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Gut microbiome modulation through non-pharmacological therapy in psychiatric disorders: neurotransmitter synthesis, neuroplasticity, and brain-gut signaling

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ABSTRACT

Psychiatric disorders affect over 970 million people globally, with substantial personal, social, and economic costs that continue to rise despite advances in treatment. Current pharmacological approaches show limited efficacy for many patients, with significant side effects and high discontinuation rates. The integration of microbiome science with psychiatric research may offer new perspectives on disease etiology, biomarker development, and therapeutic intervention. Recent advances in microbiome research reveal that the gut microbiome directly synthesizes neurotransmitters and their precursors, while microbial metabolites produced by the microorganisms through their metabolic activities, cross the blood-brain barrier (BBB) to influence regulate microglial activation, synaptic plasticity, neurogenesis, and neural circuit development associated with our brain's function. Specific gut bacterial taxa may demonstrate causal relationships with psychiatric symptoms through vagal, immune, and metabolic pathways. Gut dysbiosis patterns consistently emerge across major psychiatric conditions associated with distinct microbial signatures. Scientific research has discovered that disrupted circadian rhythm and dysregulated stress response system especially the hypothalamic pituitary adrenal (HPA) axis both disrupt gut microbiota composition and function, leading to health issues like metabolic syndrome, gastrointestinal disorders, and mental wellness issues. Understanding these mechanisms may open unprecedented opportunities for non-pharmacological approaches that integrate microbiome analysis and targeted interventions. The authors of this article aim to explore how non-pharmacological intervention methods such as mental wellness behavioral therapy and educational therapy can be integrated with gut microbiome knowledge to enhance patient outcomes, focusing on mental health, gastrointestinal, and metabolic disorders.

Keywords: Educational therapy, mental wellness behavioral therapy, gut-brain axis, microbial metabolites, neurotransmitter synthesis, neuroplasticity

INTRODUCTION

The human gut refers to the gastrointestinal tract, which runs from our mouth through the esophagus, stomach, small intestine, large intestine (colon), rectum and anus. This gut which contains over 100 trillion of microorganisms (or gut microbiota) made up of over 1,000 bacterial species (bacteria, archaea, fungi, viruses, protozoa and helminths) is referred to as gut microbiome. The gut microbiome is responsible for many different bodily functions such as breaking down food to ensure that its nutrients are absorbed and waste materials taken out of the body. It is also responsible for immunity and general well-being of the individual.¹ The gut microbiome has emerged as a critical modulator of brain function and mental health.² This intricate ecosystem influences psychiatric disorders through direct effects on neurotransmitter

synthesis, neuroplasticity mechanisms, and interactions with host genetic factors that determine individual vulnerability to mental illness.³

The gut microbiome represents a dynamic environmental factor that influence neurodevelopment, stress response systems, and neurotransmitter pathways critical for mental health.⁴ The neurobiological mechanisms underlying gut-brain communication involve multiple interconnected pathways that directly impact neurotransmitter synthesis and neural plasticity. Gut bacteria produce gamma-aminobutyric acid (GABA), serotonin, dopamine, and other neuroactive compounds, while microbial metabolites including short-chain fatty acids (SCFAs) cross the blood-brain barrier (BBB) to

influence synaptic function, neurogenesis, and neural circuit development.⁵

Association of the Gut-Brain Axis and Enteric Nervous System

The gut microbiome communicates bidirectionally with the central nervous system (CNS) through multiple mechanisms including the vagus nerve, immune system modulation, neurotransmitter production, metabolite synthesis, and epigenetic regulation.⁶ This bidirectional communication known as gut-brain axis is not restricted only to vagus nerve, albeit the vagus nerve serves as the primary channel connecting the gut and brain (see [Figure 1](#)),⁷ transmitting bidirectional signals that influence both the peripheral nervous system (PNS) and CNS functions.⁸ Bacterial metabolites and neurotransmitters activate vagal afferent neurons in the enteric nervous system, which transmit signals to the brainstem and subsequently modulate central neurotransmitter synthesis and release. Vagotomy studies have demonstrated that severing this nerve abolishes many microbiome-induced behavioral and neurochemical changes.⁸

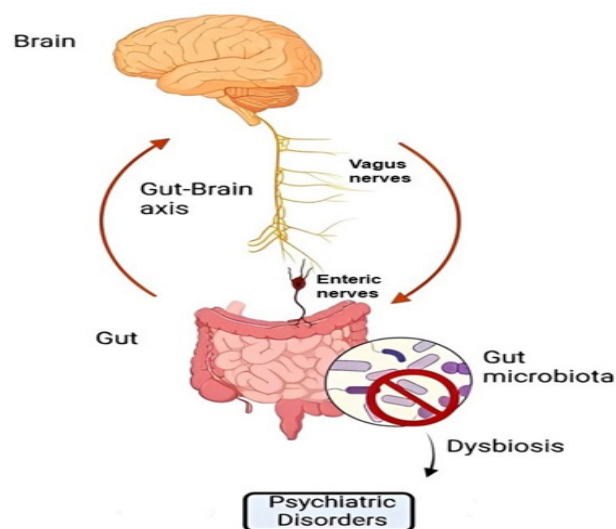


Figure 1. Bidirectional communication of the gut-brain axis

Interestingly, as estimated in the studies by Magalhães and Castelucci,⁹ there are some 500 million enteric neurons embedded on the walls of the gut. These enteric neurons range from motor neurons, sensory neurons, interneurons, vasodilator neurons to secretomotor neurons. The vast network of these neurons covering from the esophagus to anus is known as the enteric nervous system (ENS). The ENS functions autonomously like another “brain” in regulating our digestive processes (which include motility). However, this “second brain” also maintains extensive bidirectional communication with our CNS.¹⁰

GUT BACTERIA

Gut bacteria produce a variety of compounds, including microbial metabolites, neurotransmitter precursors, neurotransmitters (serotonin, GABA and dopamine) and engage in other processes that signal the brain through neural, hormonal, and immune pathways. The enteric neurons in the gut respond directly to bacterial metabolites and neurotransmitters, with specific bacterial strains capable of activating or inhibiting enteric neural circuits¹¹ (see [Table 1](#)).^{5,12-14} This local neural processing significantly influences gut-brain axis’ ascending signals to the brain and descending autonomic control of gut function.¹⁴ The vagus nerve transmits bacterial signals to the brain, influencing neurotransmitter release and mood (a direct communication line). Vagal afferent neurons also express receptors for microbial metabolites, bacterial lipopolysaccharides, and gut hormones, allowing direct sensing of microbiome composition and activity.

Gut dysbiosis (alteration to the microbiome resulting in an imbalance in the microbiota) leading to the production of inflammatory molecules and increased permeability of the intestinal barrier, disrupts enteric neural function, affecting gastrointestinal motility, barrier function, and neurotransmitter production in ways that reverberate throughout the nervous system to influence psychiatric symptoms¹⁴ (see [Figure 2](#)).¹² Gut dysbiosis may lead to

Table 1. Influence of gut bacteria on the brain

Mechanism	Description	Key processes
Direct neurotransmitter production	Gut bacteria synthesize neurotransmitters like serotonin, GABA, dopamine, and norepinephrine.	Gut bacteria produce neurotransmitters that signal the brain indirectly through blood circulation or the vagus nerve (a direct gut-brain connection).
Production of neurotransmitter precursors	Gut bacteria generate precursors (e.g., tryptophan, glutamate) used by the host to synthesize neurotransmitters.	Gut bacteria supply precursors that the host uses to synthesize neurotransmitters, modulating brain chemistry (like providing ingredients for the brain’s ‘recipes’).
Modulation of host neurotransmitter synthesis	Bacterial metabolites influence host cells to produce neurotransmitters.	Bacterial metabolites, especially SCFAs, stimulate host neurotransmitter production and can directly affect the brain (SCFAs as messengers boosting brain chemicals).
Immune system modulation	Gut bacteria interact with the immune system, indirectly affecting brain neurotransmitter levels and function.	Gut bacteria interact with the immune system; dysbiosis can trigger inflammation that affects brain function (inflammation as a false alarm).
Blood-brain barrier (BBB) integrity	Gut bacteria maintain BBB integrity, regulating what enters the brain.	Gut bacteria produce SCFAs that maintain the BBB, protecting the brain from harmful substances (reinforcing the brain’s security wall).
Hormonal regulation	Gut bacteria influence hormone production, which can affect brain signaling and neurotransmitter activity.	Gut bacteria modulate hormones like cortisol and oxytocin, which influence brain signaling (adjusting the body’s ‘mood playlist’).
Metabolic by-products	Bacterial metabolites, beyond SCFAs, influence brain function.	Bacterial metabolites modulate neurotransmitter pathways in the brain (fine-tuning brain chemistry).

GABA: Gamma-aminobutyric acid, SCFAs: Short-chain fatty acids

serotonin deficits and reduced levels of GABA, disrupting brain connectivity and functionality, affecting mood and behavior.^{15,16}

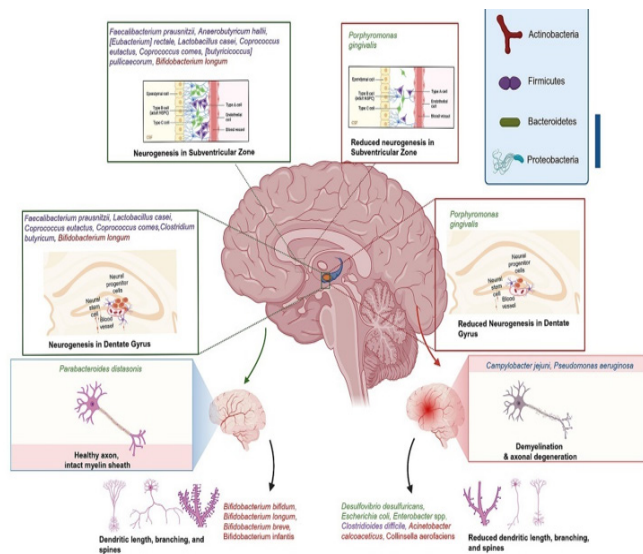


Figure 2. Gut bacteria in association with our brain & neuroplasticity functions

Table 2^{13,15,17-51} shows a comprehensive list of known contributions of gut bacteria to gut-brain axis communication associated with the brain neuroplasticity and different psychiatric disorders such as autism spectrum disorder (ASD), major depressive disorder (MDD), bipolar disorder (BD),

attention deficit-hyperactive disorder (ADHD), anxiety disorder, post-acute COVID symptoms (PACS), Alzheimer's disease (AD), Parkinson disease (PD) and schizophrenia spectrum disorder (SSD).

MICROBIAL METABOLITES AND SIGNALING

According to Zuffa et al.,⁵² when food is processed by our digestive enzymes, the gut bacteria transform this food into hundreds of different microbial metabolites through fermentation and other metabolic processes (see Table 3).^{20,53-60} These microbial metabolites enter the bloodstream and travel throughout the body, acting as molecular messengers that influence virtually every organ system such as immune function, metabolism, cardiovascular health, brain function and mood. The gut microbiome is increasingly recognized not just as a digestive aid, but as a crucial "organ" that produces hundreds of bioactive compounds essential for optimal health. The specific mix of metabolites the microbiome produces depends on factors like diet, lifestyle, genetics, medications, and the particular species of microbes the gut is harboring, making every metabolite profile uniquely related to every identity.

