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The gut-microbiome as a target for the treatment of schizophrenia: a systematic review and meta-analysis of randomised controlled trials of augmentation strategies

Amedeo Minichino1, Natascia Brondino2, Marco Solmi3,4, Cinzia Del Giovane5, Paolo Fusar-Poli2,4,6,7, Philip Burnet1, Andrea Cipriani1,8, Belinda Lennox1,8

1 Department of Psychiatry, University of Oxford, Oxford, United Kingdom
2 Section of Psychiatry, Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
3 Padua Neuroscience Center, University of Padua, Padua, Italy
4 Early Psychosis: Interventions & Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
5 Institute of Primary Health Care, University of Bern, Switzerland
6 National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health, IoPPN, King’s College London, UK.
7 OASIS Service, South London and the Maudsley NHS National Health Service Foundation Trust, UK
8 Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom.
†Joint senior authorship

Correspondence to:
Amedeo Minichino. Department of Psychiatry, University of Oxford, Oxford, UK. Email: amedeo.minichino@psych.ox.ac.uk

Abstract word length: 249 words (Limit: 250)

Text word length: 2658 (Limit: 3500)

Acknowledgment
Conflict of interest disclosure: None to report
Funding/Support: Dr. Minichino is supported by a MRC-Clarendon studentship
Access to data and data analysis: Dr. Minichino had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Abstract

The gut-microbiome has been hypothesised as a novel potential target for intervention for schizophrenia.

We tested this hypothesis with a systematic review and meta-analysis of studies investigating the efficacy and acceptability of augmentation strategies known to affect the gut-microbiome for the treatment of schizophrenia.

Following PRISMA guidelines, we searched from inception to August 2019 all the randomised double-blind controlled trials of add-on antibiotics, antimicrobials, pre/probiotics, and faecal transplant in schizophrenia. Primary outcomes were severity of negative symptoms and acceptability of treatment. Data were independently extracted by multiple observers and a random-mixed model was used for the analysis. Heterogeneity was assessed with the I² index.

We identified 28 eligible trials: 21 investigated antibiotics, 4 antimicrobials (Artemisinin, Artemether, and Sodium Benzoate), 3 pre/probiotics, none faecal transplant. Results showed no effect of D-Cycloserine (10 studies; SMD, -0.16; 95% CI -0.40, 0.08; P=0.20; I²: 28.2%), Minocycline (7 studies; SMD: -0.35; 95% CI -0.70, 0.00; P=0.05, I²:77.7%), other antibiotics (2 studies), probiotics alone (1 study), and Artemisinin (1 study) on negative symptoms of schizophrenia when compared to placebo. Limited evidence suggests efficacy on negative symptoms for Sodium benzoate (2 studies; SMD, -0.63; 95%CI -1.03, -0.23; P<0.001; I²:0%), Artemether (1 study), and probiotics combined with Vitamin D (1 study) when compared to placebo. Acceptability of intervention was similar to placebo. Currently available approaches targeting the gut-microbiome are ineffective as augmentation strategies for schizophrenia. There is a need of expanding our knowledge on the clinical relevance of gut-microbiome-host interaction in psychosis before engaging in further trials.
Introduction

Schizophrenia is the leading cause of severe functional disability among psychiatric disorders (Tandon et al., 2009). Functional impairments impact the quality of life of sufferers and their carers and impose relevant costs on wider society (Tandon et al., 2009). Treatment-resistant features of schizophrenia, such as negative symptoms, and the poor tolerability profile of antipsychotic medications have been identified as the main barrier limiting functional recovery in patients (Fusar-Poli et al., 2015; Green et al., 2012; Minichino et al., 2017b).

The gut-microbiome is a complex and balanced ecosystem of commensal micro-organisms that regulates a series of biological systems of relevance for psychotic disorders. Novel pathophysiological models suggest that the gut-microbiome might represent a novel target of intervention in schizophrenia (Cuomo et al., 2018; Minichino et al., 2017a; Nguyen et al., 2018; Zheng et al., 2019) (Figure 1). This hypothesis has been welcomed with enthusiasm by the scientific community, as shown by the rising number of commentaries and non-systematised reviews on the topic (Dinan et al., 2014; Minichino et al., 2017; Sarkar et al., 2016). This enthusiasm is clearly justified by the attractive possibility of improving the efficacy and acceptability of currently available medications with highly tolerable add-on interventions (Clarke et al., 2019).

Despite these premises, translational evidence is limited and contradictory, with only few clinical trials that tested the efficacy and acceptability of augmentation strategies in controlled randomised trials with the a-priori rationale of targeting the gut-microbiome in schizophrenia. However, there is a number of studies that used add-on compounds, such as antibiotics and antimicrobials, with a clear potential of modifying the gut-microbiome in patients (Bhalodi et al., 2019; Hrncirova et al., 2019; Willing et al., 2011). Interpreting and analysing the data from these studies will help to shed light on the potential of the gut-microbiome as a therapeutic target in schizophrenia.

In this paper, we provide the first systematic review and meta-analysis of augmentation strategies known to affect the gut-microbiome for the treatment of schizophrenia. Augmentation strategies were selected based on a preliminary search of the literature and after discussion with an expert of the field (PB). We identified four groups of add-on interventions: antibiotics, antimicrobials (i.e., non-antibiotic molecules with a well-known antimicrobial action), pre/probiotics, and faecal transplant. A summary of the included interventions with their putative mechanisms of action, can be found in Table 1.

Methods

We conducted a systematic review and meta-analysis of randomised double-blind controlled trials (RCTs-DB) comparing intervention known to affect the gut-microbiome (i.e., antibiotics, antimicrobials, pre/probiotics, and faecal transplant) and placebo as add-on treatment of schizophrenia and related psychosis (ICD and/or DSM-codified diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, first-psychotic episode). We followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (Moher et al., 2009).

