

REVIEW ARTICLE

Serotonin-interleukin pathway in neurological disorders: A mixed pathway approach

Abdullah Al Noman^{1*}, Imanul Kabir Lihu^{1†}, Ritesh Sharma^{2†},
Md. Noor Alam^{3†}, Shubham Singh⁴, Himanshu Sharma⁵, and
Zubaier Ahmed¹

¹School of Pharmacy, BRAC University, Dhaka, Bangladesh

²Department of Pharmacy, Faculty of Pharmaceutical Sciences and Nursing, Vivekananda Global University, Jaipur, Rajasthan, India

³Department of Biomedical Sciences, School of Medical and Life Sciences, Sunway University, Subang Jaya, Selangor, Malaysia

⁴Department of Pharmaceutics, School of Pharmacy, Rai University, Ahmedabad, Gujarat, India

⁵Department of Pharmacology, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India

Abstract

Neurological disorders involve complex interactions between neurotransmitters and immune signaling pathways, with serotonin (5-HT) and interleukins (ILs) playing crucial roles. This review explores the mixed pathway of 5-HT-IL signaling and its involvement in the pathophysiology of neurodegenerative and neuropsychiatric conditions. Dysregulated 5-HT and IL signaling has been implicated in Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, anxiety, schizophrenia, autism spectrum disorder, and attention-deficit/hyperactivity disorder. 5-HT influences neuroinflammation, synaptic plasticity, and cognitive function, while ILs regulate immune responses and neuronal survival. Their interplay modulates neurotransmission, neuroinflammation, and neurodegeneration through mechanisms, such as cytokine-mediated 5-HT depletion and 5-HT receptor regulation. Understanding the 5-HT-IL pathway offers new insights into disease progression and potential therapeutic strategies, including selective 5-HT reuptake inhibitors, cytokine inhibitors, and combination therapies targeting neuroimmune interactions.

[†]These authors contributed equally to this work.

***Corresponding author:**

Abdullah Al Noman
(abdullah.al.noman@g.bracu.ac.bd)

Citation: Al Noman A, Lihu IK, Sharma R, *et al.* Serotonin-interleukin pathway in neurological disorders: A mixed pathway approach. *Adv Neurol.* 2026;5(2):025220066. doi: 10.36922/AN025220066

Received: May 27, 2025

Revised: August 15, 2025

Accepted: August 25, 2025

Published online: October 3, 2025

Copyright: © 2025 Author(s).

This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Keywords: Neurological disorders; Serotonin pathway; Interleukin signaling; Neuroinflammation; Neurodegeneration

1. Introduction

Serotonin (5-HT) and interleukin (IL) possess significant roles in different physiological functions. 5-HT increases the release of several pro-inflammatory cytokines, including IL-1 and IL-6, and it has a profound impact on the body's immunity, cardiac rate, respiratory drive, vascular tone, hemostasis, and cell proliferation.¹ Moreover, 5-HT is crucial for intestinal secretion, visceral sensitivity, gastrointestinal (GI) motility,² and the modulation of the sleep-wake cycle.³ In both inflammatory and adaptive immune responses, ILs play a crucial role in regulating the activation, differentiation, and proliferation of immune cells.⁴ IL-6 mediates the activation of T cells and B cells and

participates in both innate and adaptive immune responses.⁵ Furthermore, IL-10, an anti-inflammatory cytokine, is involved in 5-HT modulation through regulation of serotonin transporters (SERT) and by increasing 5-HT reuptake receptor expression.⁶ Collectively, 5-HT and IL play critical roles in the central nervous system (CNS) and are implicated in neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD),^{7,8} Huntington's disease (HD), depression, anxiety, aggressive behavior, and stress, and are also involved in physiological processes, such as blood pressure regulation, peristaltic movements, and heart rate.⁹⁻¹²

In AD, 5-HT and IL influence the production and clearance of amyloid beta (A β) aggregates and tau pathology. According to the amyloid cascade hypothesis, the etiology of AD is initiated by deposition of A β , followed by tau pathology, neuronal death, and clinical manifestations.¹³ The neurotransmitter 5-HT is essential for regulating the synthesis and removal of A β through receptors, such as 5-HT_{2R}, 5-HT_{4R}, and 5-HT_{6R}.¹⁴ Moreover, IL-1 is implicated in exacerbating A β burden, particularly in patients with a history of head trauma. IL-1 β also stimulates the synthesis of IL-6, which, in turn, activates cyclin-dependent kinase 5 and contributes to tau hyperphosphorylation.^{13,15} Dysregulated 5-HT and IL signaling disrupts the balance of A β generation and clearance systems, therefore leading to neurotoxic plaque formation and toxic A β species deposition.¹⁶ The second feature of AD is the abnormal phosphorylation of tau protein and its clustering in neurofibrillary tangles (NFTs). As mentioned previously, 5-HT and IL have been associated with tau pathology, affecting the processes of tau accumulation and phosphorylation.¹⁷ Aberrant 5-HT and IL signaling can aggravate neuronal damage and loss by promoting abnormal tau phosphorylation and interfering with tau clearance mechanisms, therefore underpinning tau pathology.¹⁸ AD is also characterized by long-term activation of microglia and astrocytes, a signal for persistent neurological inflammation.¹⁹ By intensifying chronic neurological inflammation, 5-HT and IL influence the blood-brain barrier (BBB) and neuronal survival. In AD, reduced 5-HT and IL signaling compounds neural inflammation by generating reactive oxygen species (ROS) and pro-inflammatory cytokines, which exacerbate neuronal impairments and limit cognitive capabilities.²⁰ Along with 5-HT, IL may alter the BBB, therefore regulating the flow of immune system molecules and compounds between the neurological and circulating systems. Abnormally low levels of 5-HT and IL in AD weaken the BBB, thereby allowing immune cells and inflammatory compounds from outside the brain to penetrate and exacerbate neuronal inflammation and neuronal damage.²¹⁻²³

Moreover, 5-HT and IL play complex roles in the survival of neurons and the regulation of synapse plasticity. While acute 5-HT and IL signaling can enhance synaptic plasticity and provide neural protection, abnormal or sustained signaling may lead to synapse loss and neurodegeneration. Imbalances in 5-HT and IL signaling disrupt the balance between neuronal survival and death, causing neurodegeneration in AD pathology.²⁴⁻²⁷ Dysregulated 5-HT and IL signaling also produce a myriad of undesirable effects in HD, which is characterized by impairment of motor function, loss of memory, and symptoms, such as schizophrenia.^{9,11,28} Excitotoxicity, caused by overstimulation of glutamate receptors leading to neuronal death, is initially involved in HD pathology. 5-HT and IL increase excitotoxicity by promoting the release of glutamate and inhibiting its reuptake.^{29,30} 5-HT and IL signaling has been strongly implicated in PD, a progressive neurodegenerative illness associated with both non-motor symptoms (mood changes, memory impairment) and motor symptoms (bradykinesia, rigidity, and tremor).^{17,31-35} Moreover, the toxic accumulation of neuronal iron triggered by 5-HT and IL-induced cellular iron sequestration response promotes α -synuclein-mediated neurodegeneration.³⁶ Although the specific roles of 5-HT and IL in PD remain complex, new evidence indicates their involvement in a number of aspects of the disease's pathophysiology. Neuroinflammation is a major causative factor in PD, with disrupted 5-HT and IL signaling contributing to the sustained inflammatory profile of the disease. The elevated levels of 5-HT and IL observed in the brain tissues and cerebrospinal fluid (CSF) of PD patients corroborate this association.³⁷⁻⁴⁰ Neurological illness and neuropsychiatric disorders are significantly affected by changes in the pathophysiology of the serotonergic system. 5-HT is critically involved in the regulation of stress, anxiety, and aggression. Dysregulation of 5-HT neurotransmission has been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), migraine, epilepsy, and AD.⁴¹ Similarly, cytokines are necessary for regulating the immune system and facilitating communication between cells, particularly through ILs.⁴² They coordinate immune responses to infection and inflammation, promote tissue repair, and play an essential role in neurodegenerative disease. ILs are secreted by several immune cells, such as macrophages and leukocytes.⁴³ This review examines interactions between 5-HT and ILs during the development, progression, and potential management of neurological and psychiatric disorders.

2. 5-HT in neurological disorders

The neurotransmitter 5-HT is a key regulator of serotonergic neurons and is important in mediating neural activity. The CNS critically relies on 5-HT for its proper development and function. The disruption of 5-HT level is associated with epilepsy, migraine, MS, PD, and ALS.⁴⁴ Migraine, a frequent primary headache condition affecting approximately one in eleven adults worldwide, is characterized by abnormalities in serotonergic pathways. Biogenic amines, such as catecholamines and 5-HT, aid in the regulation of autonomic processes, including blood pressure. Alterations in the 5-HT pathway could also be involved in the pathophysiology of ALS. Studies show that hyperactivity could be partially attributed to alterations in the accessibility and metabolism of 5-HT.⁴⁵

2.1. Synthesis and release of 5-HT

The CNS serotonergic neuronal system, the alimentary tract, and thrombocyte—where 5-HT is preserved—are the initial locations for 5-HT. 5-HT functions as an endogenous chemical in addition to a neurotransmitter. However, a large percentage of 5-HT is synthesized by enterochromaffin (EC) cells, also known as Kulchitsky cells, found in the mucous membrane. The stomach, the biggest endocrine organ in the human body, produces approximately 95% of all 5-HT. Acetylcholine (ACh), neural activation, and a rise in stress within the intestinal lumen can all trigger its release. 5-HT is liberated into the mucous membranes and the intestinal lumen, which contains dendritic cells, T lymphocytes, and other immune cells.¹ Tryptophan is a necessary amino acid that is obtained from the diet and is converted into 5-HT in two steps. Tryptophan hydroxylase (TPH) hydroxylates tryptophan to 5-hydroxytryptophan (5-HTP), the initial and rate-limiting enzymatic step. EC cells contain the TPH1 isoform, while central and enteric neurons contain the TPH2 isoform. An aromatic L-amino acid decarboxylase then converts it to 5-HT. Cytoplasmic vesicles, in which 5-HT is sequestered, prevent monoamine oxidase (MAO) from breaking it down quickly. The vesicular monoamine transporter then encapsulates 5-HT into vesicles. 5-HT is transported through the SERT into platelets, which are the primary storage site for 5-HT, and into presynaptic terminals in the CNS. 5-hydroxy indole acetic acid (5-HIAA), produced by MAO-mediated degradation of 5-HT, is primarily excreted in the urine. The SERT is located in the peripheral and pulmonary vessels and the GI tract.⁴⁶ 5-HT in the CNS is synthesized by neurons in the raphe nuclei of the brain (Figure 1). In addition to regulating a variety of behavioral expressions, including mood, perception, memory, and stress responses, 5-HT also affects body temperature, circadian cycles, and emesis.

However, 5-HT is mostly found outside the CNS, where it affects key organ processes, such as heart rate, respiratory drive, vasoconstriction, intestinal motility, and secretion. In addition, 5-HT is necessary for endocrine secretion, energy balance, metabolic processes, glucose homeostasis, and lipid metabolism. 5-HT also promotes the repair of physiological organs, such as the liver after resection when its volume is lost (Table 1).⁴⁷

3. Role of 5-HT in mood regulation and cognitive function

3.1. Mood regulation

One of the main signs of depression, an emotional disorder that affects 20% of the global population and a primary cause of impairment worldwide, is low mood.⁶² Antidepressants, initially selective serotonin reuptake inhibitors (SSRIs) or combination serotonin/noradrenaline reuptake inhibitors, are the main therapeutic agents used to manage depression.⁶³ These medications are believed to act partly by increasing monoamine levels in synapses, mainly noradrenaline and 5-HT, which in turn activate serotonergic and noradrenergic postsynaptic and autoreceptor.⁶⁴ While monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) shown effectiveness in managing depression in the mid-20th century, the medicinal advantages of elevated monoamine levels led to the development of the monoamine theory, which postulated that a lack of these chemical messengers was a cause of depression.⁶⁵ Nevertheless, individuals with mild to severe depression are only marginally helped by antidepressants, with response rates of roughly 48% compared to 30% for placebo.^{66,67} The monoamine theory significantly addresses depression.^{68,69} The acute tryptophan depletion (ATD) approach has been used to investigate the effect of 5-HT on mood by lowering dietary tryptophan levels, which reduces brain 5-HT levels, allowing analysis of 5-HT-dependent activity.⁷⁰ Research on tryptophan deficiency in individuals without a history of depression varies and shows little to no overall impact on mood reduction.⁷¹ Intriguingly, some research, including healthy women, indicates modest mood reductions more frequently than studies involving healthy men.⁷² Conversely, the ATD method produces measurable anomalies in mood regulation^{73,74} among healthy individuals with no history of depression but with a genetic risk factor for depression. Even temporary lowering of tryptophan levels can trigger a relapse of serious depression in previously depressed patients, as well as a temporary increase in symptoms linked with serotonergic antidepressant use.⁷⁵⁻⁷⁹ Furthermore, while low 5-HT can lead to depressed mood, it is not sufficient on its own. It is likely interacts with other factors, such

Table 1. 5-HT receptors and their functions

Receptor	Function	References
5-HT1A, 1B, 1D, 1E, 1F	1. These receptors lead to adenylyl cyclase inhibition and diminished synthesis of cAMP as the prominent functional outcome. 2. These receptors are further blocked by pertussis toxin, which prevents dissociation between the G α and G $\beta\gamma$ subunits.	48,49
5-HT2A	It is likely the main target of potent psychoactive chemicals known as psychedelics, including hallucinogens, such as LSD.	50,51
5-HT2B	The primary role of this receptor is to coordinate the development of the proper form for vital structures, such as the heart and brain.	52-54
5-HT2C	It could regulate the transport of ions between the brain and CSF.	55,56
5-HT4	1. This receptor plays a critical role in peripheral functions, especially in the intestine. It is occurred in EC cells and enteric neurons. 2. Activation of 5-HT4 stimulates Ach release and promotes colon relaxation.	57,58
5-HT6	This receptor may be implicated in mediating part of the antidepressant effects of SSRI.	59,60
5-HT7	One of the most interesting potential areas of 5-HT7 receptor activity is in depression.	61

Abbreviations: 5-HT: 5-hydroxytryptamine; Ach: Acetylcholine; cAMP: Cyclic adenosine monophosphate; CSF: Cerebrospinal fluid; EC: Enterochromaffin; LSD: Lysergic acid diethylamide; SSRI: Selective serotonin reuptake inhibitor.

