Title: Psycho-pharmacomicrobiomics: a systematic review and meta-analysis

Amedeo Minichino[1], Tabitha Preston[1], Jack Fanshawe[1], Paolo Fusar-Poli[2, 3, 4, 5], Philip McGuire[1], Philip WJ Burnet[1], Belinda R Lennox[1, 6]

Affiliations

[1]Department of Psychiatry, University of Oxford
[2]Early Psychosis: Interventions and Clinical-Detection (EPIC) Lab
[2]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom.
[2]OASIS Service, South London and Maudsley NHS Foundation Trust, London, United Kingdom.
[5]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy.
[6]National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, United Kingdom.

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Corresponding author: Dr Amedeo Minichino
Department of Psychiatry, Warneford Lane, Headington, Oxford OX3 7JX
Amedeo.minichino@psych.ox.ac.uk

Abstract

Understanding the bi-directional interplay between the gut microbiome and the effects of psychotropics drugs ("psycho-pharmacomicrobiomics") could lead to improved treatment stratification and personalised interventions strategies in psychiatry. In this systematic review and meta-analysis, we addressed the following questions: 1. Do psychotropic medications modify the gut microbiome? 2. Does the gut microbiome affect the efficacy and tolerability of psychotropic medications?

Following PRISMA guidelines, we searched from inception to November 2022 for longitudinal and cross-sectional studies investigating the effect of psychotropic medications (namely antipsychotic, antidepressants, and mood stabilisers) on the gut microbiome. The primary outcome was the difference in diversity metrics (alpha and beta) before and after treatment with psychotropics (longitudinal studies), and in medicated compared to unmedicated individuals (cross-sectional studies). Secondary outcomes included the association between gut microbiome features (at baseline and changes after treatment) with efficacy and tolerability outcomes. Random effect meta-analyses were conducted on alpha diversity metrics, while beta diversity metrics were pooled using individual patient data. Summary statistics included SMD, 95% CI, and Higgins I^2 for alpha diversity metrics, F and R values for beta diversity metrics.

Eighteen studies encompassing 885 patients were included in our synthesis; twelve investigated antipsychotics and six antidepressants. Results showed significant changes in alpha (SMD: 0.12; 95% CI: 0.01 to 0.23; P=0.04; I^2: 14%) and beta (F=15.59; R^2:0.05; P<0.001) diversity metrics following treatment with antipsychotics and antidepressants, respectively. Altered gut microbiome composition at baseline was associated with tolerability and efficacy outcomes across studies, including response to antidepressants (alpha diversity; SMD: 2.45; 95%CI: 0.50 – 4.40; P<0.001, I^2: 0%). Females, but not males, patients treated with antipsychotics showed reduced alpha diversity compared to untreated controls (SMD: -0.68; 95% CI: -1.31 to -0.04; P=0.04; I^2: 37.61%).

These findings suggest that: 1. Treatment with psychotropic medications are associated with altered gut microbiome composition; 2. Gut microbiome features may influence the efficacy and tolerability of these medications. Further studies using translational approaches to clarify mechanisms and direction of causality are indicated.

Introduction

There is accumulating evidence suggesting a bi-directional interplay between medications and the human gut microbiome.
About one in four human-targeted medications can inhibit the growth of gut bacteria, and a large proportion of these are antipsychotics [1, 2]. Medication-induced changes in the gut microbiome can significantly impact their efficacy and tolerability [3]. A seminal example is metformin, which improves glucose tolerance by modifying the gut microbiome [4]. On the other hand, gut bacteria can modify medication metabolism, which may alter their efficacy and tolerability [5]. Human gut bacteria can convert pro-medications into active compounds [6], inactivate medications [7], influence their enterohepatic recirculation via β-D-glucuronidases [8], and affect their absorption via secondary bile acids and blockage of intestinal P-glycoproteins[9]. Bacteria can also directly influence the tolerability of medications by generating toxic metabolites via bacterial enzymes [10].
The study of the interplay between gut bacteria and medications has been described as "pharmacomicrobiomics" [11]. Due to the modifiable nature of the gut microbiome, findings can also help identity modifiable targets of interventions to improve the efficacy and tolerability of existing medications.
Pharmacomicrobiomics applied to the field of psychiatry ("psycho-pharmacomicrobiomics") might help address key unmet needs, such as the high inter-individual variability in treatment response and the high burden of side effects of psychotropic medications[12]. A nationwide population study showed that the use of antibiotics, strong modifiers of the gut microbiome, is associated with increased prescriptions of psychotropics (antipsychotics, mood stabilisers, and antidepressants) and hospitalisations for mental health disorders [13]. These findings, which provide indirect evidence of the association between alterations in gut microbiome and reduced efficacy of psychotropics, are supported by findings from an animal study, showing a direct relationship between changes in gut bacteria and reduced bioavailability of olanzapine [14]. Studies on the interplay between psychotropics and the gut microbiome in clinical populations are therefore emerging. However, findings from individual microbiome studies are often hard to interpret due to inconsistencies in methodological approaches and reporting bias.
For these reasons, we conducted a systematic review and meta-analysis where we summarised the evidence from clinical studies investigating the bi-directional interplay between the gut microbiome and psychotropic medications. We addressed two key questions: 1. Do psychotropic medications modify the gut microbiome? 2. Does the gut microbiome affect the efficacy and tolerability of psychotropic medications?
Finally, we systematically appraised the quality of the included studies against the newly validated 'Strengthening The Organization and Reporting of Microbiome Studies' (STORMS) checklist [15] and provided directions for future investigations in the field.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting guidelines [16] (see Supplementary material for the checklist). We followed a pre-registered protocol (DOI 10.17605/OSF.IO/ZDE5Y).
Search for published studies was conducted from inception to 15th November 2022, in Web of Science and PubMed using a piloted search strategy available in supplementary material.

Studies that did not meet criteria for inclusion were excluded, with reasons documented in **Figure 1 (**PRISMA flowchart**)**. Search process and data extraction were conducted independently by two authors, and disagreements resolved by consensus.

Type of studies

We included: longitudinal studies in clinical populations that investigated changes in gut microbiome features before and after starting a treatment with a psychotropic medication(s), and cross-sectional studies that compared gut microbiome features in patients treated with psychotropic drugs vs untreated patients.
There was no restriction on the underlying clinical conditions being treated with psychotropic medications (i.e., antidepressants, antipsychotics, mood stabilisers, or their combination), or on the age, gender, body mass index (BMI) of participants.
We included only original studies written in English.
We excluded studies that collected gut microbiome data only in medicated patients and healthy controls, as differences in gut microbiome features reported in these studies might be related to illness mechanisms rather than to medications. For the same reason, we excluded studies that included only participants with comorbid gastrointestinal disorders (e.g., major depressive disorders and inflammatory bowel disorders).
We excluded studies that investigated gut microbiome features in healthy volunteers only ad data reported in conference abstracts and unpublished literature.

Outcomes

To address our first question (Do psychotropic medications modify the gut microbiome? – primary outcome), we summarised findings on differences in gut microbiome features (i.e., diversity, taxonomy and functionality) before and after treatment with psychotropic medications (in longitudinal studies), and in medicated compared to unmedicated patients (in cross-sectional studies).
To address our second question (Does the gut microbiome affect the efficacy and tolerability of psychotropic medications? – secondary outcome), we looked at data on the association between gut microbiome features and measures of treatment response and tolerability across the included studies. When sufficient data were available, we further looked at differences in gut microbiome features in treatment responders (as defined by individual studies) compared to not responders.
Our primary outcome measure was alpha diversity, measured with the Shannon index. This indicates how many bacterial species are represented in a sample (richness) and how well they are represented (evenness)[17]. Our secondary measure was beta diversity (see Supplementary for measurement methods). This metric indicates if certain groups (e.g., treated patients) cluster differently based on the gut microbiome structure compared to other groups (e.g., untreated patients) [17]. Other outcomes were differences in taxonomic and microbial functional analyses.

