

Suboptimal Levodopa Response During COMT Inhibitor Combination Therapy: Hidden Role of the Gut Microbiome

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ABSTRACT

Background: While levodopa is the undisputed standard in the treatment of Parkinson's disease, it is often paired with catechol-O-methyltransferase (COMT) inhibitors to see a more sustained clinical response and better central bioavailability. Yet there is new evidence to suggest that for some patients this approach can have the opposite effect, leading to a waning or substandard therapeutic outcome. The present review considers the role of microbiome-mediated drug interaction as an explanation for such variability in levodopa response.

Materials and methods: We have put together a narrative review of the literature to examine how gut microbial metabolism influences levodopa efficacy, not least in its interplay with COMT inhibitors. Our synthesis draws on mechanistic, *ex-vivo* and clinical data found in a structured search of PubMed/MEDLINE, Embase, Scopus, Web of Science and Google Scholar, covering the period from database inception through June 2026.

Results: A number of gut bacteria are at work here, most notably *Enterococcus faecalis*. By way of tyrosine decarboxylase these organisms will turn levodopa into dopamine in the intestinal lumen, something that conventional peripheral decarboxylase inhibitors do little to stop, and which serves to lower central bioavailability. At the same time, COMT inhibitors can have an unanticipated antibacterial impact on the gut ecology; they tend to put the brakes on susceptible populations while allowing levodopa-metabolising species like *E. faecalis* to flourish, establishing what might be termed a "drug-microbiome-drug" axis.

Conclusion: In effect, the gut microbiome is an active gatekeeper in the pharmacokinetics of levodopa-COMT inhibitor therapy, accounting for the progressive loss of response and differences between individuals. A clearer picture of this tripartite dynamic points to possibilities for personalised pharmacotherapy, whether by way of enzyme inhibition, targeted antimicrobials or microbiome profiling.

KEYWORDS: Parkinson's disease, Levodopa, COMT inhibitors, Gut microbiome, Tyrosine decarboxylase, *Enterococcus faecalis*, Drug-microbiome interaction, Pharmacokinetics.

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INTRODUCTION

Levodopa is the most effective symptomatic drug for Parkinson's disease because it gets transported into the central nervous system after crossing the blood-brain barrier and replenishes dopamine levels. Its clinical use is restricted, however, because of extensive peripheral metabolism including both aromatic L-amino acid decarboxylase (AADC) and catechol-O-methyltransferase (COMT) which decreases drug bioavailability and causes motor fluctuations. Peripherally decarboxylase inhibitors reduce early metabolism, although co-administration with such inhibitors is limited, COMT inhibitors like Entacapone and Opicapone are used routinely with levodopa to extend its half-life and plasma levels.¹

In both real world and population-based data, levodopa dominates Parkinson's pharmacotherapy, with studies reporting that it accounts for ~46.5% to nearly 100% of all PD prescriptions, and in large Medicare cohorts, ~90% of treated patients receive levodopa while overall 81–82% of diagnosed patients are on some anti-Parkinson drug.²

However, in contrast, COMT inhibitors (e.g., entacapone,

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opicapone) are used much less commonly, appearing in less than 10% of patients in population data (Medicare cohort) and are generally used <10% in routine practice, reflecting their role in the adjunctive treatment rather than first-line treatment.⁽³⁾ This is consistent with treatment paths, as levodopa is prescribed to >70% of incident PD cases and is almost always prescribed with disease progression, whereas COMT inhibitors (e.g., entacapone, opicapone) are added to a specific treatment pathway, namely to manage motor fluctuations (wearing-off), to augment levodopa bioavailability and to reduce off-time.

Nonetheless, a substantial proportion of patients exhibit variability in response or experience diminishing benefit over time, suggesting the presence of unrecognized modulatory factors beyond classical host metabolism.

At the same time, the new discipline of pharmacomicrobiomics has started to reshape our perception of drug disposition and make the gut microbiota an active player in the pharmacokinetics and pharmacodynamics. The intestinal microbiome is not just a passive environment for drug absorption, however, it is also a source of enzymatic machinery that can metabolize xenobiotics, thereby modifying drug efficacy, toxicity and inter-individual variability.

MATERIALS AND METHODS

This narrative review was conducted to synthesise current mechanistic, preclinical, *ex-vivo*, and clinical evidence linking the gut microbiome to variability in levodopa response, with specific emphasis on interactions between catechol-O-methyltransferase (COMT) inhibitors and gut microbial ecology. A structured literature search was conducted across PubMed/MEDLINE, Embase, Scopus, Web of Science, and Google Scholar since database inception till June 2026.

