LIFE: International Journal of Health and Life-Sciences
ISSN 2454-5872

Pan Zhang, 2019

Volume 5 Issue 3, pp. 41-62

Date of Publication: 29th November 2019

DOI- https://dx.doi.org/10.20319/lijhls.2019.53.4162

This paper can be cited as: Zhang, P., (2019). How can we Use Neurotransmitters in Emotion and Reward System to Study Depression? LIFE: International Journal of Health and Life-Sciences, 5(3), 41-62.

HOW CAN WE USE NEUROTRANSMITTERS IN EMOTION AND REWARD SYSTEM TO STUDY DEPRESSION?

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Abstract

Depression is the most common and widespread psychiatric disorder severely affecting people's lives at all ages. Factors from social, psychological, and biological aspects can contribute to depression, and many hypotheses are associated with biological factors involved in the aetiology of depression such as genes and neurotransmitters. As three monoamine neurotransmitters, dopamine, serotonin, and norepinephrine, are involved in the regulation of mood and motivation in emotion and reward system, the dysfunction of neurotransmitters of depressive patients can lead to their abnormal symptoms. This paper will discuss how the behaviour of these neurotransmitters has helped develop antidepressant drugs for treating depression. Although helpful, antidepressant drugs have other negative health outcomes on users such as side effects. Research on antidepressants has led to the development of new drugs such as nasal spray and skin patch which has shown to alleviate symptoms of depressive patients. Current treatments with a potential reduction of side effects are suggested on new applications for improving public health condition. Furthermore, other non-medical factors such as social engagement and physical activity are also involved in treating depression.

Keywords

Depression, Emotion, Monoamine Neurotransmitter, Antidepressant Drug, Side Effects

1. Introduction

Major depressive disorder (MDD), or depression for short, is gaining more attention in daily life. According to the World Health Organization, depression is the most common psychiatric disorder affecting more than 300 million people from all ages worldwide (World Health Organization, 2018). People with depression usually experience persistent low mood and loss of interest with other non-optimal health conditions, which negatively influences their education, occupation and normal wellbeing (Smith, 2019). In severe cases, depression can be associated with cognitive dysfunction, from functional impairment to motor activity, problem processing and short term memory (Lisa & Klaus, 2009; Caligiuri & Ellwanger, 2000; Lam, Kennedy, McIntyre & Khullar, 2014), as well as life-threatening behaviours, as it is considered to be a primary risk of suicide attempts (Briere, Kwon, Semple & Godbout, 2019). In 2017, suicide was the second-leading cause of death among individuals in the United States aged 10 to 34 (National Institute of Mental Health, 2019). As a result, MDD can pose a huge impairment to labour productivity with subsequent impacts on financial social burden issues (Chow, Doane, Sheehan, Alphs & Le, 2019). Due to the adverse impact of depression on individuals and society, much previous research and development on understanding depression are carried out. This paper reviews the possible aetiologies and treatments of depression, mainly focus on the monoamine neurotransmitter and antidepressants.

2. Aetiology of Depression

The exact aetiology of MDD is unknown, however, it has been suggested that causes are biopsychosocial; all factors from biological, social and psychological aspects are responsible for the development of depression (Schotte et al., 2006) which are summarised in Figure 1.

