Gut dysbiosis: An overlooked pharmacokinetic modifier in psychotropic therapy

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Abstract

Full Text

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ABSTRACT

Growing evidence over recent years has established a bidirectional relationship between gut dysbiosis and mental health. This paper proposes that gut microbial imbalance and related functional disturbances may represent a plausible, testable biological modifier of psychotropic treatment response, contributing to apparent treatment resistance rather than only constituting a primary psychiatric cause. Stratifying patients by simple clinical and laboratory markers of dysbiosis could clarify heterogeneity in treatment outcomes. Psychotropic medications—although essential in treatment—may themselves induce or exacerbate dysbiosis, potentially contributing to indirect worsening of psychiatric symptoms in susceptible individuals. Conversely, alterations in the gut microbiome may influence the pharmacokinetics and pharmacodynamics of these agents, offering a plausible explanation for inter-individual variability in response. Recognising dysbiosis as a clinically relevant factor may therefore refine our understanding of heterogeneous response profiles. Future directions should prioritise clinician education, patient awareness, and stratification of psychotropics by microbiome impact, advancing more personalised and biologically informed psychopharmacological care.

Introduction

Gut dysbiosis refers to the disruption of the normal microbial balance within the gastrointestinal tract, including the loss of beneficial bacteria or a reduction in overall microbial diversity. Fig. 1 outlines the major causes, consequences, and mechanisms associated with dysbiosis. The most commonly recognized forms involve yeast overgrowth and small intestinal bacterial overgrowth (SIBO)1. Interest in dysbiosis has grown substantially in recent years, particularly in relation to the gut–brain axis2. Accumulating evidence suggests that gut imbalance —even when asymptomatic—is associated with psychiatric symptoms such as depression and anxiety, and may contribute to secondary mood disturbances3.

These effects are mediated through several pathways, most notably systemic inflammation. In depression, gut microbiota alterations are characterized by depletion of *Faecalibacterium* and enrichment of *Bifidobacterium*, with probiotic or synbiotic interventions showing modest improvements in mood and inflammation; in schizophrenia, microbial changes involve taxa such as *Bifidobacterium*, *Lactobacillus*, and *Roseburia*, where probiotic supplementation yields small-to-moderate benefits in cognition and metabolic side effects4. Across studies, α- and β-diversity results were inconsistent, but both depression and anxiety showed a common pattern of increased pro-inflammatory taxa and reduced short-chain fatty acid (SCFA)-producing bacteria5.

Despite these connections, these pathways remain rarely integrated in clinical psychiatric practice. Current treatment guidelines do not incorporate microbiome considerations into diagnostic evaluation or psychotropic selection. Patients with gut-related psychiatric symptoms may be misdiagnosed because routine screening for dysbiosis is uncommon. Diagnostic uncertainty regarding gut dysbiosis and psychiatric symptoms, as well as inter-individual differences and variability in treatment response, may also arise from heterogeneous testing methods, episodic symptom patterns, and overlap with functional gastrointestinal disorders.

Based on that, this paper adds and argues that gut dysbiosis also functions as a clinically relevant biological determinant of drug response, such that microbiome imbalance—whether pre-existing or drug-induced—alters psychotropic pharmacokinetics, pharmacodynamics, and downstream neuroimmune signaling, thereby shape inter-individual variability in treatment response by altering drug absorption and metabolism.

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Causes

- Lifestyle (poor sleep, chronic stress, alcohol use & sedentary lifestyle)
- Environment exposure (pollution, heavy metals and additives)
- Diet (high sugar, fats & processed foods)
- Antibiotics
- Medications (proton pump inhibitors)
- Infections
- Ageing
- Immune dysfunction (food sensitivity/allergy, genetic predisposition, inflammatory bowel disease)
- Lack of breast feeding
- Cesarean birth

Effects

- Digestive disorders (irritable bowel syndrome, ulcerative colitis & Crohn' s disease)
- Metabolic disorders (obesity, insulin resistance and type-2 diabetes)
- Autoimmune diseases
- Mental health conditions
- Cancer progression (increase risk of colorectal cancer)
- Atherosclerosis (via production of trimethylamine N-oxide metabolite)
- Systematic symptoms (food sensitivities, fatigue and brain fog)

