International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Non-Motor Symptoms of Parkinson's Disease

Klaus Seppi MD,[1] Lana Chahine MD,[2] K. Ray Chaudhuri MD,[3] Miguel Coelho MD,[1] Beatrice Heim MD,[1] Eva-Maria Hametner MD,[1] Atbin Djamshidian-Tehrani MD,[1] Regina Katzenschlager MD,[4] Shen-Yang Lim MD, FRACP,[5] Santiago Perez Lloret MD,[6] Cristina Sampaio MD, PhD,[7] Susan H. Fox MRCP (UK), PhD,[8] Daniel Weintraub MD,[9, 10] on behalf of the MDS EBM Committee

1. Department of Neurology, Medical University Innsbruck, Anichstrasse 35, AT-6020 Innsbruck, Austria

2 Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA

3 Institute of Psychiatry, Psychology & Neuroscience at King's College and Parkinson Foundation International Centre of Excellence at King's College Hospital, Denmark Hill, London, United Kingdom.

4. Department of Neurology and Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders, Danube Hospital, Vienna, Austria

5. Division of Neurology and the Mah Pooi Soo & Tan Chin Nam Centre for Parkinson's & Related Disorders, University of Malaya, Kuala Lumpur, Malaysia

6. Institute of Cardiology Research, University of Buenos Aires, National Research Council (CONICET-ININCA), Buenos Aires, Argentina.

7. CHDI Management/CHDI Foundation, USA and Instituto de Medicina Molecular, University of Lisbon, Portugal

8. Edmund J Safra Program, Movement Disorder Clinic, Toronto Western Hospital, and the University of Toronto Department of Medicine, Toronto, Ontario, Canada

9. Departments of Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

10. Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA

Corresponding author: **Klaus Seppi,** Department of Neurology, Medical University Innsbruck, Anichstrasse 35, AT-6020 Innsbruck, Austria

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Abstract

Objective: To update evidence-based medicine (EBM) recommendations for treating non-motor symptoms in Parkinson's disease (PD).

Background: The International Parkinson and Movement Disorder Society (MDS) EBM Committee recommendations for treatments of PD were first published in 2002, updated in 2011, and now updated again through December 31st, 2016.

Methods: Level I studies testing pharmacological, surgical, or non-pharmacological interventions for the treatment of non-motor symptoms in PD were reviewed. Criteria for inclusion and quality scoring were as previously reported. Disorders covered were a range of neuropsychiatric symptoms, autonomic dysfunction, disorders of sleep and wakefulness, pain, fatigue, impaired olfaction, ophthalmologic dysfunction, and global non-motor symptoms. Clinical efficacy, implications for clinical practice, and safety conclusions are reported.

Results: Thirty-eight new studies qualified for review. There were no randomized controlled trials that met inclusion criteria for the treatment of anxiety disorders, REM sleep behavior disorder, excessive sweating, impaired olfaction, or ophthalmologic dysfunction. We identified clinically useful or possibly useful interventions for the treatment of depression, apathy, impulse control and related disorders, dementia, psychosis, insomnia, daytime sleepiness, drooling, orthostatic hypotension, gastrointestinal dysfunction, urinary dysfunction, erectile dysfunction, fatigue, and pain. There were no clinically useful interventions identified to treat non-dementia level cognitive impairment and global non-motor symptoms.

Conclusions: The options for treating non-motor symptoms in PD continue to expand. The recommendations contained herein help the treating physician to determine which additional interventions are efficacious and clinically useful.

Introduction

The International Parkinson and Movement Disorder Society (MDS) Evidence-Based Medicine (EBM) Committee regularly publishes recommendations on treating Parkinson's disease (PD) non-motor symptoms (NMS). An increasing number of studies have been published since the previous review, here we review these studies and present our conclusions.

Methods

The previous MDS EBM reviews on treatments for NMS of PD reviewed studies from January 2004 to December 2010. We have continued the process and included new studies published up to December 31st, 2016. If new interventions not reviewed in prior EBM publications were identified, further searches were made retrospectively to include all appropriate studies.[1]

The methodology used was the same as in prior reports:[2-4] we performed literature searches using electronic databases (Medline, Cochrane Library) and systematic checking of references from review articles and other reports. Inclusion criteria for studies were: pharmacological, surgical, and non-pharmacological interventions to treat NMS in PD, available in at least one country, assessed using level I, randomized controlled trials (RCTs), where NMS were the primary endpoint measured with an established rating scale or well-described outcome. The included studies had to have a minimum of 20 patients who were treated for a minimum of 4 weeks. Each study was rated by at least two committee members using the Rating Scale for Quality of Evidence[5] that assigns a percentage rating to the study based on the number of applicable quality criteria fulfilled. Thus, for a study to be designated high quality, it must achieve a quality score of 75% or greater. Each intervention was then assigned an efficacy conclusion—efficacious, likely efficacious, unlikely efficacious, non-efficacious, or insufficient evidence—according to the level of evidence (Supplementary Table e1). Safety was assessed and assigned as one of the following: acceptable risk with no specialized monitoring, acceptable risk with specialized monitoring, unacceptable risk, or insufficient evidence. The overall implications for clinical practice were then assessed and classed as clinically useful, possibly useful, unlikely useful, not useful, or investigational. In several instances, NMS treatment efficacy conclusions based on RCTs in PD remain inconclusive for agents with proven efficacy in the same condition outside of PD. We decided, therefore, since the last EBM review in 2011, to categorize those interventions where a signal of efficacy in PD is extrapolated by proven efficacy and license outside of PD

