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NEUROPHARMACOLOGY (G ASTON-JONES, SECTION EDITOR)

New Pharmacological Approaches to Treating Non-Motor Symptoms of Parkinson's Disease

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Abstract
Purpose of Review Non-motor symptoms in patients with Parkinson's disease (PD) are better predictors of quality of life changes, caregiver burden, and mortality than motor symptoms. Levodopa has limited, and sometimes detrimental, effects on these symptoms. In this review, we discuss recent evidence on pharmacological treatments for non-motor symptoms.
Recent Findings Breakthroughs have been made in the treatment of psychosis and sleep dysfunction. Pimavanserin has become the first FDA approved drug for PD psychosis. There is also new research supporting cholinesterase inhibitors for sleep disorders in PD. Other studies, including several novel treatments, have shown mixed results for apathy, depression, and fatigue.
Summary Further research is needed to develop treatments for non-motor symptoms in PD. Preclinical and postmortem studies indicate that non-motor symptoms in PD may arise from pathology in non-dopamine systems. Although sometimes used off-label, therapies that target such systems have been underutilized in treating non-motor symptoms and warrant further clinical investigation.

Keywords Parkinson's disease · Non-motor symptoms · Novel PD treatments · RBD · Psychosis · Depression

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Introduction

Parkinson's disease (PD) is the second most prevalent progressive neurodegenerative disease in the USA, behind only Alzheimer's [1]. Gold standard therapeutics in PD management are aimed at treating motor symptoms and primarily target canonical dopamine (DA) pathways that deteriorate. However, studies consistently find that the vast majority of PD patients, including those on DA replacement, present with at least one non-motor symptom [2•, 3]. PD patients report an average of four to eight non-motor symptoms, in which these can include sleep disturbances, psychosis, fatigue, depression, memory impairment, urinary problems, sexual dysfunction, and more [2•, 3, 4]. The prevalence of these symptoms in PD remains relatively stable across disease progression and treatment [3], indicating that non-motor symptoms in PD are persistent and poorly addressed by current therapeutic strategies.

Non-motor symptoms, especially mild to moderate symptoms, can be underdiagnosed. Neurologist accuracy ranges from 35 to 60 % for depression, anxiety, fatigue, and sleep disturbances [5]. Even when diagnosed, conventional DA replacement therapies, such as levodopa, have little effect on the burden of the symptoms and in some cases may exacerbate them [2•]. Non-motor symptoms are stronger predictors of poor quality of life and mortality than motor symptoms [4, 6•, 7]. Screening for and appropriately treating non-motor symptoms in PD have the potential to change quality of life and disease burden, for both PD patients and caregivers. With awareness of the impact of non-motor symptoms in PD increasing, questions arise as to the most appropriate treatment strategies for these symptoms. In this article, we briefly review recent advances and empirical evidence for the pharmacological management of some of the most prevalent non-motor symptoms in PD.

Sleep

One of the most commonly reported non-motor symptoms in PD are sleep disturbances [5, 8, 9]. Sleep disturbances produce some of the largest reductions in quality of life [4, 7]. Although often seen as a precursor to PD diagnosis, REM behavior disorder (RBD) co-morbidity remains high in PD patients. Additional sleep disturbances can manifest as restless leg syndrome, nocturia, arm and leg pain, nocturnal motor symptoms, and abnormal sleep architecture [10, 11•, 12–15]. PD patients who self-identify as poor sleepers are also significantly more likely to present additional non-motor symptoms [16, 17]. Neikrug et al. [17] found that PD patients with RBD reported being more depressed and fatigued with additional sensory changes in taste, smell, and unexplained weight change. Higher non-motor symptom loads in addition to RBD may not only underlie poorer quality of life scores but may also indicate a common etiology. Alleviating RBD has potential to improve quality of life scores and may provide benefits to non-motor symptoms across multiple domains for PD patients.

Benzodiazepines such as clonazepam are the standard treatment for primary RBD. Side effects such as falls and drowsiness [18], in addition to warnings for patients with a gait disorder or dementia [19], mean that alternative therapeutic strategies are needed for RBD in PD patients.

DA Agonists

Given its primary approval for PD motor symptoms, rotigotine, more than many treatments, has been tested for treating PD related sleep abnormalities. Rotigotine has shown improvements in sleep efficacy, sleep onset latency, and wakefulness after sleep onset along with reductions in episodes and severity of restless leg syndrome, nocturia, nocturnal motor symptoms, limb pain, and RBD [13–15]. Vallderiola et al. [14] also showed that rotigotine is beneficial for those with more severe sleep disturbances, as patients with higher baseline scores saw larger improvements on multiple sleep scales.

Long-term follow up studies revealed high efficacy and good tolerability in large cohorts of patients [20, 21]. Adverse events to rotigotine were predominantly mild and declined over treatment duration. This contributed to low withdrawal rates over the 6-year study period, demonstrating that rotigotine is a viable long-term strategy to treat sleep disruptions in PD.

Part of the efficacy of rotigotine may be its non-selectivity for DA receptor subtypes or possibly its affinities at other monoaminergic sites implicated in PD. In addition to DA signaling, rotigotine shows function as a serotonin (5-HT) partial agonist and antagonist on $_{2B}$-adrenergic receptors [23]. $_{2B}$-Adrenergic receptors are highly localized in locus coeruleus [24] which has reduced signal intensities in PD patients with RBD [25].

Concerns and need for alternatives arise for those who are resistant to rotigotine or those that develop side effects such as impulse control disorders. As with all DA replacements, there is potential risk of impulse control issues, although rotigotine has reduced risk compared to other DA agonists [22]. There are, however, varieties of alternative treatments for refractory sleep symptoms that highlight the multifactorial nature of this non-motor symptoms in PD.

