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Do Probiotics Play a Role in Weight Gain Caused by Antipsychotics? A Literature Review

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Abstract

Unwanted side effects of atypical antipsychotics include weight gain, which raises the risk of additional comorbidities such obesity, diabetes, and cardiovascular disease. Second-generation antipsychotics may contribute to weight gain and obesity because they affect the microbial communities in the gut. Over the past few years, obesity has been associated with changes in bacterial strains in the human colon. The South African population, children, women, patients, and autistic patients are the groups with the highest risk. Antipsychotic drugs alter the neurotransmitters and hormones that control satiety, appetite, and glucose metabolism, causing weight gain and aberrant metabolic processes. The mechanism of antipsychotic-induced weight gain may disrupt energy hemostasis and hasten chronic inflammation by altering the gut microbiota. Additionally, probiotics alter the intestinal epithelial barrier and lessen gut permeability, which is crucial in avoiding inflammation and endotoxemia brought on by the transfer of foreign bodies into the blood. Probiotics enhanced the altered gut microbiome brought on by antipsychotics, which in turn reduced the negative and positive symptoms of schizophrenia as well as the metabolic changes brought on by antipsychotics.

Introduction

Atypical antipsychotics, known as second-generation antipsychotics, are popularly known to treat psychotic disorders in adults as well as in children and adolescents with behavioral problems [1]. In most cases, atypical antipsychotics are associated with unwanted side effects such as weight gain, which further increases the risk of other comorbidities such as obesity, diabetes, and cardiovascular disease. [1]. Though there are various mechanisms of weight gain, including the effects of metabolic hormone signaling, recent studies point towards the significance of the gut microbiome in this process [1]. Second-generation antipsychotics have an impact on the microbial populations that live in the gut and may cause weight gain and obesity [1].

Body mass index (BMI) is calculated by dividing a person's weight in kilograms by their height to determine obesity. A BMI of 25 to 29 kg/m2 indicates being overweight, whereas a BMI of 30 or higher indicates being obese [2]. When using percentile scaling for children aged 2 to 18, overweight is defined as a BMI in the 85th to 94th percentile, while anything above the 95th percentile is considered obesity [2].

The cause of obesity is multifactorial and includes biological, environmental, and behavioral factors [3]. Medications also play a key role in weight gain; the most important ones contributing to it are antipsychotics, anti-depressants, anti-epileptics, beta-blockers, antihyperglycemics, and glucocorticoids [3]. Changes in bacterial strains in the human colon have been linked in recent years to obesity [4]. The gut microbiota plays a significant role in metabolic diseases and energy balance [5]. They increase hormones related to appetite and glucose tolerance, which leads to improved absorption of short-chain fatty acids [5]. Antipsychotics change the microbiota of the gut, increasing the level of lipopolysaccharide (LPS), which leads to overfeeding and metabolic side effects. Hence, improving gut microbiota with probiotics may be beneficial for antipsychotic- induced metabolic syndrome [5].

Probiotics are live microorganisms that present diverse benefits to the host [6]. They produce antimicrobial substances to inhibit the colonization of pathogenic microbes, regulate host immunity and metabolism, and enhance intestinal barrier function [6]. Indigestible dietary fiber is fermented by the gut microbiota into short-chain fatty acids, which regulate the immune system and affect satiety [7]. As an important source of nutrients for the gut microbiota, dietary fiber plays a significant role in shaping the microbiota's composition [7]. Studies show that probiotics help with weight gain associated with antipsychotics [1]. The effect of probiotics on antipsychotic-induced weight gain is reviewed in this article.

Review

This review will discuss the risk factors, the mechanisms driving antipsychotic-induced weight gain, the role of probiotics in weight loss, and the significance of probiotics in enhancing gut flora.