Data synthesis

Random effect meta-analyses were performed for alpha diversity metrics when data from more or two studies per class of psychotropic (i.e., antidepressants, antipsychotics, mood stabilisers) were available; summary statistics included standardised mean differences (SMD) 95% CI, and the Higgin's I^2. We performed sensitivity analyses by sequentially removing single studies and rerunning the analysis.

Synthesis of beta diversity data followed a different, yet validated approach [18]. In brief, we extracted individual patient data of the coordinates of the first two axes of beta diversity metrics from each study. We then performed PERMANOVA with the vegan adonis function in R on the Euclidian distance matrix of the extracted data; summary statistics included R^2, F and P values.
Quantitative analyses were conducted separately for longitudinal and cross-sectional studies, to take into account the nested structure of longitudinal studies and the inter-individual variability of gut microbiome data (see also Supplementary methods).
Pre-planned subgroup analyses were based on variables with a known impact on the gut microbiome and were conducted on the following studies: including children; including obese participants; reporting gender-specific data; using different microbial sequencing methods; using polypharmacy; investigating specific antipsychotics/antidepressants/mood stabilizers; at low risk of bias.
Microbial taxonomic and functional findings were summarised only qualitatively, following previously validated methods [19] (see also supplementary material).

Risk of Bias/Quality of included studies

Risk of bias was assessed independently by two reviewers using an adapted version of the Strengthening The Organization and Reporting of Microbiome Studies' (STORMS) checklist [15] and visualised with the robvis tool [20].

Results

A total of 18 studies met the inclusion criteria (see PRISMA flowchart, **Figure 1**).
Of these, 14 were longitudinal studies that reported data on pre and post treatment differences in gut microbiome features across 484 patients treated with either antidepressants (six studies[21-26]; N=167) or antipsychotics (eight studies[27-34]; N=317); Five studiesreported cross-sectional data on gut microbiome features in patients treated with antipsychotics (N=182) vs antipsychotic-free patients (N=165)[27, 35-38] and two on patients treated with antidepressants vs antidepressants-free patients [26, 38, 39]. No studies directly investigated mood stabilizers.
Please see **Table 1** and **Table 2** for a qualitative summary of results.

[Fig.1]

Antipsychotics

Longitudinal studies

Of the eight longitudinal studies involving antipsychotics, three investigated Risperidone [27, 31, 32], one Amisulpiride [33], one Olanzapine [30], two Quetiapine [28, 29], and one a variety of different antipsychotics [34].
Five studies reported data on gut microbiome alpha diversity before and after treatment with antipsychotics [28, 30, 32, 33, 38]. All studies reported the Shannon index as a measure of alpha diversity. One of these studies did not report analysable data [38]; it was therefore excluded from the analyses. The pooled estimate showed a significant increase in gut microbiome alpha diversity after treatment with antipsychotic medications (N=4 studies; SMD: 0.12; 95% CI: 0.01 to 0.23; P=0.04; I^2: 14%; **Fig. 2**).

[Fig.2]

Only one study included obese participants [30], precluding subgroup analyses based on obesity. None of the studies included in the quantitative synthesis on alpha diversity included children, reported analysable data on gender, none used polypharmacy, and all used the same sequencing method, follow-up timing ranged from 1 to 6 months.
Four longitudinal studies reported data on beta diversity before and after treatment with antipsychotics [28, 30, 33, 38]. When individual data from these studies were pooled no significant difference was found in beta-diversity before vs after treatment ($F=0.38$; $R^2=0.01$; $P=0.68$; **eFigure1**).
All eight longitudinal studies reported data on gut microbiome taxonomy; all, but one [30], reported significant changes at phylum, class, family, and genus levels. Across studies, the most consistent findings were of increased *Gammaproteobacteria* at class level and increased *Bifidobacteria*, *Lactobacillus*, and *Klebsiella* at genus level, after treatment with antipsychotics (see also **eTable1**).
Three studies reported data on microbiome functional analysis following treatment with antipsychotics [28, 30, 33]. Two of out three studies reported significant changes across 12 different microbiome functional pathways, including those involved in the metabolisms of short-chain free fatty acids [28, 33] (see **eTable 1).**

Cross-sectional studies

Of the five cross-sectional studies that compared antipsychotic treated vs antipsychotic-free patients, one investigated risperidone [27] and four mixed antipsychotics [35-38].
All five studies reported data on alpha diversity. The pooled effect size showed no differences in alpha diversity between antipsychotic treated vs antipsychotic-free patients (SMD: -0.08; 95% CI: -0.68 to 0.53; P=0.80) with evidence of high heterogeneity (I^2: 83.98%).
Two studies reported data on gender differences in alpha diversity metrics between antipsychotic treated vs untreated patients [35, 36]. These two studies were also the only ones including obese participants within the study population. The pooled estimate showed a significant reduction in alpha diversity in female, but not male, patients (SMD: -0.68; 95% CI: -1.31 to -0.04; P=0.04; I^2: 37.61%).
All studies included in the quantitative synthesis on alpha diversity in cross-sectional studies used the same sequencing method, none were conducted in children, all but one [37] used polypharmacy, and all included participants in “chronic” treatment with antipsychotics (i.e., > 6 months).
Three cross-sectional studies reported data on beta diversity in antipsychotic treated vs antipsychotic free patients [27, 35, 38]. When individual data from these studies were pooled together, we found a significant difference in beta diversity between antipsychotic treated and antipsychotic free patients ($F=3.31$; R^2:0.02; $P=0.03$; **eFigure2**). Across these three studies, only one study included obese participants in their study population [35], one was conducted in children and adolescents [27], all used polypharmacy, and all included participants in “chronic” treatment with antipsychotics.
All cross-sectional studies, but one [38], reported data on gut microbiome taxonomy in antipsychotic treated vs antipsychotic free participants; all reported significant between-groups differences at phylum, class, family, and genus levels. However, specific taxonomic findings were not consistent across studies (**eTable2**)
Three studies reported data on microbiome functional analysis in antipsychotic treated vs antipsychotic free participants [27, 37, 38]. Two out of three studies reported significant

differences in the expression of microbial functional pathways; both studies reported an increase in tryptophan metabolism microbial pathways in antipsychotic treated patients [27, 38] (**eTable2**).

Association with clinical outcomes

Three longitudinal studies reported data on the association between gut microbiome features and treatment response to antipsychotics [28, 30, 32].
Two out of three studies showed that gut microbiome features at baseline, including highly represented species belonging to the *Ruminococcaceae* and *Lachnospiraceae* families, were associated with a subsequent therapeutic response to antipsychotics [28, 32](**Table1**). The only study that reported negative findings was conducted in a cohort of multi-episode chronic patients with schizophrenia, which included obese participants [30].
Only one [32] out of three [28, 30, 32] studies reported that gut microbiome changes following antipsychotic treatment are associated with treatment response. This study investigated risperidone and was conducted in a large cohort of adolescents and young adults at their first psychotic episode [32].
No studies on antipsychotics reported analysable data to quantitatively compare differences in gut microbiome features in treatment responders vs not responders.
Three longitudinal studies reported data on the association between baseline gut microbiome features and tolerability of antipsychotics [30, 31, 34]
Two of these three studies reported that both baseline and changes in gut microbiome features were associated with adverse metabolic outcomes (i.e., higher blood levels of LDL and triglycerides; increased weight gain) following treatment with antipsychotics [31, 34]; the only study that reported negative findings was conducted in a cohort of multi-episode chronic patients with schizophrenia, which included obese participants [30].

