Current Neuropharmacology, 2023, *21*, 560-577

REVIEW ARTICLE

Therapeutic Approaches to Non-Motor Symptoms of Parkinson's Disease: A Current Update on Preclinical Evidence

Poornima D.E. Weerasinghe-Mudiyanselage[1,#], Sohi Kang[1,#], Joong-Sun Kim[1] and Changjong Moon[1,*]

[1]*Department of Veterinary Anatomy and Animal Behavior, College of Veterinary Medicine and BK21 FOUR Program, Chonnam National University, Gwangju 61186, South Korea*

ARTICLE HISTORY

Received: June 19, 2022
Revised: August 30, 2022
Accepted: September 02, 2022

DOI:
10.2174/1570159X20666221005090126

Abstract: Despite being classified as a movement disorder, Parkinson's disease (PD) is characterized by a wide range of non-motor symptoms that significantly affect the patients' quality of life. However, clear evidence-based therapy recommendations for non-motor symptoms of PD are uncommon. Animal models of PD have previously been shown to be useful for advancing the knowledge and treatment of motor symptoms. However, these models may provide insight into and assess therapies for non-motor symptoms in PD. This paper highlights non-motor symptoms in preclinical models of PD and the current position regarding preclinical therapeutic approaches for these non-motor symptoms. This information may be relevant for designing future preclinical investigations of therapies for non-motor symptoms in PD.

Keywords: Non-motor symptoms, Parkinson's disease, patients' quality of life, preclinical models, therapeutics, rapid eye movement (REM).

1. INTRODUCTION

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders owing to the main impairment of the nigrostriatal system with dopamine (DA) deficiency, which is characterized by a combination of motor and non-motor symptoms [1, 2]. Furthermore, PD is a chronic, progressive disease that requires continued treatment to prevent the deterioration of quality of life [3]. Although various clinical trials have been conducted for the most current symptomatic therapies [4, 5], therapies for PD are still not completely satisfactory. Moreover, continuous preclinical investigations are essential to clarify the efficacy of existing therapies in different animal models that mimic specific pathological aspects of PD.

In patients, PD is defined not only by motor symptoms but also by a complex range of non-motor symptoms present throughout disease progression [6]. The prodromal period of PD is characterized by a variety of non-motor symptoms, such as hyposmia, rapid eye movement (REM), constipation, fatigue, erectile dysfunction, pain, depression, and cognitive impairment [6, 7]. Alternatively, these and other non-motor symptoms may arise later in the disease course [6, 8]. For example, cognitive deficits may become more severe as the disease progresses [8]. Mild cognitive impairment is an intermediate stage on the gradient between normal cognitive function and dementia and is linked with an increased risk of dementia [9]. Thus, mild cognitive impairment has been suggested as an important predictor of the progression to PD dementia [10, 11]. Some non-motor symptoms remain undisclosed because patients are embarrassed or unaware that the symptoms are linked to PD [12]. Consequently, the non-motor symptoms of PD are poorly recognized and treated [6]. However, non-motor symptoms can be equally debilitating in patients [13, 14], and the majority of non-motor symptoms do not respond to treatments targeting motor symptoms [15, 16].

Non-motor symptoms of PD most likely involve different mechanisms, such as DAergic, non-DAergic, genetic, or drug-induced pathways [6]. For instance, DAergic and noradrenergic denervation of the limbic system are noted in patients with PD and depression [17, 18]. The appearance of non-motor symptoms in PD patients with Parkin [19], SNCA [20], LRRK2 [21] or GBA [22] mutations implies a genetic basis for non-motor symptoms. Long-term use of DA replacement therapies can lead to non-motor side effects, such as diarrhea, nausea, hallucination, blurred vision, and hypotension [2, 23-26]. The heterogeneous nature and differential responses to DAergic and non-DAergic treatments make the management of non-motor symptoms challenging in clinical practice. Some non-motor symptoms, such as apathy, anxiety, and primary pain, are responsive to DA replacement therapy [2]. However, PD-associated dementia is responsive to non-DAergic therapies such as cholinesterase inhibitors and N-methyl-d-aspartate receptor (NMDAR) antagonists [27].

*Address correspondence to this author at the Department of Veterinary Anatomy and Animal Behavior, College of Veterinary Medicine and BK21 FOUR Program, Chonnam National University, 77 Yongbong-ro, Buk-gu, Gwangju 61186, South Korea, Tel: +82-62-530-2838;
E-mail: moonc@chonnam.ac.kr

[#]*These first two authors contributed equally to this work.*

1875-6190/23 $65.00+.00

Recently, several innovative pharmacological [28-33] and non-pharmacological [34, 35] therapeutic strategies to ameliorate non-motor symptoms have been investigated. However, compared to the advancement in therapeutics for motor symptoms, the majority of these investigations are still in the preclinical research stage. Understanding the neurobiology and pathophysiology of non-motor symptoms in PD is essential for successful therapy. In this context, animal models have provided crucial insights into the underlying causes of non-motor symptoms and are effective in identifying novel therapeutics [36, 37]. In this review, we searched recent literature published within ten years in Google Scholar, PubMed, Web of Science, and Scopus that described therapeutic approaches to non-motor symptoms in preclinical animal PD models. The terms used in the database searches included "therapeutics," "non-motor symptoms in PD animal models," "non-motor symptoms in preclinical PD," "non-motor symptoms in PD," "neuropsychiatric symptoms in PD animal models," "sleep disorders in PD animal models," "autonomic dysfunction in PD animal models," and "sensory dysfunction in PD animal models." Original research studies that reported data on therapeutics for non-motor symptoms in PD using animal models were included. Studies were excluded if they did not use animal models for PD, they only included *in vitro* data, they used human subjects, or they were not available in English. This review aims to provide an overview and explain the importance of treatments for non-motor symptoms in PD. This review also summarizes the different non-motor symptoms seen in animal PD models and discusses recent investigations into therapeutics for non-motor symptoms in preclinical studies, thereby emphasizing future perspectives.