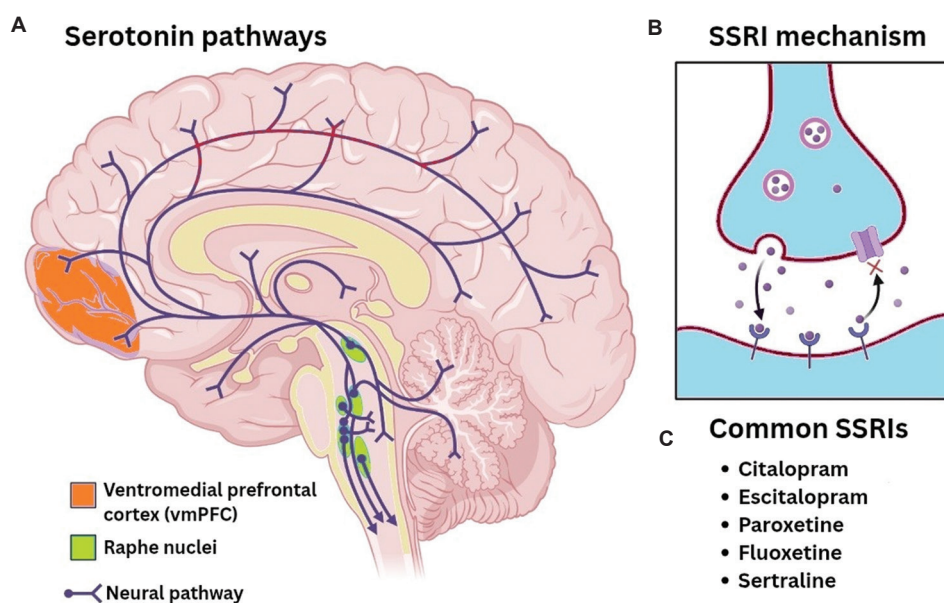


Figure 1. An overview of 5-HT pathways and the mechanistic action of SSRIs. (A) Anatomical representation of serotonergic pathways originating from the raphe nuclei (highlighted in green) and projecting to key brain regions, including the vmPFC (shown in orange). These neural circuits play critical roles in mood regulation and emotional processing. (B) Mechanistic illustration of SSRIs at the synaptic level. SSRIs inhibit the SERT, thereby inhibiting the reuptake of 5-HT into the presynaptic terminal, which increases extracellular 5-HT concentrations and enhances serotonergic neurotransmission. (C) Commonly prescribed SSRIs, including citalopram, escitalopram, paroxetine, fluoxetine, and sertraline, which are extensively employed in the management of MDD and related psychiatric conditions. Image created by the authors.

Abbreviations: 5-HT: Serotonin; MDD: Major depressive disorders; SERT: Serotonin transporter; SSRIs: Selective serotonin reuptake inhibitors; vmPFC: Ventromedial prefrontal cortex.

as neurotransmitters or genetic components, to produce mood reductions.

3.2. Cognitive function

The serotonergic system influences functions that require significant cognitive processing. 5-HT receptors are present in the grey matter, amygdaloid nucleus, and Ammon's horn, regions of the brain linked with memory and learning.⁸⁰

Numerous subclasses of 5-HT receptors have been linked to recall and cognition as putative pharmaceutical treatments for promoting or augmenting cognition. According to cumulative evidence, administration of 5-HT2A/2C or 5-HT4 receptor agonists, or 5-HT1A, 5-HT3, and 5-HT1B receptor antagonists, helps individuals to learn and resist memory loss under conditions of high cognitive demands. On the other hand, 5-HT1A, 5-HT3, and 5-HT1B agonists,

or 5-HT_{2A/2C} and 5-HT₄ receptor antagonists, typically impair learning and memory.⁸¹⁻⁸⁶ It remains unclear whether 5-HT modulates cognitive activity through particular implications on memory, executive function, and learning, although the selective functions of various 5-HT receptor subtypes in cognition may be partly responsible.⁷⁹ Experimentally lowering brain 5-HT levels through tryptophan depletion has helped to clarify the function of 5-HT in many learning processes.

3.3. 5-HT dysregulation in neurological disorders (e.g., depression, anxiety, and PD)

Numerous symptoms of depression, including mood, sexual functioning, appetite, sleep disturbances, and diurnal rhythms, have been attributed to serotonergic abnormalities.^{87,88} Serotonergic dysfunctions in blood platelets, plasma, and CSF of depressed patients, as well as in autopsy samples of individuals who died by suicide, are evidenced in a large body of research. The majority of these patients are thought to have been suffering from severe depression or bipolar depression before their deaths.^{89,90} Reduced 5-HT synthesis in depression has also been linked to normal or reduced levels of 5-HIAA, the principal metabolic product of 5-HT, in depressed patients or in those who attempted suicide.^{88,91} The response to cortisol of 5-HTP was correlated with the level of depression, likely due to an upregulation of 5-HT₂ receptors associated with a 5-HT deficit. While there is strong evidence for extensive cholinergic dysfunction in AD, cholinergic system-specific therapies have not been successful. A cholinergic theory of AD memory disturbance was proposed based on presynaptic cholinergic deficiencies consistently reported in previous post-mortem investigations in AD.⁹²⁻⁹⁴ It is still unclear how deficiencies in cholinergic and other neurotransmitter pathways relate to the mental and behavioral symptoms of AD, but post-mortem literature strongly indicates direct involvement of the 5-HT system. First, post-mortem AD brains have been demonstrated to exhibit reduced 5-HT levels and those of its metabolites.⁹⁵ 5-HT reuptake sites in the temporal cortex are also reduced in early AD patients, suggesting a loss of serotonergic nerve endings, consistent with the lower 5-HT and metabolite levels.⁹⁴ Second, NFT formation and neuronal loss in AD preferentially occur in the raphe nucleus, a region with high serotonergic neuronal activity.⁹⁶ Finally, since 5-HT_{2A} receptors are more selectively affected than 5-HT_{1A} receptors, this points to a reduction in cortical 5-HT receptors found in cholinergic nerve terminals of the hippocampus and cortex, which are linked to the 5-HT_{2A} receptor.^{97,98} Since other neurotransmitter systems, including opioid, gamma-aminobutyric acid, α 1, α 2, and β -adrenergic systems, are unaffected or minimally affected, serotonergic malfunction

in AD appears to be an isolated phenomenon rather than a result of generalized cortical degeneration.^{99,100} It is still unclear whether the common co-occurrence of depression and impairments in 5-HT cell number and neurotransmission in AD are related.^{101,102} Nonetheless, it seems that the behavioral features of AD are closely related to serotonergic impairment.¹⁰³⁻¹⁰⁵ Using [³H] paroxetine and autoradiography, evidence shows a reduction of 5-HT reuptake sites in the lateral but not frontal regions of AD brains, and such reductions were significant in AD subjects whose depressive symptoms persisted in both sites. In a small sample of AD patients with a history of depression who had committed suicide, a reduction in post-mortem imipramine binding was discovered.¹⁰⁶ Similarly, AD patients who had significant depressive symptoms in their lives showed reduced paroxetine interaction at orbitofrontal and posterior cortex 5-HT reuptake sites. Apart from depressive symptoms, serotonergic impairment has been explicitly associated with several behavioral aspects of AD. Only AD patients who exhibited pronounced violent behavior were shown to have diminished 5-HT levels in the inferior frontal cortex.¹⁰⁷ Substantial drops in 5-HT and higher rates of senile plaques in the prosubiculum have been linked to psychosis.¹⁰⁸ In addition, compared to non-agitated individuals or normal elderly controls, agitated or delusional AD patients demonstrated noticeably decreased platelet 5-HT reuptake site binding densities.¹⁰⁹ Therefore, AD patients who exhibit aggressiveness and depressive symptoms appear to have more severe 5-HT deficiencies.

4. ILs in neurological disorders

4.1. Overview of ILs and their functions

ILs are a category of cytokines essential for immune system communication and regulation.¹¹⁰ They influence cellular activities, such as proliferation, differentiation, and inflammation, playing a significant role in preserving physiological equilibrium.¹¹¹ These molecules are released from various immunologically active cells, including macrophages, lymphocytes, and glial components of the nervous system.^{112,113} In the CNS, ILs regulate neuroimmune interactions, affecting synaptic plasticity, neuronal survival, and inflammatory responses.^{114,115} Pro-inflammatory cytokines, such as IL-1, IL-6, and IL-17, amplify immune responses and contribute to neuroinflammatory conditions.¹¹⁶ Conversely, ILs with inflammation-suppressing properties, including IL-10 and IL-4, help in reducing excessive inflammation and promoting neuronal protection. The balance between these types determines the impact of immune activity on neurological health.¹¹⁷ Research indicates that ILs influence neurodegenerative diseases, brain injuries, and autoimmune disorders affecting the nervous system.¹¹⁸ Their modulation offers

potential therapeutic advancements in conditions, such as AD, MS, and PD. Understanding their multifaceted roles in neural processes may pave the way for developing targeted treatments.¹¹⁹

4.2. Synthesis and secretion of ILs in the brain

ILs in the CNS are synthesized by multiple cell types, including microglia, astrocytes, neurons, and infiltrating immune cells.^{120,121} Their production is primarily triggered by infections, injuries, or neurodegenerative processes. Microglia, the brain's primary immune cells, serve as a major source of ILs and regulate immune signaling pathways in response to different stimuli.¹²² Astrocytes also contribute to IL secretion, particularly under neuroinflammatory conditions.¹²³ Under physiological conditions, ILs support neuronal maintenance, whereas dysregulated production can lead to inflammatory damage.¹¹⁴ Various signaling pathways, such as the necrosis factor kappa-B (NF- κ B)-dependent pathway and the JAK/STAT pathway, regulate IL release and modulate inflammatory responses in the brain.^{111,124} Understanding how ILs are synthesized and released within the CNS is crucial for designing therapeutic strategies that fine-tune their effects.¹²⁵ Targeting IL production mechanisms could help in managing neuroinflammatory disorders while minimizing unwanted immune responses.¹²⁶

4.3. Role of pro-inflammatory ILs in neuroinflammation

Pro-inflammatory ILs, particularly IL-1 and IL-6, play significant roles in mediating neuroinflammatory responses.¹²⁵ These cytokines trigger immune activation, resulting in heightened synthesis of inflammatory mediators and ROS, which contribute to neuronal damage.¹²⁷ IL-1, especially IL-1 β , promotes microglial activation and leads to the secretion of additional cytokines and chemokines involved in inflammation.¹²⁸ This activation enhances increased BBB permeability, allowing infiltration of peripheral immune cells into the CNS and worsening neuroinflammation.^{129,130} IL-6 has diverse functions, including both protective and detrimental effects in the brain. While it supports neuronal survival under certain conditions, excessive IL-6 levels are associated with chronic neuroinflammation and neurodegenerative diseases.¹³¹ Its activation of the JAK/STAT signaling pathway influences inflammation-related gene expression and immune responses.¹³²

IL-8/CXCL8 is a chemotactic cytokine that facilitates the recruitment of neutrophils across the BBB and is elevated in AD and traumatic brain injury, where it contributes to prolonged neuroinflammation and synaptic loss.¹³³ IL-12 and IL-23 are heterodimeric cytokines that drive T-helper 1 (Th1) and Th17 responses, respectively. Their dysregulation

exacerbates neuroinflammatory cascades in MS, often correlating with disease severity and relapse rates.¹³⁴ IL-21 influences B-cell differentiation and has been implicated in antibody-mediated neuropathies, such as neuromyelitis optica and MS.¹³⁵ In contrast, IL-33, a nuclear cytokine, exerts a protective role in CNS injury models by enhancing T-regulatory cell infiltration and dampening microglial reactivity. IL-18 and IL-1 family cytokines are elevated in depression, schizophrenia, and AD, where they contribute to inflammasome activation, neurodegeneration, and serotonergic dysregulation. On the other hand, IL-27 and IL-37 function as anti-inflammatory agents. IL-27 has been reported to suppress IL-17 production and inhibit Th17 cell differentiation, providing potential therapeutic benefits in MS and other neuroinflammatory syndromes, while IL-37 exerts broad anti-inflammatory effects, attenuating microglial activation and oxidative stress.¹³⁴

Given their diverse roles in neuroinflammation, targeting IL-1 and IL-6 pathways has been explored as a treatment approach for neurological disorders.^{136,137} Blocking these cytokines or their downstream signaling mechanisms could help to reduce inflammatory damage in conditions, such as MS, AD, and brain injuries.¹³⁸

4.4. Anti-inflammatory ILs and their protective effects

Anti-inflammatory ILs play a vital role in regulating excessive immune activation, promoting tissue repair, and maintaining homeostasis in the CNS.¹³⁹ Among them, IL-10 is one of the most significant anti-inflammatory ILs, known for its ability in reducing pro-inflammatory cytokine production and regulate immune responses.¹⁴⁰ IL-10 is mainly produced by microglia, astrocytes, and infiltrating immune cells during CNS inflammation.^{141,142} Its protective functions are mediated by inhibiting inflammatory signaling pathways, such as NF- κ B and modulating microglial activity.¹⁴³ In addition, IL-10 enhances neuronal survival and promotes the repair of damaged tissues by reducing oxidative stress and inflammatory damage.¹⁴⁴ The therapeutic potential of IL-10 in neurological diseases has been widely studied, with evidence showing enhanced IL-10 activity improves recovery in conditions, such as MS, ischemic stroke, and TRI.¹⁴⁰ However, precise regulation of IL-10 signaling remains a challenge, requiring further investigation to fully optimize its therapeutic applications.¹⁴⁵

4.5. IL dysregulation in neurological disorders

An imbalance in IL signaling is commonly observed in neurological disorders, contributing to disease progression and severity.¹⁴⁶ Dysregulation of IL expression can result in either excess inflammation or insufficient immune

responses, both of which can have detrimental effects on neuronal activity and longevity.^{136,147,148} In AD, elevated concentrations of IL-1 β and IL-6 are related to A β plaque deposition and tau protein hyperphosphorylation, thereby exacerbating neurodegeneration.¹⁴⁹ Similarly, in MS, abnormal IL-17 and IL-6 activities contribute to autoimmune-driven demyelination, leading to neuroinflammatory damage.^{150,151} Psychiatric disorders, including depression and schizophrenia, have also been associated with altered IL levels.¹⁵² Studies suggest that chronic inflammation and cytokine imbalances may contribute to neurotransmitter dysregulation and impaired neuronal connectivity.¹³⁰ Therefore, targeting IL dysregulation in neurological diseases holds significant therapeutic potential.¹⁵³ By restoring balance in IL signaling, researchers aim to develop innovative treatment strategies that can mitigate neuroinflammation and improve neurological outcomes.¹⁵⁴

5. Interplay between 5-HT and ILs

5-HT and ILs play important roles in both the nervous and immune systems.¹⁵⁵ Their interactions regulate neuroinflammatory responses, neurotransmission, and immune signaling, thereby influencing the development and progression of neurological and psychiatric disorders. Comprehending their interplay is crucial for the design of novel therapeutic strategies in neuroimmunology.¹⁵⁶

