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A potential role for adjunctive vitamin D therapy in the management of weight gain and metabolic side effects of second-generation antipsychotics

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Abstract

Second-generation antipsychotic (SGA) medications introduced about 20 years ago are increasingly used to treat psychiatric illnesses in children and adolescents. There has been a five-fold increase in the use of these medications in U.S. children and adolescents in the past decade. However, there has also been a parallel rise in the incidence of side effects associated with these medications, such as obesity, dyslipidemia, insulin resistance, and diabetes mellitus. Despite the severity of these complications and their financial impact on the national healthcare budget, there is neither a clear understanding of the mechanisms contributing to these side effects nor the best ways to address them. Studies that examined lifestyle modification and pharmaceutical agents have yielded mixed results. Therefore, clinical studies using agents, such as vitamin D, which are inexpensive, readily available, with low side effects profile, and have mechanisms to counteract the metabolic side effects of SGA agents, are warranted. Vitamin D is a prohormone with skeletal and extraskelatal properties that could potentially reduce the severity of these metabolic side effects. Its role as an adjunctive therapy for the management of metabolic side effects of SGA agents has not been adequately studied. Effective strategies to curb these side effects will improve the overall health of youths with psychiatric illnesses who receive SGAs. Herein we present a pilot study on the use of vitamin D in patients on treatment with SGAs.

Keywords: antipsychotics; obesity; psychosis; vitamin D.

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Introduction

Second-generation antipsychotic agents and their metabolic side effects

The atypical or second-generation antipsychotic (SGA) agents were introduced approximately two decades ago. Their reduced incidence of extrapyramidal side effects and reported enhanced therapeutic benefits have rapidly led to their widespread use in the management of various psychiatric illnesses, such as schizophrenia, schizoaffective disorder, and bipolar disorder (1). However, results from studies in adults with schizophrenia, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (2), the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (3), and the European First Episode Schizophrenia Trial (EuFEST) (4), demonstrated rapid and significant weight gain in patients treated with these medications.

There is increasing evidence that SGA agents can increase the risk of metabolic abnormalities in patients (5–8). *Metabolic syndrome* is a term used to describe the coexistence of obesity, hypertension, dyslipidemia, and insulin resistance or diabetes in an individual, which confers a high degree of risk for cardiovascular disease or earlier mortality (9). The prevalence of metabolic syndrome in patients with chronic schizophrenia is 37% (8), compared with 24% in the general population (10). Patients with schizophrenia also have a three-fold increased risk of developing type 2 diabetes when compared with the general population (11).

The Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) study (12), an 8-week double-blind comparison of first- and second-generation antipsychotics in early onset schizophrenia and schizoaffective disorder demonstrated that children who were treated with SGA agents had early and significant weight gain, similar to that reported for adults. In the TEOSS study, molindone (a first-generation antipsychotic medication) was compared with two SGA agents: olanzapine and risperidone. These two SGA agents were not superior to molindone in controlling psychiatric symptoms. Moreover, the investigators found significant increases in body mass index (BMI) with the SGA agents as compared with molindone as shown in Figure 1A. Youths treated with olanzapine gained an average of 6.1 kg (SD=3.6) and increased their BMI by an average of 2.2 kg/m² (SD=1.2) over the 8-week trial. Subjects treated with risperidone gained a mean of 3.7 kg, whereas those on molindone showed no mean changes in weight. Furthermore, the olanzapine group had greater increases in total cholesterol, low-

