Review

Gut microbiota and antipsychotics induced metabolic alteration

Dong-Yu Kang[1], Su-Juan Li[1], Chen-Chen Liu[1], Ren-Rong Wu[1,2*]

[1]Mental Health Institute of the Second Xiangya Hospital, Central South University; Chinese National Clinical Research Center on Mental Disorders; Chinese National Technology Institute on Mental Disorders; Hunan Key Laboratory of Psychiatry and Mental Health, Changsha, Hunan 410011, China; [2]Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

Received 11/11/2019; Accepted 12/04/2019

ABSTRACT

Schizophrenia is a chronic and severe mental disorder with antipsychotics as primary medications, but the antipsychotics-induced metabolic side effects may contribute to the elevated risk of overall morbidity and mortality in patients with psychiatric diseases. With the development in sequencing technology and bioinformatics, dysbiosis has been shown to contribute to body weight gain and metabolic dysfunction. However, the role of gut microbiota in the antipsychotics-induced metabolic alteration remains unknown. In this paper, we reviewed the recent studies of the gut microbiota with psychiatric disorders and antipsychotic-induced metabolic dysfunction. Patients with neuropsychiatric disorders may have a different composition of gut microbiota compared with healthy controls. In addition, it seems that the use of antipsychotics is concurrently associated with both altered composition of gut microbiota and metabolic disturbance. Further study is needed to address the role of gut microbiota in the development of neuropsychiatric disorders and antipsychotic-induced metabolic disturbance, to develop novel therapeutics for both neuropsychiatric disorders and metabolic dysfunction.

KEYWORDS:

Gut microbiota, Neuropsychiatric disorder, Metabolism, Antipsychotics

INTRODUCTION

Microbes have existed hundreds of millions of years earlier than humans; there has never been a time that our body functions without microorganisms. However, not until recent decades have we started to appreciate the fact that we harbor at least 100 trillion microbial cells within (1), far more than human cells. The microbial associated that resides in and on the human body all together constitute our microbiota and the collection of genes they encode are named as microbiome (2). The human gut microbiota is dominated by two bacterial species, *Bacteroidetes* and *Firmicutes* (3). Though many factors could affect microbial composition in the human gut, it is surprisingly stable at the phylum level (4). However, when the compositions of genera and species were considered, the inter-individual variation is relatively higher (5).

Along with the development in sequencing technology and bioinformatics, the more in-depth investigations into the composition of complex microbial ecosystems and its role in neuroscience have become possible in the recent decade (6). Current researches hypothesize that the gut microbiota interacts with the host through immune, neuroendocrine and neural pathways (7), and gut microbiota can modify the synthesis of key metabolites that affect the gene expression in the prefrontal cortex and then modulate social behaviors (8). The microbiota-gut-brain communication could modulate brain development, function and even behaviors, and therefore therapeutics target at the microbiota-gut-brain could provide effective treatment for psychiatric disorders.

Antipsychotics are wildly used to treat schizophrenia and bipolar disorder, but some of them cause common metabolic side-effects, including the elevated risk for obesity, diabetes, and metabolic dysfunction, which contribute to the risk of overall morbidity and mortality(9). Accumulating evidence show an increased prevalence of obesity and metabolic dysfunction such as impaired fasting glucose and insulin resistance in drug-naïve first-episode patients

* Correspondence to: RR Wu, Email: wurenrong@csu.edu.cn

with schizophrenia, suggesting a possible co-morbidity of metabolic function in patients with schizophrenia (10). Metabolic complications such as weight gain could be distressing(11) and has become a significant concern in the selecting medications for individuals with psychotic diseases for it is often associated with a poorer functional outcome(12), more reduced quality of life(13), and more likelihood of discontinuing antipsychotic medications (14). The mechanism of antipsychotic-induced metabolic dysfunction remains unknown. Despite that, previous studies have indicated some possible pathways that might contribute to antipsychotic-induced metabolic dysfunction.

The use of antipsychotics can significantly increase appetite (15). The central and peripheral mechanism for regulating hunger and satiety plays a vital role in the maintenances of energy homeostasis, which involves gut hormones such as glucagon-like peptide 1(GLP-1), peptide YY (PYY), and ghrelin, and adipokines such as leptin (16) and adiponectin (17). Gut hormones are a group of hormones secreted by enteroendocrine cells in the stomach, pancreas, and small intestine that control various functions of the digestive organs. For example, GLP-1 increases insulin secretion; PYY inhibits food intake; ghrelin stimulates appetite and increases gastric emptying. Adipokines are cytokines secreted by adipose tissue (18). As adipokines, leptin helps regulate energy balance by inhibiting hunger, which in turn reduced fat storage in adiposities, while adiponectin is involved in regulating the levels of glucose and fatty acid breakdown. Those peripheral signals were integrated into the arcuate nucleus of the hypothalamus, which contains orexigenic neuropeptide Y (NPY) neurons and anorexigenic pro-opiomelanocortin (POMC) (19).

The antipsychotic medications may decrease the resting energy expenditure in the youth (20) and adults (21). Resting energy expenditure or fat-free mass ratio is significantly increased and correlated with the weight gain during the follow-up adolescents who took antipsychotics (22). However, after adjusting the energy expenditure for fat-free mass, there is no significant difference for individuals with schizophrenia and healthy controls, suggesting that the different body composition and impaired capacity to use fat to generate energy may play a vital role in developing weight gain (23). Besides, many studies have shown that antipsychotic medications could induce a significant risk of insulin resistance, glucose dysregulation, and the development of type 2 diabetes (9). Individuals with psychiatric disorders like drug-naive first-episode schizophrenia are reported to have an elevated risk for diabetes before using antipsychotics, suggesting a possible common underlying schizophrenia and metabolic dysfunction (24).

A recent study by Maier et al. suggests that almost one-quarter of non-antibiotic drugs used in humans, mainly antipsychotics, have antimicrobial activity, which may cause an imbalance to the gut microbiota ecosystem (25). Meanwhile, dysbiosis may contribute to bodyweight alterations and metabolic dysfunction (26). This may provide a new avenue for understanding the mechanism of antipsychotic-induced metabolic disturbance. Therefore, we prepared this review to summarize recent findings in both clinical trials and animal studies linking gut microbiota, psychotic disorders, and antipsychotic-induced metabolic alterations.

GUT MICROBIOTA AND PSYCHIATRY DISORDERS

Altered composition of gut microbiota has been found in patients with schizophrenia (27), autism spectrum disorder (ASD) (28), bipolar disorder (29), and major depressive disorder (30), which has been considered major mental health disorders (31), with a peak age of onset in children, adolescents and younger adults. Emerging researches have implicated that the gut microbiota plays a crucial role in the development of the nervous system, neuropsychiatric disorders, and drug response (32). However, the pathophysiological link with brain disorders has yet to be established. There are several bidirectional pathways through which the gut microbiota might affect the brain function(28), which as well be the potential under-lying mechanism of several neuropsychiatric disorders.

Microbiota-gut-brain-axis: communication between gut and brain

One critical pathway is the communication between the gut microbiome and the host immune system (33). The gut microbiota might trigger the production of various immune-related cytokines that could media signaling pathway (34) and is also related to the pathogenesis of inflammatory bowel disease (IBD) (35). Meanwhile, gut microbiota could communicate with the nervous system through production of neurotransmitters (Figure 1). For example, gut microbiota such as *Lactobacillus*(*L.*) *brevis* and *Bifidobacterium*(*B.*) *dentium* have been reported to produce gamma-aminobutyric acid (GABA) that might affect GABAergic neurotransmission (36), and another group of neurotransmitters such as norepinephrine, and dopamine, which has been linked to schizophrenia(37). Also, *L. reuteri* could produce histamines, which are linked to major depression and cognitive function (38).