The search combined controlled vocabulary and free-text terms using Boolean operators, including: "Parkinson's disease," "levodopa," "COMT inhibitors," "entacapone," "opicapone," "gut microbiome," "gut microbiota," "tyrosine decarboxylase," "Enterococcus faecalis," "pharmacomicrobiomics," and "drug-microbiome interaction," in varying combinations. Reference lists of relevant articles were manually screened to identify additional sources (backward citation tracking).

Studies were considered eligible if they addressed microbial metabolism of levodopa, microbiome-mediated drug interactions, COMT inhibitor effects on gut microbial ecology, or the clinical implications of these mechanisms. Mechanistic, *in-vitro*, *ex-vivo*, animal-model, observational, and interventional human studies, as well as relevant reviews, were included. Only articles published in English were considered.

Given the narrative design, formal quality appraisal and quantitative synthesis were not undertaken; sources were selected on the basis of relevance, methodological soundness, and contribution to the mechanistic narrative.

CORRELATION OF PARKINSON'S DISEASE WITH GUT MICROBIOMES

Increasing research suggests a connection between the vast number of microbes living in the human gut and neurological conditions, such as the severe neurodegenerative illness Parkinson's disease.⁽⁴⁾ The gut microbes derived from individuals with Parkinson's can worsen motor impairments when transferred into germ-free mouse models. Notably, these effects can be alleviated through antibiotic treatment, indicating a potential causal role of the microbiota in neurodegeneration. Additionally,

several investigations have identified differences in the composition of gut microbiota between Parkinson's patients and healthy individuals, with some variations appearing to correlate with disease severity.^{5–10}

Several species of the genus *Lactobacillus*¹¹ and *Enterococcus*¹² have also been discerned to contain Tyrosine decarboxylase. *E. faecium* and *E. faecalis* were found to convert levodopa to dopamine more efficiently than *L. brevis*. The proximal part of the small intestine is the main zone of levodopa absorption. Current studies indicate that the abundance of Tyrosine decarboxylase in this region of rats is negatively correlated with the levodopa content in the blood.¹³

MICROBIOME-MEDIATED LEVODOPA METABOLISM: NEWER UNDERSTANDING

Microbiome–drug interactions in Parkinson's disease: integrated mechanisms of levodopa metabolism, COMT inhibitor-induced microbial modulation and pharmacokinetic variability.

The gut microbiome is an active metabolic interface that can influence the effectiveness and safety of levodopa therapy in PD. Mechanistic evidence demonstrated that the microbial enzyme, tyrosine decarboxylase (TDC)–expressing bacteria, particularly *Enterococcus faecalis*, convert levodopa to dopamine in the intestinal lumen and this enzyme is not inhibited by standard peripheral decarboxylase inhibitors such as carbidopa, suggesting a critical therapeutic limitation.¹⁴ Within the context of a distributed metabolic network, this process is happening. Downstream organisms such as *Eggerthella lenta* are responsible for metabolizing dopamine into m-tyramine, which increases the drug loss and accounts for the inter-individual variability in the dose of levodopa.

Clinical studies also demonstrate that adjunctive COMT inhibitor therapy is associated with compositional shifts in the gut microbiota without major changes in overall diversity, indicating that the drug is associated with targeted ecological remodeling rather than global depletion.¹⁵ These changes are functionally relevant, with enrichment of taxa associated with gastrointestinal dysfunction (including constipation) and predicted alterations in amino acid metabolic pathways, including those involved in the metabolism of alanine, aspartate, and glutamate, suggesting downstream effects on luminal biochemical activity involved in levodopa handling.

Recent work builds this by elucidating that COMT inhibitors are involved in a microbiome-mediated drug-drug interaction. These agents exhibit intrinsic antimicrobial effects, with selective reshaping of gut microbial ecology and enrichment of levodopa-metabolizing organisms, such as *Enterococcus faecalis*, paradoxically increasing pre-systemic