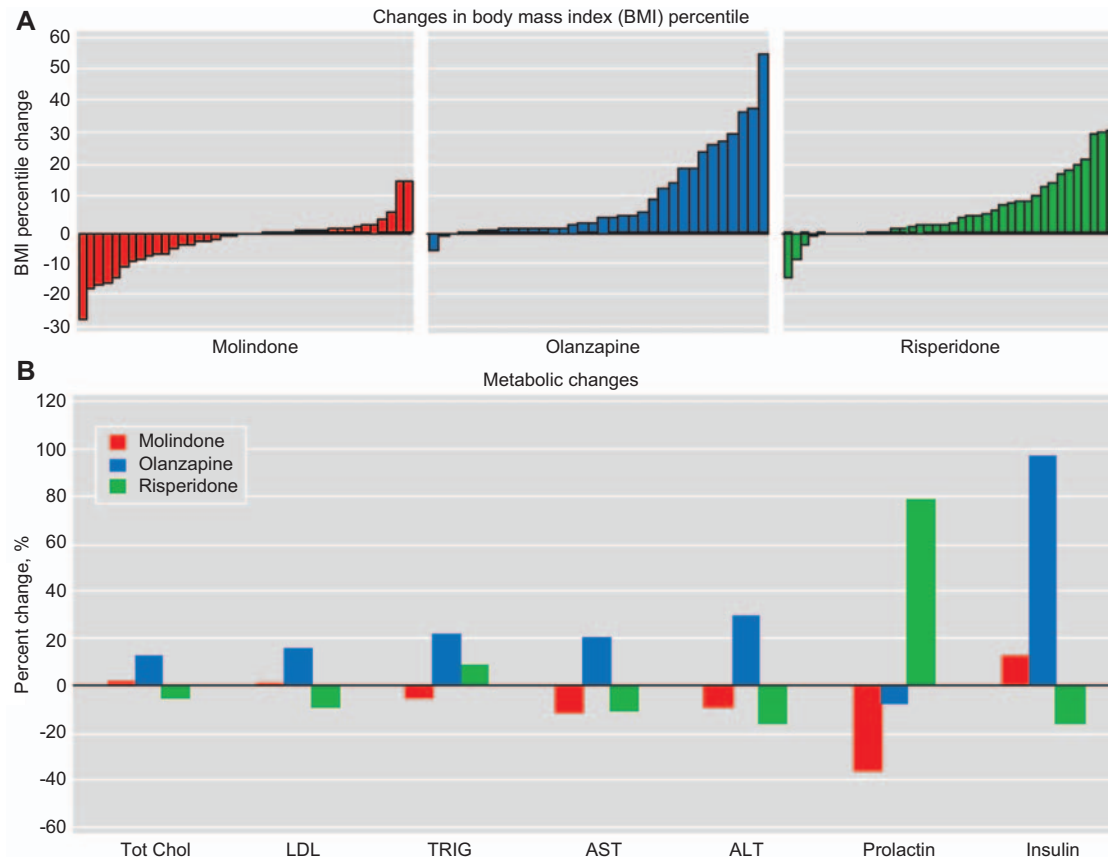


Figure 1 (A) Comparison of changes in BMI percentiles in children who received molindone as compared with those who received olanzapine and risperidone. (B) Comparison of adverse metabolic effect of antipsychotic treatment experienced in subjects with early-onset schizophrenia and schizoaffective disorder (12). Reprinted with permission from the American Journal of Psychiatry (Copyright © 2008). American Psychiatric Association.

density lipoprotein cholesterol, and insulin levels, relative to those in the molindone group (Figure 1B), suggesting a propensity for the development of metabolic syndrome. These adverse effects raise important public health concerns given the expanding use of SGA agents in children and adolescents with non-psychotic disorders, such as autism (12).

The nature of body composition changes of SGA agents associated with weight gain in children and adolescents was reported by Correll et al. (13) using bioelectric impedance analysis in a study involving 12 weeks of treatment with aripiprazole, olanzapine, quetiapine, or risperidone in pediatric patients naive to antipsychotic therapy. They reported a weight increase of 8.5 kg with olanzapine, 6.1 kg with quetiapine, 5.3 kg with risperidone, and 4.4 kg with aripiprazole. Each antipsychotic medication was associated with significant increase in fat mass and waist circumference. In a 6-week randomized, double-blind, placebo-controlled trial of olanzapine vs. placebo in adolescents with schizophrenia, Kryzhanovskaya et al. (14) demonstrated a significant weight gain in adolescents treated with olanzapine compared with placebo (4.3 vs. 0.1 kg, $p < 0.001$). The weight gain and metabolic side effects lead to reduced compliance rates, and therefore ineffective treatment of the underlying psychiatric illness (15).