as also being possibly useful for PD patients. Indeed, the definition of the implications for clinical practice allows such a procedure.

In this article, we use the terms negative and positive when referring to adequately powered trials designed to test a well-specified statistical hypothesis; we understand "positive" to signify a trial where the primary endpoint was met at the defined level of significance and "negative" to signify a trial that failed to meet the predefined primary endpoint. Each intervention was considered for the indications as outlined in table 1.

Results and conclusions

There were no RCTs that met inclusion criteria for the treatment of anxiety disorders, RBD, excessive sweating, olfactory or ophthalmologic dysfunction. For the treatment of NMS, 38 new studies[1, 6-42] qualified for review; the updated conclusions, according to indication, are presented in Tables 2–12. In all tables, interventions where new studies have been published since January 2011 or prior to this date in the case of newly identified interventions not previously reviewed, are indicated in bold, and changes in conclusions are italicized. We did not include trials that did not fulfill the inclusion criteria for review[38, 43-57] and where NMS were not an inclusion criterion, i.e. where NMS did not represent a PD-specific indication.[58-78] Unless otherwise specified, safety conclusions are "acceptable risk without specialized monitoring".

With the exception of one low-quality safety study, which lasted 76 weeks,[31] all the studies included in this review had a duration of 6 months maximum. Therefore, these recommendations do not refer to the long-term management of a given NMS in PD. Study descriptions and quality scores appear in supplementary Table e2.

1. Treatment of depression in PD—Summary and practice implications

New conclusions

A total of 6 new studies were evaluated.[8, 9, 14-17] We did not include trials that did not fulfill the inclusion criteria for review[43, 44, 55] and where depression was not an inclusion criterion.[58, 59, 61, 77] Recommendations for the treatment of depression in PD are summarized in Table 2.

Tricyclic antidepressants (TCAs)

There is "*insufficient evidence"* to make any conclusion on the efficacy of **amitriptyline** for the treatment of depression in PD.[4] Similar significant benefits were reported in the amitriptyline and sertraline arms in an open-label randomized trial, which did not include a placebo arm.[4] Moreover, a recent review on the use of antidepressants for the treatment of major depressive disorder in adults[79] concluded, based on data from head-to-head studies, that amitriptyline was more effective than other antidepressants. The practice implications have been changed so that treatment of depression with TCAs is now considered "*possibly useful"*.[79]

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs)

Venlafaxine and **paroxetine** were compared with placebo for the treatment of depression in PD. Both active groups were effective in one high-quality trial;[8] the practice implications are that **venlafaxine** is "*clinically useful"* for the treatment of depressive symptoms in PD. Due to conflicting efficacy data of paroxetine for the treatment of depression in PD,[80] there is still "*insufficient evidence"* for **paroxetine**, as for all SSRIs reviewed. All practice implications have been changed: although studies on the efficacy of **citalopram**, **paroxetine**, and **sertraline** for the treatment of PD depression report conflicting data for efficacy,[4] and although there were no placebo arms in the studies on **fluoxetine** for the treatment of PD depression,[4] the practice implications for these SSRIs is that they are "*possibly useful"* due to the established efficacy and license of SSRIs in depression outside PD.[79] Moreover, some significant benefits were reported in the active arms in the trials performed for depression in PD. [4] SSRIs, when studied in psychiatric populations, have been found to exhibit an improved safety profile over TCAs with lower incidences of anticholinergic side effects or cardiac arrhythmias. SSRIs may worsen PD tremor in up to 5% of patients and occasionally worsen parkinsonism.[4]

Dopamine agonists

Rotigotine has been evaluated in one new study[17] with negative outcomes with some effects on the primary efficacy analysis in *post hoc* analyses; the efficacy conclusion is "*unlikely efficacious"* and the practice implication is "*investigational"* for the treatment of depression in PD.

MAO-B Inhibitors

Rasagiline has been evaluated in one new study;[14] the efficacy conclusion is "*insufficient evidence",* and as there were significant benefits over the short-term, the practice implication is "*investigational*".

