First episode psychosis: the commensal gut microbiota perspective

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Abstract

Background: The rates of type 2 diabetes (T2D) in patients with schizophrenia (SCZ) are 3-5-fold higher than in the general population, contributing to a 2-fold higher risk of cardiovascular disease mortality. Antipsychotics, namely second-generation antipsychotics (SGAs), the cornerstone of treatment for this illness, induce weight gain and increase risk for diabetes. Accumulating research has demonstrated that the gut microbiome (GMB) plays a primary function in energy metabolism and could be a central factor in the pathophysiology of obesity and metabolic dysfunction. Antipsychotics are well known to contribute to metabolic dysregulation in patients with SCZ, possibly through their impact on the GMB. This effect may be mediated by changes in dietary pattern induced by antipsychotics. Alterations in the GMB therefore may be contributing to both the etiology and concurrent metabolic dysregulation observed in schizophrenia spectrum disorders.

Objective: In this review, we aim to explore how GMB affects the pathophysiology and treatment in this difficult-to-treat condition.

Methods: This paper is a narrative review. MEDLINE, Google Scholar, and PsychINFO databases were searched for articles containing the following MESH terms: first episode psychosis [AND] schizophrenia [AND] gut microbiome [AND] gut microbiota [AND] metabolic syndrome [OR] metabolic dysfunction [OR] metabolic side effects [AND] second generation antipsychotics [OR] atypical antipsychotics. Inclusion criteria for studies are full-text, English journal articles, published/in press before February 2020, and reporting changes in the gut microbiome among patients with psychosis who are receiving atypical antipsychotic treatments.

Discussion: Through this review, the GMB has been discussed in relation to patients with first episode psychosis and the changes that occur within the microbiota when antipsychotic medication is introduced. SGAs have a high propensity to cause metabolic dysfunction as well as gut dysbiosis. While mechanisms are still to be elucidated, the interactions between the GMB and SGAs largely involve neurotransmitter modulations, gastrointestinal barrier functionality, and dietary changes.

Conclusion: This commentary highlights the need for more large scale, clinical studies investigating antipsychotic-induced changes to the gut microbiome and the importance of making changes to a patient's care pathway with the GMB in mind.

Introduction

Research has demonstrated that the gut microbiome (GMB) plays a greater role than simply aiding digestion and nutrient absorption. Given its primary function in energy metabolism, the GMB is a central factor in the pathophysiology of obesity and metabolic dysfunction. Close relationships exist between GMB shifts and obesogenic profile, both in terms of diversity, which is reduced among individuals with obesity, and composition, in which the relative abundance of certain phyla change with weight gain.[1] In addition to metabolic dysfunction, the GMB has been implicated in brain structure, function, and development, ultimately influencing cognition. Pre-clinical studies have shown that changes in the GMB in mice influence cognition and brain structure.[2] There is evidence that dietary changes and inflammation contribute to this, but mechanisms have yet to be established and clinical studies assessing cognition are far and few between.[3]

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The GMB is becoming increasingly relevant to psychiatry in the prognosis and treatment of severe mental illnesses. Over the past decade, there have been numerous studies pointing to the role of the GMB in psychological processes and neuropsychiatric disorders.

An additional influence on the GMB unique to those with severe mental illness is antipsychotic medication. Antipsychotics– alongside psychosocial interventions – are the cornerstone of treatment in psychiatric illness, and influence both psychopathology and the GMB. There are two classes of antipsychotics: first generation antipsychotics and second-generation antipsychotics (SGAs). While the GMB is at the intersection of metabolic and cognitive dysfunction, there is further possibility that there may be influence of shared sites and actions between SGAs and the GMB. This perspective paper will seek to explore the GMB and metabolic changes mainly seen in patients who are considered antipsychotic-naive first episode psychosis (FEP) patients but will also include studies relating to those who have been exposed to longer term treatment with SGAs. The focus of this narrative review is to evaluate the literature on the topic of GMB dysbiosis and metabolic dysfunction among patients with psychosis receiving SGA treatment.