The protocol was registered in PROSPERO: CRD42019137715 (see also eMethods).

Outcomes and meta-analyses
Primary outcomes:
1. Severity of negative symptoms at the end of follow-up (when available) or change score
2. Acceptability of treatment, measured as drop-out rates for any cause at the end of follow-up

Secondary outcomes:
1. Severity of positive, total, and cognitive symptoms at the end of follow-up (when available) or change score
2. Impact on findings on negative symptoms of clinical subgroups: (i) stage of illness (first-episode vs multi-episode); clozapine treatment; baseline severity of negative symptoms

Individual meta-analyses were conducted when 2 or more studies per compound/intervention were available. All meta-analyses were conducted in Stata, version 13.0 (StataCorp LLC). The standardized mean difference (SMD) was used as summary statistics for continuous outcomes and Risk Ratio (RR) for dichotomous outcomes. Data were independently extracted by multiple observers and a random-mixed model was used for the analysis. Heterogeneity was assessed with the I² index and risk of bias with the Cochrane Risk of Bias Tool (Higgins et al., 2011). When 10 or more studies were included in the analysis, funnel plots and Egger’s test (Egger et al., 1997) were used to assess the possibility of publication bias. Sensitivity analyses were conducted by sequentially removing single studies and rerunning the analysis and by excluding cross-over trials, when any.

Results
A total of 28 RCTs-DB were included (Buchanan et al., 2007; Cain et al., 2014; Chaudhry et al., 2012; Deakin et al., 2018; Dickerson et al., 2011, 2014, 2009; Duncan et al., 2004; Ghaderi et al., 2018; Goff et al., 2008; Goff et al., 2005; Goff et al., 1999a; Goff et al., 1999b; Gottlieb et al., 2011; Heresco-Levy et al., 2002; Kao et al., 2019; Kelly et al., 2015; Khodaie-Ardakani et al., 2014; Lane et al., 2013; Levkovitz et al., 2010; Lin et al., 2017; Liu et al., 2014; Shibre et al., 2010; Takiguchi et al., 2017; van Berckel et al., 1999; Wang et al., 2014; Weiser et al., 2019; Zhang et al., 2018). Of these, 21 RCTs compared add-on antibiotics vs placebo (N=11 D-Cycloserine (Buchanan et al., 2007; Cain et al., 2014; Duncan et al., 2004; Goff et al., 2008; Goff et al., 1999a; Goff et al., 1999b; Gottlieb et al., 2011; Heresco-Levy et al., 2002; Kao et al., 2019; Kelly et al., 2015; Khodaie-Ardakani et al., 2014; Lane et al., 2013; Levkovitz et al., 2010; Liu et al., 2014; Weiser et al., 2019; Zhang et al., 2018); N=8 Minocycline (Chaudhry et al., 2012; Deakin et al., 2018; Kelly et al., 2015; Khodaie-Ardakani et al., 2014; Levkovitz et al., 2010; Liu et al., 2014; Weiser et al., 2019; Zhang et al., 2018); N=1 Azithromycin (Dickerson et al., 2011); and N=1 Trimethoprim (Shibre et al., 2010)); 4 RCTs compared add-on antimicrobials vs placebo (N=2 Sodium Benzoate (Lane et al., 2013; Lin et al., 2017); N=1 Artemisinin (Dickerson et al., 2011); N=1 Artemether (Wang et al., 2014)); 3 RCTs compared add-on pre- and probiotics vs placebo (N=2 probiotics (Dickerson et al., 2014; Ghaderi et al., 2018); N=1 prebiotics (Kao et al., 2019)) (see Table 2). No studies investigated faecal transplant.

Negative symptoms
It was possible to perform individual meta-analyses for the antibiotics D-Cycloserine (10 studies; SMD: -0.16; 95% CI -0.40, 0.08; P=0.20; I²: 28.2%) and Minocycline (7 studies; SMD: -0.35; 95% CI -0.70, 0.00; P=0.05, I²:77.7%) and for the antimicrobial Sodium
Benzoate (2 studies; SMD, -0.63; 95%CI -1.03, -0.23; P<0.001; I²:0%) (Figure 2).
Add-on D-Cycloserine and Minocycline were not superior to placebo for the treatment of negative symptoms of schizophrenia. In contrast, a significant beneficial effect was found for add-on Sodium Benzoate. The pooled estimates on add-on D-Cycloserine and Minocycline were calculated after excluding one study that did not assess negative symptoms (Gottlieb et al., 2011) and one outlying study (Khodaie-Ardakani et al., 2014). The 2 RCTs investigating add-on Azithromycin and Trimethoprim both reported no effect on negative symptoms at the end of follow-up when compared to placebo (Dickerson et al., 2009; Shibre et al., 2010). No effect was found for add-on Artemisinin (Dickerson et al., 2011), while one study reported a significant beneficial effect on negative symptoms of Artemether (Artemisinin-derivative) (Wang et al., 2014).

The 2 add-on probiotics trials showed contrasting results. One trial used a combination of vitamin D and probiotics, which was found effective compared to placebo for treating negative symptoms(Ghaderi et al., 2018); however, the second trial used add-on probiotics alone and reported no effect(Dickerson et al., 2014). The only add-on prebiotics trial available to date in schizophrenia(Kao et al., 2019) did not assess negative symptoms.

In summary, none of the add-on antibiotic compounds was proved effective in improving severity of negative symptoms of schizophrenia at the end of follow-up, findings on antimicrobials and prebiotics were mixed and supported by limited evidence (Table 2).