Short-Chain Fatty Acids (SCFAs)

In the studies conducted by Yassin and his colleagues,¹² the SCFAs are the most abundant and well-studied metabolites that promote BBB integrity. Particularly the acetate, propionate and butyrate, they represent critical signalling

Table 2. Roles of gut bacteria in neuroplasticity associated with psychiatric disorders

Microorganism/process	Associated psychiatric disorders	Role in brain neuroplasticity	Key findings
<i>Acinetobacter calcoaceticus</i>	No direct association	May contribute to inflammation, potentially affecting neuronal health	Part of gut microbiota, lower virulence, potential pro-inflammatory effects
<i>Actinobacteria</i>	ASD, potentially MDD, BD, SSD	May support gut barrier function, reducing inflammation	Higher in ASD, linked to GI symptoms and behavior
<i>Actinomyces naeslundii</i>	PACS (anxiety, depression)	Not directly studied	Higher in PACS, linked to psychological issues
<i>Akkermansia muciniphila</i>	ASD, MDD	Supports gut barrier integrity, aiding neuronal health	Lower in ASD and MDD, associated with metabolic health
<i>Alistipes</i>	MDD	May influence inflammation and neurotransmitter signaling	Increased in MDD, linked to systemic inflammation
<i>Anaerobutyricum hallii</i>	Anxiety, PTSD	Produces butyrate, supports synaptic plasticity and reduces neuroinflammation	Butyrate producer, linked to reduced inflammation in PTSD, potential biotherapeutic
<i>Bacillus</i> spp.	MDD, anxiety, Parkinson's disease	Supports synaptic plasticity through neurotransmitter production (dopamine, serotonin)	Synthesizes dopamine and other neurotransmitters, acts as probiotics to improve mood, influences gut-brain axis through secretome
<i>Bacillus subtilis</i>	Aggression, MDD, anxiety, Parkinson's disease	Supports synaptic plasticity through serotonin and tryptophan production	Probiotic that prevents aggression, supports serotonin synthesis, reduces neuroinflammation, potential benefits in Parkinson's disease
<i>Bacillus mycoides</i>	Potentially SSD, MDD, addiction	Supports synaptic plasticity through dopamine production	Synthesizes dopamine, a neurotransmitter critical for brain function and behavior
<i>Bacteroides</i>	ASD, ADHD, MDD, addiction (CNS stimulants)	Produces neurotransmitters and SCFAs, supports synaptic plasticity	Mixed results in ASD, increased in ADHD and PACS
<i>Bacteroides fragilis</i>	Depression, ASD, Alzheimer's, multiple sclerosis	May support or disrupt synaptic plasticity via immunomodulation and metabolic signaling	Produces polysaccharide A (PSA) with immunomodulatory effects, modulates depression-like behavior, linked to Alzheimer's and ASD
<i>Bacteriophages</i>	ASD	May modulate bacterial populations affecting brain function	Altered in ASD, influencing microbial dynamics
<i>Bifidobacterium</i>	ASD, ADHD, MDD, BD, SSD, addiction (alcohol)	Produces GABA, supports synaptic plasticity	Lower in ASD, higher in ADHD, supports neural signaling

The table continues

Table 2. Roles of gut bacteria in neuroplasticity associated with psychiatric disorders (The table continues)

<i>Bifidobacterium</i> spp.	Depression, anxiety, ASD, stress-related disorders	Supports synaptic plasticity through neurotransmitter production and anti-inflammatory effects	Key players in gut-brain axis, influence mental health via neurotransmitter production, immune modulation, stress response regulation
<i>Bifidobacterium longum</i>	MDD, anxiety, PACS	Produces GABA and SCFAs, enhances synaptic plasticity and reduces stress	Supplementation reduces depressive symptoms; lower in PACS
<i>Blautia</i>	ASD, ADHD	Produces SCFAs, supports anti-inflammatory pathways	Lower in ASD, increased in ADHD
<i>Butyricoccus pullicaecorum</i>	Anxiety	Produces butyrate, potentially supports synaptic plasticity	Decreased in anxiety, linked to reduced anti-inflammatory effects
<i>Campylobacter jejuni</i>	Anxiety	May disrupt neural signaling	Induces anxiety-like behavior in rodents
<i>Candida</i>	ASD, ADHD	May contribute to inflammation	Higher in ASD, linked to GI symptoms
<i>Clostridium</i>	ASD, MDD, BD, PASC	Produces neurotransmitter precursors (tryptophan), SCFAs, and secondary bile acids via 7 α -dehydroxylation; some species produce neurotoxins	Higher in ASD, linked to GI and behavioral symptoms; contributes to mood regulation via tryptophan metabolism
<i>Clostridium</i> spp.	Depression, anxiety, Parkinson's, multiple sclerosis	Can support or disrupt synaptic plasticity through neurotransmitter modulation and immune signaling	Influences gut-brain axis, some species linked to neurological disorders, others maintain gut homeostasis
<i>Clostridium butyricum</i>	MDD, anxiety	Produces butyrate, supports synaptic plasticity and reduces stress	Supplementation reduces depressive symptoms; enhances gut-brain signaling
<i>Clostridioides difficile</i>	ASD, Alzheimer's, Parkinson's, multiple sclerosis	May disrupt gut-brain axis, negatively affecting neuroplasticity	Linked to neurological disorders via toxins and inflammation
<i>Collinsella</i>	ASD	Associated with pro-inflammatory states	Higher in ASD, linked to inflammation
<i>Collinsella aerofaciens</i>	ASD	May contribute to inflammation, potentially affecting neuroplasticity	Higher in ASD, associated with pro-inflammatory states
<i>Coprococcus</i>	ASD, MDD	Produces butyrate, supports neuronal health	Lower in ASD and depression, anti-inflammatory
<i>Coprococcus comes</i>	ASD, MDD	Produces butyrate, supports neuronal health	Lower in ASD and depression, linked to anti-inflammatory effects
<i>Coprococcus eutactus</i>	ASD, MDD	Produces butyrate, supports neuronal health	Lower in ASD and depression, linked to anti-inflammatory effects
<i>Coriobacteriaceae</i>	BD	Linked to metabolic and inflammatory pathways	Increased in BD, associated with cholesterol metabolism
<i>Corynebacterium glutamicum</i>	Potentially SSD, MDD, anxiety	Produces glutamate, supporting GABA synthesis and synaptic plasticity	Produces L-glutamate via mechanosensitive channels, influences gut-brain axis
<i>Desulfovibrio</i>	ASD	Produces hydrogen sulfide, linked to GI issues	Mixed results in ASD, associated with gut symptoms
<i>Desulfovibrio desulfuricans</i>	ASD	Produces hydrogen sulfide, potentially disrupting neural signaling	Mixed results in ASD, linked to gut dysbiosis
<i>Dialister</i>	ASD, ADHD	Supports gut health, may influence neural signaling	Lower in ASD and unmedicated ADHD
<i>Eggerthella</i>	MDD, BD, SSD	Linked to symptom severity via inflammation	Higher in MDD, BD, SSD
<i>Enterobacteriaceae</i>	ASD	Includes pathogens, may increase inflammation	Mixed results in ASD, linked to gut dysbiosis
<i>Enterobacter</i> spp.	ASD, potentially MDD, BD, SSD	May influence neurotransmitter production and inflammation	Altered in psychiatric disorders, linked to gut-brain axis
<i>Enterococcus</i>	Addiction (alcohol), potentially MDD	Produces neurotransmitters like dopamine, influences inflammation	Increased in alcoholics, may exacerbate inflammation and mood dysregulation
<i>Escherichia coli</i>	ASD, MDD, potentially anxiety	Produces dopamine, serotonin precursors (tryptophan), and indoles, modulating mood and cognition	Supplies tryptophan for serotonin synthesis; dopamine production affects reward systems
<i>Escherichia coli</i> K-12	Potentially Parkinson's, neuroinflammation-related disorders	May disrupt synaptic plasticity through neuroinflammation and barrier disruption	Model organism, influences gut-brain axis via intestinal barrier effects and potential neuroinflammation
<i>Eubacterium rectale</i>	PTSD	Produces butyrate, potentially supports synaptic plasticity	Part of Lachnospiraceae, associated with reduced inflammation in PTSD
<i>Faecalibacterium</i>	ASD, MDD, BD, SSD, ADHD, PACS	Produces butyrate, supports anti-inflammatory pathways and neuroplasticity	Lower in multiple disorders, protective against inflammation
<i>Faecalibacterium prausnitzii</i>	ASD, MDD, BD, SSD, ADHD, PACS	Produces butyrate, enhances synaptic plasticity and reduces neuroinflammation	Lower in multiple disorders, key anti-inflammatory bacterium
<i>Firmicutes</i>	ASD, ADHD, MDD, BD, addiction	Imbalance affects gut barrier and neurotransmitter production	Mixed results, linked to gut-brain axis

The table continues

Table 2. Roles of gut bacteria in neuroplasticity associated with psychiatric disorders (The table continues)

