









Review

# Role of 5-HT and BDNF in Premature Ejaculation With Anxiety or Depression

Yi Wei<sup>1,†</sup>, Bo Ning<sup>2,†</sup>, Shengjie Wang<sup>3</sup>, Wenshuo Chen<sup>1</sup>, Lianqin Zhang<sup>1</sup>,  
Chunxiu Chen<sup>1</sup>, Junfeng Qiu<sup>1,3,\*</sup>, Zhiming Hong<sup>1,3,\*</sup><sup>1</sup>The Fourth Clinical Medical College, Guangzhou University of Chinese Medicine, 518033 Shenzhen, Guangdong, China<sup>2</sup>The Second Clinical College, Guangzhou University of Chinese Medicine, 510006 Guangzhou, Guangdong, China<sup>3</sup>Department of Andrology, Shenzhen Traditional Chinese Medicine Hospital, 518033 Shenzhen, Guangdong, China\*Correspondence: [junfeng1023@126.com](mailto:junfeng1023@126.com) (Junfeng Qiu); [hzm001983@126.com](mailto:hzm001983@126.com) (Zhiming Hong)

†These authors contributed equally.

Academic Editor: Bettina Platt

Submitted: 1 August 2025 Revised: 12 September 2025 Accepted: 24 September 2025 Published: 17 March 2026

## Abstract

Premature ejaculation (PE) accompanied by anxiety or depression is a complex clinical condition at the intersection of male reproductive dysfunction and emotional disorders. Increasing evidence suggests that serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) play central and interrelated roles in its pathogenesis. In this review we examine the bidirectional functions of 5-HT and BDNF in both the reproductive and nervous systems, highlighting their importance in regulating ejaculation, emotional stability, and synaptic plasticity. A comprehensive literature search (2010–2025) was conducted across multiple databases using relevant Medical Subject Headings (MeSH) terms, including pertinent original research and review articles, to synthesize the roles and regulatory pathways of 5-HT and BDNF in PE with comorbid anxiety or depression. We summarize the shared and distinct roles of 5-HT and BDNF in maintaining physiological balance across these systems and focus on their involvement in the major pathological processes underlying PE with anxiety or depression, including neurotransmitter imbalance, neuroendocrine dysregulation, inflammation, and oxidative stress. Furthermore, we outline the related signaling pathways through which 5-HT and BDNF exert their effects and interact. We also evaluate current pharmacological and non-pharmacological interventions targeting these molecules, demonstrating their potential to improve both ejaculatory control and emotional symptoms, and critically appraise selective serotonin reuptake inhibitor (SSRI)-related risks and highlighted the need for individualized dosing and monitoring. Emerging evidence suggests that Traditional Chinese Medicine formulations can extend intravaginal ejaculatory latency and mitigate mood symptoms and may serve as stand-alone or adjunctive options to reduce reliance on selective serotonin reuptake inhibitors (SSRIs). Overall, 5-HT and BDNF are not only deeply involved in the biological mechanisms of PE with comorbid psychological disorders, but also represent promising biomarkers and therapeutic targets, and their integrative neuro-reproductive regulatory functions provide new insights into the diagnosis and treatment of this multifaceted condition.

**Keywords:** anxiety; biomarkers; brain-derived neurotrophic factor; depression; premature ejaculation; serotonin

## 1. Introduction

Premature ejaculation (PE) is one of the most common sexual dysfunctions in men. According to the 2014 edition of the International Society for Sexual Medicine (ISSM) guidelines for the diagnosis and treatment of PE, the definition of PE includes three elements: (a) lifelong premature ejaculation (LPE), which occurs often or always before or within about 1 minute after the initiation of sexual activity. A significantly shortened intravaginal ejaculatory latency (IELT), usually less than 3 minutes, is called acquired premature ejaculation (APE); (b) these two types of PE patients cannot control and delay ejaculation almost every time they had sex; (c) PE brings negative physical and mental effects to patients, such as distress, anxiety, depression, interpersonal barriers, or avoidance of sexual life [1]. The American Urologist Association/Sexual Medicine Association of North America 2022 guideline further distinguishes between LPE and APE. LPE is defined as poor ejacula-

tion control with distress, and ejaculation within approximately 2 minutes after initial sexual activity; APE is defined as persistent poor ejaculatory control, associated distress, and significantly reduced IELT from prior sexual experience during insertion [2]. The 2021 clinical management guidelines for PE issued by the Italian Society of Andrology and Sexual Medicine (SIAMS) further delineated two important subtypes: subclinical premature ejaculation (SPE) and loss of control over erection and ejaculation (LCEE) [3]. SPE is characterized by subjectively inadequate ejaculatory control despite a normal objective IELT, accounting for approximately 15–20% of patients with suspected PE [4]. LCEE refers to the coexistence of PE with erectile dysfunction (ED) or subclinical ED; it occurs in up to 50% of patients with PE, and the two conditions exacerbate one another, creating a pathophysiological cycle [4,5]. The 2025 European Association of Urology (EAU) Guidelines did not propose their own definition of PE; instead, they



reported the ICD-11 definition based on the ISSM criteria and acknowledge variable PE and subjective PE as potential subtypes [6]. However, an additional and often overlooked presentation exists in clinical practice: some men have normal sexual performance at times, yet on other occasions experience a sudden, uncontrollable rapid ejaculation that can catch their partners off guard—this is a new concept introduced in 2025, termed intermittent premature ejaculation (IPE) [7]. A survey of 1976 Chinese men aged 18 to 50 years found a prevalence of PE of 2.3% [8]. In a study of 62,675 Danes aged 15 to 89, 10.0% of men had experienced PE in the previous year [9]. A health study of 2500 men in Bavaria, Germany, showed that the prevalence of PE was 5.2% [10]. In two surveys of samples in five countries (Turkey, the Netherlands, Spain, the United Kingdom, and the United States), only 2.95% of men had an IELT  $\leq 1$  minute and only 6.1% of men had an IELT  $\leq 2$  minutes [11,12]. PE has a negative impact on patients' self-confidence, self-esteem, and sexual relations, and is often accompanied by anxiety or depression [13–15]. A large cross-sectional study of 3016 male patients showed that the incidence of anxiety or depression in patients with PE was 18.38% and 8.84%, respectively, which was significantly higher than 9.74% and 3.26% in patients without PE [16]. Althof *et al.* [17] investigated 1010 PE patients with anxiety and depression screening scales, and found that 82.07% of them had anxiety symptoms and 74.83% had depression symptoms. Liu *et al.* [18] evaluated the correlation of psychological disorders in 270 patients and found that anxiety or depression was closely related to the onset of PE, and that they were risk factors for PE. At present, PE with anxiety or depression has become a public health burden for affected men and their partners worldwide [19].

Modern medicine has many views on the pathogenesis of PE. Initially, Jannini *et al.* [20] believed that PE had psychological factors or an interpersonal basis, and it was caused by anxiety or lack of early sexual life experience. Recent evidence has suggested that it may be related to a disorder of serotonin (5-HT) neurotransmitter in the central nervous system (CNS), reduced synthesis of brain-derived neurotrophic factor (BDNF), hypersensitivity of the glans penis, psychology, and other factors [21]. Among these factors, 5-HT is closely related to mental and psychological disorders such as anxiety or depression [22]. It is also the most widely studied inhibitory neurotransmitter in the regulation of ejaculation, and an increase in central 5-HT concentration can lead to a delay in ejaculation [23]. Selective serotonin reuptake inhibitors (SSRIs) have been used in the treatment of mental disorders, and have the side effect of delayed ejaculation. The mechanism of their action is to inhibit the reuptake of 5-HT by 5-hydroxytryptamine transporter (5-HTT), to increase the concentration of 5-HT in the synaptic cleft, and to delay ejaculation. Therefore, this class of drugs is also used in the treatment of PE [24].

BDNF is the most important member of the neurotrophic factor family. It is widely distributed in the CNS of mammals. It plays a very important role in the development and maintenance of the CNS, and can supply a variety of neurons such as 5-HT, dopamine (DA), and cholinergic neurons, and multiple brain areas such as raphe nuclei, prefrontal cortex, and hippocampus [25,26]. A clinical study conducted by Atik *et al.* [27] showed that serum BDNF levels in PE patients were significantly lower than those in healthy subjects, and with the decrease of serum BDNF levels, PE diagnostic scale scores significantly rose, suggesting that BDNF deficiency may be a potential predisposing factor for PE. In addition to its neurotrophic functions, BDNF is critically involved in the regulation of emotional states such as anxiety and depression by modulating neuronal growth, survival, apoptosis, neuroinflammatory responses, and synaptic plasticity [28]. The relationship between BDNF and 5-HT is complex and reciprocal, and Guiard *et al.* [29] demonstrated that a decrease in BDNF levels leads to an increase in baseline exogenous 5-HT levels in the ventral hippocampus of mice. However, Deltheil *et al.* [30] found that local injection of BDNF reduced exogenous 5-HT levels, and this effect was abolished by K252a, a tropomyosin-receptor-kinase B (TrkB) inhibitor. In addition, BDNF may cooperate with 5-HT homeostasis through TrkB signaling to promote the neurogenic effects of SSRIs [31]. The above studies suggest some degree of interaction between BDNF and 5-HT. The frequent coexistence of PE with anxiety or depression suggests a common pathological basis in which 5-HT and BDNF serve as key molecular mediators. They may lead to PE accompanied by anxiety or depression through a series of complex physiological and pathological processes.

In the present review, first introduced is the correlation of 5-HT and BDNF with male reproductive system and nervous system function. In the male reproductive system, 5-HT plays a pivotal role in regulating ejaculation, penile erection, and sperm quality through the modulation of intracellular messengers and hormones, including cAMP, testosterone, endothelin-1 (ET-1), and norepinephrine (NE). BDNF regulates sperm production, erectile function, and the ejaculation mechanism by activating multiple signaling pathways such as phosphatidylinositol-3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK). In the nervous system, 5-HT regulates emotion and cognitive function by regulating the 5-hydroxytryptamine 1A (5-HT<sub>1A</sub>) receptor and the 5-hydroxytryptamine 2A (5-HT<sub>2A</sub>) receptor. By influencing key brain regions such as the hippocampus and prefrontal cortex, BDNF contributes significantly to the neural mechanisms underlying anxiety and depression. Second, the review focuses on the latest research progress of the role of 5-HT and BDNF in PE with anxiety or depression, including the specific mechanisms of 5-HT and BDNF in regulating serotonergic system abnormalities, regulating dopaminergic system abnormali-

ties, regulating inflammatory response, improving oxidative stress damage, and mediating multiple signaling pathways. Last, the review summarized the potential of 5-HT and BDNF as potential biomarkers for the treatment of PE with anxiety or depression.

## 2. Literature Search and Methodology

This review adopted a narrative synthesis approach to systematically identify, screen, and integrate research evidence published since 2010 on the mechanistic roles, biomarker value, and therapeutic potential of 5-HT and BDNF in PE with comorbid anxiety or depression. We also considered established theories and emerging directions in the field to ensure scientific rigor and currency.

### 2.1 Databases and Time Frame

We conducted comprehensive searches of PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Embase (<https://www.embase.com>), the Web of Science Core Collection (<https://www.webofscience.com>), and ScienceDirect (<https://www.sciencedirect.com>). In addition, we hand-searched the reference lists of included articles to capture seminal pre-2010 studies on 5-HT and BDNF regulation of male reproductive or nervous system function. Database searches covered January 2010 to August 2025; the hand search had no time restriction to ensure completeness of foundational work.

### 2.2 Search Terms and Strategy

We combined keywords and MeSH and optimized the queries using Boolean operators (AND/OR). Representative terms included: disease-related: “premature ejaculation”, “PE”, “anxiety”, “depression”; biomarker-related: “serotonin”, “5-hydroxytryptamine”, “5-HT”, “brain-derived neurotrophic factor”, “BDNF”, “biomarker”; mechanism and therapy: “pathogenesis”, “mechanism”, “signaling pathway”, “treatment”, “selective serotonin reuptake inhibitors”, “SSRIs”, “traditional Chinese medicine”. To improve precision, we also included relevant modifiers such as “dopaminergic”, “oxidative stress”, and “inflammatory response”.

### 2.3 Inclusion Criteria

Study type: English-language original research (clinical studies and basic/preclinical experiments) and systematic reviews/meta-analyses;

Study population/models: clinical studies involving patients with PE, anxiety, or depression; preclinical studies employing animal models of PE, anxiety, or depression;

Relevance: studies explicitly examining associations of 5-HT or BDNF with PE, anxiety, or depression, including pathophysiology, diagnostic biomarker utility, or effects of targeted interventions;

Quality: published in peer-reviewed journals with complete data and clear methodological descriptions.

### 2.4 Exclusion Criteria

Study type: case reports, conference abstracts, editorials, letters, and records without full text;

Irrelevance: studies unrelated to PE or anxiety/depression or primarily focused on other mechanisms;

Quality issues: incomplete data, unclear methodology, or conclusions lacking statistical support;

Duplicates: when multiple publications from the same dataset were identified, only the most recent or most comprehensive report was included.

### 2.5 Study Selection and Quality Control

After deduplication, two reviewers independently screened titles and abstracts against the inclusion/exclusion criteria; disagreements were resolved through discussion with a third reviewer. Records deemed potentially eligible proceeded to full-text evaluation. Studies that merely described phenomena without mechanistic interrogation, or reported ambiguous efficacy data, were excluded to preserve the scientific robustness and persuasiveness of the synthesis.

## 3. The Role of 5-HT and BDNF in the Function of the Male Reproductive System and the Nervous System

Serotonin (5-HT) is a monoamine neurotransmitter that is synthesized and released by serotonergic neurons in the CNS and chromaffin cells in the gastrointestinal tract [32]. 5-HT is thought to affect a range of behavioral, physiological, and cognitive functions in the human body, such as memory, mental health, mood, sleep, appetite, sexual function, and temperature regulation [33]. The serotonergic nervous system is divided into the peripheral serotonergic system and the central serotonergic system. Peripheral 5-HT is thought to be involved in the regulation of physiological functions such as platelet aggregation, vasodilation, hypertension, and intestinal peristalsis [34]. In the CNS, 5-hydroxytryptophan (5-HTP) is generated from tryptophan (Trp) via tryptophan hydroxylase 2 (TPH<sub>2</sub>), and then 5-HT is generated by 5-hydroxytryptophan decarboxylase (5-HTPDC) [35]. The vesicular monoamine transporter (VMAT) is responsible for the transfer of 5-HT synthesized by presynaptic neurons from the cytoplasm to the vesicles, and then it is excreted to the synaptic cleft where it binds to presynaptic or postsynaptic receptors to play a physiological role [36]. 5-HT in the synaptic cleft is mainly recycled from 5-HTT to the presynaptic membrane, and then catabolized by monoamine oxidase (MAO) to form inactive 5-hydroxyindoleacetic acid (5-HIAA) [37]. 5-HT receptors are mainly divided into seven families (5-HT1 through 7), each of which is divided into different subtypes, for a total of 14 receptor subtypes. Except for 5-HT3 receptor, which is an ion-type gated channel protein, the rest are G-protein-coupled receptors (GPCRs) [38]. 5-HT receptors are highly distributed in areas related to emotion regula-

tion and memory (such as hippocampus, amygdala, and cortex). By coupling with GPCRs, 5-HT receptors increase the expression of downstream cAMP-response-element binding protein (CREB) and BDNF, thereby participating in the regulation of physiological activities [39].

BDNF is a member of the family of neurotrophin-secreting proteins that supports neuronal survival, synaptic plasticity, and neurogenesis [40]. BDNF protein is synthesized in neurons and glial cells, and then widely expressed in the CNS. It is enriched in the hippocampus and cortex, especially in the CA3 region of the hippocampus [41]. BDNF is synthesized in multiple forms—pro-pro-BDNF, pro-BDNF, and m-BDNF—with m-BDNF serving as the principal effector in promoting neuronal survival and differentiation [42]. The BDNF mRNA is first synthesized in the endoplasmic reticulum and then transported to the Golgi apparatus, where it is cleaved to remove the pro-region sequence to form pro-BDNF with certain functional activity [43]. Then, pro-BDNF can then be converted into m-BDNF in the cell through two different pathways. One, pro-BDNF is cleaved by furin, a member of the Bacillus subtilis endonuclease family, to produce m-BDNF in the Golgi network. Two, pro-BDNF can also form m-BDNF in intracellular vesicles through the action of intracellular converting enzymes such as protein convertase. The m-BDNF produced by the above two pathways is released to the outside of the cell through the presynaptic membrane [44]. BDNF, secreted into synapses, activates the p75 neurotrophin receptor [p75(NTR)], TrkB, and their downstream signaling cascades. Among them, p75(NTR)-mediated signaling pathways mainly include the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway, the c-Jun N-terminal kinase (JNK) pathway, the p38 MAPK pathway, and the RhoA/ROCK signaling pathway [45]. The signaling pathways mediated by TrkB include the rat sarcoma proto-oncogene (Ras)/MAPK/extracellular signal-regulated kinase (ERK) pathway, the IRS-1/PI3K/protein kinase B (AKT) pathway, and the Phospholipase C/Diacylglycerol/Inositol 1,4,5-trisphosphate (PLC/DAG/IP3) pathway [46]. BDNF can maintain the survival and function of sensory neurons, retinal ganglion cells, cholinergic neurons, spinal cord motor neurons, and dopaminergic neurons, and has a unique role in synaptic plasticity. The use of synaptic pathways can lead to the strengthening of connections between neurons, thereby increasing the formation of synapses at axon collaterals and dendritic spines. BDNF regulates physiological processes such as neurogenesis, synaptic plasticity and cell survival in the male nervous system and reproductive system [47]. These physiological functions and generation pathways of 5-HT and BDNF are illustrated in Fig. 1.