Methods

This paper is a narrative review. MEDLINE, Google Scholar, and PsychINFO databases were searched for articles containing the following MESH terms: first episode psychosis [AND] schizophrenia [AND] gut microbiome [AND] gut microbiota [AND] metabolic syndrome [OR] metabolic dysfunction [OR] metabolic side effects [AND] second generation antipsychotics [OR] atypical antipsychotics. Inclusion criteria for studies are full-text, English journal articles, published/in press before February 2020, and reporting changes in the gut microbiome among patients with psychosis who are receiving atypical antipsychotic treatments.

Results

Severe Mental Illness: The Patient Population

Psychosis is defined as a loss of contact with reality, manifesting with hallucinations, delusions, and disorganized thinking/behaviours. Psychotic symptoms can present in a range of psychiatric disorders, such as schizophrenia, bipolar disorder, and major depression with psychotic features. The global prevalence of psychotic disorders has been reported as 4.6 per 1000 people.[4] Prior to their first episode of psychosis, patients commonly experience a prodromal period involving subsyndromal psychotic symptoms, negative symptoms, and functional decline ranging from weeks to years.[5] In patients eventually diagnosed with schizophrenia or bipolar disorder, the first episode of psychosis typically occurs between 15 to 30 years of age.[6] Substance use disorder commonly precedes, coincides, or follows FEP and is associated with worse outcomes, including decreased treatment adherence and increased relapse, hospitalization, and suicide attempts.[5]

As the duration of untreated psychosis has been associated with negative long-term outcomes, it is imperative that intervention not be delayed. Management largely centers around pharmacologic measures, with current guidelines recommending antipsychotics, specifically SGAs, as first-line treatment of FEP patients.

Overview of second-generation antipsychotics

SGAs are commonly used for the treatment of schizophrenia, bipolar disorder, depression, and a host of additional indications under drug-specific circumstances. While the literature has not found a significant difference in efficacy of reducing positive symptoms between agents, with the exception of clozapine, systematic reviews and meta-analyses have demonstrated the superiority of SGAs over first generation antipsychotics in reducing negative symptoms and treatment discontinuation, with little difference in efficacy between SGAs.[7-9] In Canada, the prescription of antipsychotic medications was noted to have doubled, exceeding 7 million prescriptions annually between 2005 and 2012.[10] Worldwide, the number has continued to increase for both adults as well as for youths, secondary to the increase in prescription of SGAs and longer duration of use. This has important health implications when considering the nature of treatment for these disorders is often lifelong. Thus, it is imperative to consider the adverse effects these medications have. SGAs are commonly favoured over their "first generation" counterparts as they have been argued to have a lower propensity for causing extrapyramidal side effects (EPS). However, SGAs are indisputably associated with significant metabolic sequelae, including weight gain, glucose dysregulation, and dyslipidemia.[11] The illnesses associated with these metabolic disturbances negatively impact cognition, thus highlighting the complex interplay between the metabolic and cognitive adverse effects of SGAs. Beyond this, the metabolic side effects of SGAs may also contribute to lack of drug compliance, with patients who experience weight gain being more than 13 times more likely to discontinue medication than those who do not experience weight gain.[12]

Adverse metabolic effects of SGAs

Patients with mental illness suffer from high rates of cardiometabolic comorbidity, including obesity, type 2 diabetes, dyslipidemia, and hypertension,[11] which have been associated with risk factors including the use of multiple antipsychotic medications, adjunctive use of antidepressants and/or mood stabilizers, the presence of affective symptoms, younger age at FEP onset, and male gender.[13] The weight gain caused by SGAs is primarily centrally distributed, leading to an increase in waist circumference which itself has been associated with adverse outcomes, including the subsequent development of insulin resistance and metabolic syndrome.[14] A high risk of weight gain has most consistently been attributed to clozapine and olanzapine, with quetiapine and risperidone having moderate risk, and aripiprazole and ziprasidone having low risk.[14] In a systematic review by Hirsch et al., the majority of studies of olanzapine and clozapine found a significant association with type 2 diabetes mellitus.[15] While the exact mechanism for these comorbidities has not yet been elucidated, several contributory pathways have been put forth, including increased appetite and poor diet,[14] suppression of basal metabolic rate,[16] and dysregulation of glucose metabolism through blockade of the muscarinic M3 receptor.[17] Finally, recent literature has implicated the GMB in the progression of SGA's metabolic side effects, which will be the focus of the rest of this review.

