Anxiety and Depression: Ignored Neuropsychiatric Aspects of Parkinson's Disease

Rohit Doke[1*], Ajay Bhagwat[2], Kalyani Autade[3], Ganesh Lamkhade[4], Ashwini Wakchaure[5], Tejas Naik[6], Pooja Pate[7], Archana Navale[8]

[1]Research Scholar, Department of Pharmacology, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat 391760, India*
[2,5]Assistant Professor, Jaihind College of Pharmacy, Vadgaon Sahani, Pune, Maharashtra 412401, India
[3]Assistant Professor, Department of Pharmacology, N. N. Sattha College of Pharmacy, Ahmednagar, Maharashtra 414001, India
[4]Research Scholar, Indira College of Pharmacy, Tathawade, Pune, Maharashtra 411033, India
[6]Samarth College of Pharmacy, Belhe, Pune, Maharashtra 412410, India
[7]Sharadchandra Pawar College of Pharmacy, Dumbarwadi, Pune, Maharashtra 410504, India
[8]Associate Professor and Head, Department of Pharmacology, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat 391760, India

Abstract:

Millions of people worldwide are afflicted by Parkinson's disease, a kind of progressive brain condition marked by disturbed movements. Symptoms of PD include disproportionate tremors, slowness of movements, rigidity of muscle, and postural instability and non-motor manifestations such as neuropsychiatric comorbidities including anxiety, depression, sleeplessness, orthostatic hypotension, sexual dysfunction, and gastrointestinal issues. Due to the complex pathophysiology, manifestations of depression and anxiety in PD may be misidentified as PD traits and go undetected and untreated, thus posing a significant hurdle for researchers to conquer. The illusive characteristics of these condition may worsen the disease and may lead to therapeutic failure. There are various pharmacological and non-pharmacological options available to halt anxiety and depression in PD but none of them are able to address it completely. Further, most of these approaches are having several adverse impacts which directly or indirectly leads to disease progression. It is crucial to thoroughly investigate and comprehend the underlying pathways and pathophysiological mechanisms involved to the emergence of anxiety or depression in PD. The therapeutic and diagnostic advancements are explained in this review article with highlights on molecular etiology, and implications of anxiety and depression on Quality of life with PD.

Keywords: Depression, anxiety in Parkinson's, neuropsychiatric complications, anxiety, Parkinson's disease.

Corresponding author: Mr. Rohit Doke*,
Email: rohitdoke2853@gmail.com
DOI: 10.48047/ecb/2023.12.5.1202023.12/05/2023

INTRODUCTION

Parkinson disease (PD) is 2nd most prevalent multifactorial neurodegenerative disorder characterized by loss of dopaminergic neuron in substaintia nigra pars compacta (SNpc) which was earlier called as shaking palsy by the scientist James Parkinson [1]. PD has more than doubled in global prevalence over the past 25 years, 6.1 million cases in 2016 compared to 2.5 million cases in 1990. Men over 50 are more likely than women to develop the condition [2]. The progressive brain disorder marked by motor symptoms include more tremor, slow movements, rigidity, and postural difficulties and non-motor manifestations involving psychoneurological comorbidities including anxiety, depression, sleeplessness, orthostatic hypotension, sexual abnormalities, and gastrointestinal problems. Although the etiology of dopaminergic loss is still not clearly understood, but there are several factors explain below which leads to dopaminergic downregulation [3].

Genetic mutation and protein defect: Neurodegeneration is accompanied by protein misfolding, and the mitochondrial and ubiquitin proteasome systems (UPS) are controlled by the genes PINK1, parkin, DJ-1, and UCH-L1 respectively. However, the autophagy-lysosomal system, UPS, and molecular chaperone machinery all work together to eliminate misfolded proteins. Reactive oxygen species (ROS) overexpression triggers PINK1 mutation which alters mitochondrial membrane permeability and eventually mitochondrial dysfunction. When the UPS is triggered, neurotrophic factors are formed that suppress protein misfolding. SNCA, PARK2, PINK1, DJ-1, and LRRK2 genetic mutations induce severe misfolding, lowered production of neurotrophic factors, and inhibition of cellular processes that clear misfolded proteins. The alpha synuclein protein is notably impacted by the erroneous protein folding known as "Lewy Bodies"(LBs). Furthermore, alpha synuclein in LBs exacerbates neurodegeneration by influencing mitochondrial activity, autophagy, vesicular homeostasis, and neuroinflammation [4]–[6].

Environmental toxins:
Natural toxins like rotenone and MPTP leads to suppression of mitochondrial complex-I activity which results in ATP depletion in the SN and striatum, activation of neuroinflammatory and apoptotic pathways accompanied by DA neuronal death and apoptosis [7]. The blood-brain barrier is penetrated by 6-hydroxydopamine, damages 90–99% of dopaminergic neurons. The primary method by which catecholamine's are destroyed in SNpc is the production of ROS and free radicals including para-quinone, hydrogen peroxide, and hydroxyl radicals that have a direct influence on cellular oxidation and eventually result in apoptosis [8].

Oxidative stress and mitochondrial dysfunction:
Oxidative stress (OS) is due to disproportionate among ROS and the body's antioxidant status. Lipids, proteins, and DNA are among the biological components that are destroyed by an overactive OS. The mitochondria of neurons and glia are the dominant contributor of ROS formation in the brain [9]. Through caspase dependent and independent paths, ROS-induced mitochondrial dysfunction and an energy deficit state resulting in neurodegeneration. One of the main cell types implicated in inflammatory reactions is the microglia. The OS contributes to UPS dysfunction and microglia stimulation, which diminish neurotrophic factors' levels and trigger the generation of a number of inflammatory cytokines, like TNF-α, IL-1, IL-6, chemokines, and complement cascade

proteins, respectively. Dopaminergic loss is a consequence of oxidative stress and is mediated by neuroinflammation, protein aggregation, apoptosis, and mitochondrial impairment [10], [11].

Current pharmacological interventions and its limitations:

Several drugs, including L-DOPA, MAO-B inhibitors, COMT-Inhibitors, and DA agonists, which enhance dopamine (DA) levels and activity in the brain, are currently being used to treat PD[12], [13]. Despite being used as the benchmark for managing PD for many years, L-dopa administration for a prolonged period of time results in tardive dyskinesia and motor fluctuation [14]. The D1 and D2 receptors are the principal sites of action for the dopaminergic drugs, which increase DA activity while decreasing the brain's serotonin levels which triggers the depressive and anxiety symptoms[15]. The remaining drugs including cholinergic agents that modulate the levels of Ach and DA. The present pharmaceutical therapies only offer symptomatic relief yet none of them are able to cure PD and also hampered by various side effects like disorientation, hallucinations, and hepatotoxicity [16]. Surgery is advised as a therapeutic alternative when pharmacological approaches are ineffective in addressing PD. The current best surgical procedure for treating PD involves deep brain stimulation and globus pallidus internus, which especially minimizes motor instabilities and uncontrollable involuntary movements. The existing treatment has certain downsides, as it does not treat the underlying cause, merely ameliorates symptoms, has safety concerns, and is overpriced [17], [18].

Depression and anxiety:

The predominant neuropsychiatric consequence of PD includes depression and anxiety [19]. The kind of depressive signs found in PD involves major depression, minor depression, subsyndromal depression, dysthymia, however the anxiety in PD is classified as generalized, phobias, obsessive-compulsive disorder and panic disorders [20], [21]. In PD patients, depression is a significant contributor to poor mental wellbeing so the QoL. Depression is observed commonly in PD patients in between 38 to 42% [22], [23]. In PD, depression and anxiety are underlying psychiatric comorbidity that negatively impact motor and behavioral function and trigger substantial cognitive deficits which further leads to drastic changes in quality of life and increased risk of death. Since the depressive symptoms coincide with PD's cognitive and neurological characteristics, they are usually underdiagnosed. As a result, for better treatment of PD it needs earlier diagnosis and effective therapy for anxiety and depressive symptoms [24], [25]. The LRRK2 (individuals' carriers of the Gly2019Ser) and GBA gene mutations, women, severe states of PD, and cognitive impairment are all potential risk factors for depression. However, depressive moods, sleeplessness, imbalance, gait irregularities, motor abnormality are more often associated with anxiety in individuals[26], [27].

THE MECHANISMS OF ANXIETY AND DEPRESSION

The pathophysiology of depression entails a variety of causes. Numerous distinct alterations in the brain can trigger late-life depression, together with changes in toxic stress, elevated cortisol in blood, inflammation, and neuronal production and availability of neurotrophic factors, Lewy body formation, cerebrovascular disease, Alzheimer's disease, hippocampal dystrophy, and limbic and subcortical circuit modifications [28]. The below are several

elements that contribute to depression and anxiety.