Gut microbiota could directly communicate to the central nervous system to maintain a sense of homeostasis in the physiological condition through the vagus nerve in the human body (39). The beneficial effects of *L. rhamnosus* chronic treatment were not found in vagotomized mice, which may indicate the vagus as a significant modulatory pathway between gut microbiota and the brain (40). The endocrine signaling pathway may be also involved in the communication between brain and gut microbiota. Previous research reported that prebiotic treatment significantly changed the composition of gut microbiota in healthy adults, and increased the plasma concentrations of GLP-1 and PYY, which participated in appetite and glucose excursion responses after meal (41). Another focus of recent studies is that the gut microbiota metabolized short-chain fatty acids (SCFAs). Sun et al. reported that microbiota regulated Th1 cell functions to maintain intestinal homeo-stasis through gut microbiota-derived SCFAs (42). SCFAs produced by gut microbiota also links metabolic activity of the gut microbiota with host body energy homeostasis and inhibit fat accumulation in adipose tissue (43).

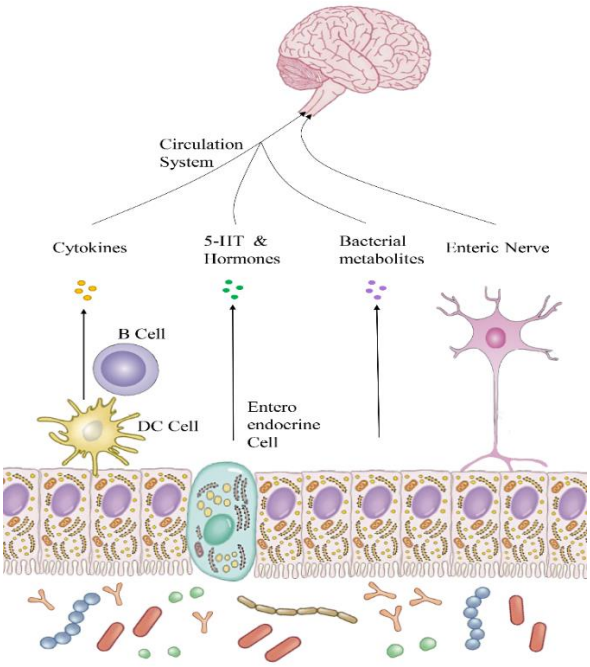

Figure 1. The various known bidirectional-signaling pathways between the gut microbiota and the brain, including immune, neuroendocrine and neural pathways. DC cell, dendritic cell; 5-HT, 5-hydroxytryptamine.

Schizophrenia

The increased morbidity of IBD and gastroenterology issues have been noted with psychiatric disorders and schizophrenia (44, 45). These may provide a theoretical basis for schizophrenia and microbiota. Recently, more studies have been focusing on the link between schizophrenia and microbiome (46, 47). For instance, the higher rate of IBD may be related to the immune origins of schizophrenia (48). One preliminary study found an altered composition of microbiota in patients with first-episode schizophrenia compared with age-matched heal-thy controls.

Meanwhile, reduced numbers of *Lactobacillus* and *Bifidobacterium* species may be correlated with the severity of negative symptoms and less likelihood of remission at 12-month follow-up in individuals with first-episode schizophrenia (49). One recent mega-genomic study of 90 drug-free patients with schizophrenia identified 26 schizophrenia-associated bacterial species, in which the discovered genes are enriched in SCFA synthesis, tryptophan metabolism, and synthesis/degradation of several neurotransmitters (50). Germ-free mice received fecal transplants from schizophrenia patients tend to have lower glutamate and higher glutamine and GABA in the hippo-campus and display schizophrenia-relevant behaviors (51). However, probiotic supplements had no effects on psychopathological symptoms measured by positive and negative symptom scales (PANSS) in individuals with schizophrenia, though it managed to reduce the possibility of severe bowel symptoms associated with antipsychotics (52). In addition, one recent systematic review also suggest that based on the current evidence there are no significant differences in psychopathological symptoms between the probiotic supplements and placebo in patients with schizophrenia (53).

Bipolar disorder

Yolken et al. reported that individuals hospitalized with acute mania have a significantly increased rate of bacterial infections (54). The hypothesis that gut microbiota related immune activation may contribute to the onset of bipolar disorder has since emerged (55). The difference in gut microbial composition has been associated with bipolar disorder and self-reported burden of diseases. *Faecalibacterium* and an unclassified member of the *Rumino-coccaceae* family, both of which belong to phylum *Firmicutes*, are reduced in individuals with bipolar disorder (29). *Faecalibacterium* is a Gram-positive butyrate-producing gut bacterium. Interestingly, both *Faecalibacterium* and *Ruminococcaceae* have relatively decreased in patients with major depressive disorder, and the reduced level of *Faecalibacterium* is correlated to the severity of depressive symptoms as measured by Hamilton's Depression Scale (56). In addition, one recent randomized controlled trial reported that adjunctive treatment with probiotics for 24 weeks was associated with a lower rate of rehospitalization in individuals with mania (57).

Major depressive disorder

One recent large cohort study show that butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria are consistently associated with a higher quality of life indicators. While *Dialister* and *Coprococcus* bacteria were depleted in depression (58), further analysis indicated that microbial synthesis potentials were positively correlated with mental quality of life. Altered hypothalamic-pituitary-adrenal (HPA) axis (59) and elevated levels inflammation(60) may be related to the mechanism of major depressive disorder. However, microbiota could have a significant influence on both HPA axis and inflammation. In 2004, Sudo, N. et al. indicated a direct link between HPA axis and microbiota by showing that an exaggerated corticosterone and adrenocorticotrophin response to stress in germ-free mice (61).

Meanwhile, increased gastrointestinal inflammation is associated with anxiety-like behavior (62) and germ-free or antibiotic treatment reduced anxiety-like behaviors in animal models (63). Several studies have indicated the alterations in microbiota is related to anxiety and depressive-like behaviors (64). When transplanting human fecal samples from people with major depressive disorder to GF mice, the recipients exhibit depressive-like behaviors compared to controls (65). One study demonstrated that feeding healthy mice with *L. rhamnosus bacteria* could decrease anxiety-like and depressive-like behaviors (40), while a similar study, the treatment with *B. infantis* bacteria showed reduction in depressive-like symptoms in rats (66). However, the clinical studies of the impact of probiotics on mood disorders are still in the early stages.

Autism spectrum disorder

Li et al. have reviewed recent evidence that gut microbiome may affect the risk of ASD, and gut microbiota plays an important role in mediating the risk of ASD (67)when

individuals are exposed to various adverse environmental factors in particular during prenatal and perinatal period (68). Reports have shown that the gut bacterial communities are different between individuals with ASD and typically developing controls (69, 70). The valproic acid (VPA)-induced rat model of autism presents with gut bacterial dysbiosis similar to that in human autism (71). While studies have been inconsistent, the richness of diff-erent species and diversity between ASD and TD controls are repeatedly reported.

In a recent study, Sharon et al. transplanted gut microbiota from human donors with ASD or TD controls into germ-free mice and revealed that colonization with ASD microbiota could induce hallmark autistic behaviors in germ-free mice. Additionally, particular candidate microbial metabolites could improve abnormal behaviors in the BTBR (Black and Tan Brachyury) mice model of ASD. They proposed that gut microbiota regulated behaviors through the production of neuroactive metabolites and thus contributed to the pathophysiology of ASD (72). Given the neurodevelopmental origin of ASD, maternal environment is also of great importance(68), Buffington et al. showed that maternal high-fat-diet-induced dysbiosis negatively affected the offspring's social behavior by altering signaling in the mesolimbic reward system. Interestingly, transferring the microbiota from control mice into offspring of high fat diet-fed mothers completely corrected the impairments in sociality and social novelty (73).

Moreover, a recent meta-analysis of nine studies with 254 patients showed children with ASD tend to have a low percentage of *Akkermansia*, *Bacteroides*, *Bifidobacterium*, and *Parabacteroides,* but a higher rate of *Faecalibacterium* among the detectable bacteria in the gut microflora compared to controls (74).

