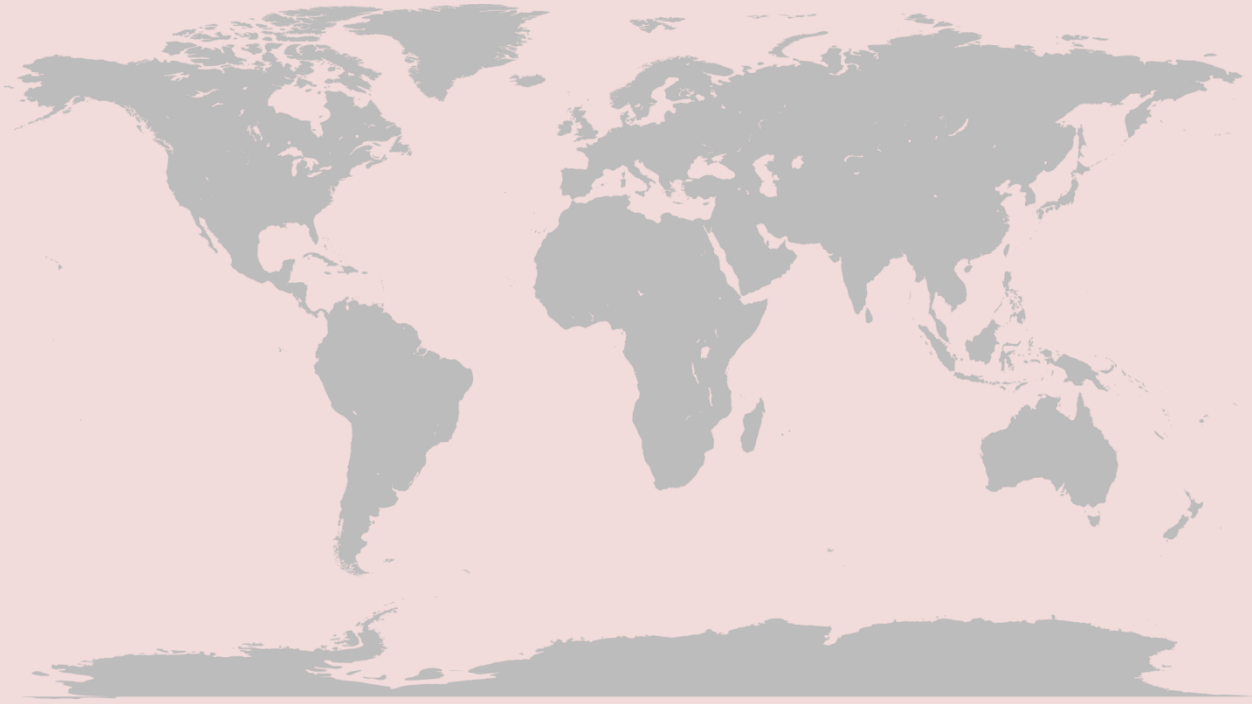
GCAT-R

ISSN 2641-7154 (Print)
ISSN 2643-8151 (Online)

Global Clinical And Translational Research

Toward an integration of genomic, environmental, and social medicine



Volume 1, Number 4

December 30, 2019

Editorial Office
P O Box 341126
Bethesda, MD
Email: journal@gcatresearch.com
Tel: 202-609-8812
Website: www.gcatresearch.com

Publisher
The journal of *Global Clinical and Translational Research* (GCAT-R) is published and printed quarterly by the Global Clinical and Translational Research Institute, Inc, MD, USA
Website: gcatreserach.org

GUIDE FOR AUTHORS

Aims and Scopes

Global Clinical and Translational Research is a new peer-reviewed, multidisciplinary scientific journal dedicated to publishing articles regarding all areas of clinical and translational research in humans or animals.

The journal aims to promote a unified platform on research communications for basic scientists, medical doctors, clinical and health professionals, social scientists and social workers to share the most recent advances in all areas of clinical and translational sciences.

The journal accepts original research articles, reviews, mini-reviews, correspondence, case reports, short notes, and rapid communications covering all aspects of clinical and translational research. Papers about novel applications of statistical methods or data science are also welcomed.

Specific fields of the papers to be published include but not limited to

- Clinical research in human or animals, including identification of genetic or molecular markers associated with diseases or traits that have clinical implications;
- Translational research that based on clinical research findings. For example, research findings provide evidence for health professionals to improve human health conditions (T1 translational research), and provide targets for basic scientists to study the biological mechanism (T2 translational research);
- Clinical trials to evaluate the effectiveness of treatment including pharmacological and non-pharmacological approach such as traditional Chinese medicine (TCM), with a molecular study to identify biomarkers that could be used to evaluate effectiveness;
- Methodology papers that improve study design, statistical analysis;
- Population-based survey on human health;
- Negative results (We also publish summary data of negative results);
- Clinical and translational research protocols.

Review process

All manuscripts are subject to peer review and are expected to meet standards of academic excellence. Upon submission, the Editorial Office will consult with associate editors to have a preliminary check on the manuscript submitted, and then decide to whether to send out for a peer review. All reviewers' identities will remain anonymous to the authors.

The journal implements a double-blinded peer review process, but the review can have access to the author information if they request and believe that could help evaluate the manuscript.

Other types of papers

Correspondence is directly related to methods and interpretation of data presented in the recent publication in our journal. While allowing to post comments on online, we also publish the correspondence as an e-content in our post categories. Commentaries and editorials are generally for invited only.

Format of manuscript

Title page

The following information should be included

- Paper title
- Full author names
- Affiliations for each author
- Email addresses and contact information on the corresponding author(s)

Abstract

Not exceed 200 words, should be structured as below for all research articles; other articles should use non-structured abstract.

- Background:
- Methods:
- Results:
- Discussion:
- Conclusion:

Keywords (3-5 keywords)

Maintext

Introduction. This section should be succinct, with no sub-headings.

Methods. Should contain all procedures with enough details so that they can be repeated.

Results. Both descriptive and analytic results.

Discussions. This should describe the implications and significance of the findings, also highlighting the limitations of the study.

Conclusion (optional).This should clearly explain the main conclusions of the work highlighting its importance and relevance.

Conflict of interest.

If there is no conflict of interest, authors should state, "The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper."

Acknowledgments (optional, including funding support if available).

References

Authors are responsible for ensuring that the information in each reference is complete and accurate. All references must be numbered consecutively and citations of references in the text should be identified using numbers in square brackets (e.g., "as discussed by Smith [1]"; "as discussed elsewhere [3, 4]"). All references should be cited within the text; otherwise, these references will be automatically removed. GCAT-R uses "Vancouver" style, as outlined in the ICMJE sample references (https://www.nlm.nih.gov/bsd/uniform _requirements.html).

Supplementary material

Supplementary material, related to the work but not critical to the publication, is encouraged and made available as e-content.

Preparation of Figures

Upon submission of an article, authors are supposed to include all figures and tables in the Word file of the manuscript. Figures and tables should not be submitted in separate files. If the article is accepted, authors will be asked to provide the source files of the figures. Each figure should be supplied in a separate electronic file. All figures should be cited in the paper in consecutive order. Figures should be supplied in bitmap formats (Photoshop, TIFF, GIF, JPEG, etc.). Bitmap images should be of 300 dpi resolution at least unless the resolution is intentionally set to a lower level for scientific reasons. If a bitmap image has labels, the image and labels should be embedded in separate layers.

Preparation of Tables

Tables should be cited consecutively in the text. Every table must have a descriptive title and if numerical measurements are given, the units should be included in the column heading. Vertical rules should not be used. A tab-le should be well annotated and easy to read and interpret with little reference to the text.

Proofs and Print

The corresponding author will receive proofs by email. Some editorial modification will be made after the manuscript is accepted, so it is important to check proofs carefully. Corrected proofs must be returned to the publisher within 48 hours of receipt. The publisher will do everything possible to ensure prompt publication. It will, therefore, be appreciated if the manuscripts and figures conform from the outset to the style of the journal.