Genetic factor:

The genetic components play prominent involvement of depression. According to some studies, the SLC6A4 gene encoding sodium-dependent serotonin transporter, is linked to depressive disorders [29], [30]. None of the genetic forms of PD appear to be linked to depression[31]. Despite the fact that study's findings imply that anxiety, depression, and several other cognitive impairments being very common in PD affected individuals with the LRRK2 G2019S mutation. In LRRK2 mutants, those with the Gly2019Ser mutation are more likely (53%) than non-carriers (16%) to have depressive symptoms [32], [33].

Monoamine theory and Neurotrophic hypothesis:

The primary monoamine neurotransmitters implicated in the pathogenesis of depression and anxiety include serotonin, noradrenaline, and DA. The decrease in the levels of these monoaminergic neurotransmitters is responsible for the depressive behaviour [34]. These all neurotransmitters along with neurotrophic factors plays crucial role in neuronal activity and regulation and so satisfactory level is necessary in order to avoid anxiety and depressive symptoms[35]. The role of these monoamine neurotransmitters is given in detail in later part of this review. The neurotrophic factors such as BDNF and GDNF are responsible for neuroplasticity, promote growth and development of neurons by providing essential components. BDNF contributes in maturity and growth of Dopaminergic neuron, hence its absence may hasten the decline of dopaminergic neurons [36]. Patients with depression also have decreased levels of BDNF in absence of PD. The BDNF promotes growth and development of immature neurons (including 5-HT, NE & DA). In depression BDNF decreases result in loss of amount/function 5-HT, NE and DA [37].

Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation

The HPA axis is essential for managing stress, malfunction in activity leads to neuropsychiatric conditions like anxiety and depression. Under stressful condition, hypothalamus produces corticotropin-releasing hormone/factor (CRH/CRF), which further acts on anterior pituitary to secret of adrenocorticotrophic hormone (ACTH). ACTH acts on adrenal cortex to produce cortisol [38], [39]. The excess of cortisol responsible for activation of several detrimental gene transcription responses which results in downregulation of neurogenesis and upregulation of neuronal apoptosis specifically 5HT, NE and DA. In addition to that excessive cortisol also stimulate glutamate mediated neuronal apoptosis. All these consequences lead to depressive symptoms [40], [41]. Mineralocorticoid and glucocorticoid receptors are primarily responsible for negative feedback control that diminishes the stress mediated overexpression of the HPA axis [42], [43]. Previous research has shown that depressive people exhibit features of a hyperactive HPA axis, indicating that depression may have a hereditary background for HPA axis malfunction[44], [45]. The primary glucocorticoid that governs metabolism, cognitive processes, and emotions particularly fear and anxiety is cortisol. Increased CRH levels or a compromised cortisol negative feedback function are two potential causes of HPA axis malfunction and thus anxiety and depression [46], [47].

Role of Dopamine

DA has a function in the motor, cognitive, behavioural, and psychological processes. The common motor complaints of PD are attributed by reduction in DA in the basal ganglia, which

interacts with the globus pallidum interna, cerebral cortex and thalamus to impact motor function [48]. Dopaminergic neurons usually operate in the SNpc and

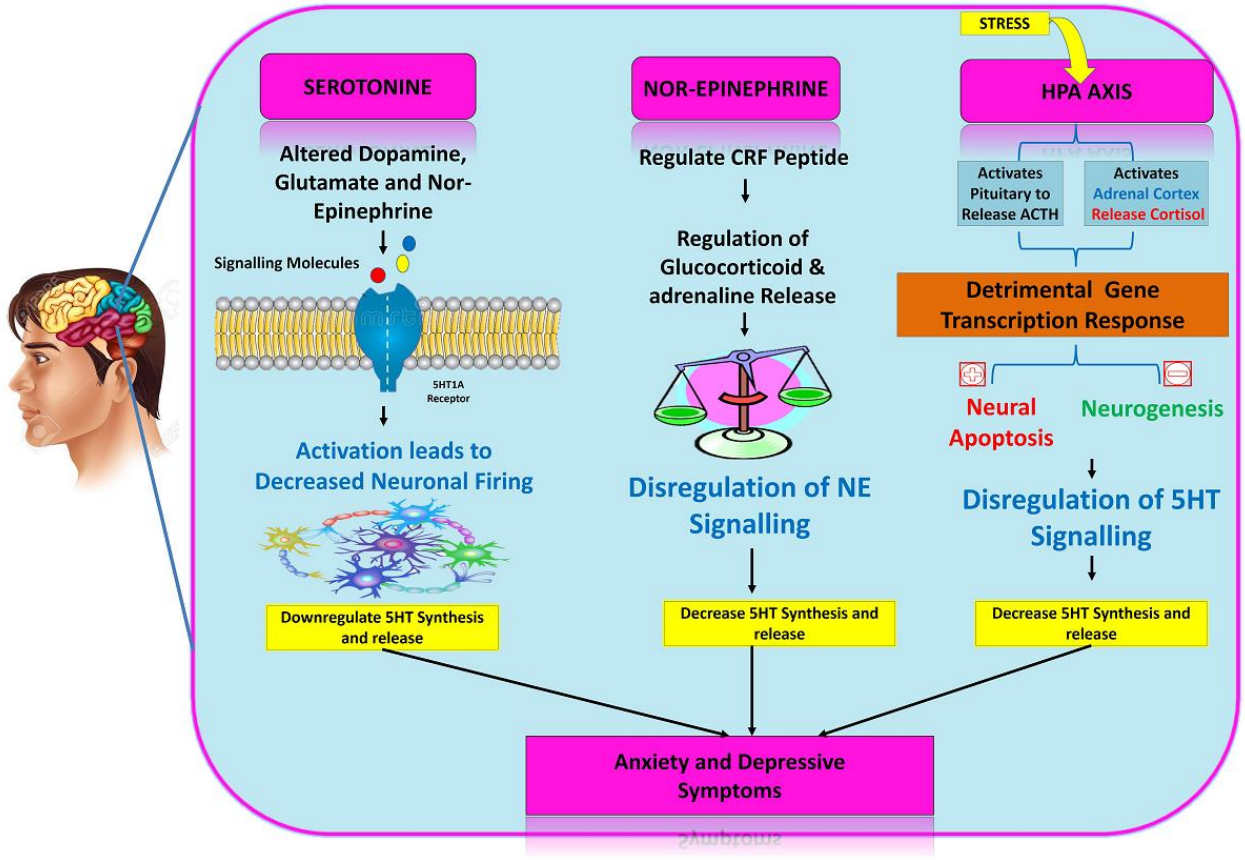

Fig.1 The Mechanisms of Anxiety and Depression

and ventral striatum, leads to motor function and reward, mood, learning, emotional functions respectively. The degeneration of DA in PD results in downregulation of ventral striatum stimulation by DA which contributes to learning, rewards and emotional problems. The complications in behavioural pathways in turns for the depressive complications which precede movement function failure in PD. The dysfunction of the cognitive function further leads to dementia as reported in earlier studies [49]. The previous studies shows that more insufficiency of DA in striatum of depressant parkinsonian patient as compared to nondepressed parkinsonian patients[50], [51]. Due to the link between the thalamus and the amygdala, the thalamus in people with PD) has less DA, which has an impact on both motor function and emotion. The reduced level of dopaminergic neurons leads to the anxiety and depression[52] and according to the monoaminergic theory of depression; the level of monoamine neurotransmitters such as DA is reduced which is responsible for producing depression in the patient[53]. Also, the reduced level of DA is responsible for the parkinsonian symptoms. So, the balancing of these dopaminergic neurotransmission is very important to prevent worsening of the condition.

Role of Serotonin

It has been observed that the level of 5HT which generally produce by raphe nuclei is also hampered not only in PD but also in depressant patient with PD [54], however it's binding to

receptors is increased. Surprisingly, people with PD lacking depression do not exhibit this observation. It is documented that both short-term and long-term distress may induce substantial increase in serotonergic and/or noradrenergic function in the cortex, striatum, and hippocampal regions of the brain [55], [56]. Impaired neuromodulation by the DA neuron may potentially contribute to the aberrant serotonergic function that has been linked to several non-motor and motor symptoms of PD. The decreased level of serotonin leads to the anxiety, depression and PD [57]. There are around 14 distinct types of serotonin receptors, including the 5-HT1A, which is found on presynaptic and post-synaptic membranes and is mostly implicated to the incidence of anxiety and depression [58], [59]. The reduction in firing rate caused by activation of serotonergic receptors in the projection regions inhibits 5-HT biosynthesis, 5-HT turnover, and 5-HT release. Since the release of GABA, glutamate, and DA are modulated by the 5HT-1A receptor, disruption of 5-HT leads to receptor modification and a neurobehavioral consequence in PD[60]–[62]. Serotonin acts as a false neurotransmitter and releases the DA from variety of serotonergic receptors in Parkinson's brain which further displaces the endogenous serotonin [63]. These mental consequences, notably anxiety and depression, can be tied to PD and are seen as the initial manifestations of PD.