<i>Fusobacteria</i>	ASD	Linked to gut dysbiosis	Increased in ASD, affects volatile organic compounds
<i>Hafnia alvei</i>	Potentially binge eating disorder, obesity-related depression	May influence synaptic plasticity through appetite regulation	Probiotic reducing food intake via ClpB protein mimicking alpha-MSH, influences gut-brain axis
<i>Klebsiella</i>	ASD	Potential pathogen, may increase inflammation	Mixed results in ASD
<i>Klebsiella pneumoniae</i>	Depression, anxiety, Alzheimer's, epilepsy	May disrupt synaptic plasticity through neuroinflammation and infection	Causes infections affecting brain, exacerbates neurological disorders like Alzheimer's and epilepsy
<i>Lactobacillus</i>	ASD, MDD, BD, SSD, anxiety	Produces GABA and serotonin, supports synaptic plasticity	Mixed in ASD, higher in MDD, BD, SSD, reduces OCD-like behaviors
<i>Lactobacillus</i> spp.	MDD, anxiety, ASD, SSD, Alzheimer's	Supports synaptic plasticity through neurotransmitter production and anti-inflammatory effects	Probiotics modulating gut-brain axis, therapeutic potential in psychiatric and neurological disorders
<i>Lactobacillus casei</i>	MDD, anxiety	Produces GABA, reduces stress and enhances neuroplasticity	Supplementation reduces depressive symptoms; modulates vagus nerve signaling
<i>Lactobacillus helveticus</i>	MDD, anxiety	Produces GABA, reduces stress and enhances neuroplasticity	Supplementation alleviates depressive symptoms; modulates vagus nerve signaling
<i>Lactobacillus rhamnosus</i>	MDD, anxiety, ASD	Produces GABA, enhances synaptic plasticity and reduces stress	Supplementation reduces anxiety and depressive symptoms, improves ASD behaviors in animal models
<i>Lactiplantibacillus plantarum</i>	ASD, MDD, anxiety	Produces serotonin, supports mood regulation and synaptic plasticity	Enhances serotonin production, reducing anxiety and depressive symptoms
<i>Lactococcus lactis</i>	Anxiety, depression	May support synaptic plasticity and brain development	Probiotic modulating gut-brain axis, reduces anxiety-like behavior in preclinical studies
<i>Methanobrevibacter</i>	ASD	Affects gut transit time via hydrogen metabolism	Mixed results in ASD
<i>Oscillibacter</i>	MDD	Linked to systemic inflammation	Increased in MDD
<i>Parabacteroides</i>	ASD	Associated with GI issues	Mixed results in ASD
<i>Parabacteroides distasonis</i>	ASD, MDD	Produces GABA, supports gut-brain axis and synaptic plasticity	Lower in ASD, induces depressive-like behavior in Crohn's disease models
<i>Peptostreptococcaceae</i>	ADHD	Produces GABA, may alter neural signaling	Increased in ADHD, linked to inattention
<i>Phascolarctobacterium</i>	ASD	Reduced SCFAs, linked to GI issues	Mixed results in ASD
<i>Porphyromonas gingivalis</i>	Alzheimer's disease (with psychiatric symptoms)	May contribute to neurodegeneration, negatively affecting neuroplasticity	Associated with Alzheimer's through neuroinflammation
<i>Prevotella</i>	ASD	Breaks down carbohydrates, linked to diet	Lower in ASD, associated with GI symptoms
<i>Proteobacteria</i>	ASD, MDD	Includes pathogens, linked to inflammation	Higher in ASD, associated with dysbiosis
<i>Proteus vulgaris</i>	Potentially Parkinson's, SSD, MDD, addiction	May influence synaptic plasticity through dopamine production	Synthesizes dopamine, part of gut microbiota, potentially influences gut-brain axis
<i>Pseudomonas aeruginosa</i>	Meningitis	Induces memory impairment, increases pro-inflammatory response, alters brain histoarchitecture	Opportunistic pathogen, potential indirect effects through infections
<i>Roseburia</i>	ASD	Produces butyrate, reduces inflammation	Lower in ASD, supports gut health
<i>Ruminococcus</i>	ASD, PACS	Involved in carbohydrate breakdown	Mixed in ASD, higher in PACS
<i>Ruminococcaceae_UCG_004</i>	ADHD	Linked to inattention symptoms	Increased in ADHD
<i>Serratia</i> spp.	Potentially SSD, MDD, addiction	May influence synaptic plasticity through dopamine production	Synthesizes dopamine, part of gut microbiota, potentially influences gut-brain axis
<i>Streptococcus</i>	MDD, BD, SSD	Linked to symptom severity via inflammation	Higher in MDD, BD, SSD
<i>Sutterella</i>	ASD	Associated with GI inflammation	Higher in ASD
<i>Tannerella</i> spp.	No direct association	Unknown	Limited evidence, primarily oral bacteria, potential indirect effects via inflammation
<i>Veillonella</i>	ASD	May contribute to gut dysbiosis	Higher in ASD
<i>Verrucomicrobia</i>	ASD, addiction (CNS stimulants)	Linked to gut dysbiosis	Increased in ASD and addiction
7α-dehydroxylation	Potentially MDD, BD, PACS	Converts primary bile acids to secondary bile acids, influencing gut-brain signaling via bile acid receptors	Secondary bile acids modulate neuroinflammation and mood; altered in PACS

GABA: Gamma-aminobutyric acid, SCFAs: Short-chain fatty acids, ASD: Autism spectrum disorder, MDD: Major depressive disorder, BD: Bipolar disorder, ADHD: Attention deficit-hyperactive disorder, PACS: Anxiety disorder, post-acute COVID symptoms, AD: Alzheimer's disease, PD: Parkinson disease, SSD: Schizophrenia spectrum disorder

Table 3. Functions of microbial metabolites in gut-brain axis

Microbial metabolites	Key components	Functions in gut-brain axis
Short-chain fatty acids (SCFAs)	Acetate, propionate, butyrate, isobutyrate, isovalerate, valerate, formate, caproate	Support energy production, reduce brain inflammation, enhance memory, strengthen BBB.
Neuroactive lipids and bile acids metabolites	Result from bacterial modification of bile acids. Primary (cholic acid, chenodeoxycholic acid), secondary (deoxycholic acid, lithocholic acid, ursodeoxycholic acid, tauroursodeoxycholic acid)	Regulate metabolism, reduce neuroinflammation, protect brain barriers, may improve cognition, though some contribute to cognitive decline.
Tryptophan and indole derivatives	Indole, Indole-3-acetic acid, Indole-3-propionic acid, kynurenic acid, indoxyl sulfate, indole-3-carbinol, indole-3-ethanol, indole-3-pyruvate, indole-3-aldehyde	Modulate brain inflammation, influence mood and behavior, some increase anxiety or oxidative stress.
Polyunsaturated fatty acids (PUFAs) metabolites	Leukotriene B4, Prostaglandin E2, 12-hydroxyheptadecatrienoic acid (from arachidonic acid), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) metabolites	Support brain cell growth, reduce inflammation, aid brain repair, with omega-3 derivatives showing cognitive benefits.
Branched-chain amino acids (BCAAs)	Come from bacterial breakdown of proteins. Leucine, isoleucine, valine	Reduce brain inflammation, support gut barrier health, protect against neurodegenerative diseases.
Nicotinamide (NMN)	Nicotinamide, nicotinic acid, NAD+	Support brain cell energy, reduce inflammation, improve motor function in diseases like ALS.
Trimethylamine N-oxide (TMAO)	TMAO	Linked to increased brain inflammation and cognitive decline, potentially worsening Alzheimer's or Parkinson's.
Phenolic compounds	Created when bacteria process plant polyphenols from foods like berries, tea, and vegetables. Urolithin A, ferulic acid, equol, enterolactone	Provide antioxidant and anti-inflammatory effects, reducing neuroinflammation and protecting brain cells.
Vitamins and cofactors	Vitamin B12, folate, riboflavin, thiamine, biotin	Support energy metabolism and neurotransmitter production, essential for brain health.
Neurotransmitter precursors and neurotransmitters	Tryptophan (serotonin precursor), choline (acetylcholine precursor), tyrosine (dopamine precursor), GABA, dopamine, serotonin	Influence mood, behavior, and cognitive function by supporting neurotransmitter production.
Other metabolites	Lactate, ethanol, polysaccharide A (PSA), endotoxins (LPS)	Lactate boosts brain energy, PSA modulates immunity, LPS may increase brain inflammation.

molecules that cross the BBB and directly influence neural function (see [Figure 3](#)).⁶¹ Butyrate demonstrates particularly robust neuroprotective and plasticity-enhancing effects. It increases brain-derived neurotrophic factor (BDNF) expression, promotes dendritic spine formation, enhances long-term potentiation, and supports adult neurogenesis in the hippocampus. BDNF exerts particular importance for depression, anxiety, and cognitive disorders where reduced neurotrophic signaling contributes to synaptic dysfunction and neural atrophy which have direct relevance for mood regulation, learning, memory, and stress resilience.

Propionate influences microglial phenotype that support synaptic plasticity and neuronal survival.⁵ This immunomodulatory effect helps explain how gut dysbiosis can lead to neuroinflammation and psychiatric symptoms through altered microglial function. The SCFAs promote oligodendrocyte differentiation and myelin synthesis, while inflammatory conditions can impair myelination and lead to white matter abnormalities. Oligodendrocyte development and myelination processes critical for neural circuit function and cognitive performance.

Neuroactive Lipids and Bile Acids

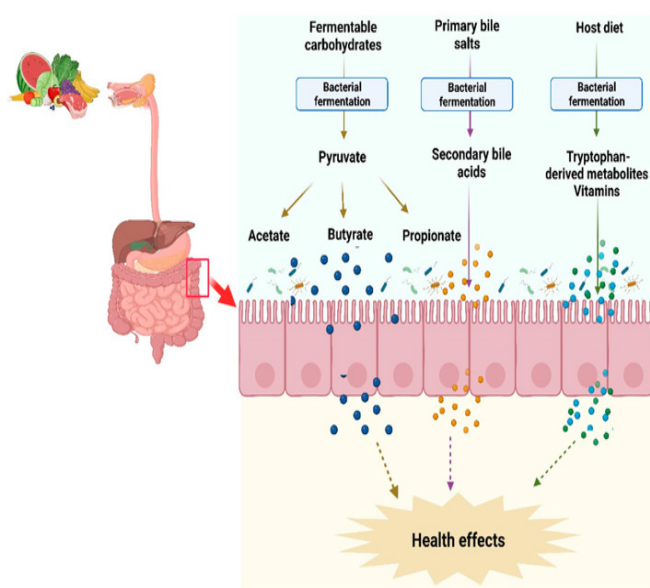
Gut bacteria influence the synthesis and metabolism of neuroactive lipids and bile acids that affect brain function through multiple mechanisms (see [Figure 3](#)).⁶¹ Secondary bile acids produced by bacterial 7 α -dehydroxylation cross the BBB and bind to nuclear receptors that regulate gene expression in neural tissues.^{62,63} Specific bacterial strains capable of bile acid metabolism show associations with depression risk and treatment response.

Tryptophan Metabolite Effects

Microbial tryptophan metabolites, including indole-3-propionic acid and indole-3-aldehyde, influence synaptic function through aryl hydrocarbon receptor activation and anti-inflammatory effects.⁵⁵ These metabolites promote microglial anti-inflammatory phenotypes and support synaptic maintenance and plasticity (see [Figure 3](#)).

Neurotransmitter-Mediated Plasticity

Microbially-produced neurotransmitters influence synaptic plasticity through both direct and indirect mechanisms.

**Figure 3.** Synthesis of microbial metabolites in the intestine

While these neurotransmitters may not directly cross the BBB, they influence vagal signaling and PNS function, indirectly modulating CNS plasticity.⁶⁴ Gut microbes function as a decentralized neurochemical factory, producing and metabolizing key neurotransmitters that shape mood, cognition, and behavior. Gut bacteria, spore-forming members of the *Clostridia* species stimulate enterochromaffin cells to ramp up tryptophan hydroxylase-1 and boost serotonin synthesis,⁶⁵ while *Enterococcus*, *Streptococcus* and *Lactobacillus* species further support serotonin production by providing critical enzymes and substrate availability.⁶⁶ Given that roughly 90% of our serotonin originates in the gut, these microbial processes can meaningfully sway central serotonergic tone and thus impact mood regulation.

Parallel to serotonin, the GABAergic pathway is under microbial control. Genera such as *Lactobacillus*, *Bifidobacterium* and *Bacteroides* synthesize GABA, the brain's chief inhibitory neurotransmitter.⁶⁷ Clinical data show that supplementing GABA-producing probiotics lowers anxiety scores and moderates stress responses, highlighting a direct gut-brain route for calming hyperarousal and rebalancing HPA axis activity.¹²⁰ Certain *Bacillus* and *Serratia* species produce dopamine and its precursor L-DOPA, offer a microbial contribution to reward, motivation, and vulnerability to addiction.¹⁴

Together, these diverse microbial neurotransmitter pathways underscore the microbiome's central role in neuropsychiatric health and highlight targeted microbial therapies as promising adjuncts for mood, anxiety, and cognitive disorders.