Copyright and Permission

When publishing in *Global Clinical and Translational Research*, the author(s) agree to assign the copyright of the article to the journal. We request that permission should be sought from the journal as the rights holder to produce any substantial part of copyrighted work. To obtain permission, please contact the editorial office as below.

Disclosure Policy

A competing interest exists when professional judgment concerning the validity of research is influenced by a secondary interest, such as financial gain. We require that our authors reveal any possible conflict of interest in their submitted manuscripts.

Clinical Studies

Global Clinical and Translational Research aims to comply with the recommendations of the International Committee of Medical Journal Editors (ICMJE) on trials registration. Therefore, authors are requested to register the clinical trial presented in the manuscript in a public trials registry and include the trial registration number at the end of the abstract. Trials must be registered prospectively before patient recruitment has begun. We promote transparency in clinical trial reporting.

In addition, the journal endorses the Principles and Guidelines for Reporting Preclinical Research by the National Institutes of Health, which a considerable number of journals have agreed to endorse (https://www.nih.gov/researc-h-training/rigor-reproducibility/principles-guidelines-re-porting-preclinical-research). The journal also promotes the core set of standards for rigorous reporting of study design (Adapted from Landis et al., Nature 2012).

CONTENTS

Article

Effects of Antipsychotic Treatment on S100B and Oxidative Stress in Patients with Schizophrenia

Xuan Wang[1], Yun Bian[1], Lei Liu[1], Yaxue Wu[1], FudeYang[1], Xianyun Li[1], Xiaole Han[1], Li Tian[2], Xingguang Luo[3], Song Chen[1], Zhiren Wang[1], Yunlong Tan[1], Yanli Li[1*]

[1]Center for Biological Psychiatry, Beijing Huilongguan Hospital, Changping district, Beijing, China; [2] The University of Helsinki, Neuroscience Center, Helsinki, Finland; [3]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Received August 15, 2019, Accepted September 7, 2019

ABSTRACT

Background: The study aimed to examine the antipsychotic treatment effect on the serum S100B and oxidative stress in patients with schizophrenia.

Methods: Subjects consisted of patients with schizophrenia of first-episode drug-naive and drug-free acute phases, and met the DSM-IV diagnostic criteria for schizophrenia. All patients were treated with risperidone for eight weeks. Positive and Negative Syndrome Scale (PANSS) was evaluated, and serum levels of S100B and parameters of oxidative stress including total oxidative status (TOS) and malondialdehyde (MDA) were measured before and after antipsychotic treatment. A general linear random-effect model was used for data analysis.

Results: Antipsychotic treatment with risperidone reduced the levels of S100B significantly in the first episode drug-naive patients with schizophrenia (Beta=24.89; p=0.0087) and marginally in the drug-free acute phase (Beta=15.65; p=0.093), no significant difference in the effect on S100B between patient groups (p=0.4785). In contrast, antipsychotic treatment increased the levels of MDA in drug-free acute phase schizophrenia (Beta=-6.55; p<0.0001) but not in the first episode drug-naive patients (beta=-0.57; p=0.6631); the effects on MDA were significantly different between two patient groups (p= 0.0020). We found that the levels of S100B were only associated with the PANSS negative score in the drug-free acute phase patients who were treated with antipsychotics.

Conclusion: Antipsychotic treatment with risperidone reduced the levels of S100B in first-episode, drug-naive patients with schizophrenia, but may increase the levels of MDA in drug-free acute phase schizophrenia.

KEYWORDS

Antipsychotic treatment, Risperidone, S100B, Oxidative stress, Schizophrenia

INTRODUCTION

Schizophrenia is a chronic mental disorder characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction (American Psychiatric Association, 2013). It has a lifetime prevalence of 0.6–1.9% across the world. (1). The etiology of schizophrenia is complex and believed to be multifactorial. Although several etiological hypotheses have been proposed, specific mechanisms are still not clearly understood. S100B is an attention-attracted pathophysiological factor that may be involved with schizophrenia(2), while the level of oxidative stress has also been a focus lately.

S100B is known to exert both paracrine and autocrine effects on neurons and glial cells(3) and has been postulated to either promote apoptotic phase or be released by astrocytes in an attempt to repair the neurodegenerative process(4). It has therefore been considered as a glial

*Correspondence to: Y Li, Email:wangjinghua6999@163.com

marker protein(5-7), even a biomarker of pathophysiology in schizophrenia. Because a risk haplotype at this gene has been identified for the risk of schizophrenia, an increase in *S100B* expression (8) suggests that S100B may be a causal link to schizophrenia(9). Recently, studies have shown that blood S100B levels in schizophrenia patients are inconsistent. Exploring the association between S100B and schizophrenia may have clinical significance.

Oxidative stress may play an essential role in the processes of many diseases, including schizophrenia. In healthy individuals, reactive oxygen species (ROS) and antioxidant system maintained at constant levels and is controlled by enzymatic and non-enzymatic antioxidants. Imbalance resulted from the excess of ROS production or decline in antioxidant levels could lead to a specific condition of oxidative stress that will cause oxidative damage, in particular in the brain, the organ that has high energy demand, a high concentration of polyunsaturated fatty acids and relatively low level of antioxidant defenses(10). Besides, oxidative stress could exert detrimental effects on socio- and neurocognitive abilities in patients with schizophrenia. So antioxidative treatment could be beneficial for individuals with schizophrenia. Oxidative stress is known to be one of the factors that lead to schizophrenia and can be used as a biomarker for disease treatment. Elevated levels of oxidative stress have been found in cerebrospinal fluid (CSF) and prefrontal cortex, in vivo. Several studies have documented the changes in oxidative parameters and antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase), but the results were not consistent, or even opposite directions have been reported (10-13).

Given the alterations in S100B and oxidative stress in patients with schizophrenia (14) as well as the intrinsic relationship between these parameters and psychopathology symptoms, it would be necessary to examine the antipsychotic effect on both S100B and Oxidant status and their association with psychopathology symptoms in patients with schizophrenia and to identify potential biomarkers for schizophrenia. The objective of the present study is to determine whether peripheral levels of S100B and oxidative stress parameters are different after treated with antipsychotics and whether the change in S100B and oxidative stress is associated with antipsychotic treatment response.

METHODS

Patients

All patients with schizophrenia were recruited from the inpatient units of Beijing HuiLongGuan Hospital, a Beijing-city owned psychiatric hospital and affiliated with Peking University. Patients comprised of first-episode drug-naive patients and drug-free acute phase patients, who met the DSM-IV criteria for schizophrenia. All patients had received dietetically balanced hospital meals. Exclusion criteria included the presence of any comorbid psychiatric disorder, severe systemic or neurologic illness, pregnancy, substance abuse or addiction, and structural brain changes apparent in magnetic resonance imaging (MRI) scan.

All subjects provided informed consents, and the study was approved by the Institutional Review Board of Beijing HuiLongGuan Hospital. All patients in both groups were treated with risperidone at the regular dose.

Clinical evaluation

Two psychiatrists, who had attended the same training session for PANSS evaluation, assessed the psycho-pathology symptoms in patients by using the Positive and Negative Syndrome Scale (PANSS). Repeated assessments of PANSS scores were performed at baseline and 8-week after antipsychotic treatment.

Measurement of oxidative stress and S100B

Venous blood was collected from the forearm vein of the patients before and 8-week after antipsychotic treatment. Plasma was separated, aliquoted, and stored at -70 °C before use. Biochemical analysis was performed by a technician who was blinded for the clinical status of the subjects. S100B and oxidative stress parameters including the total oxidants (TOS) and Malondialdehyde (MDA) were measured in the hospital laboratory center using commercially available ELISA kits from Leadman (Beijing Leadman Biotechnology Co. Ltd., Beijing, China) and an automatic biochemistry analyzer AU2700 (Olympus, Japan).

Statistical analysis

Demographic and clinical variables of patients were described by the first episode drug-naive and drug-free acute phase group. General linear regression analysis was performed to examine the effect of antipsychotic treatment on the levels of S100B and oxidative stress measured by TOS and MDA, and on the improvement of psychopathology, measured by the PANSS positive, negative and general psychopathology as well as the total score. The analysis was performed while adjusted for age, sex, education, duration of illness, and age of onset. SAS 9.4 was used for all statistical analysis. Two-tailed significance values were used, and the threshold level for significance was set at 0.05.