Role of Noradrenaline

NE, which is predominantly expressed in cells of the locus ceruleus and is projected to several cortical and subcortical brain locations, is also depleted in PD alongside DA, and numerous of these regions have indeed been associated to the origin of depression [64], [65]. The NE is widely recognized for regulating the stress response, the locus coeruleus gets signals from various different neurotransmitter pathways particularly 5-HT, GABA, CRF, DA, and glutamate, causes homeostasis. NE engages with pre- and postsynaptic α- and β-adrenergic receptors to elicit its effects. The widespread decrease in the level of noradrenaline is the result of degeneration of neurons in the locus coeruleus [66], [67]. The level of noradrenaline is found to be low in case of the depression and PD. The NE in the locus coeruleus convey stress signals to regions of the forebrain that are important in orchestrating the stress response. The NE dysregulation in the locus coeruleus results in anxiety because NE largely influences impulses transmitted by other neurotransmitters such 5HT, DA, glutamate, and GABA [68], [69].

Role of GABA

Decrease in the levels of DA alters the level of Glutamic acid decarboxylase which is important enzyme in the synthesis of an inhibitory neurotransmitter GABA. The lowered level of GABA is observed in PD and depression due to the lower levels of dopamine[70]. The activators of GABA receptors are anxiolytics and inhibitors impart anxiogenic actions. The GABAA inotropic and GABAB metabotropic receptors are the target sites for GABA. In contrast to GABAB, which influences the production of excitatory postsynaptic potential, GABAA is a ligand-gated ion channel that opens the chloride ion channel, expresses inhibitory action on neurons, and regulates brain excitability [71], [72]. Anxiety results from GABAB receptor dysfunction since this receptor is involved in the control of several healthy and unhealthy brain functions, such as sleep, memory, and emotions.[73], [74]

Treatment of anxiety and depression in Parkinson's disease

The treatment of these neuropsychiatric complications is divided into two types which

includes pharmacological and non-pharmacological treatment which is asfollows

PHARMACOLOGICAL TREATMENT

SSRIs and TCAs currently the best therapeutic classes useful for the management of depression in PD[75]. The SSRIs are popular medications for treating anxiety disorders. For PD-related problems like anxiety and depression, many neurologist favors SSRIs[76]. Fluoxetine, Sertraline and fluvoxamine are effective selective 5-HT inhibitors that have the ability to taggle major depressive conditions as panic disorders, bipolar disorders and obsessive-compulsive disorder (OCD)[77]. Although SSRIs are extensively used and have evolved as the drug of choice for the management of OCD, their effectiveness in addressing other complicated forms of anxiety and depressive states has not been established[78].SSRIs work by preventing its re-uptake, which raises the level of 5-HT in synapses, also potentiates its effect by gradually reducing postsynaptic 5-HT2 receptor and suppressing 5HT auto-receptor[79]. The possibility of developing metabolic abnormalities, hyponatremia, sexual dysfunction, loss of libido, watery stool, sleeplessness are some the side effects of SSRIs that are frequently reported by patients. The complications of withdrawal syndrome are brought on by abruptly stopping taking SSRIs [80]. An SSRI, which may be useful for both anxiety and depression, which frequently overlap. Short-term administration of benzodiazepines, such as lorazepam or clonazepam, up to 2 or 3 times day, may be helpful in cases of non-suicidal depressed individuals with extreme anxiety. It is recommended to maintain a consistent drug dose for at least six months after clinical progress has been accomplished in order to prevent relapse [81].

The TCA mainly act by downregulating synaptic reuptake predominantly of DA, NE and less predominantly of 5-HT and thus helps to elevate levels of these neurotransmitters. The Anti-muscarinic and anti-histaminergic secondary actions of TCA are proven which can be the possible mechanism behind therapeutics effectiveness of agents like nortriptyline, amitriptyline, desipramine in depressive symptoms with PD [82][83], [84]. The precise mechanisms of a handful antidepressants including bupropion, mirtazapine, and nefazodone, have also been established. Nefazodone and mirtazapine have already been investigated for the treatment of depression in PD[85]. Dopamine reuptake antagonist like bupropion could be useful for treating people with PD who are also depressed. Agitation, constipation, dry mouth, extreme perspiration, tremor, and losing weight are frequent adverse effects. Seizures and psychosis are rare at high dosages [86].

PD and anxiety problems are both treated with monoamine oxidase inhibitors (MAOI), Due to its substantial risk of complications it place the greatest safety obligation. While using MAOIs, patients are more likely to experience daytime drowsiness, weight gain, and insomnia. In individuals using levodopa concurrently along with non-selective MAOI such phenelzine, and tranylcypromine due to its potential to cause hypertensive crisis, should not be the best option[87][88]. Antidepressant and antipsychotic medication is advised for treatment. Atypical antipsychotic medication quetiapine is currently the choice treatment since it is well-tolerated and carries a negligible risk of extrapyramidal adverse effects. Quetiapine is beneficial for PD individuals carrying depression having sleeping disturbances, because of its sedating effect. PD psychosis may potentially benefit from clozapine (Clozaril) however agranulocytosis is a serious side effect of

clozapine, and patients must be closely watched for neutropenia [89], [90]

These drugs are used to manage the anxiety and depression in the PD but the drugs such as Levodopa which is widely used as a gold standard to treat the Parkinson's [91] may cause the neuropsychiatric side effects including depressive signs, possibly due to interaction with MAO's functions [92]. The higher dose of L-dopa can produce the panic attacks, dyskinesias and motor fluctuations [93]. While giving dopamine replacement therapy to the Parkinson's patients, severity of neuropsychiatric complications are increased. Giving dopamine replacement therapy and managing neuropsychiatric complication in Parkinson's patient is very challenging in the management of the disease. It is crucial for researchers to identify an alternate therapy option for fully treating the disease from every angle due to the inadequacies of the pharmacological management of anxiety and depression in PD.

NON-PHARMACOLOGICAL TREATMENT

The existing non-pharmacological treatments options are transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and cognitive behavioural therapy (CBT).

Cognitive Behavioural Therapy

CBT is a renowned psychotherapeutic technique that is used to relieve depressive symptoms in PD. It has proven effective in alleviating psychiatric disorder in people with a variety of serious chronic and neurological dysfunctions. Participants in CBT programmes for PD patients report fewer anxiety and depression symptoms than non-participants. The positive impact of CBT may have helped PD patients acquire problem-solving skills that transformed anxious thoughts and engrossed in behaviours required to deal with PD. As a result, CBT can cognitively regulate signs and behaviours to alter dysfunctional thoughts and beliefs. This may be one of the probable mechanism for the significant reduction in symptoms of anxiety and depression[94]–[96].

Transcranial magnetic stimulation

TMS is used to manage both motor and non-motor and mental issues associated with PD[97]. It is non-invasive tool for understanding the workings of the human brain. In individuals suffering from idiopathic depression who do not respond to conventional treatment, a pulsed magnetic field induces current flow in the brain and can immediately depolarize or hyperpolarize the neurons of the cerebral cortex. Patients who underwent active TMS for their mild to moderate depression and PD had better depression scores. After TMS therapy, which was well-tolerated, positive benefits on cognition and motor symptoms were also observed[98], [99].

Deep Brain Stimulation

DBS involves chronic electrical stimulation to the brain and has emerged as the surgical method of choice for movement disorders such PD, essential tremor, and dystonia that are refractory to medication[100], [101]. The mechanisms of action of DBS are yet undiscovered, despite the fact that it significantly lowers motor Dysfunction, eliminates medication related side effects, improves functional performance in daily living activities, and improves QoL [102], [103]. DBS has been linked to increased apathy as well as a decrease in mood. Additionally, it's been noted that after DBS, the suicide rates rose[104], [105].To enhance the patients' quality of life, special consideration must be given to the pharmacological and non-pharmacological treatment of anxiety and depression related to PD.