Other Monoaminergic Targets—Tricyclic Antidepressants and Melatonin

The prevalence and persistence of sleep disturbances in PD patients, including those with good management of motor symptoms, highlight involvement of non-DA systems in PD. Other monoamines, particularly 5-HT and norepinephrine (NE), are critical regulators of arousal, and PD patients show disruptions in circadian function from early in disease progression [16]. Tricyclic antidepressants prevent reuptake of monoamines, with particular affinity for 5-HT and NE transporters. A small cohort of PD patients treated with the tricyclic doxepin showed improvements on multiple sleep scales including the Insomnia Severity Index, SCOPA-night score, and Pittsburgh Sleep Quality Index-sleep disturbance subscale over 6 weeks [26]. In addition, doxepin shows potent antihistamine activity which may contribute to its effective treatment of sleep disturbances [27].

Melatonin is another circadian monoamine that is reduced in PD patients, particularly those that exhibit excessive daytime sleepiness [28]. In 2011, evidence for treatment of insomnia in PD with melatonin was deemed to be insufficient by the Movement Disorders Society Task Force [29]. More recently, a small study of 35 PD patients showed that ramelteon, a selective melatonin agonist, generated improvements in multiple aspects of sleep such as sleep latency, quality, use of sleep medication, and overall PD sleep scale version 2 score [18]. Ramelteon did not show any detrimental effects to activities of daily living or cognitive function. In light of this and other recent studies on melatonin disruption in PD, melatonin supplementation and/or melatonin agonists may warrant additional investigation for treating PD related sleep disorders.

REM Sleep and Acetylcholine

RBD is the most common type of sleep disruption in PD, and REM sleep is strongly linked to cholinergic function. Brainstem cholinergic pathways degenerate in PD [30], and a breakdown in cholinergic signaling has been associated with RBD in PD patients [31]. In preclinical studies, stimulation of brainstem cholinergic populations known to be impaired in PD drives immediate transitions to REM sleep and also

reduces dyskinesia in parkinsonian models [32, 33]. Currently available cholinesterase inhibitors such as rivastigmine seem to be useful for treating refractory RBD in PD patients. In a double blind crossover trial, rivastigmine alleviated RBD in PD patients who were resistant to both melatonin and clonazepam [11•]. It should be noted that while evidence is promising for the use of rivastigmine, its use may be limited to cases of RBD rather than other sleep disturbances.

Alternative Pharmacotherapies—Xyrem

Sodium oxybate (Xyrem) improves sleep consolidation in narcolepsy [34]. In PD patients, off-label studies of Xyrem have shown increases in slow wave sleep with decreases in nighttime and daytime sleep problems as measured by the Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index [35]. Furthermore, more recent reports on individual patients show that Xyrem is also efficacious in the treatment of refractory RBD in patients with PD [36, 37].

The mechanism by which Xyrem exerts beneficial effects on sleep disturbances in PD is unknown, and further trials are needed to confirm previous findings. Previous studies in patients with narcolepsy and/or cataplexy suggests that it has the ability to modify sleep architecture [38]. Despite the absence of a specific molecular target, Xyrem is FDA approved to treat narcolepsy and excessive daytime sleepiness.

Psychosis

Psychosis is one of the most debilitating non-motor symptoms of PD. Psychosis can not only occur as part of PD with dementia but can also be triggered by medications used to treat motor symptoms [39]. Not surprisingly, studies show significant variability in the prevalence of hallucinations and delusions as well as other psychotic symptoms in PD ranging from <15 to over 70 % [9, 40–42]. Psychotic symptoms, particularly hallucinations and delusions, often co-occur with increased depressive symptoms and are associated with worse quality of life [40]. The presence of ongoing psychosis in PD is a strong negative predictor of survival and an indicator for increased medical costs and long term care needs [6•, 43]. Much of the burdens that are due to a paucity of options for treating psychosis in PD given traditional antipsychotics are contraindicated. Atypical antipsychotics show some benefits but can worsen motor symptoms. The mainstream approach to treating psychosis in PD has been to reduce DA replacement or anticholinergic therapies which, in some cases, leads to reemergence of motor impairments [39, 44]. However, a novel atypical antipsychotic compound, pimavanserin, recently passed expedited approval by the FDA in 2016 and is showing particular promise.

Selective 5-HT_{2A} Inverse Agonist—Pimavanserin

Pimavanserin is a selective 5-HT_{2A} inverse agonist which became the first FDA approved drug for the treatment of psychosis in PD following a promising phase III trial of 185 patients that strengthened previous findings [45•]. Over a 6-week period, pimavanserin showed significant improvements on several Parkinson's disease-adapted scales for positive symptoms of psychosis. Caregivers reported a reduced burden, while patients reported additional improvements in sleep and daytime wakefulness [45•, 46]. Improvements were dramatic, with the number of patients showing more than 20 % reduction in psychosis scores with no change in motor symptom severity. Treatment was effective regardless of age, sex, and mini-mental state exam scores.

Unfortunately, many positive symptoms scales are not sensitive to the minor psychotic symptoms evident in PD psychosis [47] that affects up to 72 % of patients [42]. Another concern for pimavanserin trials are the relatively short follow up times. In a study by Mack et al. [40], the duration of minor psychotic symptoms in PD patients was 85.2 ± 71.4 weeks, and the duration of hallucinations and delusions was 173.8 ± 152.7 weeks. Both the phase II and III trials used follow-up times of less than 10 weeks [45•, 46]. The beneficial effects of pimavanserin in PD patients with psychosis of a longer duration have yet to be determined.