Non-pharmacological interventions

Repetitive transcranial stimulation (rTMS)

rTMS was evaluated in two new high-quality studies for the treatment of depression in PD, which were discrepant regarding depression outcome.[15, 16] Therefore, there is insufficient evidence for rTMS to be rated for the treatment of depression in PD. There is growing evidence that rTMS is efficacious for the treatment of depression in the general population,[81, 82] and it was approved by the Food and Drug Administration (FDA) in 2008 for the treatment of major depressive disorder. Moreover, some beneficial effects on depression outcome measures have been reported in PD patients.[4, 16] Therefore, the practice implication is "*possibly useful"*, although it should be kept in mind that the treatment effect is short-term, and treatment would need to be repeated at regular intervals.

Cognitive-behavioral therapy (CBT)

CBT[9] was evaluated in one high-quality positive study. All studies in this field, however, suffer an unavoidable risk of bias because double-blinding is not possible, and so replication of these efficacy results is required. Therefore, CBT can only be rated "*likely efficacious"* for the treatment of depression in PD, and the practice implication is "*possibly useful"*. In general, reporting of AEs in CBT trials is limited (table 2).[83, 84] Therefore, there is "*insufficient evidence"* to conclude on the safety of CBT in PD patients with depression.

2. Treatment of apathy in PD—Summary and practice implications

New conclusions

Three studies[19-21] were evaluated. We did not include a trial where apathy was not an inclusion criterion.[61] Recommendations for the treatment of apathy in PD are summarized in Table 3.

Acetylcholinesterase Inhibitors

Rivastigmine[19] was evaluated in one positive small-sized high-quality study. The efficacy conclusion is "*efficacious"* for the treatment of apathy in PD. Due to the small sample size, the practice implication is "*possibly useful"*.

Dopamine agonists

Piribedil was evaluated in one positive small-sized high-quality study[20] in PD patients following subthalamic nucleus (STN) deep brain stimulation (DBS) stimulation and initial withdrawal of dopamine agonist treatment, the efficacy conclusions is "*likely efficacious"* for the treatment of apathy in PD following STN stimulation with a practice implication of "*possibly useful"*.

One high quality trial on **rotigotine** had negative outcomes with some effects on *post hoc* analyses,[21] and thus the efficacy conclusion is "*unlikely efficacious"* and the practice implication "*investigational"*.

3. Treatment of impulse control and related disorders in PD summary and practice implications

New conclusions

Two new studies[7, 30] were evaluated. We did not include trials that did not fulfill the inclusion criteria for review.[45] Recommendations for the treatment of impulse control and related disorders (ICRDs) in PD are summarized in Table 4.

Opioid antagonists

A new negative high-quality study evaluated **naltrexone**.[7] As there were significant benefits in the active arm, there is "*insufficient evidence"* to conclude on the efficacy of naltrexone for the treatment of impulse control disorders (ICDs), the practice implication is "*investigational"*, and "*insufficient evidence"* to make any conclusions on its safety.

Cognitive-behavioral therapy (CBT)

CBT was evaluated in one low-quality positive study,[30] the efficacy conclusion is "*likely efficacious"* and the practice implication is "*possibly useful"* for the treatment of ICDs in PD. There is "*insufficient evidence"* on the safety of CBT in PD patients with ICDs (see above).

4. Treatment of dementia in PD—Summary and practice implications

New conclusions

One new study[12] fulfilled the inclusion criteria for review. In addition, one new open-label, randomized study evaluated the long-term safety of rivastigmine capsules versus patches in PD dementia.[31] Recommendations for the treatment of dementia in PD are summarized in Table 5.

Acetylcholinesterase inhibitors

A high-quality randomized open-label long-term safety study of rivastigmine capsules versus patches in PD dementia reported no new safety concerns. A new high-quality study on the use of donepezil for the treatment of dementia in PD[12] was negative on the co-primary endpoints. Therefore, there is still "insufficient evidence" for the acetylcholinesterase inhibitors donepezil and galantamine for the treatment of dementia in PD. Practice implications have been changed since the previous review. Some significant benefits were reported in the active arms in the trials performed for PD dementia,[4, 12] and a recent meta-analysis including the studies reviewed previously revealed that cholinesterase inhibitors slightly improve global impression and enhance cognitive function.[85] Moreover, due to the established efficacy and license of donepezil and galantamine outside dementia in PD, the practice implications for **donepezil** and **galantamine**, are "*possibly useful*".

5. Treatment of non-dementia cognitive impairment in PD—Summary and practice implications

New conclusions

Five studies[6, 32-35] were published fulfilling the inclusion criteria for review. We did not consider clinical trials where cognitive dysfunction was not an inclusion criterion,[58, 63-71] where cognition was not the primary endpoint,[46, 48] or which were *post hoc* analyses.[47] Recommendations for the treatment of non-dementia cognitive impairment in PD are summarized in Table 6.

Acetylcholinesterase inhibitors

Based on a high-quality negative study[35] with some trend effects and significant benefits in the rivastigmine arm compared to the placebo arm, and the lack of other RCTs, there is "*insufficient evidence"* to conclude on the efficacy of **rivastigmine** for the treatment of cognitive impairment in PD, practice implications are "*investigational*".

