The Relationship Between 5-Hydroxytryptamine and Its Metabolite Changes With Post-stroke Depression

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Post-stroke depression (PSD) is the most common and serious sequelae of stroke. Approximately 33% of stroke survivors were affected by PSD. However, many issues (e.g., incidence, diagnostic marker, and risk factor) related to PSD remained unclear. The “monoamine hypothesis” is a significant hypothesis for depression, which suggests that three monoamines play a key role in depression. Therefore, most current antidepressants are developed to modulate the monoamines on PSD treatment, and these antidepressants have good effects on patients with PSD. However, the potential mechanisms of three monoamines in PSD are still unclear. Previously, we proposed “three primary emotions,” which suggested a new model of basic emotions based on the three monoamines. It may provide a new way for PSD treatment. In addition, recent studies have found that monoamine-related emotional intervention also showed potential effects in the treatment and prevention of PSD. This study discusses these issues and attempts to provide a prospect for future research on PSD.

Keywords: post-stroke depression, 5-Hydroxytryptamine, monoamine hypothesis, three primary emotions, emotional intervention

INTRODUCTION

Post-stroke depression (PSD) is a common and serious complication after stroke, which is often regarded as the inevitable reaction toward stroke-related disability (1). A recent meta-analysis reported that the incidence of PSD within the first 5 years after stroke ranged from 25 to 33% (2). PSD adversely affects recovery and the life quality in patients with stroke. Evidence suggests that PSD is related to a large number of adverse health outcomes, such as increased morbidity, disability, and mortality (3–5). However, as the mechanisms of PSD diagnosis are unclear, the specific critical periods for most interventions are still uncertain and most antidepressants used for PSD have been reported to have serious side effects, until present some of the patients remain untreated or not be adequately treated (6).

At present, the main therapeutic approach to PSD is essentially pharmacological (7), and the most commonly used pharmacotherapeutic agents for treating PSD are antidepressants (1). Three
monoamines, namely, dopamine (DA), 5-hydroxytryptamine (5-HT), and norepinephrine (NE), play key roles in the etiology and treatment for major depressive disorders (MDD) (8). The monoamine hypothesis assumes that depression is associated with low levels of monoamines, especially DA, 5-HT, and/or NE (8, 9). So the major antidepressants for MDD are designed to increase monoamine transmission either by inhibiting neuronal reuptake or by inhibiting degradation (8, 10).

In addition, these three monoamines might be the primary substrate for emotions (11). Previously, we have proposed the "three primary color model" of basic emotions based on the three monoamines Wang et al. (2020). In the hypothesis, we suggested that all emotions are composed of some basic emotions, such as happiness, sadness, and anger and fear, which are subsided, respectively, by the three neurotransmitters: DA (happiness), 5-HT (disgust), and NE (fear and anger) (12). Depression and other affective disorders (such as PSD and anxiety) are related to the dysfunctions of the monoamine system (13, 14).

It might be easy to suggest that the etiology of PSD may be the ischemic lesions caused by stroke interrupting the projections ascending from the midbrain and brainstem, leading to a decreased bioavailability of the biogenic amines, including DA, 5-HT, and NE (4, 7). Even though traditional antidepressants are the first-line treatment used for PSD, the mechanisms of PSD are still unclear (4). Therefore, this study aims to review the relationship of PSD with three monoamines and emotions. First, we briefly introduced the incidence, risk factors, and diagnosis of PSD. Then, we reviewed the application of three monoamines in the treatment of PSD drugs and the "three primary color model" of basic emotions. Finally, we summarized the advantages of psychological therapy in recent years and posted some suggestions for the pharmacology and psychotherapy of PSD.

**POST-STROKE DEPRESSION**

Stroke and depression are two leading causes of disability worldwide (6, 15). They not only negatively affect patients' life quality but also lead to socioeconomic burden (15, 16). PSD is the most frequent and important neuropsychiatric consequence of stroke (17). According to a report by World Health Organization (WHO), approximately one-third of the 15 million patients with stroke (2) suffer from PSD every year globally (18). Despite the similarities between PSD and MMD, there are some significant differences between them (4, 15). First, PSD is a complication of stroke, which is closely linked to vascular injury (19), while MMD is majorly due to monoaminergic systems. Second, PSD and MMD are different in symptoms in that PSD tends to have more severe cognitive impairment than MMD but less anhedonia and disturbances in sleep and cyclic functions than MMD (20, 21). Third, patients with PSD have a higher prevalence of physical disability, which may be related to stroke (22). Therefore, the clinical characteristics of PSD are not identical to those of MMD, and PSD needs to be specifically discussed.