Acceptability of treatment

It was possible to perform individual meta-analyses for the antibiotics D-Cycloserine (11 studies (Buchanan et al., 2007; Cain et al., 2014; Duncan et al., 2004; Goff et al., 2008; Goff et al., 1999a; Goff et al., 1999b; Goff et al., 2005; Gottlieb et al., 2011; Heresco-Levy et al., 2002; Takiguchi et al., 2017; van Berckel et al., 1999); RR, 0.91; 95% CI, 0.64-1.30; I²:0%; P=0.62) and Minocycline (8 studies (Chaudhry et al., 2012; Deakin et al., 2018; Kelly et al., 2015; Khodaie-Ardakani et al., 2014; Levkovitz et al., 2010; Liu et al., 2014; Weiser et al., 2019; Zhang et al., 2018); RR, 1.15; 95% CI, 0.96-1.38; P=0.13; I²:0%; P=0.13) for the antimicrobial Sodium Benzoate (2 studies(Lane et al., 2013; Lin et al., 2017); RR, 0.23; 95% CI, 0.04-1.36; I²:0%; P=0.10). None of the pooled estimates suggested a significant difference between the active compounds and placebo.

Trials on add-on Azithromycin(Dickerson et al., 2009), Trimethoprim(Shibre et al., 2010), Artemether(Wang et al., 2014), Artemisinin(Dickerson et al., 2011), probiotics alone(Dickerson et al., 2014), probiotics augmented with Vitamin D(Ghaderi et al., 2018), and prebiotics(Kao et al., 2019) did not report any significant difference in drop-out rates for any cause when compared to placebo.

In summary, none of the augmentation strategies included in our review differed from placebo in terms of acceptability (Table 2).

Positive, total, and cognitive symptoms

It was possible to perform individual meta-analyses on positive, total, and cognitive symptoms for the antibiotics D-Cycloserine and Minocycline, and for the antimicrobial Sodium Benzoate. Add-on D-Cycloserine and Minocycline did not differ from placebo in improving any of the clinical domains investigated (Supplementary results).

Pooled estimates on add-on Sodium Benzoate vs placebo showed a significant effect in
improving positive (2 studies, SMD, -0.94; 95%CI -1.35, -0.53; P<0.001; I²:0%) and total symptoms (2 studies, SMD, -0.68; 95%CI -1.08, -0.28; P=0.001; I²:0%), but not cognition, in schizophrenia(Lane et al., 2013; Lin et al., 2017).

Trials on add-on Azithromycin and Trimethoprim did not report any difference from placebo in improving positive and total symptoms; cognition was not investigated(Dickerson et al., 2009; Shibre et al., 2010).

Trials on add-on Artemisinin(Dickerson et al., 2011) and Artemether(Wang et al., 2014) did not find any difference from placebo in improving positive, total, and cognitive symptoms.

The add-on of vitamin D and probiotics was found effective compared to placebo in improving total symptoms(Ghaderi et al., 2018), while no effect was found for positive symptoms. The only trial investigating add-on probiotics alone (Dickerson et al., 2014) did not find any difference with placebo in improving positive and total symptoms. Both trials on add-probiotics did not assess cognition.

The only trial published to date on add-prebiotics in schizophrenia reported a significant effect vs placebo in improving cognitive performances (in particular executive functions)(Kao et al., 2019); positive and total symptoms were not investigated.

In summary, none of the investigated compounds with the exception of Sodium Benzoate (2 studies(Lane et al., 2013; Lin et al., 2017)), prebiotics (1 study(Kao et al., 2019)), and probiotics combined with Vitamin D (1 study(Ghaderi et al., 2018)) were found superior to placebo for the treatment of positive or total or cognitive symptoms of schizophrenia (Table 2).

**Impact of clinical subgroups on findings on negative symptoms**

It was possible to compare studies based on stage of illness only for those trials investigating the efficacy of add-on Minocycline vs placebo. Pooled estimates showed no differences in efficacy when studies were grouped based on illness stage (Fig. 1). Stage of illness was not considered in the individual study analyses in any of the other included trials.

It was possible to compare studies based on the severity of negative symptoms at baseline for the trials investigating add-on Minocycline and D-Cycloserine. Add-on Minocycline, but not D-Cycloserine, was found to be effective in patients with more severe negative symptoms at baseline (Fig. 2), in particular when at an early stage of illness (Fig. 3). Severity of negative symptoms at baseline was not considered in the individual study analyses in any of the other included trials.

Three studies reported data on patients treated with Clozapine only: one investigated add-on D-Cycloserine vs placebo, and found that the active compound worsened negative symptoms of schizophrenia(Goff et al., 1999b); a second one investigated add-on Minocycline vs Placebo, reporting no differences between the active compound and placebo(Kelly et al., 2015); a third one investigated add-on Sodium Benzoate and reported a significant beneficial effect of the active compound over placebo(Lin et al., 2017).

**Methodological considerations**

We found no differences in any of the investigated outcomes when cross-over trials were excluded from the analyses. No publication bias was detected with funnel plots or Egger’s test for small study effects.
Discussion

It has been hypothesised that affecting the gut-microbiome can improve treatment outcomes in schizophrenia (Dinan et al., 2014; Minichino et al., 2017a; Sarkar et al., 2016). We tested this hypothesis in a systematic review and meta-analysis. Primary outcomes were severity of negative symptoms and acceptability of treatment. Results were mainly negative. None of the investigated add-on antibiotics was superior to placebo for the treatment of negative, positive, total, and cognitive symptoms of schizophrenia. Preliminary and limited evidence suggested efficacy for add-on Sodium benzoate (on negative, positive, and total symptoms – 2 studies (Lane et al., 2013; Lin et al., 2017)), Artemether (on negative symptoms – 1 study (Wang et al., 2014)), prebiotics (on cognition – 1 study (Kao et al., 2019)), and probiotics augmented with Vitamin D (on negative and total symptoms – 1 study (Ghaderi et al., 2018)). Finally, none of the investigated augmentation strategies resulted in improved acceptability of treatment.