Mechanisms of SGA-induced weight gain and metabolic side effects

The SGAs act by transiently occupying dopamine D2 receptors in the brain and then rapidly dissociating to allow normal dopamine transmission (16). A controversial theory of atypicality proposes that these agents simultaneously block 5-hydroxytryptamine type 2A (5-HT_{2A}) receptors and dopamine receptors, thus altering the balance of serotonin and dopamine in the brain (16). As a result of the brief D2 receptor blockade, these atypical or SGAs are believed to have enhanced therapeutic benefits and fewer dopamine-related side effects than the typical or first-generation antipsychotic agents, which have greater affinity for the D2 binding site and are associated with high risk for drug-induced movement disorders, such as tardive dyskinesia and other extrapyramidal symptoms (1, 17).

The precise mechanism of SGA-induced obesity and its complications is unclear. Some investigators have suggested that this weight gain occurs largely due to an increase in appetite (18). Fadel et al. (19) proposed that the propensity for weight gain while receiving atypical antipsychotic agents was correlated with the degree of Fos induction in orexin neurons of the lateral hypothalamic/perifornical area of

rats. Orexins are peptides expressed in neurons of the lateral hypothalamus and perifornical area that are potent regulators of feeding and other metabolic processes. Other workers have suggested that because antipsychotic medications have a broad range of activity over central neurotransmitter systems, such as serotonin, dopamine, acetylcholine, and histamine (15), it is possible that their variable antagonistic effects on receptor subtypes, such as 5-HT_{2A}, and histamine 1 (H₁), which are associated with appetite regulation and body weight, might lead to hyperphagia and obesity (20). Studies have shown that antagonism of serotonin, dopamine, and norepinephrine receptors may be associated with weight gain (21), and a robust correlation has been demonstrated between SGA medication affinity for the H₁ receptor and antipsychotic-induced weight gain (22, 23). Other reports have proposed abnormal leptin signaling as a contributor to antipsychotic agent-induced weight gain (24–26). Leptin is an adipocyte hormone that regulates food intake and energy balance and correlates closely with total body fat mass and BMI (27, 28). Leptin and insulin decrease appetite by inhibiting the production of neuropeptide Y and agouti-related protein, while stimulating melanocortin-producing neurons in the arcuate nucleus of the hypothalamus. Leptin reduces intracellular lipid concentration by decreasing the synthesis of fatty acid and triglycerides and by increasing lipid oxidation (29). However, studies with adequate statistical power and experimental controls have shown no difference in serum leptin concentrations and expression when confounding variables, such as sex and adiposity are taken into account (30, 31). Other data suggest that elevated prolactin contributes to SGA agent-induced weight gain by reducing insulin sensitivity or by altering the ratio of androgen to estrogen in the body (32).

An alternative proposed mechanism is a direct action of the antipsychotic agents on the pancreatic beta cells. It has been suggested that antipsychotic molecules could antagonize the muscarinic M3 receptors on beta cells, leading to suppression of cholinergic-stimulated insulin secretion. This will in turn inhibit glucose transport into peripheral tissues leading to hyperglycemia (33). This SGA agent-induced deficit in beta-cell function is believed to be due to a combination of increased insulin resistance and decreased glucose-stimulated insulin secretion (34). Other possible mechanisms include induction of peripheral insulin resistance, impairment of beta-cell function by serotonergic (5-HT_{1A/2A/2C}) receptor antagonism, inhibition of beta-cell function via alpha 2-adrenergic receptors, or by direct toxic effects on beta cells (35, 36). The serotonergic receptors, especially the 5-HT_{2c} receptors, are believed to be candidate target receptors for psychotropic-induced weight gain, as their antagonism leads to weight gain (20, 37).