5.1. Mechanisms of interaction between 5-HT and ILs

The interaction between 5-HT and ILs is mediated through multiple biochemical and molecular pathways.¹⁵⁷ 5-HT receptors, expressed on both neurons and immune cells, interact with cytokine signaling pathways, while ILs regulate 5-HT metabolism through enzymatic mechanisms.^{155,158,159} For instance, pro-inflammatory cytokines, such as IL-1 β , IL-6, and IL-18 stimulate indoleamine 2,3-dioxygenase (IDO), an enzyme that catalyzes the conversion of tryptophan, the pre-cursor of 5-HT, into kynurenine.¹⁶⁰ This process reduces 5-HT levels and contributes to neuroinflammation. In addition, specific 5-HT receptor subtypes, including 5-HT1A and 5-HT2A, influence IL expression in microglia and astrocytes, thereby shaping neuroinflammatory responses in the brain.¹⁶¹ SERT, which is responsible for 5-HT reuptake, is also regulated by ILs. IL-1 β and IL-6 have been shown to downregulate SERT activity, leading to increased synaptic 5-HT levels, which may contribute to altered mood states and impaired cognitive function.¹⁶² Conversely, IL-10, along with other anti-inflammatory cytokines, has the ability to modulate serotonergic pathways, restoring balance and reducing neuroinflammation.^{156,163,164}

5.2. Impact of 5-HT on IL production and release

5-HT actively modulates immune responses by regulating IL production and secretion.¹⁶⁵ Across receptor-mediated mechanisms, 5-HT regulates cytokine expression in immune cells, including microglia and astrocytes.¹⁶⁶ Stimulation of 5-HT1A and 5-HT2 receptors is generally linked to a reduction in pro-inflammatory cytokines, such as IL-1 β , IL-6, and tumor necrosis factor-alpha (TNF- α).¹⁶⁷ This anti-inflammatory effect plays a neuroprotective function in neurodegenerative conditions. Conversely, signaling through 5-HT3 receptors can enhance the exocytosis of IL-1 β and IL-6, thereby exacerbating inflammatory responses.^{168,169} 5-HT also impacts cytokine release through the hypothalamic-pituitary-adrenal axis. Prolonged stress-driven 5-HT dysregulation can elevate cortisol levels, which in turn influences cytokine expression and promote neuroinflammation.¹⁷⁰ Moreover, 5-HT levels affect the activation and differentiation of T lymphocytes, influencing the balance between pro-inflammatory and anti-inflammatory responses.¹⁷¹⁻¹⁷³

5.3. Influence of ILs on 5-HT signaling and metabolism

ILs influence 5-HT neurotransmission by regulating its synthesis, release, and receptor expression. Pro-inflammatory cytokines, such as IL-1 β , IL-6, and IL-18 impair serotonergic pathways, affecting mood and cognitive functions.¹⁷⁴ A key mechanism involves the upregulation of IDO, which shunts tryptophan metabolism toward kynurenine rather than 5-HT synthesis.¹⁷⁵ This shift results in the buildup of neurotoxic compounds, such as quinolinic acid, contributing to neurodegeneration. This mechanism is linked to conditions including depression and schizophrenia.¹⁷⁶ Furthermore, ILs modulate 5-HT receptor expression.¹⁷⁷⁻¹⁷⁹ IL-6 and IL-1 β have been demonstrated to decrease 5-HT1A receptor density, thereby impairing serotonergic transmission and increasing the risk of mood disturbances.¹⁸⁰ On the other hand, IL-10 supports 5-HT signaling and exerts neuroprotective effects.¹⁸¹ Cytokines also regulate SERT activity. IL-1 β and TNF- α can suppress SERT function, leading to prolonged 5-HT signaling, which may contribute to inflammatory neurodegenerative conditions.¹⁸²

5.4. Examples of 5-HT-IL interaction in specific neurological disorders

5.4.1. Depression and anxiety disorders

In major depressive disorder (MDD), elevated concentrations of IL-1 β , IL-6, and TNF- α correlate with 5-HT depletion due to increased IDO activity.¹⁸³ This reduction in 5-HT availability leads to depressive

symptoms. Antidepressant treatments often restore 5-HT function while also reducing cytokine levels.¹⁸³

5.4.2. AD

In AD, neuroinflammation driven by IL-1 β and IL-6 contributes to amyloid plaque accumulation and tau protein hyperphosphorylation.¹⁸⁴ Impaired 5-HT signaling worsens cognitive decline. Serotonergic drugs, such as SSRIs, have been shown to influence IL levels and may offer potential therapeutic benefits.¹⁸⁵

5.4.3. PD

In PD, neuroinflammation characterized by increased IL-1 β and IL-6 levels is linked to degeneration of serotonergic neurons.¹⁸¹ This contributes to both motor and non-motor symptoms, including mood disorders. Therapeutic strategies targeting IL pathways may offer neuroprotective benefits.¹⁸⁶

5.4.4. MS

MS involves chronic neuroinflammation mediated by IL-6 and IL-17.¹⁷⁷ The role of 5-HT in regulating immune responses in MS has gained increasing attention, with SSRIs showing potential in reducing inflammation and demyelination.^{187,188}

5.4.5. Schizophrenia

Schizophrenia involves both immune and serotonergic dysfunctions. Elevated IL-6 and IL-1 β levels have been linked to cognitive and psychotic symptoms, while modulation of 5-HT receptor remains a key target of antipsychotic treatments.¹⁸⁹ Understanding 5-HT-IL interactions may help enhance therapeutic approaches.^{190,191}

5.5. 5-HT-IL pathway in neurological disorders

5.5.1. Pathway overview

The biochemical and neurological processes involved in the production, release, action, reuptake, and metabolism of 5-HT are collectively referred to as the 5-HT pathway. 5-HT regulates a wide range of physiological functions, including appetite, sleep, thermoregulation, and pain reception, as well as psychological processes in the CNS, including mood and emotion regulation. Dysregulation of 5-HT has been implicated in numerous conditions, including depression, obsessive-compulsive disorder, mania, migraine, schizophrenia, and anxiety. The first rate-limiting step in the two-step metabolic pathway that produces 5-HT is the hydroxylation of tryptophan to 5-HTP by TPH. Aromatic L-amino acid decarboxylase then decarboxylates 5-HTP to yield 5-HT. ILs are a group of cytokines produced by various cells in the body, including leukocytes, endothelial cells, fibroblasts, and

epithelial cells. They function as messengers between cells to initiate, enhance, or suppress immune responses and aid in immune system regulation. The 5-HT-IL pathway is important in modulating neuroinflammation and influences the pathophysiology of various neurological and psychiatric disorders through different mechanisms that include activation of IDO, JAK/STAT signaling, SERT modulation, and cytokine-mediated neurotoxicity.

5.5.2. Contribution to neurodegenerative diseases (AD and PD)

Several CNS disorders, including anxiety, depression, schizophrenia, and AD, have been associated with pathological changes in 5-HT metabolism and/or an imbalance in serotonergic signaling. AD is the most prevalent progressive neurodegenerative disease, characterized by the loss of neurons in the brain. Impaired cognitive function, personality and behavior abnormalities, and memory loss are characteristic features of AD. A decrease in serotonergic neurons in the raphe nuclei has been associated with AD. In addition, post-mortem AD brains show lower levels of 5-HT and its metabolites.⁹⁵ Similarly, 5-HT reuptake sites in the temporal cortex are depleted in patients with early AD, consistent with a loss of serotonergic nerve terminals.¹⁹² The serotonin 6 receptor (5-HT₆R) is among the most recently cloned 5-HT receptors and is positively coupled to adenylate cyclase through the G_s protein.¹⁹³ The receptor is highly expressed in the cortex, striatum, and hippocampus of the CNS.¹⁹⁴ However, significant declines in 5-HT₆R density have been observed in the cortical regions of AD patients.¹⁹⁵ Pro-inflammatory cytokines, including IL-1 β , IL-12, IL-6, IL-17, and IL-23, have immunoregulatory functions in AD.¹⁹⁶⁻²⁰⁰ Elevated plasma levels of IL-1 β have been found in AD patients, indicating a connection between the etiology of AD and systemic chronic inflammation. Furthermore, soluble IL receptors (sIL-1R1, sIL-1R3, and sIL-1R4) as well as IL-33, IL-1Ra, and IL-18BP, are more prevalent in AD patients.¹⁹⁷ In the AD brain, IL-17 is widely present and plays a significant part in the disease development and progression.²⁰⁰ Elevated levels of IL-6 are found in both the brain and plasma of AD patients. In late-stage AD, IL-6 is genetically overexpressed,^{199,201} suggesting its role in disease progression and severity. PD is the second most common progressive neurodegenerative disorder, characterized by motor symptoms, such as tremor, rigidity, postural instability, and bradykinesia, as well as non-motor symptoms, including fatigue, depression, and sleep disturbances. Dysregulation of serotonergic neurotransmission is thought to contribute to both the motor and non-motor manifestations of PD.²⁰² Moreover, the increased concentration of inflammatory cytokines

leads to cognitive impairment. IL-1, a well-known pro-inflammatory cytokine, plays a role in both brain trauma and PD.²⁰³ Elevated levels of IL-6 may accelerate muscle catabolism, contributing to the development of sarcopenia. In addition to heightened weakness and exhaustion, this process has been linked to functional impairments in PD patients.³⁴

5.5.3. Role in neurodevelopmental disorders (ASD, ADHD)

ASD is linked to dysregulation of the IL-6 signaling pathways and the 5-HT system. Imbalances in 5-HT impact the development of the brain and cause ASD-like abnormalities in behavior, such as anxiety, depression-like behavior, and stereotyped behavior. A 1961 study of 23 individuals with autism reported elevated blood 5-HT levels in six participants,²⁰⁴ suggesting a potential link between 5-HT and autism. The first biomarker identified for ASD was hyperserotonemia, or high whole-blood 5-HT, which is seen in more than 25% of children with the disorder.²⁰⁵ A comprehensive literature review indicates that both high and low levels of 5-HT are linked to ASD. However, the relationship is not yet fully understood. Low 5-HT levels are associated with increased aggressive behavior. According to a recent study combining human and animal research, lower 5-HT levels may contribute to aggression in ASD, when social risks are present.²⁰⁶ Imbalanced cytokines during childhood and/or throughout the lifespan may influence brain activity and mediate the behavioral characteristics of ASD. IL-8 shows promise as an ASD biomarker, as it is associated with social abilities in children with ASD and may contribute to the disorder's pathophysiology.²⁰⁷ In addition, elevated serum IL-17A and IL-22 levels are linked to ASD.²⁰⁸ Both high-functioning children with ASD and adults with severe ASD exhibit elevated plasma levels of IL-1 β .²⁰⁹⁻²¹¹ Higher levels of IL-6 have also been detected in the blood plasma of children with ASD and adults with severe autism, while post-mortem analysis of brain tissue from individuals with ASD revealed elevated IL-6 level.²¹² ADHD, a common neurodevelopmental disorder in children, presents with symptoms, such as inattention, hyperactivity, and impulsivity. 5-HT also plays a role in mood regulation. Impaired maternal 5-HT production may increase the likelihood that children will experience symptoms and behaviors associated with ADHD and may have long-term effects on brain development.²¹³ Research suggests that individuals with ADHD may have reduced 5-HT levels in the brain, which can exacerbate symptoms, such as impulsivity, hyperactivity, and difficulty focusing.^{214,215} Low 5-HT levels may also result in frequent mood swings and impaired cognitive abilities. However, ADHD is caused

by a number of additional factors. Given the substantial neurological foundation that has been established, the pathophysiology remains poorly understood. The onset and progression of ADHD are influenced by pro-inflammatory IL cytokines. According to Darwish *et al.*,²¹⁶ serum IL-6 levels were higher in ADHD patients in comparison to healthy controls, suggesting that IL-6 may play a role in the pathogenesis of ADHD.²¹⁶ It has been noted that anti-inflammatory cytokines, particularly IL-2 and IL-4, are less prevalent in individuals with ADHD.

5.6. Impact on neuropsychiatric disorders (depression, anxiety, schizophrenia)

The term neuropsychiatric disorders refer to a group of conditions in which neurological symptoms are closely related to psychiatric conditions. The most common types of neuropsychiatric disorders include depression, anxiety, and schizophrenia. 5-HT and ILs play important roles in various neuropsychiatric disorders, particularly in mood regulation and cognitive functions. Autism, mood disorders, schizophrenia, and depression are among the neuropsychiatric illnesses that can result from deficits in the serotonergic system.²¹⁷ The World Health Organization estimates that 5% of adults worldwide experience depression. Generalized anxiety disorder (GAD) is a widespread neuropsychiatric disorder marked by chronic and pervasive anxiety that is difficult to control, often accompanied by excessive worries about daily, family, social, and professional life. Numerous studies have shown that the serotonergic system plays a role in the pathophysiology of anxiety and depression, with 5-HT and its receptors serving as main therapeutic targets.²¹⁸ The pathophysiological mechanisms of GAD are complex and involve a wide range of neurological, genetic, and environmental factors.²¹⁹ The onset and progression of anxiety and depression are also influenced by the inflammatory cytokine. A case-control study in Bangladesh, which included 50 individuals with GAD and 38 healthy controls, suggested a possible association between peripheral serum levels of IL-17A and IL-23A and the pathophysiology and development of GAD.²²⁰ Schizophrenia is a complex and chronic psychiatric disorder defined by a wide range of symptoms, including hallucinations, delusions, disorganized behavior and speech, negative symptoms, such as emotional blunting and anhedonia, and cognitive deficits. The 5-HT-IL pathway has been implicated in the development and progression of schizophrenia. Schizophrenia may arise from changes in 5-HT concentrations, which can gradually affect the brain's serotonergic systems.²²¹ A significant contributing factor to the early onset of abnormalities in the schizophrenic brain is the imbalance in the ratio of 5-HT_{1A} to 5-HT_{2A} receptors,

which are involved in modulating negative symptoms.²²² The pleiotropic cytokine IL-6 plays important roles in neurogenesis and development, neuroprotection, synaptic transmission and plasticity, and cognitive function. Reale *et al.*²²³ claimed that IL-6 is considered a state marker of schizophrenia.²²³ According to Sasayama *et al.*,²²⁴ elevated IL-6 levels in the CSF of individuals with schizophrenia suggest the presence of inflammatory activity within the CNS.²²⁴ Furthermore, IL-1 β is recognized for its significant role in the etiology and pathophysiology of schizophrenia. Alongside elevated serum levels of IL-2 and IL-6, individuals with schizophrenia have also shown increased serum levels of IL-8.²²³ Thus, disturbances in 5-HT and cytokine homeostasis appear to be major contributing factors to the development of neuropsychiatric illnesses.