ANTIPSYCHOTICS INDUCED WEIGHT GAIN AND GUT MICROBIOTA

The second-generation antipsychotics (SGA) are the mainstream treatment for schizophrenia and bipolar disorder. However, almost all antipsychotics induce weight gain (75, 76), and the risk for type 2 diabetes is significantly elevated in individuals who used medications of antipsychotics (77), in particular, olanzapine and clozapine (9). In the early stage of schizophrenia, the risk for cardiovascular disease, diabetes, and pre-diabetes is lower than that in chronic schizophrenia, which is likely due to antipsychotic-induced weight gain (78).

Human-target non-antibiotic drugs such as antipsychotics may have antibiotics-like side effects on gut microbiota. In a systematic screen on 1000-marketed drugs against 40 gut microbial strains in vitro, Maier et al. reported that 24% of non-antibiotics, including all class for human medicines, inhibited the growth of at least one strains, and the chemically diverse antipsychotics were over-represented (25). Antipsychotics may alter composition of gut microbiota and induce body weight gain and metabolic disturbance (79). The potential mechanism of antipsychotic-induced metabolic disturbance could be due to the interactions between antipsychotics and neurotransmitter receptors, altered eating habits or appetite increase, a different expression of orexigenic and anorexigenic neuropeptides, histamine H1 receptor-mediated hypothalamic AMPK activeation, increased blood leptin, ghrelin and pro-inflammatory cytokines (80).

Olanzapine is one of the widely used antipsychotics that may induce the most metabolic disturbance in patients with schizophrenia. Davey et al. reported an increase in *Firmicutes* and a decrease in *Bacteriodetes*, reduced microbiota diversity, and significant weight gain in female Sprague Dawley rats after administrated with olanzapine (81). Interestingly, co-administration of the antibiotic cocktail in olanzapine-treated rat attenuated body weight gain and metabolic dysfunction (82). However, in germ-free mice, no significant difference in body weight was observed between a high-fat diet and high fat plus olanzapine (83); after microbial colonization in the gut, the olanzapine group gained significantly more weight than placebo group did. This demonstrates that gut microbiota is necessary and sufficient for olanzapine-induced weight gain.

Risperidone, also commonly used antipsychotics, may have a significant impact on weight gain due to the suppression of energy expenditure, which correlated with an altered gut microbiome in mice (84) and children (85). Risperidone inhibited the growth of cultured fecal bacteria those are grown anaerobically more than those grown aerobically did. Transplantation of the fecal phage fraction from risperidone treated mice to naïve recipients could cause excess weight gain through reduced energy expenditure (84). A study showed that patients with drug-naïve first-episode schizophrenia treated with risperidone for 24-week have a significant increase in body weight and in the numbers of fecal *Bifidobacterium* and *Escherichia coli* , but decreases in the number of fecal *Clostridium coccoides* and *Lactobacillus*; only fecal *Bifidobacterium* are associated with the changes in weight (86). However, previous study investigating the effect of risperidone on microbiome structure in males indicated a decreased ratio of bacteroidetes to Firmicutes in those chronic treated psychiatric children compared with those antipsychotic-naive controls (85).

One study suggested that people with bipolar disorder who treated with SGAs had decreased Simpson diversity and change in specific gut microbiota with significant weight gain compared to those who did not receive a treatment of SGAs treatment (87). So far, most of the studies have focused on olanzapine and risperidone, the two commonly used SGAs with higher efficacy (88) but more induced metabolic disturbance. These may provide evidence for a clinical translational research in human patients.

PROBIOTIC AND PREBIOTIC AS INTERVENTION

Probiotics

The term "probiotics" which derived from the Greek word meaning "for life" first appeared in 1974. Its definition evolved over the time and the latest consensus definition was termed by the Food and Agriculture Organization of the United Nations (FAO) and WHO as "Live micro-organisms which when administered in adequate amounts confer

a health benefit to the host" (89). In 1907, Élie Metchnikoff from the Pasteur Institute proposed lactic acid bacteria being beneficial to human health (90). In humans, lactic acid bacteria are the most widely used probiotics, and they mainly include *Lactobacillus*, *Enterococcus*, *Pediococcus*, *Streptococcus*, *Lactococcus, Leuconostoc*, and *Oenococcus*. Microorganisms claimed with probiotic properties include specific probiotic strains of the follwing genera of *Lactobacillus*, *Bifidobacterium* (also known as *Lactobacillus bifidus* before 1960), *Saccharomyces*, *Enterococcus*, *Streptococcus*, *Pediococcus, Leuconostoc*, *Bacillus*, *Escherichia coli* (91-93), in which *Lactobacillus* and *Bifidobacterium* are the most common in the gut microbiota (94) (**Table 1**).

Table 1. The most frequently used microorganisms as probiotics.

Lactobacillus	*Bifidobacterium*	Other lactic acid or other bacteria*
L. acidophilus	*B. animalis*	*Enterococcus faecalis*
L. casei	*B. bifidum*	*Enterococcus faecium*
L. crispatus	*B. infantis*	*Escherichia coli Nissle*
L. gasseri	*B. lactis*	*Lactococcus lactis*
L. reuteri	*B. adolescentis*	*Pediococcus acidilactici*
L. rhamnosus	*B. breve*	*Streptococcus thermophilus*
L. paracasei	*B. longum*	*Saccharomyces bounlardi*
L. bulgaricus		*Saccharomyces cerevisiae*
L. fermentum		*Bacillus cereus*
L. johnsonii		*Bacillus subtilis*
L. lactis		
L. plantarum		
L. prausnitzii		

Probiotic supplements have been used in clinical practice for the prevention and treatment of several medical conditions, particularly for gastrointestinal diseases and benefits for general health (95). Different *Lactobacillus* strains can help treat diarrhea and have benefits for people who cannot digest lactose or sugar in milk. *Bifidobacterium* can be found in some dairy products and help ease the symptoms of irritable bowel syndrome (IBS) and some other conditions.

Probiotic supplements can attenuate obesity through members of the genus *Lactobacillus* (96, 97) and *Bifidobacterium* (98, 99). In animal models of obesity, certain distinctive strains of *Lactobacillus* and *Bifidobacterium* species affect reducing obesity. One recent review suggests that supplementation of the probiotics mentioned above in mice and rats show less weight gain, fat accumulation, and adipose tissue compared to the placebo (100). Clinically, several strains of *Lactobacillus* showed beneficial effect against metabolic dysfunction. For example, compared with those who received placebo, pregnant women received *L. rhamnosus* supplements from four weeks before the date of expected delivery to six months of postnatal had a significant modulation of the weight gain in children during the first few years, based on a follow-up study of cohort from birth to 10 years (101); *L. gasseri* SBT2055, when administrated to obese individuals, can significantly lower abdominal adiposity and body weight in 12 weeks (102). In addition, *B. lactis* HN019 showed a beneficial effect on reducing obesity, blood lipids, and specific inflammatory markers when administrated to people with metabolic dysfunction (103). When combined, both species of *Lactobacillus* and *Bifidobacterium* as probiotic yogurt significantly reduced body weight and body mass index (BMI) in individuals with metabolic syndromes (104). Furthermore, *Bacteroides uniformis* (105) and *Akkermansia muciniphila* (106) have been identified as beneficial probiotics for metabolic dysfunction, adipose tissue inflammation, and insulin resistance.

Some studies have shown that *L. plantarum* DSM15313 (107), *B. animalis subsp lactis* BB-12 (108), and *B.* M13-4(109) have excellent properties as probiotics and improves digestion, immunity and gastrointestinal health. *L. plantarum* is a helpful probiotic that can attack pathogenic and harmful bacteria and survives stomach acid with ease; while *B. animalis subsp lactis* BB-12 may have pathogen inhibition, barrier function enhancement, and immune interaction, and clinically have demonstrated benefits for gastrointestinal health and immune function.