Role of Ayurveda in management of the disease

Ayurveda is a traditional healthcare practice that has been used since ancient times and offers a conceptual framework and therapeutic modalities for managing a number of health issues[106]. It offers basic, affordable methods without the hazardous side effects seen with existing synthetic treatment options [107]. There are Ayurvedic medicines that assist in the functioning of different bodily organs and systems. Multiple disease can be treated with these organ-specific herbs[108]. Ayurveda can offer new information for improved management of the illness in the treatment of neuropsychiatric problems including anxiety and depression. The most popular natural medications are:

Table.1 List of Herbs used in management of neuropsychiatric complications of PD

Sr. No	Herbs	Possible Mechanism	Therapeutic application	Ref.
1	***Hypericum Perforatum***	• Modulation of monoamine neurotransmission • Nonselective re-uptake inhibitior of serotonin, dopamine, norepinephrine	• Anxiety • Depression • Parkinson's Disease	[109] , [110]
2	***Borage (Echium amoenum)***	• Neuroprotection via downregulating apoptosis and oxidative stress • Modulation of GABA	• Anxiety, • Depression • Alzheimer's Disease	[111]
3	***Cannabis Sativa***	• Modulation of dopaminergic neurons • Inhibitory GABA-nergic neurons and excitatory glutamatergic neurons	• Anxiety • Psychosis, • Neuropathic Pain, • Alzheimer Disease, • Parkinson Disease, • Huntington Disease, • Epilepsy	[112]
4	***Bacopa monnieri***	• Acts on β-amyloid • increased cerebral blood flow • modulation of ACh ,5-HT, DA neurotransmitter	• Neurodegenerative diseases • Parkinson Disease • Alzheimer Disease	[113]
5	***Passion Flower***	• Regulate GABA system mediated anxiolysis and shows non-sedative anxiolytic effects	• Anxiety	[114]
6	***Chamomile Tea***	• Inhibition of GAD activity	• Anxiety • Depression	[115]
7	***Ginkgo Biloba***	• Modification of the neurotransmitters Ach, 5-HT, and DA	• Anxiety • Depression • Parkinson's Disease	[116]

8	***Akebia Quinata***	• Catecholamine activity enhancers • Monoamine oxidase inhibitors	• Anxiety • Depression	[117], [118]
9	***Matrica Recutita***	• Regulate GABA Receptor function • Controls monoamines neurotransmission	• Anxiety • Depression	[119]

The management of these complications such as anxiety and depression can be possible with the help of Ayurveda. It offers fresh perspective for treating these mental consequences and can enhance the patients' QoL. It will also help in reducing the mortality rates. The ignored aspects of the Parkinson's disease when properly managed or treated the improvement in the condition can be observed and life of the patients can be saved. So understanding the causes and occurrence of the motor and non-motor symptoms of Parkinson's disease and proving better therapeutic management is of great importance to maintain the QoL.

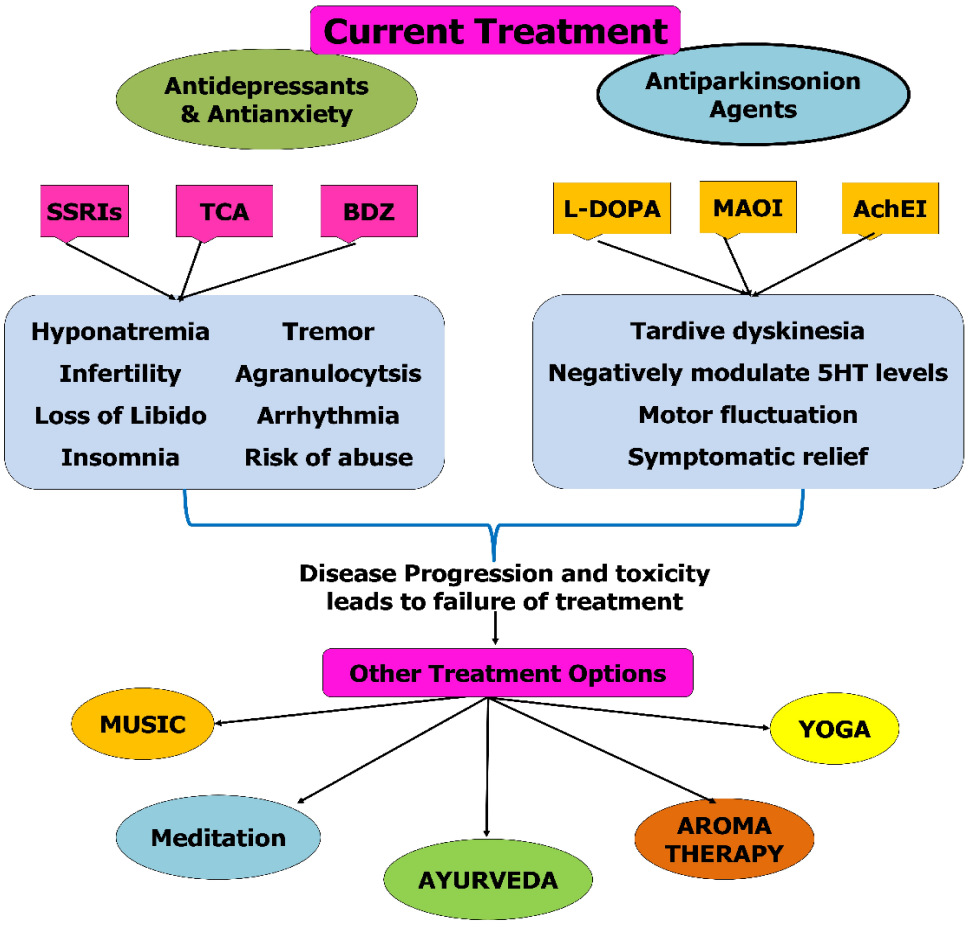

Fig.2 Currently available therapy and alternatives for management of Depression and Anxiety in PD

Aroma Therapy:

Aromatherapy is the practise of addressing a wide range of conditions with concentrated oils from that are extracted from herbs, flowers, and other plant components [120]. Aromatherapy with lavender and chamomile essential oils helps lower degree of stress, anxiety, and depression. The aromatic oils are applied mostly topically and via inhalation route [121]. The limitations of commonly used pharmacological therapy are not present when using essential oils to treat depression and anxiety. The anxiolytic effects of these essential oils and the interactions of their main constituents with CNS receptors have been confirmed by in-vivo studies in animals. Thus, it is acceptable to claim that the sedative, anxiolytic, and other beneficial effects of these neurotransmitters are likely caused by the acting on glutamate and GABA neurotransmitter systems [122].

Music Therapy and dance therapies may be effective at lowering anxiety, stress, and depression symptoms concurrently[123]. All people diagnosed with depressed symptoms benefited from dance therapy. Particularly in the last five years, music therapy has gained popularity as a treatment for a number of medical diseases and mental health issues [124]. Individuals with mental problems may benefit from using music therapy to lessen their stress and depression as well as to maintain and improve their health [125].

Meditation and Yoga:

Mantra-based meditation (MBM) often entails the constant repetition of a word, phrase, or sequence of syllables with or without religious or spiritual content [126]. It can change the thinking of the person. It is very useful in treating anxiety like complication of the PD [127]. After understanding the therapeutic limitation of existing treatment options, complementary treatment like aromatherapy, music, yoga and meditation can unquestionably benefit in the management of the disease and thereby improve the patient's quality of life [128].

CONCLUSION:

Common psychotic illnesses like depression and anxiety can make things worse by drastically lowering the effectiveness of current treatments, leading to fast impairment and functional comorbidities, which further lead to poor quality of life. Because PD is a complex disease and some of its symptoms are similar to those of anxiety and depression, it often goes undiagnosed and untreated, creating a big challenge for researchers to overcome disease. Timely diagnosis and appropriate therapy might considerably improve the condition of PD patients. Only symptomatic alleviation is offered by the use of L-dopa and other therapeutic agents. The SSRIs, SNRIs, TCA, benzodiazepines, and other anti-depressants are available therapeutics commonly used to overcome both anxiety and depression. Non-pharmacological therapeutic interventions entail Cognitive Behavioural Therapy (CBT), Repetitive Transcranial Magnetic Stimulation, and Deep Brain Stimulation. The conventional pharmacological intervention does not provide enough relief from the problems of PD as well as having many unexpected adverse effects. Therefore, using alternative therapies like exercise to strengthen functional abilities, naturopathy, aromatherapy, and psychosocial interventions such as music, dance can greatly improve quality of life of PD patient. The association among PD, anxiety and depression needs further investigation in order to develop more focused approach for detection and treatment of anxiety and depression in PD patients.