MAOB-inhibitors

Rasagiline was evaluated in one positive low-quality exploratory study [32] and one negative high-quality study,[6] therefore, there is "*insufficient evidence"* to conclude on the efficacy of rasagiline for the treatment of cognitive impairment in PD and the practice implication is "*investigational*".

Non-pharmacological interventions

Active **transcranial Direct Current Stimulation (t-DCS)** over the left dorsolateral prefrontal cortex versus sham t-DC was evaluated for improving cognitive impairment in PD patients receiving computer-based cognitive training in one low-quality study,[33] and therefore, despite significant effects the efficacy conclusion is "*insufficient evidence*" and the practice implication "*investigational*". No safety data were reported in this study and reports on the use of t-DCS in PD are scarce,[86] there is, therefore, "*insufficient evidence*" to conclude on the safety of t-DCS in PD, even though a recent systematic review[86] found little evidence to suggest that repeated sessions of active t-DCS pose increased risk to participants compared to sham t-DCS within the limits of parameters used to date.

One low-quality exploratory study[34] evaluated **cognitive rehabilitation** for improving cognitive impairment in PD patients receiving computer-based cognitive training; some significant effects were reported. Due to the exploratory character of the study and the small sample size, the efficacy conclusion is "*insufficient evidence*". Due to the limited data available for MCI in PD,[33] the practice implication is "*investigational*". Due to the lack of safety data,[33, 87] there is "*insufficient evidence*" to conclude on the safety of cognitive rehabilitation for cognitive impairment in PD.

6. Treatment of psychosis in PD—Summary and practice implications

New conclusions

Three new studies[1, 27, 36] were evaluated. Trials which did not fulfill the inclusion criteria for review were excluded.[49] Recommendations for the treatment of psychosis in PD are summarized in Table 7. Although there is insufficient evidence for **quetiapine** to be rated for the treatment of psychosis in PD, practice implications have been changed since the previous review.[4] There are no high-quality RCTs available for quetiapine for the treatment of psychosis in PD; quetiapine was similarly efficacious to clozapine in a clozapine-controlled trial that did not include a placebo arm.[4] Therefore, the practice implication is "*possibly useful*" for the treatment of psychosis in PD.

Olanzapine was evaluated in a low□quality negative study,[36] as such the conclusions are "*non-efficacious"* and "*not useful".*

Pimavanserin, a selective serotonin 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic affinity was evaluated in two level I studies.[1, 27] While the larger high-quality study had a positive outcome for antipsychotic efficacy,[27] the smaller low-quality study reported a negative outcome for the primary antipsychotic endpoint,[1] although there were several significant antipsychotic effects in the active arm. Moreover, it was unclear if the primary endpoint was motor safety or antipsychotic efficacy in this study.[1] Indeed, the study was powered for motor function and as such may have been underpowered for antipsychotic efficacy. Therefore, pimavanserin is considered "*efficacious"* over the short-term of 6 weeks for the treatment of psychosis in PD. There is a lack of safety data regarding durability beyond 6 weeks and therefore there is "*insufficient evidence"* to conclude on the safety of pimavanserin for the treatment of PD psychosis (Table 7). The FDA is currently conducting an evaluation of available information about pimavanserin after the publication of reports of post-marketing AEs.[88] Therefore, pimavanserin is considered "*possibly useful"* for the treatment of psychosis in PD.

Generally, all atypical antipsychotics must be used with great caution in demented patients with psychosis due to risk of AEs that include falls, cognitive worsening, pneumonia, cardiovascular effects, stroke, and death.[89]

7. Treatment of disorders of sleep and wakefulness in PD—Summary and practice implications

New conclusions

Three new studies[41, 42, 90] were evaluated. We did not include trials that did not fulfill the inclusion criteria for review[51, 54] and where disorders of sleep and wakefulness were not an inclusion criterion.[76] Recommendations for the treatment of sleep and wakefulness in PD are summarized in Table 8. Although there is "insufficient evidence" for the efficacy of **eszopiclone** and **melatonin** for the treatment of insomnia in PD,[4] practice implications have been changed since the previous review: both eszopiclone and melatonin have been reported to significantly improve clinical measures of insomnia compared to placebo in patients with PD and insomnia.[4] Therefore, the practice implication is "*possibly useful"* for both drugs. Moreover, eszopiclone improves global and sleep outcomes for insomnia disorder in general,[91] while **melatonin** has not only been approved in the European Union (EU) for patients aged 55 or over suffering from primary insomnia, but has been available over-the-counter in the US States since the mid-1990s.