NEUROPLASTICITY AND SYNAPTIC FUNCTION INFLUENCED BY GUT BACTERIA

As claimed by Agnihotri & Mohajeri,⁶⁸ the gut microbiome significantly influences the production and signaling of neurotrophic factors that regulate neurogenesis, dendritic morphology, neuroplasticity, neuronal survival, neuronal circuitry and synaptic function. Brain derived neurotrophic factor (BDNF), the most abundant neurotrophic factor in the brain, is modulated by multiple microbial metabolites and inflammatory mediators. *Lactobacillus helveticus* and *Bifidobacterium longum* have been shown in animal studies to enhance BDNF expression in the hippocampus and cortical regions, likely through their anti-inflammatory actions and their role in supporting gut barrier integrity. While SCFAs may contribute indirectly to these neuroprotective effects, the primary mechanisms appear to involve modulation of immune signaling and reduction of pro-inflammatory cytokines.

Glial Cell Modulation

According to Anbalagan,⁶⁹ the gut microbiota exerts a vital influence on glial cells (including microglia, astrocytes, and oligodendrocytes). These glial cells are essential for neuronal integrity, synaptic plasticity, and the maintenance of healthy neural circuits. Gut dysbiosis can impair these glial functions, leading to structural and functional neuronal abnormalities (see Figure 4). For example, altered microglial activity may result in excessive synaptic pruning, changes

in dendritic spine architecture, and disrupted circuit formation. Dysbiosis also appears to affect oligodendrocyte-driven myelination, slowing neuronal signal transmission, and can compromise astrocyte regulation of BBB integrity, particularly under conditions of heightened inflammation. Gut-derived lipopolysaccharides further drives microglia toward pro-inflammatory states, enhancing cytokine production, reducing synaptic support, and accelerating synaptic elimination. This contributes to depressive behaviors, cognitive deficits, and diminished neuroplasticity through pathways involving reduced BDNF and heightened inflammatory signaling.

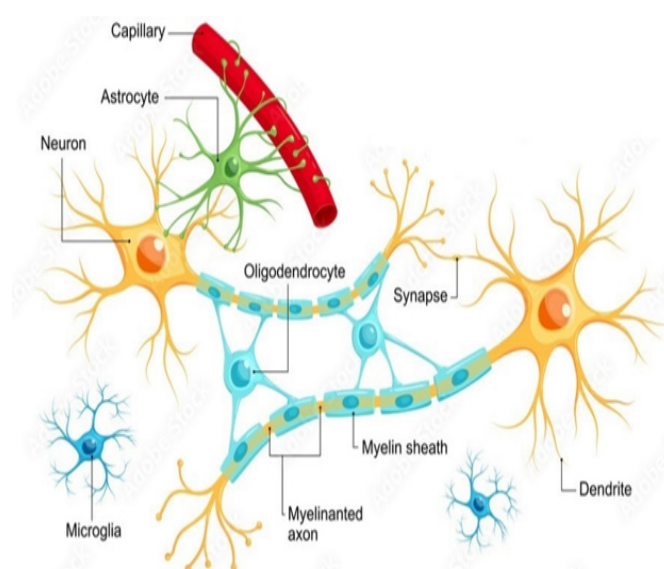


Figure 4. Glial cells and functions

In contrast, beneficial microbial metabolites such as SCFAs and tryptophan-derived compounds encourage microglia to adopt anti-inflammatory, neuroprotective states that help preserve synaptic plasticity and neuronal integrity.⁷⁰ These discoveries emphasize how the gut microbiome helps regulate the brain's immune environment, with significant consequences for mental health and resilience against neuropsychiatric disorders.

GUT MICROBIOME ALTERATIONS IN PSYCHIATRIC DISORDERS

Psychiatric disorders affect over 970 million people globally, with substantial personal, social, and economic costs that continue to rise despite advances in treatment.^{71,72} In the study conducted by Mitrea and her team,⁷³ their findings show that MDD, anxiety disorders, SSD, BD, and ASD are all distinct from each other, yet their overlapping patterns of gut microbiome alterations contribute to their pathophysiology through the gut-brain axis. In MDD, studies consistently report reduced microbial diversity, lower levels of beneficial bacteria such as *Faecalibacterium*, *Coprococcus*, and *Dialister*, and an increase in pathogenic species like *Eggerthella*. These changes result in decreased production of SCFAs (e.g., butyrate), compromising BBB integrity and lowering BDNF levels.⁷⁴ The changes also result in an increase in lipopolysaccharide-producing bacteria fuel neuroinflammation and disrupt serotonin synthesis via activation of the kynurenine pathway. Anxiety disorders are linked to reductions in GABA-producing bacteria like

Lactobacillus and *Bifidobacterium*, alongside increases in pro-inflammatory species such as *Escherichia*. These imbalances contribute to heightened stress responses, altered neurotransmitter regulation and HPA axis dysregulation. Probiotic interventions targeting these microbial deficits have shown promise in reducing anxiety symptoms and enhancing stress resilience.⁶⁸

In schizophrenia and psychotic disorders, patients typically exhibit reduced microbial diversity, disrupted tryptophan metabolism, and increased intestinal permeability. These gut changes contribute to dopaminergic dysfunction, immune activation, and metabolic disturbances that correlate with the severity of psychiatric symptoms. Antipsychotic medications further disrupt gut microbiota composition, sometimes exacerbating metabolic side effects such as weight gain.⁷³

BD displays dynamic microbiome patterns that shift between manic and depressive states, with unique alterations in bacterial species involved in circadian rhythm regulation and inflammation.⁷⁴ Meanwhile, ASD is characterized by some of the most pronounced gut-brain axis disruptions, with marked reductions in beneficial bacteria, increased pathogenic species, and a high prevalence of gastrointestinal symptoms. Across these conditions, gut microbiome dysregulation emerges as a key factor in neuroinflammation, neurotransmitter imbalance, and metabolic dysfunction, pointing to the potential of microbiome-targeted therapies as promising adjunctive strategies.⁷⁵

HPA Axis Dysregulation in Psychiatric Disorders

Chronic hyperactivation of the HPA axis, commonly seen in psychiatric disorders, leads to sustained cortisol elevation, hippocampal atrophy, reduced BDNF levels, and impaired stress adaptation.⁷⁶ Evidence suggests that inflammatory signals from gut dysbiosis, particularly elevated lipopolysaccharide and pro-inflammatory cytokines, are key contributors to this cascade, sustaining HPA dysfunction and neurodegeneration (see [Figure 5](#)).⁷⁷ When this microbial imbalance increases intestinal permeability ("leaky gut"), bacterial lipopolysaccharides can leak into the bloodstream, triggering a persistent inflammatory response. Pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) are then able to cross the BBB, impairing neuroplasticity and neuronal health and thereby contributing to depressive symptoms.^{78,79} They also disrupt neural networks involved in emotion regulation, memory, and cognition. For instance, elevated peripheral cytokines in depression and stress-related disorders have been linked to dysfunction in corticolimbic circuits, including the prefrontal cortex and hippocampus, leading to emotional and cognitive deficits.

Anxiety disorders similarly show excessive HPA activity, where microbiome-induced inflammation and loss of beneficial bacteria amplify stress responses and cortisol secretion.⁸⁰ In MDD, SSD, and BD, leaky gut facilitates microbial translocation, resulting in systemic inflammation that further perpetuates HPA-axis hyperactivity and heightens vulnerability to stress and symptom severity. In ASD, early-life HPA hyperreactivity is frequently seen, with gut-derived inflammatory triggers contributing to heightened stress sensitivity and poor glucocorticoid feedback control. In

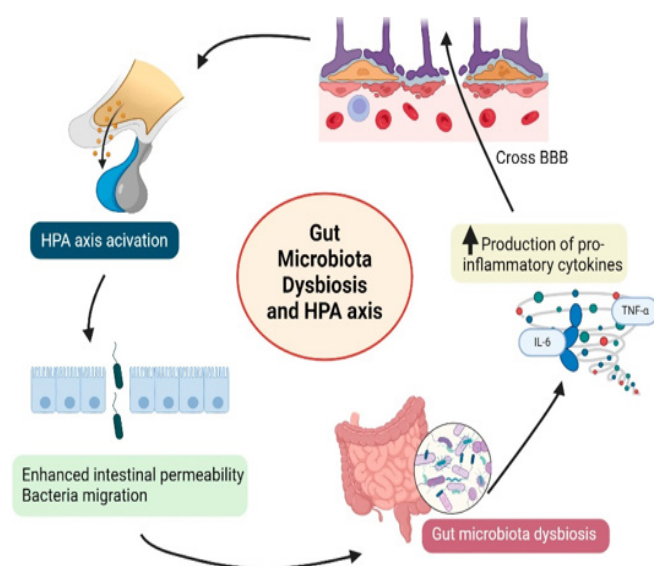


Figure 5. HPA dysregulation and gut dysbiosis
HPA: Hypothalamic pituitary adrenal

all these conditions, gut dysbiosis amplifies HPA dysfunction through immune activation, loss of SCFA-mediated regulation, and disrupted neuroendocrine feedback loops.⁸¹

By integrating these insights, we gain a more comprehensive understanding of MDD's underlying biology and open the door to multifaceted treatment strategies. Techniques to recalibrate HPA axis function such as stress-management practices and cognitive behavioral therapy (CBT), promises a more holistic approach to both preventing and managing depression.⁸² Ultimately, a collaborative, body-mind treatment paradigm may offer the greatest promise for alleviating this challenging condition.

Circadian Rhythm Disruption Association with Gut Microbiome in Psychiatric Disorders

Circadian rhythm (see [Figure 6](#))⁸³ disruption and misalignment manifests as disturbed sleep-wake cycles, altered melatonin production, and flattened cortisol rhythms across MDD, BD, SSD and anxiety disorder, is a pervasive feature deeply intertwined with mood, cognition, and behavior. Insomnia is a common and clinically important feature across several psychiatric disorders, often both a symptom and a contributing factor to illness severity.⁸⁴ Circadian disruption decouples the synchronized daily rhythms of the gut microbiome, promoting dysbiosis and barrier dysfunction. These changes trigger inflammation and metabolic imbalance and potentially worsen neuropsychiatric symptoms. Dysbiotic gut microbiota, which normally show diurnal oscillations and influence peripheral clock gene expression, lose this synchrony in these conditions, further desynchronizing the central and peripheral clocks.⁸⁵

Substance Addiction in Psychiatric Disorders

The co-occurrence of psychiatric disorders and substance use disorders (SUDs) remains a major challenge in mental health care, with around half of individuals diagnosed with one also experiencing the other. This overlap is especially pronounced in serious mental illnesses such as SSD, BD, ADHD and MDD.⁸⁶ Individuals may turn to substances to alleviate symptoms of a psychiatric disorder, while substance use can

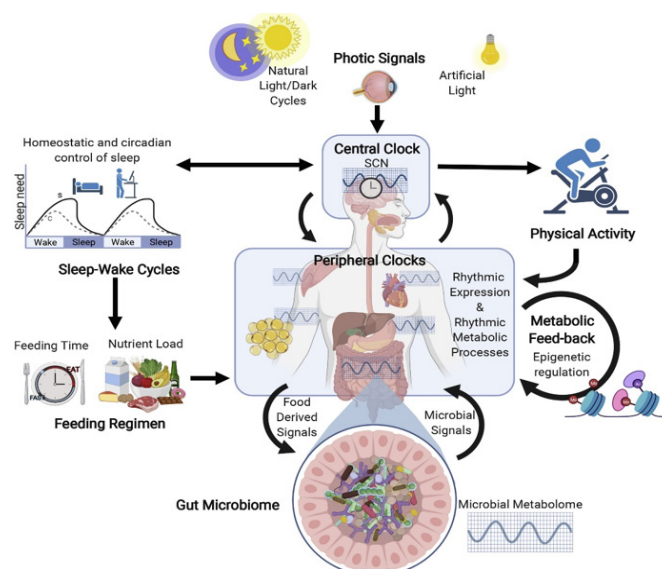


Figure 6. Circadian rhythm and gut microbiome synchrony

itself trigger or exacerbate mental health conditions. These combined comorbid conditions lead to more complicated diagnoses, lower rates of recovery, higher relapse risk, and greater strain on treatment systems.⁸⁷

According to Martinez and his team,⁸⁸ smoking, heavy alcohol use, and other substance abuse frequently induce gut dysbiosis through direct chemical effects on microbiota, epithelial damage, and immune activation. These changes can be persistent, although lifestyle modifications like smoking cessation or non-pharmacological therapies (e.g., behavioural therapy and probiotics) have shown promise in partially reversing dysbiosis and related health impacts.