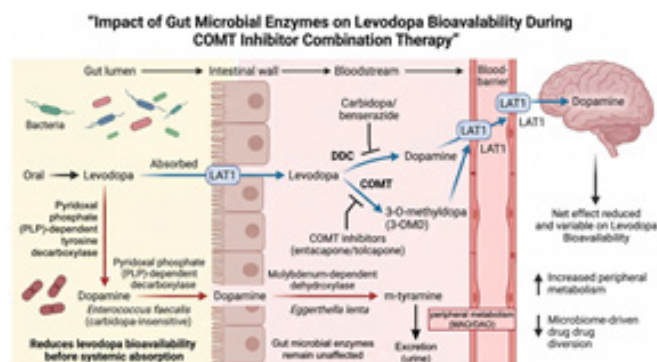


Figure 1: Microbiome-mediated levodopa metabolism and the effect of COMT inhibitor co-therapy. Bacterial tyrosine decarboxylase (TDC) (mainly from *Enterococcus faecalis*) converts luminal levodopa into dopamine, which decreases its central bioavailability; *Eggerthella lenta* further metabolizes dopamine to m-tyramine. COMT inhibitors have antibacterial effects that can alter the microbial ecology and enrich taxa involved in levodopa metabolism, thus contributing to enhanced presystemic drug loss.

levodopa degradation despite the pharmacological intent to preserve it.¹⁵ Mechanistically, this effect is associated with bacterial iron homeostasis, as COMT inhibitors induce iron starvation responses, and the availability of this element modulates microbiome susceptibility and drug activity. *Ex-vivo* human microbiome experiments, in turn, demonstrate that combined levodopa-COMT inhibitor therapy results in individualized microbiome-dependent alterations in drug metabolism, establishing the concept of a personalized "microbial pharmacokinetic phenotype".

FUTURE SCOPE

The immediate research need is to identify specific microbial taxa (e.g., tyrosine decarboxylase-harboring species) and metabolomic signatures that would predict reduced bioavailability of levodopa or increased GI intolerance with COMT inhibitors. This paves the way to microbiome-guided personalization; baseline microbiome profiling might dictate the type of therapy for a patient who should receive levodopa-COMT inhibitor therapy, adjunctive use of antibiotics/enzyme inhibitors, or even microbiota-targeted approaches such as probiotics, bacteriophages or dietary modifications. A second frontier is drug development, particularly peripherally restricted inhibitors of bacterial levodopa metabolism that do not disrupt host catecholamine pathways—an idea seeded in the 2019 work,⁽¹⁴⁾ but still underexplored clinically. Third, longitudinal and interventional human trials are needed to move beyond associative findings (as in the pilot study) toward causality, especially integrating multi-omics (metagenomics + metabolomics + pharmacokinetics) to map how COMT inhibition reshapes gut ecology over time. Further, given the consistent signal of GI adverse effects, future work must define whether these are merely tolerability issues or biomarkers of microbiome-mediated pharmacokinetic failure, which would fundamentally reframe diarrhea from a side effect into a clinically actionable

signal.

It would also be of interest to study other variants like foslevodopa which have shown potential in advanced Parkinson's disease from the lens of microbiomes. Foslevodopa is often given in combination with foscarnidopa as continuous subcutaneous infusion demonstrating increased "on" time and reducing "off" time.⁽¹⁶⁾ However, high possibility of infusion site reactions limits their usage.

A serious chunk of the next breakthroughs here may come from in silico and computational pharmacology, not just wet lab work. The most immediate opportunity is to perform genome-scale metabolic modeling of gut microorganisms, i.e., simulation of the competition between bacterial and human enzymes for levodopa and the effect of COMT inhibitors on this competition. Screening selective inhibitors of bacterial tyrosine decarboxylase using AI docking and molecular dynamics could speed up the drug discovery process, drastically. On the systems level, multi-omics integration platforms (metagenomics + metabolomics + PK data) can be applied to create predictive models of 'levodopa loss' or GI toxicity, which can enable virtual patient simulations in advance of clinical trials. Another high-yield area is digital twin modelling, in which a person's pharmacokinetics and microbiome can be virtually modelled to enable prediction of response to combination therapy and tailor dosing strategies. Lastly, network pharmacology methods can be used to map out the network of drug-microbe-host interactions, where they can find non-intuitive intervention points (e.g., dietary cofactors, enzyme co-substrates, or microbial cross-feeding pathways).