6. Therapeutic implications and future directions

6.1. Targeting the 5-HT–IL pathway for therapeutic interventions

Targeting the 5-HT–IL pathway holds promise for treating various neuropsychiatric and neurodegenerative disorders, including ASD, ADHD, anxiety, depression, AD, PD, and schizophrenia. Progressive degeneration and damage of nerve cells are hallmarks of neurodegenerative diseases. Researchers suggest that modulating the 5-HT system could potentially ease symptoms and slow the progression of both AD and PD. In AD, drugs that target the 5-HT pathway can help to improve cognitive impairment. For instance, idalopirdine, a 5-HT₆ receptor antagonist, has been shown to improve memory and learning abilities.²²⁵ Moreover, they provide neuroprotection, regulate neurotransmitter release, improve synaptic function, and reduce inflammation in AD patients.²²⁶ Similarly, the selective 5-HT_{2A} receptor antagonist, loratadine, has shown potential in AD mouse models by reducing inflammation, improving microglial function, facilitating clearance of neurotoxic substances, decreasing A β deposition, and ultimately mitigating pathological progression.²²⁷ In AD patients with severe psychosis, 5-HT_{2A} receptor antagonists, such as pimavanserin and brexpiprazole have also shown clinical efficacy.²²⁵ The 5-HT_{1A} and 5-HT_{1B} receptors have also been implicated in glial cell formation linked to PD. In chronic neuroinflammatory diseases, IL-17 and its receptors play a crucial role in regulating neuroinflammation and are therefore considered as major therapeutic targets.²²⁸

6.2. Present pharmacological approaches

SSRIs are the first-line treatment for various neuropsychiatric and neurodegenerative conditions. Their safety, effectiveness, and tolerability make them popular

first-line pharmacotherapy for depression and many other psychiatric disorders. SSRIs function by blocking the 5-HT reuptake in presynaptic neurons, which subsequently increases serotonergic activity within the synaptic cleft (Figure 2). The most common SSRIs include citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. According to the monoamine hypothesis, depression is attributed to a functional deficit of the monoamine neurotransmitter 5-HT in the brain. Because SSRIs primarily target 5-HT, they are referred to as selective. SSRIs work by increasing 5-HT availability in the brain and preventing its reuptake. The SERT, an integral membrane protein produced in the raphe nuclei of the brain, is the main target of SSRIs. SERT rapidly removes 5-HT from the synapse, stopping its signal in serotonergic neurons.²²⁹ Overactive SERTs lead to excessive 5-HT reuptake from the synapse, resulting in diminished serotonergic signaling. Inhibition of SERT at the presynaptic axon terminal by SSRIs prevents 5-HT from being reuptake into the presynaptic neuron. This leads to an increased concentration of 5-HT remaining in the synaptic cleft, allowing it to bind to and stimulate postsynaptic receptors for a longer duration.²³⁰ SSRIs have demonstrated efficacy in treating mood disorders and are considered the first-line treatment for MDD. A meta-analysis of 57 trials found that SSRIs are effective for anxiety disorders, with higher dosages associated with improved symptom relief.²³¹ SSRIs are superior to other antidepressants due to their highly specific mechanism of action. They exert minimal influence on the dopamine and norepinephrine neurotransmitters. Furthermore, SSRIs exhibit significantly lower affinity for adrenergic, cholinergic, and histaminergic receptors compared to TCAs and MAOIs. This receptor selectivity contributes to their lower side effect profile. Neuroinflammation is one of the primary causes of the pathophysiology of neurodegenerative diseases. By suppressing the cyclooxygenase enzyme, non-steroidal anti-inflammatory drugs (NSAIDs) decrease inflammation through reduced prostaglandin production. It has been demonstrated that long-term NSAID use lowers the risk of AD, likely due to its impact on neuroinflammation.^{232,233} In numerous animal models, NSAIDs have demonstrated promise in lowering the risk of neurodegenerative diseases. However, these results have mostly not been confirmed in human clinical studies.²³⁴

6.3. Potential novel therapies (cytokine inhibitors, combination therapies)

Cytokine inhibitors represent potential new treatments for neurodegenerative disorders. The use of monoclonal antibodies (mAbs) or small-molecule inhibitors against IL-1 β and IL-6 in targeted therapy provides a more accurate means of modulating neuroinflammation. In

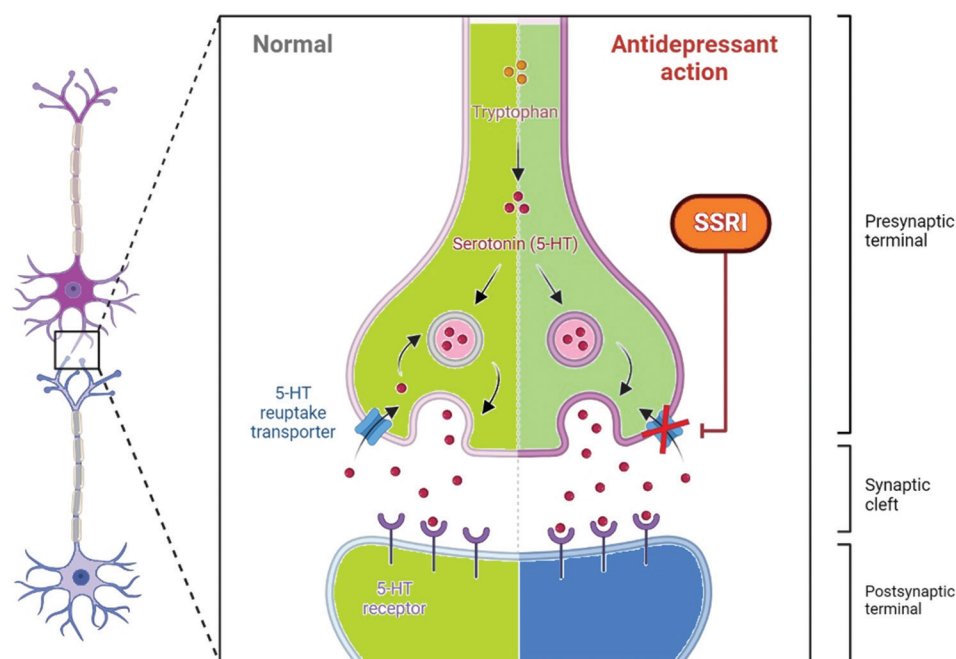


Figure 2. Mechanisms of 5-HT receptor signaling and the modulatory effects of SSRIs in neurological disorders. The illustration demonstrates synaptic 5-HT transmission under normal physiological conditions (left panel) and the antidepressant effect following SSRI treatment (right panel). Tryptophan is metabolized into 5-HT within the presynaptic terminal, where it is sequestered within synaptic vesicles and subsequently released into the synaptic cleft. In the absence of pharmacological intervention, 5-HT is reabsorbed into the presynaptic neuron through SERT. SSRIs selectively inhibit these transporters, blocking 5-HT reuptake and thereby enhancing serotonergic pathway through increased activation of postsynaptic receptors. This mechanism underlies their therapeutic efficacies in mood and anxiety disorders. Image created by the authors.

Abbreviations: 5-HT: Serotonin; SERT: Serotonin transporter; SSRI: Selective serotonin receptor inhibitor.

patients with schizophrenia, the anti-IL-6 receptor mAb Tocilizumab, which was developed and approved for rheumatoid arthritis, improved cognitive function but did not significantly alter psychological scores.²³⁵ The anti-IL-6 mAbs siltuximab and sirukumab have been shown to effectively reduce the severity of depressive symptoms in patients with rheumatoid arthritis and multicentric Castleman disease.²³⁶ Studies indicate that IL-6 drives induced pluripotent stem cell-derived neural stem cell expansion within a short timeframe and governs neuronal outgrowth, primarily through JAK-STAT signaling.²³⁷ Furthermore, IL-1 α has been proposed as a new biomarker for the early identification of AD pathologies.²³⁸ Similarly, IL-3, a multifunctional cytokine, has shown therapeutic effectiveness in AD. Combination therapy can be useful in neurological and psychiatric disorders where multiple pathological processes are involved. AD has a wide range of underlying causes, which may change as the disease progresses. These include the accumulation of misfolded proteins into hazardous plaques and tangles, oxidative stress, vascular issues, mitochondrial dysfunction, inflammation, and epigenetic alterations. An effective therapeutic approach may involve combining multiple drugs that target different pathways. In 2014,

the co-administration of donepezil and memantine was approved for the management of moderate-to-severe AD.²³⁹ Memantine, an NMDA receptor antagonist, and donepezil, a cholinesterase inhibitor, showed significant improvement in cognition, daily functioning, and behavior in AD patients. Furthermore, based on the PD Questionnaire-39 and the Unified PD Rating Scale, a recent randomized controlled trial in Vietnamese patients with PD showed that combination treatment with levodopa and pramipexole improved clinical symptoms and quality of life.²⁴⁰ Recently, the Food and Drug Administration approved the use of trospium chloride, a muscarinic antagonist, and xanomeline, an M1/M4 muscarinic agonist, for the treatment of schizophrenia.²⁴¹ Therefore, combination therapies that address multiple mechanisms represent a promising strategy in the management of brain disorders. Moreover, exercise appears to reduce depression by increasing 5-HT release, which has antidepressant effects. A study examining the exercise habits of over 600,000 individuals found that 5-HT boosts from exercise may help lower the risk of depression.²³⁴ Similarly, a recent study indicates that anti-inflammatory diets, such as the Brain Anti-Inflammatory Nutrition diet, may help manage mental and neurological diseases by reducing

inflammation, enhancing gut health, and promoting neuroprotection.²⁴² C-reactive protein (CRP) and IL-6 are inflammatory markers that are reduced by diets rich in whole foods, such as fruits, vegetables, whole grains, and sources of lean meat and poultry. In contrast, high-fat and processed diets are associated with increased inflammation and a higher risk of neurological disorders, while whole-food diets are associated with lower CRP and IL-6 levels.²⁴³ Therefore, lifestyle modifications play a key role to overcome depression and other mental disorders.

7. Challenges and opportunities in translational research

Despite their efficacy in treating mood disorders, SSRIs present several challenges. Excessive 5-HT activity in the nervous system causes 5-HT syndrome (also known as 5-HT toxicity), a life-threatening condition characterized by shivering, confusion, muscle twitching, agitation, and diarrhea. The treatment includes a combination of serotonergic medications. However, 5-HT syndrome can also result from SSRI monotherapy.^{244,245} Higher levels of 5-HT uptake inhibition in antidepressants may result in more abnormal bleeding than lower levels of inhibition.²⁴⁶ One study found that individuals taking SSRIs had a higher risk ratio (RR) of 3.0 for GI bleeding (RR = 3.0), while those on antidepressants without SSRI properties had a lower RR of 0.8.²⁴⁷ The SSRIs have cardiovascular side effects, with studies identifying that they can cause QTc prolongation. According to a meta-analysis of 16 prospective controlled trials, SSRIs prolonged the QTc interval by 6 ms compared to placebo.²⁴⁸ Adverse effects of SSRIs include weight gain, hyponatremia, GI bleeding, dry mouth, and sexual dysfunction.²⁴⁹ A notable characteristic of SSRIs in depression treatment is their delayed therapeutic onset, which can take up to 6 weeks for individuals to experience the clinical benefits of SSRIs. According to a systematic review, SSRI use for depression leads to initial symptomatic improvement within the 1st week, which then persists for at least 6 weeks with a gradually diminishing rate of improvement.²⁵⁰ Even though NSAIDs have been investigated as neuroprotective medications, their off-target effects and poor BBB penetration make this approach less successful.^{251,252} Moreover, combination therapy has proven effective in treating symptoms of many complicated diseases. However, finding clinically effective disease-modifying medicines for neurodegenerative and other brain diseases remains a challenge, as there is still no standardized framework for developing such therapies. A logical approach involves several key steps. First, individual components and their combinations require evaluation in animal models to assess efficacy, safety, potential synergies, drug-drug interactions, or added

toxicity. Phase I trials in humans then focus on safety, tolerability, and interactions. Next, Phase II trials explore dosing by examining dose-response relationships and target engagement for each agent and the combination. Synergistic effects may allow the use of lower individual doses, thereby reducing toxicity. If Phase II results are promising, confirmatory Phase III trials follow to establish clinical benefit. Therefore, the challenges of combination therapy lie in the complexity of drug development. Furthermore, the lifestyle changes require high adherence and long-term commitment to achieve a positive impact on mental health. Given the significant and continuing burden of neurological and psychiatric disorders, the development of efficacious, disease-modifying medicines continues to be a crucial issue for this discipline. By connecting basic research with clinical practice, translational research is critical in advancing the understanding of these conditions. In addition, it provides a crucial platform for researchers to share their discoveries and developments in this field. Pre-clinical models are the key to understanding brain disorders, such as AD and autism, as they reveal their underlying mechanisms. This helps develop personalized treatments and support the advancement of brain imaging for clinical use. Ultimately, pre-clinical research is crucial for dissecting these illnesses, testing therapies, and enabling tailored, innovative medicine.²⁵³ New translational research involves a variety of high-throughput patient analytics, clinical data integration, personalized diagnostics, and treatment through multiomics-based target discovery.²⁵⁴

8. Conclusion

The 5-HT-IL signaling pathway is critically involved in the pathophysiology of neurological and psychiatric disorders. Therefore, advancing the development of personalized treatment strategies for disorders associated with the 5-HT-IL axis will require more rigorous translational research that integrates technological innovations and interdisciplinary collaboration.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Abdullah Al Noman