Mechanisms

- Chronic inflammation
- Immune dysregulation (*cytokines*)
- Bile acids
- Tryptophan metabolites
- Lipopolysaccharides (*LPS*)
- Toxin production
- Impaired nutrition metabolism
- Impaired glucose and lipid metabolism
- Changes in short chain fatty acid (*SCFA*) production
- Impaired gut barrier (*leaky gut*)
- Altered gut-brain communication

Fig. 1. Major causes and downstream mechanisms of gut dysbiosis, highlighting pathways that intersect with psychiatric symptoms and drug metabolism.

[Figure diagram labels: "Gut Dysbiosis" ; "Psychotropic drugs" ; "Mental Disorders" .]

Fig. 2. A simplified conceptual model of the bidirectional cycle linking gut dysbiosis, psychotropic medications, and psychiatric disorders. Dysbiosis both arises from and modifies drug response, reinforcing treatment resistance and symptom persistence.

Discussion

The gut–brain axis is bidirectional; thus, psychiatric disorders may also provoke gut imbalance. Depression slows gastrointestinal motility and alters appetite, leading to shifts in microbial composition and downstream effects on hormonal and neurotransmitter metabolism. Disrupted sleep patterns and cortisol fluctuations further influence dietary behaviors, particularly sugar cravings[6]. Anxiety similarly elevates cortisol and activates the sympathetic nervous system, altering the gut environment. These changes can influence bile acid metabolism, short-chain fatty acid (SCFA) production, vagal signaling, and immune modulation. In addition, this bidirectionality is evident in neurodegenerative disease, where neurodegeneration can disrupt autonomic and neuroendocrine regulation of the gut, thereby altering microbial composition and metabolic signaling; conversely, gut dysbiosis contributes to metabolic disorders, with inflammation serving as a key mediator that accelerates neurodegenerative processes[7].

As a result, dysbiosis may develop secondary to psychiatric illness and subsequently contribute to the persistence or exacerbation of depressive and anxious symptoms, while also potentially influencing pharmacokinetics. Patients may enter a self-perpetuating cycle (Fig. 2) in which gut imbalance and psychiatric distress continuously exacerbate one another. This mechanism is rarely acknowledged in routine practice, yet it may plausibly contribute to some proportion of treatment resistance, non-responders or individuals with incomplete remission. Some patients may be experiencing microbiota-mediated interference with drug metabolism, inflammatory pathways, or gastrointestinal motility—factors seldom evaluated clinically.

Among the three main types of dysbiosis—structural (taxonomic shifts that define baseline metabolic pathways), ecological, and functional—functional dysbiosis is proposed as the central determinant of drug–microbiome interactions. It involves changes in microbial enzymes such as reductases, hydrolases, and deaminases, leading to altered metabolic outputs (e.g., bile acids) that directly affect drug solubility, absorption, bioavailability, and ultimately therapeutic response, depending on whether a drug requires activation as a prodrug. Structural and ecological dysbiosis act as modifiers, alongside subtypes such as genetic, genetic-related, temporal, and spatial dysbiosis. Of these, spatial dysbiosis may be the key limiting factor, as drug absorption occurs primarily in the small intestine while microbiota are concentrated in the colon. Conditions like small intestinal bacterial overgrowth (SIBO) exemplify this, highlighting the underrecognized concept of pre-absorptive metabolism and a microbiome-mediated "first-pass effect," where luminal microbial activity may induce drug loss before absorption.

Table 1
Pharmacokinetic Pathways, Dysbiosis Effects and Fluoxetine Interplay.