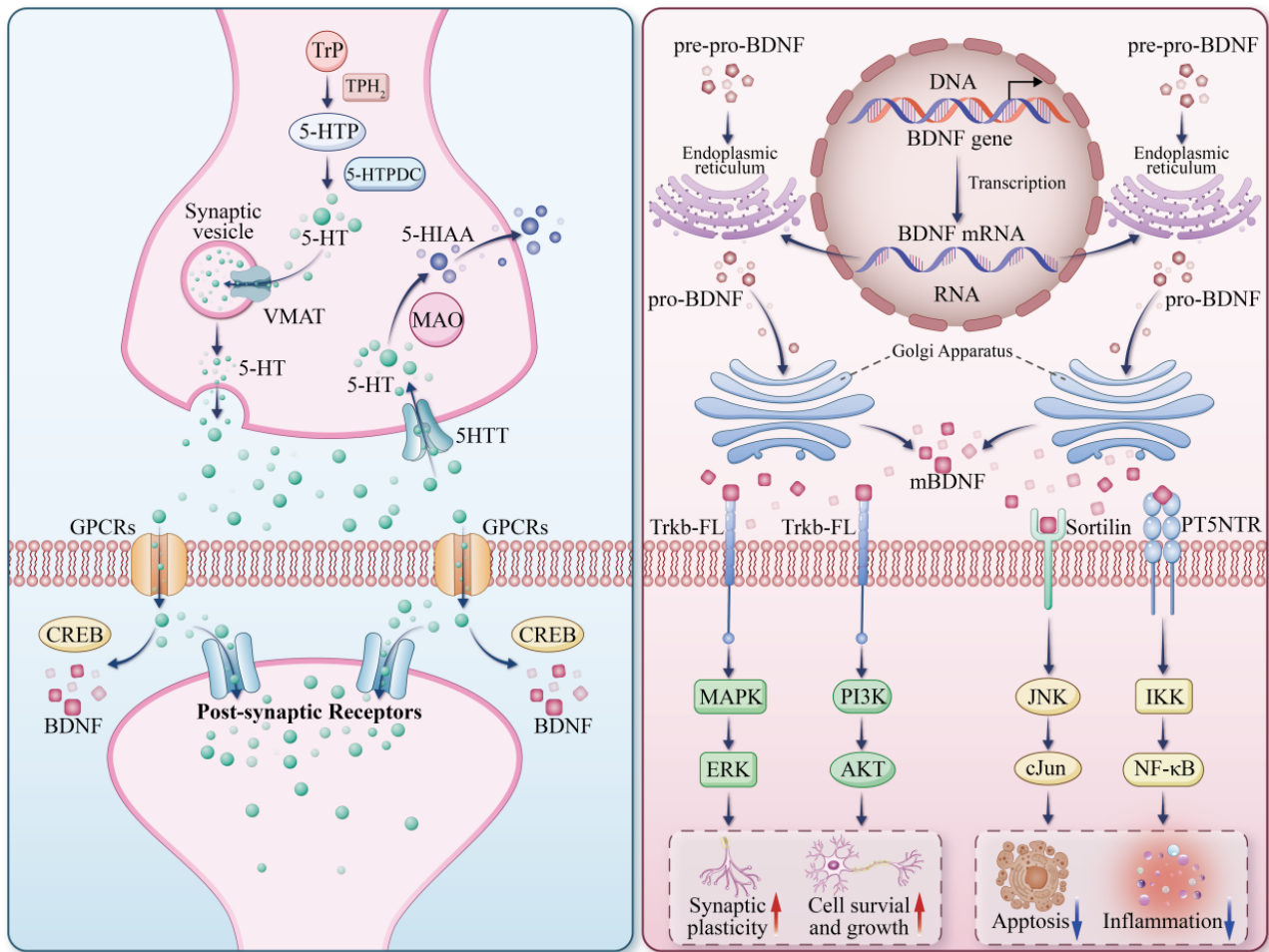
### *3.1 Correlation Between 5-HT and BDNF and Male Reproductive Function*

5-HT and BDNF are key molecular regulators involved in maintaining normal physiological function within

the male reproductive system. 5-HT affects male reproductive health by regulating ejaculation and erectile function. The disturbance of 5-HT in the CNS can lead to ejaculation disorders, and different receptors of 5-HT, such as 5-HT1A and 5-HT2A, play different roles in ejaculation and erection. For example, 5-HT2A receptor activation is associated with ED because it leads to blocked penile blood flow. In addition, 5-HT affects sperm motility and fertilization rate by regulating cAMP and testosterone levels. On the other hand, BDNF is equally important in the development and function of the male reproductive system. By binding to TrkB and p75(NTR), BDNF activates multiple signaling pathways (such as PI3K/Akt and MAPK) to promote the proliferation of Leydig cells, thereby increasing sex hormone levels and enhancing sperm motility. In addition, BDNF may be involved in the regulation of ejaculation by affecting 5-HT synthesis. Therefore, the interaction between 5-HT and BDNF, as well as their effects on male reproductive function, becomes an important direction of current research.

#### *3.1.1 Role of 5-HT in the Male Reproductive System*

The effect of central 5-HT neurotransmitter disorder on ejaculation has been a research hotspot in recent years [48]. The neural areas involved in ejaculation include the spinal ejaculatory center, the ascending fibers of the spinal ejaculatory center and the descending fibers of some brain regions. Ejaculation is regulated by a variety of neurotransmitters including 5-HT [49]. The 5-HT system consists of 5-HT, 5-HTT and the 5-HT receptors. In the hypothalamic synaptic cleft, 5-HT is regulated by 5-HTT and regulates ejaculation by binding to the 5-HT receptor. The greater the transport activity of 5-HTT, the lower the 5-HT concentration in the synaptic cleft and the shorter IELT [50]. Different 5-HT receptors have different biological functions: 5-HT2 receptors inhibit ejaculation, whereas 5-HT1A receptors promote ejaculation [51]. This suggests that 5-HT, 5-HTT, and the 5-HT receptor are closely related to the occurrence of PE. It should be noted that the widespread distribution of the 5-HT system renders interventions prone to nonspecific effects. With clinical use of SSRIs, peripheral adverse effects such as hyperhidrosis and gastrointestinal discomfort are common, and excessive activation of central 5-HT receptors may precipitate a risk of serotonin syndrome, including symptoms such as anxiety or confusion [52]. In addition, 5-HT is also associated with ED. A related study has shown that diabetes can cause a significant increase in the serum concentration of 5-HT, which enhances the vasoconstriction effect of 5-HT through the 5-HT2A receptor, and this process leads to the blockage of penile blood flow, resulting in ED [53]. Studies have shown that 5-HT and the 5-HT2A receptor can indirectly enhance the vasoconstrictor effect of vasoconstrictor substances such as ET-1 and NE, and change the normal vasoconstriction activity of blood vessels [54,55]. 5-HT elevates intracellular



**Fig. 1. Physiological functions of 5-HT and BDNF.** The downward arrow indicates a decrease (downregulation) and the upward arrow represents an increase (upregulation). 5-HT, 5-hydroxytryptamine; BDNF, brain-derived neurotrophic factor; Trp, tryptophan; TPH<sub>2</sub>, tryptophan hydroxylase 2; 5-HTP, 5-hydroxytryptophan; 5-HTPDC, 5-hydroxytryptophan decarboxylase; 5-HIAA, 5-hydroxyindoleacetic acid; MAO, monoamine oxidase; VMAT, vesicular monoamine transporter; 5-HTT, 5-hydroxytryptamine transporter; GPCRs, G protein-coupled receptors; CREB, cAMP response element-binding protein; TrkB, tropomyosin receptor kinase B; p75NTR, p75 neurotrophin receptor; PI3K, phosphatidylinositol-3-kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal Kinase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; IKK, inhibitor of kappaB kinase; ERK, extracellular signal-regulated kinase. The figure was drawn using Adobe Illustrator (2025 version 29.6.1, Adobe Inc., San Jose, CA, USA).

calcium levels in penile smooth muscle cells, thereby inducing muscle contraction. This effect can be suppressed by 5-HT<sub>2A</sub> receptor antagonists, implicating 5-HT and its 5-HT<sub>2A</sub> receptor in the development of ED [56]. Furthermore, 5-HT acts as a neural signal carrier capable of triggering the acrosome reaction in sperm, which in turn facilitates reproductive system maturation and enhances sperm functionality [57,58]. In humans, 5-HT also controls sexual desire and regulates sexual behavior through hormonal action, and improves sperm motility and fertilization rate by regulating cAMP, testicular blood flow and testosterone in the reproductive system [59].

### 3.1.2 Role of BDNF in the Male Reproductive System

BDNF has a wide range of effects on the mammalian nervous system and gonadal development. It can enhance sperm motility, increase sex hormone levels, and promote the regeneration of blood vessels and nerve fibers. Robinson *et al.* [60] demonstrated the expression and cellular localization of BDNF and its receptors in fetal Leydig cells and adult testis by immunohistochemical methods.

Spermatogenic dysfunction is one of the important causes of male infertility by leading to decreased sperm quantity, decreased quality, or insufficient motility [61]. Safari *et al.* [62] showed that exogenous BDNF supplementation significantly enhanced sperm motility. Gao *et al.* [63] demonstrated that BDNF induced the proliferation of TM3 Leydig cells by upregulating proliferating cell nuclear

antigen and enhancing the phosphorylation of extracellular signal-regulated protein kinase 1/2, thereby promoting sperm production by increasing sex hormone levels. The cavernous nerve (CN), originating from the pelvic plexus, is the main autonomic nerve that regulates penile erection. ED caused by cavernous nerve injury is a common complication of prostate cancer surgery or other pelvic surgery, and has a negative impact on the prognosis and quality of life of patients [64,65]. During ED repair and regeneration, stem cells promote angiogenesis and nerve fiber regeneration by releasing active factors such as vascular endothelial growth factor (VEGF) and BDNF. Chen *et al.* [66] injected BDNF into the cavernous body of CN-injured rats, and the erectile function of the treated group was improved over that of the control group. Lin *et al.* [67] used a combination of different molecular pathway inhibitors in the presence of BDNF and showed that the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway was the main signal transduction pathway for BDNF to promote CN fiber growth. In addition, BDNF expression may also be involved in the regulation of the male ejaculation mechanism. Huang *et al.* [68] observed that rapid ejaculation in rats was associated with reduced TPH<sub>2</sub> expression, decreased 5-HT synthesis, and diminished endogenous BDNF levels in the raphe nuclei, indicating that BDNF may modulate ejaculatory function by enhancing central 5-HT synthesis.

### 3.2 Correlation Between 5-HT and BDNF and Nervous System

Within the nervous system, 5-HT and BDNF contribute significantly to the regulation of mood and cognition. 5-HT neurons are mainly located in the raphe nucleus of the brain stem and project to a variety of areas such as substantia nigra, striatum, and prefrontal cortex, which are involved in the regulation of cognition and emotion. Depression and anxiety are closely related to changes in 5-HT levels in the brain, especially to the dysfunction of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors. The role of the 5-HT<sub>1A</sub> receptor in anxiety regulation is prominent, and its reduction may lead to mood disorders, whereas the 5-HT<sub>2A</sub> receptor is closely linked to the symptoms of schizophrenia. Relatively high levels of BDNF expression in the hippocampus and prefrontal cortex have also been associated with emotional stability. The decrease of BDNF has been significantly associated with the pathogenesis of various psychological disorders such as depression and anxiety disorders. In addition, BDNF genetic polymorphisms such as Val66Met have been significantly associated with the development of anxiety disorders, and low serum BDNF levels may be a biomarker for anxiety disorders. In summary, emotional and cognitive processes within the nervous system are profoundly influenced by 5-HT and BDNF, whose dysregulation has been implicated in the etiology of multiple psychiatric conditions.

#### 3.2.1 Role of 5-HT in the Nervous System

In the brain, the cell bodies of 5-HT neurons are primarily distributed in the raphe nuclei of the brainstem, with efferent projections extending to the substantia nigra, striatum, globus pallidus, hypothalamus, thalamus, and cortex, which are regions critically involved in cognitive and emotional processing [69]. The effects of 5-HT on cognition and emotion regulation are achieved through a number of different 5-HT receptors, and almost all 5-HT receptor subtypes are involved in the regulation of depression or anxiety [70]. The 5-HT<sub>1A</sub> receptor is the receptor subtype that has been studied more in anxiety. Patients with panic disorder have been found to have reduced 5-HT<sub>1A</sub> receptors in the forebrain and raphe nucleus [71]. Mice with anxiety-like behaviors were also found to have reduced 5-HT<sub>1A</sub> receptors in the amygdala, suggesting that 5-HT<sub>1A</sub> receptors are involved in the regulation of anxiety-like behaviors [72]. The decrease of 5-HT level in the brain is considered to be the main pathogenic factor of depression [73]. 5-HT<sub>1A</sub> receptors exert inhibitory effects on serotonergic neurons, so these autoreceptors may limit the response of serotonergic neurons to afferent excitation. Chen *et al.* [74] showed that mice develop depressive-like behaviors in response to uncontrollable stress, which is associated with up-regulation of 5-HT<sub>1A</sub> autoreceptors. However, when mice face repetitive, predictable stress, they adapt to the stress and down-regulate 5-HT<sub>1A</sub>, resulting in increased extracellular 5-HT concentration and increased transmission of monoamine neurotransmitters.

Nevertheless, the extensive projection patterns of serotonergic neurons make pharmacological interventions susceptible to off-target effects on non-target brain regions; in addition to therapeutic actions, they may provoke central adverse effects—such as insomnia and appetite loss—by disrupting sleep-wake cycles or appetite-regulatory pathways [75]. In addition, 5-HT dysfunction is associated with schizophrenia. Lysergic acid diethylamide (LSD) causes schizophrenia-like hallucination and delusional symptoms by activating 5-HT receptors, particularly 5-HT<sub>2A</sub> receptors [76]. Diez-Alarcia *et al.* [77] used three radiotracers with different pharmacological properties to study the conformation of the 5-HT<sub>2A</sub> receptor in the prefrontal cortex (PFC) of patients with schizophrenia. They found that under normal physiological conditions, the active conformation of the 5-HT<sub>2A</sub> receptor is in dynamic equilibrium with the inactive conformation. However, the proportion of 5-HT<sub>2A</sub> receptors in the active conformation is higher in the brain of schizophrenia patients, and the dynamic balance is broken, causing 5-HT<sub>2A</sub> receptors to be in a state of excessive activation.

#### 3.2.2 Role of BDNF in the Nervous System

Under normal circumstances, BDNF content is high in hippocampus, prefrontal cortex, and other brain regions related to emotion, and is closely related to the reg-

ulation of a variety of emotions. Stress can lead to a decrease in BDNF levels. In rats experiencing unpredictable, chronic mild stress, proBDNF is upregulated in the neocortex and hippocampus, thereby inducing depression-like behaviors [78]. Injection of anti-proBDNF antibody reversed depression-like behaviors in chronic-stress rats [79]. BDNF has a pathway with a number of molecules such as TrkB, p75(NTR), peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$ , and adjustable type III fibronectin component containing protein 5, which are closely related to depression [80]. Xu *et al.* [81] found that the expression of BDNF in the hippocampus of PE rats was significantly reduced, and they showed anxiety behavior, suggesting that the reduction of BDNF levels may mediate the pathological process of psychological diseases such as anxiety by impairing neuroplasticity. Zhang *et al.* [82] showed that BDNF content was decreased in the hippocampus and prefrontal cortex of depressed mice. Moreover, decreased hippocampal volume, decreased neuronal proliferation in the CA3 region, and decreased neuronal apoptosis in the dentate gyrus were closely related to decreased BDNF content. In addition, Han *et al.* [83] found that a single nucleotide polymorphism at position 66 of the *BDNF* gene (*Val66Met*), where methionine replaced valine, is considered to be the key genetic factor of anxiety disorders. There is also a close relationship between the development of anxiety disorders and changes in the expression of BDNF. The observation of 324 subjects also showed that there was a significant correlation between low serum BDNF level and the presence of anxiety disorder as reflected by temperament survey. Therefore, the decrease of serum BDNF level may be a biochemical marker of anxiety disorder [84]. Notably, exogenous BDNF supplementation warrants caution due to dose-dependent risks; excessive BDNF may down-regulate TrkB expression and induce hyperexcitability in the hippocampus and other regions, thereby adversely affecting synaptic circuitry as well as learning and memory [85]. However, BDNF, as an important biological factor of neurodevelopment, is involved in the pathogenesis of bipolar disorder (BD), and mediates cognitive impairment in BD. BDNF may be a biomarker of BD [86]. Zhang *et al.* [87] compared the cognitive function and serum BDNF levels of patients with unipolar and bipolar depression and found that patients with bipolar depression had worse cognitive function and lower BDNF levels.

