

# Major depressive disorder and the gut microbiome: what is the link?

Vania Modesto Lowe <sup>1</sup>, Margaret Chaplin,<sup>1,2</sup> Deanna Sgambato<sup>3</sup>

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## INTRODUCTION

Major depressive disorder (MDD) manifests by persistent depressed mood, anhedonia, changes in sleep and appetite, fatigue, guilt as well as hopelessness and suicidality.<sup>1</sup> MDD is quite prevalent and remains a leading cause of disease burden worldwide.<sup>2</sup> Antidepressants in combination with psychotherapies are helpful but do not work for all persons with MDD. In fact, 30%–50% of depressed patients exhibit only a partial response to antidepressants with significant residual symptoms.<sup>3</sup> Conversely, about 10%–30% of patients with MDD are resistant to the therapeutic effects of antidepressants and are classified as treatment non-responders.<sup>3</sup> This variability in treatment response among these patients may reflect diverse pathogenesis of yet undetermined subgroups of MDD.<sup>4</sup> Biological markers have implicated multiple mechanisms including neuroinflammation, neuroendocrine changes and gut microbiome abnormalities.<sup>2,4</sup> While there is no clear pathway unifying these theories, the mapping of the human microbiota offers new avenues of exploration.<sup>5–7</sup>

The gut microbiota is an ecosystem containing some 100 trillion microorganisms that enjoy a symbiotic relationship with the host in times of good health.<sup>5</sup> Firmicutes and Bacteroidetes are the two dominant bacterial phyla that constitute 90% of the total ecosystem.<sup>5</sup> Genes, age, sex, diet, life experiences, the environment and stress levels can all impact the development of the gut microbiota.<sup>5</sup> The microbiota influences digestion, vitamin production, the permeability of the intestinal barrier and immunity. The gut microbiome also has a bidirectional effect on the brain through the gut-brain axis.<sup>2,5</sup> The gut-brain axis refers to the bidirectional crosstalk between the gut and the brain and is implicated in hormonal, immunological and neural homeostasis. This means that changes in the gut microbes can affect the central nervous system (CNS), including response to stress, mood and anxiety states.<sup>2,5</sup> Similarly, persistent stress may alter

the composition of the microbiota resulting in the so-called stress-related dysbiosis (ie, a relative abundance of proinflammatory gut microbes). Persistent stress can also affect the intestinal barrier, causing a ‘leaky gut’, which allows toxic microbial products into the systemic circulation and ultimately the brain.<sup>5</sup> This intricate relationship remains largely uninvestigated in human samples but shows promise in providing different approaches through which to view and treat MDD.<sup>2,6,8</sup>

## EFFECTS OF GUT MICROBIOTA ON THE CNS AND MOOD

The gut microbiota is composed of 300–500 different species of bacteria; each species possesses its own characteristics and abilities with some synthesising neurotransmitters.<sup>9</sup> *Escherichia* and *Enterococcus* have been known to produce serotonin, while certain strains of *Bifidobacterium* and *Lactobacillus* produce gamma-aminobutyric acid (GABA).<sup>9</sup> As depicted in [figure 1](#), the gut microbiota can also stimulate the CNS via the production of bacterial metabolites, such as short-chain fatty acids (SCFAs).<sup>2</sup> Certain gut microbes, such as *Coprococcus* and *Faecalibacterium*, ferment non-digestible carbohydrates to create SCFAs including acetate, butyrate and propionate.<sup>10</sup> SCFAs target endocrine cells, the immune system and neurons.<sup>2</sup> The SCFAs likely mediate gut and brain interactions through multiple pathways, such as immune signals, hormones and the vagus nerve.<sup>2</sup> Furthermore, SCFAs directly stimulate tryptophan hydroxylase resulting in serotonin (5-HT) synthesis from intestinal enterochromaffin cells. Serotonin is released from neurons in the enteric nervous system to modulate motility and appears to be an important mediator of the gut-brain axis. Precisely how gut serotonin communicates with the brain remains to be fully elucidated. One theory is that the vagus nerve fibres have receptors for serotonin (5-HT<sub>3</sub>, 5-HT<sub>4</sub>) and other bacterial products. These receptors allow the vagus nerve to sense microbial signs and message the brain via the



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<sup>1</sup>Department of Psychiatry, University of Connecticut Health Center, Farmington, Connecticut, USA

<sup>2</sup>Farrell Treatment Center, New Britain, Connecticut, USA

<sup>3</sup>School of Health Sciences, Quinnipiac University, North Haven, Connecticut, USA

### Correspondence to

Dr Vania Modesto Lowe; modestolowe@uchc.edu

**NO FIGURE FOUND** **Figure 1** Effects of gut microbiome on brain physiology. GABA, gamma-aminobutyric acid; SCFAs, short-chain fatty acids.

nucleus of the solitary tract, which houses the majority of 5-HT neurons. Interestingly, SCFAs can pass through the blood-brain barrier (BBB), whereas GABA and serotonin do not appear to do so except in inflammatory conditions that may alter BBB permeability.<sup>11</sup> Of note, ‘depressed and stressed’ rodents have abnormally low levels of SCFAs in their gut.<sup>2</sup> Such findings are consistent with the Flemish Gut Flora Project, a large microbiome human study (n=1 054) that showed reduced levels of butyrate-producing species *Coprococcus* spp and *Dialister* in patients with MDD.<sup>9</sup> In this study, high levels of butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria were consistently associated with a higher quality of life measures.<sup>10</sup>