**INCIDENCE OF PSD**

As a common stroke complication, PSD has been investigated by many scientists in many countries around the world (23). In addition, many meta-analysis studies have investigated the incidence and etiology of PSD (2, 24, 25). In his pioneering studies of PSD, Hackett et al. (26) conducted a systemic review and meta-analysis, which included 17,934 patients from 20 studies and revealed a pooled frequency estimation of PSD of 33%. Hackett et al. (2) updated the systematic review with a meta-analysis about the frequency of PSD in the next 10 years. They revealed that the pooled frequency was estimated to be 31%, which was consistent with the results found in a 10-year earlier review. Recently, a new study reported the incidence of PSD within the first 5 years following stroke to be 39–52%, which is far higher than the incidence of MDD (about 4.4% of the world's population) (27).

Similar to Hackett et al., Ayerbe and his colleagues revealed a similar pooled frequency of PSD of 29% and a cumulative incidence of 39–52% within 5 years of the stroke (24). The interesting finding of this research is that the frequency of PSD remained quite consistent for the first year but then started to decline. However, another study has provided an opposite result as to the time course of PSD. Werheid et al. (28) reported a two-phase pathogenetic model of PSD based on 10 prospective longitudinal studies, which revealed a rise in the incidence of PSD within the first 6 months, a slight drop at about 1 year, and a new increase within the second year following a stroke.

In a recent study, Eman et al. (29) used DSM-IV TR as diagnosis criteria of depressive disorders, they found that the frequency of PSD was 36.9%, and 21.4% of which had MDDs, meanwhile 15.5% had minor depressive disorders. Even though these studies have provided the frequency and severity of PSD, still there exist one limitation in these studies because there were no standard diagnostic criteria for specific mood disorders in most studies (16). In other words, these meta-analyses did not distinguish major depression from other forms of depressive disorders occurring after stroke (23). In addition, an obvious finding was that there were differences in the results of different PSD incidence studies due to the differences in sample size, geographical location, the selection of patients, etc. (30).

**DIAGNOSIS OF PSD**

A longstanding problem was that a vast majority of patients with stroke are not screened for PSD (15) because PSD was confused with many mood disorders in symptoms, such as post-stroke apathy (PSA) (31) and catastrophic reaction (32). PSA is generally defined as a disorder of diminished motivation caused by a stroke (31). The symptoms of PSA are loss of interest, diminished emotional response, and loss of initiative (33), which are quite similar to those of PSD. In addition, based on physiology, both PSD and PSA are related to frontostriatal circuit dysfunction and small vessel ischemia (34, 35). A catastrophic reaction is also a common emotional reaction
after stroke. The definition of catastrophic reaction is an intense emotional reaction to the inability to perform tasks after neurological damage (36), which is characterized by severe frustration, sadness, anger, or aggression (15). Although these symptoms are similar to those of post-stroke diseases, the treatments are quite different. For example, substantial evidence shows that PSA is better treated by psychotherapy interventions instead of antidepressants (37), but antidepressants in fact have shown good therapeutic effects in PSD treatment (7). Therefore, the diagnosis and treatment of PSD are particularly important. The diagnosis and screening of PSD mainly use the traditional depression scales (38), such as Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS) (39). We summarized the main PSD diagnosis instruments in Table 1 according to recent reports; however, Nick et al. (40) conducted a meta-analysis on these diagnostic methods for PSD. They found that all the tools used in the clinics were not so correct for case findings. In all these scales, the Center of Epidemiological Studies-Depression Scale (CESD), HAM-D, and the Patient Health Questionnaire (PHQ-9) showed the best results. PHQ-9 is the shortest of these options, with only nine questions based on the DSM-IV criteria for MDD (41). As a result, the PHQ-9 is one of the fastest and most practical tools that can be administered in the screening and diagnosis of PSD (15) (Table 1).

### RISK FACTORS OF PSD

Depression is a common symptom following a stroke; however, the risk factors and predictors are yet to be delineated (1). The benefit of understanding PSD risk factors is beneficial to the...
prevention and treatment of this disease. Many studies during the past decades have reported many causing factors for PSD. The main factors are summarized in the following sections.