RESULTS

Demographics and baseline characterstics of patients with schizophrenia

Table 1 presents the demographics of the first episode drug-naive and drug-free acute phase patients with schizophrenia. The mean age was 27.83 (range from 19 to 52) and 26.34 (range from 18 to 48) years for the first episode drug-naive and drug-free acute phase groups, respectively, and 60% of the patients were males. The mean duration of illness was 28.16 months for the first episode drug-naive group and 48 months for drug-free acute phase patients. There was no significant difference in education, MCCB total score, or the age of onset ($p>0.05$).

Table 1. Demographics of the first episode drug-naive and drug-free acute phase patients with schizophrenia

	First episode drug-naive group (N=29)					Drug-free acute phase (N=29)				
	Mean	Med	SD	Min	Max	Mean	Med	SD	Min	Max
Age (year)	27.83	27	7.53	190	52	26.34	24	7.61	18	48
Sex (male=1)	0.59	1	0.50	0	1	0.62	1	0.49	0	1
Duration of illness(month)	28.16	20	27.87	1	98	48.00	36	49.11	3	193
Education (years)	12.66	12	2.92	4	19	12.48	12	2.31	8	16
Age of onset (years)	25.37	24	7.09	17	51.61	22.67	22	5.51	14	34..5
PANSS Positive	24.86	24	5.15	17	34	21.52	20	6.25	12	34
PANSS Negative	21.76	22	5.44	9	37	22.55	21	4.88	15	32
PANSS General	40.97	40	5.77	30	52	35.76	35	6.32	26	50
PANSS total score	87.59	87	11.70	68	117	79.83	79	13.00	59	106
MCCB total score	45.56	46	11.26	25	71	44.65	44	11.07	26	66
S100B	234.91	239.1	79.33	136.9	406.4	210.2	203	72.53	97.08	373.6
Total Oxidant status	8.83	7.69	2.89	5.51	15.96	10.08	9.94	2.02	6.46	14.58
Malondialdehyde	8.35	5.74	5.69	3.64	25.62	8.06	7.04	4.48	4.05	24.81

Antipsychotic effect on psychopathology symptoms

Psychopathology symptoms improved significantly after eight weeks of antipsychotic treatment (Table 2). In the first episode, drug-naive patients, PANSS positive symptoms decreased most significantly from 24.86 to 12.26 (p<0.01), with an improvement by more than 50%. We also noted that the PANSS negative score decreased from 21.76 to 15.56, PANSS general score from 40.97 to 26.04, PANSS total score from 87.59 to 53.85. All changes were statistically significant (p<0.001). Comparatively, the symptom improvements were less in the drug-free acute phase patients, likely due to the relatively lower levels of symptom score at the baseline, but they were still significant (p<0.01).

Table 2. Summary of psychopathology symptoms before and after treatment in both first-episode drug-naive and drug-free acute phase patients with schizophrenia

	Before treatment					After treatment					
	Mean	Med	SD	Min	Max	Mean	Med	SD	Min	Max	P
First episode drug-naive											
PANSS positive	24.86	24	5.15	17	34	12.26	11	4.83	7	23	<0.001
PANSS negative	21.76	22	5.44	9	37	15.56	16	5.04	8	25	<0.001
PANSS general	40.97	40	5.77	30	52	26.04	27	5.28	17	36	<0.001
PANSS total score	87.59	87	11.70	68	117	53.85	56	12.78	33	77	<0.001
Drug-free acute phase											
PANSS positive	21.52	20	6.25	12	34	11.97	11	4.25	7	21	<0.001
PANSS negative	22.55	21	4.88	15	32	17.41	17	5.76	7	30	<0.001
PANSS general	35.76	35	6.32	26	50	26.24	26	5.79	19	39	<0.001
PANSS total score	79.83	79	13.00	59	106	55.62	55	14.04	35	86	<0.001

P, P-value for testing the difference while adjusting for age, sex, education, duration of illness, and age of onset.

Antipsychotic effect on protein S100B and oxidative stress

Table 3 shows the effect of antipsychotic treatment on the levels of protein S100B and oxidative stress. As a result, antipsychotic treatment for eight weeks significantly reduced the level of S100B (Beta=24.89; p=0.0087) in the first episode drug-naive patients with schizophrenia and exhibited a marginal effect on the levels of S100B (Beta= 15.65; p=0.0929) in the drug-free acute phase patients with schizophrenia. While the later was at a marginal signi-ficance, there was no difference in the effect between patient groups (p=0.4785). When combining two groups, the antipsychotic treatment had a more significant effect on the S100B (Beta=20.27; p=0.0026).

Interestingly, we observed a slightly different pattern of antipsychotic treatment effect on two parameters of oxidative stress between two different groups of patients. The treatment showed no significant effect on TOS in either of the two groups (p>0.1). However, antipsychotic treatment slightly increased the level of TOS in the first episode, drug-naive patients (Beta=-1.08; p=0.1055) but not in the drug-free acute phase patients (Beta=-0.73;p=0.2683). Conversely, the antipsychotic treatment significantly increased the levels of MDA in the drug-free acute phase patients (Beta=-6.55; p<0.0001). The mean of MDA increased by more than 80% after antipsychotic treatment (LS mean =14.38) compared to the mean of 7.83 before treat-ment in the first episode drug-naive group. However, there had little influence on MDA in the first episode drug-naive patients with schizophrenia (Beta=-0.57*; p*=0.6631).

The effects were significant between two groups as there was a significant interaction (p=0.0020) between two groups on the increase in the levels of MDA. The analysis of log-transformed TOS and MDA showed mostly consistent results.

Table 3. The effect of antipsychotic treatment on the levels of S100B and oxidative stress in first-episode drug-naive and drug-free acute phase patients with schizophrenia

	LS Mean							
Patient group	Before	After	Beta	SE	DF	t Value	P	P_int
S100B								
First episode drug-naive	239.05	214.16	24.89	9.16	56	2.72	0.0087	0.4785
Drug-free acute phase	207.56	191.91	15.65	9.16	56	1.71	0.0929	
Total oxidants (TOS)								
First episode drug-naive	8.66	9.73	-1.08	0.65	56	-1.65	0.1055	0.7107
Drug-free acute phase	10.11	10.84	-0.73	0.65	56	-1.12	0.2683	
Malondialdehyde (MDA)								
First episode drug-naive	8.53	9.10	-0.57	1.30	56	-0.44	0.6631	0.0020
Drug-free acute phase	7.83	14.38	-6.55	1.30	56	-5.02	<.0001	

P_int, the interaction between the patient group and treatment.

Association between serum parameters and psychopathology symptoms

We also performed an analysis to examine whether the levels of S100B and oxidative stress would affect the psychopathology symptoms in the patients treated with antipsychotics (**Table 4**). Although the level of protein S100B significantly reduced after antipsychotic treatment in the first episode drug-naive patients, as shown above, no significant association of S100B with psychopathology symptoms of all three sub-clusters or total PANSS scores (p>0.1). Instead, the levels of S100B were associated with the improvement of PANSS negative (Beta=0.0397; p= 0.0039) in the drug-free acute phase patients with schizophrenia.

While the antipsychotic treatment had no significant effect on TOS in either of the groups, as shown above, the TOS was associated with PANSS positive (Beta=0.535;p=0.0283) and PANSS total (Beta=1.434; p=0.0238) in the first episode drug-naive patient. However, no clear association appeared between changes in MDA and PANSS symptom (p>0.05).

