



Parkinson's Disease and Depression - Together or Apart: A Review

Atul Kabra^{1,2*}, Shivani Thakur³, Rohit Sharma⁴, Ruchika Garg² and Uttam Singh Baghel²

¹Research Scholar, I. K. Gujral Punjab Technical University, Kapurthala, Punjab, INDIA

²Kota College of Pharmacy, Kota, Rajasthan, INDIA

³School of Pharmacy, Maharaja Agrasen University, Baddi, H.P., INDIA

⁴Central Ayurveda Research Institute for Drug Development, CCRAS, Ministry of AYUSH, Government of India, Bidhannagar, Kolkata, West Bengal, INDIA

* Correspondence: E-mail: atul.kbr@gmail.com

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ABSTRACT: Depression is a standout amongst the most widely recognized non-motor side effects in Parkinson's disease (PD). Depression in PD is related with a progressively quick decline in motor and as well as intellectual execution. The frequency of PD increments with age and many age-related comorbid conditions, including cardiovascular ailment. The pathophysiological mechanism involved in depression in PD includes abnormalities of serotonergic, noradrenergic and dopaminergic functions. The utilization of serotonin reuptake inhibitors and tricyclic antidepressants in the management of depression in PD is boundless in clinical practice. Dopamine agonists can likewise be powerful in the management of mild depression. An online search for information has been conducted on several articles, including Web of Science, PubMed, Scopus, Bentham Science, Science Direct, Springer, Google Scholar, and other allied databases, from January 1959 to December 2018. This review includes in-depth information about the risk factors, pathophysiology, pharmacological, non-pharmacological and phytotherapeutic approach for the treatment of depression in PD. This review can be used for future research as well as for clinical purposes.

Keywords: Parkinson disease; depression; pathophysiology; dopamine and antidepressant.

INTRODUCTION: Parkinson's disease (PD) is a progressive, chronic and age-dependent neurodegenerative disease¹. The pathologic indication of PD is a gradual and progressive loss of dopaminergic neuron in the substantia nigra that particularly affects the ventral component of the pars compacta and a decrease in dopamine levels in the striatum (caudate and putamen) of the basal ganglion^{2,3}. As a result, the capacity of nigrostriatal dopaminergic neurons is low, while the capacity of cholinergic neurons turns out to be generally prevailing, which causes the development of movement disorders^{4,5,6}. PD is the second most basic neurodegenerative sickness after Alzheimer's disease and influences over 1% of the populace over 55 and nearly 3% of the populace over years⁷.

From a clinical perspective, PD is depicted by methods for through cardinal motor signs, for example, bradykinesia, postural feebleness, resting tremors and stiffness, comparatively as non-motor signs including neuropsychiatric responses, rest issue, dysautonomia, gastrointestinal side effects, and tactile disturbances^{8,9}. Depression is the most widely recognized neuropsychiatric confusion in Parkinson's sickness and can significantly affect the quality of life¹⁰. Depression can occur at any time in the PD. Early diagnosis and suitable management of depression in patients with

PD are fundamental for enhancing the personal satisfaction and safeguarding every day working¹¹⁻¹³.

Several reviews published on PD and depression, but to date, no review describes updated and complete information on their risk factors, pathophysiology, pharmacology, and non-pharmacological, complementary and alternative therapies. Therefore, the main objective of this review is to expand the therapeutic profile and provide further clues to nourish our thinking on the relationship between PD and depression.

MATERIALS AND METHODS: Published information from several articles, of which few review articles and cross-references were collected. Several resources searched, including Technical Reports, Conference proceedings, web-based scientific databases such as PubMed, Bentham Science, Science Direct, Springer, Google Scholar, MEDLINE, SCOPMED, other allied databases were rationally reviewed and taken into a study for the report. The search term or keywords Parkinson; neurodegenerative; neuropsychiatric; antidepressant; antiparkinson; TCA; SSRI; SNRI; MAOI; and DA were either used alone or in combination to search the articles. The publication with available abstract or full text was reviewed for

this study. This review encompassed the available literature from January 1967 to December 2018.