Antidepressants

Longitudinal studies

Of the six longitudinal studies on antidepressants, four investigated Escitalopram [21-23, 25], one Vortioxetine [24], one mixed antidepressants [26]
Five studies reported data on gut microbiome alpha diversity before and after treatment with antidepressants [22-26]. The pooled estimate showed a non-significant increase in alpha diversity following antidepressant treatment (N=5 studies; SMD: 0.06, 95%CI: -0.21 to 0.33; P=0.54) with evidence of high heterogeneity (I^2: 97.84%). Similar results were obtained when analyses were restricted to the three studies investigating Escitalopram [22, 23, 25].
Four longitudinal studies on antidepressants reported data on beta-diversity [22, 25, 38]. When individual data from these studies were pooled together, they evidenced a significant difference in beta diversity following antidepressant treatment (F=15.59; R^2:0.05; P<0.001; **Figure 3**).

[Figure 3]

Similar findings were obtained when analyses were restricted to the two studies investigating Escitalopram [22, 25] (F=8.30; R^2:0.09; P<0.01).
None of the studies included in the quantitative analyses included obese participants, none

was conducted in children or adolescents, none reported data on gender differences, none used polypharmacy, and all used the same sequencing method, follow-up timing ranged from 1.5 to 6 months.
Four longitudinal studies reported data on gut microbiome taxonomy following antidepressant treatment [22-25]. Two studies reported significant changes at phylum, class, family, and genus levels, with converging findings on the increase in the abundance of *Christensenellaceae* following antidepressant treatment [24, 25] **(eTable3**), while two studies reported negative findings [22, 23].
Two studies reported data on microbiome functional analysis following treatment with antidepressants [22, 25]. One reported significant changes in microbial pathways related to biosynthesis of secondary metabolites, while the other found no changes following antidepressant treatment [28, 33].

Cross-sectional studies

Two cross-sectional studies compared gut microbiome features in antidepressant treated vs antidepressant free participants [38, 39].
None reported data on alpha or beta diversity. One study reported data on gut microbiome taxonomy, showing significant differences in the abundance of a number of bacterial species in antidepressant treated vs antidepressant free participants [39] (**Table 2**). One study reported data on gut microbiome functionality, reporting no differences between antidepressant treated vs antidepressant free participants [38].

Association with clinical outcomes

Two longitudinal studies reported data on baseline alpha diversity and subsequent treatment response to antidepressants, both studies investigated Escitalopram [21, 23]. The pooled estimate showed that patients that remitted from depression following treatment with Escitalopram had higher alpha diversity at baseline compared to those with did not remit (SMD: 2.45; 95%CI: 0.50 – 4.40; P<0.001).
Three longitudinal studies reported taxonomic data on the association between gut microbiome features and treatment response to antidepressants [21, 23, 24]. Two out of three studies showed that baseline and changes in gut microbiome taxonomic features were associated with treatment response to antidepressants [21, 24] (**Table1**),
These findings were consistent with the only cross-sectional study that investigated differences in gut microbiome taxonomy in antidepressant responders vs not responders [39].

Methodological considerations and risk of bias

Following the STORMS checklist, we consistently identified the following methodological limitations across the included studies: lack of a protocol with power calculation and analytic plan; small sample size; lack of reporting of microbiome collection method; lack of reporting of measures used to minimise contamination of samples and results; lack of supporting metatranscriptomics or metabolomics data; reporting bias of differentially abundant taxa; differences between groups in terms of polypharmacy and other confounders (e.g., BMI)
None of the included studies was at low risk of bias.
See also Supplementary material.

Discussion

To our knowledge, this is the first systematic review and meta-analysis of the effects of psychotropic medications on the gut microbiome in clinical populations.
The main findings were that: 1. Treatment with antipsychotics and antidepressants is associated with significant changes in gut microbiome features (diversity indices, taxonomy, and functionality); 2. Baseline gut microbiome features are associated with subsequent therapeutic response to both antidepressants and antipsychotics; 3. There are gender specific differences in gut microbiome features associated with exposure to antipsychotics; 4. Majority of included studies present significant methodological limitations

Our pooled estimates on longitudinal studies suggest that treatment with antipsychotics increases alpha diversity in patients. Low alpha diversity has been associated with a number of detrimental health outcomes, including mood and psychotic disorders [40-42]. A recent meta-analysis showed that patients with mental health disorders have a lower alpha diversity when compared to healthy controls [19]. One hypothesis is that antipsychotics might increase and "normalise" the diversity of the gut flora, making it closer to the one of healthy controls, with downstream potential benefits for patients [37, 43]. The qualitative summary on antipsychotics-related changes in taxonomy and functionality of the gut microbiome seem to point towards a similar direction. Antipsychotic-related gut microbiome changes included an increase in butyrate-producing bacteria, such as *Bifidobacteria* and *Lactobacillus*, and in the expression of butyrate metabolic pathways, which have known pro-cognitive and anti-inflammatory actions [19]. However, to date, only a few studies have directly investigated the relevance of these antipsychotic-related gut microbiome changes for treatment outcomes. Those that reported data on drug-naïve early psychosis patients suggest that gut microbiome changes might be clinically informative [31, 32], in line with findings from a recent study showing an association between increased serum levels of butyrate and treatment response to risperidone in drug-naïve first episode psychosis patients [44].
Evidence from in vitro and animal studies suggests that some antipsychotics can directly inhibit or enhance the growth of gut bacteria [1, 2]. This has led some authors to hypothesise that antipsychotics might act via the gut microbiome [45]. However, the observed antipsychotic-related increase in alpha diversity and in the butyrate-producing activity of gut bacteria might simply be a consequence of an improvement in illness severity. A better symptom profile (e.g., less paranoia) might increase patients' sociability and habits (e.g, more interpersonal interactions, more active lifestyle, increase exposure to outdoor spaces), which in turn could increase alpha diversity [46]. Future studies using translational approaches, such as patients-to mice faecal microbiome or specific pathogen transplants [47], are needed to clarify the direction of causality.

Although it was not significant, the pooled estimate from cross-sectional studies showed reduced alpha diversity in patients treated with antipsychotics compared to untreated patients, a finding that went in an opposite direction to the one observed in longitudinal studies. Many of the side effects of antipsychotics are metabolic, and include weight gain [48], which is known to reduce gut microbial alpha diversity[49]. As all cross-sectional studies on antipsychotics were conducted on chronically treated patients, it is possible that the observed reduction in alpha diversity might mirror the longer-term consequences of antipsychotic treatment, where chronicity related mechanisms (including, but not limited to weight gain) might counteract the initial increase in alpha diversity reported in longitudinal studies. In support of this hypothesis, the most significant increase in alpha diversity following antipsychotic treatment was observed in drug-naïve first-episode psychotic patients [32], while negative findings were reported by the only longitudinal study including multi-episode chronic patients with schizophrenia and comorbid obesity [30]. A longer exposure to

medications might also be responsible for the observed significant differences in gut microbiome structure (beta diversity) in cross-sectional, but not in longitudinal studies.