DECLARATIONS

Competing interests: The authors report no relationships that could be construed as a conflict of interest

Funding: Not applicable

Acknowledgements: Not applicable

REFERENCES

1. S. R. Sainani, P. A. Pansare, K. Rode, V. Bhalchim, R. Doke, and S. Desai, "Emendation of autophagic dysfuction in neurological disorders: a potential therapeutic target," *Int. J. Neurosci.*, vol. 132, no. 5, pp. 466–482, 2022, doi: 10.1080/00207454.2020.1822356.
2. Doke RR, Pansare PA, Sainani SR, Bhalchim VM, Rode KR, "Natural products: An emerging tool in parkinson's disease," *IP Indian J. Neurosci.*, vol. 5, no. 3, pp. 95–105, 2019
3. S. Selvaraj and S. Piramanayagam, "Impact of gene mutation in the development of Parkinson's disease," *Genes Dis.*, vol. 6, no. 2, pp. 120–128, 2019, doi: 10.1016/j.gendis.2019.01.004.
4. W. Akram, V. Kumar, S. Arora, S. Alam, and R. Kumar, "Neurotoxin models and treatments of Parkinson's disease," *Int. J. Health Sci. (Qassim).*, pp. 10316–10341, 2022, doi: 10.53730/ijhs.v6ns2.7649.
5. R. M. Kostrzewa, "Neonatal 6-hydroxydopamine lesioning of rats and dopaminergic neurotoxicity: proposed animal model of Parkinson's disease," *J. Neural Transm.*, vol. 129, no. 5–6, pp. 445–461, 2022, doi: 10.1007/s00702-022-02479-4.
6. K. H. Lee, M. Cha, and B. H. Lee, "Crosstalk between neuron and glial cells in oxidative injury and neuroprotection," *Int. J. Mol. Sci.*, vol. 22, no. 24, 2021, doi: 10.3390/ijms222413315.
7. D. S. A. Simpson and P. L. Oliver, "Ros generation in microglia: Understanding oxidative stress and inflammation in neurodegenerative disease," *Antioxidants*, vol. 9, no. 8, pp. 1–27, 2020, doi: 10.3390/antiox9080743.
8. da F. A.C.C. *et al.*, "The impact of microglial activation on blood-brain barrier in brain diseases," *Front. Cell. Neurosci.*, vol. 8, no. November, pp. 1–13, 2014, [Online]. Available: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L600348153%0Ahttp://dx.doi.org/10.3389/fncel.2014.00362
9. K. Kalinderi, L. Fidani, Z. Katsarou, and S. Bostantjopoulou, "Pharmacological treatment and the prospect of pharmacogenetics in Parkinson's disease," *Int. J. Clin. Pract.*, vol. 65, no. 12, pp. 1289–1294, 2011, doi: 10.1111/j.1742-1241.2011.02793.x.
10. Y. H. et al., "Treatment strategies for Parkinson's disease," Neurosci. Bull., vol. 26, no. 1, pp. 66–76, 2010,http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010107428
11. A. Dekundy, M. Lundblad, W. Danysz, and M. A. Cenci, "Modulation of l-DOPA-induced abnormal involuntary movements by clinically tested compounds: Further validation of the rat dyskinesia model," *Behav. Brain Res.*, vol. 179, no. 1, pp. 76–89, 2007, doi: 10.1016/j.bbr.2007.01.013.
12. L. N. Yatham *et al.*, "Atypical antipsychotics in bipolar depression: Potential mechanisms of action," *J. Clin. Psychiatry*, vol. 66, no. SUPPL. 5, pp. 40–48, 2005.
13. F. K. Salawu, A. Danburam, and A. B. Olokoba, "Non-motor symptoms of Parkinson's disease: diagnosis and management.," *Niger. J. Med.*, vol. 19, no. 2, pp. 126–131, 2010, doi: 10.4314/njm.v19i2.56496.
14. V. D. Sharma, M. Patel, and S. Miocinovic, "Surgical Treatment of Parkinson's Disease: Devices and Lesion Approaches," *Neurotherapeutics*, vol. 17, no. 4, pp. 1525–1538, 2020, doi: 10.1007/s13311-020-00939-x.
15. O. Rascol *et al.*, "Limitations of current Parkinson's disease therapy," *Ann. Neurol.*, vol. 53, no. SUPPL. 3, 2003, doi: 10.1002/ana.10513.
16. D. Aarsland and M. G. Kramberger, "Neuropsychiatric symptoms in Parkinson's disease," *J. Parkinsons. Dis.*, vol. 5, no. 3, pp. 659–667, 2015, doi: 10.3233/JPD-150604.
17. E. C. Penick, E. J. Nickel, E. Othmer, C. Desouza, W. F. Gabrielli, and E. E. Hunter,

"Minor versus major depression: a comparative clinical study.," *Prim. Care Companion J. Clin. Psychiatry*, vol. 12, no. 1, p. PCC-08m00752, 2010.

18. K. Walsh and G. Bennett, "Parkinson's disease and anxiety," *Postgrad. Med. J.*, vol. 77, no. 904, pp. 89–93, 2001, doi: 10.1136/pmj.77.904.89.
19. J. R. Slaughter, "Prevalence, Clinical Manifestations, Etiology, and Treatment of Depression in Parkinson's Disease," *J. Neuropsychiatr.*, vol. 13, no. 2, pp. 187–196, 2001, doi: 10.1176/appi.neuropsych.13.2.187.
20. S. Cong, C. Xiang, S. Zhang, T. Zhang, H. Wang, and S. Cong, "Prevalence and clinical aspects of depression in Parkinson's disease: A systematic review and meta‑analysis of 129 studies," *Neurosci. Biobehav. Rev.*, vol. 141, 2022, doi: 10.1016/j.neubiorev.2022.104749.
21. J. P. Bach, O. Riedel, J. Klotsche, A. Spottke, R. Dodel, and H. U. Wittchen, "Impact of complications and comorbidities on treatment costs and health-related quality of life of patients with Parkinson's disease," *J. Neurol. Sci.*, vol. 314, no. 1–2, pp. 41–47, 2012, doi: 10.1016/j.jns.2011.11.002.
22. J. K. Garlovsky, P. G. Overton, and J. Simpson, "Psychological Predictors of Anxiety and Depression in Parkinson's Disease: A Systematic Review," *J. Clin. Psychol.*, vol. 72, no. 10, pp. 979–998, 2016, doi: 10.1002/jclp.22308.
23. S. Q. Shu L, Zhang Y, Pan H, Xu Q, Guo J, Tang B, "Clinical heterogeneity among LRRK2 variants in Parkinson's disease: a meta-analysis.," *Front. Aging Neurosci.*, vol. 19, no. 10, p. 283, 2018.
24. P. Gonzalez-Latapi, E. Bayram, I. Litvan, and C. Marras, "Cognitive impairment in parkinson's disease: Epidemiology, clinical profile, protective and risk factors," *Behav. Sci. (Basel).*, vol. 11, no. 5, 2021, doi: 10.3390/bs11050074.
25. S. P. Aarsland D, Påhlhagen S, Ballard CG, Ehrt U, "Depression in Parkinson disease—epidemiology, mechanisms and management.," *Nat. Rev. Neurol.*, vol. 8, no. 1, p. 35, 2012.
26. C. Fabbri and A. Serretti, "Pharmacogenetics of Major Depressive Disorder: Top Genes and Pathways Toward Clinical Applications," *Curr. Psychiatry Rep.*, vol. 17, no. 7, 2015, doi: 10.1007/s11920-015-0594-9.
27. Z. Zhou, J. Zhen, N. K. Karpowich, C. J. Law, M. E. A. Reith, and D. N. Wang, "Antidepressant specificity of serotonin transporter suggested by three LeuT-SSRI structures," *Nat. Struct. Mol. Biol.*, vol. 16, no. 6, pp. 652–657, 2009, doi: 10.1038/nsmb.1602.
28. G. M. Halliday, J. B. Leverenz, J. S. Schneider, and C. H. Adler, "The neurobiological basis of cognitive impairment in Parkinson's disease," *Mov. Disord.*, vol. 29, no. 5, pp. 634–650, 2014, doi: 10.1002/mds.25857.
29. B. S. *et al.*, "LRRK2 G2019S mutation in Parkinson's disease: A neuropsychological and neuropsychiatric study in a large Algerian cohort," *Park. Relat. Disord.*, vol. 16, no. 10, pp. 676–679, 2010, [Online]. Available:http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L51100481%0Ahttp://dx.doi.org/10.1016/j.parkreldis.2010.09.003
30. E. Tolosa, M. Vila, C. Klein, and O. Rascol, "LRRK2 in Parkinson disease: challenges of clinical trials," *Nat. Rev. Neurol.*, vol. 16, no. 2, pp. 97–107, 2020, doi: 10.1038/s41582-019-0301-2.
31. B. Haenisch and H. Bönisch, "Depression and antidepressants: Insights from knockout of dopamine, serotonin or noradrenaline re-uptake transporters," *Pharmacol. Ther.*, vol. 129, no. 3, pp. 352–368, 2011, doi: 10.1016/j.pharmthera.2010.12.002.
32. S. Cohen-Cory, A. H. Kidane, N. J. Shirkey, and S. Marshak, "Brain-derived neurotrophic factor and the development of structural neuronal connectivity," *Dev. Neurobiol.*, vol. 70, no. 5, pp. 271–288, 2010, doi: 10.1002/dneu.20774.
33. F. Angelucci, S. Brenè, and A. A. Mathé, "BDNF in schizophrenia, depression and corresponding animal models," *Mol. Psychiatry*, vol. 10, no. 4, pp. 345–352, 2005, doi: 10.1038/sj.mp.4001637.
34. H. . P. Rang, M. M. Dale, J. M. Ritter, R. J.