Treatment with antibiotics is one of the most extreme perturbations to the human gut-microbiome (Willing et al., 2011). When exposed to antibiotics, microbial communities respond not only by changing their composition, but also their functional features (e.g., gene expression) (Maurice et al., 2013). The antibiotics tested so far as augmentation therapies for schizophrenia (D-Cycloserine, Minocycline, Azithromycin, and Trimethoprim) have broad-spectrum activities (Palleja et al., 2018). To date, there is a limited understanding of the effects of individual antibiotics on the human gut-microbiome (Spanogiannopoulos et al., 2016). However, preliminary evidence suggests that wide-spectrum antibiotics reduce species richness and promote the depletion of Bifidobacterium species and butyrate producers in the gut-microbiome (Palleja et al., 2018). Bifidobacterium species produce gamma-aminobutyric acid, the main inhibitory neurotransmitter in the human brain (Barrett et al., 2012). Depletion of these bacterial species has been therefore hypothesised to affect the excitatory/inhibitory balance in the brain, which is altered in schizophrenia and manifesting with clinical symptoms (Mazzoli and Pessione, 2016). Similarly, low blood levels of butyrate are believed to play a role in pathophysiological models of schizophrenia (“Sodium Butyrate For Improving Cognitive Function In Schizophrenia - ClinicalTrials.gov”). Supplementation strategies aimed at normalising peripheral butyrate levels and improving symptoms of schizophrenia are currently being tested in ongoing randomised controlled trials (“Sodium Butyrate For Improving Cognitive Function In Schizophrenia - ClinicalTrials.gov”).

Based on these considerations we would expect that affecting the gut-microbiome with add-on antibiotics would have, if any, a worsening effect on symptoms of schizophrenia. The lack of any significant effect in any of investigated domains strongly suggests that antibiotic-induced modifications of the gut-microbiome in schizophrenia do not affect clinical outcomes.

One could argue that some of the antibiotics included in this review (namely, D-Cycloserine and Minocycline) also have a beneficial effect on key brain dysfunctional mechanisms associated with schizophrenia (Table 1); this central beneficial effect might counteract the peripheral modifications related to antibiotic use. However, this hypothesis is in contrast with
the lack of findings on add-on antibiotics trials that have no-known central effect (namely, Azithromycin and Trimethoprim).

The only compounds included in this review that showed efficacy as add-on treatment for schizophrenia were Sodium benzoate, Artemether, probiotics augmented with Vitamin D, and prebiotics.

Sodium Benzoate is an antimicrobial compound used as a preservative in food products (Chen and Zhong, 2018; Sershen et al., 2016). Our pooled estimate, based on only two studies, suggested that Sodium benzoate is effective for the treatment of negative, positive, and total symptoms of schizophrenia. Recent evidence suggests that human gut microbes, such as Bifidobacterium Longum and Lactobacillus Paracasei, are susceptible to Sodium benzoate(Hrncirova et al., 2019). These bacterial species are commonly described as “beneficial” for the host’s health, and can be commonly found in dairy product fermentations and some probiotics formulations(Jones, 2017; Wang et al., 2019). Therefore, we would expect that the effect of Sodium Benzoate on the gut-microbiome would be to reduce the relative abundance of beneficial bacteria in patients with schizophrenia. Thus, if any, the expected effect on clinical outcomes would be an increase in severity of symptoms.

In contrast, we found that add-on Sodium benzoate was an effective augmentation strategy for the treatment of schizophrenia. This is likely the result of its central rather than peripheral effect. Sodium Benzoate is known to cross the blood-brain barrier (BBB) and to inhibit D-AminoAcid Oxidase (DAOO); this in turns enhance the activity of receptors (namely, N-methyl-D-aspartate receptors) believed to hypo function in schizophrenia.

Artemether is anti-parasitic compound known to cross the BBB(Dickerson et al., 2011; Wang et al., 2014). The only study conducted so far on add-on Artemether for the treatment of schizophrenia, showed a beneficial effect on negative symptoms. These findings are unlikely related to its peripheral effect, considering the lack of efficacy in schizophrenia of add-on Artemisinin (similar peripheral effect and no central effect) and azithromycin and trimethoprim, which also have anti-parasitic peripheral effect, with no known central action (Table 1).

Probiotics and prebiotics are live bacteria and nutrients for bacteria, respectively, with a putative central indirect effect on glutamatergic neurotransmission(Kao et al., 2018; Sarkar et al., 2016). The available evidence to date suggests no effect of probiotics alone (Dickerson et al., 2014)on symptoms of schizophrenia, while the augmentation with vitamin D was beneficial for negative and total symptoms(Ghaderi et al., 2018). These preliminary findings advocate for the lack of a peripheral effect of probiotics of clinical relevance for schizophrenia. The positive findings reported by the latter study are in fact likely to be related to central action of Vitamin D (Ghaderi et al., 2018).

The only add-on prebiotics trial conducted to date in schizophrenia showed an interesting pro-cognitive effect in patients, which is worth of further investigation. Unfortunately, no measure of negative symptoms were collected(Kao et al., 2019).

Findings on clinical subgroups were mainly limited to Minocycline and suggested that patients with more severe negative symptoms may benefit from this augmentation, especially if early in the course of illness. Based on the considerations on the antibiotic action on the
gut-microbiome, it is unlikely that these findings are related to the gut-microbiome targeted action of Minocycline.

**Conclusions**

This systematic review and meta-analysis suggests that the currently available approaches targeting the gut-microbiome in schizophrenia are ineffective. Preliminary and limited evidence suggested that some of the augmentation strategies with a known effect on the gut-microbiome improved clinical symptoms of schizophrenia. However, the effect of these compounds, when any, was likely to be related to their central, rather than gut-microbiome targeted, action.