**Stroke-Related Factors**

A series of studies have found that the type, severity, and lesion location of stroke were related to the PSD (30). Jørgensen et
al. (42) conducted a large sample study by collecting data from 157,243 patients with stroke between January 2001 and December 2011. They reported that patients with ischemic stroke had a higher incidence of PSD than patients with hemorrhagic stroke. In another study, Vataja et al. (43) also found that patients with PSD had more sites and a larger volume of infarcts. However, another study did not find different rates of PSD based on the type of stroke (44).

A lot of studies have provided evidence for the relationship between stroke severity and PSD incidence (24, 45, 46). One meta-analysis study of PSD by Hackett et al. (26) found that there was a positive correlation between stroke severity and PSD. Recently, a multiple regression analysis from Taiwan also found a correlation between the severity of stroke and the incidence of PSD (46). Another study by Jørgensen et al. (42) also found that a higher depression score was significantly associated with PSD, regardless of gender.

In addition, the lesion location of the brain was strongly associated with PSD. In a series of studies (23, 47, 48), Robinson and his colleagues revealed that patients with stroke in the left hemisphere had a higher incidence of PSD and the severity correlated significantly with the proximity of the lesion to the frontal pole. Meanwhile, Starkstein et al. (49) found that the location of subcortical lesions had a greater influence than cortical lesions on PSD. Similarly, in patients with subcortical damage, the closer the lesion to the frontal lobe, the more severe the PSD. Therefore, the frontal pole may play a key role in the severity of PSD. In other ways, Jorge et al. (50) found that focal brain stimulation using repetitive transcranial magnetic stimulation is only effective when it is applied to the left dorsolateral prefrontal cortex in patients with vascular depression. Robinson (23) also considered that PSD is associated with left frontal or left basal ganglia lesions within 2 months of a first clinical stroke. Therefore, left frontal or left basal ganglia lesions may be used as the screen basis of PSD.

**Demographic Factors**

Similar to MDD, many demographic factors, such as sex, age, and history of psychiatric illness, are related to the PSD. During the past decades, there was no agreement on sex as a risk factor for PSD. Some studies identify female sex as a risk factor for PSD. In a meta-analysis study of the risk factors for PSD, Shi et al. (17) found that sex (female) was significantly associated with PSD [OR = 1.77, 95% CI = 1.26–2.49]. This result was also reported in other studies (46, 51, 52). However, a systematic review by Ryck (44) found that gender was not a significant risk factor for PSD in 13 out of all 21 studies.

Age was another factor that yielded the most controversial results. In a study of 216 patients with ischemic stroke, Li et al. (53) revealed a difference in age between patients with PSD and patients without PSD. Carota et al. (54) also found the association between PSD and age. However, Ryck et al. (44) revealed that age was not associated with PSD in 16 studies. Therefore, the relationship between age and PSD is still unclear.

Finally, the history of psychiatric disorders was also associated with PSD, particularly MDD and anxiety disorders. A meta-analysis study by Ried and his colleagues found the rate of PSD was found to be 5–6 times higher among those with pre-stroke depression (55). A recent study has also revealed depression before stroke notably increased odds of PSD (56). Anxiety disorder is also a risk factor for PSD. De Ryck reported that a personal history of anxiety was a significant risk factor in some studies (44).

**Social Support**

Apart from the above risk factors, social support is also associated with the PSD. But, the available studies concerning PSD and social support are contradictory (23). A systematic review of the relationship between social support and PSD reported that some factors (such as family life, friends, acquaintances, and social participation) of social support were associated with PSD, and lack of social support may cause more severe PSD symptoms (57). Other studies have reached similar results (18, 58). Even though a lot of evidence indicated that social support was related to PSD, Jessica et al. (59) reported that living conditions and marital status have not been consistently associated with PSD.

**MONOAMINE TRANSMITTERS IN THE TREATMENT OF PSD**

In their study performed 2,500 years ago, Hippocrates and Galen suggested that individual differences are due to fluid components in the body, and that a balanced mixture of these vital chemicals can induce at least four kinds of temperaments: choleric (aggressive), melancholic (depressive), phlegmatic (fear and social detached), and sanguine (cheerful) (60). The further that research in the neurochemistry of emotionality advances, the more that neurochemical systems are linked to emotional regulation (61). In fact, dysregulation in practically all neurochemical families, especially monoamines, hormones, neuropeptides, opioid receptors, and transcription factors, appears to contribute to PSD (62). There are two main theoretical views about the determinants of PSD. One of them focuses on brain locations such as the amygdala and hippocampus, prefrontal cortex, and hypothalamus. Another one emphasizes neurochemicals such as disruption of biogenic amine neurotransmission and release of proinflammatory cytokines (63). The monoamine hypothesis assumed that PSD was related to abrupt damage of cortical circuits involved in mood regulation and monoamine production (64). Dopamine (DA), 5-HT (5-HT) and norepinephrine (NE) are the three main monoamine transmitters in emotion regulation (11), which play a key role in antidepressant drugs for PSD treatment. In the following section, the roles of 5-HT, DA, and NE in the treatment of PSD are discussed.