Of note, when analyses on cross-sectional studies were restricted to female participants only, we found a significant reduction in alpha diversity compared to untreated female controls. Compared to males, female patients are at greater risk of developing metabolic side effects from antipsychotics [50, 51]. Some authors suggest that this might be due to use of excessive doses in female patients or to hormonal factors [52]. As the gut microbiome has been causally involved in the development of metabolic disorders[53], future studies should investigate if the observed gender differences in alpha diversity associated with antipsychotic treatment might drive the metabolic side effects experienced by patients.

Pooled data on longitudinal studies on antidepressants showed a non-significant increase in alpha diversity and a significant difference in beta diversity following treatment.
The lack of significance in the pooled effect size for alpha diversity might be due to the low number of participants across studies (1/3 of those available for antipsychotics) rather than a complete lack of effect, as beta diversity metrics suggest that antidepressants are significantly associated with changes in gut microbiome structure. The majority of included studies suggested that antidepressant-related changes in gut microbiome may be clinically informative. Our taxonomic summary showed an increase in *Christensenellaceae* following treatment with antidepressants. Low levels of this bacteria have been found in patients with mood disorders and associated with more severe depressive symptoms [54, 55]; novel probiotics formulations containing *Christensenellaceae* are currently being tested as antidepressants[56]. These findings suggest that antidepressants might act via the gut microbiome. However, as discussed for antipsychotics, it also is possible that antidepressants-related changes in gut microbiome might just represent an indirect consequence of symptoms improvement.

Pooled data from two longitudinal studies investigating baseline gut microbiome features in treatment responders compared to not responders, showed that lower alpha diversity at baseline was associated with a lack of response to subsequent treatment with antidepressants. The qualitative summary on longitudinal studies on antipsychotics also corroborated this finding, further suggesting that baseline gut microbiome features might affect the tolerability of this class of psychotropics.
Gut bacteria have the potential to significantly affect the bioavailability of drugs [57]. A recent study reported that modifications in the gut microbiome can double the bioavailability of olanzapine [14]. This could occur via direct and indirect mechanisms. Indirect mechanisms include the ability of gut bacteria to modify the activity of human cytochromes [58] and the enterohepatic recycling of drugs [8]; direct mechanisms include catabolism [59] and bioaccumulation [60]. Recently, it has been shown that the expression of gut bacterial tyrosine decarboxylase can reduce the bioavailability of levodopa, a drug used for the treatment of Parkinson's disease, and increase the level of m-tyramine, with direct consequences on its efficacy and tolerability [59].
Changes in gut microbiome, such as low alpha diversity, have been associated with an increased chronic a-specific pro-inflammatory status (i.e., increased C - reactive protein, CRP, and cytokines levels) [41, 61], which may underlie certain forms of treatment resistance in both mood and psychotic disorders [62, 63]. However, the precise mechanisms by which inflammation should drive treatment resistance is unknown, and treatment stratification strategies based on CRP/cytokines havenot prove effective so far [64, 65]. One possibility is that patients with this increased chronic pro-inflammatory status might just have an

“unfavourable” gut microbiome composition [61], which might drive - with more specific mechanisms - certain aspects of treatment resistance.

Majority of included studies was at medium to high risk of bias (see supplementary material) and failed to meet key requirements of the newly published STORM checklist. A main issue is that findings from individual studies were often unaccounted for really important variables such as metabolic changes, obesity, and gender. This limits the robustness of conclusions that can be drawn.

Limitations

It was not always possible to analyse data from individual psychotropics due to lack of data. Data from antipsychotics and antidepressants were pooled together based on their similarities on central, brain, effects. However, it is possible that, within the same category, psychotropics might greatly differ in terms of effects on the gut microbiome. At the same time, it is possible that gut bacteria might contribute to the metabolism of only few compounds rather than the whole class of psychotropics. Pooled effects on both baseline and psychotropic-related changes in gut microbiome and their relationship with clinical outcomes might therefore have been driven by specific drugs and might not extend to the whole class. A large amount of included studies were conducted in the same geographic area (China), this might limit the generalisability of findings. However, all our quantitative estimates included data from different catchment areas.

Conclusions and future directions

In conclusion, this systematic review and meta-analysis showed that psychotropic medications are associated with altered gut microbiome in patients with psychotic and mood disorders and that the interaction between psychotropics and gut bacteria can potentially be informative for efficacy and tolerability outcomes in psychiatric illness.
As about one third of patients do not respond to antipsychotic and antidepressants [66], clarifying if and how the gut microbiome contributes to the efficacy of these compounds is of upmost importance. For antipsychotics, this may also contribute to their poor metabolic tolerability, a key unmet need in psychotic disorders.
Future studies should focus on minimally medicated/drug-naïve patients to avoid chronicity related biases. Gut microbiome taxonomic data should be always enriched with functional and metabolomics analysis, as same taxa could differ significantly in terms of their physiological role and, at the same time, distinct taxa could fulfil the same functional role [17]. Multi-omics and integrative analytic approach such as genomic scale metabolic modelling [67], should be adopted to clarify the precise contribution of gut bacteria to the host’s physiology. Standardised procedures, such as the STORMS guidelines [15], should be adopted to increase reproducibility of findings. Pre-specified hypotheses, ideally driven by in vitro or animal data, have the highest potential for replication in clinical settings and would require smaller sample sizes than generic, nonspecific, gut microbiome mapping approaches. Translational studies using germ-free or specific pathogen-free mice should be used to determine direction of causality.

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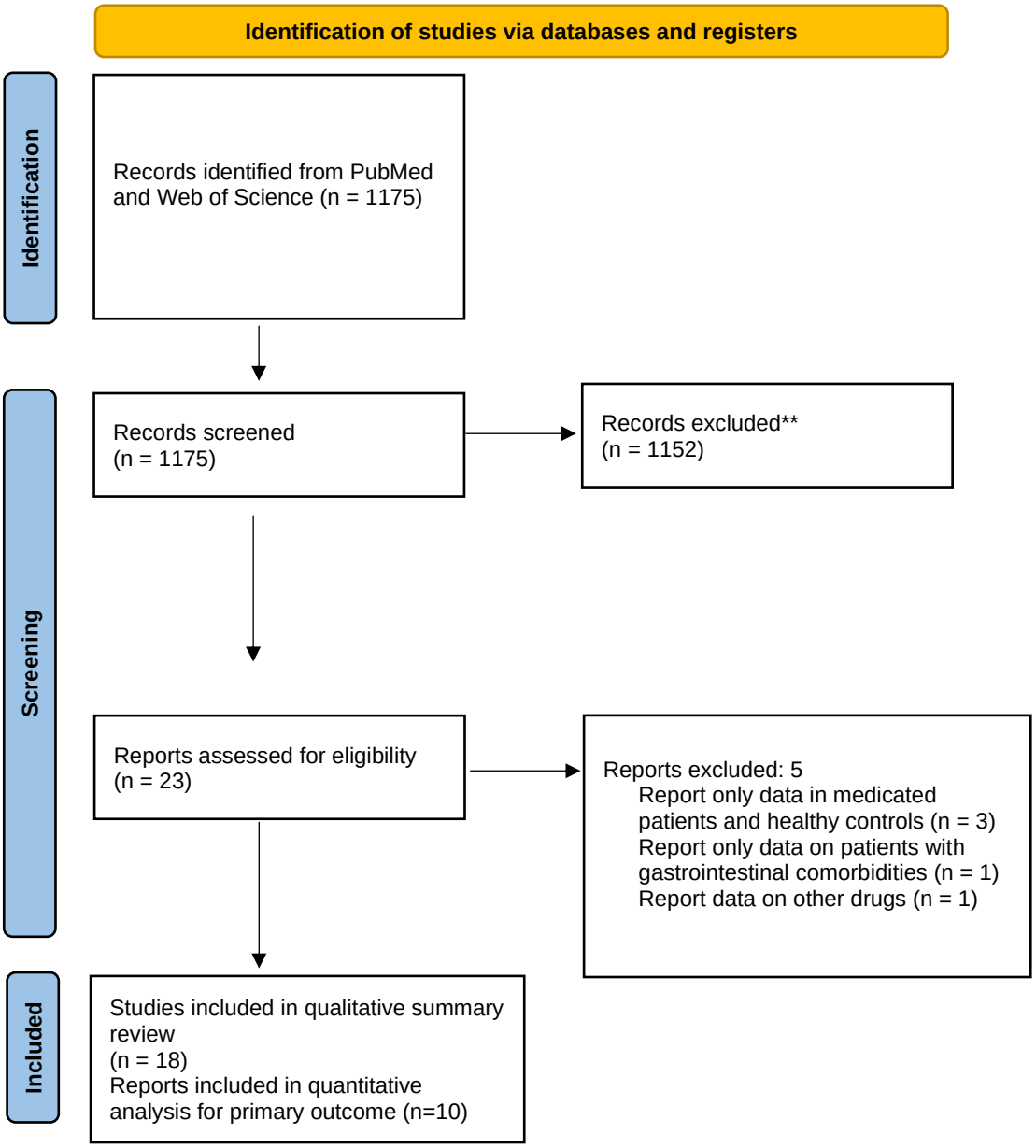
Figures and Tables