Thus, to date, there is no consensus on the mechanism of SGA-mediated weight gain, as all of the above mechanisms are speculative. One potential mechanism that has not been explored is the role of vitamin D deficiency in the propagation of SGA-mediated obesity. This is informed by studies suggesting that serum vitamin D concentrations might have a direct effect on body weight. Sibley (38) demonstrated a correlation between weight loss and vitamin D levels in an

11-week study of 38 patients on caloric restriction diets who lost 0.196 kg for every 1 ng/mL increase in serum concentrations of 25-hydroxyvitamin D (25-OHD). They also showed that higher levels of 25-OHD at baseline predicted increased abdominal subcutaneous fat loss.

Current modalities of management of SGA-induced weight gain and metabolic side effects

Various modalities and medications have been proposed as adjunctive therapies to attenuate the weight gain associated with treatment with SGA agents. Studies examining the effects of lifestyle interventions and pharmaceutical agents, such as sibutramine (39), metformin (40–44), orlistat (45), amantadine (46), and topiramate (47) have had mixed results. Moreover, sibutramine is now unavailable, and the use of orlistat is limited by its severe gastrointestinal and systemic side effects. Lifestyle interventions, such as psychoeducational, dietary, and exercise programs can be effective in the short term (48), but no large-scale study has been performed to evaluate long-term effectiveness (15), and lifestyle interventions are difficult to sustain, especially for individuals with severe psychiatric illness. In general, pharmacologic treatment modalities for weight loss are sparse with only a few Food and Drug Administration-approved medications. Even then, some of these approved medications stimulate central serotonin and norepinephrine systems (49), a mechanism of action that is opposite to the desired actions of the SGA agents.

In a randomized, double-blind, placebo-controlled trial, Klein et al. (42) studied the effectiveness of metformin in managing weight gain associated with the initiation of SGA agents in children and adolescents, ages 10–17 years, who had gained >10% of body weight during <1 year of olanzapine, risperidone, or quetiapine therapy. They reported the children treated with placebo continued to gain weight at a rate of 0.31 kg/week (mean=4.01 kg, SD=6.23), over 16 weeks, despite three family sessions of dietary counseling. In contrast, the weight of the subjects treated with metformin showed little change over the treatment period (mean –0.13 kg, SD=2.88).

In a 12-week, open-label trial of metformin for the treatment of weight gain and metabolic profiles in pediatric patients, Shin et al. (50) studied 11 children and adolescents ages 10–18 years who received metformin orally up to 2000 mg/day. They reported no statistically significant reductions in mean weight, waist circumference, BMI, serum glucose, and insulin even though 5 of the 11 subjects lost weight. This is in contrast to another open-label metformin study by Morrison et al. (40) who studied 19 patients of ages 10–18 years for 12 weeks. In this study, 15 subjects lost weight, 3 gained weight, and 1 patient had no weight change. They reported a significant decrease in mean weight (–2.93 kg, SD=3.13, p=0.008) and BMI (–2.22 kg/m², SD=1.98, p=0.003) at 12 weeks.

Although these small studies are promising, there is no consensus recommendation supporting the use of metformin in the management of weight gain associated with SGA

agents. The use of metformin is limited by its gastrointestinal side effects, which include stomach upset and nausea; contraindication in patients with renal and hepatic dysfunction, and concerns regarding its rare but severe side effect of lactic acidosis. Therefore, alternative safe and inexpensive agents with a high safety profile that has efficacy in preventing SGA-mediated weight gain would be a valuable adjunct to the management of children with psychiatric disorders requiring SGA therapy.