**Monoamine Hypothesis**

The “monoamine hypothesis” of depression originated from early clinical observations (8), which posited that depression was caused by an alteration in one or more of the monoamines (65). Robinson (48) assumed that ischemic lesions may interrupt the biogenic amine-containing axons ascending from the brainstem to the cerebral cortex and lead to a decreased availability of monoamines (5-HT, DA, and NE) in limbic structures of frontal,
temporal lobes, and basal ganglia. Monoaminergic neurons in the midbrain dynamically alter their firing patterns, which were associated with motivation-related behavior in animal studies (66). Motivation-related behavior included salience, reward and punishment learning, incentive processing, decision-making, goal-directed behavior, and anxiety (67). Recent studies have revealed three different monoaminergic dynamics that regulate diverse aspects of motivation-related behavior (68–71). Therefore, it appeared that specific aspects of motivation-related behavior were regulated by distinct synaptic and cellular mechanisms in specific brain regions that underlie the transient and sustained effects of the monoamine signaling (66). The different neural systems of three monoamines may involve different symptoms of depression (mood, cognition, and pain). Serotonergic (5-HT) neurons originate from the median raphe nucleus and innervate the limbic system, prefrontal cortex, and other related structures involved in the regulation of mood (4). In addition, 5-HT projected to the basal ganglia has been confirmed to be associated with motor control (72). Dopaminergic projections originated from the ventral tegmental area (VTA) and substantia nigra (SN), reaching different regions of nucleus accumbens (Nac), had been proven to be related to reward and aversion (73). Norepinephrinergic neurons originated from the locus coeruleus (LC) project to the limbic system to participate in the regulation of emotional arousal (74). Furthermore, the monoaminergic descending pathways projecting through the dorsolateral spinal column played an important role in the regulation of pain.

Since the 1950s, reserpine has been found to inhibit vesicular monoamine transporters and deplete brain monoamines, which provided evidence for the role of monoamines in the treatment of depression. In 1959, the Food and Drug Administration (FDA) approved imipramine for the treatment of MDD, which established the class of drugs called tricyclic antidepressants (TCA) as the first class of drugs to target monoamines. Later, selective 5-HT reuptake inhibitors (SSRIs) and 5-HT and norepinephrine reuptake inhibitors (SNRIs), which are based on the “monoamine hypothesis,” were approved for depression in 1987 and 1993, respectively. In recent years, some drugs targeting the glutamate system (such as ketamine) showed good effects (75). In all, the introduction of TCAs and monoamine oxidase inhibitors based on the monoamine hypothesis revolutionized the treatment of depression. Since then, most of antidepressants have been developed by primarily acting through modulation of monoaminergic neurotransmission (76). Even though the monoamine hypothesis alone was no more generally accepted (16), the current main treatment of PSD drugs is still based on the monoamine hypothesis (77).

Serotonin (5-HT)
5-Hydroxytryptamine is a significant neuromodulator with unique neuroplastic capabilities (78). The main gathering area for 5-HT neurons is the dorsal raphe nucleus (DRN). The 5-HTergic neurons of the DRN send projection to the entire brain and throughout the neuraxis and receive major inputs from the hypothalamus, amygdala, midbrain, and anterior neocortex (66). There are 14 types of serotonergic receptors, which can be divided into seven main families according to differently coupled G-proteins (79). Each group of receptors may have different functions. For example, 5-HT_{1A} and 5-HT_{1B} receptors are associated with anxiety (80) and reward behaviors (81); 5-HT_{2A} receptors are correlated to appetite control, thermoregulation, and sustained attention (82); 5-HT_{3} receptors are related to aggression behaviors (83); and 5-HT_{4} receptors affect memory, depression, and feeding (84).