Visualization: Zubaier Ahmed

Writing – original draft: Imanul Kabir Lihu, Ritesh Sharma, Md. Noor Alam

Writing – review & editing: Shubham Singh, Himanshu Sharma

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

- Kanova M, Kohout P. Serotonin-its synthesis and roles in the healthy and the critically ill. *Int J Mol Sci*. 2021;22(9):4837. doi: 10.3390/IJMS22094837
- Costedio MM, Hyman N, Mawe GM. Serotonin and its role in colonic function and in gastrointestinal disorders. *Dis Colon Rectum*. 2007;50(3):376-388. doi: 10.1007/s10350-006-0763-3
- De Pontes ALB, Engelberth RCGJ, Da Nascimento ES, et al. Serotonin and circadian rhythms. *Psychol Neurosci*. 2010;3(2):217-228. doi: 10.3922/J.PSNS.2010.2.011
- Kmieć Z. Cooperation of liver cells in health and disease. *Adv Anat Embryol Cell Biol*. 2001;161:III-XIII, 1-151. doi: 10.1007/978-3-642-56553-3
- Choy E, Rose-John S. Interleukin-6 as a multifunctional regulator: Inflammation, immune response, and fibrosis. *J Scleroderma Relat Disord*. 2017;2:S1-S5. doi: 10.5301/JSRD.5000265
- Zhou M, Li YJ, Tang YC, et al. Apoptotic bodies for advanced drug delivery and therapy. *J Control Release*. 2022;351:394-406. doi: 10.1016/J.JCONREL.2022.09.045
- Pons-Espinal M, Blasco-Agell L, Fernandez-Carasa I, et al. Blocking IL-6 signaling prevents astrocyte-induced neurodegeneration in an iPSC-based model of Parkinson's disease. *JCI Insight*. 2024;9(3):e1633599. doi: 10.1172/jci.insight.163359
- Diaz K, Kohut ML, Russell DW, Stegemöller EL. Peripheral inflammatory cytokines and motor symptoms in persons with Parkinson's disease. *Brain Behav Immun Health*. 2022;21:100442. doi: 10.1016/j.bbih.2022.100442
- Eide S, Misztal M, Feng ZP. Interleukin-6 as a marker of Huntington's disease progression: Systematic review and meta-analysis. *Brain Behav Immun Health*. 2023;30:100635. doi: 10.1016/j.bbih.2023.100635
- Bensadoun JC, Pereira De Almeida L, Dréano M, Aebischer P, Déglon N. Neuroprotective effect of interleukin-6 and IL6/IL6R chimera in the quinolinic acid rat model of Huntington's syndrome. *Eur J Neurosci*. 2001;14(11):1753-1761. doi: 10.1046/j.0953-816X.2001.01802.x
- Wertz MH, Pineda SS, Lee H, Kulicke R, Kellis M, Heiman M. Interleukin-6 deficiency exacerbates Huntington's disease model phenotypes. *Mol Neurodegener*. 2020;15(1):1-8. doi: 10.1186/s13024-020-00379-3
- Dorszewska J, Prendecki M, Oczkowska A, Rozycka A, Lianeri M, Kozubski W. Polymorphism of the *COMT*, *MAO*, *DAT*, *NET* and *5-HTT* Genes, and biogenic amines in Parkinson's disease. *Curr Genomics*. 2014;14(8):518-533. doi: 10.2174/1389202914666131210210241
- Gulisano W, Maugeri D, Baltrons MA, et al. Role of amyloid- β and tau proteins in Alzheimer's disease: Confuting the amyloid cascade. *J Alzheimers Dis*. 2018;64(Suppl 1):S611. doi: 10.3233/JAD-179935
- Wu Q, He Q, Zhang X, Chen S, Xue X. Systemic modulators: Potential mechanism for the 5-HT system to mediate exercise amelioration in Alzheimer's disease. *Aging Dis*. 2024;16:2770-2802. doi: 10.14336/AD.2024.0834
- Quintanilla RA, Orellana DI, González-Billault C, Maccioni RB. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. *Exp Cell Res*. 2004;295(1):245-257. doi: 10.1016/j.yexcr.2004.01.002
- Lin W, Song H, Shen J, et al. Functional role of skeletal muscle-derived interleukin-6 and its effects on lipid metabolism. *Front Physiol*. 2023;14:1110926. doi: 10.3389/fphys.2023.1110926
- Spooren A, Kolmus K, Laureys G, et al. Interleukin-6, a mental cytokine. *Brain Res Rev*. 2011;67(1-2):157-183. doi: 10.1016/j.brainresrev.2011.01.002
- Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's Dement (NY)*. 2018;4:575-590. doi: 10.1016/j.trci.2018.06.014
- Kaur D, Sharma V, Deshmukh R. Activation of microglia and astrocytes: A roadway to neuroinflammation and Alzheimer's disease. *Inflammopharmacology*. 2019;27(4):663-677. doi: 10.1007/s10787-019-00580-x

20. Shan C, Zhang C, Zhang C. The role of IL-6 in neurodegenerative disorders. *Neurochem Res.* 2024;49(4):834-846.
doi: 10.1007/S11064-023-04085-6
21. Yang J, Ran M, Li H, *et al.* New insight into neurological degeneration: Inflammatory cytokines and blood-brain barrier. *Front Mol Neurosci.* 2022;15:1013933.
doi: 10.3389/fnmol.2022.1013933
22. Huang Z, Wong LW, Su Y, *et al.* Blood-brain barrier integrity in the pathogenesis of Alzheimer's disease. *Front Neuroendocrinol.* 2020;59:100857.
doi: 10.1016/j.yfrne.2020.100857
23. Takeshita Y, Fujikawa S, Serizawa K, *et al.* New BBB model reveals that IL-6 blockade suppressed the BBB disorder, preventing onset of NMOSD. *Neurol Neuroimmunol Neuroinflamm.* 2021;8(6):e1076.
doi: 10.1212/NXI.0000000000001076
24. März P, Cheng JG, Gadiant RA, *et al.* Sympathetic neurons can produce and respond to interleukin 6. *Proc Natl Acad Sci U S A.* 1998;95(6):3251-3256.
doi: 10.1073/pnas.95.6.3251
25. Omedul I, Xiandi G, Stefan RJ, Heese K. Interleukin-6 and neural stem cells: More than gliogenesis. *Mol Biol Cell.* 2009;20:188-199.
doi: 10.1091/mbc.e08-05-0463
26. Mousa A, Bakhiet M. Role of cytokine signaling during nervous system development. *Int J Mol Sci.* 2013;14(7):13931-13957.
doi: 10.3390/ijms140713931
27. Kummer KK, Zeidler M, Kalpachidou T, Kress M. Role of IL-6 in the regulation of neuronal development, survival and function. *Cytokine.* 2021;144:155582.
doi: 10.1016/j.cyto.2021.155582
28. Irina K, Rodrigo PA, Thais VWCBM. *Advances in Cellular and Cell-Free Therapy Medicinal Products for Huntington Disease Treatment.* Vol. 11. London: IntechOpen; 2016. p. 13.
29. Palpagama TH, Waldvogel HJ, Faull RLM, Kwakowsky A. The role of microglia and astrocytes in Huntington's disease. *Front Mol Neurosci.* 2019;12:258.
doi: 10.3389/fnmol.2019.00258
30. Jia Q, Li S, Li XJ, Yin P. Neuroinflammation in Huntington's disease: From animal models to clinical therapeutics. *Front Immunol.* 2022;13:1088124.
doi: 10.3389/fimmu.2022.1088124
31. Conroy SM, Nguyen V, Quina LA, *et al.* Interleukin-6 produces neuronal loss in developing cerebellar granule neuron cultures. *J Neuroimmunol.* 2004;155(1-2):43-54.
doi: 10.1016/j.jneuroim.2004.06.014
32. Ma J, Gao J, Niu M, Zhang X, Wang J, Xie A. P2X4R overexpression upregulates interleukin-6 and exacerbates 6-OHDA-induced dopaminergic degeneration in a rat model of PD. *Front Aging Neurosci.* 2020;12:580068.
doi: 10.3389/fnagi.2020.580068
33. Dufek M, Rektorova I, Thon V, Lokaj J, Rektor I. Interleukin-6 may contribute to mortality in Parkinson's disease patients: A 4-year prospective study. *Parkinsons Dis.* 2015;2015:898192.
doi: 10.1155/2015/898192
34. Scalzo P, Kümmer A, Cardoso F, Teixeira AL. Serum levels of interleukin-6 are elevated in patients with Parkinson's disease and correlate with physical performance. *Neurosci Lett.* 2010;468(1):56-58.
doi: 10.1016/j.neulet.2009.10.062
35. Kozina E, Byrne M, Smeyne RJ. Mutant LRRK2 in lymphocytes regulates neurodegeneration via IL-6 in an inflammatory model of Parkinson's disease. *NPJ Parkinsons Dis.* 2022;8(1):24.
doi: 10.1038/s41531-022-00289-9
36. Sterling JK, Kam TI, Guttha S, *et al.* Interleukin-6 triggers toxic neuronal iron sequestration in response to pathological α -synuclein. *Cell Rep.* 2022;38(7):110358.
doi: 10.1016/j.celrep.2022.110358
37. Müller T, Blum-Degen D, Przuntek H, Kuhn W. Interleukin-6 levels in cerebrospinal fluid inversely correlate to severity of Parkinson's disease. *Acta Neurol Scand.* 1998;98(2):142-144.
doi: 10.1111/j.1600-0404.1998.tb01736.x
38. Qin XY, Zhang SP, Cao C, Loh YP, Cheng Y. Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: A systematic review and meta-analysis. *JAMA Neurol.* 2016;73(11):1316-1324.
doi: 10.1001/jamaneurol.2016.2742
39. Karpenko MN, Vasilishina AA, Gromova EA, Muruzheva ZM, Bernadotte A. Interleukin-1 β interleukin-1 receptor antagonist, interleukin-6, interleukin-10, and tumor necrosis factor- α levels in CSF and serum in relation to the clinical diversity of Parkinson's disease. *Cell Immunol.* 2018;327:77-82.
doi: 10.1016/j.cellimm.2018.02.011
40. Dzamk N. Cytokine activity in Parkinson's disease. *Neuronal Signal.* 2023;7(4):NS20220063.
doi: 10.1042/NS20220063
41. Shad KF, Shad KF. Serotonin - a chemical messenger between all types of living cells. In: *Serotonin a Chemical Messenger between All Types of Living Cells.* London: IntechOpen; 2017.
doi: 10.5772/65233

42. Levraut M, Bourg V, Capet N, *et al.* Cerebrospinal fluid IL-17A could predict acute disease severity in non-NMDA-receptor autoimmune encephalitis. *Front Immunol.* 2021;12:673021.
doi: 10.3389/fimmu.2021.673021
43. Zeng C, Chen L, Chen B, *et al.* Th17 cells were recruited and accumulated in the cerebrospinal fluid and correlated with the poor prognosis of anti-NMDAR encephalitis. *Acta Biochim Biophys Sin (Shanghai).* 2018;50(12):1266-1273.
doi: 10.1093/abbs/gmy137
44. Dorszewska J, Florczak-Wypianska J, Kowalska M, *et al.* Serotonin in neurological diseases. In: *Serotonin - a Chemical Messenger between All Types of Living Cells.* London: IntechOpen; 2017.
doi: 10.5772/INTECHOPEN.69035
45. Oades RD. The role of serotonin in attention-deficit hyperactivity disorder (ADHD). *Handb Behav Neurosci.* 2010;21:565-584.
doi: 10.1016/S1569-7339(10)70101-6
46. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. *Annu Rev Med.* 2009;60:355-366.
doi: 10.1146/annurev.med.60.042307.110802
47. Wu H, Denna TH, Storkersen JN, Gerriets VA. Beyond a neurotransmitter: The role of serotonin in inflammation and immunity. *Pharmacol Res.* 2019;140:100-114.
doi: 10.1016/j.phrs.2018.06.015
48. Reisine T. Pertussis toxin in the analysis of receptor mechanisms. *Biochem Pharmacol.* 1990;39(10):1499-1504.
doi: 10.1016/0006-2952(90)90513-K
49. Gierschik P. ADP-ribosylation of signal-transducing guanine nucleotide-binding proteins by pertussis toxin. *Curr Top Microbiol Immunol.* 1992;175:69-96.
doi: 10.1007/978-3-642-76966-5_4
50. Branchek T, Adham N, Macchi M, Kao HT, Hartig PR. [³H]-DOB(4-bromo-2,5-dimethoxyphenylisopropylamine) and [³H] ketanserin label two affinity states of the cloned human 5-hydroxytryptamine₂ receptor. *Mol Pharmacol.* 1990;38(5):604-609.
51. Nichols DE. Hallucinogens. *Pharmacol Ther.* 2004;101(2):131-181.
doi: 10.1016/j.pharmthera.2003.11.002
52. Nebigil CG, Choi DS, Dierich A, *et al.* Serotonin 2B receptor is required for heart development. *Proc Natl Acad Sci U S A.* 2000;97(17):9508-9513.
doi: 10.1073/pnas.97.17.9508
53. Choi DS, Ward SJ, Messaddeq N, *et al.* 5-HT_{2B} receptor-mediated serotonin morphogenetic functions in mouse cranial neural crest and myocardiac cells. *Development.* 1997;124(9):1745-1755.
54. Nebigil CG, Etienne N, Schaerlinger B, Hickel P, Launay JM, Maroteaux L. Developmentally regulated serotonin 5-HT_{2B} receptors. *Int J Dev Neurosci.* 2001;19(4):365-372.
doi: 10.1016/s0736-5748(01)00022-3
55. Clemett DA, Punhani T, Duxon MS, Blackburn TP, Fone KCF. Immunohistochemical localisation of the 5-HT_{2C} receptor protein in the rat CNS. *Neuropharmacology.* 2000;39(1):123-132.
doi: 10.1016/S0028-3908(99)00086-6
56. Pasqualetti M, Ori M, Castagna M, Marazziti D, Cassano GB, Nardi I. Distribution and cellular localization of the serotonin type 2C receptor messenger RNA in human brain. *Neuroscience.* 1999;92(2):601-611.
doi: 10.1016/S0306-4522(99)00011-1
57. Gershon MD. Nerves, reflexes, and the enteric nervous system: Pathogenesis of the irritable bowel syndrome. *J Clin Gastroenterol.* 2005;39(5 Suppl 3):S184-S193.
doi: 10.1097/01.mcg.0000156403.37240.30
58. Irving HR, Tan YY, Tochon-Danguy N, *et al.* Comparison of 5-HT₄ and 5-HT₇ receptor expression and function in the circular muscle of the human colon. *Life Sci.* 2007;80(13):1198-1205.
doi: 10.1016/j.lfs.2006.12.025
59. Svenningsson P, Tzavara ET, Qi H, *et al.* Biochemical and behavioral evidence for antidepressant-like effects of 5-HT₆ receptor stimulation. *J Neurosci.* 2007;27(15):4201-4209.
doi: 10.1523/JNEUROSCI.3110-06.2007
60. Wesolowska A, Nikiforuk A. Effects of the brain-penetrant and selective 5-HT₆ receptor antagonist SB-399885 in animal models of anxiety and depression. *Neuropharmacology.* 2007;52(5):1274-1283.
doi: 10.1016/j.neuropharm.2007.01.007
61. Guscott M, Bristow LJ, Hadingham K, *et al.* Genetic knockout and pharmacological blockade studies of the 5-HT₇ receptor suggest therapeutic potential in depression. *Neuropharmacology.* 2005;48(4):492-502.
doi: 10.1016/j.neuropharm.2004.11.015
62. Somers JM, Goldner EM, Waraich P, Hsu L. Prevalence and incidence studies of anxiety disorders: A systematic review of the literature. *Can J Psychiatry.* 2006;51(2):100-113.
doi: 10.1177/070674370605100206
63. Cleare A, Pariante CM, Young AH, *et al.* Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British association for psychopharmacology guidelines. *J Psychopharmacol.* 2015;29:459-525.
doi: 10.1177/0269881115581093
64. Morrisette DA, Stahl SM. Modulating the serotonin system