Depression in Parkinson's Disease: Depression is more incessant in patients with PD than in the general population^{14,15}. Most of these studies do not correlate the prevalence of depression with the lifespan of patients with PD. One study found that patients with PD onset before age 50 had a higher rate of depression than older patients¹⁶. Despite its high incidence and known impact on quality of life, there are no specific diagnostic criteria for PD depression. Most diagnosis is based on the criteria of major depression in the Diagnostic and Statistical Manual of Mental Disorders^{17,18}. [11C]RTI-32 PET, an in vivo dopamine marker and the binding of the norepinephrine transporter, to localize the differences between depressed and non-depressed patients¹⁹. Fatigue, lack of energy, weight loss, psychomotor retardation, lack of facial expression, insomnia or excessive sleep, motor deceleration, difficulty in concentration, decreased appetite and decreased sexual function in both depression and PD²⁰. Depression in PE shows features other than major depression unrelated to PE. Symptoms like irritability, sadness, dysphoria, pessimism and suicidal ideation (consider suicide without necessarily trying) are more common in patients with PD depression, while guilt, self-blame, feelings of failure and suicide attempts they are less common²¹. In fact, it has been reported that only a small percentage of patients with PD suffer from major depression (from 2 to 7%); most of them have a slight depression or only some depressive symptoms²².

Risk Factors: About 25% of cases, patients had just been depressed before the beginning of PD²³. The improvement of PD in depressed patients was about three times more frequent than on account of non-depressed patients²⁴. This backs the theory that PD is a biological risk factor for depression. Several studies have shown that, in addition to PD, depression can also predispose to other diseases, such as Alzheimer's, cardiovascular diseases and cancer²⁵⁻²⁸. Depression can prompt decay of nerve cells in the brain which thusly prompts neurodegenerative infections²⁹. Possible risk factors for the development of depression with PD include early age, female sex, right-side hemiparkinsonism, akinesia, increased severity of disability, anxiety, psychosis, high doses of levodopa, and the presence of fluctuations on / off³⁰⁻³². According to the ayurvedic concept 'Vata' and 'Kapha' are predominantly involved in depression. Vata is responsible for depression symptoms such as sadness of mood, sleep disturbances, appetite changes, easy fatigability, guilty feeling, poor concentration, and sui-

cidal ideation, while Kapha induces symptoms such as lack of pleasure and psychomotor retardation³³.

Pathophysiology: The mechanism underlying depression in PD is complex. Numerous theories attempt to give a pathophysiological clarification to the more noteworthy pervasiveness of depression in patients with PD. The well-known hypothesis involves a series of subcortical nuclei (substantia nigra, ventral tegmental area, basal nucleus, hypothalamus, rigid nucleus dorsal, locus coeruleus, caudate nucleus, etc.) which are the guideline wellsprings of neurotransmitters⁷. The pathological process of these subcortical structures leads to a distant neurochemical depletion of these nuclei. It reported a moderate to marked decrease in PD (i.e. a 40-90% reduction) of dopamine, noradrenaline, and serotonin in these nuclei. Furthermore, as in cases of primary major depression, several studies have found low levels of 5-hydroxy CSF (5-HIAA) in PD patients with major depression compared to those without mood disorders³⁴. Therefore, the pathophysiology of depression in PD may correlate mainly these neurotransmitter abnormalities (and changes accompanying the receptor) since alteration of central serotonin, noradrenaline and dopamine metabolism is showing primarily coherent depressive disorders without medical comorbidity³⁵. Neurobiological studies also show that alteration of PD mood may be mediated by a malfunction of the mesocortical and prefrontal, motivational and stress response systems³⁶.