In addition, abundant evidence has justified the role of 5-HT in depression (85), as well as in patients with PSD (86). Furthermore, 5-HT levels can be affected by three neurobiologically related factors of PSD: increased inflammation and trauma, decreased cerebral brain-derived neurotrophic factor (BDNF), and dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis. Raison et al. (87) reported that the metabolisms of 5-HT are affected by the central nervous system (CNS) inflammatory response (88). A peripherally administered cytokine could activate a CNS inflammatory response in humans that interacted with 5-HT metabolism, which was associated with depression. The association of BDNF and 5-HT also showed a special feature in depression (89). BDNF injected into the midbrain increased the level of 5-HT and also enhanced the expression of genes encoding 5-HT_{1A} and 5-HT_{2A} receptors. These changes can only be observed in depression mice but not in nondepression mice (90). In patients with PSD, 5-HT and other monoamine (DA and NE) release might be affected by abnormal HPA axis activity after stroke. Therefore, Guo et al. (30) posted a model of the PSD mechanism based on four main hypotheses of PSD: the monoamine hypothesis, HPA hypothesis, neurotrophic hypothesis, and inflammation hypothesis. The model considered that stroke could trigger a robust inflammatory response and severe monoamine system damage in the injured brain region (91). Then, this change would increase the activity of HPA, which works through the following processes. First, the inflammatory response and the 5-HT decrease made the paraventricular nucleus of the hypothalamus release more corticotropin-releasing hormone (CRH), which stimulated the pituitary to release more adrenocorticotropic hormone (ACTH). The increase in ACTH release causes an increase in glucocorticoid synthesis and release in the adrenal cortex (92). Glucocorticoid is also called cortisol in the human body, which is the major component of the HPA axis. Many studies have shown that the cortisol levels were higher in depression patients (93, 94). An increase in cortisol, in turn, could lead to a decrease in BDNF, which played a key role in the emotion system. On the one hand, lacking cerebral BDNF contributed to the development of negative mood states (95). On the other hand, BDNF was closely associated with 5-HT, and the functional activity of the 5-HT system was linked with depression and suicide (89). 5-HT decrease in the limbic system and cerebral cortex might be an important factor for depression in patients with stroke. Therefore, 5-HT and its receptors can be used as a biomarker for PSD (Figure 1).

Furthermore, the major antidepressant drugs mainly target 5-HT and its receptors. Currently, there are three main types of antidepressant drugs, including tricyclic antidepressants (TCAs),
selective 5-HT reuptake inhibitors (SSRIs), and 5-HT and norepinephrine reuptake inhibitors (SNRIs) (96). The first-line therapeutic treatment for PSD is using antidepressants, as can be seen in a recent meta-analysis, which confirmed that antidepressant drugs had a significant effect in the treatment of PSD vs. placebo (97). TCAs are a group of traditional antidepressant drugs, and some drugs of this kind are still used in PSD treatment, such as amitriptyline and nortriptyline, which are 5-HT$_2$ receptor antagonists. Xu et al. (97) found a significant advantage of TCAs over placebo in a meta-analysis study. However, both amitriptyline and nortriptyline have been reported to have serious side effects. Some elderly patients with stroke showed orthostatic hypotension, cardiac arrhythmia, glaucoma, or prostate hyperplasia after using the two drugs (98). SSRIs and SNRIs are two groups of new antidepressant drugs, which is introduced after the 1980s (7). Nowadays, there are at least 6 SSRI drugs (fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram) and 3 SNRI drugs (i.e., milnacipran, duloxetine, and duloxetine) available in PSD treatment. Anyway, a series of studies have shown that the SSRI drugs also had great effects on PSD treatment (99–105), such as gastrointestinal symptoms, headache, sexual dysfunction, and insomnia (7).

In addition, using SSRIs may increase mortality in patients with stroke (24). However, these studies did not reach a consensus result, even opposite results (106, 107). Compared with SSRIs, SNRIs may be useful in improving painful physical symptoms due to their noradrenergic action. Some studies have also found that SNRIs show a great effect on PSD prevention and treatment (103, 108, 109). In addition to these three types of drugs, some new antidepressant drugs also target 5-HT receptors and show great effects on patients with PSD. For example, vortioxetine, a new antidepressant with multimodal activity, shows great therapeutic effects on cognition. It can act on multiple 5-HT receptors, including 5-HT$_1A$, 5-HT$_1B$, 5-HT$_1D$, 5-HT$_3$, 5-HT$_7$, and 5-HT transporter (SERT) (110). In addition, vortioxetine shows fewer side effects than current first-line antidepressants. In all, these studies showed that antidepressant drugs targeting 5-HT can play a role in the treatment of PSD (Table 2).