Vitamin D

General effects of vitamin D

Vitamin D is a safe, well-tolerated, and easily available agent with no central stimulatory properties. Its primary skeletal function is the promotion of calcium absorption from the gut and phosphorus reabsorption from the kidneys for the maintenance of the skeleton (51). Although controversial (52), there are many reports of extraskeletal effects of vitamin D, such as boosting of immune system by modulating B- and T-lymphocyte function (53), prevention of certain malignancies, such as colon cancer (54), the association of a reduction in the prevalence of psychiatric illnesses, such as schizophrenia in offspring of vitamin D-sufficient mothers (55), and the prevention of diabetes mellitus (56).

Effects of vitamin D on glucose metabolism

Normal insulin secretion is partly dependent on 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$) concentrations in both intact animals and isolated islets (57, 58). Limited evidence suggests that vitamin D deficiency increases insulin resistance and thus may play a role in the early stages of the development of type 2 diabetes (59). Low serum vitamin D concentrations correlate with impaired glucose tolerance (60–63), whereas administration of supplemental vitamin D to subjects with elevated blood glucose levels increases insulin secretion (64, 65). Similar improvements have been observed in vitamin D-deficient subjects following supplementation (61, 66). Even though there are reports of a correlation between hypovitaminosis D and insulin resistance in obese adolescents (67), clinical trials with vitamin D supplementation are sparse (59, 65, 68), especially in patients with psychiatric illnesses who receive adipogenic SGA agents.

The circulating concentration of 25-OHD is regarded as the best index of nutritional vitamin D status. There are differing definitions for suboptimal serum concentration of 25-OHD (51). In general, hypovitaminosis D is defined as serum 25-OHD concentrations <75 nmol/L (31.25 ng/mL), and vitamin D deficiency as serum 25-OHD concentration <50 nmol/L (20.8 ng/mL) (67).

Vitamin D deficiency has been reported in obese individuals (69–72), although the etiology is unclear. Proposed causative factors include poor general nutrition, which results from low intake of vitamin D-containing foods, such as salmon, inadequate exposure to sunlight, and the sequestration of vitamin

D in fat stores in obese individuals, which makes the vitamin D unavailable for biological activities (70).

It is possible that vitamin D deficiency acts synergistically with other pathways to propagate the weight gain associated with SGA agents. Although a direct catabolic effect on vitamin D molecule by SGA agents has not been demonstrated, certain drugs directly impair vitamin D metabolism and reduce its levels. Pascucci et al. (73) conducted both in vivo (using human hepatocytes) and in vitro (in mice) experiments showing that antiepileptic drugs that activate pregnane X receptor (PXR) enhance CYP24 expression and accelerate the catabolism of 25-OHD, leading to vitamin D deficiency. Similarly, xenobiotic drugs, including rifampin, glucocorticoids, and antiretroviral drugs, may induce vitamin D deficiency through the same pathway (74). It is likely that other families of drugs also are activators of PXR and may increase vitamin D catabolism (74) in the liver, leading to vitamin D deficiency and osteomalacia (73, 75). Interestingly, treatment with SGA agents has also been associated with both vitamin D deficiency and osteomalacia (76, 77). Given the above findings, it is possible that SGA agents might activate PXR and induce vitamin D deficiency, which in turn results in weight accrual.