Figure 1. PRISMA Flowchart



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 2. Pooled estimate for alpha diversity before vs after treatment with antipsychotics

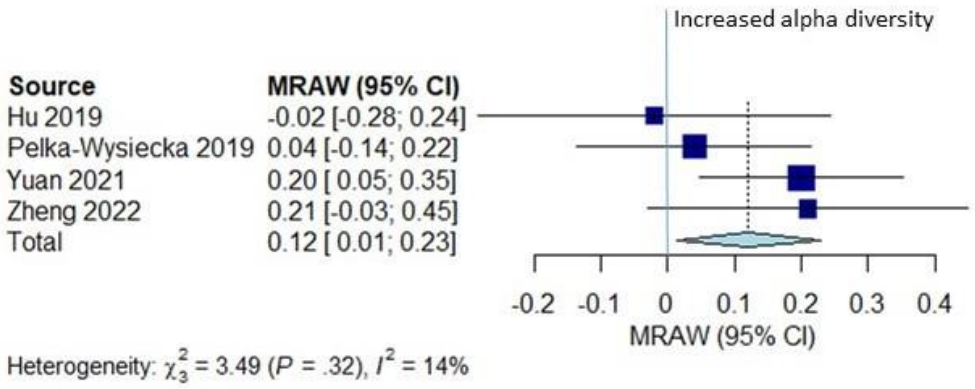


Figure 3. Beta diversity before vs after treatment with antidepressants: pooled individual patients data

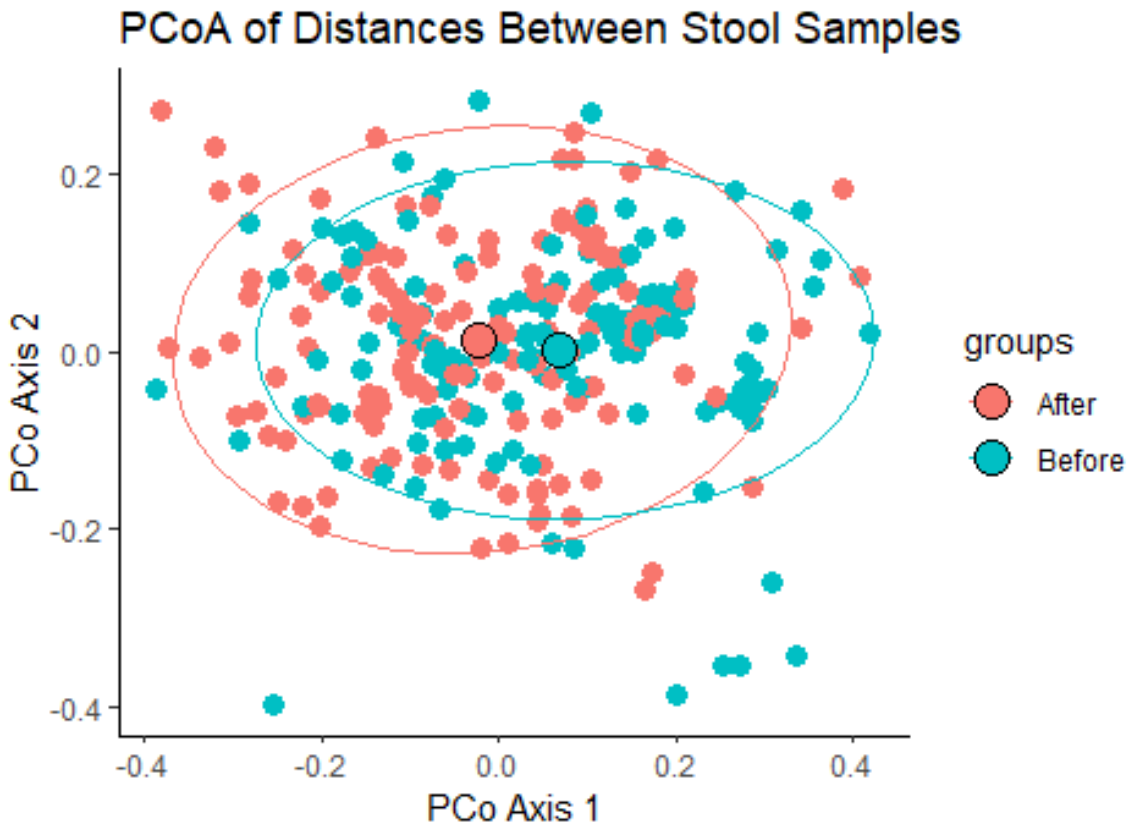


Table 1. Qualitative summary of longitudinal (within comparison) studies

Study (Country)	**Study design**	**N** (Medication status)	**Age** Mean ± SD/ Range	**Analysis**	**Medication type**	**Physical comorbidities and polypharmacy**	**BMI at baseline (changes after treatment)**	**Substance abuse**	**FU**	**Changes in gut microbiome following treatment**	**Gut microbiome features (baseline or changes) associated with clinical outcomes**
Antidepressants											
Bharwani et al 2020 (Canada) [21]	Longitudinal	N=15 MDD (Medication free at baseline)	37 ± 13	Taxonomy: 16S V4 OTUs	Citalopram (N=4) Escitalopram (N=11)	Excluded "Medical conditions known to affect microbiota"	Not reported	Excluded "current substance abuse"	3, 6 months	= alpha diversity after 6-months of treatment = beta diversity after 6-months of treatment	*Baseline* ↑ alpha diversity at baseline in **remitters vs non-remitters** (6-months FU) 22 OTUs differentially abundant at baseline in **remitters vs non-remitters** (6-months FU) *After treatment* ↑ *Clostridiales* at 6-months **in remitters** = OTUs at 6 months i**n non remitters** 42 OTUs differently abundant **in remitters vs non remitters** (6 months FU) **Remitters** = MADRS < 12 at 6 months
Dong et al., 2022 (China) [26]	Longitudinal	N = 63 MDD Drug-naive	28 ± 8	Taxonomy: 16S V4 OTUs Metabolomics	Citalopram, Escitalopram, Paroxetine, Venlafaxine	Excluded physical comorbidities	22 ± 4 (no significant change after treatment)	Excluded "substance abuse"	1.5 months	= alpha diversity after 1.5 months of treatment ≠ beta diversity After 1.5 months of treatment OTUs differences not reported	*Baseline* ≠ beta diversity in **responders** vs not **responders** **Responders**: 50% HDRS24 at 1.5 months Report taxonomic difference within groups (e.g., pre vs post within responders,