2. NON-MOTOR SYMPTOMS IN ANIMAL MODELS OF PD

Indeed, it is challenging to replicate preclinical, prodromal, and advanced stages of PD in a single animal model. Therefore, several animal models have been utilized to explain symptoms, explore pathogenesis, and develop therapeutics for PD [38, 39]. A wide range of non-motor symptoms have been observed in animal models, which correlate in part with the symptomatic categories of patients with PD [2, 40, 41]: a) neuropsychiatric symptoms, b) sleep disorders, c) autonomic symptoms, and d) sensory symptoms.

Non-motor symptoms have been observed at different time points of the disease progression in different animal models for PD. For instance, neuropsychiatric symptoms have often been observed in the prodromal stage in α-synuclein (α-Syn) transgenic (TG) mice [42], bilateral 6-hydroxydopamine (6-OHDA)-lesioned rats [43] and mice [44], and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys [28]. Sleep disorders have been reported in the prodromal and motor stages in α-Syn TG mice [45, 46] and the prodromal stage in 6-OHDA-lesioned rats [47]. Autonomic dysfunction has been observed in the motor stage of α-Syn TG mice [48, 49] and the prodromal and motor stages of 6-OHDA-lesioned rats [50]. Olfactory deficits have been observed in both prodromal and motor stage of α-Syn TG mice [51] and motor stage of MPTP-lesioned mice [52]. In brief, neuropsychiatric symptoms have been noted predominantly in the prodromal stage in animal models, congruent with patients with PD [39]. Researchers avoid the confounding motor stage to measure non-motor symptoms in animal models. However, the continuation of neuropsychiatric symptoms into the motor stage in preclinical animal models should be confirmed with novel assessment methods not influenced by motor deficits. Sleep disorders, autonomic dysfunction, and sensory symptoms have been reported throughout the prodromal and motor stages in preclinical models and are consistent with the heterogeneous time window for the appearance of these symptoms in patients with PD [53, 54]. However, unlike in human patients, non-motor behavioral assessment in the presence of motor dysfunction is challenging, and such results are less reliable. Overall comparison of different animal models for non-motor symptoms and the time window of appearance with respect to patients with PD has been previously discussed [39, 55, 56].

2.1. Neuropsychiatric Symptoms

Currently, PD is also considered as a neuropsychiatric disorder, owing to the prevalence of neuropsychiatric symptoms [57]. The predominant neuropsychiatric symptoms of PD include cognitive impairment, depression, and anxiety [2]. These symptoms have been observed in genetic- and toxin-induced animal models of PD. Cognitive deficits have been observed in α-Syn TG mice [42, 58, 59]; intrahippocampal α-Syn fibril-injected mice [60]; 6-OHDA-lesioned rats [61] and mice [44]; and MPTP-lesioned rats [62, 63], mice [64-66] and monkeys [28, 67]. Conversely, leucine-rich repeat kinase 2 (LRRK2) TG mice did not differ from their control littermates in terms of learning and memory [68]. Depression is a non-specific but frequent non-motor symptom of PD [69-71]. Similar phenotypes have been observed in animal models, including α-Syn TG mice [72, 73], MitoPark mice [74], 6-OHDA-lesioned rats [61, 75-81] and mice [44, 82], MPTP-lesioned rats [63] and mice [83, 84], and rotenone-lesioned rats [32, 85, 86] and mice [87]. However, contradictory findings have also been reported. For example, depressive behavior was not observed in LRRK2 TG mice [68], whereas antidepressive behavior was observed in MPTP-lesioned mice [88]. Anxiety in PD may be a psychological reaction to the development of other symptoms throughout the disease progression since PD patients experience higher stress than healthy individuals of the public stigma associated with the disease [89, 90]. Various animal models of PD, including α-Syn TG mice [34], CD157/BST1 knockout (KO) mice [29], 6-OHDA-lesioned rats [75, 76, 79, 91], and MPTP-lesioned mice [83, 84], have also been shown to develop anxiety. Nonetheless, anxiety was not observed in LRRK2 TG mice [68]. However, anxiolytic behavior was reported in α-Syn TG mice [92, 93] and MPTP-lesioned mice [88]. Except for these discrepancies in neuropsychiatric symptoms in animal models, which may be explained by the progressive and age-dependent nature of these symptoms [55, 94], the neuropsychiatric symptoms of PD are effectively recapitulated in many animal models.

2.2. Sleep Disorders

Up to 90% of patients with PD experience sleep disturbances, including insomnia, daytime sleepiness, restless leg

syndrome, and REM-sleep behavior disorder [2, 95]. However, only a few preclinical studies have reported these symptoms. Sleep dysregulation has only been reported in α-Syn TG mice [45, 46], 6-OHDA-lesioned rats [47], and mice injected with preformed α-Syn fibrils in the sublaterodorsal tegmental nucleus [96]. Dysregulation of REM sleep and increased daytime sleepiness have been observed in MPTP-lesioned rhesus monkeys [97] and macaque monkeys [31, 98]. Interestingly, sleep disorders have also been observed in human LRRK-expressing *Drosophila* [99], a model of PD. This overview demonstrates that the existing animal models have not been sufficiently studied to provide the requisite construct and face, and hence, the predictive validity for sleep disorders associated with PD [100]. This gap should influence future research on non-motor symptoms in preclinical animal models. In addition, it is crucial to investigate the malfunctioning neural network that causes sleep disorders in PD patients to enhance the face validity of animal models.