**Dopamine and NE**

Dopamine and NE are two other monoamines and also play a key role in the emotion system. The dopaminergic system is a unique modulatory system in the brain as it has discrete projections to specific brain regions, including motor behavior, cognition, and emotion (110). Unlike 5-HT or NE, separate groups of DA neurons project to different brain regions. Different groups of DA neurons project to different brain regions to moderate and regulate different behaviors and functions (129). Dopaminergic neurons are mainly located in the VTA and SN (130). Dopaminergic neurons in these two areas project to the reward-related Nac and ventral striatum (VS), which is called the mesolimbic DA system (22). In addition, the dopaminergic neurons in the lateral SN primarily project to the dorsomedial striatum and participate in the formation of motor learning and habit behavior (131). The functions of DA are mainly mediated by DA receptors, which are composed of five different but closely related G protein-coupled receptors, D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors (Beaulieu, Gainetdinov, & Sibley, 2011). D1-like receptors can enhance the activity by activating the Gs/ol family, but the D2-like receptors activate Gs/ol family and inhibit the activity (79, 132). More and more studies have shown that dopaminergic system dysfunction is linked to the pathology of depression (133–136). Anhedonia and amotivation are two main symptoms seen in depression, which are related to dysfunctions in the dopaminergic system (137). Animal models of depression showed stress-induced impairments of VTA dopaminergic neurons are related to the increasing susceptibility of depression in rats (138), which is due to stress increased activity of dopaminergic neurons in the circuit of the hippocampus—VS-ventral pallidum. However, increased activity in the ilPFC-amygdala-ventral pallidum circuit caused a compensatory, long-duration downregulation of the VTA. The downregulation of the VTA was maintained after stress, which might be the reason for anhedonia and depression (139). Therefore, we could speculate that stroke led to serious monoaminergic system damage, which led to reduced release of VTA dopamine to the reward-related Nac and VTA, and thus anhedonia and depression. In addition, antidepressant drugs targeting DA and its receptors also showed great benefits in

| Drugs | 5-HT receptors | Clinical application | References |
|-------|----------------|----------------------|------------|
| Fluoxetine | 5-HT$_2C$ (-) | depression, premenstrual dysphoric disorder, hypochondriasis, bulimia nervosa | (111) |
| Paroxetine | 5-HT$_2C$ (-), 5-HT$_2A$ (-) | depression, PTSD, OCD, generalized anxiety disorder, premenstrual dysphoric disorder | (112, 113) |
| Fluvoxamine | 5-HT$_1A$ (-) | anxiety disorders, schizophrenia, delusional depression | (114, 115) |
| Sertraline | 5-HT$_2C$ (-) | major depression, panic disorder, OCD, PTSD | (116) |
| Citalopram | 5-HT$_3$ (-), 5-HT$_1A$ (-), 5-HT$_2C$ (-) | major depression, OCD | (117, 118) |
| Escitalopram | 5-HT$_1A$ (+) | depression, anxiety disorder | (119) |
| Amitriptyline | 5-HT$_2$ (-) | schizophrenia, | | |
| Nortriptyline | 5-HT$_2$ (-) | depression | (121) |
| Clomipramine | 5-HT$_1A$ (+), 5-HT$_1B$ (-) | OCD, major depression | (122) |
| Milnacipran | 5-HT$_1A$ (-) | major depression | (123) |
| Duloxetine | 5-HT (-) | generalized anxiety disorder, major depression | (124) |
| Mirtazapine | 5-HT$_2A$ (-) | depression, PTSD | (125, 126) |
| Venlafaxine | 5-HT$_1B$ (-) | major depression, OCD | (127) |
| Doxepin | 5-HT$_2A$ (-), 5-HT$_2C$ (+) | insomnia | (128) |
PSD treatment. For example, fluoxetine and paroxetine, two of the most commonly used drugs in PSD treatment, could prevent the degeneration of nigrostriatal dopaminergic neurons (140). A recent study has revealed that SNRIs achieve a fast antidepressant effect by elevating the DA concentrations in the mPFC and the Nac (96). Furthermore, a new antidepressant drug, bupropion, which primarily acts through the NE transporter and DA transporter, shows a significant therapeutic effect (141).