Probiotics may attenuate symptoms of anxiety and depression, and beneficial for antipsychotics-induced weigh gain. Ryo Okubo et al. reported that the addition of the treatment of *B. breve* A-1 in individuals with schizophrenia could improve anxiety and depressive symptoms, but did not mention the change in weight (110). The administration of probiotic supplements may help attenuate the gut discomfort in male individuals with schizophrenia (111, 112). One study of mice showed that administration of probiotic mixture VSL#3 could confer beneficial for olanzapine-induced weight gain (113); a randomized clinical trial (RCT) also showed the beneficial effects of probiotics and vitamin D supplements on metabolic profiles and psychopathological symptoms in individuals with chronic schizophrenia (114). More studies are expected to determine the potential effect of probiotics as an add-on treatment for schizophrenia on metabolic profiles and clinical psychopathological symptoms.

Prebiotics

The concept of prebiotics was evolving as it elaborated in the 1990s, and the current definition typically refers to nutrient-rich and nondigestable fibers found in plants and vegetables. They can pass through intestines unchanged and end up in the deep colon and maintain for a certain

period and can stimulate the growth and activity of health-promoting bacteria that colonize the large bowel (115). Prebiotics found in supplements are usually fibers or starches; fructo-oligosaccharides (FOS), inulin, galactooligosaccharides (GOS), and 4G-β-D-galactosylsucrose (also known as Lacto sucrose) are commonly prebiotics.

Prebiotics has been known to contribute to weight loss and improved metabolic parameters in overweight or obese individuals(116). One recent randomized-controlled trial with 105 overweight and obese adults, dividing into rice bran, rice husk powder or placebo group, indicated that prebiotics could lead to a decrease in weight, BMI, waist circumference and pro-inflammatory markers (117). Cani et al. reported that 2-weeks intervention of prebiotics-supplemented diet in adults could increase the levels of GLP-1 and PYY, and decrease the ratings of the hunger assessed with visual analogue scales (VAS) (41); A rand-omized placebo-controlled study showed that intake of inulin for 8 weeks seemed to modulate inflammation and metabolic endotoxemia in women with type 2 diabetes (118); In one-month randomized placebo-controlled trial, de Luis et al showed that prebiotics (Inulin and FOS) together with alpha linolenic acid (ALA), the metabolic precursor of the long chain n-3 fatty acid eicosapentaenoic acid (20: 5n-3) that has anti-inflammatory properties, could improve total cholesterol, LDL cholesterol and C reactive protein levels in obese men(119). However, inconsistent of prebiotics was also observed (120).

The beneficial effects of prebiotics against obesity and metabolic dysfunction may be through different mechanisms. One popular hypothesis is that prebiotic supplements increase the growth of specific gut microbiota, for example, *Lactobacillus* and *Bifidobacterium*, but not pathogenic microorganisms (121). These changes might be related to better enteroendocrine cell activity, glucose homeostasis, and leptin sensitivity in obese and diabetic mice treated with prebiotics (122). Supplementation with α-cyclo-dextrins also increases lactic acid and SCFAs levels in obese mice, which is likely associated with lipid metabolism and appetite (123). Besides, the increased intestinal permeability and microbial dysbiosis in the high fat diet in mice could be prevented with an addition of prebiotics, which may be related to a beneficial effect on weight gain (124).

However, not until recently, few studies have focused on the effectiveness and safety of prebiotic modulation on antipsychotic-induced weight gain and metabolic dysfunction. Kao et al. (125)conducted a study in which adult female Sprague-Dawley rats were administered a Bimuno™ galacto-oligosaccharide (B-GOS, 0.5 g/kg/day) or water for 21 days while received an intraperitoneal injection of olanzapine during day 8 and 21. The use of B-GOS significantly attenuated olanzapine-induced weight gain, followed by a decrease in the plasma acetate concentrations, elevation of fecal *Bifidobacterium* but reduction in bacteria in phylum *Firmicutes.* Kao et al (126) further finds that the prebiotic reduction of brain histone deacetylase (HDAC) activity and OIWG in rats is independent of acetate major short-chain fatty acid (SCFA) that is produced by G-BOS fermentation. Later, Kao et al. published a letter based on a double-blind placebo-controlled crossover study of thirty-nine non-hospitalized participants randomized to B-GOS or placebo group, a significant increase in the cognitive composite T-score, which was driven by subtests of execu-tive function, was observed after 24 weeks trial. However, supplementation of B-GOS did not affect weight, BMI, central adiposity, circulating candidate metabolic or immune markers (127).

In addition, a clinical study of 16 Japanese in-patients with chronic schizophrenia suggests that Lactosucrose as a prebiotic could improve underweight accompanied by increased *Bifidobacterium* in fecal microbiota (128). However, there was report showing no difference in body weight before and after a supplementation of the resistant starch in individuals with schizophrenia (129). Further studies with adequate sample size are required to determine the potential effects of prebiotics on antipsychotic-induced weight gain and metabolic dysfunctions.

Synbiotics

Synbiotics are defined as "mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract of the host."(130) When prebiotics was introduced, researchers speculated the potential benefits if prebiotics combined with probiotics to form what then defined as synbiotics (131). Prebiotics are indigestible foods such as dietary fibers that have a beneficial effect on the microbiome for the host, and probiotics are live microbes that have a positive impact on host health when ingested in adequate quantity (47). Most human interventions of synbiotics show a beneficial effect on glucose and insulin metabolism, however, there is only very limited number of researches discussing the impact in clinical practice (132). As far as we knew, currently there is no research about the potential effect of synbiotics on antipsychotic-induced weight gain or metabolic dysfunction.

Since recent studies have indicated that gut microbiota has played an important role in individuals' health and diseases, especially metabolic dysfunction and obesity (133), it would be of interest to discover new therapeutics to treat or prevent obesity and related metabolic disorders by a modulation of the gut microbiota to mimic that found in healthy non-obese individuals. So far there have been a few published animal studies (Table 2) and clinical trials (Table 3**)** on prebiotic and probiotic supplements in individuals with schizophrenia.

CONCLUSION AND FUTURE DIRECTIONS

In this paper, we provide a summary of the recent studies of the gut microbiota with psychiatric disorders and antipsychotic-induced metabolic dysfunction. Bidirectional communication between the brain and the gut has recently been recognized. Patients with neuropsychiatric disorders such as schizophrenia, bipolar disorder, ASD, and major depressive disorder have different patterns of altered gut microbiota composition compared with healthy controls. It is critical to determine the role and elucidate possible mechanism of microbiota in the developing neuropsychiatric disorders, with advanced study design and adequate power. The development in sequencing technology and bioinfor-

matics could allow us to conduct an in-depth investigation of brain and the gut.

While the mechanism has yet to be elucidated, interventional study can help assess the benefit and safety of prebiotics and probiotics and provide causal evidence for the effective response. Studies have shown effects of prebiotics or probiotics on obesity or metabolic disturbance, but few have examined the impact of probiotics in antipsychotic-induced weight gain and metabolic dysfunction. In addition, understanding the mechanism of the effective response would help discover novel therapeutics.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this paper.

ACKNOWLDGEMENTS

The National Key R&D Program of China (Grant No. 2016-YFC1306900) and the National Natural Science Foundation of China (Grant No.81622018) supported the research.