Pimavanserin demonstrates a high specificity toward 5-HT_{2A} receptors and lower affinity for other monoaminergic receptors [48]. Clozapine, a 5-HT_{2A} antagonist with limited D_2 binding and extrapyramidal side effects [49], was rated as efficacious for the treatment of PD psychosis by the Movement Disorders Society Task Force [29] based on older studies. Prior success with clozapine and new evidence from pimavanserin identifies 5-HT_{2A} function as a specific target for further pharmaceutical development in PD psychosis. Additional support comes from PET studies in which PD patients with visual hallucinations show increased 5-HT_{2A} receptor binding in visual pathways [50].

Further insight into future treatments for PD psychosis may come from treatments for PD related sleep dysfunction such as RBD. PD patients who present with RBD or probable RBD are at an increased risk for developing PD psychosis [41, 42]. The common factor linking PD psychosis and sleep disturbances has yet to be determined, although degeneration of brainstem cholinergic populations (pedunculopontine and laterodorsal tegmental nuclei) that receive strong 5-HT innervation are a prime candidate. Cholinesterase inhibitors including rivastigmine are effective at alleviating RBD and may have added benefits in treating PD psychosis, as do reductions of anticholinergic treatment [11•, 44]. Targeting co-morbid RBD may benefit patients with PD psychosis, including minor psychotic presentations. Future research should focus on additional treatments for common minor psychotic presentations

and performing long-term follow-ups on pimavanserin and other 5-HT_{2A}-directed treatments.

Fatigue

Fatigue was voted as the symptom most in need of further research by patients attending the 2013 World Parkinson's Congress [51], and despite efforts to uncover a specific pathology, fatigue is not fully understood and there are few effective treatment options. Most studies find that fatigue affects 40 % or more of PD patients and is one of the most underdiagnosed non-motor symptoms in PD [5, 52, 53]. PD patients report higher overall fatigue and increased symptoms on various subscales such as general fatigue, physical fatigue, and mental fatigue compared to age-matched peers [54]. Fatigue is associated with a higher burden of non-motor symptoms and worse health-related quality of life [2•, 52]. Some risk factors for fatigue include depression, higher levodopa dose, and advanced disease stage and duration [52, 53]. Despite evidence that mental and physical fatigue manifest separately in PD [54], there are few studies that have attempted to define or treat the two independently.

Monoamine Oxidase Inhibitors

Rasagiline is an irreversible monoamine oxidase B inhibitor that is often used in PD patients alone or as an adjunct. Recent studies assessing the effect of rasagiline on fatigue in PD have been mixed. One study found that co-treatment with rasagiline and antidepressants resulted in significantly less progression of fatigue compared to placebo and noted no evidence for serotonin syndrome [55]. Specific antidepressants paired with rasagiline included selective serotonin reuptake inhibitors (SSRIs), amitriptyline, and trazodone hydrochloride. Another study found a similar result with rasagiline monotherapy, where fatigue symptoms stabilized but did not improve, suggesting that beneficial effects of rasagiline are independent of antidepressant use [56]. Compared to rasagiline, the placebo group saw significant worsening of 15 out of 16 items of the Parkinson's Disease Fatigue Scale. A third study found that 12 weeks of rasagiline treatment improved multiple fatigue scales including the Fatigue Severity Scale, Modified Fatigue Impact Scale, and Objective Physical and Mental Fatigue Testing. Although a number of studies have investigated rasagiline to treat fatigue in PD, most evidence implies that rasagiline does not improve fatigue symptoms but maintains them, suggesting the need for alternative treatments.

Deficiencies in 5-HT availability in the basal ganglia and limbic areas of the brain may play a role in PD fatigue [57]. Serotonergic neurons of the dorsal raphe that express monoamine oxidase A and B mRNA send projections to the basal ganglia [58]. This warrants additional research into monoamine oxidase A inhibitors or SSRIs for the treatment of PD fatigue. Serotonergic targeting strategies may provide relief for depression and anxiety [59], in addition to fatigue, although care should be taken in patients at risk for psychosis.

Adenosine Antagonists

A recent small study tested the adenosine antagonist istradefylline in 40 patients with moderate to severe PD for 8 weeks. There was a significant improvement on the Fatigue Severity Scale in addition to a significant improvement to patient and caregiver quality of life [60]. Istradefylline was previously denied FDA approval as an adjunctive PD treatment, although it is approved in some countries for this purpose [61]. Istradefylline represents a novel target in the treatment of PD fatigue. Istradefylline is a competitive antagonist that selectively binds adenosine A_{2A} receptors more favorably than other adenosine receptors [62]. Caffeine, another adenosine antagonist, is thought to promote wakefulness by affecting A_{2A} receptors specifically in the nucleus accumbens shell but not the core [63]. Despite primary DA innervation from the relatively spared ventral tegmental area neurons, the accumbens shows reduced DA levels in PD patients [64]. Adenosine blockades caused by caffeine increase DA release, which may reduce fatigue and have added benefits in PD, such as reductions in dyskinesia [65]. A newer adenosine antagonist, JNJ-40255293, shows similar binding occupancy to istradefylline at adenosine A_2 receptors in rodent models while also showing lower relative affinity for adenosine A_1 receptors [66]. Based on its binding profile and clinical effects of other adenosine antagonists, JNJ-40255293 may help alleviate fatigue in PD patients in a similar manner to istradefylline and caffeine. Whether selective adenosine antagonists potentially share the disease modifying or neuroprotective benefits in PD that have been attributed to caffeine is yet to be determined [67].