Table 4. Association of S100B and oxidative stress with psychopathology symptoms in both groups of schizophrenia patients

	S100B			TOS			MDA		
	Beta	SE	P	Beta	SE	P	Beta	SE	P
Drug naïve first episode									
PANSS positive	0.0115	0.0099	0.2554	0.5352	0.2299	0.0283	0.1228	0.1112	0.2797
PANSS negative	0.0048	0.0119	0.6934	0.3059	0.2487	0.2301	0.1324	0.1247	0.2984
PANSS general	0.0105	0.0123	0.4026	0.5316	0.2709	0.061	0.2279	0.1299	0.0917
PANSS total	0.0259	0.0259	0.3258	1.4338	0.5958	0.0238	0.5418	0.2776	0.0622
Drug-free acute phase									
PANSS positive	0.0095	0.0144	0.5121	0.2801	0.2613	0.2933	0.0346	0.1091	0.7535
PANSS negative	0.0397	0.0126	0.0039	0.1429	0.2633	0.5918	0.0445	0.1088	0.6859
PANSS general	0.0105	0.0123	0.4026	0.5316	0.2709	0.061	0.2002	0.1253	0.1216
PANSS total	0.0575	0.035	0.1117	0.1431	0.6811	0.8351	0.205	0.2797	0.47

DISCUSSION

In this study, we found that antipsychotic treatment reduced the levels of S100B in serum significantly in the first-episode drug-naive but marginally significantly in drug-free acute phase patients with schizophrenia. The antipsychotic treatment had no significant effect on total oxidant status in either of two groups, but it significantly increased the serum level of MDA in the drug-free acute phase only. We noted that S100B was positively associated with the antipsychotic response of PANSS negative in the drug-free acute phase, but TOS had a positive association with PANSS positive and total score in first-episode drug-naive patients.

S100B, a calcium-binding protein, is mainly synthesized by and released from astrocytes and oligodendrocytes(15, 16), and can pass the blood-brain barrier(17, 18). Reportedly, its peripheral levels correlate well with those in the central nervous system extensively investigated in psychotic disorders (4, 19). This protein has been considered as a surrogate marker for brain and astrocyte-specific damage or dysfunction in neurologic disorders such as stroke and traumatic brain injury (15, 16, 20). Reports on S100B levels in schizophrenia patients have been inconsistent. Accurately, some reported no diff-erences in S100B bet-

ween schizophrenia patients and healthy controls (21, 22), while others reported an increased (23) or decreased S100B (16) in patients with schizophrenia compared with healthy controls. Both the first-generation antipsychotic drug (haloperidol) and the second-generation drug (risperidone) are shown to inhibit interleukin-6-induced S100B secretion in C6 glioma cells (24). Another study also suports that S100B levels reduced during convalescence from acute paranoid schizophrenia that is regulated by its scavenger, a soluble receptor for advanced glycation end products (RAGE)(25). Previous studies of patients with the negative symptom or deficit schizophrenia find that the reduced levels of S100B are associated with negative symptom in patients treated with antipsychotics for six weeks (26). These are mostly consistent with our findings that the levels of S100B positively associated with PANSS negative score after antipsychotic treatment for eight weeks.

However, there are inconsistent reports that antipsychotic treatment leads to an increased level of serum S100B in early treatment(20), medicated and unmedicated patients (27), and older patients (>50 years) with long-term treatment of clozapine and typical antipsychotics. There was no association between S100B and PANSS, which was similar between atypical and typical drugs (28). These contradictory seemed to have some underlying explanation. Most antipsychotics such as clozapine and olanzapine have a side effect such as weight gain and impaired glucose tolerance, which may contribute to the elevated level of S100B (29, 30). While the treatment with anti-psychotics may reduce the psychotic symptoms and S100B levels simultaneously, the improvement of psychotic symptoms could not be determined by the level change of S100B, and no correlations have been detected for S100B levels with PANSS total, positive, negative, or general scores (21, 25, 28). This suggests that antipsychotic drugs could improve symptoms in patients with schizophrenia through other mechanisms rather than S100B, although the level of S100B was also affected by antipsychotic treatment. Moreover, two recent meta-analyses found no differences in S100B concentrations between medicated and non-medicated patients (31, 32). These inconsistencies could be due to the relatively small sample size or clinical heterogeneity of the patients with schizophrenia.

Recent data suggest a convergence of redox dysregulation and oxidative stress in promoting the emergence of psychosis. Many studies have identified that patients with schizophrenia increase in oxidative stress in the blood plasma, cerebrospinal fluid (CSF) and postmortem samples, including increased lipid and protein oxidation and alterations in antioxidant defense systems, such as catalase and superoxide dismutase (33-37). In contrast, a study showed that antipsychotic treatment reduced the index of oxidative stress, including the total level of peroxides in the first episode drug-naive patients treated with olanzapine and risperidone for three months (38). Anti-psychotics do not have a significant effect on the oxidative and antioxidative system parameter after treatment for six weeks (39). We noted limited evidence that risperidone antipsychotic treatment affects oxidative stress and their associations with PANSS symptoms. In this study, the levels of TOS had no significant change before and after antipsychotic treatment in both groups of patients but were associated with PANSS positive and total scores only in the first episode drug-naive patients with schizophrenia.

In healthy individuals, oxidant and antioxidant systems are maintained at constant levels and balanced, and such a balance could be disturbed in patients with schizophrenia. A significant association between antioxidant enzyme levels and clinical features of schizophrenia has been previously reported in several studies (26, 40-48). For instance, abnormalities in the antioxidant system lipid peroxidation have been associated with negative(43)and positive symptoms(47). However, most studies did not identify a significant association between oxidative stress biomarkers and clinical severity among chronic schizophrenia patients or first-episode psychosis (49-52). For drug-free acute phase patients with schizophrenia, there was no change in TOS levels before and after treatment or no correlation between TOS levels and PANSS scores, which perhaps is confounded by medication history in the non-acute phase.

Malondialdehyde (MDA) is deemed as another parameter of oxidative stress, representing the level of Lipid peroxidation (LPO). So LPO on erythrocyte membranes was assessed through determining the levels of reactive alde-hyde MDA, an end product of lipid peroxidation cascade(53). In the current study, MDA levels increased in the drug-free acute phase patients but did not in the first episode drug-naive ones; MDA has no medication effect on psychopathology symptoms in all patients after treatment. Such a phenomenon might be explained by the fact that antipsychotics leads to stress, although the previous study based on small patients showed that treatment with typi-cal antipsychotics increased the level of MDA(54). While LPO levels seemed to be lower in patients showing higher severity of negative symptoms, according to both PANSS and BNSS scales(55), the majority of relevant studies failed to replicate any correlation between MDA and clinical features(36).

Lacking association of antipsychotics treatment with the oxidative stress parameters and oxidative stress parameters with PANSS symptoms could be caused by complicated reasons. *First*, the therapeutic actions of antipsychotic drugs are heterogeneous. For example, antipsychotics may have different antioxidant and oxidant properties. Typical antipsychotics were likely to have a higher level of the neurotoxicity, which may be through the lipid peroxidation which induced oxidative injury in the brain and led to the development of extrapyramidal symptoms including tardive dyskinesia(56). Even among the atypical drugs, there were marked differences in the induced oxidative stress. Clozapine was shown to have higher antioxidant properties than risperidone and perphenazine, especially increasing the levels of antioxidants (e.g., superoxide dismutase, SOD; glutathione, GSH) and reducing levels of lipid peroxidation in patients with schizophrenia (57); olanzapine and clozapine may increase antioxidant activities, which may contribute to therapeutic actions (58). Unfortunately, we did not measure the antioxidants in this study.

Also, the alteration of a single oxidative stress parameter maybe not representtative for the anti-psychotic effect, which may be determined by the balance of oxidant and antioxidant systems at a constant level.

Given that, an increase in oxidative stress may be detrimental to cognition (59), which, in the long run, may affect the prognosis of patients with schizophrenia. Therefore, it is crucial to keep oxidative stress under control for patients treated with antipsychotics. It will be an interesting topic to see if antipsychotics plus antioxidant supplement would increase the therapeutic efficacy in patients with schizophrenia.

Limitation and strength

Several limitations of this study should be noted. The number of enrolled patients may not provide enough power for this type of study. In addition, we only measured two parameters of oxidative stress, which may not be able to assess the ultimately oxidative stress system. Oxidative and antioxidative parameters should be included simul-taneously in the analysis. Despite those limitations, some strength in the current study was noteworthy. The patients were from inpatient units and stayed in the hospital throughout the treatment. Despite a relatively short period of patients' hospitalization, they acquired good clinical improvement.