NON-PHARMACOLOGICAL THERAPEUTIC INTERVENTIONS

Psychiatric medications (or pharmacotherapy), while essential in many treatment plans, can inadvertently disrupt gut health. For instance, second-generation antipsychotics (SGAs; e.g., risperidone and aripiprazole) are associated with reduced microbial diversity and shifts in key bacterial phyla, typically decreasing *Firmicutes* and *Actinobacteria*, while increasing *Proteobacteria*.^{89,90} These microbial changes lead to diminished short-chain fatty acid (SCFA) production, compromising gut barrier function and contributing to metabolic side effects like weight gain, hyperlipidemia, and insulin resistance. Similarly, SSRIs like fluoxetine and citalopram have been shown to deplete beneficial genera such as *Lactobacillus*, *Bifidobacterium*, and *Ruminococcus*, while promoting proliferation of *Enterobacteriaceae*.⁹¹ Given these challenges, non-pharmacological interventions targeting gut-brain mechanisms have gained prominence.

Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) involves the transfer of fecal material from a screened healthy donor to a recipient with dysbiosis. The transfer can be accomplished through several routes, including colonoscopy (allowing direct delivery to the colon), upper gastrointestinal endoscopy (delivering to the duodenum or jejunum), nasogastric or

nasoduodenal tubes, oral capsules containing lyophilized or frozen fecal material, or enema administration. Recent advances have made oral encapsulated FMT increasingly popular due to its non-invasive nature and comparable efficacy to colonoscopic delivery for certain indications, with frozen or freeze-dried preparations showing similar success rates. The choice of delivery method depends on factors including the target intestinal location, patient tolerance, clinical indication, and institutional protocols, with upper GI delivery potentially offering advantages for small intestinal colonization while lower GI routes may better establish colonic microbiota.

Originally developed for refractory *Clostridioides difficile* infections, FMT is now being explored for its neuropsychiatric implications, especially in disorders involving gut-brain axis disruptions.⁹² Preliminary evidence suggests FMT may improve gastrointestinal and behavioral symptoms, although the precise microbial profiles required for optimal psychiatric benefit remain unclear. Longitudinal, placebo-controlled trials are needed to refine donor selection criteria, administration protocols, and define target microbiome signatures linked to mental health outcomes.⁵²

Dietary and Psychobiotic Interventions

Dietary modification is one of the most accessible and modifiable interventions for gut-brain health. High-fibre diets help to enhance SCFA production, strengthen gut barrier integrity, and reduce systemic inflammation.^{93,94} The Mediterranean diet, which is rich in vegetables, whole grains, polyphenols, and omega-3 fatty acids, has demonstrated efficacy in reducing depressive and anxiety symptoms.⁹⁵ For individuals with gastrointestinal sensitivities, elimination diets or low-FODMAP protocols can help identify triggers that exacerbate both GI and psychiatric symptoms.

The emerging field of psychobiotics focuses on specific probiotic strains with mental health benefits. For example, *Lactobacillus helveticus* and *Bifidobacterium longum* have shown anxiolytic and antidepressant effects in clinical studies.⁶⁸ Personalized psychobiotic therapy, guided by microbiome profiles and host genetic markers, provides a promising future intervention approach.⁹⁶

Prebiotics (e.g., inulin or galacto-oligosaccharides) nourish beneficial bacteria and suppress pathogenic strains. Supplementation with prebiotics has shown particular benefit in stress-related disorders and mild-to-moderate anxiety.⁹⁷ Synbiotic interventions, which combine probiotics and prebiotics, provide a dual mechanism, delivering beneficial microbes while enhancing their survival and colonization. Together, these microbiome-targeted strategies may offer additive or synergistic benefits in complex psychiatric presentations.^{98,99}

Educational Therapy (EdTx)

EdTx, long endorsed by the WHO,¹⁰⁰ plays a foundational role in empowering patients to understand the biological and lifestyle factors influencing their mental health. In this context, EdTx includes structured psychoeducation around the gut-brain axis, helping individuals comprehend how

dietary choices, stress, inflammation, and microbial balance interact to influence mood, cognition, and systemic health.¹⁰¹

Core components of EdTx also address chronobiology and stress physiology. Techniques such as mindfulness-based stress reduction (MBSR), which incorporates breathwork, body scanning, and mindful movement, have been shown to reduce salivary cortisol levels and improve emotional regulation.¹⁰² Similarly, cognitive appraisal training helps individuals reframe maladaptive stress responses, lowering cortisol reactivity during acute stress exposures.¹⁰³

Chrono-education, another pillar of EdTx, teaches patients about the biological importance of maintaining regular sleep-wake cycles, consistent meal timing, and exposure to natural light.¹⁰⁴ These strategies promote dim-light melatonin onset, stabilize hormonal rhythms, and support sleep hygiene.¹⁰⁵ When paired with diet literacy, such as understanding the benefits of high-fibre and fermented foods, EdTx equips patients with the tools to make informed, sustainable changes.

Mental Wellness & Behavior Therapy (MWBT)

Behavioral therapy (BeTx) and mental wellness techniques (MWTech) complement EdTx by translating knowledge into action. Interventions, e.g., CBT,¹⁰⁶ behavioral activation (a form of short-term out-patient therapy),¹⁰⁷ and acceptance and commitment therapy (ACT),¹⁰⁸ target maladaptive behaviors like emotional eating, irregular meal patterns, and sleep dysregulation. Notably, a study in patients with irritable bowel syndrome (IBS) showed that CBT not only improved GI and mood symptoms but also led to shifts in gut microbiota and brain connectivity, highlighting the bi-directional influence of psychological therapy on gut-brain physiology.⁸²

Further, mindfulness-based techniques, yoga, and group-based interventions foster vagal tone and reduce stress-induced microbial disruptions.^{109,110} For example, CBT for insomnia (CBT-I) has been shown in meta-analyses to improve sleep latency and efficiency, while normalizing nocturnal cortisol rhythms.¹¹¹ MBSR protocols have also demonstrated reductions in inflammatory markers such as IL-6 in both clinical and non-clinical populations.

Lifestyle Coaching and Circadian Health

Lifestyle coaching supports the sustained adoption of behavior changes by integrating personalized strategies that align with circadian and microbiome rhythms. Time-restricted feeding (limiting daily food intake to an 8-10 hour window) can restore microbial diurnal oscillations, enhance metabolic health, and regulate clock gene expression.¹¹² Similarly, morning bright-light therapy helps entrain circadian rhythms by activating the suprachiasmatic nucleus, improving sleep-wake cycles, and reducing depressive symptoms.¹¹³

Physical activity, especially in the morning, not only promotes sleep consolidation but also enhances microbiome diversity and circadian stability. Coaching patients on practical steps such as fixed bedtimes, reducing caffeine/alcohol intake before sleep, limiting daytime naps, and optimizing sleep

environments (cool, dark, and quiet) can support long-term autonomic balance and gut-brain harmony.

Integrative Framework and Outcomes

Taken together, these non-pharmacological interventions form a robust, integrative model comprising four interdependent domains: (i) EdTx, which builds the foundational understanding and motivation around gut-brain health; (ii) behavior therapy (BeTx), which installs actionable, sustainable lifestyle changes; (iii) mental Wellness techniques (MWTech), which supports emotional regulation, stress resilience, and autonomic balance; and (iv) microbiome science (MbSc), which anchors all interventions in evidence-based biological mechanisms. The authors of this paper have termed it biopsychosocial-educational (BPSE) model (see Figure 7).

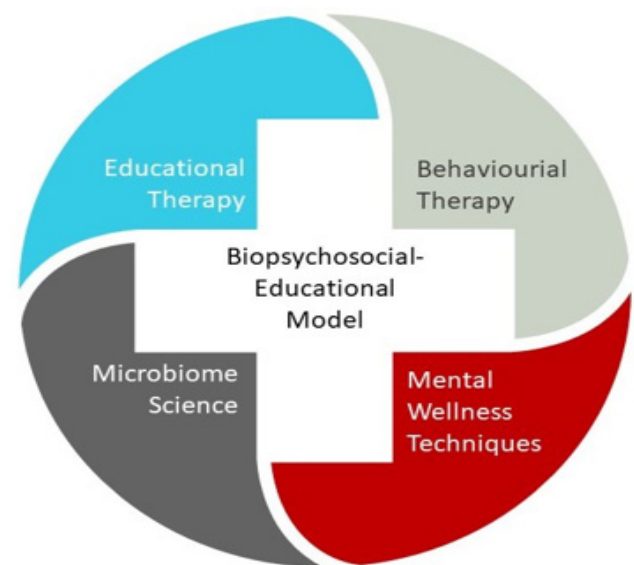


Figure 7. The biopsychosocial-educational (BPSE) model

This BPSE framework is particularly suited for populations with IBS and anxiety, mood disorders with metabolic features, or neurodevelopmental conditions, e.g., in the context of ASD, where the gut-brain axis plays a pronounced role.¹¹⁴ The outcomes from such integrated care models can be measured across multiple domains, e.g., (i) psychiatric symptoms: can improve scores on PHQ-9¹¹⁵ and/or GAD-7,¹¹⁶ for example; (ii) GI symptoms: can be tracked via IBS-SSS and stool form scales;¹¹⁷ (iii) Behavioral and cognitive functioning: can enhance executive function and consistency in self-care;¹¹⁸ and (iv) microbiome health: can increase in beneficial taxa (e.g., *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium prausnitzii*), and corresponding reductions in inflammation. By bridging cognitive, emotional, behavioral, and biological domains, this BPSE model empowers patients to actively participate in their own healing process and fosters sustainable, whole-person wellness.¹¹⁹

CONCLUSION

The gut microbiome represents a paradigm shift in understanding psychiatric disorders, revealing complex bidirectional relationships between microbial communities and brain functions. The evidence consistently demonstrates that gut dysbiosis is associated with various mental health

conditions, with mechanistic pathways involving neural signalling, metabolite production, immune modulation associated with stress response system, circadian rhythm, nutritional options, lifestyle habits and substance addiction.