Central and peripheral mechanisms of the antiobesity effects of vitamin D

Peripheral mechanism Vitamin D deficiency is marked by low serum 25-OHD and elevated parathyroid hormone (PTH) and $1,25(\text{OH})_2\text{D}_3$ (70–72, 78) to maintain normocalcemia. This compensatory increase in $1,25(\text{OH})_2\text{D}_3$ level is the principal proposed mechanism of vitamin D deficiency-related adipogenesis. Elevated serum concentrations of $1,25(\text{OH})_2\text{D}_3$ are believed to promote obesity by binding to a membrane vitamin D receptor called the membrane-associated rapid response to steroid receptor (79, 80) and inducing a rapid influx of calcium ions into adipocytes (Figure 2). Intracellular Ca^{2+} , a key regulator of adipocyte lipid metabolism, stimulates the expression and activity of fatty acid synthase (FAS), a key enzyme for de novo lipogenesis, while inhibiting basal and agonist-stimulated lipolysis in adipocytes (81). This results in increased lipid accumulation in adipocytes (82) and attendant obesity, which leads to a further decrease in 25-OHD as a result of sequestration of vitamin D in fat depots. This establishes a vicious cycle of worsening obesity and vitamin D deficiency.

Therefore, pharmacologic interventions aimed at normalizing serum concentrations of 25-OHD may prevent both PTH elevation and compensatory activation of 25-OHD to $1,25(\text{OH})_2\text{D}_3$, which in turn will preclude the elevation of intracellular calcium ion concentrations and consequently reduces the activity of FAS. This breaks the vicious cycle of obesity and vitamin D deficiency.

Central mechanism FAS activity is present peripherally in adipocytes and centrally in the hypothalamus (81, 83). Hypothalamic fatty acid metabolism plays a major role in the modulation of energy balance, affecting both feeding and energy expenditure (84). Treatments with FAS inhibitors, such

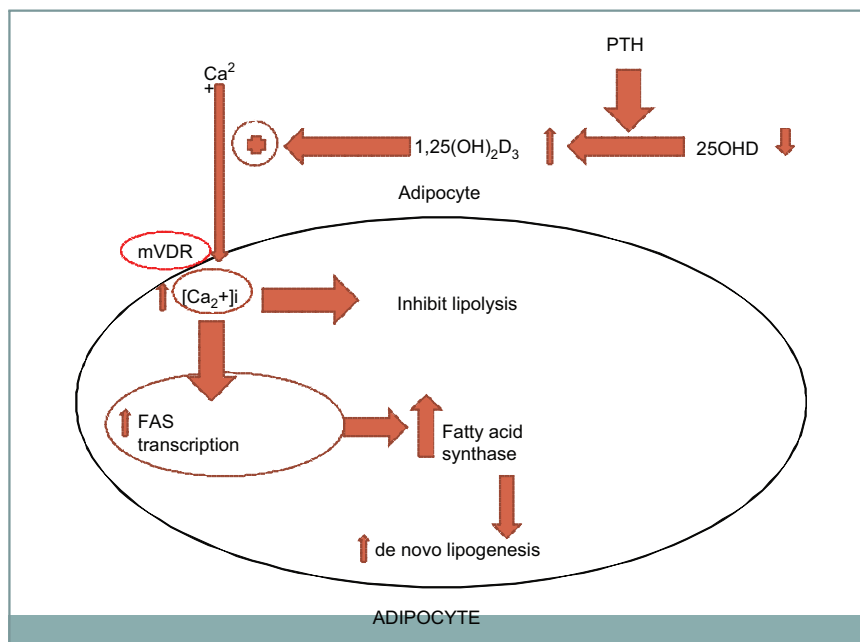


Figure 2 In vitamin D-deficient states, PTH accelerates the conversion of 25-OHD to 1,25(OH)₂D₃, which results in a compensatory increase in serum 1,25-dihydroxyvitamin D level, which drives the influx of calcium ions into the cell and consequent activation of FAS. Adapted from Zemel (81).

as cerulenin, or drugs that down-regulate FAS expression, such as tamoxifen, induce remarkable weight loss and hypophagia (85). The anorectic effect of these drugs requires the accumulation of malonyl-CoA in the hypothalamus, which may serve as a signal of nutrient abundance by critical neurons regulating food intake (84), decreased expression of orexigenic (agouti-related protein, neuropeptide Y), and elevated expression of anorexigenic (cocaine- and amphetamine-regulated transcript, proopiomelanocortin) neuropeptides in the arcuate nucleus (86, 87). It is possible, therefore, to induce similar effects as drugs that down-regulate FAS activity by preventing the up-regulation of FAS through optimal vitamin D supplementation. One study demonstrated a correlation between weight loss and vitamin D levels in adults receiving caloric restriction diets who lost 0.196 kg for every 1 ng/mL increase in serum concentrations of 25-OHD (38).