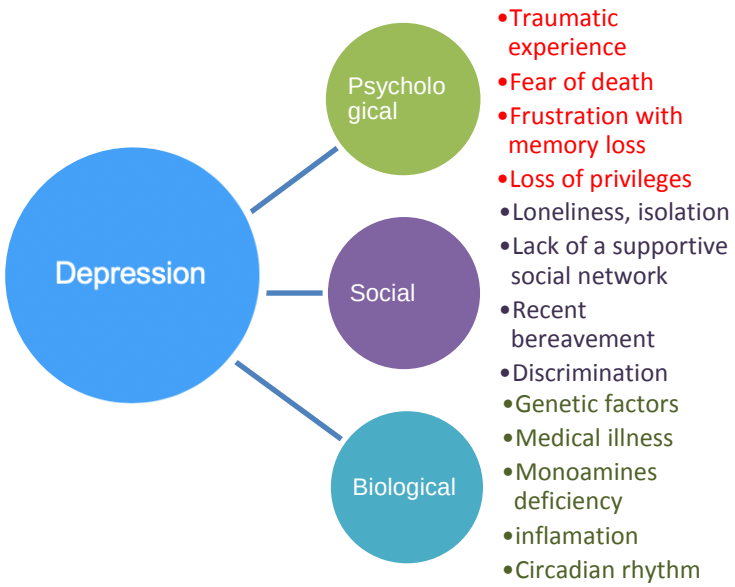

Figure 1: *The Biopsychosocial Model of Causes of Depression. Some Examples are Provided Biologically, Socially and psychologically, which all potentially contribute to Depression. In Different Cases, MDD Patients are affected by the Single Factor, but most of the Time Multiple Combinations Result in MDD*

Psychological hypotheses suggest that traumatic experiences such as childhood maltreatment and sexual abuse result in a high rate of depression (Comijs et al., 2013; Gerke et al., 2018). Besides, lack of social interactions, for example, loneliness, is also thought to be a risk factor contributing to depression (Cacioppo, Hughes, Waite, Hawkley & Thisted, 2006). Noticeably, socioeconomic status also plays a significant role in depression formation as people with low financial and social background have a higher prevalence of depression in Europe (Freeman et al., 2016).

More importantly, depression also implicates in biological factors including genetic alternation (Shadrina, Bondarenko & Slominsky, 2018). Through whole-genome studies on 807,553 individuals from the three largest genome-wide association studies of depression in 2019, 102 genetic variants possibly associated with depression were discovered (Howard et al., 2019). For instance, a gene encoding the receptors of the serotonin-transporter-linked polymorphic region is predicted to have a relationship with depression, though the findings are mixed and no candidate genes are identified with an exact allele that will cause depression (Bleys, Luyten, Soenens & Claes, 2018; Karg, Burmeister, Shedden & Sen, 2011).

Another major and more commonly accepted theory from biological aspect causing depression is the dysfunctional reward system (Admon & Pizzagalli, 2015) and associated monoamines

neurotransmitters deficiency (aan het Rot, Mathew & Charney, 2009). Depression is manifested by many different observable behavioural phenotypes. One of the core symptoms of depression is anhedonia (Paykel, 2008), described as an absence of pleasure and motivation, which is also known as a deficit of reward-processing system (Der-Avakian & Markou, 2012). The role of monoamines neurotransmitter in depression is important for mood regulation, thus the relationship between depression and neural pathways in the emotion, motivation and reward system can be explained.

3. Neurotransmitters and Depression

The role of neurotransmitters, which are chemical messengers that enable neural communication within the synapses of the nervous system, is crucial for the information transmission from the presynaptic neuron to the postsynaptic neuron, ensuring the stimulus arrives at the right place at the corresponding region of the reward system at the right time (Lodish and National Library Of Medicine, 2000).

Three monoamine neurotransmitters involved in depression are dopamine (DA), serotonin (5-HT) and norepinephrine (NE) (Hamon & Blier, 2013). Behavioural and neurological evidence indicate a deficiency of monoamines in patients with depression (Belmaker & Agam, 2008). As the neurotransmitters in the reward system are mainly responsible for the generation and regulation of emotion and motivation (Salamone & Correa, 2012) (Figure 2), the symptoms of depressive patients such as low mood can be linked to abnormal behaviour of neurotransmitters and their receptors.

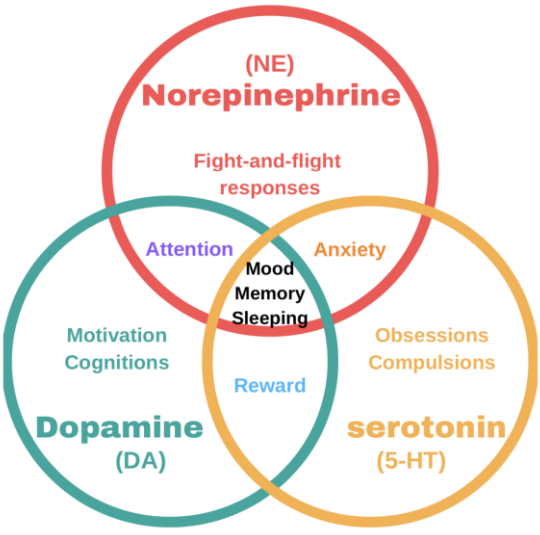

Figure 2: *The Role of Monoamines Neurotransmitters in Regulation of Mood Behaviour (Nutt, 2008). While Each Neurotransmitter has its Own Role, they also Share some Overlapping Activities with each other*