In summary, after antipsychotic treatment, while the levels of S100B decreased in both groups. S100B had no significant meditational effect on psychopathology symptoms in the first episode drug-naive patients, but on PANSS negative symptoms in the drug-free acute phase patients with schizophrenia. However, the level of MDA increased in drug-free acute phase schizophrenia patients but not associated with psychopathology symptoms. These findings warrant a further study in a larger sample size.

CONFLICT OF INTERESTS

The authors reported no biomedical financial interests or potential conflict of interest regarding the publication of this paper.

ACKNOWLEDGMENTS

This work was funded by the grant from Dengfeng Project of Beijing Medical Administration(DFL20151901). The source of findings had no further role in study design, the collection, analysis, and interpretation of data, writing of the report, and has not been involved with the decision to submit the paper for publication.

REFERENCES

1. Long J, Huang G, Liang W, Liang B, Chen Q, Xie J, et al. The prevalence of schizophrenia in mainland China: evidence from epidemiological surveys. Acta Psychiatr Scand. 2014; 130(4):244-56.
2. Monji A, Kato TA, Mizoguchi Y, Horikawa H, Seki Y, Kasai M, et al. Neuroinflammation in schizophrenia especially focused on the role of microglia. Prog Neuropsychopharmacol Biol Psychiatry. 2013;42:115-21.
3. Donato R. Intracellular and extracellular roles of S100 proteins. Microsc Res Tech. 2003;60(6):540-51.
4. Rothermundt M, Falkai P, Ponath G, Abel S, Burkle H, Diedrich M, et al. Glial cell dysfunction in schizophrenia indicated by increased S100B in the CSF. Mol Psychiatry. 2004;9(10):897-9.
5. Steiner J, Bernstein HG, Bielau H, Berndt A, Brisch R, Mawrin C, et al. Evidence for a wide extra-astrocytic distribution of S100B in human brain. BMC Neurosci. 2007;8:2.
6. Schroeter ML, Steiner J. Elevated serum levels of the glial marker protein S100B are not specific for schizophrenia or mood disorders. Mol Psychiatry. 2009;14(3):235-7.
7. Steiner J, Bernstein HG, Bogerts B, Gos T, Richter-Landsberg C, Wunderlich MT, et al. S100B is expressed in, and released from, OLN-93 oligodendrocytes: Influence of serum and glucose deprivation. Neuroscience. 2008;154(2):496-503.
8. Liu J, Shi Y, Tang J, Guo T, Li X, Yang Y, et al. SNPs and haplotypes in the S100B gene reveal association with schizophrenia. Biochem Biophys Res Commun. 2005;328(1): 335-41.
9. Rothermundt M, Falkai P, Ponath G, Abel S, Bürkle H, Diedrich M, et al. Glial cell dysfunction in schizophrenia indicated by increased S100B in the CSF. Molecular Psychiatry. 2004;9:897.
10. Bitanihirwe BK, Woo TU. Oxidative stress in schizophrenia: an integrated approach. Neurosci Biobehav Rev. 2011;35(3): 878-93.
11. Pedrini M, Massuda R, Fries GR, de Bittencourt Pasquali MA, Schnorr CE, Moreira JC, et al. Similarities in serum oxidative stress markers and inflammatory cytokines in patients with overt schizophrenia at early and late stages of chronicity. J Psychiatr Res. 2012;46(6):819-24.
12. Boll KM, Noto C, Bonifacio KL, Bortolasci CC, Gadelha A, Bressan RA, et al. Oxidative and nitrosative stress biomarkers in chronic schizophrenia. Psychiatry Res. 2017; 253:43-8.
13. Morera-Fumero AL, Diaz-Mesa E, Abreu-Gonzalez P, Fernandez-Lopez L, Cejas-Mendez MD. Low levels of serum total antioxidant capacity and presence at admission and absence at discharge of a day/night change as a marker of acute paranoid schizophrenia relapse. Psychiatry Res. 2017;249:200-5.
14. Liu L, Li Y, Bian Y, Yang F, Li X, Han X, et al. Serum levels of oxidants and protein S100B were associated in the first-episode drug naïve patients with schizophrenia. . Glob Clin Transl Res 2019;1(2):84-92.
15. Rothermundt M, Missler U, Arolt V, Peters M, Leadbeater J, Wiesmann M, et al. Increased S100B blood levels in unmedicated and treated schizophrenic patients are correlated with negative symptomatology. Mol Psychiatry. 2001;6(4):445-9.
16. Gattaz WF, Lara DR, Elkis H, Portela LV, Goncalves CA, Tort AB, et al. Decreased S100-beta protein in schizophrenia: preliminary evidence. Schizophr Res. 2000;43(2-3):91-5.
17. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology. 1998;37(12):1553-61.
18. Marchi N, Cavaglia M, Fazio V, Bhudia S, Hallene K, Janigro D. Peripheral markers of blood-brain barrier damage. Clin Chim Acta. 2004;342(1-2):1-12.
19. Steiner J, Bogerts B, Schroeter ML, Bernstein HG. S100B protein in neurodegenerative disorders. Clin Chem Lab Med. 2011;49(3):409-24.
20. Schroeter ML, Abdul-Khaliq H, Fruhauf S, Hohne R, Schick G, Diefenbacher A, et al. Serum S100B is increased during early treatment with antipsychotics and in deficit schizophrenia. Schizophr Res. 2003;62(3):231-6.
21. Hendouei N, Hosseini SH, Panahi A, Khazaeipour Z, Barari F, Sahebnasagh A, et al. Negative Correlation between Serum S100B and Leptin Levels in Schizophrenic Patients During