2.3. Autonomic Symptoms

Autonomic symptoms of PD include abnormalities of the cardiovascular, urinary, and gastrointestinal systems; sexual dysfunction; and impaired thermoregulation [15]. In animal models of PD, cardiovascular symptoms include either an increase or decrease in blood pressure, heart rate variability, and baroreflex sensitivity [36]. Previously, α-Syn TG mice [48, 49], 6-OHDA-lesioned rats [101-104] and rhesus monkeys [105, 106], and rotenone-lesioned rats [107] have been shown to have these cardiovascular symptoms. However, there is no indication of cardiovascular autonomic impairment in animal models with ablation genes for PD, including *DJ-1, PINK1*, and *PARKIN* [108-110]. Bladder dysfunction and urodynamic effects have been reported in 6-OHDA-lesioned rats [111-114] and MPTP-lesioned marmosets [115]. Furthermore, α-Syn TG mice had expanded postmortem bladders; however, bladder function has not been examined [48]. Gastrointestinal symptoms associated with animal models of PD are swallowing difficulties, delayed gastric emptying, and constipation [116]. The α-Syn TG mice [117], *PINK1* KO mice [118], *DJ*-1 KO rats [119], 6-OHDA-lesioned rats [50, 120-123] and rhesus monkeys [124], paraquat-lesioned rats [125], and rotenone-lesioned mice [126-128] exhibited these symptoms. However, there was no change in gastric emptying in α-Syn TG [129] or rotenone-lesioned mice [130]. Thermoregulatory dysfunction is not frequently observed in PD animal models. The MPTP-lesioned mice produced acute hypothermia [131], but neither paraquat-lesioned mice [131] nor α-Syn TG mice [132]. However, sexual dysfunction has not been reported in animal models of PD. There is a difference between species or modeling strategies in recapitulating autonomic symptoms in PD. Despite the conserved autonomic nervous system across many species, neuroanatomical differences should also be considered when selecting animal models [116]. Toxin-induced models can also have confounding off-target effects such as vascular damage and myocardial degeneration [133]. Additionally, it is important to implement appropriate parameters and techniques to assess autonomic function in each animal model. Collectively, these steps will ensure the improvement of preclinical studies to recapitulate the autonomic symptoms in PD.

2.4. Sensory Symptoms

Numerous sensory abnormalities, including olfactory and visual impairments and pain patterns, have been associated with PD [134, 135]. Olfactory impairment and hyperalgesia have been observed in several animal models. Olfactory impairments have been described in α-Syn TG mice [51], LRRK2 TG mice [136], and intranasally [137] and intraperitoneally [52] MPTP-lesioned mice. However, the olfactory function is preserved in *PARKIN* KO mice [137, 138], α-Syn TG mice [137], LRRK2 TG mice [68], and intraperitoneal MPTP-lesioned mice [137]. Pain is one of the distressing non-motor symptoms of PD [139, 140]. DAT-Cnr2-LoxP TG mice [141], 6-OHDA-lesioned rats [142-145], and MPTP-lesioned mice [52, 84, 146] exhibit hyperalgesia. However, the thermal threshold was not altered in LRRK2 TG mice [68, 136] or rotenone-lesioned rats [147]. Together, rodent models of PD offer a good level of both face and predictive validity for sensory symptoms. Moreover, there is scope for furthering the face validity and hence, the utility of rodent models of sensory symptoms in PD. In addition, non-human primate models should not be neglected and should be evaluated for a variety of sensory symptoms in future studies.

3. PRECLINICAL THERAPEUTIC APPROACHES TO NON-MOTOR SYMPTOMS OF PD

The DAergic system is the main pharmacological target for PD, as PD pathophysiology is defined by the loss of DAergic neurons in the substantia nigra of the brain, which is associated with motor impairment [3]. Such DAergic damage is successfully reproduced in rodent and primate models, and these models are widely used to study the motor and non-motor symptoms of PD, comprehend the relevant pathophysiology, develop novel therapeutics, and assess the adverse effects of DAergic medication. Due to their complicated, diverse, and multi-neurotransmitter-driven nature [36], the non-motor symptoms of PD are emerging as one of the defining challenges for understanding and therapy. Furthermore, the potential interactions of novel therapeutics with other drugs that are in clinical use to resolve non-motor symptoms should be investigated in preclinical models. Here, we discuss the current position of preclinical studies for the treatment of these non-motor symptoms as well as the proposed underlying mechanisms. Table **1** summarizes the current preclinical studies on pharmacological and non-pharmacological therapeutic approaches for treating non-motor symptoms in PD [148-161].

3.1. Pharmacological Therapeutic Approaches to Non-Motor Symptoms in Preclinical PD Models

3.1.1. DAergic Therapies

The DA precursor L-3,4-dihydroxy-L-phenylalanine (L-DOPA) has long been considered the gold standard treatment for PD in clinical practice. Subsequently, alternative treatments, such as DA receptor agonists and DA metabolism inhibitors, have been developed because L-DOPA treatment is associated with motor function fluctuations [162]. The DAergic basis for non-motor symptoms, including mood, apathy, sleep disorders, and perceptional disorders, has recently been reviewed [163]. In preclinical studies, L-DOPA

Table 1. Recent evidence of therapeutic approaches to non-motor symptoms of PD in animal models.