A feasibility study on the role of vitamin D in patients receiving SGAs

Given the paucity of data on the role of vitamin D supplementation in children and adolescents with SGA-induced obesity, we designed a feasibility study to evaluate the relationship between changes in anthropometry and serum concentrations of 25-OHD in overweight and obese patients on treatment with SGA agents. Our primary objective was to establish the feasibility of enrolling adolescents with major psychiatric disorders in an in-patient setting in a treatment study. Our secondary aim was to conduct an open-label pilot study to determine the safety profile and efficacy of supplemental vitamin D in

psychiatric patients receiving SGA medications. We believed that the results of such a study would form the framework for the development of a longer-term clinical study.

All subjects had a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (88) Axis 1 diagnosis and had been receiving treatment with SGA medication for more than 3 months. All had a BMI of >85th percentile and had a 25-hydroxyvitamin D level of <75 nmol/L (30 ng/mL). Subjects were excluded from participation if they met the criteria for an eating disorder, substance abuse/dependence, significant medical or neurological illness, IQ <70, pregnancy, recent history of suicidality, or being psychiatrically unstable on their current medication regimen. The study was approved by the University of Massachusetts Medical School and the Department of Mental Health Services Institutional Review Boards. Signed parental informed consent with signed assent of the youth were obtained before study enrollment and baseline eligibility assessment.

All participants were residents of a chronic care facility for adolescents with psychiatric disorders. All received 10 drops (2000 IU) of ergocalciferol every morning before breakfast for 8 weeks. Anthropometric measures, height (cm), weight (kg), BMI (kg/m²), as well as laboratory evaluations were performed in the fasting state.

Of the 12 participants, 4 were males and 8 were females. Of these, eight were white, two were Hispanic, and two were African American. All participants completed the study. The average age was 16.6±1.65 years, with a range of 13–18 years. At the end of the study, there was a non-significant decrease in body weight standard deviation score from baseline to the end

of study, 2.56 ± 1.32 vs. 2.49 ± 1.38 ($p=0.18$) (95% confidence interval -0.200 to 0.058). One subject experienced no change in weight, five subjects gained weight, and six subjects lost weight. When analyzed by sex, two males gained weight, one lost weight, and one had no weight change. Three females gained weight, whereas five lost weight. Serum concentrations of 25-OHD increased significantly from baseline to the end of study 46.5 ± 18.65 vs. 72.75 ± 21.12 nmol/L (18.6 ± 7.46 vs. 29.1 ± 8.45 ng/mL) ($p=0.0001$). There were no side effects from the vitamin D supplementation. Thus, we achieved our primary objective, which was to establish the feasibility of enrolling adolescents with major psychiatric disorders in an in-patient setting in a treatment study. We also demonstrated that adjunctive vitamin D supplementation is safe in psychiatric patients receiving SGA medications. We did not design the study with sufficient power or long enough duration to detect significant changes in weight or BMI, as this was a feasibility study. We are now planning a trial of longer duration with vitamin D supplementation, which is inexpensive, readily available, with a low side effect profile, which could counteract the metabolic side effects of SGA agents.

Summary and conclusion

In summary, SGA medications are increasingly being prescribed to treat psychiatric illnesses in children and adolescents. However, the use of these agents is limited by their severe metabolic side effects. The mechanism(s) of these adverse events are unknown, and there is a lack of consensus on the best approach to address these problems. In conclusion, adjunctive vitamin D therapy may play a role in counteracting the adipogenic effects of SGA agents.

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