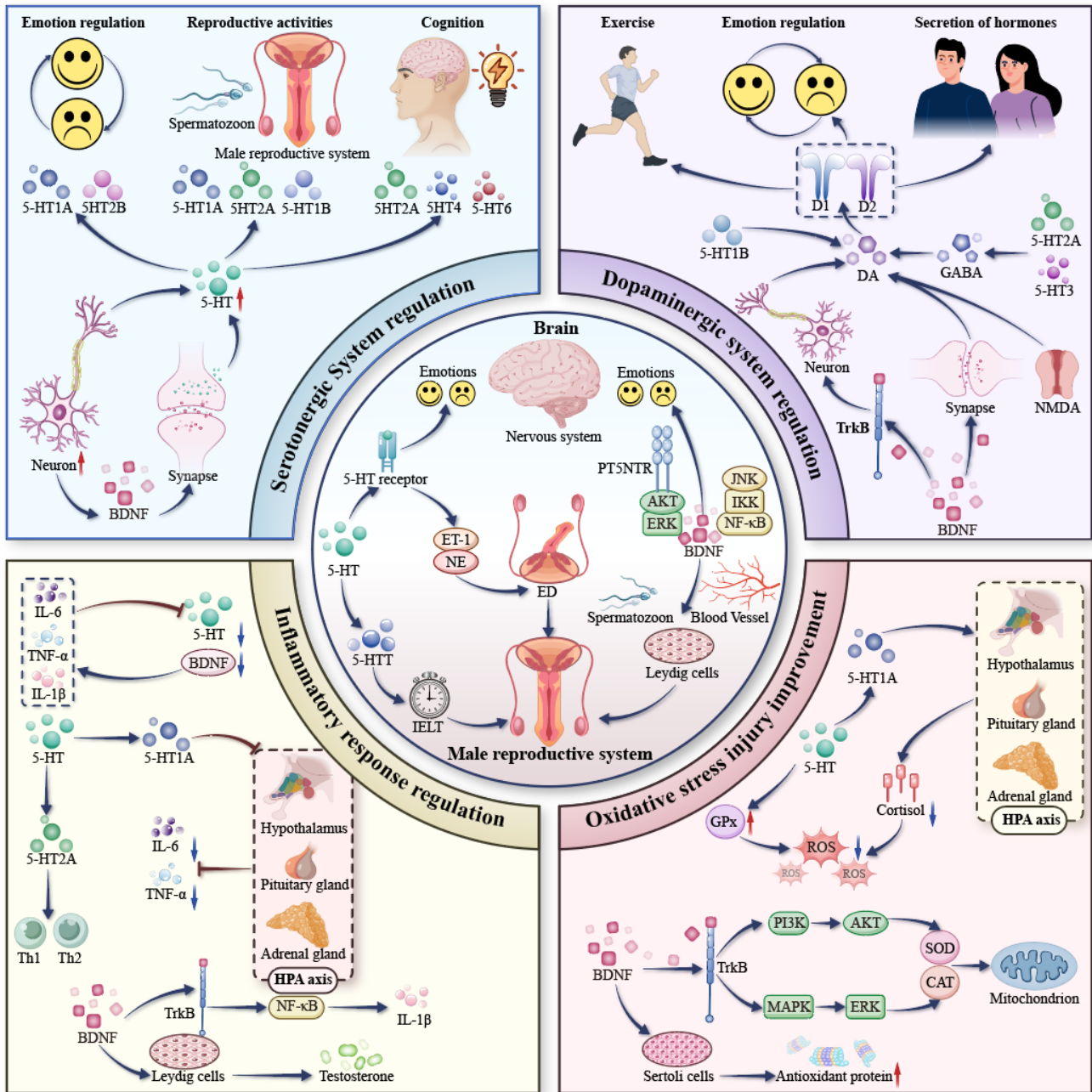
#### 4. The Mechanism of 5-HT and BDNF in PE With Anxiety or Depression

At present, the relationship of the pathological mechanism of PE with anxiety or depression is believed to be closely related to abnormalities in the serotonergic system, imbalance of dopaminergic system, neuroinflammatory response, and oxidative stress injury. The abnormality in the serotonergic system mainly leads to the disorder of ejaculation control and to anxiety and depression

through insufficient synthesis or a metabolic disorder of 5-HT. The imbalance of the dopaminergic system is mainly manifested as excessive activation of the DA signal to accelerate the ejaculatory reflex, which interacts with 5-HT to regulate emotion. The neuroinflammatory response is mainly caused by the interference of proinflammatory factors (IL-6, TNF- $\alpha$ , etc.) with neurotransmitter metabolism and synaptic function. Oxidative-stress damage is caused by the accumulation of reactive oxygen species (ROS), which disrupts neuroendocrine homeostasis. This process may be substantially influenced by the coordinated actions of 5-HT and BDNF. 5-HT regulates ejaculation and mood mainly by activating different receptors. Spinal 5-HT1B receptors inhibit the ejaculatory reflex, whereas defects in prefrontal 5-HT1A receptor function aggravate anxiety or depression. PE in patients is often accompanied by decreased central 5-HT levels and decreased peripheral 5-HT1A receptor-mediated anti-inflammatory effects. SSRIs increase synaptic 5-HT concentration by blocking serotonin transporter (SERT) and synergistically regulating dopamine D4 receptor expression to delay ejaculation. BDNF activates PI3K/Akt and MAPK pathways through the TrkB receptor to maintain 5-HT/DA neuron survival and synaptic plasticity. A decrease in the level of BDNF can lead to damage to the synaptic connections between hippocampus and prefrontal lobe, and aggravate 5-HT-signal-transmission disorder. In addition, BDNF can reduce the inflammatory response by inhibiting the NF- $\kappa$ B pathway and up-regulating superoxide dismutase (SOD)/catalase (CAT) to protect against oxidative stress. Fig. 2 provides a schematic overview of the mechanistic role of 5-HT and BDNF in PE with anxiety or depression.

##### 4.1 5-HT and BDNF Regulate Serotonergic-System Abnormalities

The serotonergic system is an important neurotransmitter system in the human body. With serotonin as the core, it is widely involved in the regulation of emotion, cognition, sleep, and other physiological and psychological functions [88]. The cell bodies in the raphe nuclei neurons are the main source of 5-HT in the brain. They are divided into nine nuclei, named B1-B9. Most of these nuclei contain 5-HT neurons. However, ascending fibers from more medullary clusters (B5-B9) are connected with cerebral cortex, hypothalamus, thalamus, basal ganglia, hippocampus, etc. [89]. Because of this extensive neuronal network, 5-HT may be viewed as one of the major regulators of the CNS. 5-HT directly regulates the serotonergic system by activating different receptors, these include reproductive activities (5-HT1A, 5-HT2A, 5-HT1B, etc.), emotional regulation (5-HT1A, 5-HT2B, etc.), appetite and digestion (5-HT2B, 5-HT4, etc.), and pain perception (5-HT1A, 5-HT2B, 5-HT1F, etc.), cognition and decision making (5-HT2A, 5-HT4, 5-HT6, etc.) [90]. Although BDNF has an indirect regulatory effect on the serotonergic system,



**Fig. 2. The mechanistic role of 5-HT and BDNF in PE with anxiety or depression.** The downward arrow indicates a decrease (downregulation), and the upward arrow represents an increase (upregulation). DA, dopamine; GABA, gamma-aminobutyric acid; TrkB, tropomyosin receptor kinase B; NMDA, N-methyl-D-aspartate; HPA, hypothalamic-pituitary-adrenal; ED, erectile dysfunction; IELT, intravaginal ejaculatory latency time; ET-1, endothelin-1; NE, norepinephrine; IL-6, Interleukin-6; TNF- $\alpha$ , tumor necrosis factor-alpha; IL-1 $\beta$ , interleukin-1 beta; Th1, T helper 1 cell; Th2, T helper 2 cell; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase. The figure was drawn using Adobe Illustrator.

BDNF can support the survival of raphe nucleus neurons and axonal growth by promoting the development of neurons [91]. In addition, BDNF is involved in the regulation of synaptic plasticity, which affects emotional and memory functions by enhancing synaptic connectivity between the hippocampus and prefrontal cortex and improving the efficiency of serotonergic signaling [47]. Therefore, there

is a close interaction between 5-HT and BDNF in the regulation of serotonergic system function, and an abnormality of 5-HT or BDNF may lead to male sexual dysfunction, mood disorders, cognitive deficits, and other pathological problems. Maillet *et al.* [92] showed that the degree of depression and anxiety was mainly related to the degree of serotonergic disruption in the bilateral subgenual por-

tion or the right dorsal aspect of the anterior cingulate cortex. Huang *et al.* [93] found that aerobic exercise can significantly increase the expression of 5-HT and BDNF and prolong IELT by ameliorating abnormalities of the serotonergic system, thus improving the symptoms of PE in rats, which was used as an auxiliary treatment for PE along with the SSRIs dapoxetine. Liu *et al.* [94] confirmed through experiments that high-frequency repetitive transcranial magnetic stimulation (rTMS) could regulate the abnormal regulatory effect of 5-HT and BDNF on the serotonergic system in rats, thereby significantly prolonging IELT and reducing the symptoms of PE in rats. da Fonseca *et al.* [95] found that probiotics significantly increased the expression of serotonergic-system proteins in the hippocampus and prefrontal cortex of food-deprived rats by correcting abnormal serotonergic regulation—through restoring 5-HT and BDNF signaling—and finally improved the anxiety- and depression-related behavior of those rats. Diniz *et al.* [96] found that BDNF overexpression in the ventral hippocampus could significantly reduce depression and anxiety behaviors in serotonin-transporter-deficient rats, which revealed the potential of BDNF in the treatment of depression and anxiety in the regulation of serotonergic system abnormalities.

#### 4.2 5-HT and BDNF Regulate Dopaminergic-System Abnormalities

The dopaminergic system is a neurotransmitter system that regulates motor function, emotion regulation, and stress responses. With DA as the core, it is widely involved in the regulation of movement, emotion, hormone secretion, and other important physiological and psychological activities in the CNS [97]. DA mainly acts through four pathways, among which the mesocortical channels are involved in regulating cognitive decision-making, the mesolimbic channels drive motivational behavior, the nigrostriatal pathway controls motor coordination, and the nodular-infundibular pathway regulates endocrine homeostasis [98]. DA acts by binding to receptors on the cell membrane. DA exerts a variety of physiological effects by activating D1-like (DRD1, DRD5) and D2-like (DRD2, DRD3, DRD4) receptor families [99]. Among them, D1-like receptors enhance neuronal excitability through the cAMP-PKA signaling pathway, whereas D2-like receptors inhibit this pathway by coupling Gi/o proteins [100,101]. 5-HT exerts bidirectional influence on the dopaminergic system via distinct receptor-mediated mechanisms. For example, 5-HT<sub>1B</sub> receptors, located at the axon terminals of striatal dopaminergic neurons, suppress dopamine release and thereby attenuate dopaminergic signaling efficiency [102]. In contrast, 5-HT<sub>2A</sub> and 5-HT<sub>3</sub> receptors indirectly promote the release of dopamine by activating striatal gamma-aminobutyric acid (GABA)ergic interneurons [103]. The development, function, and synaptic remodeling of dopaminergic circuits are strongly influenced

by BDNF-mediated signaling mechanisms. BDNF promotes the survival of dopaminergic neurons and axonal outgrowth by activating the TrkB receptor [31,104]. BDNF regulates the synaptic plasticity of dopaminergic neurons by enhancing synaptic connectivity and N-methyl-D-aspartate (NMDA) receptor function [47,105]. Gao *et al.* [106] demonstrated that the SSRI dapoxetine upregulates the expression of DRD4 to delay ejaculation by increasing the level of 5-HT and mediating the synergistic effect of histone serotonization, and myeloid zinc finger protein 1, on the promoter region of the DRD4 receptor. By establishing a gradient-overpressure-explosion-trauma model, Ma *et al.* [107] showed that high-pressure shock waves could induce sequential fluctuations in serum 5-HT, BDNF, and DA levels in rats (the levels of 5-HT and DA decreased in the acute phase, and the level of BDNF decreased continuously in the chronic phase), which were significantly correlated with the bipolar recurrence of anxiety-like behavior. Chen *et al.* [108] demonstrated that saffron essential oil significantly alleviated depressive symptoms and partially reduced hippocampal neuronal damage by activating the MAPK-CREB1-BDNF signaling axis and upregulating serum 5-HT, DA, and BDNF levels, in mice that had been exposed to chronic, unpredictable, mild stress.

#### 4.3 5-HT and BDNF Regulate Inflammatory Response

Inflammation is a complex and highly coordinated defense response of the body to tissue injury, infection, or harmful stimuli, in order to clear pathogens, repair damaged tissues, and restore body homeostasis [109]. In the male reproductive system, inflammatory activity contributes to homeostatic regulation by eliminating pathogens and promoting tissue repair via cytokine-mediated signaling under normal physiological conditions [110]. Under pathological conditions, chronic inflammation can trigger oxidative stress and apoptosis, leading to reproductive-system dysfunction [111]. In the male reproductive system, glandular tissue such as that in the prostate and seminal vesicle is particularly sensitive to inflammation; inflammatory diseases such as chronic prostatitis are closely related to male conditions such as PE and ED [112,113]. As an important neurotransmitter in men, 5-HT can be involved in the regulation of male inflammatory response. In the CNS, 5-HT inhibits the hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis by activating the 5-HT<sub>1A</sub> receptor, thereby reducing the release of pro-inflammatory factors IL-6 and TNF- $\alpha$  [114,115]. In the peripheral circulation, gut- and platelet-derived 5-HT can directly act on 5-HT<sub>2A</sub> receptors on the surface of immune cells to regulate Th1/Th2 cell balance [116]. The regulatory influence of BDNF on male inflammatory responses has been increasingly recognized. It not only promotes neuronal viability and synaptic remodeling through TrkB signaling, but also inhibits NF- $\kappa$ B activation and downregulates pro-inflammatory cytokines such as IL-1 $\beta$  [117]. In addition, the supporting effect of BDNF

on Leydig cell function may increase or decrease testosterone synthesis, potentially leading to inflammation and endocrine disorders [118,119].

There are interactions among 5-HT, BDNF, and the inflammatory response. On the one hand, inflammatory microenvironment can lead to the damage of central 5-HT neurons and the decrease of BDNF expression [68]. On the other hand, decreased 5-HT levels aggravate inflammation and decrease the availability of BDNF [120]. Zhang *et al.* [121] showed that experimental autoimmune prostatitis induces disorders of 5-HT metabolism in the CNS by increasing serum levels of proinflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$ , which leads to decreased serum 5-HT content and abnormal expression of the 5-HT1A receptor in rats. However, anti-inflammatory treatment can partially reverse this inflammation-mediated dysregulation of the 5-HT system and reduce the symptoms of PE in rats. In BDNF-deficient mice, Parrott *et al.* [122] observed exaggerated neuroinflammatory responses and behavioral anhedonia after peripheral immune activation, which indicated the involvement of BDNF in buffering inflammation-driven depressive-like states through regulation of neuroimmune cascades. Zhuang *et al.* [123] reported that IL-33 inhibited BDNF expression in the basolateral amygdala by activating the NF- $\kappa$ B pathway, thereby impairing GABAergic neurotransmission and inducing anxiety-like behaviors, suggesting that the imbalance of BDNF-mediated neuroplasticity and neuroinflammation may be the core mechanism of inflammation-driven anxiety disorders.