Treatment of Depression in Pd: Drugs such as serotonin inhibitors selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase type B inhibitors (MAOBI) and tricyclic antidepressants (TCAs) can be effective pharmacological agents. Treat depression in Parkinson's disease. Antiparkinsons agents impact dopaminergic or anticholinergic exercises and are recommended in various combinations as per the necessities of the patients. Co-careldopa (Levodopa/carbidopa) enhances dopamine synthesis by giving more substrate. Co-careldopa is accessible in regular and sustained release forms. Amantadine acts presynaptically to invigorate an expansion in dopamine discharge and represses re-take-up when pergolide and bromocriptine act specifically on postsynaptic dopamine receptors. Pramipexole, a non-ergot dopamine agonist, binds to dopamine D₂ and D₃ receptors. The monoamine oxidase (MAO) inhibitors attenuate the catabolism of dopamine and other catecholamines. Selegiline (deprenyl) hinders MAO-B, while entacapone (OR-611) represses catechol-o-methyl (COMT), another enzyme that catabolises dopamine. Anticholinergic medications, for example, (benztropine) and

triexphenidyl (benhexol), constrict the tremor of PD components³⁷. PD surgery includes deep brain stimulation, pallidotomy, thalamotomy, gamma surgery. In addition to pharmacological and non-pharmacological approaches, many herbs also have the potential to treat depression with PD³⁸.

Pharmacological treatment: There is evidence to suggest that SSRIs, SNRIs, MAOBI, and TCAs may

be pharmacological agents effective for depression in PD. The antidepressants with the most proof for treating depression in Parkinson's infirmity incorporates amitriptyline, sertraline, fluoxetine, citalopram, paroxetine, nortriptyline, venlafaxine, and desipramine^{39,40} were shown in Table 1 and different antidepressant drugs that were embraced by the US FDA^{41,42} in recent five years are presented in Table 2.

Table 1: FDA approved drug for Depression in last five year⁵⁶.

S. No	Class	Name of Drug	Brand Name	MOA	Use	Approval Year	Company Name
1	AAP	Pimavanserin	Nuplazid	Inverse agonist and antagonist activity at serotonin 5-HT _{2A} receptors	Hallucinations and delusions associated with Parkinson's disease psychosis	2016	Acadia Pharmaceuticals
2	AAP	Aripiprazole lauroxil	Aristada	Unknown	Depression and schizophrenia	2015	Alkermes Pharmaceuticals
3	AAP	Brexipiprazole	Rexulti	Unknown	Major depressive disorder and schizophrenia	2015	Otsuka Pharmaceuticals
4	AAP	Cariprazine	Vraylar	Unknown	Schizophrenia and bipolar disorder	2015	Allergan Pharmaceuticals
5	SMS	Vortioxetine	Brintellix	Enhancement of serotonergic activity in the CNS	Major Depressive Disorder	2013	Takeda Pharmaceuticals
6	SNA-RI	Levomilnacipran	Fetzima	Potential of serotonin and norepinephrine in the CNS	Major depressive disorder	2013	Forest Laboratories
7	SSRI	Vilazodone hydrochloride	Viibryd	Enhancement of serotonergic activity in the CNS	Major depressive disorder	2011	Clinical Data

AAP: Atypical antipsychotic; SMS: Serotonin modulator and stimulator; SNARI: Selective norepinephrine and serotonin reuptake inhibitor; SSRI: Selective serotonin reuptake, MOA: Mechanism of action; CNS: Central nervous system; 5-HT_{2A}.

Table 2: Pharmacological treatments of depression in PD⁵⁷⁻⁵⁹.

Class	Drug name	Dose (mg/day)	Side effects
Tricyclic antidepressants	Amitriptyline	25–300	Orthostatic hypotension, Anticholinergic side effects, weight gain, dizziness and sexual dysfunction
	Desipramine	25–200	
	Nortriptyline	25–150	
Selective serotonin reuptake inhibitors	Sertraline	25–200	Gastrointestinal side effects, sexual dysfunction, insomnia
	Fluoxetine	10–60	
	Citalopram	10–40	
	Paroxetine	10–50	
Serotonin norepinephrine reuptake inhibitors	Venlafaxine Duloxetine	37.5–225 20–120	Gastrointestinal side effects, sexual dysfunction, insomnia, dose-dependent increased blood pressure
Monoamine oxidase type B inhibitors	Rasagiline	1–2	Nausea, headache, orthostatic hypotension, dyskinesia
Dopamine agonists	Pramipexole	1–3	Nausea, dyskinesia
Other agents	Bupropion	100–450	Nausea, anxiety, weight loss, agitation, insomnia
	Mirtazapine	7.5–45	Sedation, elevated cholesterol, increased appetite, weight gain

Table 3: Commonly Used Herbs in Depression with Parkinson's Disease^{55,60}.