- in the treatment of major depressive disorder. *CNS Spectr.* 2014;19:57-67; quiz 54-7, 68.
doi: 10.1017/S1092852914000613
65. Mulinari S. Monoamine theories of depression: Historical impact on biomedical research. *J Hist Neurosci.* 2012;21(4):366-392.
doi: 10.1080/0964704X.2011.623917
 66. Melander H, Salmonson T, Abadie E, Van Zwieten-Boot B. A regulatory apologia--a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *Eur Neuropsychopharmacol.* 2008;18(9):623-627.
doi: 10.1016/j.euroneuro.2008.06.003
 67. Timothy Walsh B, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: Variable, substantial, and growing. *JAMA.* 2002;287(14):1840-1847.
doi: 10.1001/jama.287.14.1840
 68. Hindmarch I. Beyond the monoamine hypothesis: Mechanisms, molecules and methods. *Eur Psychiatry.* 2002;17(Suppl 3):294-299.
doi: 10.1016/S0924-9338(02)00653-3
 69. Owens MJ. Selectivity of antidepressants: From the monoamine hypothesis of depression to the SSRI revolution and beyond. *J Clin Psychiatry.* 2004;65(Suppl 4):5-10.
 70. Young SN. Acute tryptophan depletion in humans: A review of theoretical, practical and ethical aspects. *J Psychiatry Neurosci.* 2013;38(5):294-305.
doi: 10.1503/jpn.120209
 71. MacE JL, Porter RJ, Dalrymple-Alford JC, Wesnes KA, Anderson TJ. The effects of acute tryptophan depletion on neuropsychological function, mood and movement in the healthy elderly. *J Psychopharmacol.* 2011;25(10):1337-1343.
doi: 10.1177/02698811110389094
 72. Ellenbogen MA, Young SN, Dean P, Palmour RM, Benkelfat C. Mood response to acute tryptophan depletion in healthy volunteers: Sex differences and temporal stability. *Neuropsychopharmacology.* 1996;15(5):465-474.
doi: 10.1016/S0893-133X(96)00056-5
 73. Feder A, Skipper J, Blair JR, *et al.* Tryptophan depletion and emotional processing in healthy volunteers at high risk for depression. *Biol Psychiatry.* 2011;69(8):804-807.
doi: 10.1016/j.biopsych.2010.12.033
 74. Van Der Veen FM, Evers EAT, Deutz NEP, Schmitt JAJ. Effects of acute tryptophan depletion on mood and facial emotion perception related brain activation and performance in healthy women with and without a family history of depression. *Neuropsychopharmacology.* 2007;32(1):216-224.
doi: 10.1038/sj.npp.1301212
 75. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet.* 1997;349(9056):915-919.
doi: 10.1016/S0140-6736(96)07044-4
 76. Moreno FA, Gelenberg AJ, Heninger GR, *et al.* Tryptophan depletion and depressive vulnerability. *Biol Psychiatry.* 1999;46(4):498-505.
doi: 10.1016/S0006-3223(99)00095-5
 77. Booij L, Van Der Does AJW, Haffmans PMJ, Riedel WJ, Fekkes D, Blum MJB. The effects of high-dose and low-dose tryptophan depletion on mood and cognitive functions of remitted depressed patients. *J Psychopharmacol.* 2005;19(3):267-275.
doi: 10.1177/0269881105051538
 78. Booij L, Van Der Does AJW, Haffmans PMJ, Riedel WJ. Acute tryptophan depletion in depressed patients treated with a selective serotonin-noradrenalin reuptake inhibitor: Augmentation of antidepressant response? *J Affect Disord.* 2005;86(2-3):305-311.
doi: 10.1016/j.jad.2005.01.012
 79. Haynes PL, McQuaid JR, Kelsoe J, Rapaport M, Gillin JC. Affective state and EEG sleep profile in response to rapid tryptophan depletion in recently recovered nonmedicated depressed individuals. *J Affect Disord.* 2004;83(2-3):253-262.
doi: 10.1016/j.jad.2004.05.010
 80. Meneses A. 5-HT system and cognition. *Neurosci Biobehav Rev.* 1999;23(8):1111-1125.
doi: 10.1016/S0149-7634(99)00067-6
 81. Buhot MC, Martin S, Segu L. Role of serotonin in memory impairment. *Ann Med.* 2000;32(3):210-221.
doi: 10.3109/07853890008998828
 82. Ögren SO, Eriksson TM, Elvander-Tottie E, *et al.* The role of 5-HT(1A) receptors in learning and memory. *Behav Brain Res.* 2008;195(1):54-77.
doi: 10.1016/j.bbr.2008.02.023
 83. Sharma T, Mockler D. The cognitive efficacy of atypical antipsychotics in schizophrenia. *J Clin Psychopharmacol.* 1998;18(2 Suppl 1):12S-19S.
doi: 10.1097/00004714-199804001-00004
 84. Bockaert J, Claeysen S, Compan V, Dumuis A. 5-HT(4) receptors, a place in the sun: Act two. *Curr Opin Pharmacol.* 2011;11(1):87-93.
doi: 10.1016/j.coph.2011.01.012
 85. Wolf H. Preclinical and clinical pharmacology of the 5-HT₃ receptor antagonists. *Scand J Rheumatol.* 2000;113:37-45.
doi: 10.1080/030097400446625
 86. Cowen P, Sherwood AC. The role of serotonin in cognitive function: Evidence from recent studies and implications

- for understanding depression. *J Psychopharmacol.* 2013;27(7):575-583.
doi: 10.1177/0269881113482531
87. Blundel JE. Serotonin and appetite. *Neuropharmacology.* 1984;23(12B):1537-1551.
doi: 10.1016/0028-3908(84)90098-4
 88. Lesch KP, Beckmann H. The serotonin hypothesis of depression. *Fortschr Neurol Psychiatr.* 1990;58(11):427-438.
doi: 10.1055/s-2007-1001206
 89. Robins E, Murphy GE, Wilkinson RH Jr., Gassner S, Kayes J. Some clinical considerations in the prevention of suicide based on a study of 134 successful suicides. *Am J Public Nations Health.* 1959;49(7):888-899.
doi: 10.2105/ajph.49.7.888
 90. Barraclough B, Bunch J, Nelson B, Sainsbury P. A hundred cases of suicide: Clinical aspects. *Br J Psychiatry.* 1974;125(10):355-373.
doi: 10.1192/bjp.125.4.355
 91. Åsberg M, Bertilsson L, Mårtensson B, Scalia-Tomba GP, Thorén P, Träskman-Bendz L. CSF monoamine metabolites in melancholia. *Acta Psychiatr Scand.* 1984;69(3):201-219.
doi: 10.1111/j.1600-0447.1984.tb02488.x
 92. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet.* 1976;2(8000):1403
doi: 10.1016/s0140-6736(76)91936-x
 93. DeKosky ST, Scheff SW, Markesbery WR. Laminar organization of cholinergic circuits in human frontal cortex in Alzheimer's disease and aging. *Neurology.* 1985;35(10):1425-1431.
doi: 10.1212/WNL.35.10.1425
 94. Bergmann K, Tomlinson BE, Blessed G, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Br Med J.* 1978;2(6150):1457-1459.
doi: 10.1136/bmj.2.6150.1457
 95. Reinikainen KJ, Soininen H, Riekkinen PJ. Neurotransmitter changes in Alzheimer's disease: Implications to diagnostics and therapy. *J Neurosci Res.* 1990;27(4):576-586.
doi: 10.1002/jnr.490270419
 96. Curcio CA, Kemper T. Nucleus raphe dorsalis in dementia of the Alzheimer type: Neurofibrillary changes and neuronal packing density. *J Neuropathol Exp Neurol.* 1984;43(4):359-368.
doi: 10.1097/00005072-198407000-00001
 97. Cheng AVT, Ferrier IN, Morris CM, *et al.* Cortical serotonin-S2 receptor binding in Lewy body dementia, Alzheimer's and Parkinson's diseases. *J Neurol Sci.* 1991;106(1):50-55.
doi: 10.1016/0022-510X(91)90193-B
 98. Quirion R, Richard J, Dam TV. Evidence for the existence of serotonin type-2 receptors on cholinergic terminals in rat cortex. *Brain Res.* 1985;333(2):345-349.
doi: 10.1016/0006-8993(85)91590-2
 99. Bowen DM, Allen SJ, Benton JS, *et al.* Biochemical assessment of serotonergic and cholinergic dysfunction and cerebral atrophy in Alzheimer's disease. *J Neurochem.* 1983;41(1):266-272.
doi: 10.1111/j.1471-4159.1983.tb11838.x
 100. Nordberg A. Clinical studies in Alzheimer patients with positron emission tomography. *Behav Brain Res.* 1993;57(2):215-224.
doi: 10.1016/0166-4328(93)90138-G
 101. Michelsen KA, Prickaerts J, Steinbusch HWM. The dorsal raphe nucleus and serotonin: implications for neuroplasticity linked to major depression and Alzheimer's disease. *Prog Brain Res.* 2008;172:233-264.
doi: 10.1016/S0079-6123(08)00912-6
 102. Santulli C. Beyond buttons: repurposing of casein-based materials in education and industry—A review. *Academia Materials Sci.* 2024;1(3):1-13.
doi: 10.20935/ACADMATSCI7286
 103. Paudel K, Gautam K, Bhandari P, *et al.* Suicidal ideation, plan, and attempt among men who have sex with men in Nepal: Findings from a cross-sectional study. *PLOS Glob Public Health.* 2023;3(11):e0002348.
doi: 10.1371/journal.pgph.0002348
 104. Gottfries CG. Clinical and neurochemical aspects of diseases with cognitive impairment. *Rev Neurosci.* 1992;3(3):191-206.
doi: 10.1515/REVNEURO.1992.3.3.191
 105. Chen CPLH, Alder JT, Bowen DM, *et al.* Presynaptic serotonergic markers in community-acquired cases of Alzheimer's disease: Correlations with depression and neuroleptic medication. *J Neurochem.* 1996;66(4):1592-1598.
doi: 10.1046/j.1471-4159.1996.66041592.x
 106. Crow TJ, Cross AJ, Cooper SJ, *et al.* Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicides. *Neuropharmacology.* 1984;23(12 B):1561-1569.
doi: 10.1016/0028-3908(84)90100-X
 107. Palmer AM, Stratmann GC, Procter AW, Bowen DM. Possible neurotransmitter basis of behavioral changes in Alzheimer's disease. *Ann Neurol.* 1988;23(6):616-620.
doi: 10.1002/ana.410230616
 108. Zubenko GS, Moossy J, Martinez AJ, *et al.* Neuropathologic and neurochemical correlates of psychosis in primary dementia. *Arch Neurol.* 1991;48(6):619-624.

- doi: 10.1001/archneur.1991.00530180075020
109. Schneider LS, Severson JA, Chui HC, Pollock VE, Bruce Sloane R, Fredrickson ER. Platelet tritiated imipramine binding and MAO activity in Alzheimer's disease patients with agitation and delusions. *Psychiatry Res.* 1988;25(3):311-322.
doi: 10.1016/0165-1781(88)90101-1
110. Durum SK. Interleukins: An overview. In: *Lipid Mediators in the Immunology of Shock*. Berlin: Springer; 1987. p. 311-319.
doi: 10.1007/978-1-4613-0919-2_34
111. Trotta PP. Cytokines: An overview. *Am J Reprod Immunol.* 1991;25(3):137-141.
doi: 10.1111/J.1600-0897.1991.TB01082.X
112. *Immunology CDS in, 2013 Undefined. Overview of the Interleukin-1 Family of Ligands and Receptors*. Elsevier. Available from: <https://www.sciencedirect.com/science/article/pii/S1044532313000821> [Last accessed on 2025 Mar 31].
113. Taga T. *Immunology TKA Review of, 1997 Undefined. gp130 and the Interleukin-6 Family of Cytokines*. Available from: <https://www.annualreviews.org/content/journals/10.1146/annurev.immunol.15.1.797> [Last accessed on 2025 Mar 31].
114. Mizel SB. The interleukins¹. *FASEB J.* 1989;3(12):2379-2388.
doi: 10.1096/FASEBJ.3.12.2676681
115. Vaillant A. *Interleukin*; 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/nbk499840> [Last accessed on 2025 Mar 31].
116. Nicod LP. Cytokines. 1. Overview. *Thorax.* 1993;48:660-667.
doi: 10.1136/thx.48.6.660
117. Snick JV. Interleukin-6: An overview. *Annu Rev Immunol.* 1990;8:253-278.
doi: 10.1146/annurev.iy.08.040190.001345
118. Gaffen SL, Liu KD. Overview of interleukin-2 function, production and clinical applications. *Cytokine.* 2004;28:109-123.
doi: 10.1016/j.cyto.2004.06.010
119. Maher JJ. Cytokines: Overview. *Semin Liver Dis.* 1999;19(2):109-116.
doi: 10.1055/S-2007-1007103
120. Durum SK. *Interleukins: An Overview*. Springer; 1987. Available from: https://link.springer.com/chapter/10.1007/978-1-4613-0919-2_34 [Last accessed on 2025 Mar 31].
121. NZPA. *Interleukin 35: An Overview*; 2020. Available from: <https://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=12308013&an=148532767&h=7ouugfhti5n%2fcj8yage2cfdiubjv5hystwnbv5c6zfi6yicr188ruu6pfquqen2y%2foigbff%2b2ai0g98anre9g%3d%3d&url=c> [Last accessed on 2025 Mar 31].
122. Disease JMS. *Cytokines: Overview*; 1999. Available from: <https://www.thieme/connect.com/products/ejournals/html/10.1055/s-2007-1007103> [Last accessed on 2025 Mar 31].
123. Newsletter DACI. *The Interleukins, Interferons, Transforming Growth Factors, and their Assays: An Overview*. Elsevier; 1990. Available from: <https://www.sciencedirect.com/science/article/pii/019718599090005s> [Last accessed on 2025 Mar 31].
124. Gulati K, Guhathakurta S, Joshi J, Rai N, Immunol ARM. Cytokines and their role in health and disease: A brief overview. *MOJ Immunol.* 2016;4:00121.
doi: 10.15406/moji.2016.04.00121
125. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol.* 2009;27:519-550.
doi: 10.1146/ANNUREV.IMMUNOL.021908.132612
126. Rosenwasser LJ. Interleukin-1: An overview. In: *IUPHAR 9th International Congress of Pharmacology London 1984*. Berlin: Springer; 1984. p. 301-306.
doi: 10.1007/978-1-349-17615-1_44
127. Kaneko N, Kurata M, Yamamoto T, Morikawa S, Masumoto J. The role of interleukin-1 in general pathology. *Inflamm Regen.* 2019;39:12.
doi: 10.1186/s41232-019-0101-5
128. Briukhovetska D, Dörr J, Endres S, Dinarello CA, Libby P, Kobold S. Interleukins in cancer: From biology to therapy. *Nat Rev Cancer.* 2021;21:481-499.
doi: 10.1038/s41568-021-00363-z
129. Mertowska P, Mertowski S, Smarz-Widelska I, Grywalska E. Biological role, mechanism of action and the importance of interleukins in kidney diseases. *Int J Mol Sci.* 2022;23:647.
doi: 10.3390/ijms23020647
130. Greene WC. An overview of the human interleukin-2 receptor: Molecular, biochemical, and functional properties. *Cancer Investig.* 1987;5(4):369-376.
doi: 10.1080/07357908709170110
131. Rosenwasser LJ. *Interleukin-1: An Overview*. Berlin: Springer; Available from: https://link.springer.com/chapter/10.1007/978-1-349-17615-1_44 [Last accessed on 2025 Mar 31].
132. Saleh RO, Jasim SA, Kadhum WR, *et al.* Exploring the detailed role of interleukins in cancer: A comprehensive review of literature. *Pathol Res Pract.* 2024;257:155284.
doi: 10.1016/j.prp.2024.155284
133. Fietta P, Costa E, Delsante G. Interleukins (ILs), a fascinating family of cytokines. Part I: ILS from IL-1 to IL-19. *Theor Biol Forum.* 2014;107:13-45.
134. Houwing DJ, Buwalda B, Van Der Zee EA, De Boer SF,