Pathway	Normal State	Alteration in Dysbiosis	Evidence for Fluoxetine	Effect of Fluoxetine on Microbiome
Absorption	Solubility and uptake in small intestine; bile acids aid emulsification	Functional dysbiosis alters bile acid metabolism → reduced solubility and absorption	Rat studies show altered fluoxetine absorption with microbiota shifts (e.g., bile acid changes)	modifies bile acid related microbial pathways, reducing microbial diversity
Metabolism	Microbial enzymes transform drugs before hepatic metabolism	Dysbiosis alters enzyme activity → altered pre-absorptive metabolism	*Enterococcus faecalis* metabolizes fluoxetine in vitro	Fluoxetine inhibits certain microbial enzymatic functions, shifting metabolic outputs
Distribution	Microbiota indirectly modulate host CYP450 and transporters	Dysbiosis alters host gene expression	Animal models show germ-free vs conventional mice differ in fluoxetine distribution	Fluoxetine exposure changes microbial composition, which feeds back into host CYP regulation
Excretion	Microbial deconjugation of metabolites in colon affects enterohepatic recycling	Dysbiosis alters recycling → may change drug half-life	Preclinical data suggest altered fluoxetine metabolite recycling under microbiome shifts	Fluoxetine reduces microbial taxa involved in deconjugation

Psychotropic drugs involvement

Antidepressants, the primary pharmacological treatment for

depression and anxiety, vary in their effects on the gut microbiota6. Some possess antimicrobial properties that may be beneficial in select cases but can worsen dysbiosis in susceptible individuals. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine8 and sertraline9, illustrate this complexity, as demonstrated in the findings of an in vitro study8. Fluoxetine can slow gut motility—thereby potentially influencing absorption—alter microbial composition, disrupt bile acid metabolism—thus indirectly may be affecting first pass metabolism—reduce SCFA-producing bacteria, and interfere with vagal pathways. Similarly, sertraline alters microbial composition, yet mainly influences vagal serotonin signaling and modulates immune activity along the gut–brain axis.

Table 1 illustrates the major pharmacokinetic pathways under normal and dysbiotic states, highlighting how psychotropic drugs may interact with and conversely reshape the microbiome. Fluoxetine is presented as the primary example given its widespread use, although most evidence remains preclinical; sertraline (with very high lipophilicity) and fluoxetine (high lipophilicity) are less studied in some contexts compared to duloxetine, yet due to their shared cationic amphiphilic nature, similar behavior is expected. Regarding SCFAs and bioaccumulation, they influence absorption and distribution, respectively: SCFAs regulate transporters and tight junction integrity, while bioaccumulation reflects the microbiome' s ability to sequester lipophilic drugs, thereby reducing free luminal concentrations and enhancing degradation, ultimately lowering systemic exposure. Conversely, microbial metabolites can modulate hepatic CYP enzymes and drug metabolism, which may increase AUC (Area Under Curve), in some cases representing the sole mechanism for enhanced systemic drug levels.

The net impact of microbiome–drug interactions is highly context-dependent, determined by factors such as dose, baseline microbiome composition, and treatment duration. At low doses, microbial degradation or bioaccumulation may predominate, reducing systemic exposure, whereas higher doses may saturate microbial capacity and shift the balance toward host metabolism. Baseline microbiome composition dictates the availability of key enzymatic activities, thereby influencing which pathway is most affected. Treatment duration further shapes outcomes, as prolonged exposure allows psychotropics to remodel microbial communities. Thus, the predominance of any given effect reflects a dynamic interplay between drug properties and microbiome ecology, underscoring the need for individualized assessment of pharmacokinetic variability in psychotropic therapy.

In cases of treatment resistance, clinicians often escalate therapy by switching to serotonin–noradrenaline reuptake inhibitors (SNRIs) or adding antipsychotics. However, many of these agents further reduce gut motility and may worsen dysbiosis, thereby aggravating psychiatric symptoms or diminishing drug efficacy.

Tricyclic Antidepressants (TCAs), venlafaxine10 and quetiapine11,12 exemplify this pattern in preclinical animal studies; the latter' s metabolic side effects, including weight gain, may be linked to microbiome alterations. This has been also suggested by a perspective paper13 highlighting the bidirectional relationship among metformin, antipsychotic treatment, and the gut–brain axis, wherein metformin modulates gut microbiota composition and metabolic signaling while gut-derived alterations reciprocally influence metformin' s efficacy in mitigating antipsychotic-induced metabolic dysfunction.