3.1 Neurotransmission and Antidepressants

First, neurotransmitters are synthesised from precursors and stored in the vesicles in neurons (Wurtman, Hefti & Melamed, 1980). Monoamines neurotransmitters are endogenous chemicals that are synthesised from amino acid precursors, as tables 1, 2, and 3 show. Once the action potential reaches the axon terminal, it triggers the fusion of vesicles with the presynaptic membrane (Wurtman, Hefti & Melamed, 1980), causing the release of neurotransmitters into the synapse by exocytosis (Figure3).

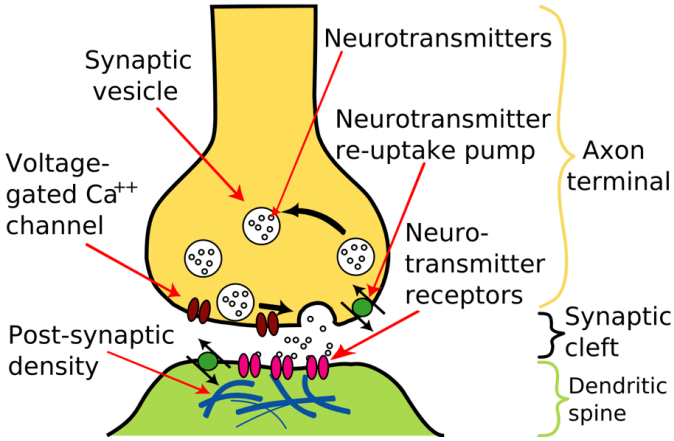

Figure 3: *The Structure of the Neuronal Synapse Consisting of Presynaptic Neuron, Synaptic Cleft, and Postsynaptic Neuron. Neurotransmitters are Released into the Cleft and Absorbed by the Postsynaptic Receptors*

There are specific receptors on the dendrites of postsynaptic cells (Wurtman, Hefti & Melamed, 1980). Owing to their specificity, the neurotransmitter molecules diffuse and bind to the exhibitory or inhibitory receptors (Elias & Saucier, 2005), which then either open the voltage-gated ion channels and generate another action potential or block the stimulus (García-Cazorla & Artuch, 2015). In this way, the stimulus can be passed from the sensory neurons to interneurons until the target cell (Lodish and National Library of Medicine, 2000). The receptors for DA, 5-HT and NE are summarised in the tables below.

Table 1: *A Summary of Dopamine and Dopamine Receptors found in the Nervous System (Neve, 2009)*

Neurotransmitter	**Precusor**	**Position**	**Role**	**Dopamine Receptors**			
				Type		***Position***	***Function***
Dopamine	Phenylalanine	Central nervous system (eg.	Reward-related	D1-like family	D1	Presynaptic and	Excitatory

		Basal ganglia, hippocampus)	cognition			postsynaptic	
	Tyrosine		Motor control		D5	Postsynaptic	Excitatory
			Emotional responses and motivation	D2-like family	D2	Postsynaptic and presynaptic	Inhibitory
	L-DOPA	Other part of the body	Blood-flow modulation		D3	Postsynaptic and presynaptic	Inhibitory
			Immune response		D4	Postsynaptic and presynaptic	Inhibitory

Table 2: *A Summary of Serotonin and 5-HT Receptors (Barnes & Sharp, 1999)*

Neurotransmitter	**Precusor**	**Position**	**Role**	**5-HT Receptors**			
				Type		***Position***	***Function***
Serotonin	5-HTP	Nervous system (raphe nuclei)	Sensorimotor	5-HT1 receptor family	5-HT1A	Presynaptic	Inhibitory
			Mood regulation		5-HT1B	Presynaptic	
					5-HT1D	Presynaptic	
					5-HT1E	Postsynaptic	
					5-HT1F	Postsynaptic	
				5-HT2 receptor family	5-HT2A	Postsynaptic	Excitatory
		Outside the nervous system	Gastrointestinal function regulation		5-HT2B	Postsynaptic	
			Bone metabolism		5-HT2C	Postsynaptic	
			Organ development	Other 5-HT receptors	5-HT3	Presynaptic	Excitatory and inhibitory
					5-HT4	Postsynaptic	Excitatory