There is a need of expanding our knowledge on the clinical relevance of gut-microbiome-host interaction in psychosis before engaging in further trials. In particular, there is a clear gap in knowledge about which features of the gut-microbiome might be relevant (e.g., beneficial or harmful) for the disease status. Given the clinical heterogeneity of schizophrenia it will be crucial to understand if and how gut-microbiome features relate and contribute to different phenotypes. Lastly, there is evidence suggesting that the gut-microbiome might be involved in the metabolism of specific antipsychotics (i.e., risperidone and derivatives, olanzapine).

Future studies should aim at clarifying if this interaction is clinically relevant and whether and how we can translate this knowledge to improve treatment outcomes.

**Limitations**

Limitations include relatively small sample sizes in a number of studies. Furthermore, only 2–3 studies were meta-analysed for a number of secondary outcomes and for the primary outcome on Sodium Benzoate. The use of different scales to assess endpoint scores represent another limitation. Finally, acceptability measures were limited to drop-out rates.

**References**


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https://doi.org/10.1016/j.schres.2009.03.005

https://doi.org/10.1016/S0893-133X(99)00014-7


\textbf{Figure 1.} The gut-brain axis: putative relevance for negative symptoms in schizophrenia.
The gut-brain axis is a bidirectional communication network that contributes to the regulation of both peripheral and central physiological functions. The gut-microbiota is a complex and balanced ecosystem of commensal micro-organisms that regulates a series of biological system of relevance for psychotic disorders, including biological barriers permeability, pro-inflammatory responses and central neurotransmitter modulation.


The hypofunction of N-methyl-D-aspartate (NMDA) in the brain are believed to play a central role in the pathophysiology of schizophrenia. Perturbations in the gut microbiota (“gut dysbiosis”) result in increased synthesis and release in the blood stream of a series of molecules that have the potential to reduce central N-methyl-D-aspartate (NMDA) receptor activity, including pro-inflammatory molecules (e.g., Interleukin-1, Il-1) and neurotransmitters-derivatives (kynurenine acid).

The passage of these molecules from the blood stream to the central nervous system seems to be facilitated by the increased permeability of biological barriers – a phenomenon related to gut dysbiosis and triggered by activation of pathways 1, 2 and 3.

Based on these considerations, a number of authors suggested that the gut-microbiome might represent a new treatment target in schizophrenia (references in main text).
**Figure 2.** Forest plot of standardised mean difference in end-point negative symptoms in patients treated with augmentation strategies known to affect the gut-microbiome vs placebo.

In this forest plot are reported all the included trials that assessed negative symptoms at end of follow-up. NR: Data were not reported AND not retrievable (i.e., no replies from authors).
Table 1. Augmentation strategies included in the systematic review: putative mechanisms of actions on the gut-microbiome-brain axis