Risk Factors for Antipsychotic Induced Weight Gain

Second-generation antipsychotics cause significant weight gain compared to first-generation antipsychotics, with an increase of 2.6 kg and a BMI of 1.6 kg/m2 in the first 6 to 10 weeks of treatment initiation. Weight gain progresses during the entire duration of treatment, with 12kg in 2-year treatment and 18kg in 4-year treatment [8]. Risk is most remarkable in adolescents, patients with autism, pediatric patients, female patients, and the South African population [9, 10]. Interest in antipsychotic-induced weight gain became known after a first study by Allison [11] over 10 weeks, where patients on placebo lost weight when compared to those on antipsychotics who gained weight [11].

Schizophrenia alone is associated with metabolic syndrome and cardiovascular disease, a threefold increase in obesity, and a two- to fourfold increase in

type 2 DM [12]. Antipsychotic drugs have an independent disposition to weight gain; in a meta-analysis of twenty-two studies, olanzapine compared to placebo in adolescence showed a weight gain of 4.1 kg compared to 0.9 kg with aripiprazole, 1.3 kg with quetiapine, and 1.9 kg with risperidone. Ziprasidone causes the least weight gain [8]. Antipsychotic-induced weight gain causes significant distress in patients and may lead to discontinuation [8]. The names of the medications and the proportion of weight gain linked to them are listed in Table 1.

Medication name	Percentage of weight gain
Olanzapine	25%
Clozapine	18%
Risperidone	19%
Quetiapine	17%
Lurasidone	18%
Aripiprazole	14%
Ziprasidone	11%
Haloperidol	12%

Table 1: Percentage of weight gain in relation to antipsychotics [13]

Antipsychotics and Weight Gain: Mechanism

The mechanism of antipsychotic-induced weight gain is not yet totally analyzed; it is assumed that the interaction is multifactorial. Increased appetite, energy intake, storage, metabolic and endocrine disturbances, and low physical activity led to reduced energy expenditure, all of which contributed to weight gain [14].

Antipsychotic medications have an impact on the neurotransmitters and hormones involved in the regulation of satiety, eating, and glucose metabolism, which results in weight gain and metabolic abnormalities [15]. The most significant hormones associated with antipsychotics are leptin, ghrelin, and adiponectin [14]. Leptin is a protein that acts to inhibit food intake. Studies have shown that antipsychotics can induce leptin resistance, which may accelerate obesity [15]. Additionally, adiponectin works by reducing appetite. According to a meta-analysis by Bartoli [16] the use of clozapine and olanzapine is linked to lower levels of adiponectin, and lower adiponectin levels may possibly play a role in insulin resistance and obesity [17].

According to some studies the effects of second-generation antipsychotics, particularly clozapine and olanzapine, on adiponectin levels are time-dependent, with initial rises, neutral levels, and then declining levels [15]. Ghrelin is a hunger-inducing hormone. A study report on the effect of antipsychotics on ghrelin is disagreeable; however, three long-term studies showed increased ghrelin levels in patients on 2nd-generation ASA [18].

Increased eating is influenced by neurotransmitters, namely the H1 receptor antagonistic effects of clozapine and olanzapine [19]. The hypnotic effects of H1 receptor antagonism, which eventually lead to decreased mobility, have also been claimed to promote weight gain [20]. Serotonin triggers a satiety signal at the 5HT2c receptor via the melanocortin and leptin pathways, which also aid in energy hemostasis [21]. Ziprasidone, which has a strong affinity for the HT2c receptor and only slightly increases body weight, shows that several neurotransmitters are involved in antipsychotic-induced weight gain by acting as 5HT2c inverse agonists, and second-generation ASA increase appetite [22]. Aripiprazole Lurasidone and Ziprasidone are partial agonists at the 5HT1a receptor and are less likely to develop metabolic syndrome [23]. Cholinergic M3 receptors on pancreatic beta cells control the synthesis of insulin. Olanzapine and Clozapine, M3 antagonists, inhibit insulin synthesis in isolated rat cells, leading to DM [24].