Several mood stabilizers also share common gut effects while some exert differential and indirect impact14: carbamazepine15 impairs motility, valproate16 alters bile metabolism, lamotrigine17 reduces SCFA production, and lithium18 affects immune communication. Most of these findings derive from preclinical animal models and are rarely considered, even though such interactions may inadvertently worsen outcomes in patients already struggling with treatment failure.

Preclinical studies consistently show that gut microbiota can degrade psychotropic drugs19–21. Fluoxetine is metabolized by commensals such as Enterococcus faecalis in vitro, producing less active derivatives and reducing bioavailability. Olanzapine undergoes microbial transformation in animal models, where conventional mice display altered metabolism and weight gain compared to germ-free counterparts, implicating microbial enzymatic reduction and indirect modulation of hepatic CYP450. Diazepam degradation has been observed in rodents, with antibiotic depletion of gut flora shifting its pharmacokinetics, indicating microbial enzymatic breakdown into inactive metabolites. These mechanisms—direct enzymatic cleavage and indirect host-microbiome signaling—highlight a bidirectional loop. This dynamic interplay underscores the microbiome as both a sink and a modulator of psychotropic action, offering a mechanistic basis for interindividual variability.

Recommendations and clinical implications

A critical need exists for the integration (e.g. validation and implementation of biomarkers) of gut–brain axis knowledge into practice and psychiatric training. Psychiatrists currently receive limited instruction on microbiota-related mechanisms, leaving a significant gap in practice.

In clinical practice, dysbiosis can be assessed through structured gastrointestinal symptom questionnaires, targeted laboratory biomarkers (e.g., serum inflammatory cytokines, metabolite ratios such as kynurenine/tryptophan), and non-invasive breath tests for small intestinal bacterial overgrowth (SIBO). These tools enable stratification of patients into microbiome-risk categories, allowing clinicians to anticipate altered pharmacokinetics and adjust psychotropic therapy accordingly—for instance, selecting agents with lower dependence on bile acid metabolism or modifying dose in patients with confirmed dysbiosis.

Future research

While systematic reviews and meta-analyses22–24 support the role of gut microbiota in psychiatric disorders, and most clinical studies focus on outcomes such as symptom improvement and metabolic side effects, evidence directly linking dysbiosis to psychotropic pharmacokinetics (e.g., AUC, Cmax, t½, bioavailability) remains limited. Recent reviews25,26 highlight microbiota-mediated modulation of SCFA, bioaccumulation and bile acid metabolism, suggesting plausible mechanisms by which gut imbalance may alter drug absorption and metabolism, but quantitative pharmacokinetic synthesis is still lacking. Stronger evidence exists for non-psychotropics (as seen with the inactivation of digoxin by *Eggerthella lenta* in humans27), and this may be used as proof-of-principle that similar magnitude effects could potentially occur with psychotropics.

Future research should prioritize the systematic study of psychotropic effects on the gut microbiota, enabling classification of drug classes based on their human microbiome impact. Rifaximin merits investigation as an adjunct in controlled trials because it has a favorable, luminally restricted resistance profile for certain SIBO subtypes; however, routine off-label use for psychiatric indications is not currently supported by robust evidence28. While it may reduce luminal bacterial load and improve absorption, potential risks include further perturbation of microbial diversity, off-target metabolic effects (as bile acid signaling alterations) and the emergence of antimicrobial resistance or opportunistic infections. Controlled trials are therefore necessary to establish both efficacy and safety before clinical adoption. Additional studies should explore how gut microbiota influence psychotropic pharmacokinetics (as seen with an abstract tackling lamotrigine17) and treatment response. Gut dysbiosis may alter bioavailability and first-pass metabolism—mechanisms pending further validation—contributing to inconsistent clinical response, which may explain inter-individual differences in drug tolerability. This highlights the potential of personalized medicine, where microbiome profiling can help predict drug efficacy and side effects. Finally, genomic and

inter-individual variations in microbiome composition warrant investigation to better understand how genetic diversity shapes dysbiosis and interacts with psychiatric medications.