#### 4.4 5-HT and BDNF Improved Oxidative Stress Injury

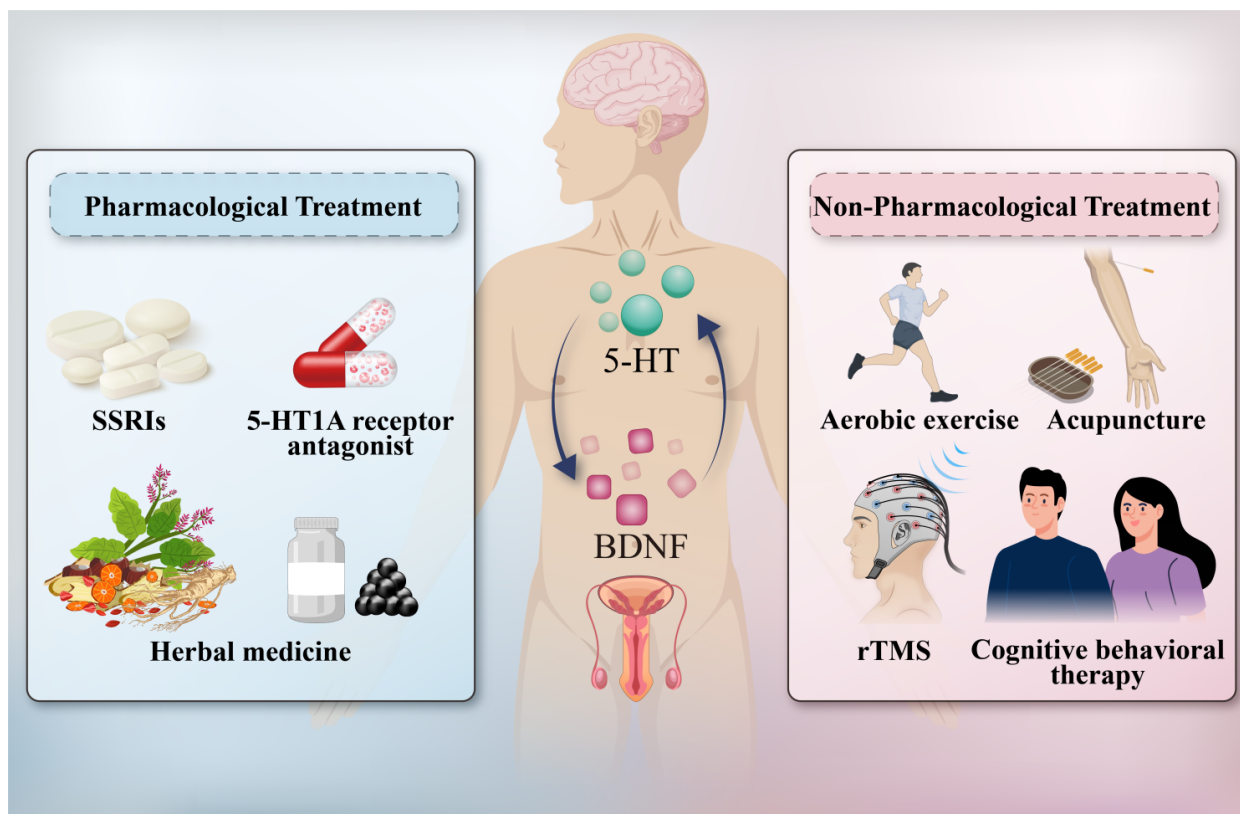
Oxidative stress is a pathological state caused by excessive production of oxides or imbalance of the antioxidant defense system. Its core mechanism is lipid, protein, and DNA damage caused by excessive accumulation of ROS [124]. In the male reproductive system, oxidative stress is an important cause of male diseases such as decreased sperm quality and chronic prostatitis [125,126]. Testicular tissue is particularly sensitive to oxidative damage due to its active metabolism and low levels of antioxidant enzymes. Chronic oxidative stress can damage the function of the hypothalamic-pituitary-testis axis, reduce the synthesis of testosterone, and induce apoptosis of germ cells; this has become the potential pathological basis of male infertility, ED, and PE [127,128]. 5-HT exerts antioxidant effects in both CNS and peripheral tissue. 5-HT inhibits excessive activation of the HPA axis by activating the 5-HT1A receptor and reducing cortisol release, thereby decreasing ROS generation [129]. In addition, 5-HT enhances glutathione peroxidase (GPx) activity, directly scrubbing free radicals and protecting Leydig cells from oxidative damage [130].

BDNF ameliorates oxidative stress by regulating neuroplasticity and mitochondrial function. The binding of BDNF to the TrkB receptor can activate PI3K/Akt and MAPK/ERK pathways, up-regulate the expression of SOD

and CAT, and enhance the antioxidant-defense ability of cells [131,132]. In the male reproductive system, BDNF can maintain the synaptic function between hippocampus and prefrontal cortex and alleviate oxidative stress induced by anxiety or depression [133]. It also directly acts on the Sertoli cells of the testis to promote the synthesis of antioxidant proteins [119]. However, the decreased BDNF level caused by chronic stress may impair the ability of the reproductive system to remove ROS, resulting in inflammation and neuronal apoptosis [134]. Jiang *et al.* [135] found that plasma luteinizing hormone levels were significantly increased in male patients with hypersexual disorder, suggesting dysfunction of the hypothalamic-pituitary-gonadal axis, and suggesting that 5-HT and BDNF may participate in abnormal regulation of sexual behavior including PE through oxidative-stress-mediated neuroendocrine disorders. Xia *et al.* [136] showed that sesamol significantly restored hippocampal 5-HT and NE levels and alleviated depression and anxiety-like behaviors by activating the Nrf2 antioxidant pathway and up-regulating the BDNF/TrkB/CREB signaling axis. The results suggested that mood disorders associated with gut-brain interaction may be alleviated through the combined actions of 5-HT and BDNF in regulating oxidative stress and neuroinflammatory pathways. Keshavarzi *et al.* [137] established a methamphetamine-induced neurotoxicity model in rats and confirmed that metformin significantly improved oxidative stress and neuroinflammation by activating the CREB/BDNF and Akt/GSK3 signaling axes, and reversed methamphetamine-induced anxiety, depression, and cognitive impairment. Those findings indicate that neurotransmitter metabolism and mood regulation may be modulated through BDNF-associated signaling pathways.

#### 4.5 5-HT and BDNF Mediated Related Signaling Pathways

Emerging evidence has suggested that 5-HT and BDNF exert their physiological and pathological effects through complex intracellular signaling cascades that govern neurotransmission, synaptic plasticity, inflammation, and oxidative stress. Table 1 (Ref. [138–147]) summarizes key studies that elucidate the mechanisms by which 5-HT-related pathways contribute to PE with comorbid anxiety or depression. Pharmacological and non-pharmacological interventions, including SSRIs (e.g., dapoxetine, fluoxetine), 5-HT receptor agonists/antagonists, acupuncture, and pulsed radiofrequency, have been shown to modulate serotonergic signaling via diverse pathways such as TPH<sub>2</sub>-mediated 5-HT synthesis, 5-HT1A/1B/2A/2BR/6 receptor activity, SERT modulation, and downstream cascades involving ERK1/2, CREB, and BDNF expression. Those findings have demonstrated the ability of serotonergic interventions to regulate both ejaculatory control and emotional behaviors through central and peripheral mechanisms. Table 2 (Ref. [68,94,126,148–154]) focuses



**Fig. 3. Clinical application of 5-HT and BDNF in the treatment of PE with anxiety or depression.** SSRIs, selective serotonin reuptake inhibitors; rTMS, repetitive transcranial magnetic stimulation. The figure was drawn using Adobe Illustrator.

on BDNF-mediated signaling pathways involved in the neurobiological regulation of PE accompanied by anxiety or depression. Various treatment modalities—including rTMS, herbal compounds, antidepressants, acupuncture, and neurostimulation—activate canonical BDNF signaling via TrkB, CREB, ERK1/2, PI3K/Akt, mTOR, and Nrf2 axes. These pathways contribute to the restoration of hippocampal and prefrontal synaptic plasticity, dendritic integrity, neurogenesis, and antioxidative defense, thereby alleviating ejaculatory dysfunction and affective symptoms. Additionally, synergistic regulation of 5-HT and BDNF—such as BDNF-enhanced TPH<sub>2</sub> expression—further underscores their coordinated role in modulating serotonergic tone.

## 5. Clinical Application of 5-HT and BDNF in the Treatment of PE With Anxiety or Depression

Although no standardized therapy directly targeting 5-HT and BDNF has been established for PE with comorbid anxiety or depression, accumulating evidence has indicated that several existing pharmacological and non-pharmacological approaches may exert therapeutic effects by modulating these pathways. The following summarizes representative treatments, their mechanisms, and related experimental or clinical findings (Fig. 3).

### 5.1 Pharmacotherapy in Modern Medicine

In a randomized clinical trial, Siroosbakht *et al.* [155] compared four SSRIs (sertraline, fluoxetine, paroxetine, and citalopram) for the treatment of PE and found that each significantly prolonged IELT via inhibition of 5-HT reuptake. Although adverse effects such as somnolence and dyspepsia were observed, no serious complications occurred and no treatment discontinuations were reported; nonetheless, interindividual differences in tolerability warrant clinical attention. Animal experiments showed that the SSRI fluoxetine reduced anxiety and depression behavior in mice by activating the 5-HT<sub>1A</sub> receptor (5-HT<sub>1A</sub>R) to disrupt the nNOS-CAPON interaction, up-regulating the BDNF/ERK/CREB signaling pathway in the hippocampus, and enhancing neural plasticity [156]. Migliorini *et al.* [157] demonstrated in a double-blind controlled trial that GSK958108, a 5-HT<sub>1A</sub> receptor antagonist, significantly prolonged IELT in PE patients by 16% in the 3-mg group and 77% in the 7-mg group by blocking the central 5-HT<sub>1A</sub> autoreceptor and enhancing 5-HT neurotransmission. A study on rats demonstrated that combining the SSRI paroxetine with the 5-HT<sub>1A</sub> receptor antagonist Atlas987 synergistically modulated the 5-HT system to acutely, on-demand, prolong IELT, suggesting a novel, potentially on-demand strategy for treating LPE [158]. Although SSRIs—by elevating 5-HT concentrations in the

**Table 1. Mechanistic studies of 5-HT-mediated signaling pathways associated with PE and with anxiety or depression.**

Signaling pathways/mechanisms	Study drugs/treatments	Subjects	Indicators of observation	Ref.
Trp→5-HTP→5-HT	Dapoxetine (SSRI)	LPE patients and healthy controls	Trp/LNAAs ratio ↓; KYN/Trp ratio ↑; central 5-HT level ↓; serotonergic metabolic abnormality ↑	[138]
Tph <sub>2</sub> -mediated signaling pathways for 5-HT synthesis	Dapoxetine (SSRI)	Rats	TPH <sub>2</sub> -mediated 5-HT synthesis pathway ↑; central 5-HT level ↑; IELT ↑; premature ejaculation behavior ↓	[139]
The excitability of 5-HT1B receptor was enhanced	Acupuncture needle	PE patients and controls	5-HT1B receptor excitability ↑; spinal ejaculation-related pathway activity ↓; frontal cortical activation ↑; IELT ↑	[140]
Inhibition mediated by peripheral 5-HT1A receptors	Selective 5-HT receptor agonists	Wistar rats	Peripheral 5-HT1A receptor activation ↑; electrostimulation-induced seminal vesicle contraction ↓	[141]
Enhanced 5-HT1A receptor-mediated neurotransmission	Imipramine (tricyclic), fluoxetine (SSRI)	Wistar rats	5-HT1A receptor-mediated neurotransmission in dPAG ↑; anxiety-like behavior ↓	[142]
ERK1/2 phosphorylation mediated by 5-HT2A receptor hyperactivity was enhanced	Fluoxetine (SSRI), doxorubicin combined with cyclophosphamide	Rats	5-HT2A receptor activation ↑; ERK1/2 phosphorylation ↑; anxiety-like behavior ↑; hippocampal 5-HT level ↑ (ineffective in reversing ERK1/2 ↑)	[143]
5-HT2BR/ $\beta$ -arrestin2	Fluoxetine (SSRI)	CMS model mice	5-HT2BR/ $\beta$ -arrestin2 signaling pathway ↑; A1-type reactive astrocyte activation ↓; depressive-like behavior ↓	[144]
5-HT/SERT	Pulsed radio frequency (PRF)	Wistar rats	SERT density in descending 5-HTergic pathway ↑; IL-6 level ↓; mechanical allodynia ↓; cold allodynia ↓; depressive-like behavior ↓	[145]
5-HT6/AC-cAMP-PKA-MEK-CREB-BDNF	EMD-386088; SB-258585; SQ-22536; H89; U0126	Rats	VLO 5-HT6 receptor activation ↑; AC-cAMP-PKA-MEK-CREB-BDNF signaling pathway ↑; p-ERK expression ↑; p-CREB expression ↑; BDNF expression ↑; anxiety-like behavior ↓; depression-like behavior ↓	[146]
5-HT3R/NK-1/NK-2	Plant alkaloids (Berberine)	Patients with neuropathic pain	5-HT3 receptor activity ↓; substance P release ↓; NK-1/NK-2 pathway activation ↓; IL-6 level ↓; TNF- $\alpha$ level ↓; depressive-like behavior ↓	[147]

LPE, lifelong premature ejaculation; IELT, intravaginal ejaculatory latency time; dPAG, dorsal periaqueductal gray; CMS, chronic mild stress; SERT, 5-hydroxytryptamine transporter; AC, Adenylyl cyclase; cAMP, Cyclic adenosine monophosphate; PKA, Protein kinase A; MEK, Mitogen-activated protein kinase; VLO, ventrolateral orbital cortex; NK, neurokinin; ↑, increase; ↓, decrease.

synaptic cleft—are first-line agents for PE, recent studies underscored multiple clinical risks, including off-label use, adverse effects, long-term safety concerns, and contraindications in special populations [159]. In addition to their ejaculatory-delay efficacy, SSRIs may induce multiple adverse events during treatment, chiefly manifesting as neurologic symptoms (e.g., dizziness, headache), gastrointestinal disturbances (e.g., nausea, diarrhea), and sexual adverse

effects such as decreased libido and secondary sexual dysfunction [160,161]. Although SSRIs can modulate the 5-HT system to improve both mood and ejaculatory function, clinicians should be aware that excessive serotonergic activity may exacerbate anxiety; therapy should be initiated at low doses with close monitoring of mood changes [162]. Moreover, studies have indicated a strong association between SSRIs and severe hyponatremia, with the highest risk

**Table 2. Mechanistic studies of BDNF-mediated signaling pathways associated with PE and with Anxiety or depression.**

Signaling ways/mechanisms	path- drugs/treatments	Study	Subjects	Indicators of observation	Ref.
BDNF/TrkB	High frequency rTMS (10 Hz)		PE rats and sham stimulation control group	Hippocampal 5-HT concentration ↑; BDNF–TrkB signaling ↑; SYN expression ↑; PSD95 expression ↑; neural plasticity ↑	[94]
BDNF/TPH <sub>2</sub> /5-HT	Observation of natural behavior		Male rats	Dorsal raphe BDNF level ↓; 5-HT level ↓; TPH <sub>2</sub> mRNA expression ↓; TPH <sub>2</sub> protein expression ↓; 5-HT synthesis ↓	[68]
BDNF/TrkB/CREB	2-phenylethylamine (PEA) combined with/against CORT		Cort-induced hippocampal neurons/depression model mice	Dendritic spine damage ↓; BDNF/TrkB/CREB pathway activation ↑; depressive-like behavior ↓; hippocampal BDNF expression ↑; hippocampal TrkB expression ↑	[148]
BDNF/MAPK	Bladder Meridian Acupressure (ABM)		Chronic stress-induced anxiety in rats	MAPK signaling in hippocampus ↓; BDNF signaling ↑; proinflammatory cytokines ↓; neurotransmitter balance ↑; anxiety-like behavior ↓	[149]
BDNF/ERK1/2/CREB	Spinoposin		C57BL/6J male mice	ERK1/2/CREB/BDNF signaling ↑; neuroprotective protein expression in hippocampus ↑; neuroprotective protein expression in prefrontal cortex ↑; neurotransmitter balance ↑; inflammatory response ↓; anxiety-like behavior ↓	[150]
BDNF–TrkB–Akt	Imipramine		Female SERT KO rats	BDNF–TrkB–Akt signaling in subcortical limbic cortex ↑; depressive-like behavior ↓	[151]
BDNF/TrkB–ERK1/2	Bilateral vmPFC DBS		Male CUS model rats and non-stressed rats	BDNF/TrkB signaling ↑; ERK1/2 phosphorylation ↑; depressive-like behavior ↓ (reversal of CUS-induced symptoms)	[152]
BDNF/AKT/mTOR	Esketamine (ESK)		Maternal rats with postpartum depression	BDNF/AKT/mTOR pathway integrity in prefrontal cortex ↑; BDNF/AKT/mTOR pathway integrity in hippocampus ↑; anxiety-like behavior ↓; depressive-like behavior ↓	[126]
eIF4E/BDNF	Ketamine		Cort-induced depression in male mice	eIF4E phosphorylation ↓ (via eFT508); MNK1 expression ↓ (via eFT508); TrkB/BDNF signaling ↑ (via 7,8-DHF); eIF4E phosphorylation ↑; MNK1 expression ↑	[153]
Nrf2–BDNF	Chlorphenamine (CPA)		Male Wistar rats	Nrf2–BDNF signaling in hippocampus ↑; Nrf2–BDNF signaling in cortex ↑; oxidative stress ↓ (SOD activity ↑, MDA ↓); inflammation ↓ (IL-6 ↓, IL-1β ↓); 5-HT level in brain ↑; norepinephrine level ↑; anxiety-like behavior ↓	[154]

SYN, synapsin; PSD95, postsynaptic density protein 95; TPH<sub>2</sub>, tryptophan hydroxylase 2; PEA, 2-phenylethylamine; CORT, corticosterone; ABM, bladder Meridian Acupressure; CREB, cAMP response element-binding protein; SERT KO, serotonin transporter knockout; vmPFC DBS, ventromedial prefrontal cortex deep brain stimulation; CUS, chronic unpredictable stress; ESK, esketamine; mTOR, mammalian target of rapamycin; eIF4E, eukaryotic translation initiation factor 4E; MNK1, MAP kinase-interacting serine/threonine-protein kinase 1; 7,8-DHF, 7,8-dihydroxyflavone; Nrf2, nuclear factor erythroid 2-related factor 2; CPA, chlorphenamine; MDA, malondialdehyde; ↑, increase; ↓, decrease.

occurring within the first two weeks after initiation; the risk also increases with age, warranting particular vigilance for early-treatment hyponatremia in older patients [163].