The mechanism of antipsychotic-induced weight gain

through disturbances in the gut microbiota may affect energy hemostasis and accelerate chronic inflammation icrobiota in the gut, which has an impact on gut hormones like ghrelin, peptides, glucagon-like peptides, and CCK, which are crucial for energy hemostasis related to glucose metabolism, fat storage, and appetite regulation [25]. Antipsychotics that promote dysbiosis also produce inflammatory cytokines such as interleukin 1, interleukin 6, and tumor necrosis factor alpha. The relationship between anomalies in the gut microbiota and metabolic diseases is significantly regulated by these cytokines [28].

[25, 26]. According to Maier et al. [27], antipsychotics have antimicrobial activity and may disturb the

One theory holds that SGAs' antagonistic activities on the 5-HT2c, muscarinic, and H1 neurohormone receptors alter the gut flora. As a result, weight gain happens more quickly. However, SGAs that boost caloric intake may change the gut microbiota's makeup and cause weight gain [29,30,31]. It is still crucial to investigate how SGAs, neurohormones, and microbiota interact. Figure 1 explains the mechanism of weight gain caused by second-generation antipsychotics [25,26,27].

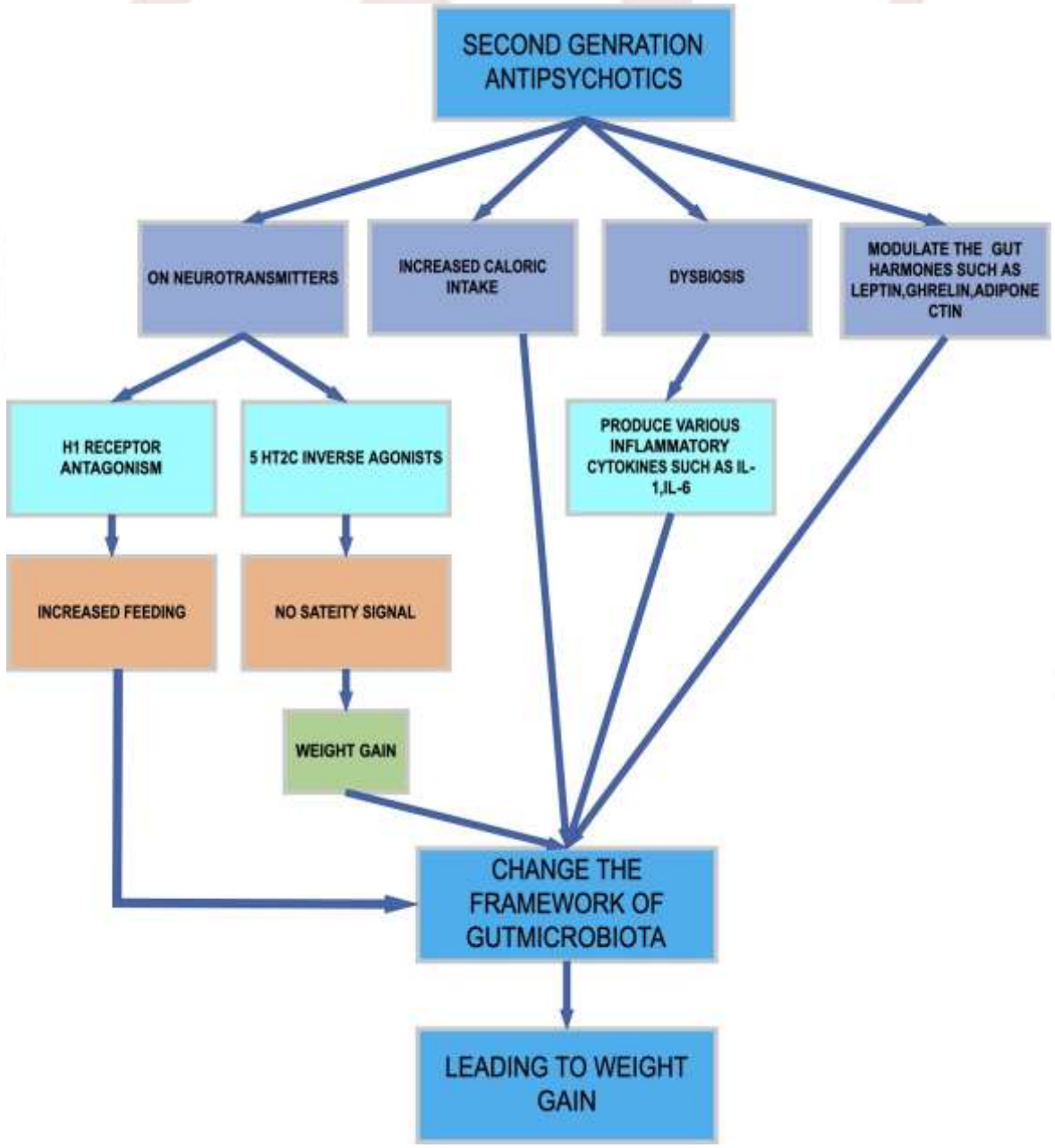

Figure 1: Mechanism of weight gain caused by second-generation antipsychotics.

Role of Probiotics in Antipsychotic-Induced Weight Gain

Live bacteria are included in probiotics, particularly Lactobacilli and Bifidobacterium, which support the host's health by enhancing the structure of the intestinal microbiota [32]. Compared to gram-negative bacteria, probiotics, including Lactobacilli and Bifidobacterium appear to have an advantage in avoiding the expansion of pathogenic bacteria in the flora [32]. Probiotics also modify the intestinal epithelial barrier and decrease gut permeability, which plays a significant role in preventing inflammation and endotoxemia due to foreign body transfer into the blood [32]. Pre-diabetics' glycemic control was reported to improve when probiotics and dietary fiber were administered [33].

A Review of Studies Demonstrating the Role Of Probiotics In Antipsychotic-Induced Weight Gain