											rather than differences between groups)
Liskiewicz et al., 2019 (Poland) [22]	Longitudinal	N=17 MDD (7-day washout from all medication before baseline)	42 ± 14	Taxonomy: 16S –V4 OTUs	Escitalopram	"Poor general health, including cancer and gastrointestinal diseases", diabetes, thyroid dysregulation excluded.	25 ± 4 (not reported)	N=6 Smokers	1.5 months	↑ alpha diversity after 1.5 months of treatment = beta diversity after treatment (6 weeks) No differences in taxa abundance after treatment (6 weeks)	No investigation of clinical outcomes.
Liskiewicz et al., 2021 (Poland) [23]	Longitudinal	N=16 MDD Inpatients, medicateda (7-day washout from all medication before baseline)	44 ± 16	Taxonomy: 16S V4 ASVs Function: PICRUSt2-KEGG 16S-based	Escitalopram	Excluded gastrointestinal diseases, diabetes, thyroid dysfunctions	25 ± 3 (not reported)	Not reported	1.5 months	= alpha diversity after 1.5 months of treatment = beta diversity after 1.5 months of treatment = ASVs and MetaCyc pathways after 1.5 months of treatment	*Baseline* = alpha diversity at baseline in **remitters vs not remitters; responders vs not responders** (1.5 months FU). = beta diversity at baseline in **remitters vs not remitters; responders vs not responders** (1.5 months FU). = ASVs and MetaCyc pathways **remitters vs not remitters; responders vs not responders** (1.5 months FU). *After treatment* = alfa, beta, ASVs, MetaCyc pathways in **remitters vs not remitters; responders vs not responders** (1.5 months FU). **Remitters** = HDRS24 ≤ 8 at 1.5 months **Responders** = -50% HDRS24 at 1.5 months

Shen et al., 2021 (China) [25]	Longitudinal	N=30 MDD Drug-naïve at baseline	45 ± 11	Taxonomy: 16S V3-V4 OTUs Function: PICRUSt-KEGG 16S-based	Escitalopram	Excluded gastrointestinal disorders, diabetes, "immune system diseases"	24 ± 2 (not reported)	Reported tobacco (46.7%) and alcohol use (53.3%)	1.5 months	↓ alpha diversity after 1.5 months of treatment ≠ beta diversity after 1.5 months of treatment ↑ abundance of *Bacteroides*, *Christensenellaceae*, *Eubacterium*, *Fusobacterium* after 1.5 months of treatment ↓ abundance of *Lactobacillus* after 1.5 months of treatment ↑ "Biosynthesis of other secondary metabolites" (KEGG annotation) after 1.5 months of treatment	No investigation of clinical outcomes.
Ye et al., 2021 (China) [24]	Longitudinal	N = 26 MDD	26 ± 7	Taxonomy: 16S – V3/V4 OTUs	Vortioxetine	"Major physical disease history" excluded	26 ± 2 (not reported)	"Drug and alcohol abuse in the previous year" excluded	2 months	= alpha diversity after 2 months of treatment ≠ beta diversity after 2 months of treatment At *phylum* level: ↑ *Firmicutes*, *Actinobacteria* after 2 months of treatment ↓ *Acidobacteria*, *Bacteroidetes*, *Proteobacteria* after 2 months of treatment At *family* level: ↑*Lachnospiraceae*, *Ruminococcaceae*, *Bifidobacteriaceae*, *Coriobacteriaceae*, *Akkermansiaceae*, *Acidaminococcaceae*, *Erysipelotichaceae* after 2 months of treatment	*Baseline* ↓ *Dialister*, *Bacteroides*, *Prevotella-9*, and *Agathobacter* associated with improvement in HAMD after 2 months of treatment *After treatment* ↑ *Lachnospira*, *Roseburia*, *Subdoligranulum*, *Faecalibacterium*, and *Blautia* associated with improvement in HAMD after 2 months of treatment

										↓ *Prevotellaceae* after 2 months of treatment At *genus* level: ↑ *Bacteroides, Faecalibacterium, Roseburia, Fusicatenibacter,* and *Bifidobacterium* after 2 months of treatment ↓ *Parasutterella, Prevotella-9, Dialister, and Agathobacter* after 2 months of treatment	
Antipsychotics											
Bahr et al. 2015 (USA) [27]	Longitudinal	N=5 FEP baseline gut microbiome collected within a few days of starting risperidone treatment	12 ± 1	Taxonomy: 16S V1-V2 Function: PICRUSt-KEGG 16S-based	Risperidone	Unclear (psychostimulants and α-2 agonists)	z-score 0.12 ± 0.8 (significant increase)	Not reported	10 months	No data on diversity measures. ↑ *Firmicutes* after 10 months of treatment ↓ *Bacteroidetes* after 10 months of treatment Do not report data on microbial function	No investigation of clinical outcomes.
Hu et al., 2019 (Australia) [28]	Longitudinal	N=52 BPD Drug-free at baseline	24 ± 10	Taxonomy: 16S –V4 OTUs Function: PICRUSt-KEGG 16S-based	Quetiapine	Excluded physical comorbidities No medications other than APs	22 ± 3 (no significant increase)	Not reported	1 month	= alpha diversity after 1 month of treatment = beta diversity after 1 month of treatment At phylum level: ↑ *Proteobacteria* after 1 month of treatment At genus level: ↑*Klebsiella, Lactobacillus, Anaeroglobus, Collinsella,*	*Baseline* ↑ *Paraprevotella, Lachnospira, TM7* in **responders** (<50% in HAMD-17 total score) vs **not responders** ↓ *Acinetobacter, Asaccharobacter, Eubacterium, Lactococcus, Lactobacillus, Achromobacter, Bifidobacterium*