Treatment	Animal Model	Neuropsychiatric Symptoms	Sleep Disorders	Autonomic Symptoms	Sensory Symptoms
Pharmacological Treatments					
DAergic Treatments					
L-DOPA	6-OHDA-lesioned rats [143]	-	-	-	↑Pain threshold
L-DOPA	MPTP-lesioned monkeys [31]	-	↑Sleep quality	-	-
SKF38393	MPTP-lesioned monkeys [98]	-	↑EDS & REM	-	-
L-DOPA	6-OHDA-lesioned mice [148]	No effect on anxiety & depression	-	-	-
-	6-OHDA-lesioned rats [149]	↑Anxiety	-	-	-
MAO-B Inhibitors					
Selegiline	CD157/BST1 KO mice [29]	↓Anxiety & ↓Depression	-	-	-
Imidazole	MPTP-lesioned mice [84]	↓Anxiety & ↓Depression	-	-	↑Pain threshold
Immunotherapy					
Anti-α-Syn	α-Syn TG mice [150-152]	↑Cognition	-	-	-
A2AR Antagonists/Genetic Ablation					
Istradefylline	MPTP-lesioned monkeys [28]	↑Cognition	-	-	-
KW6002	MPTP-lesioned monkeys [67]	↑Cognition	-	-	-
A2AR KO	Intra-hippocampal α-Syn fibril-infused mice [60]	↑Cognition	-	-	-
A2AR KO	6-OHDA-lesioned rats [153]	↑Cognition	-	-	-
mGluR5 Antagonists					
MPEP	α-Syn TG mice [42]	↑Cognition	-	-	-
MPEP	MPTP-lesioned rats [62]	↑Cognition	-	-	-
Anti-Oxidative and Anti-Inflammatory Treatments					
Cu^{II}(atsm)	α-Syn TG mice [58]	↑Cognition	-	-	-
Resveratrol	α-Syn TG mice [59]	↑Cognition	-	-	-
Apocynin	LRRK2 TG mice [136]	↓Anxiety & ↓Depression	-	-	-
Melatonin	LRRK2 TG mice [99]	-	↑Sleep quality	-	-
PLX3397	6-OHDA-lesioned rats [77]	↓Depression	-	-	-
Curcumin	Rotenone-lesioned rats [32, 85]	↓Depression	-	-	-
Quercetin	Rotenone-lesioned rats [86]	↑Cognition & ↓Depression	-	-	-
Baicalein	Rotenone-lesioned mice [87]	↓Depression	-	-	-
TLR4 KO	6-OHDA-lesioned mice [82]	↑Cognition & ↓Depression	-	-	-
Rapamycin	6-OHDA-lesioned mice [44]	↑Cognition, ↓Anxiety & ↓Depression	-	-	-
TLR4 KO	MPTP-lesioned mice [83]	↓Anxiety & ↓Depression	-	-	-
Thioredoxin-1	MPTP-lesioned mice [154]	↑Cognition	-	-	-
Other Pharmacological Treatments					
Neuropeptide-S	6-OHDA-lesioned rats [75]	↑Cognition, ↓Anxiety & ↓Depression	-	-	-
Apamin	6-OHDA-lesioned rats [76]	↑Cognition, ↓Anxiety & ↓Depression	-	-	-
Exendin-4	6-OHDA-lesioned rats [81]	↑Cognition & ↓Depression	-	-	-

(Table 1) Contd….

Treatment	Animal Model	Neuropsychiatric Symptoms	Sleep Disorders	Autonomic Symptoms	Sensory Symptoms
Other Pharmacological Treatments					
Atorvastatin	MPTP-lesioned rats [63]	↑Cognition & ↓Depression	-	-	-
Nobiletin	MPTP-lesioned mice [64]	↑Cognition	-	-	-
Ethyl pyruvate	MPTP-lesioned mice [65]	↑Cognition	-	-	-
NTRC 3531-0	Rotenone-lesioned mice [155]	↑Cognition	-	↑Intestinal transit	-
Oligonucleotide	α-Syn TG mice [73]	↓Depression	-	-	-
GDNF	MitoPark mice [74]	↓Depression	-	-	-
Pramipexole	6-OHDA-lesioned rats [156]	↓Depression	-	-	-
Reboxetine	6-OHDA-lesioned mice [148]	↓Anxiety & ↓Depression	-	-	-
Desipramine	6-OHDA-lesioned mice [148]	No effect on anxiety & depression	-	-	-
Clioquinol	MPTP-lesioned monkeys [157]	-	-	↓Constipation	-
Citalopram	6-OHDA-lesioned rats [142]	-	-	-	↑Pain threshold
Mulberry fruit	MPTP-lesioned mice [52]	-	-	-	↑Olfaction
Non-Pharmacological Treatments					
Exercise	AAV-α-Syn overexpressing rats [35]	↑Cognition	-	-	-
	6-OHDA-lesioned rats [61]	↑Cognition & ↓Depression	-	-	-
	MPTP-lesioned mice [66]	↑Cognition	-	-	-
	MPTP-lesioned mice [158]	No effect on cognition	-	-	-
Environmental enrichment	α-Syn TG mice [34]	↓Anxiety	-	-	-
STN-DBS/ Duloxetine	6-OHDA-lesioned rats [144, 145, 159, 160]	-	-	-	↑Pain threshold
Stem cell therapy	6-OHDA-lesioned rats [113, 161]	-	-	↑Voiding function	-

Abbreviations: 6-OHDA, 6-hydroxydopamine; AAV, adeno-associated virus; A2AR, adenosine A2A receptor; α-Syn, α-synuclein; Cu^{II}(atsm), diacetyl*bis*(*N*(4)-methylthiosemicarbazonato) copper(II); DA, dopamine; EDS, excessive daytime sleepiness; GDNF, glial-derived neurotrophic factor; KO, knockout; KW6002, A2AR antagonists; L-DOPA, l-3,4-dihydroxy-L-phenylalanine; LRRK2, leucine-rich repeat kinase 2; MAO-B, monoamine oxidase B; mGluR5, metabotropic glutamate receptor 5; MPEP, 2-methyl-6-(phenylethynyl)pyridine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDAR, N-methyl D-aspartate receptor; NTRC 3531-0, tryptophan 2,3-dioxygenase inhibitor; PLX3397, pexidartinib; REM, rapid eye movement; SKF38393, DAergic D1-like receptor agonist; STN-DBS, Subthalamic deep brain stimulation; TG, transgenic; TLR, Toll-like receptor.

or the DA (D1) receptor agonist SKF38393 decreased hyperalgesia in 6-OHDA-lesioned rats [143] and enhanced sleep quality in MPTP-lesioned monkeys [31, 98]. In contrast, L-DOPA did not ameliorate depression- and anxiety-like behaviors in 6-OHDA-lesioned mice [148]. Further, there are concerns that these DAergic therapies may aggravate various non-motor symptoms in PD [23, 24, 164]. Chronic L-DOPA treatment aggravated anxiety-like behavior in 6-OHDA-lesioned rats [149]. The negative or positive effect of DA treatment may depend on the dose and duration of treatment. Lower doses of L-DOPA or DA agonists improve sleep quality, whereas higher doses of the same drugs cause insomnia and excessive daytime sleepiness [95]. Thus, our understanding of the mechanisms underlying the therapeutic and adverse effects of DAergic therapies is inadequate. DA therapy does not only act on the DAergic system but also on the noradrenergic and serotonergic systems [143, 165, 166]. Understanding the complex mechanisms behind DAergic therapies will allow us to target multiple non-motor symptoms and improve patients' quality of life. Furthermore, new formulations of DAergic therapies and adjunct treatment with other pharmacological or non-pharmacological interventions may help manage the limiting side effects of DAergic therapies. These novel aspects of DAergic therapies should be the focus of future preclinical investigations to advance the treatment of non-motor symptoms of PD.