Apathy

Apathy is present in 18 to 54 % of PD patients, and multiple studies find that apathy is commonly concomitant with depression, with published rates between 28 and 43 % [68–70]. Despite overlapping symptoms between apathy and depression, they are clinically and pathologically distinct constructs. Apathy is associated with higher levodopa dosage at earlier Hoehn and Yahr stages [69]. Although apathy has limited impact on quality of life, it remains an important non-motor symptom because apathetic PD patients have increased motor and cognitive impairments [68, 70]. Apathy has also been linked with other non-motor symptoms such as fatigue and hallucinations [70]. In animal models, apathy and anhedonia can be generated by selective lesions of substantia nigra

pars compacta [71], indicating that apathy is a core DA based symptom of PD unlike most other non-motor symptoms. Furthermore, non-pharmacological PD treatments such as deep brain stimulation that allows reductions of DA replacement can precipitate apathy [72].

DA Agonists

As apathy can result from insufficient DA replacement therapy, DA agonists are a first-line therapy for the treatment of apathy in PD. Although there are no FDA approved treatment specifically for apathy in PD, DA agonists have long shown safety and efficacy in treating PD motor symptoms. In a post hoc analysis of the RECOVER study, patients treated with rotigotine showed significant improvement in the mood/apathy domain of the non-motor symptom scale [73]. Apathy-related items including "lost interest in surroundings" and "lost interest in doing things" showed the greatest effect sizes. A more recent investigation of rotigotine showed no effect on apathy as rated by patients or caregivers, despite some improvements in clinical apathy scores [74]. This may signal difficulties in patients' ability to accurately qualify their apathetic status and subsequent changes.

In preclinical animal models, pramipexole reversed motivational deficits, which returned upon cessation [75]. A large study of non-demented PD patients tested pramipexole as a mono or adjunctive therapy and saw an improvement in apathy on the Neuropsychiatric Inventory [76].

One of the most effective DA agonist treatments, piribedil, was utilized in a 12-week study of apathy after subthalamic nucleus deep brain stimulation [72]. Piribedil reduced apathy scores by 34.6 % compared to a 3.2 % reduction in the placebo group. Apathy was deemed to have disappeared in 47.4 % of patients on piribedil compared to 16.7 % of patients in the placebo group with results typically occurring within the first 6 weeks of treatment. Piribedil can also improve cognition in older individuals [77], potentially leading to additional benefits when used for the treatment of apathy in PD.

Piribedil shows $_2$ antagonist activity in addition to functioning as a partial agonist at D_2 and D_3 receptors [78]. Apathy scores are inversely correlated to the binding potential of DA and NE in the ventral striatum [79]. Other DA agonists that have less selective binding profiles or do not target both catecholamine systems appear to be less effective in treating apathy in PD.

Cholinesterase Inhibitors

Apathetic patients without depression have an increased risk of cognitive decline and development of dementia [80]. Cognitive decline has been linked with forebrain cholinergic loss and decreased cortical choline acetyltransferase [81]. Therefore, apathy may be an early sign of cholinergic pathway breakdown and signal the onset of cognitive decline in PD patients. In preclinical studies, cholinergic interneurons in the striatum have been shown to regulate DA signaling and motivation [82]. A cholinesterase inhibitor such as rivastigmine could be a novel strategy in the treatment of apathy and may help offset these cholinergic deficits.

In a 6-month trial on dementia and depression-free, apathetic PD patients, rivastigmine decreased apathy scores [83], specifically in the domains of intellectual curiosity and action initiation. By the end of the trial, only 37 % of patients treated with rivastigmine were categorized as apathetic compared to 83 % of placebo patients. An extension of this study showed significant improvements in apathy after the original placebo group initiated rivastigmine treatment. However, benefits were not maintained over a 12-month continuation period in the original treatment group, demonstrating transient benefits.

Depression

Depression is a problematic and underdiagnosed non-motor symptom in PD, significantly impacting patient health related quality of life and symptom burden [2•, 3, 4]. Around half of all PD patients report depressive symptoms; rates of major depressive disorder in PD are around 17 %, while minor depression is around 22 % and dysthymia 13 % [84]. Even after initial treatment, as many as 47 % of PD patients will still meet the criteria for depression [85]. Despite a medical need, few patients are prescribed the highest recommended doses of antidepressants and as few as one third will try more than one antidepressant [85]. Therapeutic approaches to alleviate the burden of depression are essential, as depression is the best predictor of poor compliance in PD patients [86]. Compliance in PD is startling, with one fifth of patients showing less than 80 % compliance. Additionally, as low as 3 % of patients show compliance for drugs prescribed twice or more per day [87]. Dopamine-based treatments such as pergolide [88] and rasagiline monotherapies [89] have been ineffective in treating PD depression, indicating the involvement of non-DA systems in the pathophysiology of PD depression. Effectively treating depression in PD may enhance patient compliance for other medications, in turn facilitating better overall treatment and reduced symptom burdens.

Canonical Antidepressants

Recently, there have been mixed reviews of antidepressants to treat depression in PD. SSRIs and tricyclic antidepressants are used as a first line therapy for PD depression [90]. Several large-scale meta-analyses have shown that tricyclic antidepressants are significantly more effective at treating comorbid PD depression than SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) [91, 92]. This

may be due to additional benefits of tricyclics on other non-motor symptoms like sleep disturbances, discussed above. However, a number of new studies provide increasing evidence for effective treatment with SSRIs or SNRIs [93].