GMB changes associated with SGAs

The literature has linked specific changes in GMB to weight gain and metabolic disturbances. These same changes are seen with SGA treatment. GMB diversity appears to decrease with longer SGA use, as illustrated in both pre-clinical and clinical studies.[18,19] Diversity also appears to decrease during the early stages of SGA treatment.[19] In connection to obesity, decreased diversity is a characteristic of an obesogenic profile (i.e. greater adiposity, dyslipidemia, impaired glucose homeostasis, and low-grade inflammation).[20]

A systematic review by Zydecka et al. of 10 articles, including 15 experiments of SGAs in both humans and animals, found that in studies examining bacterial content of stool, dysbiosis was demonstrated in all but one study.[16] More specifically, an increase in the Firmicutes/Bacteroidetes (F/B) ratio was not only the most common abnormality, but was also demonstrated in all of the studies that examined for that parameter.[16] This is significant as animal studies have largely demonstrated that an increase in the F/B ratio is strongly associated with an increase in body fat, obesity, and metabolic syndrome. In humans, this relationship has been more difficult to demonstrate, with some studies finding no such association,[8,21] while others have found a similar increase in the F/B ratio in obese individuals,[20,22,23] and still some have not reported bacterial phyla. Some of the other known taxonomic alterations that are influenced by SGAs in humans include *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* phyla, as well as bacteria that are members of the *Bifidobacterium* genus. Increases in *Proteobacteria* and *Actinobacteria* abundance coupled with decreases in *Verrucomicrobia* have been illustrated with risperidone use among adolescents.[24] Decreases in *Akkermansia* have been reported in non-obese adults with SGAs[19] and increases in *Bifidobacterium* seen in adults with first episode psychosis treated with risperidone.[25]

While the mechanism by which SGAs alter the GMB remains uncertain, several have been proposed (see Figure 1).

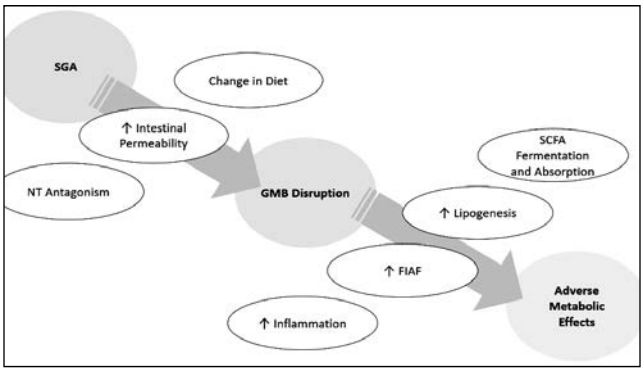

Figure 1. A summary of putative mechanisms by which SGAs cause adverse metabolic effects via disruption of the GMB. SGA: second generation antipsychotic, NT: Neurotransmitter, SCFA: short chain fatty acid, FIAF: fasting-induced adipocyte factor.

SGAs compromise the gastrointestinal barrier

SGAs may be antimicrobial. Prebiotic treatment has previously been shown to decrease intestinal permeability through increased integrity of tight junction proteins.[26] Because the GMB plays a part in maintaining the gastrointestinal barrier, SGAs could cause an increase in intestinal permeability. Increased intestinal permeability in turn allows movement of pathogens and antigens beyond the gut, inducing inflammation and culminating in metabolic side effects.[27,28]