- Olivier JDA. The serotonin transporter and early life stress: Translational perspectives. *Front Cell Neurosci.* 2017;11:117. doi: 10.3389/fncel.2017.00117
135. Bremshey S, Groß J, Renken K, Maseck OA. The role of serotonin in depression-A historical roundup and future directions. *J Neurochem.* 2024;168:1751-1779. doi: 10.1111/jnc.16097
136. Boraschi D. What is IL-1 for? The functions of interleukin-1 across evolution. *Front Immunol.* 2022;13:872155. doi: 10.3389/FIMMU.2022.872155
137. Kurzrock R, Talpaz M. *Cytokines: Interleukins and their Receptors*; 2012. Available from: https://books.google.com/books?hl=en&lr=&id=zucybwaqbaj&oi=fnd&pg=pa1&dq=overview+of+interleukins+and+their+functions&ots=ag22hnynck&sig=xspnyjfubrkk6ok_6atfjwcti0 [Last accessed on 2025 Mar 31].
138. Strober W, James P. The interleukins. 1988;4(5):549-557. doi: 10.1203/00006450-198811000-00001
139. Prados-Carmona A, Navarro-Triviño FJ, Ruiz-Villaverde R, Corell A. Role of interleukins in dermatology: Exploring the immune mechanisms in skin diseases. *J Eur Acad Dermatol Venereol.* 2024;3:1381-1398. doi: 10.1002/jvc2.537
140. Weber A, Wasiliew P, Kracht M. Interleukin-1 (IL-1) pathway. *Sci Signal.* 2010;3(105):cm1. doi: 10.1126/scisignal.3105cm1
141. Keller E, Wanagat J, Ershler WB. Molecular and cellular biology of interleukin-6 and its receptor. *Front Biosci.* 1996;1:340-357.
142. Uciechowski P, Dempke WC. Interleukin-6: A masterplayer in the cytokine network. *Oncology.* 2020;98:131-137. doi: 10.1159/000505099
143. Banchereau J, Briere F, Galizzi JP, Miossec P, Rousset F. Human interleukin 4. *J Lipid Mediat Cell Signal.* 1994;9(1):43-53. doi: 10.1201/9781003067405-12
144. Schett G, Dayer JM, Manger B. Interleukin-1 function and role in rheumatic disease. *Nat Rev Rheumatol.* 2016;12:14-24. doi: 10.1038/nrrheum.2016.166
145. Peters M. Actions of cytokines on the immune response and viral interactions: An overview. *Hepatology.* 1996;23(4):909-916. doi: 10.1002/hep.510230436
146. Yang M, Zhang CY. Interleukins in liver disease treatment. *World J Hepatol.* 2024;16(2):140-145. doi: 10.4254/wjh.v16.i2.140
147. Gaffen SL. An overview of IL-17 function and signaling. *Cytokine.* 2008;43:402-407. doi: 10.1016/j.cyto.2008.07.017
148. *Human Interleukin-3: An Overview*; 2020. Available from: <https://www.taylorfrancis.com/chapters/edit/10.1201/9781003067405/12/human/interleukin/3/yang-yu-chung> [Last accessed on 2025 Mar 31].
149. Dinarello CA. Historical insights into cytokines. *Eur J Immunol.* 2007;37(Suppl 1):S34-S35. doi: 10.1002/eji.200737772
150. Taga T, Kishimoto T. Gp130 and the interleukin-6 family of cytokines. *Annu Rev Immunol.* 1997;15:797-819. doi: 10.1146/ANNUREV.IMMUNOL.15.1.797
151. Litwack G. *Interleukins*; 2011. Available from: https://books.google.com/books?hl=en&lr=&id=6oxndu7dlisc&oi=fnd&pg=pp2&dq=overview+of+interleukins+and+their+functions&ots=atuwlableh&sig=rusyqru_rmv2nmekqqbuylz3y [Last accessed on 2025 Mar 31].
152. Negreva M, Georgiev S, Vitlianova K. Interleukin response in cardiovascular diseases: An overview. *Sci Online Resour Syst.* 2015;47(2):9-13.
153. Dinarello CA, Novick D, Puren AJ, et al. Overview of interleukin-18: More than an interferon-gamma inducing factor. *J Leukoc Biol.* 1998;63(6):658-664. doi: 10.1002/jlb.63.6.658
154. Lederer JA, Czaprynski CJ. *Interleukin-1*; 2020. Available from: <https://www.taylorfrancis.com/chapters/edit/10.1201/9781003067382/2/interleukin/1/james/leder-er-charles-czaprynski> [Last accessed on 2025 Mar 31].
155. Shajib MS, Khan WI. The role of serotonin and its receptors in activation of immune responses and inflammation. *Acta Physiol (Oxf).* 2015;213(3):561-574. doi: 10.1111/APHA.12430
156. Herr N, Bode C, Duerschmied D. The effects of serotonin in immune cells. *Front Cardiovasc Med.* 2017;4:48. doi: 10.3389/FCVM.2017.00048
157. Mössner R, Daniel S, Schmitt A, Albert D, Lesch KP. Modulation of serotonin transporter function by interleukin-4. *Life Sci.* 2001;68:873-880. doi: 10.1016/S0024-3205(00)00992-9
158. Su S, Zhao J, Douglas Bremner J, et al. Serotonin transporter gene, depressive symptoms, and interleukin-6. *Circ Cardiovasc Genet.* 2009;2(6):614-620. doi: 10.1161/CIRCGENETICS.109.870386
159. Kopp SK. The influence of neuropeptides, serotonin, and interleukin 1 β on temporomandibular joint pain and inflammation. *J Oral Maxillofac Surg.* 1998;56:189-191. doi: 10.1016/S0278-2391(98)90867-9
160. Martino M, Rocchi G, Escelsior A, Fornaro M. Immunomodulation mechanism of antidepressants:

- Interactions between serotonin/norepinephrine balance and Th1/Th2 balance. *Curr Neuropsychopharmacol.* 2012;10:97-123.
doi: 10.2174/157015912800604542
161. Müller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. *Mol Psychiatry.* 2007;12:988-1000.
doi: 10.1038/sj.mp.4002006
162. Delgado SG, Garza-Veloz I, Trejo-Vazquez F, Martinez-Fierro ML. Interplay between serotonin, immune response, and intestinal dysbiosis in inflammatory bowel disease. *Int J Mol Sci.* 2022;23:15632.
doi: 10.3390/ijms232415632
163. Kubera M, Maes M, Kenis G, Kim Y, Lason W. Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor α and interleukin-6. *Psychiatry Res.* 2005;134:251-258.
doi: 10.1016/j.psychres.2004.01.014
164. Song C, Merali Z, Anisman H. Variations of nucleus accumbens dopamine and serotonin following systemic interleukin-1, interleukin-2 or interleukin-6 treatment. *Neuroscience.* 1999;88:823-836.
doi: 10.1016/s0306-4522(98)00271-1
165. Kubera M, Maes M. *Serotonin-Immune Interactions in Major Depression.* Berlin: Springer; 2000. p. 79-87.
doi: 10.1007/978-3-642-59643-8_8
166. Haase J, Brown E. Integrating the monoamine, neurotrophin and cytokine hypotheses of depression--a central role for the serotonin transporter? *Pharmacol Ther.* 2015;147:1-11.
doi: 10.1016/j.pharmthera.2014.10.002
167. Yang CJ, Liu CL, Sang B, Zhu XM, Du YJ. The combined role of serotonin and interleukin-6 as biomarker for autism. *Neuroscience.* 2015;284:290-296.
doi: 10.1016/j.neuroscience.2014.10.011
168. Kubera M, Maes M. *Serotonin-Immune Interactions in Major Depression;* 2000. Springer. Available from: https://link.springer.com/chapter/10.1007/978-3-642-59643-8_8 [Last accessed on 2025 Mar ³¹].
169. Merali Z, Lacosta S, Anisman H. Effects of interleukin-1 β and mild stress on alterations of norepinephrine, dopamine and serotonin neurotransmission: A regional microdialysis study. *Brain Res.* 1997;761:225-235.
doi: 10.1016/S0006-8993(97)00312-0
170. Ménard G, Turmel V, Bissonnette EY. Serotonin modulates the cytokine network in the lung: Involvement of prostaglandin E2. *Clin Exp Immunol.* 2007;150:340-348.
doi: 10.1111/j.1365-2249.2007.03492.x
171. Bull SJ, Huezo-Diaz P, Cubells JF, *et al.* Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. *Mol Psychiatry.* 2009;14(12):1095-1104.
doi: 10.1038/mp.2008.48
172. Mössner R, Heils A, Stöber G, *et al.* Enhancement of serotonin transporter function by tumor necrosis factor alpha but not by interleukin-6. *Neurochem Int.* 1998;33:251-254.
doi: 10.1016/S0197-0186(98)00026-6
173. Myint A, Kim YK. Cytokine-serotonin interaction through IDO: A neurodegeneration hypothesis of depression. *Med Hypotheses.* 2003;61:519-525.
doi: 10.26481/dis.20070118am
174. Kubera M, Kenis G, Bosmans E, Scharpé S, Maes M. Effects of serotonin and serotonergic agonists and antagonists on the production of interferon-gamma and interleukin-10. *Neuropsychopharmacology.* 2000;23(1):89-98.
doi: 10.1016/S0893-133X(99)00150-5
175. Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1 β and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology.* 2006;31:2121-2131.
doi: 10.1038/sj.npp.1301029
176. Correia A, Cardoso A, Vale N. Highlighting immune system and stress in major depressive disorder, Parkinson's, and Alzheimer's diseases, with a connection with serotonin. *Int J Mol Sci.* 2021;22:8525.
doi: 10.3390/ijms22168525
177. Anderson G, Kubera M, Duda W, Lason W, Berk M, Maes M. Increased IL-6 trans-signaling in depression: Focus on the tryptophan catabolite pathway, melatonin and neuroprogression. *Pharmacol Rep.* 2013;65(6):1647-1654.
doi: 10.1016/S1734-1140(13)71526-3
178. Lindqvist D, Janelidze S, Hagell P, *et al.* Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol Psychiatry.* 2009;66:287-292.
doi: 10.1016/j.biopsych.2009.01.030
179. Szelenyi J, Vizi ES. The catecholamine cytokine balance: Interaction between the brain and the immune system. *Ann N Y Acad Sci.* 2007;1113:311-324.
doi: 10.1196/annals.1391.026
180. Brebner K, Hayley S, Zacharko R, Merali Z, Anisman H. Synergistic effects of interleukin-1 β , interleukin-6, and tumor necrosis factor-alpha: Central monoamine, corticosterone, and behavioral variations. *Neuropsychopharmacology.* 2000;22(6):566-580.
doi: 10.1016/S0893-133X(99)00166-9
181. Miura H, Ozaki N, Sawada M, Isobe K, Ohta T, Nagatsu T. A link between stress and depression: shifts

- in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression. *Stress*. 2008;11(3):198-209.
doi: 10.1080/10253890701754068
182. Wang J, Dunn AJ. Mouse interleukin-6 stimulates the HPA axis and increases brain tryptophan and serotonin metabolism. *Neurochem Int*. 1998;33:143-154.
doi: 10.1016/S0197-0186(98)00016-3
 183. Amitai M, Taler M, Carmel M, *et al*. The relationship between plasma cytokine levels and response to selective serotonin reuptake inhibitor treatment in children and adolescents with depression and/or anxiety disorders. *J Child Adolesc Psychopharmacol*. 2016;26(8):727-732.
doi: 10.1089/cap.2015.0147
 184. Li N, Ghia JE, Wang H, *et al*. Serotonin activates dendritic cell function in the context of gut inflammation. *Am J Pathol*. 2011;178:662-671.
doi: 10.1016/j.ajpath.2010.10.028
 185. Shajib MS, Wang H, Kim JJ, *et al*. Interleukin 13 and serotonin: Linking the immune and endocrine systems in murine models of intestinal inflammation. *PLoS One*. 2013;8(8):e72774.
doi: 10.1371/journal.pone.0072774
 186. Ramamoorthy S, Ramamoorthy J, Prasad PD, *et al*. Regulation of the human serotonin transporter by interleukin-1 β . *Biochem Biophys Res Commun*. 1995;216:560-567.
doi: 10.1006/bbrc.1995.2659
 187. Cloëz-Tayarani I, Petit-Bertron AF, Venters HD, Cavaillon JM. Differential effect of serotonin on cytokine production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells: Involvement of 5-hydroxytryptamine2A receptors. *Int Immunol*. 2003;15:233-240.
doi: 10.1093/intimm/dxg027
 188. Postal M, Appenzeller S. The importance of cytokines and autoantibodies in depression. *Autoimmun Rev*. 2015;14:30-35.
doi: 10.1016/j.autrev.2014.09.001
 189. Jaffré F, Callebort J, Sarre A, *et al*. Involvement of the serotonin 5-HT_{2B} receptor in cardiac hypertrophy linked to sympathetic stimulation: Control of interleukin-6, interleukin-1 β , and tumor necrosis. *Circulation*. 2004;110(8):969-974.
doi: 10.1161/01.CIR.0000139856.20505.57
 190. Zhang J, Terreni L, De Simoni MG, Dunn AJ. Peripheral interleukin-6 administration increases extracellular concentrations of serotonin and the evoked release of serotonin in the rat striatum. *Neurochem Int*. 2001;38:303-308.
doi: 10.1016/s0197-0186(00)00099-1
 191. Myint AM, Schwarz MJ, Steinbusch HWM, Leonard BE. Neuropsychiatric disorders related to interferon and interleukins treatment. *Metab Brain Dis*. 2009;24(1):55-68.
doi: 10.1007/S11011-008-9114-5
 192. Cross AJ. Serotonin in Alzheimer-type dementia and other dementing illnesses. *Ann N Y Acad Sci*. 1990;600(1):405-415; discussion 415-417.
doi: 10.1111/j.1749-6632.1990.tb16897.x
 193. Kohen R, Metcalf MA, Khan N, *et al*. Cloning, characterization, and chromosomal localization of a human 5-HT₆ serotonin receptor. *J Neurochem*. 1996;66(1):47-56.
doi: 10.1046/j.1471-4159.1996.66010047.x
 194. Woolley ML, Marsden CA, Fone KCF. 5-HT₆ receptors. *Curr Drug Targets CNS Neurol Disord*. 2004;3(1):59-79.
doi: 10.2174/1568007043482561
 195. Garcia-Alloza M, Hirst WD, Chen CPLH, Lasheras B, Francis PT, Ramírez MJ. Differential involvement of 5-HT_{1B/1D} and 5-HT₆ receptors in cognitive and non-cognitive symptoms in Alzheimer's disease. *Neuropsychopharmacology*. 2004;29(2):410-416.
doi: 10.1038/sj.npp.1300330
 196. Di Bona D, Candore G, Franceschi C, *et al*. Systematic review by meta-analyses on the possible role of TNF- α polymorphisms in association with Alzheimer's disease. *Brain Res Rev*. 2009;61(2):60-68.
doi: 10.1016/j.brainresrev.2009.05.001
 197. Italiani P, Puxeddu I, Napoletano S, *et al*. Circulating levels of IL-1 family cytokines and receptors in Alzheimer's disease: New markers of disease progression? *J Neuroinflammation*. 2018;15(1):342.
doi: 10.1186/s12974-018-1376-1
 198. Vom Berg J, Prokop S, Miller KR, *et al*. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. *Nat Med*. 2012;18(12):1812-1819.
doi: 10.1038/nm.2965
 199. Haddick PCG, Larson JL, Rathore N, *et al*. A common variant of IL-6R is associated with elevated IL-6 pathway activity in Alzheimer's disease brains. *J Alzheimers Dis*. 2017;56(3):1037-1054.
doi: 10.3233/JAD-160524
 200. Yan XZ, Lai L, Ao Q, Tian XH, Zhang YH. Interleukin-17A in Alzheimer's disease: Recent advances and controversies. *Curr Neuropharmacol*. 2021;20(2):372-383.
doi: 10.2174/1570159x19666210823110004
 201. Griciuc A, Patel S, Federico AN, *et al*. TREM2 acts downstream of CD33 in modulating microglial pathology in Alzheimer's disease. *Neuron*. 2020;103(5):820-835.e7.
doi: 10.1016/j.neuron.2019.06.010.TREM2