Treatment with Clozapine and Risperidone: Preliminary Evidence. Iran J Pharm Res. 2016;15(1):323-30.
22. Uzbay T, Goktalay G, Kayir H, Eker SS, Sarandol A, Oral S, et al. Increased plasma agmatine levels in patients with schizophrenia. J Psychiatr Res. 2013;47(8):1054-60.
23. Milleit B, Smesny S, Rothermundt M, Preul C, Schroeter ML, von Eiff C, et al. Serum S100B Protein is Specifically Related to White Matter Changes in Schizophrenia. Front Cell Neurosci. 2016;10:33.
24. de Souza DF, Wartchow K, Hansen F, Lunardi P, Guerra MC, Nardin P, et al. Interleukin-6-induced S100B secretion is inhibited by haloperidol and risperidone. Prog Neuropsychopharmacol Biol Psychiatry. 2013;43:14-22.
25. Steiner J, Walter M, Wunderlich MT, Bernstein HG, Panteli B, Brauner M, et al. A new pathophysiological aspect of S100B in schizophrenia: potential regulation of S100B by its scavenger soluble RAGE. Biol Psychiatry. 2009;65(12):1107-10.
26. Sarandol A, Kirli S, Akkaya C, Altin A, Demirci M, Sarandol E. Oxidative-antioxidative systems and their relation with serum S100 B levels in patients with schizophrenia: effects of short term antipsychotic treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(6): 1164-9.
27. Zhang XY, Xiu MH, Song C, Chen DC, Wu GY, Haile CN, et al. Increased serum S100B in never-medicated and medicated schizophrenic patients. J Psychiatr Res. 2010;44(16):1236-40.
28. Qi LY, Xiu MH, Chen DC, Wang F, Kosten TA, Kosten TR, et al. Increased serum S100B levels in chronic schizophrenic patients on long-term clozapine or typical antipsychotics. Neurosci Lett. 2009;462(2):113-7.
29. Steiner J, Myint AM, Schiltz K, Westphal S, Bernstein HG, Walter M, et al. S100B Serum Levels in Schizophrenia Are Presumably Related to Visceral Obesity and Insulin Resistance. Cardiovasc Psychiatry Neurol. 2010;2010: 480707.
30. Steiner J, Walter M, Guest P, Myint AM, Schiltz K, Panteli B, et al. Elevated S100B levels in schizophrenia are associated with insulin resistance. Mol Psychiatry. 2010;15(1):3-4.
31. Schumberg K, Polyakova M, Steiner J, Schroeter ML. Serum S100B Is Related to Illness Duration and Clinical Symptoms in Schizophrenia-A Meta-Regression Analysis. Front Cell Neurosci. 2016;10:46.
32. Aleksovska K, Leoncini E, Bonassi S, Cesario A, Boccia S, Frustaci A. Systematic review and meta-analysis of circulating S100B blood levels in schizophrenia. PLoS One. 2014; 9(9):e106342.
33. Do KQ, Cabungcal JH, Frank A, Steullet P, Cuenod M. Redox dysregulation, neurodevelopment, and schizophrenia. Curr Opin Neurobiol. 2009;19(2):220-30.
34. Yao JK, Keshavan MS. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxid Redox Signal. 2011;15(7):2011-35.
35. Martins-de-Souza D, Harris LW, Guest PC, Bahn S. The role of energy metabolism dysfunction and oxidative stress in schizophrenia revealed by proteomics. Antioxid Redox Signal. 2011;15(7):2067-79.
36. Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. Biol Psychiatry. 2013;74(6):400-9.
37. Coughlin JM, Ishizuka K, Kano SI, Edwards JA, Seifuddin FT, Shimano MA, et al. Marked reduction of soluble superoxide dismutase-1 (SOD1) in cerebrospinal fluid of patients with recent-onset schizophrenia. Mol Psychiatry. 2013;18(1):10-1.
38. Kriisa K, Haring L, Vasar E, Koido K, Janno S, Vasar V, et al. Antipsychotic Treatment Reduces Indices of Oxidative Stress in First-Episode Psychosis Patients. Oxid Med Cell Longev. 2016;2016:9616593.
39. Sarandol A, Sarandol E, Acikgoz HE, Eker SS, Akkaya C, Dirican M. First-episode psychosis is associated with oxidative stress: Effects of short-term antipsychotic treatment. Psychiatry Clin Neurosci. 2015;69(11):699-707.
40. Peet M, Laugharne J, Rangarajan N, Reynolds GP. Tardive dyskinesia, lipid peroxidation, and sustained amelioration with vitamin E treatment. Int Clin Psychopharmacol. 1993; 8(3):151-3.
41. Zhang XY, Zhou DF, Cao LY, Chen DC, Zhu FY, Wu GY. Blood superoxide dismutase level in schizophrenic patients with tardive dyskinesia: association with dyskinetic movements. Schizophr Res. 2003;62(3):245-50.
42. Arvindakshan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP. Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. Schizophr Res. 2003;62(3):195-204.
43. Skosnik PD, Yao JK. From membrane phospholipid defects to altered neurotransmission: is arachidonic acid a nexus in the pathophysiology of schizophrenia? Prostaglandins Leukot Essent Fatty Acids. 2003;69(6):367-84.
44. Tsai G, Goff DC, Chang RW, Flood J, Baer L, Coyle JT. Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. Am J Psychiatry. 1998; 155(9):1207-13.
45. Yao JK, Reddy R, van Kammen DP. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia. Psychiatry Res. 2000;97(2-3):137-51.
46. Khan MM, Evans DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. Schizophr Res. 2002;58(1):1-10.
47. Zhang XY, Zhou DF, Cao LY, Zhang PY, Wu GY. Elevated blood superoxide dismutase in neuroleptic-free schizophrenia: association with positive symptoms. Psychiatry Res. 2003; 117(1):85-8.
48. Kunz M, Gama CS, Andreazza AC, Salvador M, Cereser KM, Gomes FA, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(7):1677-81.
49. Devanarayanan S, Nandeesha H, Kattimani S, Sarkar S. Relationship between matrix metalloproteinase-9 and oxidative stress in drug-free male schizophrenia: a case control study. Clin Chem Lab Med. 2016;54(3):447-52.
50. Noto C, Ota VK, Gadelha A, Noto MN, Barbosa DS, Bonifacio KL, et al. Oxidative stress in drug naive first episode psychosis and antioxidant effects of risperidone. J Psychiatr Res. 2015;68:210-6.
51. Reyazuddin M, Azmi SA, Islam N, Rizvi A. Oxidative stress and level of antioxidant enzymes in drug-naive schizophrenics. Indian J Psychiatry. 2014;56(4):344-9.
52. Fraguas D, Diaz-Caneja CM, Rodriguez-Quiroga A, Arango C. Oxidative Stress and Inflammation in Early Onset First Episode Psychosis: A Systematic Review and Meta-Analysis. Int J Neuropsychopharmacol. 2017;20(6):435-44.
53. Esterbauer H, Dieber-Rotheneder M, Waeg G, Puhl H, Tatzber F. Endogenous antioxidants and lipoprotein oxidation. Biochem Soc Trans. 1990;18(6):1059-61.
54. Gunes M, Camkurt MA, Bulut M, Demir S, Ibiloglu AO, Kaya MC, et al. Evaluation of Paraoxonase, Arylesterase and Malondialdehyde Levels in Schizophrenia Patients Taking Typical, Atypical and Combined Antipsychotic Treatment. Clin Psychopharmacol Neurosci. 2016;14(4):345-50.
55. Zhang XY, Chen DC, Tan YL, Tan SP, Wang ZR, Yang FD, et al. The interplay between BDNF and oxidative stress in chronic schizophrenia. Psychoneuroendocrinology. 2015;51: 201-8.
56. Kropp S, Kern V, Lange K, Degner D, Hajak G, Kornhuber J, et al. Oxidative stress during treatment with first- and second-

generation antipsychotics. J Neuropsychiatry Clin Neurosci. 2005;17(2):227-31.
57. Hendouei N, Farnia S, Mohseni F, Salehi A, Bagheri M, Shadfar F, et al. Alterations in oxidative stress markers and its correlation with clinical findings in schizophrenic patients consuming perphenazine, clozapine and risperidone. Bio-med Pharmacother. 2018;103:965-72.
58. Sadowska-Bartosz I, Galiniak S, Bartosz G, Zuberek M, Grzelak A, Dietrich-Muszalska A. Antioxidant properties of atypical antipsychotic drugs used in the treatment of schizophrenia. Schizophr Res. 2016;176(2-3):245-51.
59. Hajjar I, Hayek SS, Goldstein FC, Martin G, Jones DP, Quyyumi A. Oxidative stress predicts cognitive decline with aging in healthy adults: an observational study. J Neuroinflammation. 2018;15(1):17.

How to cite this article:

Wang X, Bian Y, Liu L, Wu Y, Yang F, Li X, Han X, Tian L, Luo X, Chen S, Wang Z, Tan Y, Li Y. Effects of antipsychotic treatment on S100B and oxidative stress in patients with schizophrenia. Glob Clin Transl Res. 2019; 1(4): 120-128. DOI:10.36316/gcatr.01.0018.

Perspective

A Pediatrician's Opinion on the Need for More Data on Medicines in Pregnancy

Susan P Tansey*

Accepted November 8, 2019

The safety of medicines in pregnancy and the neonatal period cannot be taken into consideration in isolation. Medicines given in pregnancy, as we all know can produce adverse events that only become apparent in the neonate/baby at a much later stage, e.g. diethylstilboestrol and clear cell adenocarcinoma of the vagina. In this historical case, the medicine was given to prevent or treat pregnancy-related problems (such as miscarriage), but medicines may also be needed for non-pregnancy related reasons in women of child-bearing age who either are pregnant or could become pregnant. Of course, it is also important to take into account the maternal and obstetric medical history when administering an investigational medicine to a neonate in order to be able to fully assess the risks and benefits of that medicine and the causality of any adverse event that occurs.

During pregnancy, the women's body undergoes many physiological changes, which makes it particularly important to study the pharmacokinetics of medicine during pregnancy since the clearance and thus the drug levels in the bloodstream are not necessarily the same as they would be in a non-pregnant woman. It is also important to consider clinical trials looking at the level of drug in cord blood at birth and/or the placenta. Similarly, a premature neonate at different gestations will have a different body composition from a term baby, and this will change as the baby develops.