Table 2. Animal studies of prebiotic or probiotic supplements and antipsychotics

Author	Species	N	Intervention	Result	Conclusion
Dhaliwal N,(113), 2019	Female Swiss albino LACA mice	20	Randomized into four groups: -Control -Olanzapine+VSL#3 -Olanzapine -VSL#3 Olanzapine (3 mg/kg, p.o) once daily for 28 days. Probiotic mixture VSL#3 ($20*10^9$ CFU/day, p.o) once daily for 28 days.	VSL#3 administration attenuate OLZ-induced body weight gain, uterine fat deposition, impaired glucose tolerance, and insulin resistance. Olanzapine treatment decreased inflammatory markers, abolished oxidative stress in vWAT, and prevented shifts in gut microbiota abundance levels	VSL#3 via its ability to manipulate gut microbiome confers beneficial metabolic effects and represent a novel therapeutics for reversing antipsychotic-induced metabolic dysfunction
Kao A.C (125), 2018	Female adult Sprague-Dawley rats	24	Randomized into four groups: -saline/water, -B-GOS®/saline, -water/ olanzapine, -B-GOS®/olanzapine. rats were given water or water plus B-GOS® (0.5 g/kg/day) for 1 week, followed by a 2-week, daily intraperitoneal injection of olanzapine (10 mg/kg) or saline, during which water or B-GOS® administration continued.	B-GOS® feeding attenuated olanzapine-induced weight gain without influencing the reduction of central 5-HT2AR levels. Olanzapine increased levels of GluN1 in the frontal cortex and GluN1 mRNA expression in CA3 with the presence of B-GOS®, Olanzapine alone or with B-GOS® did not affect the abundance of some specific genera of enteric bacteria, while B-GOS® alone had some notable effects.	B-GOS® reduced weight gain when adjunctively with second-generation antipsychotic drugs, without affecting their central molecular actions.
Kao A.C (126), 2019	Female adult Sprague-Dawley rats, 220-250g (6-8weeks),	48	Randomized to four groups: -saline/water (n=6), -acetate/saline (n= 6), -water/olanzapine (n = 6), -acetate/olanzapine (n = 6) Sodium acetate was administered to rats via their drinking water at a dose of 500mg/kg/day; Olanzapine (10 mg/kg) was intraperitoneal injected daily.	Ingestion of sodium acetate inhibited HAT activity in brain, and increased hippocampal levels of HDAC-3 and HDAC-4 mRNAs. Acetate administration did not affect olanzapine-mediated weight gain, alter the expression of NMDAR subunits, or influence abundance of fecal microbial genera.	B-GOS®-mediated benefits on central and peripheral physiology are not entirely, if at all, mediated by acetate produced from fermentation of B-GOS.

Table 3. Clinical trials of probiotic or prebiotic supplements in patients with Schizophrenia

Author, Year	Design	Subjects	Intervention	Control	Results	Conclusions
Okubo R (110), 2018	Open-label single-arm study	N=30, outpatient with schizophrenia, BPRS anxiety and depressive symptoms>=10 points, aged >20 years	Probiotics: 2 sachets of B. breve A-1 at 5.0×10^{10} colony-forming units each per day for first 4 and evaluated 4 weeks after.	No control	HADS was improved at 4 weeks but not at 8 weeks, PANSS anxiety/depression score was improved at both 4 and 8 weeks.	B. breve A-1 improves anxiety and depressive symptoms in patients with schizophrenia, which is related to TRANCE and IL-22.
Nagamine T (128),2018	Open-label single-arm study	N=16, underweight Japanese schizophrenia inpatients	Prebiotics: 3.0 g/day 4G-β-D-galactosylsucrose as a food supplement for 6 months.	No control	Bodyweight and BMI Blood glucose or triglyceride level	4G-β-Dgalactosylsucrose had a weight gain effect in underweight schizophrenia inpatients accompanied by a bifidobacteria-enhancing result.
Kao KC (127),2019	Randomized double-blind placebo-controlled crossover trial	N=39, outpatient with psychosis on stable antipsychotic medication, global cognitive score was 0.5 standard deviations below healthy average	Prebiotics: One sachet (3.5g) of galactooliogosaccharides (B-GOS®) daily during breakfast for 12 weeks	Maltodextrin (3.5g) daily during breakfast for 12 weeks	Composite T-score (Cohen'sd=0.443), Subtests of executive function, mood, anthropometric indices or serum levels of acetate, CRP and IL6	Consumption of the prebiotic B-GOS® confers significant cognitive benefits but did not affect weight, BMI, central adiposity or circulating candidate metabolic/immune markers
Dickerson FB (52),2014	Randomized double-blind placebo-controlled trial	N=65, outpatients with schizophrenia with at least moderately severe psychotic symptoms	Probiotics: 2-week placebo run-in period, 14 weeks adjunctive probiotic tablet supplement once per day	Control tablets identical in appearance for once per day	No significant difference in PANSS total symptom score	Probiotic supplementation may help prevent a common somatic symptom associated with schizophrenia
Severance EG (111), 2017	Randomized, placebo-controlled pilot study	N=56, outpatients with schizophrenia with at least moderately severe psychotic symptoms	Probiotics: 2 weeks placebo run-in period, and 14 weeks adjunctive probiotic tablet supplement once per day	Control tablets identical in appearance for once per day	C. albicans IgG levels reduced in male schizophrenia with probiotics, improved bowel function	Administration of probiotics may help normalize C. albicans antibody levels and associated gut discomfort in male individuals
Ghaderi A (48), 2019	Randomized, double-blind, placebo-controlled trial	N=60, schizophrenia PANSS score 55 or higher, treated with chlorpromazine and anticholinergic	Probiotics: 50,000 IU of vitamin D3 every 2 weeks plus 8 × 109 CFU/day of probiotics for 12 weeks	Capsules in a similar shape and packaging as vitamin D and probiotics for 12 weeks	25-OH-vitamin D levels, PANSS scores; Plasma TAC and decreased MDA; FPG, serum insulin concentrations, HOMA-IR, triglycerides, cholesterol, HDL	Probiotic and vitamin D for 12 weeks had impacts effects on the general and total PANSS scores, as well as other metabolic profiles.
Tomasik J (112),2015	Randomized double-blind placebo-controlled trial	N=65, outpatients with schizophrenia at least moderately severe psychotic symptoms	Probiotics: 2 weeks placebo run-in period, and 14 weeks adjunctive probiotic supplement daily	Control tablets identical in appearance for once per day	levels of MCP-1, BDNF, T-cell-specific protein RANTES	Probiotics have immunomodulatory effects in schizophrenia patients and improve bowel functioning through IL-17-related immune responses.
Flowers SA (129),2019	Cross-sectional cohort study	N=37, adults with a diagnosis of bipolar disorder or schizophrenia who were treated with an AAP or lithium and/or lamotrigine	Prebiotics: raw, unmodified potato starch (resistant starch) daily (48 g/day)	No control	Actinobacteria phylum increased with resistant starch administration. Increase in the OTU corresponding to resistant starch degrading. Inverse Simpson Diversity Index.	Resistant starch supplements increased organisms associated with starch degradation and SCFA.

HADS, Hospital Anxiety and Depression Scale.