					5-HT5A	Postsynaptic	Inhibitory
					5-HT6	Postsynaptic	Excitatory
					5-HT7	Postsynaptic	Excitatory

Table 3: *A Summary of Norepinephrine and Adrenergic Receptors (Banerjee, Kung, Riggi & Chanda, 1997)*

Neurotransmitter	**Precusor**	**Location**	**Role**	**Noradrenergic Receptors**		
				Type	***Position***	***Function***
Norepinephrine	Dopamine	Sympathetic nervous system	Fight-or-flight response,	α1	Postsynaptic membrane	Excitatory
		Central nervous system (eg. locus coeruleus)	Attention, alertness, arousal	α2	presynaptic membrane	Inhibitory
			Sleep/wake cycle	β1	Postsynaptic membrane	Excitatory
			Regulating mood/anxiety	β2	Postsynaptic membrane	Excitatory
			Enhances formation and retrieval of memory	β3	Postsynaptic membrane	Excitatory

Neither all neurotransmitters binding to the postsynaptic receptors nor they are remaining at the synapse clefts increase of further excitatory or inhibitory signal transduction (Davies & Morris, 2006). The level of neurotransmitters that released is regulated by negative feedback via auto-receptors (Timmermans & Thoolen, 1987). The auto-receptors are receptors in the presynaptic membrane of the terminal button, where some neurotransmitters bind and thereby inhibit further release or synthesis (Nautiyal et al., 2016). The excess neurotransmitters in the synaptic cleft are got rid of via three ways, re-uptake, degeneration, absorption (Fon & Edwards, 2001), while the mechanisms of antidepressants mainly focus on reuptake and degeneration (Harmer, Duman & Cowen, 2017).

Through re-uptake, extracellular neurotransmitters are repackaged back into the presynaptic neurons via monoamine transporters (MATs) and are stored in the vesicles of axon terminals

(Wurtman, Hefti & Melamed, 1980). Monoamine transporters (MATs) are classified into three types, each is responsible for one type of neurotransmitter (Bönisch, Sitte & Bönisch, 2016), the dopamine transporter, the norepinephrine transporter, and the serotonin transporter. Apart from re-uptake, excess neurotransmitters in the synapses can be broken down. Monoamines undergo oxidative deamination attached by the catalytic enzymes, which are monoamine oxidase (MAOA/B) and catechol-O-methyltransferase (COMT) and they are essential due to their function on regulation the level of neurotransmitters (Mathew et al., 2016), which directly related to the major depression (Krishnan, 2009).

Similar to any other diseases and abnormalities, MDD patients are required to visit trained doctors to seek treatment. Multiple methods exist for the treatment of depressive patients. With acquiring a better understanding of chemical interactions between the neurotransmitters and the corresponding receptors in the reward system, along with the knowledge of molecular biology obtained over the past few decades, many antidepressant drugs have been developed to treat depression (Jennings, 2018). The most commonly prescribed antidepressants in the treatment of depressive patients include selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs). Sometimes, not enough neurotransmitters are synthesised in depression patients, thus antidepressants are developed to help increase the level of precursors of DA (Andrade and Rao, 2010). For SSRIs and SNRIs, which both work as antagonist medicine, bind on MATs to prevent reuptake of 5-HT and NE in order to prolong the preservation of neurotransmitters at the synapses (Weilburg, 2004). Monoamine oxidase inhibitors (MAOIs) are antidepressants that binding to enzymes so that fewer monoamines are broken down and achieve similar effects as SSRI and SNRI (Blier, 2016). By imitating or altering the release and clearance of the neurotransmitters, antidepressants manipulate the reward system (Carlson & Birkett, 2017).