As a pediatrician, one of the first times I was introduced to the close interplay between obstetrics and neonatal research was when I was the research fellow on an antenatal trial in the mid-1990s(1). This was a trial looking at the use of antenatal Thyrotrophin Releasing Hormone (TRH) to try and reduce the incidence of respiratory distress syndrome in premature neonates. I was in the privileged position of being the only pediatrician work-ing in the University of Liverpool Obstetric Department as there was a need to ensure data on the babies born to the mothers included in the study was collected accu-rately. Many years later, I also had the pleasure of work-ing closely with obstetricians in an industry-sponsored antenatal trial to try and prevent recurrent miscarriage. In both these cases, I felt it was invaluable to have a neonatology experienced pediatrician involved. By coincidence neither of those studies had a positive outcome, but I think this also emphasized to me that negative trials can be just as important – not least to avoid the use of medicines in pregnancy when there is insufficient evidence of the benefit/risk to justify their use. In this article I am going to focus on the need for more evidence on medicines given in pregnancy and why I feel this is so important.

An area of particular interest for me is the maternal immunization. Up until quite recently, it would not have been considered feasible to conduct randomized controlled trials with an investigational vaccine in pregnant women. However, the worldwide H1N1 flu pandemic in 2009 led to the recognition that there was a high rate of hospitalization and some deaths when influenza was contracted in pregnancy (2). Subsequently, there was a change in perception concerning the vaccination of pregnant women against influenza, and the current recommendations by the Center for Disease Control and Prevention in pregnancy are for both influenza and TDaP (tetanus, diphtheria and acellular pertussis) vaccinations to be given during pregnancy since the benefits outweigh the risks(3).

In addition, there are currently several investigational vaccines in development for maternal immunization. These include vaccinations to protect against Respiratory Syncytial Virus and neonatal Group B streptococcal infections. These two infections account for much morbidity and mortality in the neonatal period globally, and their prevention would be welcomed by neonat-ologists and obstetricians alike. Benefits could include not only the reduction of these infections in newborn babies but might also help in the fight against antimicrobial resistance, and the term preventative neonatology has been applied to refer to this type of intervention(4).

An interesting recent target for vaccination is the Zika virus. Although the main aim of immunization would be to reduce the serious impact of maternal infection on the developing fetus, the target population, in this case, would be adolescent girls so that they are protected in advance of a pregnancy. It is the most effective way of prevention since the harmful effects of the Zika virus occur very early in pregnancy. There are several Zika vaccines currently in development (5).

Whereas in the past, the approach has been to avoid all medicines in pregnancy, there is increasingly a recognition that there are several situations where it is either essential or desirable to give medicines during pregnancy. This includes situations where the mother has epilepsy when the risk of fits in pregnancy will often

*Correspondence to: SP Tansey, MRCP MRCPCH FFPM, Email: spt.research@btinternet.com

outweigh the risk of taking medication for pregnant women or those planning a pregnancy. Medication during pregnancy may also be needed in other conditions such as cystic fibrosis, multiple sclerosis, or in HIV infected mothers, where there may also be risks to the unborn child of transmission of infection.

As an example, sodium valproate has been used for many years in the treatment of epilepsy and although some of the adverse effects were well known, the full extent of the risks to the unborn child when it is taken in pregnancy have only recently been fully acknowledged and addressed (6). Although for epileptic women planning a pregnancy there are other anti-epileptics drugs (AEDs) available, the dilemma for a doctor considering changing anti-epileptic medication (apart from the risk of a change in fit frequency) includes the lack of data for use in pregnancy for many of the other AEDs. In many cases, the data comes from registries where there can be difficulties interpreting the data because of the problem to find an appropriate comparator group (which should ideally be untreated epileptic mothers and their babies), and lack of data on terminations carried out for fetal abnormalities, etc. A recent publication (7) presented a descriptive drug utilization study covering a 10-year period (1st Jan 2007 – 31st December 2016) of anti-epileptic prescribing in 3 European countries (Italy, France, and the UK). This study found that of the pregnant women prescribed AEDs (incidence between 3 and 7.8 per 1000 pregnancies), there was a slight decrease in valproate prescriptions over the study period. About a third of the women in the UK and France were on lamotrigine. Worryingly there was an increase in prescriptions of gabapentin and pregabalin in pregnancy where the risks to the embryo or fetus are not well known.

Similarly, the MHRA (Medicines & Healthcare products Regulatory Agency) recently published a statement on the use of Fingolimod (a disease-modifying treatment for multiple sclerosis) in pregnancy advising against use in pregnancy and in women trying to get pregnant due to the increased risk of major congenital malformations(8). However, there is limited data available on other disease-modifying agents in pregnancy.

These 2 cases illustrate the need to investigate not only new investigational products that are anticipated to be prescribed in pregnancy and/or women of childbearing potential but also to review the evidence available for older medications such as sodium valproate and consider whether new trials should be conducted. Clinical trials may not always be feasible, so other ways to collect evidence for use in pregnancy may need to be considered, e.g. registries or real-world studies (recognizing the limitations that were mentioned earlier). The Food and Drug Administration (FDA) has a list of pregnancy exposure registries available on its website (9).

To emphasize the need to include pregnant women in clinical trials, the FDA has published draft Guidance in 2018 (10). This document mentions the need to focus on medication indicated for conditions that occur commonly in women of childbearing potential and the guidance points out that currently most labeling information for pregnant women is based on nonclinical data with limited human safety data. We have seen through the examples I mention, the potential consequences for mothers and babies if we fail to include pregnant women in clinical trials. I hope that as we have increasingly seen maternal immunization clinical trials being conducted, we will now start to see an increase in clinical trials of new medicines in pregnancy. This should enable an adequate assessment of the benefit/risk to be made available for physicians and women planning a pregna-ncy and result in better outcomes for mothers and babies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper

REFERENCES

1. Alfirevic Z, Boer K, Borcklehurst P, Buimer M, Elbourne D, Kok J, et al. Two trials of antenatal thyrotrophin-releasing hormone for fetal maturation: stopping before the due date. Antenatal TRH Trial and the Thyroneth Trial Groups. Br J Obstet Gynaecol. 1999;106(9):898-906.
2. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009; 374(9688):451-8.
3. National Center for Immunization and Respiratory Diseases. General recommendations on immunization -- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011; 60 (2):1-64.
4. Bergin N, Murtagh J, Philip RK. Maternal Vaccination as an Essential Component of Life-Course Immunization and Its Contribution to Preventive Neonatology. Int J Environ Res Public Health. 2018;15(5).
5. Barrett ADT. Current status of Zika vaccine development: Zika vaccines advance into clinical evaluation. NPJ Vaccines. 2018;3:24.
6. https://www.gov.uk/government/news/valproate-banned-without-the-pregnancy-prevention-programme. Accessed on October 15, 2019.
7. Hurault-Delarue C, Morris JK, Charlton R, Gini R, Loane M, Pierini A, et al. Prescription of antiepileptic medicines including valproate in pregnant women: A study in three European countries. Pharmacoepidemiol Drug Saf. 2019.
8. https://www.gov.uk/drug-safety-update/fingolimod-gilenya-increased-risk-of-congenital-malformations-new-contraindication-during-pregnancy-and-in-women-of-childbearing-potential-not-using-effective-contraception. Accessed on October 15, 2019.
9. https://www.fda.gov/science-research/womens-health-research/pregnancy-registries. Accessed on October 15, 2019.
10. FDA Draft Guidance: Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry, April 2018 Revision 1. https://www.fda.gov/media/112195/download. Accessed on October 30,2019.

How to cite this article:

Tansey SP. A pediatrician's opinion on the need for more data on more data on medicines in pregnacy. Glob Clin Transl Res. 2019; 1(4):129-130. DOI:10.36316/gcatr.01.0019

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

Since microbes have existed hundreds of millions to billions of years, multicellular animals including humans arose in a microbiologically complex environment. However, not until recent decades have we started to appreciate the fact that we harbor at least 100 trillion microbial cells (1), far more than the number of human cells in the body. The microbes that reside in and on the human body all together constitute our microbiota and the collection of genes they encode are named as the microbiome (2). The human gut microbiota is dominated by two bacterial phyla, *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 was relatively higher (5).