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cross Blood-Brain Barrier</th>
<th>Effect on the central nervous system</th>
<th>Effect on the gut-microbiome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre/Probiotics</td>
<td>No</td>
<td><strong>Indirect effect</strong> Modulates expression of NMDA-R and GABA-R in hippocampus and frontal cortex(Kao et al., 2018; Sarkar et al., 2016)</td>
<td>↑ Bifidobacterium and Lactobacillus families(Sarkar et al., 2016)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Yes</td>
<td><strong>No direct effect</strong></td>
<td>↓Species richness  ↓Bifidobacterium species ↓Butyrate producers(Willing et al., 2011)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Yes</td>
<td><strong>No direct effect</strong></td>
<td>↓Species richness  ↓Bifidobacterium species ↓Butyrate producers(Willing et al., 2011)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Yes</td>
<td><strong>Unclear</strong> Proposed direct effect: inhibition of microglia activation AND inhibition of NOS(Garrido-Mesa et al., 2013)</td>
<td>↓Species richness  ↓Bifidobacterium species ↓Butyrate producers(Willing et al., 2011)</td>
</tr>
<tr>
<td>D-Cycloserine</td>
<td>Yes</td>
<td><strong>Direct effect</strong> NMDA-R partial agonist(Goff et al., 2016)</td>
<td>↓Species richness  ↓Bifidobacterium species ↓Butyrate producers(Willing et al., 2011)</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Yes</td>
<td><strong>Direct</strong> D-amino acids oxidase (DAAO) inhibitor – modulates NMDA-R activity(Sershen et al., 2016)</td>
<td>↓Bifidobacterium Longum and Lactobacillus Paracasei (Chen and Zhong, 2018; Hrncirova et al., 2019)</td>
</tr>
<tr>
<td>Artemisinin</td>
<td>Yes</td>
<td><strong>Direct (Artemether only)</strong> ↑NMDA-R expression(Singh et al., 2019)</td>
<td>Anti-parasitic activity (Ke et al., 1990)</td>
</tr>
<tr>
<td>Artemether</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend. ↑:increase; ↓:decrease; GABA: Gamma-Aminobutyric acid; NMDA-R: N-Methyl-d-aspartic acid receptors; NOS: Nitric Oxide Synthase
## Table 2. Main characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>In/outpatients</th>
<th>Stage</th>
<th>Gender</th>
<th>N (%)-Female</th>
<th>Inclusion criteria</th>
<th>Duration</th>
<th>Add-on</th>
<th>Add-on dose</th>
<th>TAU</th>
<th>N add-on</th>
<th>N placebo</th>
<th>Negative Symptoms Scale (main)</th>
<th>NS Baseline Score Mean (SD)</th>
<th>Main findings Efficacy</th>
<th>Main findings Tolerability</th>
<th>Funding</th>
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<tr>
<td><strong>In. D-Cycloserine</strong></td>
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<tr>
<td>Goff 1999a</td>
<td>RDCBT</td>
<td>Mixed</td>
<td>Multi-episode</td>
<td>12 (17.4)</td>
<td>1. Primary Deficit Syndrome (Kirkpatrick 1989) 2. SANS≥30 3. SAS &lt; 8 4. HAM-D 18 &lt; 25</td>
<td>8 weeks</td>
<td>D-Cycloserine</td>
<td>50 mg once daily</td>
<td>Typical APs</td>
<td>23</td>
<td>24</td>
<td>SANS</td>
<td>52.6 (13.8)</td>
<td>At 8 weeks, D-Cycloserine vs placebo: 1. ↓ Negative symptoms 2. = Positive symptoms 3. = Total symptoms 4. = Cognition</td>
<td>No differences in acceptability</td>
<td>1. NIMH</td>
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<tr>
<td>Goff 1999b</td>
<td>RCDBT crossover</td>
<td>Outpatients</td>
<td>Multi-episode</td>
<td>2 (28.5)</td>
<td>1. SANS &gt; 30</td>
<td>6 weeks</td>
<td>D-Cycloserine</td>
<td>50 mg once daily</td>
<td>Clozapine</td>
<td>17</td>
<td>17</td>
<td>SANS</td>
<td>49.5 (NA)</td>
<td>At 6 weeks, D-Cycloserine vs placebo: 1. ↑ Negative symptoms</td>
<td>No differences in acceptability</td>
<td>1. PHS</td>
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<tr>
<td>Van Berckel 1999</td>
<td>RCDBT</td>
<td>Mixed</td>
<td>Multi-episode</td>
<td>4 (15.4)</td>
<td>1. At least &quot;moderate&quot; scores on two items of the PANSS Negative</td>
<td>8 weeks</td>
<td>D-Cycloserine</td>
<td>100 mg daily</td>
<td>Typical APs</td>
<td>13</td>
<td>13</td>
<td>PANSS Negative</td>
<td>25.2 (4.7)</td>
<td>At 8 weeks, D-Cycloserine vs placebo: 1. = Negative symptoms 2. ↑ Positive symptoms 3. = Total symptoms</td>
<td>No differences in acceptability</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Design</td>
<td>Method</td>
<td>Patients</td>
<td>Duration</td>
<td>Drug</td>
<td>Dose</td>
<td>Comparator</td>
<td>Endpoints</td>
<td>Outcome</td>
<td>Notes</td>
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<tr>
<td>Duncan</td>
<td>2004</td>
<td>RCDBT</td>
<td>Mixed</td>
<td>Multi-episode</td>
<td>0 (0)</td>
<td>1. Primary Deficit Syndrome (Kirkpatrick 1989) 2. SANS≥30</td>
<td>4 weeks</td>
<td>D-Cycloserine</td>
<td>50 mg once daily</td>
<td>Mixed typical and atypical APs</td>
<td>10</td>
<td>SANS</td>
<td>69.1 (16.7)</td>
<td>At 4 weeks, D-Cycloserine vs placebo: 1. = Negative symptoms 2. = Positive symptoms 3. = Total symptoms 4. = Cognition</td>
<td>No differences in acceptability</td>
<td>Not stated</td>
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<tr>
<td>Goff</td>
<td>2005</td>
<td>RCDBT</td>
<td>Outpatients</td>
<td>Multi-episode</td>
<td>11 (20.0)</td>
<td>1. SANS≥40</td>
<td>6 months</td>
<td>D-Cycloserine</td>
<td>50 mg once daily</td>
<td>Typical APs</td>
<td>27</td>
<td>SANS</td>
<td>50 (11.6)</td>
<td>At 6 months, D-Cycloserine vs placebo: 1. = Negative symptoms 2. = Positive symptoms 3. = Total symptoms 4. = Cognition</td>
<td>No differences in acceptability</td>
<td>1. NIMH</td>
<td></td>
</tr>
<tr>
<td>Goff</td>
<td>2008</td>
<td>RCDBT</td>
<td>Outpatients</td>
<td>Multi-episode</td>
<td>15 (39.4)</td>
<td>None</td>
<td>8 weeks</td>
<td>D-Cycloserine</td>
<td>50 mg once weekly</td>
<td>Mixed typical and atypical APs</td>
<td>19</td>
<td>19</td>
<td>SANS-Modified (SANS total minus Attention subscale)</td>
<td>At 8 weeks, D-Cycloserine vs placebo: 1. ↓ Negative symptoms 2. ↓ Positive symptoms 3. ↓ Total symptoms 4. ↓ Cognition</td>
<td>No differences in acceptability</td>
<td>1. NIMH</td>
<td></td>
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<tr>
<td>Gottlieb</td>
<td>2011</td>
<td>RCDBT- crossover</td>
<td>Outpatients</td>
<td>Multi-episode</td>
<td>7 (35)</td>
<td>1. SAPS ≥ 3 &quot;on the global measure of delusional severity&quot;</td>
<td>2 weeks</td>
<td>D-Cycloserine</td>
<td>50 mg once weekly</td>
<td>Mixed typical APs</td>
<td>11</td>
<td>9</td>
<td>Not measured</td>
<td>At 2 weeks, D-Cycloserine vs placebo:</td>
<td>No differences in tolerability</td>
<td>1. Harvard Medical School NIMH</td>
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</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Group</td>
<td>Type</td>
<td>Primary Outcome</td>
<td>Comparator</td>
<td>Follow-up</td>
<td>Treatment</td>
<td>Comparator</td>
<td>Follow-up</td>
<td>Outcome 1</td>
<td>Outcome 2</td>
<td>Outcome 3</td>
<td>Outcome 4</td>
<td>Outcome 5</td>
<td>Notes</td>
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<tr>
<td>Cain 2014</td>
<td>RCDBT</td>
<td>Outpatients</td>
<td>Mixed-episode</td>
<td>5 (13.9)</td>
<td>None</td>
<td>8 weeks</td>
<td>D-Cycloserine</td>
<td>50 mg once weekly</td>
<td>Mixed typical and atypical APs</td>
<td>18</td>
<td>18</td>
<td>SANS-Modified (SANS total minus Attention subscale)</td>
<td>25.2 (12.1)</td>
<td>At 8 weeks, D-Cycloserine vs placebo: 1. ↓ Negative symptoms (overall group) 2. ↓ Negative symptoms (patients with SANS≥20) 3. = Positive symptoms 4. = Total symptoms 5. = Cognition 6. ↑ performances in auditory discrimination task</td>
<td>No differences in acceptability</td>
<td>1. NARSAD 2. NIH 3. NIMH</td>
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<tr>
<td>Levkovitz 2010</td>
<td>RCDBT</td>
<td>Mixed?</td>
<td>Early-phase</td>
<td>14 (25.9)</td>
<td>1. PANSS Total≥60</td>
<td>6 months</td>
<td>Minocycline</td>
<td>200mg once daily</td>
<td>Mixed typical and atypical APs</td>
<td>36</td>
<td>18</td>
<td>SANS</td>
<td>42.9 (18.5)</td>
<td>At 24 weeks, Minocycline vs placebo: 1. ↓ Negative symptoms 2. = Positive symptoms 3. = Total symptoms 4. ↑ Cognition (Executive functions)</td>
<td>At 24 weeks, Minocycline vs placebo: 1. ↓ Weight gain</td>
<td>1. NIMH</td>
<td></td>
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<tr>
<td>Chaudry 2012</td>
<td>RCDBT</td>
<td>Mixed?</td>
<td>Early-phase</td>
<td>58 (40.3)</td>
<td>12 months</td>
<td>Minocycline</td>
<td>200mg once daily</td>
<td>Mixed typical and atypical APs</td>
<td>71</td>
<td>73</td>
<td>PANSS Negative</td>
<td>21.9 (7.3)</td>
<td>At 1 year, Minocycline vs placebo: 1. ↓ Negative symptoms 2. = Positive symptoms</td>
<td>No differences in acceptability</td>
<td>1. PHS</td>
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<tr>
<td>Study</td>
<td>RCDBT</td>
<td>Design</td>
<td>Phase</td>
<td>N</td>
<td>Follow-up</td>
<td>Treatment</td>
<td>Comparator</td>
<td>Follow-up Symptom Change</td>
<td>Notes</td>
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<tr>
<td>Liu 2014</td>
<td>RCDFT</td>
<td>Not stated</td>
<td>Early-phase</td>
<td>30 (38.0)</td>
<td>4 months</td>
<td>Minocycline 200mg once daily</td>
<td>Risperidone only</td>
<td>39</td>
<td>40 (14.7)</td>
<td>At 6 weeks, Minocycline vs placebo: 1. ↓ Negative symptoms 2. = Positive symptoms 3. = Total symptoms 4. ↑ Cognition (attention) No difference in acceptability</td>
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<tr>
<td>Khodaie-Ardakani 2014</td>
<td>RCDFT</td>
<td>Outpatients</td>
<td>Multi-episode</td>
<td>11 (27.5)</td>
<td>2 months</td>
<td>Minocycline 200mg once daily</td>
<td>Risperidone only</td>
<td>20</td>
<td>20</td>
<td>At 8 weeks, Minocycline vs placebo: 1. ↓ Negative symptoms 2. ↓ Positive symptoms 3. ↓ Total symptoms No difference in acceptability</td>
<td></td>
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<tr>
<td>Kelly 2015</td>
<td>RCDFT</td>
<td>Mixed</td>
<td>Multi-episode</td>
<td>13 (25.4)</td>
<td>2.5 months</td>
<td>Minocycline 100 mg twice daily</td>
<td>Clozapine</td>
<td>29</td>
<td>23 (12.9)</td>
<td>At 10 weeks, Minocycline vs placebo: 1. ↓ Avolition 2. = Negative symptoms (total score) 3. = Positive symptoms 4. = Total symptoms 5. ↑ Cognition (working memory) No difference in acceptability</td>
<td></td>
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<tr>
<td>Deakin 2018</td>
<td>RCDFT</td>
<td>Mixed</td>
<td>Early-phase</td>
<td>57 (27.5)</td>
<td>12 months</td>
<td>Minocycline 100mg twice daily for 2 weeks, 100mg three times daily for the Mixed typical and atypical APs</td>
<td>PANSS Modified (SANS total score minus &quot;global items, inappropriate affect, poverty of content of speech, attention&quot;)</td>
<td>104</td>
<td>103 (5.7)</td>
<td>At 15 months, Minocycline vs placebo: 1. = Negative symptoms No difference in acceptability</td>
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Notes:
1. National R&D Special Fund for Health Profession National Natural Science Foundation of China National Science and Technology Major Projects for "Major New Drugs Innovation and Development 
2. No difference in acceptability
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Treatment Duration</th>
<th>Treatment Details</th>
<th>Control Group Details</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Acceptability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang 2018</td>
<td>RCDBT</td>
<td>Mixed Multi-episode</td>
<td>38 (50-6)</td>
<td>Minocycline 1.00mg once daily 2. 100mg twice daily</td>
<td>PANSS negative &gt; 20 2. PANSS Positive &gt; PANSS Negative</td>
<td>At 3 months, Minocycline 200 mg/daily vs placebo: 1. ↓ Negative symptoms 2. = Positive symptoms 3. = Total symptoms</td>
<td></td>
</tr>
<tr>
<td>Weser 2019</td>
<td>RCDBT</td>
<td>Mixed Mixed</td>
<td>43.4 (10.1)</td>
<td>Minocycline 100 mg twice daily</td>
<td>PANSS Delusions ≥ 4 or 2. PANSS Conceptual disorganisation ≥ 4 or 3. PANSS Hallucinatory behaviour ≥ 4 or 4. PANSS Suspiciousness ≥ 4 or 5. PANSS Negative ≥ 18</td>
<td>At 3 months, Minocycline 200mg/daily vs placebo: 1. = Negative symptoms 2. = Total symptoms 3. = General symptoms</td>
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### 1c. Other antibiotics