3.1.2. Monoamine Oxidase-B (MAO-B) Inhibitors

The enzyme, MAO-B, metabolizes DA released from synaptic vesicles [167]. MAO-B inhibitors are now available in several countries for managing motor symptoms in patients with PD; however, their effect on static and fluctuating non-motor symptoms is yet to be elucidated [168]. In preclinical studies, the MAO-B inhibitors selegiline and imidazole restored anxiety- and depression-like behavior in CD157/BST1 KO mice [29] and MPTP-lesioned mice [84]. Moreover, treatment with imidazole enhances the pain threshold in MPTP-lesioned mice [84]. MAO-B inhibition increases striatal DAergic activity and decreases the production of free

radicals resulting from DA oxidation [169]. Thus, MAO-B inhibitors potentiate the responsiveness of striatal neurons to DA [170, 171] and are regularly used in DAergic medicines [172]. Additionally, MAO-B inhibitors exert an anti-apoptotic function [173], delaying the nucleation phase of α-Syn aggregation *in vitro* [174], and thus have the potential to slow the progression of PD. Furthermore, MAO-B inhibitors restore striatal 5-hydroxytryptamine (5-HT) and cortical norepinephrine levels [29], which have been linked to mood disorders [29]. This association between MAO-B inhibitors and multiple neurotransmitter levels suggests that the mechanism underlying the therapeutic benefits of MAO-B inhibitors on neuropsychiatric symptoms is multimodal. These effects can be used in appropriate preclinical animal models to understand the pathophysiology underlying the non-motor symptoms of PD and to investigate the potential of utilizing MAO-B inhibitors in the more complex and advanced phases of the disease in the future. MAO-B inhibitors are safer and have a better tolerance than DA agonists or L-DOPA [172]. Existing knowledge on MAO-B inhibitors provides an additional impetus for developing novel therapies with increased selectivity, safety, and neuroprotection to alleviate non-motor symptoms in the advanced stages of PD.

3.1.3. Anti-α-Syn Immunotherapy

The pathology of α-Syn is a hallmark of PD [175]. The accumulation of α-Syn in synaptic terminals [176], axons [177] and neuronal cell bodies [178] causes neurodegeneration and neuron-to-neuron transmission, similar to prion-like propagation [179]. Anti-α-Syn immunotherapy can repair cognitive impairment in α-Syn TG mice [150-152]. Specific antibodies against α-Syn may promote the clearance of extracellular α-Syn. When α-Syn aggregates are complexed with specific antibodies, they are internalized *via* Fc receptors on microglia and transported to lysosomes, thereby reducing cell-to-cell propagation [180] and enhancing synaptic function and axonal transport [152]. Although immunotherapy has theoretical advantages over traditional therapies, there are currently no entirely effective and safe antibody-based medications [181]. Further studies utilizing a range of animal models are necessary to improve the efficacy and safety of immunotherapy against α-Syn pathology in PD. Nanobodies represent a novel field of immunotherapy that can reach intracellular targets, as opposed to traditional antibodies that can only reach extracellular targets. Proteasome-targeted nanobodies successfully targeted α-Syn misfolding and aggregation in a PD animal model [182]. Thus, nanobodies represent a new area of immunotherapy that remains to be assessed for the treatment of non-motor symptoms in PD. These innovative immunotherapy strategies are awaiting testing to treat various non-motor symptoms. In this context, various α-Syn-based animal models, ranging from rodents to non-human primates, offer useful tools [183]. Furthermore, a recently created α-Syn origin and connectome model of PD [184] will serve as an intriguing preclinical model for investigating a wide range of non-motor symptoms affecting the brain and body.

3.1.4. Adenosine A2A Receptor (A2AR) Antagonists and Genetic Ablation

The A2AR is known to affect α-Syn aggregation and toxicity, and vice versa, since α-Syn can enhance A2AR signaling [185]. In preclinical studies, treatment with A2AR antagonists (istradefylline and KW6002) improved cognition in MPTP-lesioned non-human primates [28, 67], and genetic ablation of A2AR rescued cognitive impairments in intrahippocampal α-Syn fibril-infused mice [60] and 6-OHDA-lesioned rats [153]. Recently, an A2AR antagonist (istradefylline) was approved for clinical use as an adjunct treatment for motor disabilities to extend the therapeutic action of L-DOPA [186, 187]. Thus, A2AR antagonists and genetic deletions may ameliorate α-Syn-induced brain dysfunction and neurodegeneration. Although the precise mechanism by which A2AR antagonism mediates cognitive improvement in PD remains to be elucidated, several possible mechanisms have been implicated in the anti-parkinsonian effects of A2AR antagonism. First, A2AR antagonism may dampen the excessive activity of striatopallidal neurons and restore the balance between striatonigral and striatopallidal neurons [188]. The A2AR antagonism may modulate GABAergic synaptic transmissions in the caudate-putamen [189] and the globus pallidus [190] as a second possible mechanism. Third, because the activation of A2ARs can directly inhibit D2 DAergic receptors and limit coupling to G1 proteins [191, 192], inhibiting A2ARs may reduce the hyper inhibition generated by striatopallidal projections. Additionally, A2AR can form heteromers with metabotropic glutamate receptors (mGluRs) [193]; however, the underlying mechanism is unclear. A2AR antagonists also interact with non-DAergic and non-glutamatergic receptors, such as cannabinoids and serotonin receptors, which have the potential to induce behavioral alterations [194-196]. Future studies should address the precise mechanisms associated with A2AR antagonism and potential non-motor symptoms associated with A2AR in PD.