The association between intestinal bacterial diversity and psychiatric or neurological diseases represents a complex bidirectional relationship rather than a unidirectional causal pathway. Emerging evidence demonstrates that gut dysbiosis may function as a contributory etiological factor through several mechanisms: microbial synthesis of neurotransmitters and neuroactive metabolites that modulate CNS function, bacterial metabolite-mediated regulation of systemic inflammation and BBB integrity, and vagal nerve transmission of gut-derived signals that influence mood, cognition, and behavior.

Conversely, psychiatric and neurological conditions reciprocally alter gut microbiome composition through multiple pathways. Chronic psychological stress induces HPA axis hyperactivation and sustained cortisol elevation, directly disrupting microbial ecosystems. Mental illness-associated behavioral changes, including altered dietary patterns, reduced physical activity, and sleep disruption that substantially reshape the microbiome. Additionally, psychotropic medications exert antimicrobial effects that modify bacterial communities, while autonomic dysfunction in neurological disorders affects gastrointestinal motility and secretion, creating selective pressures on microbial populations. This creates a self-reinforcing cycle wherein initial dysbiosis increases neuropsychiatric vulnerability, while the disease state subsequently exacerbates microbial imbalance through behavioral, neuroendocrine, and pharmacological mechanisms.

The therapeutic implications of gut-brain axis research extend far beyond traditional pharmacological approaches to include personalized interventions targeting microbiome optimization. The integration of microbiome science with non-pharmacological intervention such as EdTx, CBT, MBSR, FMT, dietary options and psychobiotic intervention may offers unprecedented new opportunities for precision medicine approaches that consider individual biological profiles when selecting treatments.

These clinical implementations must also address regulatory considerations, healthcare provider education, and economic factors that will influence widespread adoption of microbiome-based therapeutics. This implementation will likely include routine assessment of gut microbiome status alongside traditional clinical evaluations, with treatment plans incorporating both conventional therapies and microbiome-targeted interventions. This integrated approach holds promise for improving treatment outcomes while reducing side effects and healthcare costs. The gut-brain axis represents one of the most exciting frontiers in mental health research, offering hope for more effective, personalized treatments that address the underlying biological mechanisms of psychiatric disorders and addiction. Continued investment in this research area will be essential for translating scientific discoveries into clinical benefits for patients worldwide.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

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Author Contributions

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Diagnosis and management of carotid artery stenosis: pathophysiology, advanced imaging, and evolving revascularization strategies

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ABSTRACT

Carotid artery stenosis is a major and potentially preventable cause of ischemic stroke worldwide. Although the degree of luminal narrowing has traditionally guided risk stratification and treatment decisions, accumulating evidence indicates that plaque composition, biomechanical forces, and hemodynamic factors play a critical role in determining cerebrovascular risk. Atherosclerotic lesions preferentially develop at the carotid bifurcation due to disturbed flow patterns and low wall shear stress, promoting endothelial dysfunction and plaque instability. Recent advances in imaging have shifted diagnostic paradigms beyond luminal assessment toward detailed plaque characterization. Magnetic resonance imaging, particularly with T1-weighted sequences, enables reliable detection of intraplaque hemorrhage and fibrous cap status, both of which are strongly associated with embolic events independent of stenosis severity. These insights have important implications for individualized patient management. Medical therapy remains the cornerstone of treatment for all patients with carotid artery disease. Antiplatelet agents and high-intensity statin therapy play a central role in stroke prevention by reducing thromboembolic risk and promoting plaque stabilization. For patients requiring revascularization, carotid endarterectomy continues to represent the gold standard in appropriately selected symptomatic individuals. Carotid artery stenting has emerged as an alternative for high-risk surgical candidates, although embolic complications associated with transfemoral access remain a concern. Transcarotid artery revascularization, utilizing flow reversal for cerebral protection, has expanded the therapeutic armamentarium and offers a promising hybrid approach with favorable safety profiles. This review provides a comprehensive overview of the epidemiology, pathophysiology, diagnostic advances, and evolving treatment strategies for carotid artery stenosis. Emphasis is placed on multidisciplinary decision-making, patient-specific risk assessment, and the integration of advanced imaging to optimize outcomes in both symptomatic and asymptomatic disease.

Keywords: Carotid artery stenosis, ischemic stroke, plaque vulnerability, carotid endarterectomy, carotid artery stenting, transcarotid artery revascularization

INTRODUCTION AND EPIDEMIOLOGY

Extracranial carotid artery disease accounts for approximately 15–20% of ischemic strokes worldwide. Its prevalence increases markedly with age, exceeding 10% in individuals older than 80 years. Symptomatic carotid artery stenosis represents a particularly high-risk subgroup, as it is associated with a substantially increased likelihood of recurrent ischemic stroke.^{1,2}

The development and progression of carotid artery disease are strongly influenced by modifiable risk factors, including cigarette smoking, hypertension, diabetes mellitus, hyperlipidemia, and a sedentary lifestyle.^{1,3} Consequently, contemporary management strategies extend beyond

the treatment of existing stenosis and emphasize both primary and secondary prevention aimed at halting disease progression and reducing future cerebrovascular events (Figure 1).

ETIOPATHOGENESIS AND BIOMECHANICAL BACKGROUND

Atherosclerosis constitutes the fundamental pathological substrate of carotid artery stenosis. However, the preferential localization of atherosclerotic plaques at the carotid bifurcation cannot be explained solely by systemic risk factors and is best understood through biomechanical principles.²⁻⁴

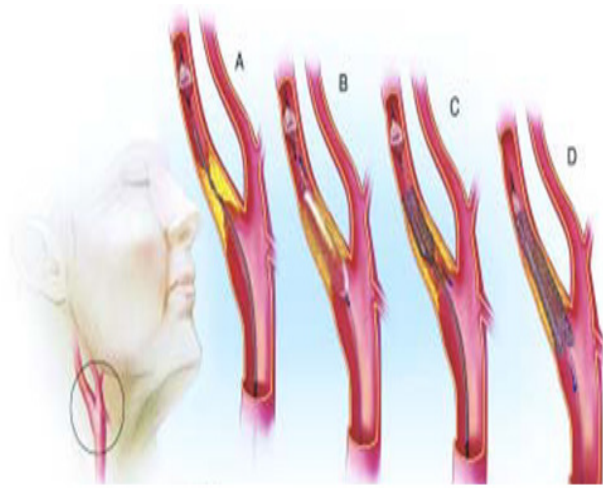


Figure 1. Anatomical localization of extracranial carotid artery stenosis

Hemodynamic Factors and Endothelial Dysfunction

At the carotid bifurcation, abrupt changes in vessel geometry lead to flow separation and disturbed blood flow patterns. These regions are characterized by low and oscillatory wall shear stress. Reduced shear stress suppresses endothelial nitric oxide (NO) production, promotes pro-inflammatory gene expression, and facilitates monocyte adhesion. As a result, the transendothelial migration of low-density lipoprotein (LDL) particles is enhanced, creating a microenvironment conducive to atherogenesis.³⁻⁵ These biomechanical mechanisms influence not only plaque initiation but also the subsequent evolution of plaque phenotype, determining whether lesions remain stable or progress toward an unstable, rupture-prone configuration (Figure 2).

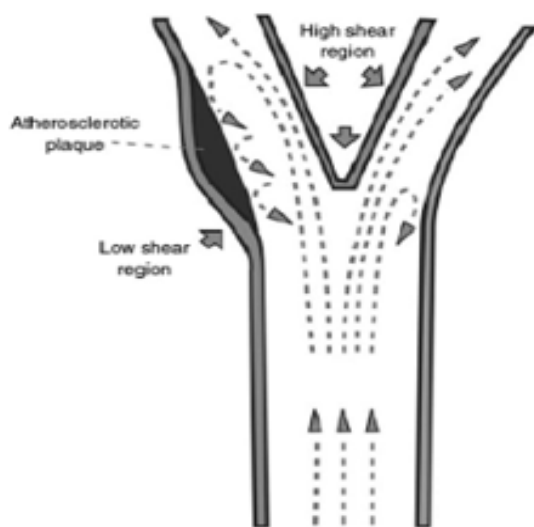


Figure 2. Physiopathogenesis of carotid artery stenosis

DIAGNOSTIC APPROACHES: BEYOND LUMINAL NARROWING

Traditionally, the diagnosis and risk stratification of carotid artery stenosis have relied primarily on the percentage of luminal narrowing. Current evidence, however, indicates that stroke risk is determined not only by the degree of stenosis but also by the structural and biological characteristics of the atherosclerotic plaque.⁴⁻⁸

Ultrasonography and Computed Tomography Angiography

Color Doppler ultrasonography remains the first-line modality for screening and follow-up. Peak systolic velocities and spectral waveform analysis allow for noninvasive estimation of stenosis severity.⁶⁻⁸ Computed tomography angiography (CTA) provides high-resolution visualization of vascular anatomy and calcific burden, offering valuable information for surgical or endovascular planning (Figure 3, 4).



Figure 3. Three-dimensional computed tomography angiographic findings

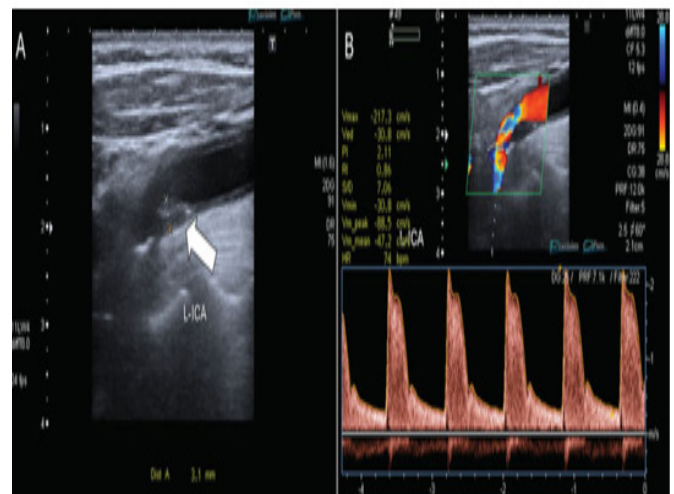


Figure 4. Corresponding Doppler ultrasonography evaluation

Magnetic Resonance Imaging and Plaque Characterization

Magnetic resonance imaging (MRI) has emerged as a powerful tool for assessing plaque biology. In particular, intraplaque hemorrhage (IPH), detected using T1-weighted MP-RAGE sequences, is recognized as one of the strongest predictors of plaque rupture and embolic events. The presence of IPH significantly increases stroke risk, independent of the degree of luminal stenosis.^{7,8}

Contrast-enhanced MRI further enables assessment of fibrous cap thickness and lipid-rich necrotic core volume. These parameters have become increasingly influential in guiding treatment decisions in both symptomatic and asymptomatic patients.^{7,8}

PHARMACOLOGICAL MANAGEMENT AND PLAQUE STABILIZATION

Medical therapy constitutes the cornerstone of carotid artery disease management and should be implemented in all patients, regardless of whether surgical or endovascular intervention is performed.⁹⁻¹¹

Antithrombotic Therapy

Antiplatelet therapy represents the standard antithrombotic strategy in carotid artery stenosis. Aspirin or clopidogrel is selected based on clinical context and patient characteristics. Anticoagulation is reserved for specific indications, such as concomitant atrial fibrillation or the presence of a free-floating thrombus.^{9,11}

The Role of Statin Therapy

Beyond lipid lowering, statins exert pleiotropic effects that are critical in carotid disease. By attenuating vascular inflammation, reducing lipid core size, and increasing fibrous cap thickness, statins promote plaque stabilization. High-intensity statin therapy is therefore a fundamental component of stroke prevention strategies.⁹⁻¹²

SURGICAL AND ENDOVASCULAR TREATMENT OPTIONS

Carotid Endarterectomy (CEA)

Carotid endarterectomy remains the most evidence-based intervention for reducing stroke risk in patients with symptomatic high-grade carotid stenosis. Following the publication of large randomized trials comparing endarterectomy with best medical therapy alone, CEA became the preferred treatment for recently symptomatic patients with severe carotid stenosis. Landmark studies such as NASCET and ACST clearly demonstrated the superiority of CEA over medical therapy when appropriate patient selection is applied. CEA may be performed using conventional longitudinal arteriotomy with patch angioplasty or via the eversion technique. The choice of technique is largely determined by surgeon experience and individual vascular anatomy.^{6,10-15}

Carotid Artery Stenting (CAS)

Carotid artery stenting was developed as an alternative to CEA, particularly for patients at high surgical risk. The potential benefit of endovascular treatment, with or without stenting, as an alternative to endarterectomy was first highlighted by the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).¹⁰ However, embolic complications associated with the transfemoral approach remain a major limitation.