Although there is "insufficient evidence" to conclude on the efficacy of **modafinil** in the treatment of excessive daytime somnolence and sudden onset of sleep in PD,[4] the practice implications for modafinil for the treatment of insomnia have been changed since the previous review [92] with the practice implication "*possibly useful*". Indeed, a recent meta-analysis of three trials evaluating modafinil, which were also included in the previous review, [4] showed a significant reduction in sleepiness, as assessed by the Epworth Sleepiness Scale.[92])

Based on a low-quality positive study,[42] continuous positive airway pressure (CPAP) therapy is considered "*likely efficacious*" and "*possibly useful*" in improving sleep and daytime sleepiness in patients with PD and obstructive sleep apnea (OSA). No safety concerns were identified in this study, and given its wide availability,[93] CPAP therapy is considered safe with an "*acceptable risk without specialized monitoring*".

Caffeine has been evaluated for the treatment of daytime sleepiness in PD in a high-quality negative study.[13] There were some significant effects for caffeine compared to placebo, and as such the efficacy conclusion is "*insufficient evidence*" and the practice implication "*investigational*." Given its wide availability and over-the-counter use in many countries, caffeine can be used with an "*acceptable risk without specialized monitoring*".

Dopamine agonists

Based on a low-quality negative study[41] with some significant benefits in the **piribedil** arm and the lack of further RCTs, there is "*insufficient evidence"* to conclude on the efficacy of piribedil for improving vigilance and cognitive performance in those experiencing EDS while being treated for PD with the oral dopamine agonists pramipexole or ropinirole and who have been switched overnight from their oral dopamine agonists to an equivalent dose of piribedil. The practice implication is "*investigational*." Based on a low-quality positive study, **rotigotine** is "*likely efficacious*" and "*possibly useful*" in improving sleep as it has shown to have significant effects on sleep quality and maintenance in patients with PD.[94]

8. **Treatment of orthostatic hypotension (OH) PD—Summary and practice implications**

New conclusions

Two publications[25, 26] based on data from one trial were evaluated. We did not include trials that did not fulfill the inclusion criteria for review.[57] Recommendations for the treatment of OH in PD are summarized in Table 9. Although there is "insufficient evidence" for the efficacy of midodrine and fludrocortisone for the treatment of OH in PD,[4] practice implications for the treatment of insomnia have changed since the previous review. Midodrine provided significant benefits on measures of OH in RCTs in a mixed population of patients of which only a subgroup had PD[95] and there were also some significant benefits for fludrocortisone.[4] Therefore, the practice implications for both **midodrine** and **fludrocortisone** are "*possibly useful*". Safety conclusions for domperidone have been changed to "*acceptable risk with specialized monitoring*" because domperidone may cause QT prolongation and is associated with increased risk of ventricular tachyarrhythmia and sudden cardiac death (VT/SCD) in PD patients with preexisting cardiac disease.[96]

Droxidopa, a norepinephrine prodrug was evaluated in a high-quality trial, which was originally designed to evaluate the clinical efficacy of droxidopa over an 8-week double-blind period.[25, 26] Because of a pre-planned interim efficacy analysis which did not demonstrate a significant difference across groups in the trial's original primary efficacy measure (i.e., change in OHQ composite score),[25] the original study was stopped for futility and, subsequently, a corresponding change in the trial's primary efficacy measure was undertaken.[26] Based on this trial, droxidopa is considered "*efficacious"* for the short-term treatment of OH in PD, while there is "*insufficient evidence"* to conclude on the efficacy of droxidopa for the treatment of OH in PD beyond 1 week. Practice implications are therefore "*possibly useful*". There were no safety concerns. The RCTs using droxidopa for neurogenic OH were consistent in showing good tolerability of droxidopa.[97] As for midodrine and fludrocortisone, the risk of supine hypertension has to be considered for droxidopa.[98] Therefore, droxidopa is considered to pose an "*acceptable risk without specialized monitoring*" over the short-term, while there is "*insufficient evidence*" to conclude on the safety of droxidopa for the treatment of OH over the long-term.

9. **Treatment of urinary dysfunction in PD—Summary and Practice Implications**

New conclusions

One study[37] was evaluated for the treatment of urinary dysfunction in PD that fulfilled review inclusion criteria. One trial that failed to meet inclusion criteria was excluded.[50] Recommendations for the treatment of urinary dysfunction in PD are summarized in Table 9.

Solifenacin for the treatment of overactive bladder was evaluated in a high-quality negative study.[37] Because there were some significant benefits in the active arm, there is "*insufficient evidence"* to make a conclusion on efficacy. The practice implications for solifenacin for the treatment of overactive bladder is "*possibly useful"* as there were some significant benefits in this trial[37] and due to the established efficacy and license of solifenacin in this indication outside PD.[99, 100] No safety concerns were reported. Systematic reviews reported typical peripheral antimuscarinic AEs in patients treated with solifenacin.[99, 100 101] Due to the data available in the geriatric population, solifenacin is considered to pose an "*acceptable risk without specialized monitoring*".