Plant Name	Family	Common Name	Part used	Chemical Constituents
<i>Asparagus recemosus</i>	Liliaceae	Wild carrot, Water roof	Fresh tuber	Shatavarin Asperagin
<i>Azadirachta indica</i>	Maliaceae	Neem, margosa	Fresh leaf	Meliacin- nimbolide, quercetin, kaempferol
<i>Breynia retusa</i>	Euphorbiaceae	Kanumu chettu	Dried bark	Triacontane, peonidin, lanosterol
<i>Celtis philippensis</i>	Ulmaceae	White Indian nettle	Fresh/ dried whole plant	Betulin, di- methyl elagic acid, gallic acid, leucocyanide glycoside
<i>Dendrophthoe falcata</i>	Loranthaceae	Honey sucklemistletoe	Fresh/ dried whole plant	Tanins, flavons, oleanolic acid, beta sitosterol, stigmasterol
<i>Emblica officinalis</i>	Euphorbiaceae	Amla, Indian goose berry	Fruit	Tannins, Phyllembelin, Pectins, Vitamin C
<i>Hypericum perforatum</i>	Hypericaceae	St.John's wort	Dried arial parts	Hypercin, pseudo hypercin
<i>Smilax perfoliata</i>	Smilacaceae	Ram damtena	Dry root	Steroidal sapogeninsdiosgenin
<i>Smilax zeylanica</i>	Smilacaceae	Rough blind weed, hill lotus	Dry root	Alpha, beta hydroxy acids

Non-pharmacological Treatment: A few non-pharmacotherapies have risen as elective methodologies for the treatment of PD patients.

Surgery: PD surgery includes fetal mesencephalic tissue transplantation, thalamotomy, pallidotomy, subthalamic stimulation, pale stimulation, and gamma-ray surgery. Out of these surgical procedures, fetal mesencephalic tissue transplantation has been accounted for as a reason for the state of mind changes. Adrenal medullary tissue transplantation causes intense, reversible psychosis or delirium and has been relinquished as a treatment for PD^{8,43,44}.

Transplantation of human fetal mesencephalic tissue for the treatment of Parkinson's disease caused depression and long-term non-specific emotional and behavioral symptoms (up to 1 year after surgery in patients without psychiatric history). This effect may have helped a drastic physical episode. The reason for the difference in neuropsychiatric outcome between adrenal medullary tissue transplantation and fetal mesencephalic tissue is unknown⁴³. Posterior ventricular pallidotomy in 24 cognitively intact PD patients did not cause depression in patients with PD referred to thalamotomy, 63% had depression; however, the author has not commented on the effect of the surgical procedure on his moods. The gamma knife (GK) is an emerging non-invasive surgical approach that is typically used in elderly patients with persistent tremor

PD, patients with PD with medical co-morbidities such as cardiovascular disease that prevent them from undergoing surgical procedures or patients wishing to avoid positioning of hardware as in DBS. Transplant candidates must undergo a pre-and post-operative neuropsychiatric assessment to facilitate the treatment of mood disorders^{8,45,46}.

Electroconvulsive Therapy [ECT]: The utilization of ECT has been appeared to be compelling as an antidepressant treatment, yet requires exceptional contemplations in patients with PD. ECT is helpful if patients are self-destructive or cannot wait for the time required for antidepressant drug response. ECT may likewise be helpful for patients with PD who are not depressed but rather who encounter "on-off" disorder or who don't react to treatment for PD. ECT was utilized to treat mania in patients treated with levodopa^{46,47}.