It is difficult to translate this knowledge clinically, as capturing an individual’s unique microbiota composition, or faecal signature, is complex. Finding an MDD-specific faecal signature is even more challenging.<sup>8</sup> Enterotypes such as alpha species diversity, the ratio of Firmicutes to Bacteroidetes phyla, and the relative abundance of beneficial (eg, *Coprococcus* and *Faecalibacterium*) versus proinflammatory (*Eggerthella* and *Atopobium*) genera have all been employed in this research.<sup>10</sup> Early efforts to find an MDD-specific faecal signature employed the ratio of Firmicutes to Bacteroidetes, which are two of the most prominent phyla of bacteria in the human gut.<sup>8</sup> Jiang *et al* proposes the Firmicutes to Bacteroidetes ratio as a potential biomarker, finding a substantial decrease in the phylum Firmicutes in individuals with MDD relative to healthy controls.<sup>12</sup> Therefore, the identification of microbiome composition with smaller Firmicutes to Bacteroidetes ratios could potentially serve as a biomarker for depressive symptoms.<sup>12</sup> Subsequently, a systematic review of available studies showed mixed results, which suggests difficulties in replicating these initial findings.<sup>13</sup>

Alternative methods to examine the gut use metrics of alpha and beta diversity.<sup>5 14</sup> Alpha diversity explores the number and distribution of bacterial species within the host with higher alpha diversity thought to benefit mood.<sup>14</sup> In a systematic review of 17 studies, Knudsen *et al* found that four studies revealed reduced alpha diversity in patients with MDD. If alpha diversity is diet responsive, this finding may be of clinical interest if replicated. Conversely, beta diversity focuses on similarities or dissimilarities in gut microbiota ecology between groups, such as between subjects with MDD and healthy controls.<sup>14</sup> In terms of beta diversity, the gut microbiota compositions clustered separately according to MDD status in 12 studies. More specifically, there was an increase in the relative abundance of proinflammatory bacteria such as *Eggerthella*, *Atopobium*, and a decreased relative abundance of *Faecalibacterium* in MDD subjects.<sup>14</sup> Similarly in Sanada *et al*’s<sup>15</sup> meta-analysis, patients with MDD had a decreased abundance of the genera *Coprococcus* and *Faecalibacterium*, compared with non-depressed individuals.

Of note, *Faecalibacterium* acts as a major butyrate-producing bacteria in the gut, essential for gut homeostasis and possibly decreasing depressive symptoms at least in animal models.<sup>16</sup>

## THE INFLUENCE OF MOOD ON GUT HEALTH

Preclinical research suggests possible ways by which chronic stress and depressive states may contribute to gut inflammation and leaky gut.<sup>2 5</sup> In rodents, both persistent stress and depressive behaviours alter colonic motility and foster the growth of proinflammatory bacteria.<sup>2</sup> Both chronic stress and gut inflammation appear implicated in MDD.<sup>8</sup> Hence, one line of research has sought to correlate changes in the gut microbiota ecology according to inflammatory markers and depressive status.<sup>10 12 13</sup>

Observational studies exploring the gut microbiota of MDD samples<sup>17</sup> showed a higher abundance of proinflammatory species (eg, *Desulfovibrio*) and members of the family Enterobacteriaceae along with low abundances of butyrate-producing bacteria such as *Faecalibacterium*. A review by Simpson also showed lower SCFA-producing bacteria (eg, *Faecalibacterium*) as well as a high abundance of proinflammatory (eg, Enterobacteriaceae) species in the gut of depressed subjects.<sup>18</sup> While the relative scarcity of *Faecalibacterium* in MDD samples may signify inflammation in depressive states, a lack of specificity limits the clinical value of these findings; a meta-analysis put forth by Nikolova *et al* found that depleted levels of *Faecalibacterium* and *Coprococcus*, as well as enriched levels of *Eggerthella*, are shared among other psychiatric disorders.<sup>19</sup>

## CONCLUSION

MDD remains clinically and epidemiologically relevant with a lack of effective treatment for up to two-thirds of patients. This makes it essential to consider and investigate other novel pathways of pathogenesis, including the gut microbiome. While the nature of gut microbiota in depressed humans appears complex and remains poorly investigated, advances have occurred with research displaying factors such as low butyrate production and proinflammatory bacteria as risks to MDD development and even as consequences of mood disorders. However, current research has yet to determine changes that are unique to MDD. Furthermore, at present, a significant source of available research derives from animal models. Nonetheless, there is a well-established connection between the gut and the brain and growing evidence that gut microbiome disturbances are present in MDD. Whether these are primary or secondary changes and whether there is in fact a pathological pattern unique to MDD remains to be determined. If future research can elucidate a more specific pathology, then exploration of the gut microbiome may not only find a potential biomarker but also an avenue to pursue novel treatment options.

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#### ORCID iD

Vania Modesto Lowe <http://orcid.org/0000-0003-3036-2566>

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*Dr Vania Modesto Lowe graduated from the Federal University of Paraiba, Brazil in 1985. She received a master's degree in Public Health in 1988 and completed her psychiatric residency at the University of Connecticut, USA in 1996. She has been the medical director of Hartford Behavioral Health in the USA since 2022. She has also been community faculty at UCHC and Quinnipiac University in the USA for the past 20 years. Her areas of clinical and research interest include general psychiatry and addiction psychiatry. She is also passionate about teaching students and residents to learn about the biological aspects of addiction, including pharmacotherapy such as methadone, buprenorphine, varenicline, and acamprostate.*