10. **Treatment of erectile dysfunction in PD—Summary and practice implications**

New conclusions

One study[39] was evaluated for the treatment of erectile dysfunction (ED) in PD fulfilling the inclusion criteria for review. Recommendations for the treatment of ED in PD are summarized in Table 9.

Sildenafil was evaluated in one high-quality positive study,[39] and is considered "*efficacious*" for the treatment of ED in PD and the practice implication is "*clinically useful*." There is a lack of safety data for sildenafil in PD patients. Taking into account the data available in the general population,[102] sildenafil is considered to pose an "*acceptable risk without specialized monitoring*". OH is common in PD and consequences of sildenafil treatment in this population have not been widely explored. Cautious use is advised therefore in parkinsonian patients with OH.

11. **Treatment of drooling in PD—Summary and practice implications**

Results

One study[11] was included for the treatment of drooling in PD. We did not include trials that did not fulfill the inclusion criteria for review.[52, 103] Recommendations for the treatment of sialorrhea in PD are summarized in Table 9.

Botulinum Toxin B (BoNT-B) was evaluated in one high-quality positive study,[11] and conclusions remain "efficacious" and "clinically useful". There were no new safety concerns identified in this study. Generally, BoNT-A and BoNT-B are considered to pose an "acceptable risk with specialized monitoring" of the training of the administration of BoNT-A and BoNT-B: they should be administered by well-trained physicians with access to specialized monitoring techniques.[4]

12. **Treatment of gastrointestinal dysfunction in PD—Summary and practice implications**

New conclusions

Three new studies[10, 38, 40] were included for the treatment of gastrointestinal dysfunction in PD not including trials that did not fulfill the inclusion criteria for review.[53, 56] We excluded a trial that did not meet the inclusion criteria.[104] Recommendations for the treatment of constipation in PD are summarized in Table 9.

Based on a low-quality positive trial,[10] **lubiprostone** is considered "*likely efficacious"* and "*possibly useful"* for the treatment of constipation in PD. There were no safety concerns. There is, however, a lack of safety data of lubiprostone in PD patients, but due to the data available in the general and geriatric population,[105, 106] lubiprostone is considered to pose an "*acceptable risk without specialized monitoring*". Typical AEs of lubiprostone include nausea, diarrhea and dyspnea.[105, 106]

Probiotics and **prebiotic fiber** were evaluated in one high-quality positive study.[40] The new conclusions are "*efficacious*" and "*clinically useful*". There are no safety concerns and given its wide availability and over-the-counter use in many countries, probiotics and prebiotic fiber are considered to pose an "*acceptable risk without specialized monitoring*".

Abdominal massages with lifestyle advice versus lifestyle advice alone were evaluated in one low-quality negative RCT.[38] Because there were significant signals in both arms, the conclusions are "*insufficient evidence*" and "*investigational*". Although abdominal massages should not have AEs,[107] there have been rare reports of potentially fatal complications with abdominal massages for the treatment of constipation in non-PD patients such as volvulus, small bowel intramural hematoma or peripheral embolization.[104, 108, 109] Safety was not assessed in this study, therefore there is "*insufficient evidence"* to conclude on the safety of abdominal massage in PD.

13. Treatment of fatigue in PD—Summary and practice implications

New conclusions

Two studies[22, 23] were evaluated. We did not include trials where fatigue was not an inclusion criterion.[78] Recommendations for the treatment of fatigue in PD are summarized in Table 10.

MAO-B Inhibitors

Rasagiline was evaluated in one positive small-sized low-quality study[22] and is considered "*efficacious*" for the treatment of fatigue in PD. Due to the small sample size, the practice implication is "*possibly useful*".

Non-pharmacological interventions

Acupuncture was evaluated in one negative low-quality study in PD,[23] thus there is "*insufficient evidence"* to conclude on its efficacy in PD. As there were significant benefits in the active arm, the practice implication for acupuncture is "*investigational*". There were no safety concerns in this study and a recent meta-analysis on the effectiveness and safety of acupuncture combined with levodopa and benserazide for the treatment of PD revealed no safety concerns for the use of acupuncture in patients with PD.[110] As such acupuncture is considered to pose an "*acceptable risk without specialized monitoring*".

14. Treatment of pain in PD—Summary and Practice Implications

New conclusions

Two studies [24, 29] were evaluated. Recommendations for the treatment of pain in PD are summarized in Table 11.

Oxycodone-naloxone prolonged release

Based on a high-quality negative trial with some signals in the active arm there is "*insufficient evidence*" to conclude on the efficacy of **oxycodone-naloxone PR**.[24] Because oxycodone/naloxone PR is an approved treatment option to consider in adults with severe chronic pain it is "*possibly useful"* for PD patients with chronic pain.[111, 112] There were no safety concerns in the above study. There is a lack of safety data of oxycodone-naloxone in PD patients, but due to the data available in the general and elderly population,[113] oxycodone-naloxone is considered to pose an "*acceptable risk without specialized monitoring*". Typical AEs of oxycodone-naloxone include dizziness, headache, fatigue, and gastrointestinal tract symptoms such as nausea, vomiting and constipation.[114]

Dopaminergic agents

Based on a high-quality negative trial with some signals in the active arm,[29] the conclusions for **rotigotine** are "*insufficient evidence"* and "*investigational"* for the treatment of pain in PD.