The antiparkinsonian impacts of ECT include the dopaminergic and serotonergic pathways. ECT upgrades dopamine transmission in animals, potentially through expanded endogenous MAO inhibitor action. Also, ECT lessens the neurotic increment in opioid system function, which thusly increments striatal and mesolimbic dopamine discharge. ECT downregulates presynaptic 5-HT1A receptors and upregulates postsynaptic 5-HT2 receptors. This serotonergic impact of ECT is considered to contribute fundamentally to its

antidepressant activity. In patients with PD, a lack of elevated levels of CSF homovanillic acid after ECT lessens the probability of noradrenergic impacts brought about by ECT^{48,49}.

Unfortunately, while depression and akinesia in patients with PD improve with ECT, patients are more susceptible (compared to depressed patients without PD) to prolonged delirium after bilateral and bilateral ECT. Furthermore, multiple ECT treatments increase the duration of delirium (up to 21 days) and atropine before the procedure can contribute to confusion; however, the placement of the bilateral electrode may be less harmful than unilateral placement^{49,50}.

Transcranial Magnetic Stimulation (TMS): TMS gave impermanent alleviation from depression under exploratory conditions. TMS exposes the focal regions of the brain to magnetic and electrical energy that does not cause structural changes, but rather prompts functional changes. It produces transient changes in motor function and state of mind in patients with PD. The weaknesses of utilizing TMS incorporate a temporary therapeutic impact, a headache due to muscle tension at the incitement site and danger of convulsions⁵¹. Electromyography performed at the same time with rapid TMS (rTMS) demonstrates that patients with PD have a drawn-out excitation period that goes before

the potential evoked by the motor and this prolongation can be settled with rTMS, which reduces akinesia. Researchers have possessed the capacity to prompt subjective "sadness" by administering rTMS in the left prefrontal territories, while "happiness" results from the incitement of the right prefrontal areas⁵².

Sandyk and Derpapas noted that relaxation, laziness, improvement of inclination, expanded dreams and improvement of the electroencephalogram movement due to the external application of magnetic fields in the pT-range were also found in healthy persons taking melatonin and proposed that these effects have occurred from the pineal gland⁵³. Although this remains speculative, there is a large addition in the plasma prolactin level after TMS, which would demonstrate an effect on the hypothalamic tuberoinfundibular dopaminergic frame⁵⁴.

Herbal Approaches: Apart from the pharmacological and non-pharmacological treatment, herbal remedies are also used to cure depression in PD. The greatest advantage of adapting herbal remedies is that lack of side effects. The most commonly used herbs for treatment of depression in PD⁵⁵ were summarized in Table 3 and their macroscopic features presented in Figure 1.



Figure 1: Macroscopic features of some plants (A) *Asparagus recemosus*; (B) *Azadirachta indica*; (C) *Breynia retusa*; (D) *Celtis philippensis*; (E) *Dendrophthoe falcate*; (F) *Emblica officinalis*; (G) *Hypericum perforatum*; (H) *Smilax perfoliata* (I) *Smilax zeylanica*.

CONCLUSION: Depression is a standout amongst the most neuropsychiatric complication of PD. Depression often accompanies PD and can have a negative impact on quality of life. For the reason that symptoms overlap between two disorders, it can be difficult to recognize depression in PD. However, the current evidence that drives depression treatment in PD is limited. Non-pharmacological approaches, including ECT and rTMS, have been explored for the treatment of depression in Parkinson's disease, but there is insufficient evidence to support the efficacy of ECT or rTMS for depression in patients with PD. However, there is as yet a requirement for well-designed trials further assessing the adequacy of antidepressants, dopamine agonists, especially TCAs, and other agents. For TCAs, a correlation of scope of doses might be useful in deciding the best endured effective dose. More examinations on behavioral medicines would likewise be useful especially for patients who may incline toward non-pharmacologic techniques, are hesitant to take behavioral, or may have a poor reaction to pharmacotherapy. Examining the sturdiness of impacts of treatment modalities in the long haul and taking a gander at combination treatments to grow viability are different territories that can be researched. At last, an advancement and approval of a PD depression-specific scale which tends to the issue of overlapping symptoms would be ideal. Herbal medicines are also an alternative and valuable source for treating depression in PD and may serve as the most promising candidates for future research.

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