Recent studies of paroxetine (SSRI) and venlafaxine (SNRI) treatment led to significant improvements on several rating scales [94]. More patients in the treatment groups met the criteria for responsiveness to treatment and remission compared to the placebo; additionally, no worsening of PD motor symptoms were found. A secondary regression revealed that higher baseline Hamilton depression scores, lower anxiety scores, and lower Unified Parkinson's Disease Rating Scale section III scores were significant predictors of improved Hamilton scores by the end of the study [95]. This may indicate that patients with mood dominant early PD are particularly responsive to targeted therapies. Another study specifically investigated three domains of depression, namely affective, somatic, and cognitive, alongside their timetable for improvement while on paroxetine or venlafaxine [96]. Improvements were seen in all three domains, with the affective domain showing the earliest treatment-by-time interaction after week 4. The somatic domain showed after week 6 and the cognitive domain after week 8.

NE function is also linked to depression, and depressed PD patients have decreased noradrenergic innervation of limbic regions [79]. However, studies with selective NE reuptake inhibitors such as reboxetine and atomoxetine did not show clear benefits [97, 98]. Recent successes with mixed serotonin and noradrenergic reuptake inhibitors indicate that further exploration of noradrenergic involvement in PD depression may be warranted.

Conclusion

We have covered new evidence for pharmacological treatments of some of the most common non-motor symptoms that occur in PD. Recent advances have been made in the treatment of sleep disturbances and psychosis. Still, other symptoms such as depression and fatigue have few new treatment options. Many non-motor symptoms not covered here including executive dysfunction, memory, pain, hyposmia, and gastrointestinal dysfunction are problematic and also have limited therapeutic options.

The development of pharmaceutical approaches for non-motor symptoms in PD has been influenced by the precedent of PD as a dopaminergic motor disease. Some common non-motor symptoms like psychosis can be consequences of DA replacement, although most are not. Most non-motor symptoms are present when patients are receiving ongoing DA therapy. Additional DA-based treatments have been tested for a large number of non-motor symptoms, with unsurprisingly limited success. Preclinical and neuropathological evidence has made clear that non-DA systems are significantly affected. Yet clinical assessment of non-DA-targeted therapeutics for non-motor symptoms is underinvestigated. Recent successes of cholinergic and serotonergic-based treatments have led to new therapies for sleep disruption and psychosis in PD. Further investigation of pharmaceuticals that target modulatory disruptions to adrenergic, serotonergic, and cholinergic nuclei in PD may be particularly important for non-motor symptoms.

Because of the breadth of non-motor symptoms in PD, therapeutic developments may be expedited by grouping non-motor presentations into PD subtypes. Sauerbier et al. [99] argue that non-motor subtyping would enhance patient recruitment, clinical design, and treatment of PD despite some overlap between non-motor subtypes. Subtype specific treatments may identify related non-motor symptoms and effective new treatments across multiple domains. Streamlining treatments could result in the need for fewer drugs to manage PD symptoms which would have positive impacts on medication adherence [87] and economic burden [100].

Non-motor symptoms remain problematic in PD and have profound impacts on survival rates, economic burden, and quality of life for patients and caregivers. Given the growing public health burden of age related diseases like PD, future research should prioritize the development of therapeutics for untreated non-motor symptoms using neuropathological and preclinical evidence to expand the range of pharmaceutical targets.

Compliance with Ethical Standards

Conflict of Interest An immediate relative of MAK is employed by inVentiv Health. EMV has no conflict of interest to disclose. All reported studies/experiments with human or animal subjects have previously been published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. de Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. Lancet Neurol. 2006;5:525–35.

2.• Kadastik-Eerme L, Muldmaa M, Lilles S, Rosenthal M, Taba N, Taba P. Nonmotor features in Parkinson's disease: what are the most important associated factors? Parkinsons Dis. 2016;2016: 4370674. **There is a growing concern about negative health related impacts of non-motor symptoms for PD patients. This study showed almost universal prevalence of non-motor symptoms in PD as well as evidence that levodopa treatment is associated with a higher burden of non-motor symptoms.**

3. Erro R, Roberto E, Marina P, et al. Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. J Neurol Neurosurg Psychiatry. 2012;84:14–7.

4. Duncan GW, Khoo TK, Yarnall AJ, O'Brien JT, Coleman SY, Brooks DJ, et al. Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. Mov Disord. 2014;29:195–202.

5. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2002;8:193–7.

6.• de Lau LML, Verbaan D, Marinus J, van Hilten JJ. Survival in Parkinson's disease. Relation with motor and non-motor features. Parkinsonism Relat Disord. 2014;20:613–6. **This study investigated factors associated with survival rates in PD. The main finding showed that non-motor symptoms such as depression, psychosis, and cognitive impairments were associated with increased mortality even after adjusting for age, sex, and disease duration. This study highlights the importance of non-motor symptoms in a disease that is primarily defined by its motor manifestations.**

7. Prakash KM, Nadkarni NV, Lye W-K, Yong M-H, Tan E-K. The impact of non-motor symptoms on the quality of life of Parkinson's disease patients: a longitudinal study. Eur J Neurol. 2016;23:854–60.

8. Oerlemans WGH, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease. A self-reported, community-based survey. Sleep Med. 2002;3:147–9.

9. Riedel O, Oliver R, Jens K, et al. Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. J Neurol. 2010;257:1073–82.

10. Zibetti M, Rizzone M, Merola A, Angrisano S, Rizzi L, Montanaro E, et al. Sleep improvement with levodopa/carbidopa intestinal gel infusion in Parkinson disease. Acta Neurol Scand. 2013;127:e28–32.