In the last 10 years, there have been several clinical trials conducted to assess the effect of probiotics on schizophrenia and antipsychotic-induced metabolic alterations. One of the studies found that supplementation with probiotics reduced positive and negative symptoms associated with schizophrenia. In one of the studies, it was found that supplementation with probiotics containing a fusion of Bifidobacterium, Lactobacillus, and Enterococcus was shown to reduce weight gain associated with olanzapine, but it was not sustained after 8 and 12 weeks of treatment [34].

Author	Study design	Probiotics used	Major outcomes
Yadav et al [35].	Experimental study	Live Microorganisms (VSL # Probiotics)	Prevent obesity and diabetes in mice via induction of butyrate and GLP-1
Stenman et al [36].	Double blinded, parallel reatment using a computer generated sequence.	Probiotics +dietary fiber	Reduced weight circumference in overweight and obese adults after 6 months of treatment While probiotics alone did not show any change.
Flowers et al [37].	Cross Sectional Cohort study	Prebiotic raw unmodified potato starch or resistant starch	No significant difference was observed between 2nd generation antipsychotic users and non-SGA users.
Liu, C et al [5].	Randomized control study	Probiotic combination of Bifidobacterium, Lactobacillus and Enterococcus	Probiotic plus olanzapine reduced fasting. Insulin levels, BMI, and body weight, but the effects were not statistically significant.

Table 2: Summarizes the studies and shows the role of probiotics in antipsychotic- induced weight loss.

Limitations

Only PubMed and PubMed Central (PMC) were utilized as search engines for this review article. The search was limited to studies that were published during the last ten years. The long-term impacts of the therapy weren't investigated.

Future research on a large and diverse population is required because the investigations were limited to certain regions. Additionally, the studies were unable to entirely rule out the impact of meal composition and exercise regimens on antipsychotic medication-induced weight gain.

Conclusion

Antipsychotics cause weight gain through multiple mechanisms; supplementation with probiotics plus dietary fiber causes weight loss and improves metabolic disturbances. Probiotics alone prevented further weight gain but no weight loss; in addition, probiotics improved the altered gut microbe caused by antipsychotics, which also improved positive and negative symptoms associated with schizophrenia along with the antipsychotic-induced metabolic alterations. Hence, the addition of probiotics along with psychotherapy should be considered.

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