3.1.5. Metabotropic Glutamate Receptor 5 (mGluR5) Antagonists

Glutamatergic neurotransmission within the basal ganglia is implicated in the development of a wide range of motor and non-motor symptoms in PD, including mood disorders and pain [197]. Furthermore, glutamate excitotoxicity is involved in the degeneration of DAergic neurons in PD [198]. In particular, mGluR5 subtypes, which can contribute to glutamate excitotoxicity, are abundant in several brain regions, including the hippocampus and frontal cortex. These receptors have been recommended as therapeutic targets for various non-motor symptoms of PD [62, 199]. Additionally, α-Syn interacts with cellular prion protein *via* mGluR5, resulting in NMDAR activation, also contributing to glutamate excitotoxicity [42]. mGluR5 antagonists currently under preclinical and/or clinical investigations against PD include 2-methyl-6-(phenylethynyl)pyridine (MPEP) and 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) [200]. In preclinical studies, MPEP-mediated antagonism of mGluR5 ameliorated cognitive impairment in α-Syn TG mice [42] and MPTP-lesioned rats [62]. However, the effect of MTEP on non-motor symptoms in preclinical animal models of PD has not yet been elucidated. Instead, MTEP is well documented for protection against dyskinesia in PD animal models [200, 201]. Thus, mGluR blockage is a method for reducing glutamatergic hyperactivity and is a possible therapeutic strategy for PD [62]. Reduced glutamate release and inhibition of excitotoxicity in the DAergic system are likely implicated in

the mechanisms mediated by MPEP [202]. Higher doses of MPEP and another mGluR5 antagonist, SIB-1893, have been demonstrated to function as NMDA antagonists [203], modulating brain activities such as memory formation, attention, movement, anxiety, and depression [204]. In addition, MTEP has been shown to have an anti-depressive effect in animal models of depression [205]. Therefore, the therapeutic effects of mGluR5 antagonists on non-motor symptoms should be studied further.

3.1.6. Anti-Oxidative and Anti-inflammatory Treatments

Oxidative stress is increasingly being identified as a major event contributing to the degeneration of DAergic neurons in PD [206, 207]. Oxidative stress, as represented by elevated ROS, activates pro-inflammatory responses [52, 208] that together result in neurochemical imbalances [209] and, thus, behavioral alterations [210]. Therefore, neuroinflammation may contribute to the onset and progression of PD [211-213]. Inflammation-mediated pathways of neurodegeneration are linked to oxidative stress, which in turn leads to Lewy body formation and α-Syn aggregation resulting in excessive oxidative damage. Thus, oxidative stress and inflammation are two interacting components leading to neurodegeneration in the pathogenesis of PD [213]. In preclinical studies, non-motor symptoms, including cognitive dysfunction, sleep disorders, and anxiety/depression-like behaviors, have been improved in α-Syn TG mice treated with radiolabeled diacetyl*bis*(*N*(4)-methylthiosemicarbazonato) copper(II) (an imaging agent) [58] and resveratrol (a natural polyphenol compound) [59]; LRRK2 TG mice treated with mitochondrial-penetrable apocynin (an NADPH inhibitor) [136] and melatonin [99]; 6-OHDA-lesioned rats treated with PLX3397 (colony-stimulating factor inhibitor) [77]; rotenone-lesioned rats treated with curcumin [32, 85] and quercetin [86]; rotenone-lesioned mice treated with baicalein (a flavonoid) [87]; 6-OHDA-lesioned mice with TLR4 KO background [82] and treated with rapamycin [44]; and MPTP-lesioned mice with TLR4 KO background [83] and treated with thioredoxin-1 (a redox protein) [154]. The majority of the above pharmacological treatments utilize their inherent anti-oxidative and anti-inflammatory characteristics to reverse behavioral alterations in preclinical models [214]. Additionally, some of these pharmacological treatments can restore neurotransmitter levels [86] and synaptic function [99], indicating their multimodal action against PD pathology. These existing treatments need to be assessed in preclinical animal models that mimic the different pathological aspects of non-motor symptoms in PD. However, further research is needed to investigate novel therapeutics and ensure the safety and scope of existing therapeutics. Overall, there is a potential value of antioxidant supplementation as adjuvant therapy for PD.

3.1.7. Other Pharmacological Treatments

Cognitive impairment was reversed in 6-OHDA-lesioned rats treated with neuropeptide-S [75], apamin (small conductance calcium-activated K^+ channel blocker) [76], and exendin-4 (a glucagon-like peptide 1 receptor agonist) [81]; 6-OHDA-lesioned mice treated with rapamycin [44]; MPTP-lesioned rats treated with atorvastatin [63]; MPTP-lesioned mice treated with nobiletin (a flavonoid) [64] and ethyl pyruvate [65]; and rotenone-lesioned mice treated with NTRC 3531-0 (tryptophan 2,3-dioxygenase inhibitor) [155]. Anxiety- and depression-like behaviors were alleviated in α-Syn TG mice treated with oligonucleotide therapy [73], MitoPark mice treated with glial-derived neurotrophic factor (GDNF)-expressing macrophages [74], 6-OHDA-lesioned rats treated with neuropeptide-S [75], apamin [76], exendin-4 [81], and pramipexole (an anti-depressant drug) [156], and 6-OHDA-lesioned mice treated with reboxetine (a noradrenaline reuptake inhibitor) [148]. However, desipramine (a noradrenaline reuptake inhibitor) did not improve depression- and anxiety-like behavior in 6-OHDA-lesioned mice [148]. Gastrointestinal symptoms have been improved in rotenone-lesioned mice treated with NTRC 3531-0 [155] and MPTP-lesioned monkeys treated with clioquinol [157]. Hyperalgesia in 6-OHDA-lesioned rats and olfactory dysfunction in MPTP-lesioned mice were alleviated with citalopram [142] and mulberry fruit treatment [52], respectively. Multiple mechanisms may underpin the range of non-motor symptoms observed in patients with PD of unknown etiology. The aforementioned therapeutics address the reversal of one or more pathological events in PD; nobiletin rescued calcium/calmodulin-dependent protein kinase II and protein kinase A signaling in the striatum and hippocampal CA1 [64]. Neurotrophic factors, such as GDNF, have neuroprotective and neuroregenerative effects in DAergic neurons [215, 216], while citalopram [142] and oligonucleotide therapy [73] addressed serotonergic alterations. The protective mechanisms of neuropeptide-S seem to involve DAergic neurotransmission [217] and oxidative damage [218]. Accumulating preclinical evidence has demonstrated the therapeutic potential of novel candidates for PD-associated non-motor symptoms *via* several molecular mechanisms.