Treatment of non-motor symptoms in PD—Summary and Practice Implications

New conclusions

One study[28] was evaluated for the treatment of NMS in PD. We did not include four trials in which the presence of NMS was not an inclusion criterion.[72-75] Recommendations for the treatment of NMS in PD are summarized in Table 12.

Dopaminergic agents

Based on a high-quality negative trial[28] with some signals in the active arm the conclusions for **rotigotine** are "*insufficient evidence*" and "*investigational"*. There were no safety concerns.

Discussion

The present EBM review summarizes the best available evidence from RCTs published from January 2011 to December 2016. While we have identified a number of efficacious treatments, for many interventions there is insufficient evidence to make adequate conclusions on their efficacy. Indeed, for several indications further RCTs are required. Safety profiles of most of the interventions reviewed in this update are largely based on studies performed in non-PD populations without firm evidence of efficacy from RCTs in the PD population. In the absence of such data there was insufficient evidence to conclude on the safety for many (see Tables 2 to 12) of the interventions reviewed with the exception being the case of sufficient safety data available from geriatric populations, in which cases this was clearly stated.

Although common, NMS of PD are frequently missed or undeclared during routine consultations[115] and well-performed large-scale RCTs for the treatment of the different NMS in PD are lacking. Indeed, only 66 % of the trials included in this EBM review fulfilled criteria to be rated as a high-quality RCT (see supplementary table e2). Moreover, there were no RCTs that met inclusion criteria for the treatment of anxiety disorders, excessive sweating, RBD, and sensory symptoms such as olfactory and ophthalmologic dysfunction.[116, 117 118] Therefore, there is insufficient evidence for the treatment of these indications. EBM conclusions are only one component of the final dataset that clinicians must use in making treatment decisions. The usefulness of all EBM reviews in day-to-day clinical practice requires integration of level I evidence from well-conducted RCTs with a number of other

factors taken into account before deciding on the best therapy required for an individual patient. These factors include economic influences, local availability of the drug/intervention, local drug approval, physicians' individual clinical experience and judgment, and other patient-/medical-related factors such as side effects and tolerability, comorbidities and co-medications as well as patient preferences that all contribute to the final preferred treatment choice. Off-label use of an intervention is also sometimes required in the absence of firm level I evidence for a specific indication when this would benefit the individual patient, but such off-label use is not without its dangers. This is particularly important for the pragmatic treatment of NMS in PD, which become increasingly prevalent and obvious over the course of the illness and are a major determinant of quality of life, progression of overall disability and of nursing home placement in PD.[119]

NMS add to the overall burden of parkinsonian morbidity, especially in advanced stages of the disease. In practice, their management is based on careful assessment of triggering or contributing factors, including a rigorous review of the current antiparkinsonian treatment schedule or polypharmacy with other (e.g., centrally active) drugs. This is especially important for the treatment of cognitive dysfunction and psychosis, disorders of sleep-wake cycle regulation, and autonomic dysfunction.

Dopaminergic replacement therapies may have contrasting effects on NMS: some, including dopamine agonists and rasagiline, are "possibly useful" or "useful" for the treatment of depression, apathy following STN DBS, insomnia and fatigue. Indeed, several RCTs included in this review have studied the efficacy of dopaminergic replacement therapies for NMS.[14 17 20 21 6 32 41 94 22 29 28] In contrast, some NMS such as psychosis, ICRDs, EDS, or constipation can also be worsened or even induced by dopaminergic agents.[120] Therefore adapting the antiparkinsonian drug regime is empirically the first step, if feasible.

The pathophysiology of depression in PD is complex and likely to differ considerably from non-PD patients, reflecting the widespread brainstem and cortical pathology in PD, with the involvement of several neurotransmitters, including dopaminergic, serotonergic and noradrenergic systems.[121] Therefore, treatments used in general psychiatry services may not be as effective in PD.[121] Nevertheless, up to 25% of PD patients are on an antidepressant at any given time, most commonly an SSRI.[122, 123] There is now some evidence for the efficacy of SSRIs for PD depression,[8] as well as for SNRIs,[8] tricylic antidepressants,[80] and dopamine agonists.[124] For non-pharmacological treatments, there is evidence for the efficacy of CBT,[9] and many PD patients with depression may prefer psychotherapy.[125] Although not

specifically a treatment for PD depression, mood generally improves after patients have DBS surgery, perhaps more so for GPi versus STN lead placement.[126]

A variety of anatomical and metabolic abnormalities have been described in PD-related apathy, and dopaminergic and cholinergic denervation are thought to play an important role.[127, 128] Indeed, rivastigmine has been shown to improve apathy in PD and is “possibly useful”,[19] while the evidence is weaker for dopaminergic therapies.[21] [129] On the other hand, for apathy occurring in the context of STN DBS and post-operative withdrawal of PD medications, dopamine agonists can be considered[20] [130] and piribedil is "possibly useful" for this indication.