The 2022 FASEB study points toward a promising future in which treatment for Parkinson's disease shifts from intermittent pharmaceutical doses to continuous, biologically integrated drug supplies.⁽¹⁷⁾ The engineered *E. coli* Nissle platform capable of continuous localized production of L-DOPA implies that future research in this direction will focus on precision microbiome engineering: on chromosomal introduction, fine-tuning regulatory circuits, and designing safety mechanisms to prevent inappropriate dopamine production. The most crucial upcoming experiment is long-term trials in humans to assess colonization efficiency, controllability of dose, and potential adverse genetic exchange events. Another promising avenue is the combination of such engineered bacteria with other treatment approaches (COMT inhibition, diet modulation, microbiota-targeted therapies) in a concerted effort to manage both disease progression and pharmacokinetic variability. Overall, this research hints toward a future wherein drugs are not dosed in discrete temporal administrations, but continuously produced, regulated, and optimized within the patient's own body.

The narrow-spectrum, gut-restricted design of antibiotics

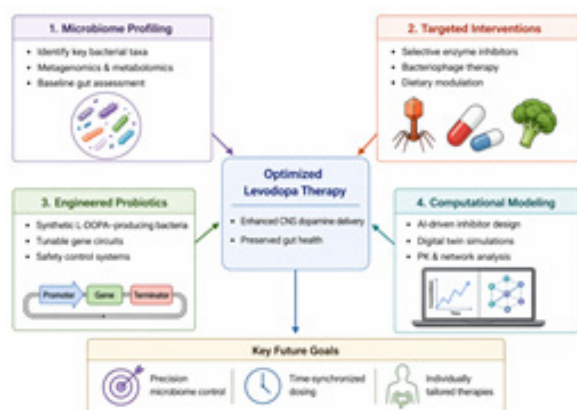


Figure 2: Emerging microbiome-targeted strategies to preserve levodopa bioavailability. Narrow-spectrum inhibitors of bacterial TDC, bacteriophages targeting *E. faecalis*, reversible metabolic blockers (e.g., honokiol-SCFA conjugates), engineered probiotics for in situ L-DOPA delivery, and baseline microbiome profiling collectively enable microbiome-guided, patient-specific optimisation of levodopa therapy.

targeting *Enterococcus faecalis* and *Eggerthella lenta* could be a novel approach for improving central levodopa bioavailability with minimal disruption of global microbiome. But enzyme-level inhibition (such as targeting bacterial TyrDC) might be more specific than organism-level eradication.

The 2024 study provides a valuable glimpse into the future by suggesting that targeted inhibition of L-DOPA-metabolizing bacteria, such as *Enterococcus faecalis*, may optimize the delivery of dopamine to the brain without altering levodopa itself.¹⁸ Mito-ortho-HNK exemplifies an innovative approach to microbiome modulation that preferentially suppresses bacterial tyrosine decarboxylase while conserving the integrity of the broader gastrointestinal microbiota. Future investigations should prioritize the development of narrow-spectrum bacterial inhibitors as well as bacteriophage targeting and metabolite-specific enzymatic blockers, coupled with time-dependent levodopa dosing regimens that maximize central nervous system availability. When combined with microbiome profiling, these strategies could facilitate a paradigm shift from standardized combination therapy to individualized levodopa optimization based on each patient's microbiome.

Recent studies expand previous microbiome-focused strategies by shifting towards more specific and reversible manipulations of levodopa metabolism. The 2024 study demonstrating the use of bacteriophages to specifically target and eliminate *Enterococcus faecalis* highlights the potential for targeted removal of specific bacterial populations contributing to L-DOPA metabolism.¹⁹ Building on these findings, a 2025 study introduced honokiol-SCFA conjugates that temporarily suppress bacterial metabolism without permanently eliminating the bacteria, creating a window during which levodopa can remain

unmetabolized and available for absorption.²⁰ These findings suggest that future therapeutic approaches should be focused on precision microbiome control tools, including bacteriophages, enzyme-specific inhibitors, and reversible metabolic blockers, over traditional co-drug strategies. The next step is to develop time-controlled patient-specific strategies for modulating the microbiota around levodopa administration, which would allow for predictable delivery of levodopa to the CNS while preserving microbiome stability.

CONCLUSION

In general, evidence was found that supports the idea that the levodopa-COMT inhibitor paradigm is not only a host-controlled pharmacokinetic process but also a host-microbiome co-regulated function. The variability in the response and the occurrence of GI adverse effects suggest that the pharmacological response is determined by bacterial metabolism and ecosystem changes. This evidence may change the current understanding of the paradigm from a clinical practice based on dose adjustments and symptomatic management to a more mechanistically informed strategy that considers microbiome interference. If this line of research holds, the future standard of care will not just ask "how much levodopa?" but "in which microbiome context?" with therapeutic strategies extending beyond COMT inhibition to include targeted modulation of gut bacterial activity.

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