## 5.2 Chinese Herbal Medicine Therapy

In recent years, Traditional Chinese Medicine (TCM)-based therapies have played a significant and increasingly recognized role in managing PE with comorbid anxiety or depression [164,165]. Xie *et al.* [166] reported that commonly used TCM monomers—such as

Cistanche (Roucongong), Epimedium (Yinyanghuo), and Lycium barbarum L. fruits (Gouqizi)—can enhance sexual function, partly by increasing testosterone and exerting antioxidant effects, thereby indirectly alleviating anxiety and depression; meanwhile, multi-component formulas including Shugan Yiyang Capsules, Bazhen Decoction, and Chaihu Shugan San have been shown to improve PE symptoms and accompanying anxiety/depressive states via multi-target actions that modulate the NOS–cGMP pathway and neurotransmitter balance. An animal study demonstrated that a five-herb TCM formula—Lycium barbarum L. fruits (Gouqizi), Epimedium koreanum Nakai leaves (Yinyanghuo), Morinda officinalis How roots (Bajitian), Cinnamomum cassia bark (Rougui), and Eugenia caryophyllata flower buds (Dingxiang)—significantly improved IELT and ejaculatory control in male rats with sexual dysfunction by activating the dopaminergic system and increasing serum testosterone levels [167]. Han *et al.* [168], in a PE rat model, demonstrated that the TCM formula Shugan Yidan Fang improved ejaculatory behavior, with its therapeutic effects likely mediated by modulation of the central dopaminergic system. Cui *et al.* [169], in a randomized controlled trial, reported that an eight-herb topical spray—comprising, among others, Radix Aconiti (Chuanwu), Herba Asari (Xixin), and Pericarpium Zanthoxyli (Huajiao)—combined with PE desensitization therapy, significantly prolonged IELT and improved sexual function indices, and outperformed monotherapy, in patients with lifelong PE. Feng *et al.* [170] demonstrated that Xiao-Chai-Hu-Tang can promote nerve regeneration, regulate neurotransmitter metabolism, and inhibit neuroinflammation by activating the BDNF/TrkB/CREB and PI3K/AKT signaling pathways, and reduce depression and anxiety-like behaviors in rats. A study using a chronic, stress-induced-depression rat model showed that the TCM formula Xiaoyao San significantly improved depressive-like behavior and locomotor activity, exerting multi-pathway antidepressant effects by modulating hepatic mitochondrial metabolomics, energy metabolism, and inflammation-related targets such as IL-6 and TNF- $\alpha$  [171].

### 5.3 Non-Drug Treatment

Huang *et al.* [93] showed that aerobic exercise enhanced ejaculatory control and prolonged ejaculatory latency in rats with PE by up-regulation of BDNF and 5-HT in the raphe nucleus, and the effect of aerobic exercise on delayed ejaculation was almost equivalent to that of dapoxetine. Seo *et al.* [172] showed that acupuncture at certain acupoints could alleviate anxiety and stress responses in rats by activating the BDNF-TrkB signaling pathway in the amygdala, and reducing corticotropin-releasing hormone (CRH) expression and inhibiting HPA-axis over-activation, suggesting that acupuncture that targets BDNF may provide a new avenue for the treatment of anxiety and depression by improving neuroplasticity and

the stress-emotion pathway. A randomized controlled trial demonstrated that both acupuncture and the SSRI paroxetine significantly prolonged IELT in patients with PE, with each factor performing significantly better than placebo; although paroxetine was superior to acupuncture in extending IELT, acupuncture still exhibited clear therapeutic potential, suggesting benefits mediated via modulation of the serotonergic system [173]. Liu *et al.* [94] demonstrated that rTMS enhanced the 5-HT level in the hippocampus and up-regulated BDNF, SYN, and PSD95 expression by activating the BDNF-TrkB-CREB pathway, thereby regulating neuroplasticity and significantly prolonging IELT in PE rats. Schosser *et al.* [174] demonstrated that cognitive behavioral therapy (CBT) regulates neuroplasticity through the BDNF gene polymorphisms; depression patients with specific BDNF variants have more significant responses to CBT treatment, suggesting that CBT may improve depressive symptoms by activating BDNF-dependent synaptic remodeling and hippocampal neurogenesis.

## 6. Conclusions and Prospects

This article reviewed the interrelationship between 5-HT and BDNF in the context of PE comorbid with anxiety or depression. The pathogenesis of PE involves disrupted central 5-HT signaling and impaired BDNF-mediated neuroplasticity, which compromise neuronal survival and synaptic integrity, thereby contributing to the emergence of negative emotional states. Both 5-HT and BDNF appear to be key molecular mediators in the neurobiological mechanisms linking PE with mood disorders.

In both the male reproductive and nervous systems, 5-HT and BDNF play essential roles. In the male reproductive system, 5-HT modulates the ejaculatory threshold via 5-HT<sub>1B</sub> receptors in the spinal ejaculatory center and promotes sex hormone synthesis, and BDNF enhances Leydig cell proliferation and sperm motility through the PI3K/Akt pathway. In the nervous system, 5-HT inhibits anxiety by regulating the HPA axis and GABAergic transmission in the amygdala via 5-HT<sub>1A</sub> receptors, whereas BDNF improves cognitive and emotional function by promoting hippocampal neurogenesis and prefrontal synaptic plasticity.

Mechanistically, their synergistic interaction is reflected in four major ways. First, 5-HT synthesis is reduced due to TPH<sub>2</sub> inhibition in the raphe nucleus, thereby weakening inhibitory input to the spinal ejaculatory center, and BDNF deficiency disrupts emotional regulation in the limbic system by impairing TrkB-mediated ERK/CREB phosphorylation. Second, dopaminergic dysregulation—characterized by D<sub>2</sub> receptor overactivation—accelerates ejaculation, whereas 5-HT<sub>2A</sub> antagonism and BDNF/TrkB signaling contribute to DA/5-HT balance. Third, inflammatory cytokines such as IL-6 and TNF- $\alpha$  suppress BDNF expression via NF- $\kappa$ B and simultaneously enhance 5-HT release from platelets, creating a feedback loop of inflammation and oxidative stress. Fourth, oxidative stress in-

creases MAO-A activity and induces Sertoli cell apoptosis through ROS, whereas BDNF counteracts this by upregulating the SOD/CAT system and Nrf2 pathway to maintain neuroendocrine-reproductive homeostasis.

With respect to clinical applications, management of PE with comorbid anxiety or depression is currently dominated by SSRIs, and no disease-specific targeted pharmacotherapies have yet been developed. Non-pharmacological interventions—including aerobic exercise, acupuncture, repetitive transcranial magnetic stimulation (rTMS), and CBT—have also been reported in clinical studies of PE with anxiety/depression. From the perspectives of physiological and pathological relevance and current therapeutic practice, 5-HT and BDNF emerge as potential biomarkers—and mechanistic nodes—for this condition, acting through multiple pathways *in vivo*. TCM shows distinctive value: multi-herb formulas such as Shugan Yidan Fang and Xiao-Chai-Hu-Tang may concurrently improve ejaculatory control and mood by rebalancing the 5-HT and dopaminergic systems and activating the BDNF/TrkB signaling pathway; moreover, an herbal spray combined with desensitization therapy can further enhance outcomes in LPE, underscoring the holistic advantage of TCM based on syndrome differentiation (bianzheng lunzhi). Additionally, *BDNF*- and *5-HT*-oriented gene therapies, exogenous BDNF protein administration, BDNF enhancers, and TCM interventions show preliminary promise; however, their precise therapeutic windows, target engagement, and mechanisms of action remain to be fully elucidated.

It is important to note that the central pleiotropy of the 5-HT and BDNF systems makes therapeutic applications unavoidably accompanied by adverse-effect risks. 5-HT is broadly involved in regulating sleep, appetite, and cognition. Although SSRIs improve PE and mood symptoms by inhibiting 5-HT reuptake, they commonly elicit neurologic and gastrointestinal adverse events (e.g., dizziness, nausea), and with long-term use, excessive activation of 5-HT receptors may lead to decreased libido and secondary sexual dysfunction; older patients warrant particular vigilance for hyponatremia. Moreover, supraphysiologic serotonergic tone can destabilize mood regulation, paradoxically exacerbating anxiety and, in severe cases, precipitating serotonin syndrome. Therefore, we propose that special attention should be paid to individual dosage, timely monitoring of mood changes, close attention to drug complications, and careful selection of drug users when using SSRIs for the treatment of PE. In addition, due to the high expression of BDNF in the hippocampus, prefrontal lobe and other key brain regions for emotion and cognition, excessive exogenous supplement of BDNF or excessive activation of TrkB signaling pathway may interfere with normal neuroplasticity, and there is a potential risk of inducing emotional fluctuations or cognitive dysfunction. Fundamentally, these adverse effects reflect the difficulty of

restricting current interventions to the pathological targets specific to PE with anxiety/depression. Developing strategies that preferentially engage specific receptor subtypes or modulate signaling within defined brain regions to reduce systemic side effects remains a key challenge for clinical translation.

As PE with anxiety or depression represents a cross-domain disorder involving both neural and male reproductive systems, investigating the roles of 5-HT and BDNF in its pathophysiology remains a central focus of current research. Moving forward, optimizing the application of these molecular targets in clinical treatment—while ensuring both efficacy and safety—will be a key objective.

## Abbreviations

PE, premature ejaculation; LPE, lifelong premature ejaculation; IELT, intravaginal ejaculatory latency time; APE, acquired premature ejaculation; 5-HT, 5-hydroxytryptamine; CNS, central nervous system; BDNF, brain-derived neurotrophic factor; SSRIs, selective serotonin reuptake inhibitors; 5-HTT, 5-hydroxytryptamine transporter; DA, dopamine; TrkB, tropomyosin receptor kinase B; ET-1, endothelin-1; NE, norepinephrine; PI3K, phosphatidylinositol-3-kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal Kinase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; 5-HTP, 5-hydroxytryptophan; 5-HTPDC, 5-hydroxytryptophan decarboxylase; Trp, tryptophan; TPH<sub>2</sub>, tryptophan hydroxylase 2; VMAT, vesicular monoamine transporter; MAO, monoamine oxidase; 5-HIAA, 5-hydroxyindoleacetic acid; GPCRs, G protein-coupled receptors; CREB, cAMP response element-binding protein; p75(NTR), p75 neurotrophin receptor; ED, erectile dysfunction; CN, cavernous nerve; VEGF, vascular endothelial growth factor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex; BD, bipolar disorder; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; rTMS, repetitive transcranial magnetic stimulation; GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; PRF, Pulsed radio frequency; PEA, 2-phenylethylamine; ABM, bladder Meridian Acupressure; ESK, esketamine; CPA, chlorphenamine; CRH, corticotropin-releasing hormone; CBT, cognitive behavioral therapy.

## Author Contributions

JFQ and ZMH designed the research study and revised the manuscript critically for important intellectual content. YW, BN, and SJW conceptualized the study, performed literature searches, drafted the manuscript, and designed the figures. WSC, LQZ, and CXC collected and sorted references, assisted in data collation, and provided technical support for figure optimization. All authors contributed to editorial changes in the manuscript. All authors read and ap-

proved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This study was supported by the National Natural Science Foundation of China (No. 82305229) and the Shenzhen Science and Technology Program (No. JCYJ20230807094759010).

## Conflict of Interest

The authors declare no conflict of interest.

## References

- [1] Althof SE, McMahon CG, Waldinger MD, Serefoglu EC, Shindel AW, Adaikan PG, *et al.* An update of the International Society of Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation (PE). *The Journal of Sexual Medicine*. 2014; 11: 1392–1422. <https://doi.org/10.1111/jsm.12504>.
- [2] Shindel AW, Althof SE, Carrier S, Chou R, McMahon CG, Mulhall JP, *et al.* Disorders of Ejaculation: An AUA/SMSNA Guideline. *The Journal of Urology*. 2022; 207: 504–512. <https://doi.org/10.1097/JU.0000000000002392>.
- [3] Sansone A, Aversa A, Corona G, Fisher AD, Isidori AM, La Vignera S, *et al.* Management of premature ejaculation: a clinical guideline from the Italian Society of Andrology and Sexual Medicine (SIAMS). *Journal of Endocrinological Investigation*. 2021; 44: 1103–1118. <https://doi.org/10.1007/s40618-020-01458-4>.
- [4] Colonnello E, Ciocca G, Limoncin E, Sansone A, Jannini EA. Redefining a sexual medicine paradigm: subclinical premature ejaculation as a new taxonomic entity. *Nature Reviews. Urology*. 2021; 18: 115–127. <https://doi.org/10.1038/s41585-020-00417-1>.
- [5] Corona G, Rastrelli G, Limoncin E, Sforza A, Jannini EA, Maggi M. Interplay Between Premature Ejaculation and Erectile Dysfunction: A Systematic Review and Meta-Analysis. *The Journal of Sexual Medicine*. 2015; 12: 2291–2300. <https://doi.org/10.1111/jsm.13041>.
- [6] Salonia A, Capogrosso P, Boeri L, Cocci A, Corona G, Dinkelman-Smit M, *et al.* European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2025 Update on Male Hypogonadism, Erectile Dysfunction, Premature Ejaculation, and Peyronie's Disease. *European Urology*. 2025; 88: 76–102. <https://doi.org/10.1016/j.eururo.2025.04.010>.
- [7] Rowland DL, Althof SE, Cote-Leger P. Intermittent premature ejaculation: exploring an understudied phenomenon. *The Journal of Sexual Medicine*. 2025; 22: 1373–1382. <https://doi.org/10.1093/jsxmed/qdaf113>.
- [8] Niu C, Ventus D, Jern P, Santtila P. Premature ejaculation among Chinese urban men: prevalence and correlates. *Sexual Medicine*. 2023; 11: qfac015. <https://doi.org/10.1093/sexmed/qfac015>.
- [9] Andresen JB, Graugaard C, Andersson M, Bahnsen MK, Frisch M. Sexual Inactivity and Dysfunction in Denmark: A Project SEXUS Study. *Archives of Sexual Behavior*. 2022; 51: 3669–3688. <https://doi.org/10.1007/s10508-022-02348-x>.
- [10] Herkommer K, Meissner VH, Dinkel A, Jahnen M, Schiele S, Kron M, *et al.* Prevalence, lifestyle, and risk factors of erectile dysfunction, premature ejaculation, and low libido in middle-aged men: first results of the Bavarian Men's Health-Study. *Andrology*. 2024; 12: 801–808. <https://doi.org/10.1111/andr.13524>.
- [11] Waldinger MD, McIntosh J, Schweitzer DH. A five-nation survey to assess the distribution of the intravaginal ejaculatory latency time among the general male population. *The Journal of Sexual Medicine*. 2009; 6: 2888–2895. <https://doi.org/10.1111/j.1743-6109.2009.01392.x>.
- [12] Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, Boolell M. A multinational population survey of intravaginal ejaculation latency time. *The Journal of Sexual Medicine*. 2005; 2: 492–497. <https://doi.org/10.1111/j.1743-6109.2005.00070.x>.
- [13] Rosen RC, Althof S. Impact of premature ejaculation: the psychological, quality of life, and sexual relationship consequences. *The Journal of Sexual Medicine*. 2008; 5: 1296–1307. <https://doi.org/10.1111/j.1743-6109.2008.00825.x>.
- [14] Sotomayor M. The burden of premature ejaculation: the patient's perspective. *The Journal of Sexual Medicine*. 2005; 2 Suppl 2: 110–114. <https://doi.org/10.1111/j.1743-6109.2005.20371.x>.
- [15] Hanafy S, Hamed AM, Hilmy Samy MS. Prevalence of premature ejaculation and its impact on the quality of life: Results from a sample of Egyptian patients. *Andrologia*. 2019; 51: e13298. <https://doi.org/10.1111/and.13298>.
- [16] Gao J, Zhang X, Su P, Peng Z, Liu J, Xia L, *et al.* The impact of intravaginal ejaculatory latency time and erectile function on anxiety and depression in the four types of premature ejaculation: a large cross-sectional study in a Chinese population. *The Journal of Sexual Medicine*. 2014; 11: 521–528. <https://doi.org/10.1111/jsm.12383>.
- [17] Althof S, Rosen R, Symonds T, Mundayat R, May K, Abraham L. Development and validation of a new questionnaire to assess sexual satisfaction, control, and distress associated with premature ejaculation. *The Journal of Sexual Medicine*. 2006; 3: 465–475. <https://doi.org/10.1111/j.1743-6109.2006.00239.x>.
- [18] Liu T, Jia C, Peng YF, Zhong W, Fang X. Correlation between premature ejaculation and psychological disorders in 270 Chinese outpatients. *Psychiatry Research*. 2019; 272: 69–72. <https://doi.org/10.1016/j.psychres.2018.12.038>.
- [19] D'Angelantonio M, Collins JL, Manchia M, Baldessarini RJ, Tondo L. Physical exercise, depression, and anxiety in 2190 affective disorder subjects. *Journal of Affective Disorders*. 2022; 309: 172–177. <https://doi.org/10.1016/j.jad.2022.04.079>.
- [20] Jannini EA, Simonelli C, Lenzi A. Sexological approach to ejaculatory dysfunction. *International Journal of Andrology*. 2002; 25: 317–323. <https://doi.org/10.1046/j.1365-2605.2002.00371.x>.
- [21] Jannini EA, Ciocca G, Limoncin E, Mollaioli D, Di Sante S, Gianfrilli D, *et al.* Premature ejaculation: old story, new insights. *Fertility and Sterility*. 2015; 104: 1061–1073. <https://doi.org/10.1016/j.fertnstert.2015.08.035>.
- [22] Stein MB, Andrews AM. Serotonin States and Social Anxiety. *JAMA Psychiatry*. 2015; 72: 845–847. <https://doi.org/10.1001/jamapsychiatry.2015.0486>.
- [23] Hampf C, Scherf-Clavel M, Weiß C, Klüpfel C, Stonawski S, Hommers L, *et al.* Effects of Anxious Depression on Antidepressant Treatment Response. *International Journal of Molecular Sciences*. 2023; 24: 17128. <https://doi.org/10.3390/ijms242417128>.