										Paraprevotella, Solobacterium, Veillonella after 1 month of treatment ↓ *Alistipes* after 1 month of treatment ↑12 microbial KEGG modules after 1 month of treatment ↓1 microbial KEGG module after 1 month of treatment	in **responders** vs **not responders**
Lu et al., 2019 (China) [29]	Longitudinal	N=36 BPD	33 ± 11	Targeted qPCR on 10 selected bacterial species (*Feacalibacterium preusnitzii, Enterococcus faecalis, Prevotella, Lactic acid bacteria, Bifidobacteria, Clostridium clusters I and IV, Eubacterium rectale, Atopobium, Enterobacter*)	Quetiapine	Excluded comorbidity with gastrointestinal diseases and "other physical diseases" No medications other than APs	22 ± 4 (No significant increase)	Excluded patients with "any history of substance abuse"	1 month	No data on diversity measures ↑ *Bifidobacteria. Eubacterium rectale*, after 1 month of treatment **Note**: Investigated only the abundance of 10 bacteria species	*Baseline and after treatment* No significant association between baseline (or change) gut microbiome features and depression scores after 1 month of treatment
Pan et al, 2022 (China) [34]	Longitudinal	N = 43 Diagnoses not reported APs naïve at baseline	12 ± 3	Taxonomy: 16S –V4 OTUs	Atypical antipsychotics (N=23 risperidone; N=10 quetiapine; n=7 aripiprazole; N=3 olazapine)	Excluded diabetes, inflammatory and irritable bowel disorders	19 ± 6	Drug excluded	3 months	No data on the overall group of participants Authors provide separate data on two groups of participants – those who gained weight (more than 5 kg) after three months of treatment and those who did not (less than 5 kg).	*Baseline* In patients that gained weight (≥5 kg) = alpha diversity = beta diversity ↑ *Parabacteroidetes, Eubacterium halii*

											After treatment In patients that gained weight (≥5 kg) = alpha diversity = beta diversity ↓ *Parabacteroidetes* In patients that did not gain weight (< 5 kg): = alpha diversity = beta diversity ↑ *Rombutsia* and *Klebsiella* ↓ *Parabacteroidetes*
Pelka-Wysiecka 2019 (Poland) [30]	Longitudinal	N = 20 SCZ inpatients (7-day washout from all medication before baseline)	33 ± 6	Taxonomy: 16S –V4 OTUs Function: PICRUSt-KEGG 16S-based	Olanzapine	"Poor general health, including cancer and gastrointestinal diseases", diabetes, thyroid dysregulation excluded. (No other medications)	29 ± 5 (No significant increase)	Inpatients (Drugs excluded)	1.5 months	= alfa diversity after 1.5 months of treatment = beta diversity after 1.5 months of treatment = OTUs and KEGG pathways after 1.5 months of treatment	*Baseline and after treatment* None of the taxonomic or microbial functional pathways correlated with any of the efficacy (measured as continuous PANSS score; and dichotomous responders' vs not responders) or tolerability (weight gain) outcomes.
Yaun et al., 2018 (China) [31]	Longitudinal	N=41 FEP drug-naïve at baseline	23 ± 4	Targeted qPCR on 5 selected bacterial species *Bifidobacterium spcc, Clostridium coccoides, Escherichia coli, Lactobacill*	Risperidone	Excluded comorbidity with gastrointestinal diseases and "other physical diseases" (No other medications)	21 ± 3 (significant increase)	Not reported	6 months	No data on diversity measures ↑*Bifidobacterium, Escherichia coli* after treatment ↓ *Clostridium coccoides, Lactobacillus* after treatment	*Baseline* ↓ *Bifidobacterium* associated with ↑ LDL levels ↓ *Escherichia coli* associated with ↑ triglycerides and CRP *After treatment*

				us, *Bacteroides*							↑ *Bifidobacterium* associated with ↑ BMI and weight gain
Yuan et al., 2021 (China) [32]	Longitudinal	N= 107 FEP drug-naïve at baseline	19 ± 4	Taxonomy: 16S V3-V4 OTUs	Risperidone	Excluded diabetes and gastrointestinal, autoimmune, cardiovascular, neurological, hepatobiliary disorders (No other medications)	21 ± 3 (significant increase)	Reported tobacco use (5%)	6 months	↑ alpha diversity after 6 months of treatment Do not report data on beta diversity pre vs post-treatment at any time point ↓ *Lachnoclostridium* after 6 months of treatment ↑ *Romboutsia* after 6 months of treatment	*Baseline* ↑ *Lachnoclostridium* and *Romboutsia* associated with more severe symptoms after 6 months of treatment (PANSS total) *After treatment* ↑ *Lachnoclostridium* associated with more severe negative symptoms after 6 months of treatment (PANSS negative) ↓ *Romboutsia* associated with more severe negative symptoms after 6 months of treatment (PANSS negative)
Zheng et al., 2022 (China) [33]	Longitudinal (within comparison)	N=33 SCZ inpatients (at least 4 weeks without receiving drugs)	39 ± 12	Taxonomy: 16S –V4 OTUs Function: PICRUSt-KEGG 16S-based	Amisulpride	"Presence of infection, diarrhoea, or gastrointestinal diseases" excluded (No other medications)	23 ± 3 (no significant increase)	Inpatients (Drugs excluded)	1 month	= alfa diversity after 1 month of treatment ≠ beta diversity after 2 month of treatment ↑*Dorea, Desulfovibrio*,, and *Butyricicoccus* after 1 month of treatment ↓ *Actinomyces*, *Porphyromonas* after 1 month of treatment ↓ microbial functional pathway (butanoate metabolism) after 1 month of treatment	No investigation of clinical outcomes

Legend. ADs: Antidepressants; APs: Antipsychotics; ASV: amplicon sequence variant; BMI: Body Mass Index; BPD: Bipolar Disorder; CRP: C-reactive protein; FEP: First Episode Psychosis; HAMD: Hamilton depression rating scale; HAMD17: Hamilton depression rating scale 17 items; HDRS24: Hamilton Depression Rating Scale 24 items; KEGG: Kyoto Encyclopaedia of Genes and Genomes; LDL: Low

Density Lipoproteins; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major Depressive Disorder; OTU: Operational Taxonomic Unit; PANSS: Positive and Negative Symptoms Scale; PICRUSt: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; qPCR: quantitative polymerase chain reaction; SCZ: Schizophrenia.

Table 2. Qualitative summary of cross-sectional (between comparisons) studies

Study	**Study design**	**N** (Medication status**)**	**Age**	**Analysis**	**Medication type**	**Physical comorbidities and polypharmacy**	**BMI (significant differences)**	**Substance abuse**	**Main findings**	**Gut microbiome features associated with clinical status/ tolerability of medications**
Antipsychotics										
Bahr et al., 2015 (US) [27]	Cross-sectional	N=18 APs-treated (patients treated with risperidone for at least one year-multiple diagnoses) N=10 APs-free (“psychiatric controls”-comparable diagnoses to the risperidone group)	Overall sample: 12 ± 3	Taxonomy: 16S V1-V2 Function: PICRUSt-KEGG 16S-based	Risperidone	Unclear/not reported Both groups had participants on psychostimulants, alfa-2 agonists, SSRIs (no significant between-group differences) Significant differences in exposure to benzodiazepines	APs-group: 0.3* ± 1.1 APs-free: 0.1* ± 0.6 *z-score (no significant differences)	Not reported	↑ alpha diversity in AP-treated vs AP-free ≠ beta diversity in APs-treated vs APs-free ↓ *Bacteroidetes/Firmicutes* ratio in APs-treated vs AP-s free (regardless of BMI) ↑47 OTUs in AP-treated vs APs-free (most abundant: Clostridium, Collinsella, Lactobacillus, Ralstonia, Erysipelotrichaceae family) ↓ 3 OTUs of the Bacteroidetes phylum in APs-treated vs APs-free ↑ KEGG modules – SCFA and tryptophan metabolism in APs-treated vs APs-free	*Within the APs-treated group* ↑*Clostridium, Lactobacillus, Ralstonia*, in AP-treated patients with weight gain vs those AP-treated patients with no weight gain ↓*Coriobacteriales (C.aerofacies)* in AP-treated patients with weight gain vs those AP-treated patients with no weight gain
Flowers et al., 2017 (US) [35]	Cross-sectional (Between comparison)	N= 49 APs-treated BPD	APs-treated: 46 ± 12	Taxonomy: 16S V4 OTUs	Antipsychotics	Unclear/not reported Both groups had participants on	APs-treated: 31 ± 7	Excluded current substance abuse	↓ alpha diversity in APs-treated vs APs-free ≠ beta diversity in AP-treated vs APs-free	*Within the APs-treated group* In females, but not in males, ↓ alpha diversity in APs-treated vs AP-free