SGAs alter diet, and diet modifies the GMB

Independent of SGAs, diet has been implicated in determining the structure and function of the GMB. Changes in GMB composition due to diet can happen as quickly as within 24 hours of an alteration in diet.[22] Looking at specific diets, those which are high in fat have been linked to changes in the GMB, namely an increase of Firmicutes to Bacteroidetes,[29] which has also been correlated with obesity.[22] In pre-clinical studies, high fat and high sugar diets (modeling the human "western diet") increased *Roseburia spp.* and *Ruminococcus gnavus*, which have been positively correlated with insulin levels and a homeostatic model of insulin resistance, two key markers of metabolic dysfunction.[30] Plant-based versus animal-based diets also impact the GMB. Animal-based diets have illustrated increases in *Alistipes spp., Bilophila spp.* and *Bacteroidetes spp.*, and decreases in *Roseburia spp., Eubacterium rectale* and *Ruminococcus bromii*, the latter group all sharing a common feature of being fermenters of dietary plant polysaccharides.[31] Alterations in the GMB strongly associated with the "western diet" have been proposed to occur through lower consumption of microbiota-accessible carbohydrates (MACs).[28] MACs promote diversity in the gut, and are fermented by microbiota to form short chain fatty acids (SCFAs).[28,32] One food which has been discussed frequently in conjunction with the GMB is yogurt. Consumption of yogurt modifies GMB composition depending on the strain of bacteria. For instance, yogurt with *Bifidobacterium lactis* has been shown to have immunomodulatory effects.[33]

SGAs modify diet, so it follows that changes in diet may account for SGA-mediated changes in the GMB. Additionally, clozapine and olanzapine have been shown to induce food craving and binge eating in patients.[34,35] Looking to "hunger hormones", SGAs also affect serum ghrelin and leptin levels. In a study assessing five SGAs (clozapine, olanzapine, risperidone, quetiapine, and amisulpride), elevated serum ghrelin levels were associated with all but quetiapine.[27] With regards to leptin, the consensus is that SGAs such as olanzapine and clozapine increase serum levels.[32,36] Taken together, dietary choices greatly influence the composition of the GMB independently of SGAs, and the introduction of an SGA potentially causes GMB-altering dietary changes.

SGAs disrupt the GMB through neurotransmitter antagonism

Gut bacteria produce and are receptive to the neurotransmitters gamma aminobutyric acid (GABA), serotonin, dopamine, and norepinephrine.[37] As examples, *Lactobacillus* are capable of producing GABA, *Streptococcus* has been shown to produce serotonin, and *Proteus vulgaris* can produce dopamine and norepinephrine. A recent review by Strandwitz has identified several studies showing species of bacteria beyond those mentioned that are able to produce neurotransmitters.[38] Along with neurotransmitter production, both gram positive and negative bacteria have been shown to respond to norepinephrine and dopamine with increased growth (in culture) and virulence.[39-41]

SGAs function as antagonists at serotonin (mainly the 5-HT2A receptor subtype), norepinephrine (alpha and beta),

and dopamine D2 receptors, thereby inhibiting reuptake of these neurotransmitters. While this improves psychopathology, it also changes the structure and function of the GMB, and may be a pathway by which weight gain and other forms of metabolic dysfunction occur.[42]

Metabolic consequences of GMB disruption

SGAs have been shown to cause gut dysbiosis resembling illness, antibiotic treatment, or dietary changes.[43,44] While several mechanisms of action have been suggested by which GMB dysbiosis deleteriously affects metabolism, a precise mechanism of action has yet to be determined. The following putative mechanisms will be discussed in detail given the literature supporting them: increases in lipogenesis, absorption of short chain fatty acids (SCFA), inflammation, and fasting-induced adipocyte factor (FIAF) (see Figure 1).

Lipogenesis

Dysbiotic changes in GMB composition and function strongly affect major organ systems. Colonized mice show upregulated absorption of monosaccharides compared to germ-free mice.[45] When these monosaccharides reach the liver, it responds with an increase in carbohydrate response element binding protein (chREBP) and sterol regulatory element binding protein-1c (SREBP), which is followed by increased lipogenesis and lipoprotein lipase.[23,32,36,45]

SCFA

SCFAs are produced by the GMB and gut and absorbed into the blood, making available an otherwise inaccessible source of nutrients like butyrate, acetate, and propionic acid. The extent to which this occurs depends in part upon the abundance of phyla that ferment MACs into SCFAs.[28,32]