3.2 Monoamines Neurotransmitter Deficiency in Emotion and Reward System

According to National Institute of Mental health (2019), the typical symptom of MDD is a continuously low mood for at least 2 weeks, along with anhedonia, a loss of energy, difficulties in eating, sleeping and concentration, and pain without any physical causes. The symptoms of depression can be related to a dysfunction of the reward system. Reward system is a set of anatomical structures of the brain, which are mainly present along with mesocorticolimbic projection, responsible for emotions and motivational cognition (Naranjo, Tremblay and Busto, 2001) (Figure 4).

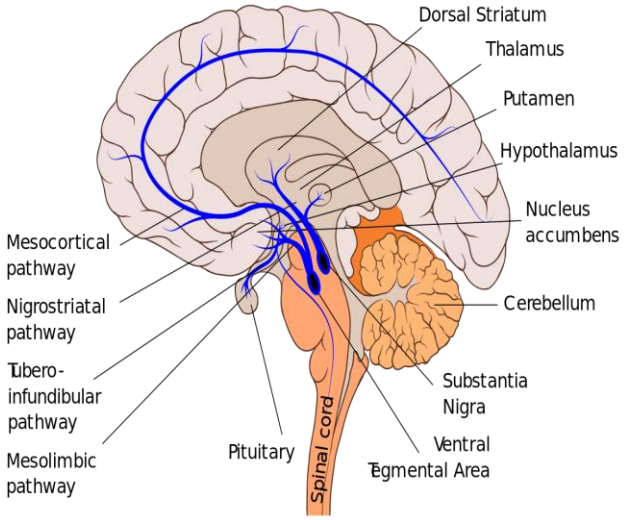

Figure 4: *The Dopaminergic Pathways. Two Blue Lines Start from the Lower Blue Dots, which represents Ventral Tegmental Area, are Mesocortical and Mesolimbic Pathways*

3.2.1 Dopamine (DA)

One of the most remarkable symptoms of MDD is anhedonia, an inability to experience pleasure with a response to stimulus and interest. It has been suggested that anhedonia, is related to the abnormality of the dopaminergic pathway of the reward system (Beauchaine, Klein, Knapton & Zisner, 2019). In 2009, By scanning the brain of MDD patients while conducting monetary incentive delay tasks, Functional magnetic resonance imaging studies showed that patients with MDD have a reduced ventral striatal volume in the reward system, which might indicate a reduction in dopaminergic receptors and dopamine synthesis (Pizzagalli et al., 2009). Antidepressants such as Pramipexole and Bupropion are effective for reducing anhedonia of depressive patients and helping them seek for motivation by acting on DA and modulating striatal function (Goldstein-Piekarski & Williams, 2019).

3.2.2 Serotonin (5-HT)

5-HT used to be considered as the most essential monoamine in MDD patient. 5-HT is responsible for the mood regulation, sleep, appetite and cognitive response (Figure 2), which corresponding to abnormalities in the symptoms of MDD patients (Meltzer, 1990). There was evidence of a rise in the risk of depression by decreasing 5-HT receptors in the serotonergic pathway (Fakhoury, 2015). However, it has been later shown that depletion of 5-HT does not reduce mood in healthy people (Ruhé, Mason and Schene, 2007), which suggested the serotonergic involvement in MDD is more complicated and can be related to decreasing in exhibitory serotonergic receptors and decrease activity in MAOs (Hasler, 2010).

Noticeably, 5-HT plays a role in the reward system and regulation of DA (Fischer and Ullsperger, 2017). 5-HT level controls the role of motivational and affective reward processing in DA (Fischer and Ullsperger, 2017), as the absence of DA and presence of 5-HT are associated with punishing process. Therefore, monoamines are influencing each other, which can lead to antidepressants misusage. Patients cannot intake a mixed combination of antidepressant randomly. The prescribed antidepressants should be taken under the guidance of physicians, or it can cause excessively stimulate the production and release of monoamines and inhibit MAOs (Foong, Grindrod, Patel & Kellar, 2018). For instance, increasing dosages of serotonergic medication will lead to serotonin toxicity within 6 to 8 hours, which hyperactive the nervous system, resulting in different symptoms such as agitation, clonus and fever (Isbister, Bowe, Dawson & Whyte, 2004). What is more, drug interactions can occur with a mixed intake of antidepressants, a combination of SSRIs, venlafaxine with MAOI may contribute to severe toxicity by decrease serotonin reuptake (Frank, 2008).