		N= 68 APs free BPD	APs-free: 52 ± 14		(clozapine, olanzapine, risperidone, quetiapine, asenapine, ziprasidone, lurasidone, aripiprazole, paliperidone,iloperidone)	mood stabilisers and antidepressants (no significant between-group differences) and benzodiazepines (greater use in APs-treated)	APs-free:28 ± 6		↑*Lachnospiraceae* in APs-treated vs AP-free ↓*Akkermansia* in APs-treated vs APs-free AP-treated BPD were younger and had higher BMI. Analyses were adjusted for age, gender, BMI	
Flowers et al., 2019 (US) [36]	Cross-sectional (Between comparison)	N=21 APs treated N=16 APs-free		Taxonomy: 16S V4 OTUs	Antipsychotics (clozapine, olanzapine, risperidone, quetiapine, ziprasidone)	Excluded participants with "uncontrolled gastrointestinal disorders" and "any serious medical condition" Both groups treated with lithium and/or lamotrigine (no significant differences).	APs-treated: 30.6 APs-free: 31.1 (no SD reported) (81% of patients were obese – equally represented across groups)	Excluded patients with "chronic heavy alcohol consumption"	= alpha diversity in APs-treated vs AP-s free = beta diversity in AP-treated vs APs-free ↓ *Alistipes* in APs-treated vs AP-s free	*Within the APs-treated group* In females, but not in males, ↓ alpha diversity in APs-treated vs AP-free
Ma et al., 2020 (China) [37]	Cross-sectional (Between comparison)	N=85 APs-treated (SCZ) N=40 APs-free (FEP drug-naive)	Overall group: 24 ± 6	Taxonomy: 16S V4 OTUs Function: PICRUSt-KEGG 16S-based	Any antipsychotic	Excluded "any physical disorder during the lifetime" FEP group was drugs-naïve SCZ – author do not mention drugs other than APs	Overall group: 18 < BMI < 25 (no significant differences between groups)	Not reported (inpatients – exclude current use)	↓ alfa diversity in APs-treated vs APs-free ≠ beta diversity in AP-treated vs APs-free At *phylum* level: ↓ *Lentisphaerae* in AP-treated vs APs-free At *family* level: ↑ *Lactobacillaceae, Enterococcaceae, Peptostreptococcaceae, Streptococcaceae, Veillonellaceae*	↑ *Actinobacillus and Veillonellacea* associated with greater rMFG volume in AP-free, but not in AP-treated.

									in APs-treated vs APs-free At *genus* level: ↑*Lactobacillus, Enterococcus, Shigella, Streptococcus, Megasphaera, Escherichia, Veillonella, Enterobacteriaceae, Citrobacter, Clostridium, Peptostreptococcaceae, Ruminococcus, Sutterella, Erysipelotrichaceae* in APs-treated vs APs-free ↓*Lachnobacterium, Barnesiellaceae* in APs-treated vs APs-free = KEGG pathways in APs-treated vs APs-free	
Antidepressants/antipsychotics										
Tomizawa 2021 (Japan) [38]	Cross-sectional (between comparison) AND Longitudinal (comparison across different treatment groups)[1]	N=40 Depression and/or anxiety (MDD; PDD; GAD; PD) *Antipsychotics* [N=9 APs-treated vs N=31 APs-free] *Antidepressants* [N=33 ADs-treated vs N=7 ADs-free]	Overall group: 54 ± 19	Taxonomy: 16S V1-V2 OTUs Function: PICRUSt-KEGG 16S-based	Any antipsychotic/ any antidepressant All patients that were taking antipsychotics were also on antidepressant	Excluded gastrointestinal disorders	Overall group: 22 ± 4	Not reported	*Cross-sectional analyses: ADs* = alpha diversity in AD-treated vs AD-free = beta diversity in AD-treated vs AD-free ↑ GABA III synthesis and GABA degradation microbial pathways in AD-treated vs AD-free *Cross-sectional analyses: APs* = alpha diversity in AP-treated vs APs-free ≠ beta diversity in AP-treated vs APs-free	Not investigated

									↑tryptophan and GABA II synthesis microbial pathways in AP-treated vs APs-free ↓tryptophan degradation microbial pathway in AP-treated vs APs-free *Longitudinal analyses*[1] APs-treated patients showed ↓ alpha diversity vs APs-free patients after 40 ± 97 days of treatment	
Antidepressants										
Fontana et al., 2021 (Italy) [39]	Cross-sectional	N=27 ADs-treated MDD N=7 ADs-free MDD	Overall group: 56 ± 19	Taxonomy: 16S V3-V4 OTUs	Any antidepressant (SSRI, SNRI, TCA)	Excluded patients with “severe comorbidities that may influence microbiota variation” Both groups had participants on mood stabilisers and antipsychotics (no significant between-group differences)	ADs-treated: 24 ± 4 ADs-free: 23 ± 3	Not reported	No measures of alpha or beta-diversity. ↑*Proteobacteria, Propionibacteriaceae, Peptococcaceae, Murimonas, Parabacteroides, Elusimirobia, Dakarella, Desulfovibrio* in APs-treated vs APs-untreated patients ↓*Candidatus Saccharibacteria, Lentisphaerae, Euryarchaeota, Acidaminococcaceae, Micrococcaceae, Fusibacteriaceae, Victivallaceae, Eggerthellaceae, Methanobacteriaceae, Sanguibacteroides, Phascolarctobacterium, Anaeromassilibacillus,*	↑*Proteobacteria, Tenericutes, Peptostreptococcaceae* in **treatment resistant*** vs responders ↓*Actinobacteria* in **treatment resistant** vs responders *defined on “retrospective assessment of longitudinally collected information”

									Streptomyces, Raoultibacter, Denitrobacterium, Prevotella sporal clone IK062, Ruminococcus torques, Sanguibacteroides justesenii, Flintibacter butyricus, Roseburia intestinalis and Dialister sp S7D in APs-treated vs APs-untreated patients	

Legend. ADs: Antidepressants; APs: Antipsychotics; ASV: amplicon sequence variant; BMI: Body Mass Index; BPD: Bipolar Disorder; CRP: C-reactive protein; FEP: First Episode Psychosis; HAMD: Hamilton depression rating scale; HAMD17: Hamilton depression rating scale 17 items; HDRS24: Hamilton Depression Rating Scale 24 items; KEGG: Kyoto Encyclopaedia of Genes and Genomes; LDL: Low Density Lipoproteins; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major Depressive Disorder; OTU: Operational Taxonomic Unit; PANSS: Positive and Negative Symptoms Scale; PICRUSt: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; qPCR: quantitative polymerase chain reaction; SCZ: Schizophrenia.

[1]Note: This study was not reported in the longitudinal (within comparison) table and longitudinal data were not used to produce meta-analytic estimates as the authors compared differences in alpha diversity between treatment groups (e.g., changes in microbial diversity after antipsychotic treatment vs changes in microbial diversity after antidepressant treatment) rather than pre-to-post differences within the same treatment group.