202. Chaudhuri KR, Martinez-Martin P, Schapira AHV, *et al.* International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: The NMSQuest study. *Mov Disord.* 2006;21(7):916-923.
doi: 10.1002/mds.20844
203. Collins LM, Toulouse A, Connor TJ, Nolan YM. Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease. *Neuropharmacology.* 2012;62(7):2154-2168.
doi: 10.1016/j.neuropharm.2012.01.028
204. Cook EH, Leventhal BL. The serotonin system in autism. *Curr Opin Pediatr.* 1996;8(4):348-354.
doi: 10.1097/00008480-199608000-00008
205. Muller CL, Anacker AMJ, Veenstra-VanderWeele J. The serotonin system in autism spectrum disorder: From biomarker to animal models. *Neuroscience.* 2016;321:24-41.
doi: 10.1016/J.NEUROSCIENCE.2015.11.010
206. Martin H, Choi JE, Rodrigues AR, Eshel N. Review: Dopamine, serotonin, and the translational neuroscience of aggression in autism spectrum disorder. *JAACAP Open.* 2025;3(1):29-41.
doi: 10.1016/J.JAACOP.2024.01.010
207. Shen Y, Li Y, Shi L, *et al.* Autism spectrum disorder and severe social impairment associated with elevated plasma interleukin-8. *Pediatr Res.* 2021;89(3):591-597.
doi: 10.1038/s41390-020-0910-x
208. Sallam DE, Shaker YS, Mostafa GA, El-Hossiny RM, Taha SI, Ahamed MAEH. Evaluation of serum interleukin-17 A and interleukin-22 levels in pediatric patients with autism spectrum disorder: A pilot study. *BMC Pediatr.* 2024;24(1):18.
doi: 10.1186/s12887-023-04484-2
209. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah IN, Van De Water J. Altered T cell responses in children with autism. *Brain Behav Immun.* 2011;25(5):840-849.
doi: 10.1016/j.bbi.2010.09.002
210. Suzuki K, Matsuzaki H, Iwata K, *et al.* Plasma cytokine profiles in subjects with high-functioning autism spectrum disorders. *PLoS One.* 2011;6(5):e20470.
doi: 10.1371/journal.pone.0020470
211. Emanuele E, Orsi P, Boso M, *et al.* Low-grade endotoxemia in patients with severe autism. *Neurosci Lett.* 2010;471(3):162-165.
doi: 10.1016/j.neulet.2010.01.033
212. Wei H, Zou H, Sheikh AM, *et al.* IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation. *J Neuroinflammation.* 2011;8(1):52.
doi: 10.1186/1742-2094-8-52
213. Halmøy A, Johansson S, Winge I, McKinney JA, Knappskog PM, Haavik J. Attention-deficit/hyperactivity disorder symptoms in offspring of mothers with impaired serotonin production. *Arch Gen Psychiatry.* 2010;67(10):1033-1043.
doi: 10.1001/ARCHGENPSYCHIATRY.2010.124
214. Oades RD. Role of the serotonin system in ADHD: Treatment implications. *Expert Rev Neurother.* 2007;7(10):1357-1374.
doi: 10.1586/14737175.7.10.1357
215. Banerjee E, Nandagopal K. Does serotonin deficit mediate susceptibility to ADHD? *Neurochem Int.* 2015;82:52-68.
doi: 10.1016/J.NEUINT.2015.02.001
216. Darwish AH, Elgohary TM, Nosair NA. Serum interleukin-6 level in children with attention-deficit hyperactivity disorder (ADHD). *J Child Neurol.* 2019;34(2):61-67.
doi: 10.1177/0883073818809831
217. Pourhamzeh M, Moravej FG, Arabi M, *et al.* The roles of serotonin in neuropsychiatric disorders. *Cell Mol Neurobiol.* 2021;42(6):1671-1692.
doi: 10.1007/S10571-021-01064-9
218. Lin J, Liu W, Guan J, *et al.* Latest updates on the serotonergic system in depression and anxiety. *Front Synaptic Neurosci.* 2023;15:1124112.
doi: 10.3389/fnsyn.2023.1124112
219. Schiele MA, Domschke K. Epigenetics at the crossroads between genes, environment and resilience in anxiety disorders. *Genes Brain Behav.* 2018;17(3):e12423.
doi: 10.1111/gbb.12423
220. Roknuzzaman ASM, Sarker R, Nayem J, *et al.* Altered serum interleukin-17A and interleukin-23A levels may be associated with the pathophysiology and development of generalized anxiety disorder. *Sci Rep.* 2024;14(1):15087.
doi: 10.1038/s41598-024-66131-9
221. Abi-Dargham A. Alterations of serotonin transmission in schizophrenia. *Int Rev Neurobiol.* 2007;78(6):133-164.
doi: 10.1016/S0074-7742(06)78005-9
222. Kim SA. 5-HT1A and 5-HT2A signaling, desensitization, and downregulation: Serotonergic dysfunction and abnormal receptor density in schizophrenia and the prodrome. *Cureus.* 2021;13(6):e15811.
doi: 10.7759/cureus.15811
223. Reale M, Costantini E, Greig NH. Cytokine imbalance in schizophrenia. From research to clinic: Potential implications for treatment. *Front Psychiatry.* 2021;12:536257.
doi: 10.3389/fpsy.2021.536257
224. Sasayama D, Hattori K, Wakabayashi C, *et al.* Increased

- cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. *J Psychiatr Res.* 2013;47(3):401-406.
doi: 10.1016/j.jpsychires.2012.12.001
225. Xing C, Chen H, Bi W, Lei T, Hang Z, Du H. Targeting 5-HT Is a potential therapeutic strategy for neurodegenerative diseases. *Int J Mol Sci.* 2024;25(24):13446.
doi: 10.3390/ijms252413446
226. De Jong IEM, Mørk A. Antagonism of the 5-HT₆ receptor - preclinical rationale for the treatment of Alzheimer's disease. *Neuropharmacology.* 2017;125:50-63.
doi: 10.1016/j.neuropharm.2017.07.010
227. Lu J, Zhang C, Lv J, *et al.* Antiallergic drug desloratadine as a selective antagonist of 5HT_{2A} receptor ameliorates pathology of Alzheimer's disease model mice by improving microglial dysfunction. *Aging Cell.* 2021;20(1):e13286.
doi: 10.1111/acer.13286
228. Singh Gautam A, Kumar Singh R. Therapeutic potential of targeting IL-17 and its receptor signaling in neuroinflammation. *Drug Discov Today.* 2023;28(4):103517.
doi: 10.1016/j.DRUDIS.2023.103517
229. Anderluh A, Klotzsch E, Reismann AWAF, *et al.* Single molecule analysis reveals coexistence of stable serotonin transporter monomers and oligomers in the live cell plasma membrane. *J Biol Chem.* 2014;289(7):4387-4394.
doi: 10.1074/jbc.M113.531632
230. Ogata N, De Souza Dantas LM, Crowell-Davis SL. Selective serotonin reuptake inhibitors. In: *Veterinary Psychopharmacology.* United States: Wiley; 2023. p. 103-128.
doi: 10.1002/9781119226253.ch8
231. Jakubovski E, Johnson JA, Nasir M, Müller-Vahl K, Bloch MH. Systematic review and meta-analysis: Dose-response curve of SSRIs and SNRIs in anxiety disorders. *Depress Anxiety.* 2019;36(3):198-212.
doi: 10.1002/DA.22854
232. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. *Aging Dis.* 2018;9(1):143-150.
doi: 10.14336/AD.2017.0306
233. Gunaydin C, Bilge SS. Effects of nonsteroidal anti-inflammatory drugs at the molecular level. *Eurasian J Med.* 2018;50(2):116-121.
doi: 10.5152/eurasianjmed.2018.0010
234. Choi KW, Chen CY, Stein MB, *et al.* Assessment of bidirectional relationships between physical activity and depression among adults a 2-sample Mendelian randomization study. *JAMA Psychiatry.* 2019;76(4):399-408.
doi: 10.1001/jamapsychiatry.2018.4175
235. Miller BJ, Dias JK, Lemos HP, Buckley PF. An open-label, pilot trial of adjunctive tocilizumab in schizophrenia. *J Clin Psychiatry.* 2016;77(2):275-276.
doi: 10.4088/JCP.15L09920
236. Sun Y, Wang D, Salvatore G, *et al.* The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. *Brain Behav Immun.* 2017;66:156-164.
doi: 10.1016/j.bbi.2017.06.014
237. Sulistio YA, Lee HK, Jung SJ, Heese K. Interleukin-6-mediated induced pluripotent stem cell (iPSC)-derived neural differentiation. *Mol Neurobiol.* 2018;55(4):3513-3522.
doi: 10.1007/S12035-017-0594-3/METRICS
238. Hu WT, Chen-Plotkin A, Arnold SE, *et al.* Novel CSF biomarkers for Alzheimer's disease and mild cognitive impairment. *Acta Neuropathol.* 2010;119(6):669-678.
doi: 10.1007/s00401-010-0667-0
239. Ekundayo BE, Obafemi TO, Adewale OB, Oyinloye BE. Donepezil-based combination therapy for Alzheimer's disease and related neuropathies. *Comp Clin Path.* 2023;32(4):699-708.
doi: 10.1007/s00580-023-03487-w
240. Le Van M, Diep DT, Tran TTT, Pham TKA, Tran BLT, Nguyen T. Levodopa and pramipexole combination therapy efficacy in Vietnamese patients with Parkinson's disease: A randomized controlled trial. *Russian Open Med J.* 2024;13(1):e0107.
doi: 10.15275/rusomj.2024.0107
241. Begni V, Marchesin A, Riva MA. IUPHAR review - novel therapeutic targets for schizophrenia treatment: A translational perspective. *Pharmacol Res.* 2025;214:107690.
doi: 10.1016/j.phrs.2025.107690
242. Van Zonneveld SM, Van Den Oever EJ, Haarman BCM, *et al.* An anti-inflammatory diet and its potential benefit for individuals with mental disorders and neurodegenerative diseases-a narrative review. *Nutrients.* 2024;16(16):2646.
doi: 10.3390/nu16162646
243. Kurowska A, Ziemichód W, Herbet M, Piątkowska-Chmiel I. The role of diet as a modulator of the inflammatory process in the neurological diseases. *Nutrients.* 2023;15(6):1436.
doi: 10.3390/nu15061436
244. Francescangeli J, Karamchandani K, Powell M, Bonavia A. The serotonin syndrome: From molecular mechanisms to clinical practice. *Int J Mol Sci.* 2019;20(9):2288.
doi: 10.3390/ijms20092288
245. Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH,

- Whyte IM. The hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):635-642.
doi: 10.1093/qjmed/hcg109
246. Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: A review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry*. 2010;71(12):1565-1575.
doi: 10.4088/JCP.09R05786BLU
247. De Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: Mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging*. 2012;28(5):345-367.
doi: 10.2165/11589340-000000000-00000
248. Mago R, Tripathi N, Andrade C. Cardiovascular adverse effects of newer antidepressants. *Expert Rev Neurother*. 2014;14(5):539-551.
doi: 10.1586/14737175.2014.908709
249. Wang SM, Han C, Bahk WM, *et al*. Addressing the side effects of contemporary antidepressant drugs: A comprehensive review. *Chonnam Med J*. 2018;54(2):101-112.
doi: 10.4068/cmj.2018.54.2.101
250. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: Systematic review and meta-analysis. *Arch Gen Psychiatry*. 2006;63(11):1217-1223.
doi: 10.1001/archpsyc.63.11.1217
251. Vieira CP, Lelis CA, Ochioni AC, *et al*. Estimating the therapeutic potential of NSAIDs and linoleic acid-isomers supplementation against neuroinflammation. *Biomed Pharmacother*. 2024;177:116884.
doi: 10.1016/J.BIOPHA.2024.116884
252. Kaduševičius E. Novel applications of nsais: Insight and future perspectives in cardiovascular, neurodegenerative, diabetes and cancer disease therapy. *Int J Mol Sci*. 2021;22(12):6637.
doi: 10.3390/ijms22126637
253. Tanaka M, Szabó Á, Vécsei L, Giménez-Llort L. Emerging translational research in neurological and psychiatric diseases: From *in vitro* to *in vivo* models. *Int J Mol Sci*. 2023;24(21):15739.
doi: 10.3390/ijms242115739
254. Yoon JH, Lee D, Lee C, *et al*. Paradigm shift required for translational research on the brain. *Exp Mol Med*. 2024;56(5):1043-1054.
doi: 10.1038/s12276-024-01218-x