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Treatment Duration</th>
<th>Treatment Details</th>
<th>Control Group Details</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Acceptability</th>
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<tr>
<td>Dickerson 2009</td>
<td>RCDBT Outpatients 15 (54.0)</td>
<td>16 weeks</td>
<td>Azithromycin 600mg once daily for the first two</td>
<td>PANSS Negative Not reported</td>
<td>At 16 weeks, Azithromycin vs placebo: No differences in</td>
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No difference in acceptability
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<th>Study</th>
<th>Design</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Recruitment Criteria</th>
<th>Intervention Duration</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Acceptability</th>
<th>Funding</th>
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<tbody>
<tr>
<td>Shibre 2010</td>
<td>RCT</td>
<td>Mixed*</td>
<td>0 (0)</td>
<td>1. PANSS Total ≥ 60</td>
<td>6 months</td>
<td>Trimethoprim</td>
<td>Mixed typical and atypical APs</td>
<td>46</td>
<td>45</td>
<td>PANSS Negative</td>
<td>35.7 (9.6)</td>
</tr>
<tr>
<td>Dickerson 2011</td>
<td>RCT</td>
<td>Outpatients</td>
<td>28 (42.0)</td>
<td>1. &quot;Psychotic symptoms which were at least moderately severe&quot; based on PANSS Positive and/or 2. PANSS Negative ≥ 4 or 3. PANSS Total ≥ 50 &quot;containing at least three positive or negative items with scores ≥ 3&quot;</td>
<td>10 weeks</td>
<td>Artemisinin</td>
<td>100 mg twice daily</td>
<td>Mixed typical and atypical APs</td>
<td>33</td>
<td>33</td>
<td>PANSS Negative</td>
</tr>
<tr>
<td>Wang 2014</td>
<td>RCT</td>
<td>Mixed*</td>
<td>33 (53.0)</td>
<td>1. PANSS Total ≥ 60</td>
<td>8 weeks</td>
<td>Artesunate</td>
<td>80 mg once daily at week 2 and week 4</td>
<td>Risperidone only</td>
<td>50</td>
<td>50</td>
<td>PANSS Negative</td>
</tr>
<tr>
<td>Lane 2013</td>
<td>RCT</td>
<td>Mixed*</td>
<td>26 (50.0)</td>
<td>1. PANSS Total ≥ 60</td>
<td>6 weeks</td>
<td>Sodium Benzoate</td>
<td>1g once daily</td>
<td>Mixed typical and atypical APs</td>
<td>25</td>
<td>27</td>
<td>SANS</td>
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### 1e. Pre/Probiotics