3.2. Non-Pharmacological Therapeutic Approaches to Non-Motor Symptoms in Preclinical PD Models

3.2.1. Voluntary Exercise and Environmental Enrichment

In addition to pharmacological treatments, non-pharmacological interventions are now emerging as novel approaches to alleviate non-motor symptoms in PD [219-222]. In preclinical studies, voluntary exercise improved cognitive dysfunction in AAV-α-Syn-overexpressing rats [35] and 6-OHDA-lesioned rats [61]. In MPTP-lesioned mice, forced exercise improved cognitive dysfunction [66], but not voluntary exercise [158]. Environmental enrichment and voluntary exercise alleviated anxiety- and depression-like behaviors in α-Syn TG mice [34] and 6-OHDA-lesioned rats [61], respectively. Behavioral improvement under physical exercise and environmental enrichment is associated with alterations in synaptic plasticity, brain-derived neurotrophic factor [61], DA receptors and transporters in the striatum [34], and hippocampal neurogenesis [35]. Although the underlying mechanisms are unclear, given that exercise can stimulate opioid signaling and increase synaptic plasticity, it can be assumed that behavioral improvement is at least partially due to exercise [223]. Nevertheless, learning and social interactions also play a key role in the recovery from non-motor behavioral deficits in PD. However, the detailed mechanisms driving this environmental enrichment-mediated behavioral improvement require further investigation, including an ultrastructural study of synaptic structural alterations as

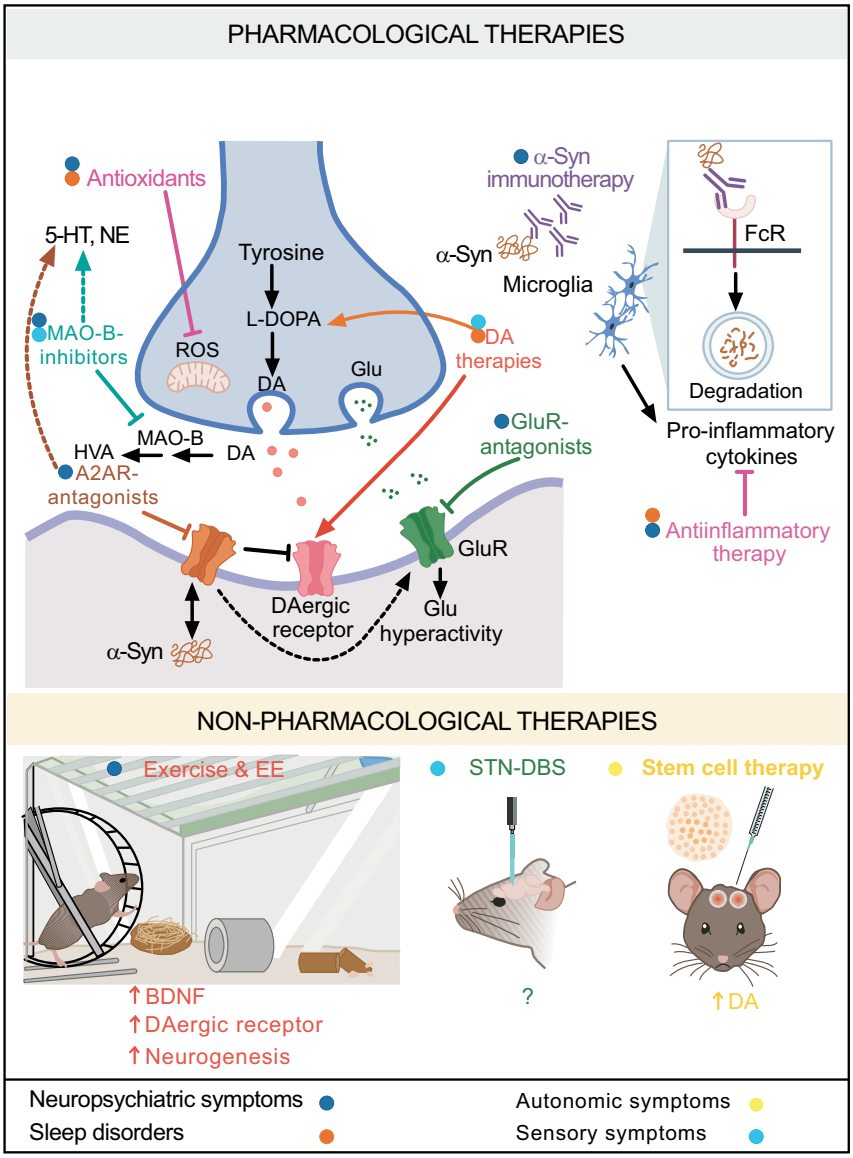

Fig (1). Graphical illustration of pharmacological and non-pharmacological therapeutics over non-motor symptoms in preclinical PD models. In pharmacological therapeutics, neuropsychiatric symptoms and sleep disorders were improved with many categories of treatments, while sensory symptoms were improved only with DA therapies and MAO-B inhibition. In non-pharmacological therapeutics, exercise and environmental enrichment improved the neuropsychiatric symptoms, while STN-DBS improved sensory symptoms and stem cell therapy improved autonomic symptoms in preclinical animal models. **Abbreviations**: 5-HT, serotonin; A2AR, Adenosine A2 receptor; α-Syn, alpha-synuclein; BDNF, brain-derived neurotrophic factor; DA, dopamine; STN-DBS, Subthalamic deep brain stimulation; EE, environmental enrichment; Glu, glutamate; GluR, glutamate receptor; HVA, homovanillic acid; L-DOPA, levodopa; MAO-B, monoamine oxidase-B; NE, norepinephrine; ROS, reactive oxygen species. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

well as postsynaptic and glial transporters [34, 223, 224]. Moreover, the therapeutic effects of exercise and environmental enrichment on sleep disorders and sensory symptoms should also be considered in future studies.