Moreover, future studies must rigorously address the difficulty of disentangling confounders that shape both dysbiosis and psychotropic response. Beyond diet, genetic polymorphisms, concomitant medications, and metabolic or gastrointestinal comorbidities, key modifiers include age-related microbiome shifts, sex-specific hormonal influences, lifestyle factors such as sleep, stress, and physical activity, environmental exposures, and early-life determinants like birth mode and antibiotic history. Research designs should incorporate standardized dietary protocols or stratification by nutritional patterns, exclude or adjust for microbiome-altering drugs, and match or statistically control for comorbidities and demographic variables. Longitudinal multi-omics approaches—integrating

microbiome sequencing, SCFA and bile acid metabolomics, and pharmacokinetic profiling—can help distinguish transient influences from stable dysbiosis signatures.

Testable hypotheses

Future investigations may predict stratified response outcomes, pharmacokinetic interaction, adjunctive treatment interventions and biomarker panel performance. For instance, among patients with major depression, those with objective markers of SIBO or reduced SCFA-producing microbiota will show lower remission rates on standard SSRI therapy compared with microbiome-normal patients, independent of baseline severity. In addition, in patients taking lamotrigine or other narrow-therapeutic-index psychotropics, documented dysbiosis will correlate with altered plasma drug concentrations and metabolite ratios, measurable in serial pharmacokinetic sampling. Moreover, in a randomized, biomarker-stratified trial, adjunctive therapy with probiotics/prebiotics or targeted treatment of confirmed SIBO (standardized rifaximin regimen) plus usual psychopharmacology will yield higher response/remission rates at 8–12 weeks than psychopharmacology plus placebo in the biomarker-positive subgroup. Also, patients with microbiome profiles enriched in bile acid–modifying taxa will show greater susceptibility to olanzapine-induced weight gain, suggesting microbiome-targeted interventions could mitigate adverse effects. Finally, a simple clinical-laboratory panel (gastrointestinal symptom checklist + breath test for SIBO + serum markers of inflammation or metabolite ratios)—also a research proposal requiring prospective validation, taking into consideration the lack of established specificity of these markers for psychiatric-specific dysbiosis and other potential confounding effects—will predict a subgroup of patients who derive clinically meaningful benefit from microbiome-directed adjuncts, for treatment augmentation response in pilot testing.

Limitations

The viewpoints advanced here are hypothesis-driven and integrate heterogeneous data from abstracts, clinical observations, preclinical models, small clinical cohorts, and case reports. Certain findings require extrapolation from preclinical to clinical contexts before they can be integrated into the proposed hypothetical model. Furthermore, key limitations include limited sample sizes, inconsistent diagnostic criteria across studies and several confounding influences —as age, gender, genetics, diet, comorbidities and medications—thus reducing generalizability.

Conclusion

Psychiatrists and pharmacologists should begin considering microbiome status as a hidden determinant of drug response rather than a psychiatric etiology only, thus representing a pragmatic step toward more individualized treatment strategies. This brief communication highlights critical gaps in the recognition

and integration of gut–brain interactions within psychiatric practice. Moreover, addressing these issues may clarify and reframe treatment resistance, improve therapeutic outcomes, enhance quality of life, inform future biomarker-stratified clinical trials, and ultimately strengthen the application of evidence-based pharmacology.

Declarations

- This manuscript is not submitted to any other media
- The manuscript has not been published earlier

Declaration of Generative AI and AI-assisted technologies in the writing process

Microsoft Co-pilot was only used for the final version of the manuscript for proofreading and enhancing readability—language copyediting purposes. Author read, edited and approved the final version of the manuscript.

Author contribution

The author (M.A.) independently conducted all aspects of the manuscript, including conceptualization, writing, and editing, without any external assistance

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Note: Figure translations are in progress. See original paper for figures.