Flower, and G. Henderson, "Φαρμακολογια (Rang & Dale's Pharmacology)," p. 802, 2013, [Online].
35. S. Watson and P. Mackin, "HPA axis function in mood disorders," *Psychiatry*, vol. 8, no. 3, pp. 97–101, 2009, doi: 10.1016/j.mppsy.2008.11.006.
36. I. Liberzon, M. Krstov, and E. A. Young, "Stress-restress: Effects on ACTH and fast feedback," *Psychoneuroendocrinology*, vol. 22, no. 6, pp. 443–453, 1997, doi: 10.1016/S0306-4530(97)00044-9.
37. E. Jesulola, P. Micalos, and I. J. Baguley, "Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model - are we there yet?," *Behav. Brain Res.*, vol. 341, pp. 79–90, 2018, doi: 10.1016/j.bbr.2017.12.025.
38. K. Chopra, B. Kumar, and A. Kuhad, "Pathobiological targets of depression," *Expert Opin. Ther. Targets*, vol. 15, no. 4, pp. 379–400, 2011, doi: 10.1517/14728222.2011.553603.
39. G. Boero *et al.*, "Impaired glucocorticoid-mediated HPA axis negative feedback induced by juvenile social isolation in male rats," *Neuropharmacology*, vol. 133, pp. 242–253, 2018, doi: 10.1016/j.neuropharm.2018.01.045.
40. B. J. Kolber, L. Wieczorek, and L. J. Muglia, "Hypothalamic-pituitary-adrenal axis dysregulation and behavioral analysis of mouse mutants with altered glucocorticoid or mineralocorticoid receptor function," *Stress*, vol. 11, no. 5, pp. 321–338, 2008, doi: 10.1080/10253890701821081.
41. E. J. Nestler, "Antidepressant treatments in the 21st century," *Biol. Psychiatry*, vol. 44, no. 7, pp. 526–533, 1998, doi: 10.1016/S0006-3223(98)00095-X.
42. H. F., L. C.J., S. W., and K. J.-C., "Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders," *Neuroendocrinology*, vol. 62, no. 4, pp. 340–347, 1995, [Online].
43. L. Arborelius, M. J. Owens, P. M. Plotsky, and C. B. Nemeroff, "The role of corticotropin-releasing factor in depression and anxiety disorders," *J. Endocrinol.*, vol. 160, no. 1, pp. 1–12, 1999, doi: 10.1677/joe.0.1600001.
44. E. A. Young, R. F. Haskett, V. Murphy Weinberg, S. J. Watson, and H. Akil, "Loss of Glucocorticoid Fast Feedback in Depression," *Arch. Gen. Psychiatry*, vol. 48, no. 8, pp. 693–699, 1991, doi: 10.1001/archpsyc.1991.01810320017003
45. G. Leisman and R. Melillo, "The basal ganglia: Motor and cognitive relationships in a clinical neurobehavioral context," *Rev. Neurosci.*, vol. 24, no. 1, pp. 9–25, 2013, doi: 10.1515/revneuro-2012-0067.
46. B. M. Roberts *et al.*, "GABA uptake transporters support dopamine release in dorsal striatum with maladaptive downregulation in a parkinsonism model," *Nat. Commun.*, vol. 11, no. 1, 2020, doi: 10.1038/s41467-020-18247-5.
47. S. J. Chung, J. J. Lee, J. H. Ham, P. H. Lee, and Y. H. Sohn, "Apathy and striatal dopamine defects in non-demented patients with Parkinson's disease," *Park. Relat. Disord.*, vol. 23, pp. 62–65, 2016, doi: 10.1016/j.parkreldis.2015.12.003.
48. H. Bernheimer, W. Birkmayer, O. Hornykiewicz, K. Jellinger, and F. Seitelberger, "Brain dopamine and the syndromes of Parkinson and Huntington Clinical, morphological and neurochemical correlations," *J. Neurol. Sci.*, vol. 20, no. 4, pp. 415–455, 1973, doi: 10.1016/0022-510X(73)90175-5.
49. R. M. Torack and J. C. Morris, "The Association of Ventral Tegmental Area Histopathology With Adult Dementia," *Arch. Neurol.*, vol. 45, no. 5, pp. 497–501, 1988, doi: 10.1001/archneur.1988.00520290025008
50. P. Jenner, M. Sheehy, and C. Marsden, "Noradrenaline and 5-hydroxytryptamine modulation of brain dopamine function: implications for the treatment of Parkinson's disease.," *Br. J. Clin. Pharmacol.*, vol. 15, no. 2 S, pp. 277S-289S, 1983, doi: 10.1111/j.1365-2125.1983.tb05876.x.
51. A. J. Emerson, D. P. Kappenman, P. J. Ronan, K. J. Renner, and C. H. Summers, "Stress induces rapid changes in serotonergic activity: Restraint and exertion," *Behav. Brain Res.*, vol.

52. 111, no. 1–2, pp. 83–92, 2000, doi: 10.1016/S0166-4328(00)00143-1.
53. R. Tomer, J. Aharon-Peretz, and Z. Tsitrinbaum, "Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease," *Neuropsychologia*, vol. 45, no. 2, pp. 357–367, 2007, doi: 10.1016/j.neuropsychologia.2006.06.014.
54. J. H. Krystal and A. Neumeister, "Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience," *Brain Res.*, vol. 1293, pp. 13–23, 2009, doi: 10.1016/j.brainres.2009.03.044.
55. D. Yadav and P. Kumar, "Restoration and targeting of aberrant neurotransmitters in Parkinson's disease therapeutics," *Neurochem. Int.*, vol. 156, 2022, doi: 10.1016/j.neuint.2022.105327.
56. A. L. Garcia-Garcia, A. Newman-Tancredi, and E. D. Leonardo, "P5-HT1A receptors in mood and anxiety: Recent insights into autoreceptor versus heteroreceptor function," *Psychopharmacology (Berl).*, vol. 231, no. 4, pp. 623–636, 2014, doi: 10.1007/s00213-013-3389-x.
57. M. Amargós-Bosch, X. López-Gil, F. Artigas, and A. Adell, "Clozapine and olanzapine, but not haloperidol, suppress serotonin efflux in the medial prefrontal cortex elicited by phencyclidine and ketamine," *Int. J. Neuropsychopharmacol.*, vol. 9, no. 5, pp. 565–573, 2006, doi: 10.1017/S1461145705005900.
58. P. M. Whitaker-Azmitia, M. Druse, P. Walker, and J. M. Lauder, "Serotonin as a developmental signal," *Behav. Brain Res.*, vol. 73, no. 1–2, pp. 19–29, 1995, doi: 10.1016/0166-4328(96)00071-X.
59. T. M. Klein Gunnewiek, J. R. Homberg, and T. Kozicz, "Modulation of glucocorticoids by the serotonin transporter polymorphism: A narrative review," *Neurosci. Biobehav. Rev.*, vol. 92, pp. 338–349, 2018, doi: 10.1016/j.neubiorev.2018.06.022.
60. U. Lueken *et al.*, "Neurobiological markers predicting treatment response in anxiety disorders: A systematic review and implications for clinical application," *Neurosci. Biobehav. Rev.*, vol. 66, pp. 143–162, 2016, doi: 10.1016/j.neubiorev.2016.04.005.
61. H. Iderberg, A. C. McCreary, M. A. Varney, M. A. Cenci, and A. Newman-Tancredi, "Activity of serotonin 5-HT1A receptor 'biased agonists' in rat models of Parkinson's disease and l-DOPA-induced dyskinesia," *Neuropharmacology*, vol. 93, pp. 52–67, 2015, doi: 10.1016/j.neuropharm.2015.01.012.
62. M. Gesi, P. Soldani, F. S. Giorgi, A. Santinami, I. Bonaccorsi, and F. Fornai, "The role of the locus coeruleus in the development of Parkinson's disease," *Neurosci. Biobehav. Rev.*, vol. 24, no. 6, pp. 655–668, 2000, doi: 10.1016/S0149-7634(00)00028-2.
63. S. M. Stahl, L. Zhang, C. Damatarca, and M. Grady, "Brain Circuits Determine Destiny in Depression: A Novel Approach to the Psychopharmacology of Wakefulness, Fatigue, and Executive Dysfunction in Major Depressive Disorder," *J. Clin. Psychiatry*, vol. 64, no. SUPPL. 14, pp. 6–17, 2003.
64. D. C., de D. P., and B. A., "Noradrenaline and Parkinson's disease," *Front. Syst. Neurosci.*, no. MAY 2011,
65. E. A. Stone, Y. Lin, Y. Sarfraz, and D. Quartermain, "The role of the central noradrenergic system in behavioral inhibition," *Brain Res. Rev.*, vol. 67, no. 1–2, pp. 193–208, 2011, doi: 10.1016/j.brainresrev.2011.02.002.
66. C. W. Berridge and B. D. Waterhouse, "The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes," *Brain Res. Rev.*, vol. 42, no. 1, pp. 33–84, 2003, doi: 10.1016/S0165-0173(03)00143-7.
67. J. C. F. Vieira *et al.*, "Anxiety-like behavior induced by 6-OHDA animal model of Parkinson's disease may be related to a dysregulation of neurotransmitter systems in brain areas related to anxiety," *Behav. Brain Res.*, vol. 371, 2019, doi: 10.1016/j.bbr.2019.111981.
68. S. E. Lee, Y. Lee, and G. H. Lee, "The regulation of glutamic acid decarboxylases in GABA neurotransmission in the brain," *Arch. Pharm. Res.*, vol. 42, no. 12, pp. 1031–1039, 2019, doi: 10.1007/s12272-019-01196-z.