- [24] Thomas RE. In premature ejaculation, SSRIs improve self-perceived symptoms and satisfaction vs. placebo. *Annals of Internal Medicine*. 2021; 174: JC90. <https://doi.org/10.7326/ACJP202108170-090>.
- [25] Bazzari AH, Bazzari FH. BDNF Therapeutic Mechanisms in Neuropsychiatric Disorders. *International Journal of Molecular Sciences*. 2022; 23: 8417. <https://doi.org/10.3390/ijms23158417>.
- [26] Gao L, Zhang Y, Sterling K, Song W. Brain-derived neurotrophic factor in Alzheimer's disease and its pharmaceutical potential. *Translational Neurodegeneration*. 2022; 11: 4. <https://doi.org/10.1186/s40035-022-00279-0>.
- [27] Atik YT, Gokce A, Halis F, Cimen HI. Can low serum brain-derived neurotrophic factor levels be associated with lifelong premature ejaculation?; A pilot study. *Andrologia*. 2020; 52: e13746. <https://doi.org/10.1111/and.13746>.
- [28] Ning B, Ge T, Wu Y, Wang Y, Zhao M. Role of Brain-Derived Neurotrophic Factor in Anxiety or Depression After Percutaneous Coronary Intervention. *Molecular Neurobiology*. 2024; 61: 2921–2937. <https://doi.org/10.1007/s12035-023-03758-1>.
- [29] Guiard BP, David DJP, Deltheil T, Chenu F, Le Maître E, Renoir T, *et al.* Brain-derived neurotrophic factor-deficient mice exhibit a hippocampal hyperserotonergic phenotype. *The International Journal of Neuropsychopharmacology*. 2008; 11: 79–92. <https://doi.org/10.1017/S1461145707007857>.
- [30] Deltheil T, Guiard BP, Guilloux JP, Nicolas L, Deloménie C, Repérant C, *et al.* Consequences of changes in BDNF levels on serotonin neurotransmission, 5-HT transporter expression and function: studies in adult mice hippocampus. *Pharmacology, Biochemistry, and Behavior*. 2008; 90: 174–183. <https://doi.org/10.1016/j.pbb.2007.09.018>.
- [31] Moliner R, Gyrych M, Brunello CA, Kovaleva V, Biojone C, Enkavi G, *et al.* Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nature Neuroscience*. 2023; 26: 1032–1041. <https://doi.org/10.1038/s41593-023-01316-5>.
- [32] Movassaghi CS, Andrews AM. Call me serotonin. *Nature Chemistry*. 2024; 16: 670. <https://doi.org/10.1038/s41557-024-01488-y>.
- [33] Salvan P, Fonseca M, Winkler AM, Beauchamp A, Lerch JP, Johansen-Berg H. Serotonin regulation of behavior via large-scale neuromodulation of serotonin receptor networks. *Nature Neuroscience*. 2023; 26: 53–63. <https://doi.org/10.1038/s41593-022-01213-3>.
- [34] Shine JM, O'Callaghan C, Walpola IC, Wainstein G, Taylor N, Aru J, *et al.* Understanding the effects of serotonin in the brain through its role in the gastrointestinal tract. *Brain: a Journal of Neurology*. 2022; 145: 2967–2981. <https://doi.org/10.1093/brain/awac256>.
- [35] Yu J, Vogt MC, Fox BW, Wrobel CJJ, Fajardo Palomino D, Curtis BJ, *et al.* Parallel pathways for serotonin biosynthesis and metabolism in *C. elegans*. *Nature Chemical Biology*. 2023; 19: 141–150. <https://doi.org/10.1038/s41589-022-01148-7>.
- [36] Carhart-Harris RL. Serotonin, psychedelics and psychiatry. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*. 2018; 17: 358–359. <https://doi.org/10.1002/wps.20555>.
- [37] Okaty BW, Commons KG, Dymecki SM. Embracing diversity in the 5-HT neuronal system. *Nature Reviews. Neuroscience*. 2019; 20: 397–424. <https://doi.org/10.1038/s41583-019-0151-3>.
- [38] Wacker D, Wang C, Katritch V, Han GW, Huang XP, Vardy E, *et al.* Structural features for functional selectivity at serotonin receptors. *Science (New York, N.Y.)*. 2013; 340: 615–619. <https://doi.org/10.1126/science.1232808>.
- [39] Teixeira CM, Rosen ZB, Suri D, Sun Q, Hersh M, Sargin D, *et al.* Hippocampal 5-HT Input Regulates Memory Formation and Schaffer Collateral Excitation. *Neuron*. 2018; 98: 992–1004.e4. <https://doi.org/10.1016/j.neuron.2018.04.030>.
- [40] Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nature Reviews. Neuroscience*. 2013; 14: 7–23. <https://doi.org/10.1038/nrn3379>.
- [41] Kowiański P, Lietzau G, Czuba E, Waśkow M, Steliga A, Moryś J. BDNF: A Key Factor with Multipotent Impact on Brain Signaling and Synaptic Plasticity. *Cellular and Molecular Neurobiology*. 2018; 38: 579–593. <https://doi.org/10.1007/s10571-017-0510-4>.
- [42] Alfonsetti M, d'Angelo M, Castelli V. Neurotrophic factor-based pharmacological approaches in neurological disorders. *Neural Regeneration Research*. 2023; 18: 1220–1228. <https://doi.org/10.4103/1673-5374.358619>.
- [43] Feetham CH, Collabolletta V, Worth AA, Shoop R, Groom S, Harding C, *et al.* Brainstem BDNF neurons are downstream of GFRAL/GLP1R signalling. *Nature Communications*. 2024; 15: 10749. <https://doi.org/10.1038/s41467-024-54367-y>.
- [44] Schanker BD. Epigenetic regulation of brain-derived neurotrophic factor: implications in neurodevelopment and behavior. *The Behavioral and Brain Sciences*. 2012; 35: 377–378. <https://doi.org/10.1017/S0140525X12001100>.
- [45] Podyma B, Parekh K, Güler AD, Deppmann CD. Metabolic homeostasis via BDNF and its receptors. *Trends in Endocrinology and Metabolism: TEM*. 2021; 32: 488–499. <https://doi.org/10.1016/j.tem.2021.04.005>.
- [46] Nikolettou V, Sidiropoulou K, Kallergi E, Dalezios Y, Tavernarakis N. Modulation of Autophagy by BDNF Underlies Synaptic Plasticity. *Cell Metabolism*. 2017; 26: 230–242.e5. <https://doi.org/10.1016/j.cmet.2017.06.005>.
- [47] Wang CS, Kavalali ET, Monteggia LM. BDNF signaling in context: From synaptic regulation to psychiatric disorders. *Cell*. 2022; 185: 62–76. <https://doi.org/10.1016/j.cell.2021.12.003>.
- [48] de Almeida Kiguti LR, Pacheco TL, Antunes E, Kempinas WDG. Lorcaserin Administration has Pro-Ejaculatory Effects in Rats via 5-HT<sub>2C</sub> Receptors Activation: A Putative Pharmacologic Strategy to Delayed Ejaculation? *The Journal of Sexual Medicine*. 2020; 17: 1060–1071. <https://doi.org/10.1016/j.jsxm.2020.02.027>.
- [49] Hentzen C, Musco S, Amarengo G, Del Popolo G, Panicker JN. Approach and management to patients with neurological disorders reporting sexual dysfunction. *The Lancet. Neurology*. 2022; 21: 551–562. [https://doi.org/10.1016/S1474-4422\(22\)00036-9](https://doi.org/10.1016/S1474-4422(22)00036-9).
- [50] Nguyen HB, Nguyen CT, Pham MQ, Hoang L, Sansone A, Jannini EA. Perceived intravaginal ejaculation latency time: The diagnosis of premature ejaculation among Vietnamese men. *Andrology*. 2024; 12: 618–623. <https://doi.org/10.1111/andr.13516>.
- [51] Ishigami T, Yoshioka K, Karicheti V, Marson L. A role for peripheral 5-HT<sub>2</sub> receptors in serotonin-induced facilitation of the expulsion phase of ejaculation in male rats. *The Journal of Sexual Medicine*. 2013; 10: 2688–2702. <https://doi.org/10.1111/jsm.12306>.
- [52] Popova NK, Tsybko AS, Naumenko VS. The Implication of 5-HT Receptor Family Members in Aggression, Depression and Suicide: Similarity and Difference. *International Journal of Molecular Sciences*. 2022; 23: 8814. <https://doi.org/10.3390/ijms23158814>.
- [53] Mazzilli R, Zamponi V, Olana S, Mikovic N, Cimadomo D, Defeudis G, *et al.* Erectile dysfunction as a marker of endocrine and glycemic disorders. *Journal of Endocrinological Investigation*. 2022; 45: 1527–1534. <https://doi.org/10.1007/s40618-022-01788-5>.
- [54] Zelinskaya I, Kornushin O, Savochkina E, Dyachuk V, Vasyutina M, Galagudza M, *et al.* Vascular region-specific changes in arterial tone in rats with type 2 diabetes mellitus:

- Opposite responses of mesenteric and femoral arteries to acetylcholine and 5-hydroxytryptamine. *Life Sciences*. 2021; 286: 120011. <https://doi.org/10.1016/j.lfs.2021.120011>.
- [55] Renden RB, Institoris A, Sharma K, Tran CHT. Modulatory effects of noradrenergic and serotonergic signaling pathway on neurovascular coupling. *Communications Biology*. 2024; 7: 287. <https://doi.org/10.1038/s42003-024-05996-y>.
- [56] Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, *et al*. Erectile dysfunction. *Nature Reviews. Disease Primers*. 2016; 2: 16003. <https://doi.org/10.1038/nrdp.2016.3>.
- [57] Fujinoki M. Serotonin-enhanced hyperactivation of hamster sperm. *Reproduction (Cambridge, England)*. 2011; 142: 255–266. <https://doi.org/10.1530/REP-11-0074>.
- [58] McKnight K, Hoang HD, Prasain JK, Brown N, Vibbert J, Hollister KA, *et al*. Neurosensory perception of environmental cues modulates sperm motility critical for fertilization. *Science (New York, N.Y.)*. 2014; 344: 754–757. <https://doi.org/10.1126/science.1250598>.
- [59] Niederberger CS. The Male Factor in Fertility and Infertility. *The Journal of Urology*. 2017; 197: S92–S93. <https://doi.org/10.1016/j.juro.2016.10.086>.
- [60] Robinson LLL, Townsend J, Anderson RA. The human fetal testis is a site of expression of neurotrophins and their receptors: regulation of the germ cell and peritubular cell population. *The Journal of Clinical Endocrinology and Metabolism*. 2003; 88: 3943–3951. <https://doi.org/10.1210/jc.2003-030196>.
- [61] Agarwal A, Baskaran S, Parekh N, Cho CL, Henkel R, Vij S, *et al*. Male infertility. *Lancet (London, England)*. 2021; 397: 319–333. [https://doi.org/10.1016/S0140-6736\(20\)32667-2](https://doi.org/10.1016/S0140-6736(20)32667-2).
- [62] Safari H, Khanlarkhani N, Sobhani A, Najafi A, Amidi F. Effect of brain-derived neurotrophic factor (BDNF) on sperm quality of normozoospermic men. *Human Fertility (Cambridge, England)*. 2018; 21: 248–254. <https://doi.org/10.1080/14647273.2017.1346301>.
- [63] Gao S, Chen S, Chen L, Zhao Y, Sun L, Cao M, *et al*. Brain-derived neurotrophic factor: A steroidogenic regulator of Leydig cells. *Journal of Cellular Physiology*. 2019; 234: 14058–14067. <https://doi.org/10.1002/jcp.28095>.
- [64] Lloyd L. The ins and outs of penile erection. *Nature Reviews. Urology*. 2024; 21: 193. <https://doi.org/10.1038/s41585-024-00870-2>.
- [65] Guimaraes EL, Dias DO, Hau WF, Julien A, Holl D, Garcia-Collado M, *et al*. Corpora cavernosa fibroblasts mediate penile erection. *Science (New York, N.Y.)*. 2024; 383: eade8064. <https://doi.org/10.1126/science.ade8064>.
- [66] Chen KC, Minor TX, Rahman NU, Ho HC, Nunes L, Lue TF. The additive erectile recovery effect of brain-derived neurotrophic factor combined with vascular endothelial growth factor in a rat model of neurogenic impotence. *BJU International*. 2005; 95: 1077–1080. <https://doi.org/10.1111/j.1464-410X.2005.05470.x>.
- [67] Lin G, Bella AJ, Lue TF, Lin CS. Brain-derived neurotrophic factor (BDNF) acts primarily via the JAK/STAT pathway to promote neurite growth in the major pelvic ganglion of the rat: part 2. *The Journal of Sexual Medicine*. 2006; 3: 821–829. <https://doi.org/10.1111/j.1743-6109.2006.00292.x>.
- [68] Huang Y, Peng D, Geng H, Dai Y, Jiang H, Zhang X. Endogenous Deficiency of Brain-Derived Neurotrophic Factor Induces the Downregulation of Tryptophan Hydroxylase-2 Expression in Raphe Nuclei of Rapid Ejaculator Rats. *The Journal of Sexual Medicine*. 2021; 18: 1491–1499. <https://doi.org/10.1016/j.jsxm.2021.07.009>.
- [69] Michely J, Eldar E, Martin IM, Dolan RJ. A mechanistic account of serotonin's impact on mood. *Nature Communications*. 2020; 11: 2335. <https://doi.org/10.1038/s41467-020-16090-2>.
- [70] Zilberg G, Parpounas AK, Warren AL, Fiorillo B, Provasi D, Filizola M, *et al*. Structural insights into the unexpected agonism of tetracyclic antidepressants at serotonin receptors 5-HT<sub>1e</sub>R and 5-HT<sub>1F</sub>R. *Science Advances*. 2024; 10: eadk4855. <https://doi.org/10.1126/sciadv.adk4855>.
- [71] Aslam SY, Zortea T, Salkovskis P. The cognitive theory of panic disorder: A systematic narrative review. *Clinical Psychology Review*. 2024; 113: 102483. <https://doi.org/10.1016/j.cpr.2024.102483>.
- [72] Yu XD, Zhu Y, Sun QX, Deng F, Wan J, Zheng D, *et al*. Distinct serotonergic pathways to the amygdala underlie separate behavioral features of anxiety. *Nature Neuroscience*. 2022; 25: 1651–1663. <https://doi.org/10.1038/s41593-022-01200-8>.
- [73] Haase J, Brown E. Integrating the monoamine, neurotrophin and cytokine hypotheses of depression—a central role for the serotonin transporter? *Pharmacology & Therapeutics*. 2015; 147: 1–11. <https://doi.org/10.1016/j.pharmthera.2014.10.002>.
- [74] Chen M, Wang C, Lin Y, Chen Y, Xie W, Huang X, *et al*. Dorsal raphe nucleus-hippocampus serotonergic circuit underlies the depressive and cognitive impairments in 5×FAD male mice. *Translational Neurodegeneration*. 2024; 13: 34. <https://doi.org/10.1186/s40035-024-00425-w>.
- [75] Brunetti L, Francavilla F, Leopoldo M, Lacivita E. Allosteric Modulators of Serotonin Receptors: A Medicinal Chemistry Survey. *Pharmaceuticals (Basel, Switzerland)*. 2024; 17: 695. <https://doi.org/10.3390/ph17060695>.
- [76] de Oliveira RP, Yokoyama T, Cardoso Thomaz LDS, de Andrade JS, Santos ADA, de Carvalho Mendonça V, *et al*. Pre-pulse inhibition of the acoustic startle reflex impairment by 5-HT<sub>2A</sub> receptor activation in the inferior colliculus is prevented by GABAA receptor blockade in the pedunculopontine tegmental nucleus. *Behavioural Brain Research*. 2023; 448: 114436. <https://doi.org/10.1016/j.bbr.2023.114436>.
- [77] Diez-Alarcia R, Muguza C, Rivero G, García-Bea A, Gómez-Vallejo V, Callado LF, *et al*. Opposite alterations of 5-HT<sub>2A</sub> receptor brain density in subjects with schizophrenia: relevance of radiotracers pharmacological profile. *Translational Psychiatry*. 2021; 11: 302. <https://doi.org/10.1038/s41398-021-01430-7>.
- [78] Zheng N, Luo S, Zhang X, Hu L, Huang M, Li M, *et al*. Haploinsufficiency of intraflagellar transport protein 172 causes autism-like behavioral phenotypes in mice through BDNF. *Journal of Advanced Research*. 2025; 73: 681–695. <https://doi.org/10.1016/j.jare.2024.08.041>.
- [79] Yang CR, Bai YY, Ruan CS, Zhou FH, Li F, Li CQ, *et al*. Injection of Anti-proBDNF in Anterior Cingulate Cortex (ACC) Reverses Chronic Stress-Induced Adverse Mood Behaviors in Mice. *Neurotoxicity Research*. 2017; 31: 298–308. <https://doi.org/10.1007/s12640-016-9687-4>.
- [80] Zhang K, Wang F, Zhai M, He M, Hu Y, Feng L, *et al*. Hyperactive neuronal autophagy depletes BDNF and impairs adult hippocampal neurogenesis in a corticosterone-induced mouse model of depression. *Theranostics*. 2023; 13: 1059–1075. <https://doi.org/10.7150/thno.81067>.
- [81] Xu C, Wu N, Song T, Dai Y. Rapid ejaculator rats are more susceptible to anxiety compared with normal ejaculator rats. *International Journal of Impotence Research*. 2025; 37: 157–162. <https://doi.org/10.1038/s41443-024-00888-5>.
- [82] Zhang HL, Sun Y, Wu ZJ, Yin Y, Liu RY, Zhang JC, *et al*. Hippocampal PACAP signaling activation triggers a rapid antidepressant response. *Military Medical Research*. 2024; 11: 49. <https://doi.org/10.1186/s40779-024-00548-1>.
- [83] Han X, Shen Q, Hou C, Yang H, Chen W, Zeng Y, *et al*. Disease clusters subsequent to anxiety and stress-related disorders and their genetic determinants. *Nature Communications*. 2024; 15: 1209. <https://doi.org/10.1038/s41467-024-45445-2>.
- [84] Minelli A, Zanardini R, Bonvicini C, Sartori R, Pedrini L, Gennarelli M, *et al*. BDNF serum levels, but not BDNF