The downstream effects of SCFAs on metabolic outcomes are variable. Colonizing germ-free adult mice with the microbiota of an obese mouse led to weight gain, without an associated increase in food or calorie consumption compared to mice colonized with the microbiota of a lean mouse.[46] Furthermore, caecal gross energy content was smaller, while butyrate levels, and acetate levels were larger in genetically obese mice, suggesting that perhaps production and absorption of SCFAs is more efficient in an 'obese' GMB.[46] In contrast, addition of butyrate and propionate to a high-fat diet prevented weight gain in mice.[47] Similarly adding MACs (which the GMB converts to SCFAs) to a high-fat diet prevented weight gain in mice.[48]

SCFAs might also lead to decreased activity of AMP-activated protein kinase (AMPK) in skeletal muscles and liver tissue, resulting in upregulated deposition of SCFAs in adipose tissue.[22,49,50] Some evidence indicates SCFAs may be anti-inflammatory in nature, which would be metabolically beneficial.[28]

Inflammation

A compromised GMB can lead to antigens crossing the gastrointestinal area into the blood, where inflammation follows. Neuroinflammation relates the brain and the gut in a gut-brain axis, causally linking gut microbiota to stress in the central and enteric nervous system enhancing sensitivity to stress and caloric intake.[51] The resulting psychological stress, proinflammatory cytokines, and hypoglycemia can activate the hypothalamus-pituitary-adrenal axis,[52] and overactivation may, in turn, deleteriously affect the GMB in a loop.[53] While the GMB influences endocrine pathways and behavior, endocrine disease and behavioural states also influence the GMB.[52,54]

Additionally, proinflammatory cytokines activate the JNK/IKK pathway, which promote the activity of obesogenic genes involved in lipid metabolism.[32]

FIAF

FIAF is secreted by adipose tissue, the liver, and the intestine. It inhibits lipoprotein lipase (LPL) which promotes the deposition of lipids in adipose tissue.[32,45] Bäckhed et al., found that conventionalized mice gained weight while germ-free mice did not, and that this effect was abolished in fiaf knockdown mice.[45] Consistent with a role as a LPL inhibitor, colonized mice displayed greater LPL activity.[45] Taken together, this suggests that GMB dysbiosis might cause weight gain by upregulating FIAF.

Impact of research involving SGAs and the GMB

Studies have suggested that the degree of weight gain attributable to SGAs may be greater in antipsychotic-naive patients than in chronically treated adult patient populations, with the greatest increases in weight and metabolic parameters occurring during the first year of treatment.[55] This is significant as many FEP patients are antipsychotic-naive and rushed by their treating team to be started on an SGA immediately, as early intervention has been associated with improved treatment outcomes.[56] However, as the majority of FEP patients are relatively young in age, they not only have to cope with the lifetime impact of the metabolic sequelae of their treatment, but are also forced to cope with weight gain at a time in their life where their appearances may be of greater personal importance. This may negatively impact their self-esteem, further taxing their mental health at a time when it is already being challenged by their primary disease state. These negative influences on quality of life may further impede medication compliance. Patients may attribute their weight gain and other adverse effects to starting their medication (often a correct association), and thus may choose to discontinue their medications in the hopes of stopping these adverse effects without appreciating the consequences on symptom control. There is significant literature, however, to suggest that antipsychotic discontinuation, even if for a brief period before being restarted, has adverse effects on long term outcomes, including time to remission and risk of relapse.[57,58] Indeed, a retrospective cohort study by Winton-Brown et al.[58] found that treatment discontinuation was associated with a five times greater risk of relapse.[58] Furthermore, a systematic review by Zipursky et al. found that patients who continued treatment with antipsychotics had one year relapse rates of 3%, while those who discontinued had relapse rates of 77% at one year and 90% at two years.[57] Relapses may then lead to increased difficulty in controlling symptoms, requiring larger antipsychotic doses or the use of clozapine, both associated with increases in negative metabolic effects. A study by Hickling et al. examining antipsychotic medication non-adherence to in FEP patients found that 34% of patients reported non-adherence, with contributory factors including younger age and less satisfaction with medication information.[59] Others have reported that up to half of patients

are non-adherent in the first year following initiation of treatment with antipsychotics.[58] The impact of research on the interplay between SGAs and the GMB therefore extends beyond attenuating metabolic side effects, and into addressing issues of medication compliancy, self-esteem, risk of psychiatric relapse, and time to remission.