REFERENCES

1. Whitman WB, Coleman DC, Wiebe WJ. Prokaryotes: the unseen majority. Proc Natl Acad Sci U S A. 1998; 95(12): 6578-83.
2. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an inte-grative view. Cell. 2012;148(6):1258-70.
3. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science (New York, NY). 2005;308(5728):1635-8.
4. Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiological revi-ews. 2010;90(3): 859-904.
5. Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, et al. Metagenomic analysis of the human distal gut microbiome. Science (New York, NY). 2006; 312(5778): 1355-9.
6. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The Central Nervous System and the Gut Micro-biome. Cell. 2016;167(4):915-32.
7. Kelly JR, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbiota axis: challenges for translation in psychiatry. Ann Epidemiol. 2016;26(5):366-72.
8. Gacias M, Gaspari S, Santos PM, Tamburini S, Andrade M, Zhang F, et al. Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. Elife. 2016;5.
9. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8(2): 114-26.
10. Cohen D, De Hert M. Endogenic and iatrogenic diabetes mellitus in drug-naive schizophrenia: the role of olanzapine and its place in the psychopharmacological treatment algorithm. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2011;36(11): 2368-9.
11. Covell NH, Weissman EM, Schell B, McCorkle BH, Summerfelt WT, Weiden PJ, et al. Distress with medication side effects among persons with severe mental illness. Adm Policy Ment Health. 2007; 34(5):435-42.
12. Vancampfort D, Sweers K, Probst M, Maurissen K, Knapen J, Minguet P, et al. Association of the meta-bolic syndrome with physical activity performance in patients with schizophrenia. Diabetes & metabolism. 2011;37(4):318-23.
13. De Hert M, Peuskens B, van Winkel R, Kalnicka D, Hanssens L, Van Eyck D, et al. Body weight and self-esteem in patients with schizophrenia evaluated with B-WISE. Schizophrenia research. 2006;88(1-3):222-6.
14. Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res. 2004;66 (1):51-7.
15. Basson BR, Kinon BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. The Journal of clinical psychiatry. 2001;62(4):231-8.
16. Cortes B, Becker J, Mories Alvarez MT, Marcos AI, Molina V. Contribution of baseline body mass index and leptin serum level to the prediction of early weight gain with atypical antipsychotics in schizophrenia. Psychiatry Clin Neurosci. 2014;68(2):127-32.
17. Wampers M, Hanssens L, van Winkel R, Heald A, Collette J, Peuskens J, et al. Differential effects of olanzapine and risperidone on plasma adiponectin levels over time: results from a 3-month prospective open-label study. Eur Neuropsychopharmacol. 2012; 22(1):17-26.
18. Conde J, Scotece M, Gomez R, Lopez V, Gomez-Reino JJ, Lago F, et al. Adipokines: biofactors from white adipose tissue. A complex hub among inflammation, metabolism, and immunity. Biofactors. 2011;37 (6): 413-20.
19. Weston-Green K, Huang XF, Deng C. Alterations to melanocortinergic, GABAergic and cannabinoid neurotransmission associated with olanzapine-induced weight gain. PloS one. 2012;7(3):e33548.
20. Gothelf D, Falk B, Singer P, Kairi M, Phillip M, Zigel L, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. Am J Psychiatry. 2002; 159(6):1055-7.
21. Cuerda C, Velasco C, Merchan-Naranjo J, Garcia-Peris P, Arango C. The effects of second-generation antipsychotics on food intake, resting energy expenditure and physical activity. Eur J Clin Nutr. 2014; 68(2): 146-52.
22. Cuerda C, Merchan-Naranjo J, Velasco C, Gutierrez A, Leiva M, de Castro MJ, et al. Influence of resting energy expenditure on weight gain in adolescents taking second-generation antipsychotics. Clin Nutr. 2011;30 (5):616-23.
23. Sharpe JK, Stedman TJ, Byrne NM, Hills AP. Low-fat oxidation may be a factor in obesity among men with schizophrenia. Acta Psychiatr Scand. 2009;119 (6): 451-6.
24. Chen DC, Du XD, Yin GZ, Yang KB, Nie Y, Wang N, et al. Impaired glucose tolerance in first-episode drug-naive patients with schizophrenia: relationships with clinical phenotypes and cognitive deficits. Psychol Med. 2016;46 (15): 3219-30.
25. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018;555 (7698):623-8.
26. Komaroff AL. The Microbiome and Risk for Obesity and Diabetes. Jama. 2017;317(4):355-6.
27. Xu R, Wu B, Liang J, He F, Gu W, Li K, et al. Altered gut microbiota and mucosal immunity in patients with schizophrenia. Brain, behavior, and immunity. 2019.
28. Li K, Hu Z, Ou J, K X. Altered Gut Microbiome in Autism Spectrum Disorder: Potential Mechanism and Implications for Clinical Intervention. Glob Clin Transl Res. 2019;1(1):45-52.
29. Evans SJ, Bassis CM, Hein R, Assari S, Flowers SA, Kelly MB, et al. The gut microbiome composition associates with bipolar disorder and illness severity. J Psychiatr Res. 2017;87:23-9.
30. Kelly JR, Borre Y, C OB, Patterson E, El Aidy S, Deane J, et al. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. Journal of psychiatric research. 2016;82:109-18.
31. Zhnag F, Zhao J. China is prepared to fight against emerging mental health disorders. International Journal of Emergency Mental Health. 2015;17(3):628-34.
32. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The Microbiota-Gut-Brain Axis. Physiological reviews. 2019;99 (4): 1877-2013.
33. Erny D, Hrabe de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nature neuroscience. 2015;18(7): 965-77.
34. Evrensel A, Ceylan ME. The Gut-Brain Axis: The Missing Link in Depression. Clinical psychopharmacology and neuroscience: the official scientific journal of the Korean College of Neuropsychopharmacology. 2015;13(3):239-44.
35. Sun M, Wu W, Liu Z, Cong Y. Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. J Gastroenterol. 2017;52(1):1-8.
36. Sherwin E, Sandhu KV, Dinan TG, Cryan JF. May the Force Be With You: The Light and Dark Sides of the Microbiota-Gut-Brain Axis in Neuropsychiatry. CNS Drugs.2016;30 (11): 1019-41.
37. Orikasa S, Nabeshima K, Iwabuchi N, Xiao JZ. Effect of

repeated oral administration of Bifidobacterium longum BB536 on apomorphine-induced rearing behavior in mice. Biosci Microbiota Food Health. 2016;35(3):141-5.
38. Chen H, Nwe PK, Yang Y, Rosen CE, Bielecka AA, Kuchroo M, et al. A Forward Chemical Genetic Screen Reveals Gut Microbiota Metabolites That Modulate Host Physiology. Cell. 2019; 177(5):1217-31 e18.
39. Fulling C, Dinan TG, Cryan JF. Gut Microbe to Brain Signaling: What Happens in Vagus. Neuron. 2019; 101(6):998-1002.
40. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2011; 108 (38): 16050-5.
41. Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, et al. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. Am J Clin Nutr. 2009;90(5):1236-43.
42. Sun M, Wu W, Chen L, Yang W, Huang X, Ma C, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. Nat Commun. 2018;9(1):3555.
43. Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, Maeda T, et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nat Commun. 2013;4:1829.
44. Fadgyas-Stanculete M, Buga AM, Popa-Wagner A, Dumitrascu DL. The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations. J Mol Psychiatry. 2014;2(1):4.
45. Severance EG, Prandovszky E, Castiglione J, Yolken RH. Gastroenterology issues in schizophrenia: why the gut matters. Curr Psychiatry Rep. 2015;17(5):27.
46. Kelly JR, Minuto C, Cryan JF, Clarke G, Dinan TG. Cross Talk: The Microbiota and Neurodevelopmental Disorders. Frontiers in neuroscience. 2017;11:490.
47. Bastiaanssen TFS, Cowan CSM, Claesson MJ, Dinan TG, Cryan JF. Making Sense of the Microbiome in Psychiatry. Int J Neuropsychopharmacol. 2019;22 (1):37-52.
48. van Kesteren CF, Gremmels H, de Witte LD, Hol EM, Van Gool AR, Falkai PG, et al. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl Psychiatry. 2017;7(3):e1075.
49. Schwarz E, Maukonen J, Hyytiainen T, Kieseppa T, Oresic M, Sabunciyan S, et al. Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. Schizophr Res. 2018;192: 398-403.
50. Zhu F, Ju Y, Wang W, Wang Q, Guo R, Ma Q, et al. Identification of gut microbiome markers for schizophrenia delineates a potential role of Streptococcus. bioRxiv. 2019:774265.
51. Zheng P, Zeng B, Liu M, Chen J, Pan J, Han Y, et al. The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. Sci Adv. 2019;5(2):eaau8317.
52. Dickerson FB, Stallings C, Origoni A, Katsafanas E, Savage CL, Schweinfurth LA, et al. Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: a randomized, placebo-controlled trial. Prim Care Companion CNS Disord. 2014;16(1).
53. Ng QX, Soh AYS, Venkatanarayanan N, Ho CYX, Lim DY, Yeo WS. A Systematic Review of the Effect of Probiotic Supplementation on Schizophrenia Symptoms. Neuropsychobiology. 2019; 78(1):1-6.
54. Yolken R, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C, et al. Individuals hospitalized with acute mania have increased exposure to antimicrobial medications. Bipolar Disord. 2016;18 (5): 404-9.
55. Dickerson F, Severance E, Yolken R. The microbiome, immunity, and schizophrenia and bipolar disorder. Brain Behav Immun. 2017;62:46-52.
56. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun. 2015;48:186-94.
57. Dickerson F, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C, et al. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial. Bipolar Disord. 2018; 20(7): 614-21.
58. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019;4(4):623-32.
59. Keller J, Gomez R, Williams G, Lembke A, Lazzeroni L, Murphy GM, Jr., et al. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry. 2017;22 (4): 527-36.
60. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22-34.
61. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol. 2004;558(Pt 1):263-75.
62. Bercik P, Verdu EF, Foster JA, Macri J, Potter M, Huang X, et al. Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. Gastroenterology. 2010;139(6):2102-12 e1.
63. Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2011;23 (3):255-64, e119.
64. Foster JA, McVey Neufeld K-A. Gut–brain axis: how the microbiome influences anxiety and depression. Trends in Neurosciences. 2013;36(5):305-12.
65. Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol Psychiatry. 2016;21(6):786-96.
66. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. Neuroscience. 2010;170(4):1179-88.
67. Li K, Hu Z, ou J, Xia K. Altered Gut Microbiome in Autism Spectrum Disorder: Potential Mechanism and Implications for Clinical Intervention. Global Clinical and Translational Research. 2019:45-52.
68. Ou J, Shen Y, Li Y, Xun G, Liu H, He Y, et al. Prenatal Environment and Perinatal Factors Associated with Autism Spectrum Disorder. Glob Clin Transl Res. 2019;1(3):100-8.
69. Strati F, Cavalieri D, Albanese D, De Felice C, Donati C, Hayek J, et al. New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome. 2017;5(1):24.
70. Ata H, Ekstrom TL, Martinez-Galvez G, Mann CM, Dvornikov AV, Schaefbauer KJ, et al. Robust activation of microhomology-mediated end joining for precision gene editing applications. PLoS Genet. 2018; 14(9):e1007652.
71. Liu F, Horton-Sparks K, Hull V, Li RW, Martinez-Cerdeno V. The valproic acid rat model of autism presents with gut bacterial dysbiosis similar to that in human autism. Mol Autism. 2018;9:61.
72. Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, et al. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. Cell. 2019;177 (6): 1600-18 e17.
73. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino

JF, Costa-Mattioli M. Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring. Cell. 2016;165(7): 1762-75.
74. Xu M, Xu X, Li J, Li F. Association Between Gut Microbiota and Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Front Psychiatry. 2019;10:473.
75. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394(10202):939-51.
76. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One. 2014;9(4):e94112.
77. Galling B, Roldan A, Nielsen RE, Nielsen J, Gerhard T, Carbon M, et al. Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2016;73(3):247-59.
78. Mitchell AJ, Vancampfort D, De Herdt A, Yu W, De Hert M. Is the Prevalence of Metabolic Syndrome and Metabolic Abnormalities Increased in Early Schizophrenia? A Comparative Meta-Analysis of First Episode, Untreated and Treated Patients. Schizophrenia bulletin. 2013;39(2):295-305.
79. Skonieczna-Zydecka K, Loniewski I, Misera A, Stachowska E, Maciejewska D, Marlicz W, et al. Second-generation antipsychotics and metabolism alterations: a systematic review of the role of the gut microbiome. Psychopharmacology. 2018.
80. Singh R, Bansal Y, Medhi B, Kuhad A. Antipsychotics-induced metabolic alterations: Recounting the mechanistic insights, therapeutic targets and pharmacological alternatives. European journal of pharmacology. 2019;844:231-40.
81. Davey KJ, O'Mahony SM, Schellekens H, O'Sullivan O, Bienenstock J, Cotter PD, et al. Gender-dependent consequences of chronic olanzapine in the rat: effects on body weight, inflammatory, metabolic and microbiota parameters. Psychopharmacology (Berl). 2012; 221(1):155-69.
82. Davey KJ, Cotter PD, O'Sullivan O, Crispie F, Dinan TG, Cryan JF, et al. Antipsychotics and the gut microbiome: olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat. Translational psychiatry. 2013; 3:e309.
83. Morgan AP, Crowley JJ, Nonneman RJ, Quackenbush CR, Miller CN, Ryan AK, et al. The antipsychotic olanzapine interacts with the gut microbiome to cause weight gain in mouse. PloS one. 2014;9 (12): e115225.
84. Bahra SM, Weidemann BJ, Castro AN, Walsh JW, deLeon O, Burnett CM, et al. Risperidone-induced weight gain is mediated through shifts in the gut microbiome and suppression of energy expenditure. EBioMedicine. 2015; 2(11):1725-34.
85. Bahr SM, Tyler BC, Wooldridge N, Butcher BD, Burns TL, Teesch LM, et al. Use of the second-generation antipsychotic, risperidone, and secondary weight gain are associated with an altered gut microbiota in children. Transl Psychiatry. 2015; 5:e652.
86. Yuan X, Zhang P, Wang Y, Liu Y, Li X, Kumar BU, et al. Changes in metabolism and microbiota after 24-week risperidone treatment in drug naive, normal weight patients with first episode schizophrenia. Schizophrenia research. 2018;201: 299-306.
87. Flowers SA, Evans SJ, Ward KM, McInnis MG, Ellingrod VL. Interaction Between Atypical Antipsychotics and the Gut Microbiome in a Bipolar Disease Cohort. Pharmacotherapy. 2017;37(3):261-7.
88. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353 (12):1209-23.
89. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature reviews Gastroenterology & hepatology. 2017; 14(8):491-502.
90. FAO/WHO. Health and Nutrition Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. 2002. Report No.: ISSN 0254-4725.
91. Williams NT. Probiotics. Am J Health Syst Pharm. 2010;67 (6):449-58.
92. Mombelli B, Gismondo M. The use of probiotics in medical practice. International journal of antimicrobial agents. 2001; 16:531-6.
93. Markowiak P, Slizewska K. Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. Nutrients. 2017;9(9).
94. Fijan S. Microorganisms with claimed probiotic properties: an overview of recent literature. Int J Environ Res Public Health. 2014;11(5):4745-67.
95. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nature medicine. 2019;25(5):716-29.
96. Kang JH, Yun SI, Park HO. Effects of Lactobacillus gasseri BNR17 on body weight and adipose tissue mass in diet-induced overweight rats. Journal of microbiology (Seoul, Korea). 2010;48(5):712-4.
97. Lee HY, Park JH, Seok SH, Baek MW, Kim DJ, Lee KE, et al. Human originated bacteria, Lactobacillus rhamnosus PL60, produce conjugated linoleic acid and show antiobesity effects in diet-induced obese mice. Biochimica et biophysica acta. 2006;1761 (7): 736-44.
98. Chen JJ, Wang R, Li XF, Wang RL. Bifidobacterium longum supplementation improved high-fat-fed-induced metabolic syndrome and promoted intestinal Reg I gene expression. Experimental biology and medicine (Maywood, NJ). 2011; 236 (7):823-31.
99. Chen J, Wang R, Li XF, Wang RL. Bifidobacterium adolescentis supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. The British journal of nutrition. 2012; 107(10):1429-34.
100. Ejtahed H-S, Angoorani P, Soroush A-R, Atlasi R, Hasani-Ranjbar S, Mortazavian AM, et al. Probiotics supplementation for the obesity management; A systematic review of animal studies and clinical trials. Journal of functional foods. 2019; 52:228-42.
101. Luoto R, Kalliomaki M, Laitinen K, Isolauri E. The impact of perinatal probiotic intervention on the development of overweight and obesity: followup study from birth to 10 years. International journal of obesity(2005). 2010;34 (10):1531-7.
102. Kadooka Y, Sato M, Imaizumi K, Ogawa A, Ikuyama K, Akai Y, et al. Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. European journal of clinical nutrition. 2010; 64(6):636-43.
103. Bernini LJ, Simao AN, Alfieri DF, Lozovoy MA, Mari NL, de Souza CH, et al. Beneficial effects of Bifidobacterium lactis on lipid profile and cytokines in patients with metabolic syndrome: A randomized trial. Effects of probiotics on metabolic syndrome. Nutrition (Burbank, Los Angeles County, Calif). 2016;32(6): 716-9.
104. Chang BJ, Park SU, Jang YS, Ko SH, Joo NM, Kim SI, et al. Effect of functional yogurt NY-YP901 in improving the trait of metabolic syndrome. European journal of clinical nutrition. 2011; 65(11):1250-5.
105. Gauffin Cano P, Santacruz A, Moya A, Sanz Y. Bacteroides uniformis CECT 7771 ameliorates metabolic and immunological dysfunction in mice with high-fat-diet induced obesity. PloS one. 2012;7 (7): e41079.
106. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, et al. Akkermansia muciniphila and improved