Norepinephrine, a catecholamine neuromodulator, projects to all the brain regions except some dopaminergic neuron regions, such as the striatum, globus pallidus, NAc, and SN (142). NE is mainly released from neurons originating from locus coeruleus (LC), a small nucleus situated in the pons of the brainstem. The LC-NE system has long been considered to be critical in arousal (71). NE exerts its effects through binding to G-protein coupled α-adrenergic receptor (α-AR) and β-adrenergic receptor (β-AR). β-ARs possess two groups: β1 and β2 (143). NE has the highest affinity for the α2 receptors and the lowest affinity for β adrenergic receptors. In addition, α1 receptor stimulation has been found to enhance excitatory processes in many brain regions (144). Animal models offered the evidence that reduction of the levels of presynaptic NE, such as 5-HT, or DA, plays a key role in the pathophysiology of depression (145). In all, the LC-NE system is also related to the low arousal state of depression (74). A meta-study showed a significant correlation between baseline 3-methoxy-4-hydroxyphenylglycol (sMHPG) levels and Beck Depression Inventory (BDI) score, and sMHPG was the major NE metabolite in the cerebrospinal fluid (146). Leonard et al. (147) proposed a model about the relationship between NE and depression. They proposed that chronic stress activated the release of corticotropin-releasing factor (CRF), leading to the increased release of pro-inflammatory cytokines, prostaglandins of the E series, and nitric oxide, which influenced the central neurotransmitter function. If these changes persisted, they may contribute to the degenerative changes in noradrenergic neurons, which would lead to depression. In patients with stroke, stroke might change NE levels and thus PSD. In terms of depression medications, SNRIs showed faster antidepressant effects than SSRIs, and the underlying mechanisms of faster antidepressant effects of SNRIs may be related to NE (96). In all, SNRIs showed a great effect in improving painful physical symptoms due to their noradrenergic action (7). A meta-study showed in recent clinical studies that NE may play an important role in aberrant regulation of cognition, arousal, and valence systems that are associated with depression (143).

### Monoamine and Related Chemicals

Even though the monoaminergic systems are implicated in the regulation of basic emotions, there is a functional overlap of neurochemical systems related to PSD. The neurochemicals involved in PSD can be divided into two groups: neuromodulators and neuropeptides (Table 3). The neuromodulators are small molecules, such as monoamines, and have specific functions, such as joy, disgust, and fear, like the three primary colors. While the peptides such as oxytocin, orexin, and neuropeptides are more complex and carry more flexible functions, which might be secondary to the neuromodulators. Anyway, the monoamines and other secondary neurochemicals can interact with each other to produce different kinds of emotions (Figure 2). The difference might be that the neuropeptides are involved in more specific functions, such as thirst, hunger, and pain (Table 3).

### THE THEORY OF THREE PRIMARY EMOTIONS

Although the “monoamine hypothesis” proposed that the mood symptoms of depression were mainly related to decreased levels of monoamines, the relationship between monoamine transmitters and emotion was never clarified. Nowadays, there are two widely accepted theories in emotional studies: basic emotion theory and dimensional theory (175). The basic emotion theory suggests that all emotions are composed of a limited number of emotions (11). Basic emotions have evolutionarily preserved biological and social functions (175). After many experimental studies, Ekman (176) suggested that people have six basic emotions: joy, sadness, fear, anger, disgust, and surprise. Robert Plutchik proposed eight primary emotions in a color wheel: anger, fear, sadness, disgust, surprise, anticipation, trust, and joy (175). In recent years, Jack et al. (177) proposed four basic emotions: fear, anger, joy, and sadness. The dimensional theory proposes that emotions could be defined by some different dimensions, and all emotions could be defined as a combination of these dimensions (178). The dimensional theory was first proposed by Wundt, who suggested...
that emotion had three independent dimensions: pleasant-unpleasant, tension-relaxation, and excitation-calm (179). The most famous dimensional theory was proposed by Russell et al., who invented the circumplex, which is composed of two dimensions: hedonic (pleasure-displeasure) and arousal (rest-activated). They proposed that all emotions could be arranged in a circle, and the different locations of each emotion in the circle reflected varying amounts of hedonic and arousal properties (180). Even though both theories were supported by more studies, no previous reports have connected emotion with neurotransmitters. Wang et al. (61, 79, 178, 179) posted a new theory of three primary emotions, which not only compromised both basic emotion theory and dimensional theory but also associated with neurotransmitters, especially monoamines, with emotions.

Basic emotions are instinctive, primitive, and developed throughout evolution (175), and each basic emotion should have a specific neural basis. Therefore, Wang et al. (12, 61, 170) proposed the theory of three primary emotions via a large number of basic emotional studies. They proposed three basic emotions: joy, disgust, and fear (anger), which were subsided, respectively, by the three monoamine neurotransmitters: DA, happiness; 5-HT, sadness; and NE, fear (anger). Fear and anger are twin emotions that are like two sides of the same coin (61). Fear and anger are associated with unanticipated ways things happen: fear is associated with uncertainty about the situation; and anger is related to trying to control the situation (181), which can induce the individuals to generate the so-called fight or flight response (182). Similarly, in the emotional dimension, DA and 5-HT represent two poles of the horizontal dimension, which is the valence dimension, while the NE represents the vertical dimension, which means arousal (11). This model might be the first theory to connect monoamine neurotransmitters with basic emotions and emotional dimensions.