Along with the development in sequencing technology and bioinformatics, the more in-depth investigations into the composition and the role of complex microbial ecosystems 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 communiction might 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 these drugs commonly cause metabolic side-effects, including the increased incidence of obesity, diabetes, and metabolic dysfunction, which contribute to the risk of overall morbidity and mortality(9). Accumulating evidence shows an increased prevalence of obesity and metabolic dysfunction such as impaired fasting glucose and insulin resistance in drug-naïve first-episode

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

patients with schizophrenia, suggesting a possible co-morbidity of metabolic dysfunction in patients with schizophrenia (10). Metabolic complications such as weight gain could be distressing(11) and has become a significant conern in selecting medications for individuals with psychotic diseases for it is often associated with a poorer functional outcome(12), reduced quality of life(13), and 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 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 of 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 have been considered major mental health disorders (31), with a peak age of onset in children, adolescents and younger adults. Emerging research indicates 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 may be the potential underlying 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 homeostasis 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).

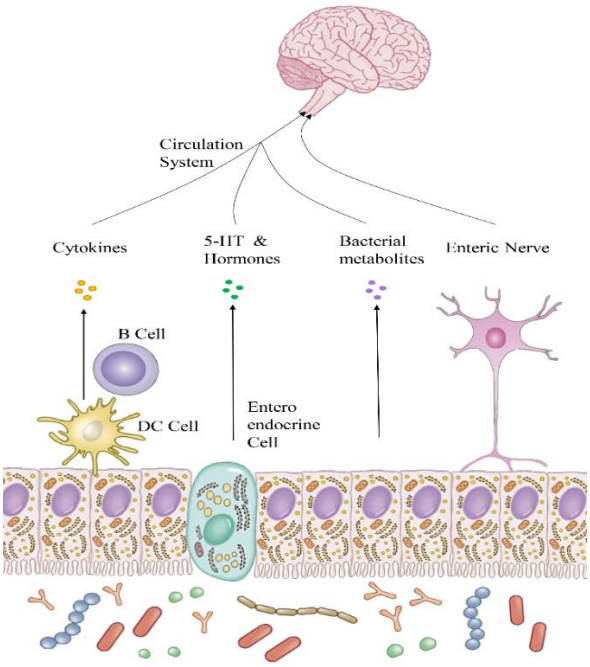


Figure 1. The various known bidirectional-signaling pathways between the gut microbiota and the brain, including immune, neuroendocrine and neural pathways. DC cell, dendritic cell; 5-HT, 5-hydroxytryptamine.

Schizophrenia

The increased morbidity of IBD and gastroenterology issues have been noted with psychiatric disorders and schizophrenia (44, 45). This association suggests that there is a plausible basis for hypothesizing that schizophrenia and microbiota have a functional relationship. 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 mi-crobiota in patients with first-episode schizophrenia com-pared with age-matched healthy 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 given fecal transplants from schizophrenia patients tend to have lower glutamate and higher glutamine and GABA in the hippocampus 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 the treatment reduced severe bowel symptoms associated with antipsychotics (52). In addition, one recent systematic review also suggests that based on the current evidence, there are no significant differences in psychopa-thological symptoms between the group of patients with schizophrenia given either probiotic supplements and placebo (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 *Ruminococcaceae* 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* are 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 shows 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 that the alterations in microbiota are 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 in 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 different 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 sociability 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 antipsychotic medications (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 of 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 antibiotic cocktail in olanzapine-treated rats 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). Microbial colonization of the gut, the olanzapine group gained significantly more weight than did the placebo group. This demonstrates that gut microbiota were necessary and sufficient for the occurrence of olanzapine-induced weight gain.

Risperidone, also a 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). Risperi-done inhibited the growth of cultured fecal bacteria, particularly those are grown anaerobically rather than aerobic-ally. Transplantation of the fecal phage fraction from risperidone treated mice to naïve recipients caused excess weight gain through reduced energy expenditure (84). A study showed that patients with drug-naïve first-episode schizophrenia treated with risperidone for 24 weeks had a significant increase in body weight and in the numbers of fecal *Bifidobacterium* and *Escherichia coli* but had decreases in the number of fecal *Clostridium coccoides* and *Lactobacillus, of which* only increase in fecal *Bifidobacterium* are associated with the weight gain (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 were 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 with SGAs (87). So far, most of the studies have focused on olanzapine and risperidone, the two commonly used SGAs with higher efficacy (88) but more likelihood of induced metabolic disturbance. These studies may provide evidence for a clinical translational research in human patients.

PROBIOTIC AND PREBIOTIC AS INTERVENTION

Probiotics

In 1907, Élie Metchnikoff from the Pasteur Institute proposed lactic acid bacteria being beneficial to human health (90). The term "probiotics" which derived from the Greek

word meaning "for life" first appeared in 1974. Its definetion 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 microorganisms which when administered in adequate amounts confer a health benefit to the host" (89). 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 following 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 heip reducing obesity. One recent review suggests that supplementation of the probiotics mentioned above in mice and rats lead to less weight gain, fat accumulation, and adipose tissue compared to the placebo group (100). Clinically, several strains of *Lactobacillus* showed beneficial effect against metabolic dysfunction. For example, compared with those who received placebo, pregnant women who received *L. rhamnosus* supplements from four weeks before the date of expected delivery to six months of postnatally had a significant modulation of the weight gain in their children during the first few years, based on a follow-up study of the 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 administered 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 properties, and clinically has demonstrated benefits for gastrointestinal health and immune function.

Probiotics may attenuate symptoms of anxiety and depression, and be 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 measure of weight (110). Probiotic supplements may help attenuate the gut discomfort in male individuals with schizophrenia (111, 112). One study of mice showed that administering of probiotic mixture VSL#3 could confer a benefit for olanzapine-induced wei-ght gain (113); a randomized clinical trial (RCT) also sho-wed the beneficial effects of probiotics and vitamin D sup-lements 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 psycho-pathological symptoms.

Prebiotics

The concept of prebiotics was evolving as it was 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,

end up in the deep colon, 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; common prebiotics include fructo-oligosaccharides (FOS), inulin, galactooligo-saccharides (GOS), and 4G-β-D-galactosylsucrose (also known as Lacto sucrose).

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, divided into rice bran, rice husk powder or placebo groups, 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 randomized 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 a 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 effects of prebiotics were 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).

Only recently, a few studies have focused on the effectiveness and safety of prebiotic modulation on anti-psychotic-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 receiving an intraperitoneal injection of olanzapine daily on day 8 through 21. The use of B-GOS significantly attenuated olanzapine-induced weight gain, followed by a decrease in the plasma acetate concentrations, and elevation of fecal *Bifidobacterium* but reduction in bacteria in phylum *Firmicutes.* Kao et al (126) further found that the prebiotic reduction of brain histone deacetylase (HDAC) activity and OIWG in rats was 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, in which after 24 weeks trial, the treatment group showed a significant increase in the cognitive composite T-score, which was driven by subtests of executive function. 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 suggested that Lactosucrose as a prebiotic could improve underweight accompanied by increased *Bifidobacterium* in fecal microbiota (128). However, there was a report showing no difference in body weight before and after a supplementation of resistant starch in individuals with schizophrenia (129). Further studies with adequate sample size are required to deter-mine 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) Soon after the concept of prebiotics was introduced, investigators speculated the potential benefits of combining prebiotics with probiotics. This combination was then called synbiotics (131). Although there are very few reported clinical trials of synbiotics, the limited results seem to suggest a beneficial effect on glucose and insulin metab-olism (132). As far as we know, currently there is no research about the potential effect of synbiotics on anti-psychotic-induced weight gain or metabolic dysfunction.

Since recent studies have indicated that gut microbiota play an important role in an individuals' health and risk of 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 models (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 in psychiatric disorders and anti-psychotic-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 by which microbiota influences the development of neuropsychiatric disorders, with more advanced study designs 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 inter-

relationship.

While the mechanism has yet to be elucidated, interventional study would help assess the potential benefit and safety of prebiotics and probiotics and provide causal evidence if efficacy is observed. 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 any effective responses could 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 schizo-phrenia. 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 repe-

ated 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.

Introduction to the editors