In the interim analysis of the International Carotid Stenting Study, which compared carotid artery stenting with endarterectomy in symptomatic patients with severe carotid stenosis suitable for surgery, CEA remained the preferred treatment option (International Carotid Stenting Study investigators, 2010).^{10,12-17}

Transcarotid Artery Revascularization (TCAR)

Transcarotid artery revascularization represents a significant advancement in endovascular therapy.^{11,12} By utilizing direct carotid access and temporary flow reversal during the procedure, TCAR effectively prevents embolic debris from reaching the cerebral circulation. This feature positions TCAR as a hybrid and potentially safer alternative between conventional surgery and transfemoral stenting. Owing to its low rates of perioperative stroke and other complications, TCAR appears to be a promising treatment option for carotid artery stenosis.¹¹

SPECIAL CLINICAL SITUATIONS: TOTAL OCCLUSION AND EC-IC BYPASS

In cases of total carotid artery occlusion, revascularization is generally not recommended.^{13,15,17,18} Nevertheless, in carefully selected patients who remain symptomatic despite maximal medical therapy and demonstrate severe hemodynamic compromise on perfusion MRI, extracranial-intracranial (EC-IC) bypass surgery, such as superficial temporal artery to middle cerebral artery (STA-MCA) bypass, may be considered as a salvage option. The Carotid Occlusion Surgery Study (COSS) has provided important insights in this context.¹⁵ However, other studies have reported no reduction in the risk of recurrent ipsilateral ischemic stroke within two years⁶ (Figure 5).

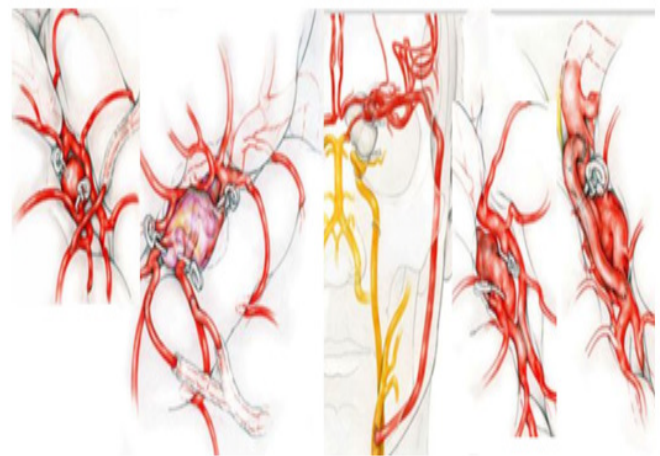


Figure 5. Extracranial-intracranial BYPASS technique

RESTENOSIS AND LONG-TERM FOLLOW-UP

Restenosis following CEA or carotid stenting is closely associated with diabetes mellitus and cigarette smoking. Diabetes accelerates neointimal hyperplasia, whereas smoking exacerbates endothelial dysfunction, significantly increasing restenosis risk. Additional factors such as dyslipidemia, female sex, renal insufficiency, hypertension, and smoking have also been shown to increase restenosis rates, while patch angioplasty during endarterectomy appears to confer a protective effect. Patients with these risk factors require closer imaging surveillance and aggressive risk factor modification.^{17,19,20}

CONCLUSION

The management of carotid artery stenosis has evolved beyond the scope of a single specialty. The optimal contemporary approach relies on a multidisciplinary team involving neurology, radiology, cardiovascular surgery, and endovascular specialists. Future research should focus on developing higher-quality evidence to refine patient selection, particularly in asymptomatic carotid stenosis, enabling individualized conservative, surgical, or endovascular treatment strategies. Advanced imaging modalities, including MRI, PET-CT, and duplex ultrasonography, will likely play an increasingly important role in the reliable identification of plaque morphologies predictive of cerebral ischemia. Despite ongoing technological advances, early diagnosis and rigorous control of vascular risk factors remain the cornerstone of successful long-term outcomes.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

All authors contributed equally to the planning, writing, and critical revision of the manuscript. All authors approved the final version for submission.

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A case of Wernicke's encephalopathy in a patient receiving teprotumumab infusions for thyroid eye disease

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ABSTRACT

A 64-year-old male with clinically active thyroid eye disease was started on teprotumumab infusion for ongoing visual symptoms in the setting of managed systemic disease. After six weeks of treatment, and 3 infusions of teprotumumab, the patient developed unexplained symptoms of anxiety, confusion, and abnormal behavior over the course of several days, for which he was hospitalized. An extensive workup was unrevealing of a cause for the onset of these symptoms, and the patient did not improve until treated with supplemental thiamine, supporting a clinical diagnosis of Wernicke's encephalopathy. The authors will describe the circumstances of this episode and briefly summarize the available literature on encephalopathies as a serious complication in patients receiving a relatively novel treatment for thyroid eye disease.

Keywords: Graves ophthalmopathy, Wernicke's encephalopathy, monoclonal antibodies

INTRODUCTION

Teprotumumab is a monoclonal antibody against insulin-like growth factor receptor (IGFR-1) that was approved for treating thyroid eye disease (TED) in January 2020. It works by blocking the activation of orbital fibroblasts, integral to TED's pathogenesis.¹ In clinical trials, patients treated with teprotumumab had a significant and sustained reduction in proptosis and subjective diplopia, as well as increased quality of life, and vision.¹ Common side effects, such as blood glucose abnormalities, auditory issues, musculoskeletal issues, hair loss, fatigue, and reproductive issues, are well documented.²⁻⁴ Nonetheless, teprotumumab's status as a relatively newly approved treatment suggests the potential for uncovering rare adverse effects. We describe a teprotumumab-treated patient who developed Wernicke's encephalopathy (WE), a neurological condition commonly characterized by nystagmus, ataxia, and confusion, and often due to a thiamine deficiency secondary to alcohol use disorder (AUD). Outside of AUD, other causes include malignancy, GI surgery and diseases, excessive vomiting, malnutrition, renal disease, transplantation, infection, intoxication, and uncontrolled thyroid diseases. Its variable presentations make WE often clinically underreported, but data from autopsies suggest the prevalence is between 0.4 and 2.8% in western countries.⁵ Collection and evaluation of protected health information was compliant with the Health Insurance Portability and Accountability Act, and this manuscript adheres to the tenets

of the Declaration of Helsinki, an informed consent form was obtained from the patient for gathering of data for research purposes.

CASE

A 64-year-old male recently diagnosed with hyperthyroidism presented with a year-long history of fluctuating diplopia and left eye exophthalmos. He denied vision loss, eye pain, tearing, or headaches. His ophthalmic history included left eye tear duct surgery six years prior. Visual acuity was 20/20 bilaterally, and examination revealed left eye esotropia and hypotropia, bilateral proptosis, eyelid edema and erythema, corneal superficial punctate keratitis, conjunctival injection, and chemosis. Measurements on Hertel exophthalmometry were 14 millimeters in the right eye, 20 on the left, and a base of 110. MRI of the orbits showed diffuse thickening and enhancement of the extraocular muscles consistent with TED. When compared to imaging from a year prior, there was an increase in left eye proptosis, crowding of the orbital apex, and size of the superior rectus; the right eye only showed mild enlargement of the inferior rectus. He had been treated with methimazole for the prior 8 months and had no history of thyroidectomy, or radioactive iodine. Direct T3 and T4 had normalized to 3.4 and 1.1 respectively, while thyroid-stimulating hormone levels remained low. The diplopia had



subjectively improved gradually since the onset of symptoms but still interfered with the patient's work. After discussing the risk and benefits of various treatment options, including symptomatic management, corticosteroids, orbital radiation, and surgical decompression, he chose to start teprotumumab for his significant diplopia and proptosis.

One week after his third infusion, the patient developed anxiety for several days, accompanied by behavioral changes like reduced speech frequency and incorrect naming of objects. His status fluctuated as he was taken to the emergency department, but he left before being worked up, reportedly feeling better. The following morning, his partner found him hard to rouse. He was admitted to the hospital for confusion. The patient's history was negative for any recent illness, fever, cough, shortness of breath, chest pain, palpitations, weakness, changes in vision, or GI/GU symptoms, as well as alcohol, tobacco, and recreational drug use. He had a history of major depressive disorder and no history of psychotic symptoms. The patient was well-appearing and in no acute distress. His cardiovascular, pulmonary, and abdominal exams were normal. His neurological exam was notable for a bilateral upper extremity intention tremor, which had begun 2 days prior. No cranial nerve deficits or weakness were noted, though the exam was limited by patient effort. There was an attempt to screen for mild cognitive impairment using the Montreal Cognitive Assessment (MoCA), however, a score could not be obtained because of a lack of patient cooperation.

Complete blood count and metabolic panels were unrevealing. The possibility of a thyroid storm was considered, but despite TSI and TrAb being elevated, TSH, free T3 and T4, and TPO antibodies were within normal limits. Toxicology reports were negative for barbiturates, opiates, benzodiazepines, amphetamines, cocaine, phencyclidine, THC, and alcohol. His urinalysis was only notable for over 80 mg/dl of ketones. Testing for HIV, syphilis, ANA, anti-dsDNA, C3/C4 hypocomplementemia, ANCA, hepatitis B and C, and COVID-19 were all negative. An ECG, head CT, and a brain MRI without contrast failed to reveal any abnormalities and ruled out a stroke.

It has been theorized that increased metabolic states associated with hyperthyroidism can lead to overutilization and depletion of thiamine reserves, predisposing patients to WE.⁶ The patient's outpatient endocrinologist urged his care team to treat presumptive WE given the patient's thyroid history. The patient was treated for 3 days with 500 mg of IV thiamine every 8 hours, during which his mental status improved. The patient was discharged home with intramuscular thiamine, followed by oral thiamine and B complex vitamins. Vitamin B1 levels drawn before initiation of this therapy were 102.2 nmol/L, in the lower half of the reference range.