11.• Di Giacopo R, Fasano A, Quaranta D, Della Marca G, Bove F, Bentivoglio AR. Rivastigmine as alternative treatment for refractory REM behavior disorder in Parkinson's disease. Mov Disord. 2012;27:559–61. **Based on the results of this study, rivastigmine represents a new alternative treatment for RBD in PD patients that is refractory to traditional treatment options such as clonazepam and melatonin.**

12. Pierantozzi M, Mariangela P, Fabio P, Claudio L, Maria A, Paola I, et al. Rotigotine may improve sleep architecture in Parkinson's disease: a double-blind, randomized, placebo-controlled polysomnographic study. Sleep Med. 2016;21:140–4.

13. Pagonabarraga J, Javier P, Gerard P, et al. Transdermal rotigotine improves sleep fragmentation in Parkinson's disease: results of the multicenter, prospective SLEEP-FRAM study. Parkinsons Dis. 2015;2015:1–7.

14. Vallderiola F, Compta Y, Aparicio J, Tarradellas J, Salazar G, Oliver JM, et al. Effects of night-time use of rotigotine on nocturnal symptoms in Parkinson's disease. Parkinsons Dis. 2015;2015: 475630.

15. Calandra-Buonaura G, Guaraldi P, Doria A, Zanigni S, Nassetti S, Favoni V, et al. Rotigotine objectively improves sleep in Parkinson's dsease: an open-label pilot study with actigraphic recording. Parkinsons Dis. 2016;2016:3724148.

16. Breen DP, Vuono R, Nawarathna U, Fisher K, Shneerson JM, Reddy AB, et al. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol. 2014;71:589–95.

17. Neikrug AB, Avanzino JA, Liu L, Maglione JE, Natarajan L, Corey-Bloom J, et al. Parkinson's disease and REM sleep behavior disorder result in increased non-motor symptoms. Sleep Med. 2014;15:959–66.

18. Kashihara K, Nomura T, Maeda T, Tsuboi Y, Mishima T, Takigawa H, et al. Beneficial effects of ramelteon on rapid eye movement sleep behavior disorder associated with Parkinson's disease—results of a multicenter open trial. Intern Med. 2016;55:231–6.

19. Aurora RN, Zak RS, Maganti RK, et al. Best practice guide for the treatment of REM sleep behavior disorder (RBD). J Clin Sleep Med. 2010;6:85–95.

20. Elmer LW, Surmann E, Boroojerdi B, Jankovic J. Long-term safety and tolerability of rotigotine transdermal system in patients with early-stage idiopathic Parkinson's disease: a prospective, open-label extension study. Parkinsonism Relat Disord. 2012;18:488–93.

21. Giladi N, Nir G, Babak B, Erwin S. The safety and tolerability of rotigotine transdermal system over a 6-year period in patients with early-stage Parkinson's disease. J Neural Transm. 2013;120: 1321–9.

22. Garcia-Ruiz PJ, Martinez Castrillo JC, Alonso-Canovas A, Herranz Barcenas A, Vela L, Sanchez Alonso P, et al. Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. J Neurol Neurosurg Psychiatry. 2014;85:840–4.

23. Scheller D, Dieter S, Christoph U, Reinhard B, Mirella G, Hermann L. The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease. Naunyn Schmiedebergs Arch Pharmacol. 2008;379:73–86.

24. Saunders C, Limbird LE. Localization and trafficking of alpha2-adrenergic receptor subtypes in cells and tissues. Pharmacol Ther. 1999;84:193–205.

25. García-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, et al. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain. 2013;136:2120–9.

26. Rios Romenets S, Creti L, Fichten C, Bailes S, Libman E, Pelletier A, et al. Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease—a randomized study. Parkinsonism Relat Disord. 2013;19:670–5.

27. Taylor JE, Richelson E. High-affinity binding of [3H]doxepin to histamine H1-receptors in rat brain: possible identification of a subclass of histamine H1-receptors. Eur J Pharmacol. 1982;78: 279–85.

28. Videnovic A, Aleksandar V, Charleston N, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 2014;71:463.

29. Seppi K, Weintraub D, Coelho M, et al. The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011;26 Suppl 3:S42–80.

30. Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc Natl Acad Sci U S A. 1987;84:5976–80.

31. Kotagal V, Vikas K, Albin RL, Martijn LT, Koeppe RA, Chervin RD, et al. Symptoms of rapid eye movement sleep behavior disorder are associated with cholinergic denervation in Parkinson disease. Ann Neurol. 2012;71:560–8.

32. Van Dort CJ, Zachs DP, Kenny JD, et al. Optogenetic activation of cholinergic neurons in the PPT or LDT induces REM sleep. Proc Natl Acad Sci U S A. 2015;112:584–9.