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<tr>
<th>Last Name</th>
<th>Designation</th>
<th>Patient Type</th>
<th>Multi-episode</th>
<th>N</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Conclusion</th>
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<tr>
<td>Lin 2017</td>
<td>RCDHT</td>
<td>Inpatients</td>
<td>Multi-episode</td>
<td>19 (31.7)</td>
<td>1. SANS-20 ≥40  2. PANSS total ≥70  3. AP-resistance  4. Clozapine-resistance (12 weeks of treatment without satisfactory response)</td>
<td></td>
<td>6 weeks Sodium Benzoate  1. 1g once daily  2. 2 g once daily</td>
<td>Clozapine  1. 20 (1g dose)  2. 20 (2g dose)</td>
<td>20</td>
</tr>
<tr>
<td>Dickerson 2014</td>
<td>RCDHT</td>
<td>Outpatients</td>
<td>Multi-episode</td>
<td>23 (35.4)</td>
<td>1. PANSS Positive≥1 or 2. PANSS Negatives ≥ 4 or 3. PANSS Total ≥ 56, “containing at least 3 positive or negative items with scores ≥ 3”</td>
<td></td>
<td>14 weeks Probiotics*  *Lactobacillus rhamnosus strain GG and Bifidobacterium animalis subsp. lactis strain Bb12</td>
<td>10-CFU Lactobacillus and 10-CFU Bifidobacterium once daily</td>
<td>Mixed typical and atypical APs</td>
</tr>
<tr>
<td>Gadheri 2018</td>
<td>RCDHT</td>
<td>Mixed?</td>
<td>Not stated</td>
<td>4 (6.7)</td>
<td>1. PANSS total ≥ 55  2. HDRS &lt;14 OR PANSS depressions&lt; 4</td>
<td></td>
<td>12 weeks Probiotics* + Vitamin D  *Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri, Lactobacillus fermentum</td>
<td>8x10 CFU once daily probiotics and 50,000 IU Vitamin D every two weeks</td>
<td>Mixed typical and atypical APs</td>
</tr>
<tr>
<td>Kao 2019</td>
<td>RCDHT</td>
<td>Outpatients</td>
<td>Multi-episode</td>
<td>1. Global cognitive score below “0.5 SD the healthy average”</td>
<td>24 weeks</td>
<td>B-GOS</td>
<td>Once daily</td>
<td>Mixed typical and atypical APs</td>
<td>21</td>
</tr>
</tbody>
</table>

1. Taiwan Department of Health  
2. Ministry of Science and Technology  
3. Welfare Clinical Trial and Research Centre of Excellence  
4. China Medical University Hospital, Taiwan
Legend. ↑: Increase; ↓: Reduce; = No effect. APs: Antipsychotics; B-GOS: galacto-oligosaccharide prebiotic; CFU: colony forming unit; HDRS: Hamilton Depression Rating Scale; NIH: National Institute of Health; NIMH: National Institute of Mental Health; NARSAD: National Alliance for Research on Schizophrenia & Depression; NSC: National Science Council; PANSS: Positive and Negative Syndrome Scale; PHS Public Health Service; RCDBT: Randomised-Controlled Double Blind Trial; SANS: Scale for the Assessment of Negative Symptoms; SAS: Simpson-Angus Scale