69. A. P. Princivalle, "GABAB Receptors in Neurodegeneration," *Curr. Top. Behav. Neurosci.*, vol. 52, pp. 267–290, 2022, doi: 10.1007/7854_2021_222.
70. D. Bassetti, "Keeping the Balance: GABAB Receptors in the Developing Brain and Beyond," *Brain Sci.*, vol. 12, no. 4, 2022, doi: 10.3390/brainsci12040419.
71. M. Nasir, D. Trujillo, J. Levine, J. B. Dwyer, Z. W. Rupp, and M. H. Bloch, "Glutamate Systems in DSM-5 Anxiety Disorders: Their Role and a Review of Glutamate and GABA Psychopharmacology," *Front. Psychiatry*, vol. 11, 2020, doi: 10.3389/fpsyt.2020.548505.
72. O. Babaev, C. Piletti Chatain, and D. Krueger-Burg, "Inhibition in the amygdala anxiety circuitry," *Exp. Mol. Med.*, vol. 50, no. 4, 2018, doi: 10.1038/s12276-018-0063-8.
73. C. G. Goetz *et al.*, "Movement Disorder Society Task Force Report on the Hoehn and Yahr Staging Scale: Status and Recommendations The Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease," *Wiley Online Libr.*, vol. 19, no. 9, pp. 1020–1028, 2004, [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.1002/mds.20213
74. K. R. Richard IH, Schiffer RB, "Anxiety and Parkinson's disease.," *J. Neuropsychiatry Clin. Neurosci.*, 1996.
75. G. Racagni and M. Popoli, "The pharmacological properties of antidepressants," *Int. Clin. Psychopharmacol.*, vol. 25, no. 3, pp. 117–131, 2010, doi: 10.1097/YIC.0b013e3283311acd.
76. L. H. Price, W. K. Goodman, D. S. Charney, S. A. Rasmussen, and G. R. Heninger, "Treatment of severe obsessive-compulsive disorder with fluvoxamine," *Am. J. Psychiatry*, vol. 144, no. 8, pp. 1059–1061, 1987, doi: 10.1176/ajp.144.8.1059.
77. J. B. Weilburg, "An overview of SSRI and SNRI therapies for depression.," *Manag. Care*, vol. 13, no. 6 Suppl Depression, pp. 25–33, 2004.
78. Haddad PM., "Antidepressant discontinuation syndromes," *Drug Saf.*, vol. 24, no. 3, pp. 183–97, 2001.
79. R. Balon and V. Starcevic, "Role of benzodiazepines in anxiety disorders," *Adv. Exp. Med. Biol.*, vol. 1191, pp. 367–388, 2020, doi: 10.1007/978-981-32-9705-0_20.
80. A. Antonini, A. Zecchinelli, S. Tesei, G. Sacilotto, N. Meucci, and G. Pezzoli, "A randomized single-blind study of sertraline vs. amitriptiline for the treatment of depression in patients with Parkinson's disease," *Mov. Disord.*, vol. 19, pp. S263–S263, 2004, [Online]. Available: wos:000221639600807
81. M. Serrano-Dueñas, "A comparison between low doses of amitriptyline and low doses of fluoxetin used in the control of depression in patients suffering from Parkinson's disease," *Rev. Neurol.*, vol. 35, no. 11, pp. 1010–1014, 2002, doi: 10.33588/rn.3511.2001044.
82. S. Ghazi-Noori, T. H. Chung, K. Deane, H. E. Rickards, and C. E. Clarke, "Therapies for depression in Parkinson's disease," *Cochrane Database Syst. Rev.*, vol. 2010, no. 1, 2003, doi: 10.1002/14651858.CD003465.
83. A. Avila, X. Cardona, M. Martin-Baranera, P. Maho, F. Sastre, and J. Bello, "Does nefazodone improve both depression and Parkinson disease? A pilot randomized trial," *J. Clin. Psychopharmacol.*, vol. 23, no. 5, pp. 509–513, 2003, doi: 10.1097/01.jcp.0000088908.24613.db.
84. A. F. Leentjens, F. R. Verhey, and F. W. Vreeling, "[Successful treatment of depression in a Parkinson disease patient with bupropion].," *Ned. Tijdschr. Geneeskd.*, vol. 144, no. 45, pp. 2157–9, 2000, [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/11086491
85. Y. M. and Y. H., "Clinical Pharmacology of MAO Inhibitors: Safety and Future," *Neurotoxicology*, vol. 25, no. 1–2, pp. 215–221, 2004, [Online]. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=2004016413
86. S. Elliot-Baker, "Monoamine oxidase inhibitors.," *Med. J. Aust.*, vol. 147, no. 6, p. 315, 1987, doi: 10.5694/j.1326-5377.1987.tb133500.x.

87. M. E. Thase *et al.*, "Efficacy of quetiapine monotherapy in bipolar I and II depression: A double-blind, placebo-controlled study (the BOLDER II study)," *J. Clin. Psychopharmacol.*, vol. 26, no. 6, pp. 600–609, 2006, doi: 10.1097/01.jcp.0000248603.76231.b7.
88. E. Bablenis, S. S. Weber, and R. L. Wagner, "Clozapine: A novel antipsychotic agent," *DICP, Ann. Pharmacother.*, vol. 23, no. 2, pp. 109–115, 1989, doi: 10.1177/106002808902300201.
89. F. M. Nilsson, L. V. Kessing, and T. G. Bolwig, "Increased risk of developing Parkinson's disease for patients with major affective disorder: A register study," *Acta Psychiatr. Scand.*, vol. 104, no. 5, pp. 380–386, 2001, doi: 10.1034/j.1600-0447.2001.00372.x.
90. K. L. Eskow Jaunarajs, K. B. Dupre, C. Y. Ostock, T. Button, T. Deak, and C. Bishop, "Behavioral and neurochemical effects of chronic L-DOPA treatment on nonmotor sequelae in the hemiparkinsonian rat," *Behav. Pharmacol.*, vol. 21, no. 7, pp. 627–637, 2010, doi: 10.1097/FBP.0b013e32833e7e80.
91. A. Vázquez, F. J. Jiménez-Jiménez, P. García-Ruiz, and D. García-Urra, "'Panic attacks' in Parkinson's disease: A long-term complication of levodopatherapy," *Acta Neurol. Scand.*, vol. 87, no. 1, pp. 14–18, 1993, doi: 10.1111/j.1600-0404.1993.tb04068.x.
92. E. S.J., L. K., and , Starkstein S, "Cognitive behaviour therapy for depression and anxiety in Parkinson's disease," *J. Parkinsons. Dis.*, vol. 5, no. 3, pp. 443–451, 2015.
93. D. Weintraub *et al.*, "The neuropsychiatry of Parkinson's disease: advances and challenges," *Lancet Neurol.*, vol. 21, no. 1, pp. 89–102, 2022, doi: 10.1016/S1474-4422(21)00330-6.
94. A. Nagy and A. Schrag, "Neuropsychiatric aspects of Parkinson's disease," *J. Neural Transm.*, vol. 126, no. 7, pp. 889–896, 2019, doi: 10.1007/s00702-019-02019-7.
95. M. Brys *et al.*, "Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease," *Neurology*, vol. 87, no. 18, pp. 1907–1915, 2016, doi: 10.1212/WNL.0000000000003279.
96. B. R.M. *et al.*, "A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression," *Biol. Psychiatry*, vol. 47, no. 4, pp. 332–337, 2000, [Online].
97. P. E., N. F., A. Z., B. E., and K. N., "The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: A randomized, double-blind, placebo-controlled study," *Mov. Disord.*, vol. 25, no. 14, pp. 2311–2317, 2010, [Online].
98. M. D. Johnson, S. Miocinovic, C. C. McIntyre, and J. L. Vitek, "Mechanisms and Targets of Deep Brain Stimulation in Movement Disorders," *Neurotherapeutics*, vol. 5, no. 2, pp. 294–308, 2008, doi: 10.1016/j.nurt.2008.01.010.
99. P. Blomstedt and M. I. Hariz, "Deep brain stimulation for movement disorders before DBS for movement disorders," *Park. Relat. Disord.*, vol. 16, no. 7, pp. 429–433, 2010, doi: 10.1016/j.parkreldis.2010.04.005.
100. [99] T. K. Lee and E. L. Yankee, "A review on Parkinson's disease treatment," *Neuroimmunol. Neuroinflammation*, vol. 8, p. 222, 2022, doi: 10.20517/2347-8659.2020.58.
101. H. C., H. H., J. J., G. M., W. M., and B. G., "Deep brain stimulation in neurologic disorders," *Park. Relat. Disord.*, vol. 13, no. 1, pp. 1–16, 2007,
102. [101] K.-D. L., Z. L.B., M. M., O. M.S., F. K.D., and B. D., "The trajectory of apathy after deep brain stimulation: From pre-surgery to 6 months post-surgery in Parkinson's disease," *Park. Relat. Disord.*, vol. 17, no. 3, pp. 182–188, 2011,
103. M. I. Gaitán, "A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease," *Rev. Neurol. Argentina*, vol. 1, no. 1, p. 59, 2009, doi: 10.1016/s0513-5117(09)79023-4.
104. H. S. Puri, "Rasayana: Ayurvedic Herbs for Longevity and Rejuvenation," vol. 3, no. 2, p. 368, 2003.
105. R. Govindarajan, M. Vijayakumar, and P. Pushpangadan, "Antioxidant approach to disease management and the role of