The patient had an otherwise excellent response to teprotumumab. Diplopia, periorbital edema, and lid retraction improved after just three infusions. His TED remained stable, with no episodes of compressive optic neuropathy and only residual diplopia. The patient suffered no permanent deficits from the episode, but because of his stable state and concerns about teprotumumab as a possible cause of his encephalopathy, infusions were discontinued.

At a 7-week follow-up, his mental status was intact, and the neurological exam was only notable for impaired abduction and elevation of the left eye, consistent with the known pathology of his extraocular muscles. The patient was also seen by oculoplastic at 2 weeks, 5 weeks, 7 months, and 1 year after his hospitalization. His exam showed sustained improvement in his proptosis (Hertels of 15/110/117) and periorbital edema. His diplopia had subjectively improved but still occurred intermittently and did not respond to prisms. A second trial of teprotumumab was considered, but due to limited data on efficacy of the medication in inactive TED, and the serious complication he had experienced, this was not done. To date, no other interventions have been taken for his TED.

DISCUSSION

This case represents a unique instance of WE arising in a context lacking common etiologies such as alcohol use, making its temporal association with teprotumumab noteworthy. The best known diagnostic criteria for WE is the Caine Criteria, which was developed specifically for patients with a history of alcohol abuse issues, and requires any two dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, and either altered mental status or mild memory impairment.⁷ Our patient demonstrated both altered mental status and memory impairment. He also presented with a new bilateral intention tremor, indicating cerebellar dysfunction. His wife confirmed there were no dietary deficiencies, and there were no new oculomotor deficits documented. It's worth noting that the patient was uncooperative during the neurological exam, hindering assessment of cranial nerves III, IV, and VI, as well as coordination, meaning that other pertinent findings may have been missed. Though his blood levels of thiamine were within the normal range, thiamine levels are not formally part of the diagnosis of WE. Measuring thiamine levels prior to treatment is recommended in the guidelines of the European Federation of Neurological Societies, but normal levels do not exclude the diagnosis, and there are other reports of normal-thiamine WE.^{5,8} The patient denied alcohol use, had a varied diet, and had stable thyroid function before developing WE, eliminating many common causes of the condition. The only major change around the onset of symptoms was the initiation of teprotumumab infusions.

Although teprotumumab use has not previously been linked with WE, there was a reported case of Hashimoto's encephalopathy and two presumed autoimmune encephalopathies associated with teprotumumab that resolved with plasmapheresis.^{2,9,10} Not much information is available in the case of Hashimoto's encephalopathy, but it was believed to be possibly related to teprotumumab, and lead to participant discontinuation from a randomized trial of the medication.² The first case of autoimmune encephalitis was a 76 year old male presenting with 6 weeks of executive dysfunction after 4 infusions of teprotumumab, later found to have high CSF protein. There was no response to steroids or IV immunoglobins, but the patient returned to baseline after 5 sessions of plasmapheresis. It is theorized that this treatment cleared teprotumumab induced autoantibodies impacting the CNS.⁹ The second case was a 62-year-old woman who presented with 1 week of fluctuating mental

status, tremors, and psychiatric symptoms after 3 infusions of teprotumumab. Her treatment team was familiar with the previous case report and used plasmapheresis early on, leading to progressively shorter episodes of altered mental status until her symptoms completely resolved.¹⁰

CONCLUSION

Though documented instances of teprotumumab-associated encephalopathy are rare, the potential for serious neurological symptoms exists, as exemplified by this case, and the other published cases of encephalopathy. This possibility necessitates vigilance and prompt recognition by healthcare providers overseeing such treatments.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

All authors made substantial contributions to the clinical documentation, interpretation, and manuscript preparation. All authors approved the final version of the manuscript.

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A wolf in stroke's clothing: the hidden face of chronic subdural haematoma

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Keywords: Chronic subdural haematoma, stroke, cranial computerized tomographic scan, burr hole, hemiplegia

Dear Editor,

We write to highlight a recurring and pertinent issue in neurosurgical practice, one which carries with it a potential for grave consequences. Patients with chronic subdural haematoma (CSDH), a neurosurgical condition, often present with symptoms and signs that may mimic a cerebrovascular event (stroke).¹ Hence, they often present initially to the neurologists, who usually institute treatment protocols for stroke, which are mostly non-operative. The stroke protocols are usually continued until a neuroimaging is eventually done. This stroke-like presentation of CSDH often leads to a delay in neurosurgical intervention with an attendant worsening of outcome.

CSDH is one of the most common intracranial pathologies that neurosurgeons grapple with. It is mostly a disease of the elderly, and the incidence continues to rise globally due to an ageing population.² The common symptoms of CSDH, such as headache and focal neurologic deficits like hemiparesis or hemiplegia, are, however, non-specific and may be easily mistaken for a stroke. This diagnostic conundrum is further complicated by the fact that both conditions i.e. stroke and CSDH occur mostly in patients with similar demographics, that is, elderly patients with comorbidities like hypertension. These patients are usually on antihypertensive medications as well as antiplatelet medications which are a recognised risk factor for CSDH.

Furthermore, a history of head trauma which is often present in patients with CSDH and may help the clinician decipher between a stroke and CSDH is usually missed at initial presentation to the neurologists. This is due to a number of reasons. The trauma typically implicated in CSDH is usually very remote from the onset of symptoms and may have been forgotten by the patients and/or their relatives. Besides, the trauma is usually trivial and mostly considered inconsequential by patients and caregivers alike; and as such

the history of trauma is not usually readily volunteered.³ Hence, a cursory inquiry about a history of trauma often yields a negative response. All these are in addition to the innate bias of the neurologist or physician to make a medical diagnosis (stroke) rather than a surgical one (CSDH).

Cranial computerized tomographic (CT) scan is the first-line imaging modality in evaluating patients with suspected stroke in most facilities and will often confirm the diagnosis of a CSDH.⁴ However, missed cases have been reported even after neuroimaging. On the one hand, subdural haematomas in the subacute phase appear isodense on cranial CT scan, blend imperceptibly with the normal brain and may be easily missed; on the other hand, CSDH may be mistaken for an infarct from an ischaemic stroke as both may have similar appearances-hypodense, wedge-shaped and dura-based.

The foregoing often leads to a delay in the diagnosis and ultimately surgical treatment of CSDH. Thus, there is a more prolonged period of sustained elevation in intracranial pressure occasioned by the CSDH. This usually leads to neurological deterioration as well as a poorer outcome when surgery is eventually done and in some cases mortality. CSDHs are generally associated with good outcomes with complete resolution of neurologic symptoms and deficits when promptly addressed and are usually amenable to burr hole and haematoma drainage, a simple neurosurgical procedure.⁵

Therefore, there is a pertinent need for heightened awareness of CSDH as a stroke-mimic and impostor. We admonish clinicians and all first responders to always consider CSDH as a possible differential diagnosis in all patients presenting with stroke-like symptoms, especially those with risk factors such as advanced age, patients on antiplatelets or those with a history of trauma, even if trivial. We also recommend a very

low threshold for plain cranial CT scan or brain MRI in these patients. This will influence commencement of definitive treatment like thrombolytics for ischaemic stroke, facilitate timely diagnosis of CSDH and prompt referral for appropriate treatment, thus improving outcomes.

ETHICAL DECLARATIONS

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

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Intranasal bromocriptine in Parkinson's disease: a nasocerebral leap in dopaminergic therapy

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Keywords: Bromocriptine mesylate, Parkinson's disease, neurobiology

Dear Editor,

We write to bring to the foremost awareness and consideration, a novel modality of Parkinson's disease (PD) treatment. This novel, non-invasive brain-targeted therapy, offers a promising milieu for the clinical management of PD.

PD remains one of the most debilitating neurodegenerative disorders, characterized by dopaminergic neuronal loss in the substantia nigra and the consequent motor and non-motor manifestations.¹ Despite pharmacologic advances, oral dopaminergic therapies, including bromocriptine, have been limited by erratic gastrointestinal absorption, extensive first-pass metabolism, and dose-dependent adverse effects such as nausea, hypotension, and neuropsychiatric symptoms.²

In this context, the intranasal route of bromocriptine (Bromocriptine Mesylate Loaded Nanostructured Lipid Carriers) administration presents a transformative pharmacotherapeutic proposition using precision nanomedicine as its vector. The nasal mucosa offers a direct conduit to the central nervous system via the olfactory and trigeminal pathways, bypassing the blood-brain barrier and hepatic metabolism.³ This not only enhances central bioavailability but also shortens onset time and reduces systemic side effects. A visual illustration of this is displayed below in [Figure](#).

Preclinical studies have demonstrated superior dopaminergic receptor activation and behavioral improvement following intranasal bromocriptine delivery compared to its oral counterpart.⁴ Additionally, early pharmacokinetic data indicate that nasal formulations achieve therapeutically relevant cerebrospinal fluid concentrations within minutes,

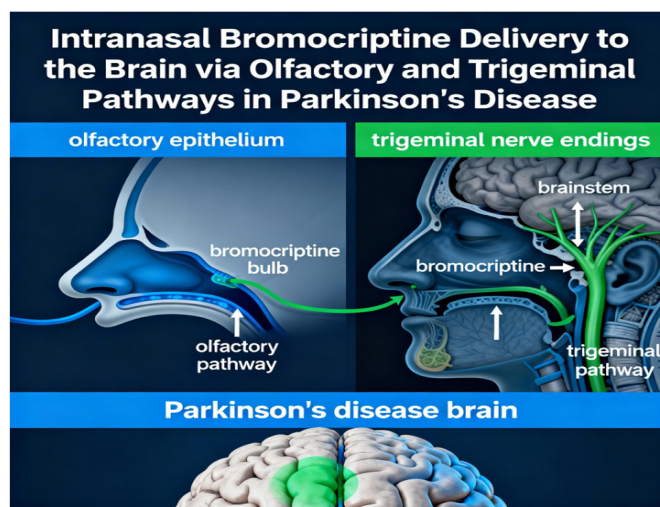


Figure. A visual illustration of the delivery mechanism of intranasal bromocriptine

suggesting potential utility for both continuous symptom management and acute “off” episodes in PD.^{3,4}

While the therapeutic rationale is compelling, several translational challenges warrant attention. These include optimizing formulation stability, minimizing mucociliary clearance, improving patient tolerability, and ensuring long-term nasal safety. Addressing these issues will be essential before large-scale trials can fully validate efficacy and safety.

We therefore, using this journal as a vantage point of outreach to strategic stakeholders in the neurobiological landscape, advocate for rigorous clinical investigations

that will check and confirm the therapeutic promise of intranasal bromocriptine as an adjunct or alternative to established dopaminergic regimens. This approach, if successful, could herald a “nasocerebral” era of precision dopaminergic modulation, optimizing therapeutic outcomes while minimizing systemic burdens across several affected demographics in developed and developing nations.

ETHICAL DECLARATIONS

Peer Review Process

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Author Contributions

All authors contributed to the conceptualization and drafting of this correspondence and approved the final version for publication.

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