Clinical importance of understanding the GMB in SGA treatment

FEP patients typically respond well to treatment initiation with APs, having relatively rapid resolution of psychotic symptoms, as antipsychotic sensitivity is increased in the early stages of psychosis as compared to later.[58] Given the evidence in the literature demonstrating the metabolic adverse effects of SGAs, physicians should be cognizant of the weight gain and cardiometabolic risks associated with starting patients on such medications, particularly FEP patients who are most commonly antipsychotic-naive and thus in the position to experience the greatest metabolic insult. Monitoring metabolism is important in the initial stages of treatment, but must be continued throughout. Since treatment regimens for this patient population are often long term, if not lifelong, it is imperative that physicians make efforts to reduce untoward metabolic effects. Strategies to reduce weight gain and cardiometabolic risk include choosing SGAs with better cardiometabolic risk profiles whenever possible (i.e. aripiprazole or ziprasidone). Although behavioural modifications are often recommended as first line interventions to combat metabolic comorbidities, they may be challenging to adopt in a patient population that is often limited in motivation and by the inherent nature of their disorder and the medications used to treat it. However, physicians should not be deterred and should continue to work with their patients to incorporate various health-risk behavioural modifications, such as involving caloric intake, choosing healthier food options, and increasing physical activity. Lastly, in light of the metabolic sequelae described above, including increases in fasting plasma glucose, cholesterol levels, triglyceride levels, blood pressure, and weight, physicians should routinely screen their patients according to current guidelines and begin treatment of abnormal values and subsequent disease states appropriately.[60]

As described above, factors associated with antipsychotic non-adherence include younger age and less satisfaction with medication information.[59] To promote adherence, physicians should endeavour to provide better information about antipsychotics to their patients, especially those who are younger and at greater risk for non-adherence.

Current commonly employed methods of reducing SGA-induced weight gain include metformin and topiramate.[61,62] Omega-3 fatty acids have also proven to be protective against metabolic syndrome in schizophrenia patients.63 The facility with which the GMB changes in response to diet, probiotics, and prebiotics, as well as the role it plays in metabolic symptom progression, make the GMB an attractive target for the future development of SGA-adjuvant treatments.

Discussion

Summary: Present understandings and future directions

A limitation of this study is that it is a narrative review rather than a systematic one. It is also worth bearing in mind that the GMB and metabolism both seem to be disrupted in psychiatric patients prior to beginning SGAs.[13] This means that the extent to which observed changes in the GMB are uniquely attributable to SGAs rather than the progression of the disease itself is difficult to assess in human subjects, where ethical implications of withholding treatment preclude a placebo-controlled patient group in many instances. However, in studies where first-generation antipsychotics or other pharmacological treatments are compared to SGAs, the GMB and weight were adversely affected by SGAs.[19,64]

Pre-clinical studies have been able to illustrate clearer relationships between SGAs, obesity, metabolic dysfunction, and the GMB. Currently, four studies (see Table 1) have been conducted in humans reporting on SGAs in relation to microbiome diversity and metabolic changes.[19,20,25,64] From pre-clinical and clinical studies, it is understood that SGAs have their effects on the GMB by blocking neurotransmitter receptors, altering diet, and increasing intestinal permeability. While we are slowly beginning to recognize pathways for the GMB's involvement in SGA-induced metabolic dysfunction, there is more to be understood, namely through exploration with larger sample sizes and longer follow up among FEP patients and those who have been chronically treated.