metabolic health during a dietary intervention in obesity: relationship with gut micro-biome richness and ecology. Gut. 2016;65 (3):426-36.
107. Andersson U, Branning C, Ahrne S, Molin G, Alenfall J, Onning G, et al. Probiotics lower plasma glucose in the high-fat fed C57BL/6J mouse. Beneficial microbes. 2010;1(2):189-96.
108. Bomhof MR, Saha DC, Reid DT, Paul HA, Reimer RA. Combined effects of oligofructose and Bifidobacterium animalis on gut microbiota and glycemia in obese rats. Obesity (Silver Spring, Md). 2014;22 (3): 763-71.
109. Yin YN, Yu QF, Fu N, Liu XW, Lu FG. Effects of four Bifidobacteria on obesity in high-fat diet induced rats. World journal of gastroenterology. 2010;16(27): 3394-401.
110. Okubo R, Koga M, Katsumata N, Odamaki T, Matsuyama S, Oka M, et al. Effect of bifidobacterium breve A-1 on anxiety and depressive symptoms in schizophrenia: A proof-of-concept study. J Affect Disord. 2019;245:377-85.
111. Severance EG, Gressitt KL, Stallings CR, Katsafanas E, Schweinfurth LA, Savage CLG, et al. Probiotic normalization of Candida albicans in schizophrenia: A randomized, placebo-controlled, longitudinal pilot study. Brain Behav Immun. 2017;62:41-5.
112. Tomasik J, Yolken RH, Bahn S, Dickerson FB. Immunomodulatory Effects of Probiotic Supplementation in Schizophrenia Patients: A Randomized, Placebo-Controlled Trial. Biomark Insights. 2015;10: 47-54.
113. Dhaliwal N, Dhaliwal J, Singh DP, Kondepudi KK, Bishnoi M, Chopra K. The Probiotic Mixture VSL#3 Reverses Olanzapine-Induced Metabolic Dysfunction in Mice. Methods Mol Biol. 2019;2011:531-44.
114. Ghaderi A, Banafshe HR, Mirhosseini N, Moradi M, Karimi MA, Mehrzad F, et al. Clinical and metabolic response to vitamin D plus probiotic in schizophrenia patients. BMC Psychiatry. 2019;19 (1):77.
115. Bindels LB, Delzenne NM, Cani PD, Walter J. Towards a more comprehensive concept for prebiotics. Nature reviews Gastroenterology & hepatology. 2015;12(5): 303-10.
116. Parnell JA, Reimer RA. Weight loss during oligo-fructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. The American Journal of Clinical Nutrition. 2009;89(6):1751-9.
117. Edrisi F, Salehi M, Ahmadi A, Fararoei M, Rusta F, Mahmoodianfard S. Effects of supplementation with rice husk powder and rice bran on inflammatory factors in overweight and obese adults following an energyrestricted diet: a randomized controlled trial. European journal of nutrition. 2018; 57(2):833-43.
118. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. Int J Food Sci Nutr. 2014;65(1):117-23.
119. de Luis DA, de la Fuente B, Izaola O, Conde R, Gutierrez S, Morillo M, et al. Double blind randomized clinical trial contrlled by placebo with an alpha linoleic acid and prebiotic enriched cookie on risk cardiovascular factor in obese patients. Nutr Hosp. 2011;26(4):827-33.
120. Seidel C, Boehm V, Vogelsang H, Wagner A, Persin C, Glei M, et al. Influence of prebiotics and antioxidants in bread on the immune system, antioxidative status and antioxidative capacity in male smokers and nonsmokers. Br J Nutr. 2007; 97(2): 349-56.
121. Nicolucci AC, Hume MP, Martinez I, Mayengbam S, Walter J, Reimer RA. Prebiotics Reduce Body Fat and Alter Intestinal Microbiota in Children Who Are Overweight or With Obesity. Gastroenterology. 2017; 153(3):711-22.
122. Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Neyrinck AM, et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. Diabetes. 2011;60(11):2775-86.
123. Nihei N, Okamoto H, Furune T, Ikuta N, Sasaki K, Rimbach G, et al. Dietary alpha-cyclodextrin modifies gut microbiota and reduces fat accumulation in high-fat-diet-fed obese mice. BioFactors (Oxford, England). 2018.
124. Hamilton MK, Ronveaux CC, Rust BM, Newman JW, Hawley M, Barile D, et al. Prebiotic milk oligosaccharides prevent development of obese phenotype, impairment of gut permeability, and microbial dysbiosis in high fat-fed mice. American journal of physiology Gastrointestinal and liver physiology. 2017;312 (5):G474-g87.
125. Kao AC, Spitzer S, Anthony DC, Lennox B, Burnet PWJ. Prebiotic attenuation of olanzapine-induced weight gain in rats: analysis of central and peripheral biomarkers and gut microbiota. Transl Psychiatry. 2018; 8(1):66.
126. Kao AC, Chan KW, Anthony DC, Lennox BR, Burnet PW. Prebiotic reduction of brain histone deacetylase (HDAC) activity and olanzapine-mediated weight gain in rats, are acetate independent. Neuropharmacology. 2019;150:184-91.
127. Kao AC, Safarikova J, Marquardt T, Mullins B, Lennox BR, Burnet PWJ. Procognitive effect of a prebiotic in psychosis: A double blind placebo controlled crossover study. Schizophrenia research. 2019;208:460-1.
128. Nagamine T, Ido Y, Nakamura M, Okamura T. 4(G)-beta-D-galactosylsucrose as a prebiotics may improve underweight in inpatients with schizophrenia. Bioscience of microbiota, food and health. 2018; 37(2):45-7.
129. Flowers SA, Baxter NT, Ward KM, Kraal AZ, McInnis MG, Schmidt TM, et al. Effects of Atypical Antipsychotic Treatment and Resistant Starch Supplementation on Gut Microbiome Composition in a Cohort of Patients with Bipolar Disorder or Schizophrenia. Pharmacotherapy. 2019;39 (2): 161-70.
130. Andersson H, Asp N-G, Bruce Å, Roos S, Wadström T, Wold AE. Health effects of probiotics and prebiotics A literature review on human studies. Food and nutrition research. 2001;45(1): 58-75. DOI:10.3402 /fnr. v45i0.1790
131. Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics- a review. Journal of food science and technology. 2015;52(12):7577-87.
132. Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, synbiotics and insulin sensitivity. Nutrition research reviews. 2018; 31(1):35-51.
133. Villanueva-Millan MJ, Perez-Matute P, Oteo JA. Gut microbiota: a key player in health and disease. A review focused on obesity. Journal of physiology and biochemistry. 2015;71(3): 509-25.

How to cite this article:
Kang, DY, Li SJ, Liu CC, Wu RR. Gut microbiota and antipsychotics induced metabolic alteration. Glob Clin Transl Res. 2019; 1(4): 131-144. DOI:10.36316/gcatr.01.0020.