointestinal symptoms.[2,17,18,20] There are no reports of significant sedation or neuropsychiatric effects with metformin.[2,17,18,20] However, the FDA issued a warning recently that metformin's specific form contains a potential carcinogenic nitrosodimethylamine above the acceptable intake limit and requested a recall on those specific batches of medicine.[21] Adverse effects reported with topiramate including mild-to-moderate sedation, psychomotor agitation, nephrolithiasis, hyperactivity, irritability, paresthesia, worsening of the underlying mental condition, and cognitive impairment have been reported [Table 2].[2,20,22]

Currently, two active clinical trials, "GRATITUDE" and "GRATITUDE II," are studying the selective glucocorticoid receptor blocking properties of miricorilant to decrease AIWG in adults with schizophrenia and bipolar disorder.[23,24] Miricorilant selectively blocks glucocorticoid receptors only.[23,24] Hopefully, these clinical trials will help us determine the glucocorticoid antagonist's role as a potential treatment option for AIWG.

Limitations

We base our findings on two clinical trials limiting our research data and external validity. The clinical trial duration of 28 days raises concerns for long-term safety, efficacy, and adverse effects of mifepristone. The study population in the two studies is young males, from the same geographical region, not of diverse race or sex, with normal-weight healthy volunteers with no psychiatric disease. Our search was limited to English-language publications. We had no access to unpublished mifepristone and AIWG studies/data. These limitations restrict the generalizability of the study findings.

Conclusions

Mifepristone shows potential in managing AIWG. Glucocorticoid antagonists can be a viable alternative to address AIWG. Future prospective, well-designed, more diverse, and large-scale clinical studies are warranted to determine the medication's safety and efficacy based on this mechanism of action.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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