3.2.3 Norepinephrine (NE)

NE is an essential chemical presented in human body (Table 3). In the central nervous system, NEs are mainly responsible for the motor responses and memory (Dean and Keshavan, 2017). The correlation of NE and MDD is still remain mystery, but it is hypothesised that NE is involved in the lack of energy and reduced ability to concentre in patients with MDD (Briley and Chantal, 2011). In peripheral nervous system, NE activates the sympathetic system (Table 3), such as fight and flight response (Tank and Wong, 2014). Antidepressants including desvenlafaxine that associated with NE is usually SNRIs, which block the reuptake of both 5-HT and NE.

4. Limitation of Antidepressants

Indeed, antidepressants can help reduce the symptoms of MDD patients, but they have limitations. First, antidepressants are not effective on all people; only about one third to a half of people demonstrate a varying level of recovery from the prescribed medications and it takes as long as 4 to 6 weeks until the positive effects of antidepressants are visible (Baghai, Moller & Rupprecht, 2006). During the first 2 weeks of medication, some symptoms such as anxiety and dizziness can even worsen, and the incremental suicidal thoughts of depressive patients increases (Nordqvist, 2018). Additionally, antidepressants also can cause nausea, insomnia, sleepiness or fatigue, dry mouth and diarrhoea (Shankman et al., 2017). What is more, antidepressants are particularly ineffective among

teenagers and adolescents aged 9 to18 (Zhou et al., 2018). According to the research, among 34 types of antidepressants and placebo present, some of them such as imipramine and venlafaxine even result in more severe adverse effects on children with low tolerance and acceptance (Cipriani et al., 2016).

5. Novel Drugs for Treating Depression

Due to the limitations of existing antidepressants based on the monoamine hypothesis, new types of antidepressants are under research and development.

5.1 Esketamine

Another type of neurotransmitter, glutamate, is also involved in the regulation of mood, and dysfunction in binding to its receptors, N-methyl-D-aspartate (NMDA) receptors, is known to cause MDD (Jaso et al., 201). Hence, esketamine nasal spray as a new form of fast-acting clinical medicine is developed in 2019 based on the mechanism of blocking NMDA receptors and releasing glutamate (Elliott & Chan, 2019). Esketamine nasal spray can subsequently activate another receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and increases the signalling of neurotrophic factors, thereby increasing mood (U.S. Food & Drug Administration, 2019)

Esketamine nasal spray is used with other oral antidepressants in depressive patients who show resistance to at least two antidepressant treatments (U.S. FDA, 2019). Esketamine demonstrates significant impact on mood improving within 2 to 4 hours of usage with the high maintenance of efficacy, which has improved the problem of long onset of action and low durability shown in conventional antidepressant (Popova et al.,2019). However, the nasal spray can also cause inevitable negative effects on depressive patients. Similar to the conventional antidepressant, esketamine increases suicidal thoughts in patients aged 24 or younger (Spravato® (esketamine), 2019). In more severe cases, esketamine also shows much more serious side effects, such as increasing blood pressure, declining short-term cognitive ability and lose in motor coordination (U.S. Food & Drug Administration, 2019; Kim, Farchione, Potter, Chen & Temple, 2019). Nonetheless, esketamine has brought a new insight into linking anaesthesia to the treatment of depression, which provides us with possible medical treatment based on this mechanism.

5.2 EMSAM

Other innovative methods of MDD treatment are available. While most of the antidepressants described above are tablets that need oral intake, Selegiline transdermal system (EMSAM), a new form of FDA-approved skin patch is developed recently to treat depression (Emsam.com, 2017). EMSAM is

the first antidepressant that utilises a transdermal delivery system, acting as an MAOI that binds to adrenergic α2B receptors to inhibit the degeneration of neurotransmitters NE (Emsam.com, 2017). Rather than swallowing MAOI pills, which might cause a digestive disturbance with a certain food (López-Muñoz, Álamo, Juckel & Assion, 2007), people with depression can relieve the symptoms of MDD with minimal side effects by adhering the patch to their skin (Asnis & Henderson, 2014). Therefore, EMSAM is a more convenient, effective and safer antidepressant to treat depression, especially in those people who are resistant to medicine ingestion.