33. Pienaar IS, Gartside SE, Sharma P, De Paola V, Gretenkord S, Withers D, et al. Pharmacogenetic stimulation of cholinergic pedunculopontine neurons reverses motor deficits in a rat model of Parkinson's disease. Mol Neurodegener. 2015;10:47.
34. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep. 2006;29:939–46.
35. Ondo WG, Perkins T, Swick T, Hull Jr KL, Jimenez JE, Garris TS, et al. Sodium oxybate for excessive daytime sleepiness in Parkinson disease: an open-label polysomnographic study. Arch Neurol. 2008;65:1337–40.
36. Moghadam KK, Fabio P, Alberto P, Raffaele F, Giuseppe P. Sodium oxybate for idiopathic REM sleep behavior disorder: a report on two patients. Sleep Med. 2016. doi:10.1016/j.sleep.2016.04.014.
37. Liebenthal J, Valerio J, Ruoff C, Mahowald M. A case of rapid eye movement sleep behavior disorder in Parkinson disease treated with sodium oxybate. JAMA Neurol. 2016;73:126–7.
38. Mamelak M, Black J, Montplaisir J, Ristanovic R. A pilot study on the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. Sleep. 2004;27:1327–34.
39. Friedman JH. Parkinson's disease psychosis 2010: a review article. Parkinsonism Relat Disord. 2010;16:553–60.
40. Mack J, Joel M, Peter R, et al. Prevalence of psychotic symptoms in a community-based Parkinson disease sample. Am J Geriatr Psychiatry. 2012;20:123–32.
41. Forsaa EB, Larsen JP, Wentzel-Larsen T, Goetz CG, Stebbins GT, Aarsland D, et al. A 12-year population-based study of psychosis in Parkinson disease. Arch Neurol. 2010;67:996–1001.
42. Pacchetti C, Claudio P, Raffaele M, et al. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. Mov Disord. 2005;20:1439–48.
43. Hermanowicz N, Edwards K. Parkinson's disease psychosis: symptoms, management, and economic burden. Am J Manag Care. 2015;21:s199–206.
44. Friedman JH, Factor SA. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord. 2000;15:201–11.
45.• Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383:533–40. **Successful phase III trial of pimavanserin to treat PD psychosis. Since this study, pimavanserin has become the first FDA approved drug for treatment of PD psychosis.**
46. Meltzer HY, Roger M, Stephen R, Hilde W, Ann J, Daun B, et al. Pimavanserin, a Serotonin2A receptor inverse agonist, for the treatment of Parkinson's disease psychosis. Neuropsychopharmacology. 2009;35:881–92.
47. Fernandez HH, Aarsland D, Fénelon G, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. Mov Disord. 2008;23:484–500.
48. Vanover KE. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine2A receptor inverse agonist. J Pharmacol Exp Ther. 2006;317:910–8.
49. Kapur S, Shitij K, Philip S. Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics?: a new hypothesis. Am J Psychiatry. 2001;158:360–9.
50. Ballanger B, Benedicte B, Strafella AP, van Eimeren T, Mateusz Z, Rusjan PM, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. Arch Neurol. 2010. doi:10.1001/archneurol.2010.35.
51. Kluger BM, Karen H, Chou KL, Jau-Shin L, Goetz CG, Lang AE, et al. Parkinson's disease-related fatigue: a case definition and recommendations for clinical research. Mov Disord. 2016;31:625–31.
52. Herlofson K, Larsen JP. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand. 2003;107:1–6.
53. Gołąb-Janowska M, Monika G-J, Dariusz K, Krzysztof S, Agnieszka M, Anna B, et al. Risk factors of fatigue in idiopathic Parkinson's disease in a Polish population. Parkinsons Dis. 2016;2016:1–8.
54. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. Mov Disord. 2001;16:190–6.
55. Smith KM, Eyal E, Weintraub D, Investigators ADAGIO. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. JAMA Neurol. 2015;72:88–95.
56. Stocchi F, The ADAGIO investigators. Benefits of treatment with rasagiline for fatigue symptoms in patients with early Parkinson's disease. Eur J Neurol. 2013;21:357–60.
57. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. Brain. 2010;133:3434–43.
58. Lanciego JL, Luquin N, Obeso JA. Functional neuroanatomy of the basal ganglia. Cold Spring Harb Perspect Med. 2012. doi:10.1101/cshperspect.a009621.
59. Grady MM, Stahl SM. Practical guide for prescribing MAOIs: debunking myths and removing barriers. CNS Spectr. 2012;17:2–10.
60. Abe K, Kazuo A, Masashi F, Hiroo Y. Effectiveness of istradefylline for fatigue and quality of life in Parkinson's disease patients' and of their caregivers'. Adv Parkinson's Disease. 2016;05:24–8.
61. Dungo R, Deeks ED. Istradefylline: first global approval. Drugs. 2013;73:875–82.
62. Saki M, Yamada K, Koshimura E, Sasaki K, Kanda T. In vitro pharmacological profile of the A2A receptor antagonist istradefylline. Naunyn Schmiedebergs Arch Pharmacol. 2013;386:963–72.
63. Lazarus M, Shen H-Y, Cherasse Y, et al. Arousal effect of caffeine depends on adenosine A2A receptors in the shell of the nucleus accumbens. J Neurosci. 2011;31:10067–75.
64. Bokobza B, Ruberg M, Scatton B, Javoy-Agid F, Agid Y. [3H]spiperone binding, dopamine and HVA concentrations in Parkinson's disease and supranuclear palsy. Eur J Pharmacol. 1984;99:167–75.
65. Zheng X, Hasegawa H. Administration of caffeine inhibited adenosine receptor agonist-induced decreases in motor performance, thermoregulation, and brain neurotransmitter release in exercising rats. Pharmacol, Biochem Behav. 2016;140:82–9.
66. Atack JR, Shook BC, Rassnick S, et al. JNJ-40255293, a novel adenosine A2A/A1 antagonist with efficacy in preclinical models of Parkinson's disease. ACS Chem Neurosci. 2014;5:1005–19.
67. Xu K, Di Luca DG, Orrú M, Xu Y, Chen J-F, Schwarzschild MA. Neuroprotection by caffeine in the MPTP model of Parkinson's disease and its dependence on adenosine A2A receptors. Neuroscience. 2016;322:129–37.
68. Skorvanek M, Rosenberger J, Gdovinova Z, Nagyova I, Saeedian RG, Groothoff JW, et al. Apathy in elderly nondemented patients with Parkinson's disease: clinical determinants and relationship to quality of life. J Geriatr Psychiatry Neurol. 2013;26:237–43.
69. Ziropadja L, Lj Z, Stefanova E, Petrovic M, Stojkovic T, Kostic VS. Apathy and depression in Parkinson's disease: the Belgrade PD study report. Parkinsonism Relat Disord. 2012;18:339–42.
70. Dujardin K, Langlois C, Plomhause L, Carette A-S, Delliaux M, Duhamel A, et al. Apathy in untreated early-stage Parkinson