- Val66Met genotype, are correlated with personality traits in healthy subjects. *European Archives of Psychiatry and Clinical Neuroscience*. 2011; 261: 323–329. <https://doi.org/10.1007/s00406-011-0189-3>.
- [85] Szarowicz CA, Steece-Collier K, Caulfield ME. New Frontiers in Neurodegeneration and Regeneration Associated with Brain-Derived Neurotrophic Factor and the rs6265 Single Nucleotide Polymorphism. *International Journal of Molecular Sciences*. 2022; 23: 8011. <https://doi.org/10.3390/ijms23148011>.
- [86] Vega-Núñez A, Gómez-Sánchez-Lafuente C, Mayoral-Cleries F, Bordallo A, Rodríguez de Fonseca F, Suárez J, *et al*. Clinical Value of Inflammatory and Neurotrophic Biomarkers in Bipolar Disorder: A Systematic Review and Meta-Analysis. *Biomedicines*. 2022; 10: 1368. <https://doi.org/10.3390/biomedicines10061368>.
- [87] Zhang SF, Chen HM, Xiong JN, Liu J, Xiong J, Xie JZ, *et al*. Comparison of cognitive impairments with lipid profiles and inflammatory biomarkers in unipolar and bipolar depression. *Journal of Psychiatric Research*. 2022; 150: 300–306. <https://doi.org/10.1016/j.jpsychores.2022.04.002>.
- [88] Liu Z, Lin R, Luo M. Reward Contributions to Serotonergic Functions. *Annual Review of Neuroscience*. 2020; 43: 141–162. <https://doi.org/10.1146/annurev-neuro-093019-112252>.
- [89] Cheng HM, Gao CS, Lou QW, Chen Z, Wang Y. The diverse role of the raphe 5-HTergic systems in epilepsy. *Acta Pharmacologica Sinica*. 2022; 43: 2777–2788. <https://doi.org/10.1038/s41401-022-00918-2>.
- [90] Zweckstetter M, Dityatev A, Pomimaskin E. Structure of serotonin receptors: molecular underpinning of receptor activation and modulation. *Signal Transduction and Targeted Therapy*. 2021; 6: 243. <https://doi.org/10.1038/s41392-021-00668-3>.
- [91] Chen B, Gao C, Liu C, Guo T, Hu J, Xue J, *et al*. Heat acclimation in mice requires preoptic BDNF neurons and postsynaptic potentiation. *Cell Research*. 2025; 35: 224–227. <https://doi.org/10.1038/s41422-024-01064-6>.
- [92] Maillat A, Krack P, Lhommée E, Météreau E, Klinger H, Favre E, *et al*. The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain: a Journal of Neurology*. 2016; 139: 2486–2502. <https://doi.org/10.1093/brain/aww162>.
- [93] Huang YY, Peng DW, Liu QS, Jiang H, Zhang XS. Aerobic exercise improves ejaculatory behaviors and complements dapoxetine treatment by upregulating the BDNF-5-HT duo: a pilot study in rats. *Asian Journal of Andrology*. 2023; 25: 637–642. <https://doi.org/10.4103/aja2022121>.
- [94] Liu Q, Wang M, Wang W, Yue S, Jannini TB, Jannini EA, *et al*. Repetitive transcranial magnetic stimulation via the hippocampal brain-derived neurotrophic factor-tyrosine kinase receptor B pathway to affect sexual behavior and neuroplasticity in rapid ejaculation rats. *Andrology*. 2024; 12: 1429–1438. <https://doi.org/10.1111/andr.13595>.
- [95] da Fonseca STO, Alves CC, Dias CT, Mendes-da-Silva C. Probiotics and undernourishment impact on brain 5-Hydroxytryptamine system and neurotrophin BDNF in rats: Risk of depression and anxiety? *Nutrition (Burbank, Los Angeles County, Calif.)*. 2025; 132: 112680. <https://doi.org/10.1016/j.nut.2024.112680>.
- [96] Diniz DM, Calabrese F, Brivio P, Riva MA, Grandjean J, Homberg JR. BDNF Overexpression in the Ventral Hippocampus Promotes Antidepressant- and Anxiolytic-Like Activity in Serotonin Transporter Knockout Rats. *International Journal of Molecular Sciences*. 2021; 22: 5040. <https://doi.org/10.3390/ijms22095040>.
- [97] Hou M, Herold F, Zhang Z, Ando S, Cheval B, Ludyga S, *et al*. Human dopaminergic system in the exercise-cognition link. *Trends in Molecular Medicine*. 2024; 30: 708–712. <https://doi.org/10.1016/j.molmed.2024.04.011>.
- [98] Jovanoski KD, Duquenoy L, Mitchell J, Kapoor I, Treiber CD, Crosset V, *et al*. Dopaminergic systems create reward seeking despite adverse consequences. *Nature*. 2023; 623: 356–365. <https://doi.org/10.1038/s41586-023-06671-8>.
- [99] Misganaw D. Heteromerization of dopaminergic receptors in the brain: Pharmacological implications. *Pharmacological Research*. 2021; 170: 105600. <https://doi.org/10.1016/j.phrs.2021.105600>.
- [100] Mota É, Bompierre S, Betolngar D, Castro LRV, Vincent P. Pivotal role of phosphodiesterase 10A in the integration of dopamine signals in mice striatal D<sub>1</sub> and D<sub>2</sub> medium-sized spiny neurones. *British Journal of Pharmacology*. 2021; 178: 4873–4890. <https://doi.org/10.1111/bph.15664>.
- [101] Chen H, Xiong XX, Jin SY, He XY, Li XW, Yang JM, *et al*. Dopamine D2 receptors in pyramidal neurons in the medial prefrontal cortex regulate social behavior. *Pharmacological Research*. 2024; 199: 107042. <https://doi.org/10.1016/j.phrs.2023.107042>.
- [102] Burke DA, Alvarez VA. Serotonin receptors contribute to dopamine depression of lateral inhibition in the nucleus accumbens. *Cell Reports*. 2022; 39: 110795. <https://doi.org/10.1016/j.celrep.2022.110795>.
- [103] Conde KM, Wong H, Fang S, Li Y, Yu M, Deng Y, *et al*. Serotonin neurons integrate GABA and dopamine inputs to regulate meal initiation. *Metabolism: Clinical and Experimental*. 2025; 163: 156099. <https://doi.org/10.1016/j.metabol.2024.156099>.
- [104] Kang SS, Zhang Z, Liu X, Manfredsson FP, Benskey MJ, Cao X, *et al*. TrkB neurotrophic activities are blocked by  $\alpha$ -synuclein, triggering dopaminergic cell death in Parkinson's disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2017; 114: 10773–10778. <https://doi.org/10.1073/pnas.1713969114>.
- [105] Lituma PJ, Kwon HB, Alviña K, Luján R, Castillo PE. Presynaptic NMDA receptors facilitate short-term plasticity and BDNF release at hippocampal mossy fiber synapses. *eLife*. 2021; 10: e66612. <https://doi.org/10.7554/eLife.66612>.
- [106] Gao P, Liu X, Zhu T, Gao R, Gao J, Zhang Y, *et al*. Vital function of DRD4 in dapoxetine medicated premature ejaculation treatment. *Andrology*. 2023; 11: 1175–1187. <https://doi.org/10.1111/andr.13390>.
- [107] Ma N, Wang H, Lu Q, Liu J, Fan X, Li L, *et al*. Temporal changes of neurobehavior in rats following varied blast magnitudes and screening of serum biomarkers in early stage of brain injury. *Scientific Reports*. 2024; 14: 30023. <https://doi.org/10.1038/s41598-024-81656-9>.
- [108] Chen Z, Gu J, Lin S, Xu Z, Xu H, Zhao J, *et al*. Saffron essential oil ameliorates CUMS-induced depression-like behavior in mice via the MAPK-CREB1-BDNF signaling pathway. *Journal of Ethnopharmacology*. 2023; 300: 115719. <https://doi.org/10.1016/j.jep.2022.115719>.
- [109] Nathan C. Nonresolving inflammation redux. *Immunity*. 2022; 55: 592–605. <https://doi.org/10.1016/j.immuni.2022.03.016>.
- [110] Sengupta P, Dutta S, Roychoudhury S, D'Souza UJA, Govindasamy K, Kolesarova A. COVID-19, Oxidative Stress and Male Reproduction: Possible Role of Antioxidants. *Antioxidants (Basel, Switzerland)*. 2022; 11: 548. <https://doi.org/10.3390/antiox11030548>.
- [111] Dutta S, Sengupta P, Roychoudhury S, Chakravarthi S, Wang CW, Slama P. Antioxidant Paradox in Male Infertility: 'A Blind Eye' on Inflammation. *Antioxidants (Basel, Switzerland)*. 2022; 11: 167. <https://doi.org/10.3390/antiox11010167>.
- [112] Li XC, Zhang XB, Liao ZC, Tang ZY, Li DJ. Is mild erectile dysfunction associated with severe psychological symptoms in Chinese patients with moderate-to-severe chronic prostatitis/chronic pelvic pain syndrome? *Asian Journal of Andrology*.

- 2021; 23: 319–324. [https://doi.org/10.4103/aja.aja\\_71\\_20](https://doi.org/10.4103/aja.aja_71_20).
- [113] Wang H, Zhao M, Zhang J, Yan B, Gao Q, Guo J. Traditional Chinese medicine regulates inflammatory factors in chronic prostatitis/chronic pelvic pain syndrome: A review. *Integrative Medicine in Nephrology and Andrology*. 2023; 10: e1. <http://doi.org/10.1097/IMNA-D-22-00001>.
- [114] Qiu X, Lu P, Zeng X, Jin S, Chen X. Study on the Mechanism for SIRT1 during the Process of Exercise Improving Depression. *Brain Sciences*. 2023; 13: 719. <https://doi.org/10.3390/brainsci13050719>.
- [115] Munawar N, Bitar MS, Masocha W. Activation of 5-HT1A Receptors Normalizes the Overexpression of Presynaptic 5-HT1A Receptors and Alleviates Diabetic Neuropathic Pain. *International Journal of Molecular Sciences*. 2023; 24: 14334. <https://doi.org/10.3390/ijms241814334>.
- [116] Martino M, Rocchi G, Escelsior A, Fornaro M. Immunomodulation Mechanism of Antidepressants: Interactions between Serotonin/Norepinephrine Balance and Th1/Th2 Balance. *Current Neuropharmacology*. 2012; 10: 97–123. <https://doi.org/10.2174/157015912800604542>.
- [117] Serra MP, Sanna F, Boi M, Poddighe L, Secci L, Trucas M, *et al.* Acute Stress Induces Different Changes on the Expression of BDNF and trkB in the Mesocorticolimbic System of Two Lines of Rats Differing in Their Response to Stressors. *International Journal of Molecular Sciences*. 2022; 23: 14995. <https://doi.org/10.3390/ijms232314995>.
- [118] Gao S, Li C, Xu Y, Chen S, Zhao Y, Chen L, *et al.* Differential expression of microRNAs in TM3 Leydig cells of mice treated with brain-derived neurotrophic factor. *Cell Biochemistry and Function*. 2017; 35: 364–371. <https://doi.org/10.1002/cbf.3283>.
- [119] Tan X, Zhao L, Tang Y. The Function of BDNF and Its Receptor in the Male Genitourinary System and Its Potential Clinical Application. *Current Issues in Molecular Biology*. 2022; 45: 110–121. <https://doi.org/10.3390/cimb45010008>.
- [120] Tsybko AS, Ilchibaeva TV, Filimonova EA, Eremin DV, Popova NK, Naumenko VS. The Chronic Treatment With 5-HT<sub>2A</sub> Receptor Agonists Affects the Behavior and the BDNF System in Mice. *Neurochemical Research*. 2020; 45: 3059–3075. <https://doi.org/10.1007/s11064-020-03153-5>.
- [121] Zhang Y, Li X, Zhou K, Zhou M, Xia K, Xu Y, *et al.* Influence of Experimental Autoimmune Prostatitis on Sexual Function and the Anti-inflammatory Efficacy of Celecoxib in a Rat Model. *Frontiers in Immunology*. 2020; 11: 574212. <https://doi.org/10.3389/fimmu.2020.574212>.
- [122] Parrott JM, Porter GA, Redus L, O'Connor JC. Brain derived neurotrophic factor deficiency exacerbates inflammation-induced anhedonia in mice. *Psychoneuroendocrinology*. 2021; 134: 105404. <https://doi.org/10.1016/j.psyneuen.2021.105404>.
- [123] Zhuang X, Zhan B, Jia Y, Li C, Wu N, Zhao M, *et al.* IL-33 in the basolateral amygdala integrates neuroinflammation into anxiogenic circuits via modulating BDNF expression. *Brain, Behavior, and Immunity*. 2022; 102: 98–109. <https://doi.org/10.1016/j.bbi.2022.02.019>.
- [124] Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC, Touyz RM. Oxidative Stress and Hypertension. *Circulation Research*. 2021; 128: 993–1020. <https://doi.org/10.1161/CIRCRESAHA.121.318063>.
- [125] Evans EPP, Scholten JTM, Mzyk A, Reyes-San-Martin C, Llumbet AE, Hamoh T, *et al.* Male subfertility and oxidative stress. *Redox Biology*. 2021; 46: 102071. <https://doi.org/10.1016/j.redox.2021.102071>.
- [126] Roychoudhury S, Chakraborty S, Choudhury AP, Das A, Jha NK, Slama P, *et al.* Environmental Factors-Induced Oxidative Stress: Hormonal and Molecular Pathway Disruptions in Hypogonadism and Erectile Dysfunction. *Antioxidants (Basel, Switzerland)*. 2021; 10: 837. <https://doi.org/10.3390/antiox10060837>.
- [127] Odetayo AF, Akhigbe RE, Bassey GE, Hamed MA, Olayaki LA. Impact of stress on male fertility: role of gonadotropin inhibitory hormone. *Frontiers in Endocrinology*. 2024; 14: 1329564. <https://doi.org/10.3389/fendo.2023.1329564>.
- [128] Mora AR, Firth A, Blareau S, Vallat A, Helfenstein F. Oxidative stress affects sperm performance and ejaculate redox status in subordinate house sparrows. *The Journal of Experimental Biology*. 2017; 220: 2577–2588. <https://doi.org/10.1242/jeb.154799>.
- [129] Villas-Boas GR, Lavorato SN, Paes MM, de Carvalho PMG, Rescia VC, Cunha MS, *et al.* Modulation of the Serotonergic Receptosome in the Treatment of Anxiety and Depression: A Narrative Review of the Experimental Evidence. *Pharmaceuticals*. 2021; 14: 148. <http://doi.org/10.3390/ph14020148>.
- [130] Emre Kızıl H, Gür C, Ayna A, Darendelioğlu E, Küçükler S, Sağ S. Contribution of Oxidative Stress, Apoptosis, Endoplasmic Reticulum Stress and Autophagy Pathways to the Ameliorative Effects of Hesperidin in NaF-Induced Testicular Toxicity. *Chemistry & Biodiversity*. 2023; 20: e202200982. <https://doi.org/10.1002/cbdv.202200982>.
- [131] Jeong GB, Mojsilovic-Petrovic J, Boccitto M, Kalb R. Signaling events in axons and/or dendrites render motor neurons vulnerable to mutant superoxide dismutase toxicity. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2011; 31: 295–299. <https://doi.org/10.1523/JNEUROSCI.4824-10.2011>.
- [132] Yao C, Zhang Y, Sun X, Pei H, Wei S, Wang M, *et al.* Arca catechu L. ameliorates chronic unpredictable mild stress-induced depression behavior in rats by the promotion of the BDNF signaling pathway. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*. 2023; 164: 114459. <https://doi.org/10.1016/j.biopha.2023.114459>.
- [133] Luhach K, Kulkarni GT, Singh VP, Sharma B. Vinpocetine amended prenatal valproic acid induced features of ASD possibly by altering markers of neuronal function, inflammation, and oxidative stress. *Autism Research: Official Journal of the International Society for Autism Research*. 2021; 14: 2270–2286. <https://doi.org/10.1002/aur.2597>.
- [134] Jeong HR, Kim JM, Lee U, Kang JY, Park SK, Lee HL, *et al.* Leaves of *Cedrela sinensis* Attenuate Chronic Unpredictable Mild Stress-Induced Depression-like Behavior via Regulation of Hormonal and Inflammatory Imbalance. *Antioxidants (Basel, Switzerland)*. 2022; 11: 2448. <https://doi.org/10.3390/antiox11122448>.
- [135] Jiang L, Dong R, Xu M, Liu Y, Xu J, Ma Z, *et al.* Inhibition of the integrated stress response reverses oxidative stress damage-induced postoperative cognitive dysfunction. *Frontiers in Cellular Neuroscience*. 2022; 16: 992869. <https://doi.org/10.3389/fn cel.2022.992869>.
- [136] Xia B, Liu X, Li X, Wang Y, Wang D, Kou R, *et al.* Sesamol ameliorates dextran sulfate sodium-induced depression-like and anxiety-like behaviors in colitis mice: the potential involvement of the gut-brain axis. *Food & Function*. 2022; 13: 2865–2883. <https://doi.org/10.1039/d1fo03888e>.
- [137] Keshavarzi S, Kermanshahi S, Karami L, Motaghinejad M, Motevalian M, Sadr S. Protective role of metformin against methamphetamine induced anxiety, depression, cognition impairment and neurodegeneration in rat: The role of CREB/BDNF and Akt/GSK3 signaling pathways. *Neurotoxicology*. 2019; 72: 74–84. <https://doi.org/10.1016/j.neuro.2019.02.004>.
- [138] Wu C, Huang S, Liu Z, Wang Y, Zhu Y, Zang ZJ. Correlation between serum tryptophan metabolism and treatment efficacy of dapoxetine in patients with premature ejaculation: A pilot study. *Andrology*. 2024; 12: 1830–1840. <https://doi.org/10.1111/andr>