6. Non-Medication Methods for Treating Depression

In addition to medication, changes in the lifestyle, diet, and social behaviour can also improve the health condition of people with depression (Sarris, Neil, Coulson, Schweitzer & Berk, 2014). Different approaches such as having a healthy diet, routine physical exercise, engaging in mental activities, and social activities can regulate the mental and physical states of patients with depression by influencing the level of neurotransmitters synthesis and releases (Briguglio et al., 2018; Chakrabarti & Mohanakumar, 2016). For instance, it has been shown that dietary improvement like consumption of low-fat vegan and nutritious food to have a positive effect on mood and help depressive patients to recover faster (Firth et al., 2019) as many foods are a rich source of monoamines precursors, which are the chemicals that are essential for synthesising neurotransmitters (Briguglio et al., 2018). Moreover, physical exercises up-regulate the level of monoamines (Lin and Kuo, 2013), therefore it can be considered as a method for modulation of the reward system and alleviate the symptoms of depression. More importantly, social supports and cognitive behaviour therapy (CBT) should be given to people with depression so that they can try to communicate to people about their problems and feel more relieved (Steven, 2011; Santini, Koyanagi, Tyrovolas, Mason & Haro, 2015).

7. Discussion

As new forms of antidepressants are invented, such as the nasal spray and skin patch, their future alternative usages in daily lives for improvement in people's mood can be suggested. If any side effects are eliminated, any form of esketamine in moderate amounts can be used as a comforting gas not only for depressive patients but also for students and workers who are under huge stress and anxiety, noticeably in undergraduate medical students facing their final examinations (Noerhidajati, Makarim & Albab, 2018). The gas-releasing device can be equipped in the air conditioner in the

patients waiting rooms, in schools, in workplaces and even in toilets. Hence, people can be calmed down and their efficiency and productivity will increase.

What is more, since EMSAM skin patch can relieve the symptom of depression in only a few hours and last for a day, similar material that contains the reduced side-effect substances in skin patch can be designed and industrialised to provide clothes for depressive people to achieve mood-lifting effects, for instance disposable underwear for women who experience Premenstrual Syndrome (Alan, Bakir, Surucu & Yildirim, 2018). Furthermore, if the time of efficacy is shortened, it can be used as a cover on touchable items such as door handles, on the computer mouse. Moreover, other forms of oral antidepressants with minimal side effects can be developed, for example chewing gums and drinking, which can be commonly and widely used for alleviating the low mood and improve people's health.

8. Conclusion

MDD is a common but serious mental disorder affecting millions of people worldwide. Factors from social, psychological and biological aspects can contribute to depression, while one of the most popular biological hypotheses for aetiology of depression is monoamines neurotransmitters deficiency. Three major monoamine neurotransmitters, dopamine, serotonin and norepinephrine, involved in the pathology of depression are mainly responsible for the regulation of emotion and motivation in the reward system and most depressive patients with relative symptoms are suffering from neurotransmission problems in terms of these monoamines. Antidepressants such as SSRIs and SNRIs are effective on alleviating the symptoms of depression, though side effects are not being neglected. Therefore, new types of drugs minimising the negative impact are developed. Moreover, non-medication treatments are also important for relieving symptoms of depression.

At present, most studies on antidepressant focus on studying the mechanism of antidepressants for their mood-lifting functions, while the research on other symptoms of depression is relatively understudied. Therefore, as there are more symptoms of MDD patients than continuously low mood, such as sleep disturbance and anhedonia, there is a question about the curative efficacy of antidepressants against depression. Can they treat depression, or is it just a potentially more obvious improvement on mood-lifting emotion instead of general symptoms of depression? This blind spot affects the use of antidepressants, which is indicated by more severe side effects that increase the risk of comorbidities. Subsequently, MDD patients can easily lose faith in mediation. Hence, it is suggested that more effective antidepressants are in need with a wider consideration of other symptoms besides

mood. Therefore, only after thoroughly understanding the cause of depression can a truly new generation of antidepressants for curing depression be developed.

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