disease: relationship with other non-motor symptoms. Mov Disord. 2014;29:1796–801.
71. Drui G, Carnicella S, Carcenac C, Favier M, Bertrand A, Boulet S, et al. Loss of dopaminergic nigrostriatal neurons accounts for the motivational and affective deficits in Parkinson's disease. Mol Psychiatry. 2013;19:358–67.
72. Thobois S, Lhommée E, Klinger H, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain. 2013;136:1568–77.
73. Ray Chaudhuri K, Martinez-Martin P, Antonini A, Brown RG, Friedman JH, Onofrj M, et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. Parkinsonism Relat Disord. 2013;19:660–5.
74. Hauser RA, Jaroslaw S, Paolo B, Elisabeth D, Erwin S, Mahnaz A, et al. Evaluation of rotigotine transdermal patch for the treatment of apathy and motor symptoms in Parkinson's disease. BMC Neurol. 2016. doi:10.1186/s12883-016-0610-7.
75. Favier M, Mathieu F, Theo D, Carole C, Guillaume D, Marc S, et al. Pramipexole reverses Parkinson's disease-related motivational deficits in rats. Mov Disord. 2014;29:912–20.
76. Pérez-Pérez J, Jesús P-P, Javier P, Saül M-H, Ramón F-B, Salvador S, et al. Head-to-head comparison of the neuropsychiatric effect of dopamine agonists in Parkinson's disease: a prospective, cross-sectional study in non-demented patients. Drugs Aging. 2015;32:401–7.
77. Nagaraja D, Jayashree S. Randomized study of the dopamine receptor agonist piribedil in the treatment of mild cognitive impairment. Am J Psychiatry. 2001;158:1517–9.
78. Millan MJ. From the cell to the clinic: a comparative review of the partial D2/D3 receptor agonist and α2-adrenoceptor antagonist, piribedil, in the treatment of Parkinson's disease. Pharmacol Ther. 2010;128:229–73.
79. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain. 2005;128:1314–22.
80. Dujardin K, Sockeel P, Delliaux M, Destée A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinson's disease. Mov Disord. 2009;24:2391–7.
81. Perry EK, Curtis M, Dick DJ, Candy JM, Atack JR, Bloxham CA, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1985;48:413–21.
82. Cachope R, Mateo Y, Mathur BN, Irving J, Wang H-L, Morales M, et al. Selective activation of cholinergic interneurons enhances accumbal phasic dopamine release: setting the tone for reward processing. Cell Rep. 2012;2:33–41.
83. Devos D, Moreau C, Maltête D, et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. J Neurol Neurosurg Psychiatry. 2014;85:668–74.
84. Reijnders JSAM, Uwe E, Weber WEJ, Dag A, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2007;23:183–9.
85. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. J Geriatr Psychiatry Neurol. 2003;16:178–83.
86. Daley DJ, Myint PK, Gray RJ, Deane KHO. Systematic review on factors associated with medication non-adherence in Parkinson's disease. Parkinsonism Relat Disord. 2012;18:1053–61.
87. Grosset KA, Bone I, Grosset DG. Suboptimal medication adherence in Parkinson's disease. Mov Disord. 2005;20:1502–7.
88. Rektorova I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol. 2003;10:399–406.
89. Barone P, Santangelo G, Morgante L, et al. A randomized clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients. Eur J Neurol. 2015;22:1184–91.
90. Richard IH, Kurlan R, Parkinson Study Group. A survey of antidepressant drug use in Parkinson's disease. Neurology. 1997;49:1168–70.
91. Liu J, Dong J, Wang L, Su Y, Yan P, Sun S. Comparative efficacy and acceptability of antidepressants in Parkinson's disease: a network meta-analysis. PLoS One. 2013;8, e76651.
92. Troeung L, Lakkhina T, Egan SJ, Natalie G. A meta-analysis of randomised placebo-controlled treatment trials for depression and anxiety in Parkinson's disease. PLoS One. 2013;8, e79510.
93. Bomasang-Layno E, Emily B-L, Iris F, Murray AN, Seth H. Antidepressive treatments for Parkinson's disease: a systematic review and meta-analysis. Am J Geriatr Psychiatry. 2016;24:S102–3.
94. Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology. 2012;78:1229–36.
95. Moonen AJH, Wijers A, Leentjens AFG, et al. Severity of depression and anxiety are predictors of response to antidepressant treatment in Parkinson's disease. Parkinsonism Relat Disord. 2014;20:644–6.
96. Broen MPG, Leentjens AFG, Köhler S, Kuijf ML, McDonald WM, Richard IH. Trajectories of recovery in depressed Parkinson's disease patients treated with paroxetine or venlafaxine. Parkinsonism Relat Disord. 2016;23:80–5.
97. Eyding D, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010;341:c4737.
98. Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology. 2010;75:448–55.
99. Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disord. 2016;22 Suppl 1:S41–6.
100. Noyes K, Liu H, Li Y, Holloway R, Dick AW. Economic burden associated with Parkinson's disease on elderly Medicare beneficiaries. Mov Disord. 2006;21:362–72.