.13632.

- [139] Zhu T, Gao P, Gao J, Liu X, Jiang H, Zhang X. The upregulation of tryptophan hydroxylase-2 expression is important for premature ejaculation treatment with the selective serotonin reuptake inhibitor. *Andrology*. 2022; 10: 595–603. <https://doi.org/10.1111/andr.13135>.
- [140] Wang A, Wang H, Ma D, Chang H, Zhao Z, Luo D, *et al.* The role of acupuncture in treating premature ejaculation and its probable neurobiological mechanism. *Basic and Clinical Andrology*. 2024; 34: 20. <https://doi.org/10.1186/s12610-024-00239-w>.
- [141] Hsieh JT, Liu SP, Chang HC, Tsai VFS, Chien CT, Yu HJ, *et al.* The activation of peripheral 5-HT<sub>1A</sub> receptors can inhibit seminal vesicle contraction: an in vivo animal study. *Urology*. 2011; 78: 376–379. <https://doi.org/10.1016/j.urology.2011.04.009>.
- [142] Vilela-Costa HH, Maraschin JC, Casarotto PC, Sant’Ana AB, de Bortoli VC, Vicente MA, *et al.* Role of 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors of the dorsal periaqueductal gray in the anxiety- and panic-modulating effects of antidepressants in rats. *Behavioural Brain Research*. 2021; 404: 113159. <https://doi.org/10.1016/j.bbr.2021.113159>.
- [143] Tabuchi H, Kitamura Y, Ushio S, Kan S, Wada Y, Sumiyoshi Y, *et al.* Influence of 5-HT<sub>2A</sub> receptor function on anxiety-like behavior induced by a combination treatment with doxorubicin and cyclophosphamide in rats. *Psychopharmacology*. 2021; 238: 3607–3614. <https://doi.org/10.1007/s00213-021-05979-5>.
- [144] Fang Y, Ding X, Zhang Y, Cai L, Ge Y, Ma K, *et al.* Fluoxetine inhibited the activation of A1 reactive astrocyte in a mouse model of major depressive disorder through astrocytic 5-HT<sub>2B</sub>R/ $\beta$ -arrestin2 pathway. *Journal of Neuroinflammation*. 2022; 19: 23. <https://doi.org/10.1186/s12974-022-02389-y>.
- [145] Ma KH, Cheng CY, Chan WH, Chen SY, Kao LT, Sung CS, *et al.* Pulsed Radiofrequency Upregulates Serotonin Transporters and Alleviates Neuropathic Pain-Induced Depression in a Spared Nerve Injury Rat Model. *Biomedicines*. 2021; 9: 1489. <https://doi.org/10.3390/biomedicines9101489>.
- [146] Zhao YL, Yi HY, Baba SS, Guo YX, Yuan XC, Hou XM, *et al.* Activation of 5-HT<sub>6</sub> Receptors in the Ventrolateral Orbital Cortex Produces Anti-Anxiodepressive Effects in a Rat Model of Neuropathic Pain. *Molecular Neurobiology*. 2025; 62: 1136–1150. <https://doi.org/10.1007/s12035-024-04314-1>.
- [147] Akotkar L, Aswar U, Ganeshpurkar A, Rathod K, Bagad P, Gurav S. Phytoconstituents Targeting the Serotonin 5-HT<sub>3</sub> Receptor: Promising Therapeutic Strategies for Neurological Disorders. *ACS Pharmacology & Translational Science*. 2024; 7: 1694–1710. <https://doi.org/10.1021/acsptsci.4c00084>.
- [148] Lee YJ, Kim HR, Lee CY, Hyun SA, Ko MY, Lee BS, *et al.* 2-Phenylethylamine (PEA) Ameliorates Corticosterone-Induced Depression-Like Phenotype via the BDNF/TrkB/CREB Signaling Pathway. *International Journal of Molecular Sciences*. 2020; 21: 9103. <https://doi.org/10.3390/ijms21239103>.
- [149] Lu P, Yin Z, Fang M, Yao L, Zhang N, Zhang S, *et al.* Acupressure bladder meridian alleviates anxiety disorder in rats by regulating MAPK and BDNF signal pathway. *Physiology & Behavior*. 2024; 283: 114534. <https://doi.org/10.1016/j.physbeh.2024.114534>.
- [150] Guo Y, Wei F, Lv Y, Wu H, Li Y, Tang R, *et al.* Spinosin improves anxiety disorders in mice with chronic restraint stress via the ERK1/2-CREB-BDNF pathway. *International Immunopharmacology*. 2024; 143: 113517. <https://doi.org/10.1016/j.intimp.2024.113517>.
- [151] Sadighi M, Mai L, Xu Y, Boillot M, Targa G, Mottarlini F, *et al.* Chronic exposure to imipramine induces a switch from depression-like to mania-like behavior in female serotonin transporter knockout rats: Role of BDNF signaling in the infralimbic cortex. *Journal of Affective Disorders*. 2024; 351: 128–142. <https://doi.org/10.1016/j.jad.2024.01.186>.
- [152] Liu F, Huang S, Guo D, Li X, Han Y. Deep brain stimulation of ventromedial prefrontal cortex reverses depressive-like behaviors via BDNF/TrkB signaling pathway in rats. *Life Sciences*. 2023; 334: 122222. <https://doi.org/10.1016/j.lfs.2023.122222>.
- [153] Yang C, Ali T, Li A, Gao R, Yu X, Li S, *et al.* Ketamine reverses chronic corticosterone-induced behavioral deficits and hippocampal synaptic dysfunction by regulating eIF4E/BDNF signaling. *Neuropharmacology*. 2024; 261: 110156. <https://doi.org/10.1016/j.neuropharm.2024.110156>.
- [154] Alamri HS, Mufti R, Sabir DK, Abuderman AA, Dawood AF, ShamsEldeen AM, *et al.* Forced Swimming-Induced Depressive-like Behavior and Anxiety Are Reduced by Chlorpheniramine via Suppression of Oxidative and Inflammatory Mediators and Activating the Nrf2-BDNF Signaling Pathway. *Current Issues in Molecular Biology*. 2023; 45: 6449–6465. <https://doi.org/10.3390/cimb4508407>.
- [155] Siroosbakht S, Rezakhaniha S, Rezakhaniha B. Which of available selective serotonin reuptake inhibitors (SSRIs) is more effective in treatment of premature ejaculation? A randomized clinical trial. *International Braz J Urol: Official Journal of the Brazilian Society of Urology*. 2019; 45: 1209–1215. <https://doi.org/10.1590/S1677-5538.IBJU.2019.0121>.
- [156] Shi HJ, Wu DL, Chen R, Li N, Zhu LJ. Requirement of hippocampal DG nNOS-CAPON dissociation for the anxiolytic and antidepressant effects of fluoxetine. *Theranostics*. 2022; 12: 3656–3675. <https://doi.org/10.7150/thno.70370>.
- [157] Migliorini F, Tafuri A, Bettica P, Ziviani L, Lund J, Poggesi I, *et al.* A Double-Blind, Placebo-Controlled Parallel Group Study to Evaluate the Effect of a Single Oral Dose of 5-HT<sub>1A</sub> Antagonist GSK958108 on Ejaculation Latency Time in Male Patients Suffering From Premature Ejaculation. *The Journal of Sexual Medicine*. 2021; 18: 63–71. <https://doi.org/10.1016/j.jsxm.2020.09.012>.
- [158] Olivier JDA, Janssen JA, Esquivel-Franco DC, de Prêtre S, Olivier B. A new approach to ‘on-demand’ treatment of lifelong premature ejaculation by treatment with a combination of a 5-HT<sub>1A</sub> receptor antagonist and SSRI in rats. *Frontiers in Neuroscience*. 2023; 17: 1224959. <https://doi.org/10.3389/fnins.2023.1224959>.
- [159] Jannini TB, Lorenzo GD, Bianciardi E, Niolu C, Toscano M, Ciocca G, *et al.* Off-label Uses of Selective Serotonin Reuptake Inhibitors (SSRIs). *Current Neuropharmacology*. 2022; 20: 693–712. <https://doi.org/10.2174/1570159X19666210517150418>.
- [160] Giatti S, Cioffi L, Diviccaro S, Chrostek G, Piazza R, Melcangi RC. Transcriptomic Profile of the Male Rat Hypothalamus and Nucleus Accumbens After Paroxetine Treatment and Withdrawal: Possible Causes of Sexual Dysfunction. *Molecular Neurobiology*. 2025; 62: 4935–4951. <https://doi.org/10.1007/s12035-024-04592-9>.
- [161] Healy D, Mangin D. Post-SSRI sexual dysfunction: barriers to quantifying incidence and prevalence. *Epidemiology and Psychiatric Sciences*. 2024; 33: e40. <https://doi.org/10.1017/S2045796024000441>.
- [162] Turcotte-Cardin V, Vahid-Ansari F, Luckhart C, Daigle M, Geddes SD, Tanaka KF, *et al.* Loss of Adult 5-HT<sub>1A</sub> Autoreceptors Results in a Paradoxical Anxiogenic Response to Antidepressant Treatment. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2019; 39: 1334–1346. <https://doi.org/10.1523/JNEUROSCI.0352-18.2018>.
- [163] Issa I, Skov J, Falhammar H, Roos M, Lindh JD, Mannheimer B. The association of selective serotonin reuptake inhibitors and venlafaxine with profound hyponatremia. *European Journal of Endocrinology*. 2025; 193: 179–187. <https://doi.org/10.1093/ej>

endo/lvaf140.

- [164] Xie Z, Lu J, Zhang X, Jia H, Zhang Y. Efficacy of Chinese herbal medicine in the treatment of anxiety and depression in male sexual dysfunction: a systematic review and meta-analysis. *Sexual Medicine*. 2025; 13: qfaf048. <https://doi.org/10.1093/sexmed/qfaf048>.
- [165] Ma D, Wang A, Wang H, Yang J, Luo D, Zhao Z, *et al.* A Review of Studies on the Treatment of Premature Ejaculation with Traditional Chinese Medicine. *Integrative Medicine in Nephrology and Andrology*. 2024; 11: e24–e28. <http://doi.org/10.1097/IMNA-D-24-00008>.
- [166] Xie Z, Zhang X, Jia H, Zhang Y. Efficacy of Chinese herbal medicine in the treatment of anxiety and depression in male sexual dysfunction: a systematic review and meta-analysis protocol. *Frontiers in Psychiatry*. 2025; 16: 1584306. <https://doi.org/10.3389/fpsy.2025.1584306>.
- [167] Zanolì P, Benelli A, Zavatti M, Rivasi M, Baraldi C, Baraldi M. Improved sexual behavior in male rats treated with a Chinese herbal extract: hormonal and neuronal implications. *Asian Journal of Andrology*. 2008; 10: 937–945. <https://doi.org/10.1111/j.1745-7262.2008.00437.x>.
- [168] Han Q, Guo J, Wang R, Li J, Wang F, Gao Q, *et al.* Mechanism of Shugan Yidan fan, a Chinese herbal formula, in rat model of premature ejaculation. *Basic and Clinical Andrology*. 2023; 33: 25. <https://doi.org/10.1186/s12610-023-00200-3>.
- [169] Cui YD, Hu SB, Wu B, Li SJ, Xiang K, Liao ZL, *et al.* Efficacy of combined traditional Chinese medicine spray with premature ejaculation desensitization therapy for the treatment of primary premature ejaculation. *African Health Sciences*. 2017; 17: 603–613. <https://doi.org/10.4314/ahs.v17i3.2>.
- [170] Feng Y, Wang W, Zhang Y, Feng Y, Zhao Y, Zhang Z, *et al.* Xiao-Chai-Hu-Tang Ameliorates Depressive Symptoms via Modulating Neuro-Endocrine Network in Chronic Unpredictable Mild Stress-Induced Mice. *CNS Neuroscience & Therapeutics*. 2025; 31: e70290. <https://doi.org/10.1111/cns.70290>.
- [171] Zhao W, Ji C, Zheng J, Zhou S, Tian J, Han Y, *et al.* Effects of Xiaoyao San on exercise capacity and liver mitochondrial metabolomics in rat depression model. *Chinese Herbal Medicines*. 2023; 16: 132–142. <https://doi.org/10.1016/j.chmed.2023.09.004>.
- [172] Seo SY, Bang SK, Kang SY, Cho SJ, Choi KH, Ryu YH. Acupuncture Alleviates Anxiety and 22-kHz Ultrasonic Vocalizations in Rats Subjected to Repeated Alcohol Administration by Modulating the Brain-Derived Neurotrophic Factor/Corticotropin-Releasing Hormone Signaling Pathway. *International Journal of Molecular Sciences*. 2021; 22: 4037. <https://doi.org/10.3390/ijms22084037>.
- [173] Sunay D, Sunay M, Aydoğmuş Y, Bağbancı S, Arslan H, Karabulut A, *et al.* Acupuncture versus paroxetine for the treatment of premature ejaculation: a randomized, placebo-controlled clinical trial. *European Urology*. 2011; 59: 765–771. <https://doi.org/10.1016/j.eururo.2011.01.019>.
- [174] Schosser A, Fischer-Hansal D, Swoboda MM, Ludwig B, Carlberg L, Swoboda P, *et al.* BDNF gene polymorphisms predicting treatment response to CBT-based rehabilitation of depression: to be submitted to: *European Neuropsychopharmacology*. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*. 2022; 58: 103–108. <https://doi.org/10.1016/j.euroneuro.2022.03.005>.