3.2.2. Subthalamic Deep Brain Stimulation

The STN (subthalamic nucleus) has functional connections with cortical areas involved in pain processing and with brainstem nuclei implicated in nociception and descending modulation of pain transmission [225, 226]. STN-DBS alone and/or in combination with duloxetine (selective serotonin and noradrenaline reuptake inhibitor) treatment in 6-OHDA-lesioned rats increased the pain threshold [144, 145, 159, 160]. As the effects of STN-DBS may be found in a variety of pain-related cortical locations, certain STN territories may be engaged in specific pain processing [224]. However, there are controversies over the type of pain relief offered by STN-DBS and how neurostimulation may affect pain processing in PD [224]. Moreover, the site of subthalamic stimulation influences the emergence of neuropsychiatric symptoms [227, 228]. Preclinical animal models will be useful tools for understanding the different subtypes of pain, how nociception is controlled with STN-DBS and specifying the role of distinct subthalamic regions in pain processing. Such a detailed understanding will be a promising approach to treating pain in PD and eliminating or minimizing side effects.

3.2.3. Stem Cell Therapy

Preclinical investigations of non-motor responses to stem cell therapy are rare. Advances in stem cell technology have facilitated the development of first-generation human pluripotent stem cell-derived DAergic neuron technologies that are now in the pipeline for clinical trials [229, 230]. However, there are only a few preclinical investigations on stem cell therapy against the non-motor symptoms of PD. Nevertheless, it remains unclear whether stem cell therapy affects non-motor symptoms or the progression of the disease. In preclinical studies, bone marrow-derived mesenchymal stromal cell therapy improved the voiding function in 6-OHDA-lesioned rats [113, 161]. These findings suggest the potential of stem cell therapy for the treatment of autonomic symptoms in PD. Moreover, these studies explain the neuroprotective and neuroregenerative effects of bone marrow-derived stromal cells *via* a juxtacrine interaction, thereby normalizing the neural control of micturition [113], although the detailed mechanisms are yet to be studied in the future. For cell therapy to be optimized, effective, and clinically relevant, the key limitations must be addressed in the future. Therefore, without being limited to autonomic symptoms, we recommend further preclinical investigations of stem cell therapy in different preclinical models that capture different aspects of non-motor symptoms in PD.

CONCLUSION

Among the different categories of non-motor symptoms, neuropsychiatric symptoms, as seen in clinical PD, have been successfully recapitulated in various preclinical animal models. However, sleep disorders, autonomic symptoms, and sensory disorders have not been sufficiently recapitulated in animal models. In particular, inconsistent autonomic symptoms across preclinical animal models suggest a considerable influence of species and modeling strategies. Future studies should address these points to increase the face validity of existing animal models while developing novel preclinical models that capture multiple aspects of PD pathogenesis.

To date, several pharmacological and non-pharmacological therapeutics have been clinically evaluated (Fig. **1**). New formulations of DAergic therapies and adjunct treatments with other pharmacological/non-pharmacological strategies for non-motor symptoms will be the focus of future preclinical investigations. As novel candidates for monotherapy against non-motor symptoms, MAO-B inhibitors or anti-α-Syn immunotherapy needs to be investigated in the advanced stages of different animal models of PD. Moreover, we suggest considering other non-motor symptoms, including sleep disorders, autonomic symptoms, and sensory symptoms, in future preclinical studies of A2AR and mGluR5 antagonists, as they are already resolving neuropsychiatric symptoms. Anti-inflammatory and anti-oxidative therapies are useful supportive therapies for PD. However, the possibility of developing them as monotherapies against non-motor symptoms in PD remains to be elucidated. In addition to the aforementioned pharmacological categories, several uncategorized therapeutics have emerged as novel candidates in preclinical studies, although their efficacy in resolving non-motor symptoms should be confirmed in further studies. This should be addressed in the future, as non-pharmacological treatment methods may offer useful approaches for managing symptoms such as pain and sensory and autonomic symptoms that are difficult to manage pharmacologically.

This review summarizes the non-motor symptoms observed in preclinical animal models and recent studies on therapeutics against these non-motor symptoms. We also discuss the inadequacies and discrepancies in recapitulating non-motor symptoms in animal models. Moreover, we discuss the future possibilities of therapeutic approaches to the non-motor symptoms of PD. Ultimately, the future aim is to improve the patient's quality of life by resolving the non-motor symptoms of PD, which should be addressed in future preclinical studies.

LIST OF ABBREVIATIONS

A2AR	=	Adenosine 2A Receptor
AAV	=	Adeno-Associated Virus
BDNF	=	Brain-Derived Neurotrophic Factor
Cu^{II}(atsm)	=	Diacetyl*bis*(*N*(4)-methylthiosemicarbazonato) Copper(II)
DA	=	Dopamine
DBS	=	Deep Brain Stimulation
EDS	=	Excessive Daytime Sleepiness
GDNF	=	Glial-Derived Neurotrophic Factor
5-HT	=	5-Hydroxytryptamine
KO	=	Knockout
L-DOPA	=	L-3,4-dihydroxy-L-phenylalanine
LRRK2	=	Leucine-Rich Repeat Kinase 2
MAO-B	=	Monoamine Oxidase B
mGluR	=	Metabotropic Glutamate Receptor
MPEP	=	2-Methyl-6-(phenylethynyl) pyridine
MPTP	=	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NMDAR	=	N-methyl D-aspartate Receptor
NTRC 3531-0	=	Tryptophan 2,3-dioxygenase Inhibitor
6-OHDA	=	6-Hydroxydopamine
PD	=	Parkinson's Disease
PLX3397	=	Pexidartinib
REM	=	Rapid Eye Movement
RLS	=	Restless Legs Syndrome
SKF38393	=	DAergic D1-like Receptor Agonist
STN-DBS	=	Subthalamic Deep Brain Stimulation
α-Syn	=	α-Synuclein
TG	=	Transgenic
TLR4	=	Toll-like Receptor

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by the National Research Foundation (NRF) of Korea grant funded by the Korean Government (Grant nos. NRF-2020R1A4A1019395; NRF-2022R1A2C1004022).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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