'Rasayana' herbs of Ayurveda," *J. Ethnopharmacol.*, vol. 99, no. 2, pp. 165–178, 2005, doi: 10.1016/j.jep.2005.02.035.

106. H. Sharma, H. M. Chandola, G. Singh, and G. Basisht, "Utilization of Ayurveda in health care: An approach for prevention, health promotion, and treatment of disease. Part 2 - Ayurveda in primary health care," *J. Altern. Complement. Med.*, vol. 13, no. 10, pp. 1135–1150, 2007, doi: 10.1089/acm.2007.7017-B.
107. E. C. Hirsch, P. Jenner, and S. Przedborski, "Pathogenesis of Parkinson's disease," *Mov. Disord.*, vol. 28, no. 1, pp. 24–30, 2013, doi: 10.1002/mds.25032
108. V. Butterweck, "Mechanism of action of St John's wort in depression: What is known?," *CNS Drugs*, vol. 17, no. 8, pp. 539–562, 2003, doi: 10.2165/00023210-200317080-00001.
109. Y. Chang and S. J. Wang, "Hypericin, the active component of St. John's wort, inhibits glutamate release in the rat cerebrocortical synaptosomes via a mitogen-activated protein kinase-dependent pathway," *Eur. J. Pharmacol.*, vol. 634, no. 1–3, pp. 53–61, 2010, doi: 10.1016/j.ejphar.2010.02.035.
110. W. A. Rocca, "The burden of Parkinson's disease: a worldwide perspective," *Lancet Neurol.*, vol. 17, no. 11, pp. 928–929, 2018, doi: 10.1016/S1474-4422(18)30355-7.
111. J. Jankovic, "Parkinson's disease: Clinical features and diagnosis," *J. Neurol. Neurosurg. Psychiatry*, vol. 79, no. 4, pp. 368–376, 2008, doi: 10.1136/jnnp.2007.131045.
112. [111] M. Nouri *et al.*, "A Close Look at Echium amoenum Processing, Neuroactive Components, and Effects on Neuropsychiatric Disorders," *Galen Med. J.*, vol. 8, p. 1559, 2019, doi: 10.31661/gmj.v8i0.1559.
113. [112] S. Chayasirisobhon, "Cannabis and neuropsychiatric disorders: An updated review," *Acta Neurol. Taiwan.*, vol. 28, no. 2, pp. 27–39, 2019.
114. [113] S. Aguiar and T. Borowski, "Neuropharmacological review of the nootropic herb Bacopa monnieri," *Rejuvenation Res.*, vol. 16, no. 4, pp. 313–326, 2013, doi: 10.1089/rej.2013.1431.
115. [114] T. Takara, K. Yamamoto, N. Suzuki, M. Hirano, N. Shimizu, and H. Shimoda, "Passionflower extract improves diurnal quality of life in Japanese subjects with anxiety: A randomized, placebo-controlled, double-blind trial," *Funct. Foods Heal. Dis.*, vol. 9, no. 5, pp. 312–327, 2019, doi: 10.31989/ffhd.v9i5.593.
116. [115] J. K. Srivastava, E. Shankar, and S. Gupta, "Chamomile: A herbal medicine of the past with a bright future (review)," *Mol. Med. Rep.*, vol. 3, no. 6, pp. 895–901, 2010, doi: 10.3892/mmr.2010.377.
117. [116] S. Singh, G. Barreto, G. Aliev, and V. Echeverria, "Ginkgo biloba as an Alternative Medicine in the Treatment of Anxiety in Dementia and other Psychiatric Disorders," *Curr. Drug Metab.*, vol. 18, no. 2, pp. 112–119, 2016, doi: 10.2174/1389200217666161201112206.
118. [117] M. Bhattacharjee and E. Perumal, "Potential plant-derived catecholaminergic activity enhancers for neuropharmacological approaches: A review," *Phytomedicine*, vol. 55, pp. 148–164, 2019, doi: 10.1016/j.phymed.2018.07.010.
119. D. Maciąg, E. Dobrowolska, M. Sharafan, H. Ekiert, M. Tomczyk, and A. Szopa, "Akebia quinata and Akebia trifoliata - a review of phytochemical composition, ethnopharmacological approaches and biological studies," *J. Ethnopharmacol.*, vol. 280, 2021, doi: 10.1016/j.jep.2021.114486.
120. J. Sarris, A. Panossian, I. Schweitzer, C. Stough, and A. Scholey, "Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence," *Eur. Neuropsychopharmacol.*, vol. 21, no. 12, pp. 841–860, 2011, doi: 10.1016/j.euroneuro.2011.04.002.
121. B. Cooke and E. Ernst, "Aromatherapy: A systematic review," *Br. J. Gen. Pract.*, vol. 50, no. 455, pp. 493–496, 2000.
122. H. Ebrahimi, A. Mardani, M. H. Basirinezhad, A. Hamidzadeh, and F. Eskandari, "The effects of Lavender and Chamomile essential oil inhalation aromatherapy on depression, anxiety and stress in older community-dwelling people: A

randomized controlled trial," *Explore*, vol. 18, no. 3, pp. 272–278, 2022, doi: 10.1016/j.explore.2020.12.012.

123. Agatonovic-Kustrin, E. Kustrin, V. Gegechkori, and D. W. Morton, "Anxiolytic terpenoids and aromatherapy for anxiety and depression," *Adv. Exp. Med. Biol.*, vol. 1260, pp. 283–296, 2020, doi: 10.1007/978-3-030-42667-5_11.
124. Q. Zhang, J. Hu, L. Wei, Y. Jia, and Y. Jin, "Effects of dance therapy on cognitive and mood symptoms in people with Parkinson's disease: A systematic review and meta-analysis," *Complement. Ther. Clin. Pract.*, vol. 36, pp. 12–17, 2019, doi: 10.1016/j.ctcp.2019.04.005.
125. M. Ishak, N. Herrera, C. Martin, and J. Jeffrey, "Music Therapy for Depression in Adolescents: A Systematic Review of Randomized Controlled Trial," *Int. J. Psychiatry Res.*, vol. 4, no. 1, 2021, doi: 10.33425/2641-4317.1085.
126. M. Hartmann *et al.*, "Musical interaction in music therapy for depression treatment," *Psychol. Music*, vol. 51, no. 1, pp. 33–50, 2023, doi: 10.1177/03057356221084368.
127. Y. Álvarez-Pérez *et al.*, "Effectiveness of Mantra-Based Meditation on Mental Health: A Systematic Review and Meta-Analysis," *Int. J. Environ. Res. Public Health*, vol. 19, no. 6, 2022, doi: 10.3390/ijerph19063380.
128. A. G.N., G. J., and G. B.N., "Complementary Therapies for Mental Health Disorders," *Med. Clin. North Am.*, vol. 101, no. 5, pp. 847–864, 2017, [Online]. Available: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L616889199%0Ahttp://dx.doi.org/10.1016/j.mcna.2017.04.004
129. E. Ernst, J. I. Rand, and C. Stevinson, "Complementary therapies for depression: An overview," *Arch. Gen. Psychiatry*, vol. 55, no. 11, pp. 1026–1032, 1998, doi: 10.1001/archpsyc.55.11.1026.