Table 1. A summary of studies featuring GMB and metabolic changes associated with SGAs

Authors	Population	Tx	GMB Changes	Metabolic Outcomes
Bahr et al., 2015	9-15 year old males with and without psychosis	Risperidone (in the psychosis group)	↓ Bacteroidetes:Firmicutes	↑ BMI
Yuan et al., 2018	FEP patients	Risperidone	↑ *Bifidobacterium spp.* and Escherichia coli ↓ *Lactobacillus spp.* and *Clostridium coccoides*	↑ BMI, fasting glucose, triglycerides, LDL, hs-CRP, SOD, and HOMA-IR in Risperidone group
Flowers et al., 2017	Bipolar disorder patients	Any SGA or no SGA	↓ diversity among females ↓ *Akkermansia* ↓ *Sutterella* ↑ *Lachnospiraceae*	↓ relative abundance of *Akkermansia* in SGA group was only found among non-obese patients. Obese patients had ↑ *Lachnospiraceae* abundance ↑ BMI in SGA group
Flowers et al., 2019	Bipolar disorder or schizophrenia patients	Raw unmodified potato starch, SGA, or lithium or lamotrigine	↓ *Alistipes* abundance among SGA users ↓ diversity among females ↑ *Actinobacteria* with starch	Not examined

BMI: body mass index, FEP: first episode psychosis, LDL: low density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, HOMA-IR: homeostatic model assessment of insulin resistance

Interpretation of literature

In summary, the literature to date illustrates the potential importance of targeting the GMB for the treatment of metabolic costs of SGAs. The literature also highlights the potential mechanistic role played by the GMB in mediating SGA-induced weight gain. Finally, further research into the interplay between the GMB, SGAs, and metabolism may allow earlier diagnosis and better monitoring and treatment of schizophrenia, other psychotic disorders, co-morbid obesity, and obesity-related conditions (i.e. type 2 diabetes, metabolic syndrome). As has been reviewed, there appear to be baseline differences in metabolic as well as GMB parameters that differentiate FEP from healthy individuals. This separation becomes even more apparent as a psychotic illness progresses and with the introduction of SGAs. Common characteristics which occur among FEPs when starting SGAs include decreases in GMB diversity, transition of the GMB towards that of an obesogenic profile, and an increase in Firmicutes with a corresponding decrease in Bacteroidetes at the phyla level. It should be noted, however, that although many studies illustrate these findings, there are several that do not or that show conflicting results, therefore drawing the importance of continuing research.

In addition to exploring differences between FEP and healthy individuals, as well as changes in the GMB while FEP individuals progress through their treatment, the literature points to the importance of increasing clinical trials which focus on interventions for metabolic adversities among this population, be them pharmacotherapy or diet-based. Clinical trials should also explore how GMB-based interventions may complement SGA treatment and potentially improve SGA efficacy. Furthermore, the literature surrounding this topic also points to the importance of research in patients who are most vulnerable to metabolic dysfunction (i.e. youth and those who have never been exposed to SGAs), especially because they are at the greatest risk for long-term changes and therefore long-term metabolic complications.

Finally, while this review as well as the literature surrounding this topic focus on the interplay between the GMB, SGAs, and metabolic dysfunction among FEP patients, these investigations also present an opportunity to understand host-microbial interactions, psychotic illness, and metabolic dysfunction in general.

Future directions

We suggest that future research initiatives explore metabolomic, proteomic, and lipidomic assessments. Going further than metabolic side effects, we suggest that future research initiatives explore how GMB alterations correlate with changes in cognition (both structural and functional) and psychopathology, as this relationship has yet to be reported in this patient population. Collectively, an understanding of the interplay between SGAs and the GMB which includes metabolic, psychopathological, and cognitive changes, is the ultimate goal. In addition, discussion of GMB changes when starting chronic treatment with an SGA was limited to studies assessing GMB composition due to the limited available literature. Future research directions should thus focus on other ways to analyze the GMB. Future research directions could explore novel options for co-therapy to prevent or reduce metabolic adverse effects. For example, clinical trials could explore if benefit could be derived from the simultaneous treatment of SGAs with probiotic, prebiotic or symbiotic therapy. Further research is also needed to better understand co-therapy options that can mitigate SGA-induced metabolic dysfunction, such as the oral hypoglycemic agent Metformin,65 in a patient population with severe mental illness.

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