**EMOTION-BASED INTERVENTIONS IN TREATING PSD**

If patients are diagnosed with PSD, they are usually treated with antidepressants (183). However, the effectiveness of antidepressants in clinical practice is only approximately 50% (184). Therefore, it is necessary to provide additional effective and safe treatment for PSD. Emotional control for PSD showed great potential in the treatment and prevention of PSD in recent studies (7). The effects of several major psychotherapies in recent studies are summarized in the following section.

Cognitive reappraisal is an effective and common intervention therapy for the treatment of depression (185). In a recent meta-study, cognitive behavioral therapy (CBT) interventions yielded a larger short-term decrease in depression scores (126). CBT was also widely used in clinical treatment for PSD (186). A
single-blind randomized controlled trial of PSD revealed that CBT was as effective as citalopram for late-onset post-ischemic depression and was more effective than rehabilitation alone (100). A recent meta-study also reported that both CBT alone and CBT with antidepressants all showed significantly improved depressive symptoms in PSD (18). However, most studies have not considered the time of depression onset. Hou et al. (187) found that antidepressants and psychological therapy may not improve the symptoms of depression in patients during the first 3 months. Gao et al. (100) also reported that the most positive results of CBT for treating post-ischemic stroke depression occurred 3 months later. It may be associated with the biological changes in the brain tissue caused by stroke. Therefore, CBT is effective in treating PSD, but this effect usually occurs after the biological changes in brain tissue stabilize. In addition, a recent study has demonstrated the relevance of the MAOA gene for the treatment outcome of CBT, while the MAOA gene plays a key role in the degradation of monoamines, especially 5-HT and NE (188).

In a recent study, mindfulness meditation showed potential benefits for PSD (189). Mindfulness is defined as a process of openly attending, with awareness, to one’s present moment experience (190). Mindfulness meditation includes at least three components: improved attention control, enhanced emotion regulation, and altered self-awareness (191). In a recent randomized controlled trial, Wang et al. (189) revealed that mindfulness intervention had positive effects on depression, social wellbeing, and emotional wellbeing of patients with PSD.

In addition, other treatments of implicit emotional control were also recommended for patients with PSD, such as literature therapy and art treatment (192–194). Literature therapy is psychotherapeutic, which helps patients develop insight and awareness of negative thoughts and emotions, provides answers to problems, and supports them to practice these approaches in their daily life (195). Art treatment is defined as the therapeutic use of verbal treatment methods, using rhythms, sensory stimulation, symbolic motions, and colors that could facilitate the addressing of the patients’ psychological issues (196). All of these treatments have been proved to work well for depression by changing the unconscious minds, which can be called implicit emotional control (194, 195, 197). Therefore, Eum et al. (195) suggested that literature therapy and art treatment could serve as a useful emotional control to help patients with stroke in their rehabilitation process (195).

Even though many studies have reported that emotional control has a great potential effect on PSD, there are still more questions that remain unanswered, e.g., the best time for emotional intervention in PSD. Most of the studies have not considered time, e.g., Hou et al. (187) found that antidepressants and psychological therapy only play a role after 3 months. In addition, there is no standard process for emotional control for PSD. Most researchers appealed to make a more individualized plan for different patients (193, 198). Therefore, a series of studies (18, 179) showed that the evidence for emotional control in PSD is still inconclusive.

**CONCLUSION AND PERSPECTIVES**

In this study, we briefly introduced the incidence, risk factors, and diagnosis of PSD. Then, we introduced the “monoamine hypothesis,” the role of three monoamines in PSD, and the antidepressant drugs primarily targeting these three monoamines and their receptors. Next, we elaborated on a new model of emotion based on the “monoamine hypothesis.” We hope to clarify the relationship between the three monoamines, emotion, and PSD. Patients with PSD have some changes in their microbiome and metabolism, and these potential biomarkers and microorganisms may aid in the diagnosis and treatment of the disease. Finally, since all drugs have side effects and the effectiveness of antidepressants in clinical practice is less than ∼50%, we introduced some emotional controls for PSD. We hope this study could help with the diagnosis and treatment of PSD.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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