Two large randomized controlled cholinesterase inhibitor (ChEI) studies in PDD have been published, one a positive study for rivastigmine and the other an equivocal study for donepezil. [4] [12] Although statistically significant, the effects of ChEIs in PD are clinically modest.[131] While rivastigmine is “clinically useful” for the treatment of PDD, the other ChEIs are “possibly useful”. ChEI treatment appears to be overall well-tolerated in PD, outside of nausea and worsening tremor in some patients. On the other hand, the use of memantine is investigational. Regarding management of PD MCI (PD-MCI) or cognitive impairment short of dementia, the evidence is much more limited, for both PD and MCI in the general population with insufficient efficacy evidence for rasagiline and rivastigmine [6, 132] [32] [35] and an unclear role of DBS surgery.[133, 134] There is preliminary evidence that physical[135] and cognitive exercise[136] may be beneficial for cognition in PD, limiting anticholinergic medication use[137] and treating psychiatric conditions might help with cognition long-term, and comorbid vascular diseases (e.g., hypertension and diabetes) may prevent or limit vascular disease-associated cognitive decline.

Dose reductions of antiparkinsonian drugs to a level that will lead to a resolution of psychotic symptoms, while maintaining sufficient symptomatic motor control, is not always feasible and start of antipsychotic therapy becomes necessary.[138] Frequently, the treatment of psychosis in PD will include the addition of an antipsychotic agent.[139] Low-dosage quetiapine, although not formally established as efficacious in RCTs, can be considered a pragmatic first choice due to its improved safety profile compared to clozapine. In countries where pimavanserin is available, this may be preferable for the treatment of psychosis in PD, as it is considered “efficacious” in this instance. Clozapine is another antipsychotic agent with proven efficacy and should be used in all cases that fail following treatment with quetiapine or pimavanserin, but can also be considered a first-line option despite onerous weekly blood count monitoring. On the other hand, pimavanserin is a “relatively” new drug, and as such, there is a lack of

safety data. Indeed, the FDA is currently evaluating the available data on pimavanserin after the publication of reports of post-marketing AEs.[88] All antipsychotics must be used with great caution in demented patients with psychosis due to risk of AEs that include falls, cognitive worsening, pneumonia, cardiovascular effects, stroke, and death.[89] Recently, preliminary research has shown an increased risk or mortality and morbidity with antipsychotic use in PD patients, too, and not specific to dementia.[140, 141] Concerns have been raised recently that pimavanserin may also increase mortality risk in PD, based on clinical trial and post-marketing data.[88] Additional controlled research is needed to determine if antipsychotics do increase mortality risk in PD, and if pimavanserin is similar to other antipsychotics in this regard. Moreover, rivastigmine may be another treatment option for psychotic behavior specifically in patients with PD and dementia, based on a *post hoc* analysis of a large placebo-controlled study of rivastigmine in PD dementia that showed improvement of hallucinations on rivastigmine.[142]

It is critical for PD patients to be monitored closely for the development of ICRDs as part of routine clinical care, which ideally would include caregiver reports, because ICRDs may have potentially devastating psychological, social, legal, and economic consequences, including divorce, bankruptcy, incarceration, and attempted suicide.[143-145] ICRDs have been most closely related to the use of dopamine agonists,[146] therefore, the first step in management is usually to try and reduce the dosage of dopamine agonist therapy; in some cases, total cessation is needed.[143] This, unfortunately, is frequently complicated by the development of a dopamine agonist withdrawal syndrome, despite compensatory increases in levodopa dosage.[147, 148] CBT was shown to be effective in one small study involving cases of moderate severity, and is considered "possibly useful",[30] while other interventions included in this EBM are investigational.[7 4] STN DBS coupled with post-operative reduction of dopaminergic medications may be effective in reducing ICRDs in a substantial proportion of patients,[149, 150] but RCTs are not available.

Chewing gum/or sucking on hard candy might provide some relief in PD patients with drooling, as these may stimulate voluntary swallowing.[151] Botulinum Toxins A and B, which block the release of acetylcholine from nerve endings, have been rated as “clinically useful” on the basis of well-designed RCTs. Special training is needed for performing the injections and ultrasound guidance may reduce the risk of toxin spread to nearby anatomical structures. Both the parotid and submandibular glands should be injected to achieve the best effects.[152] Glycopyrrolate, a muscarinic antagonist, has been considered “possibly useful” for the short-term treatment of drooling.

For the treatment of symptomatic OH, the current drug regimen should be reviewed for possible drug-induced OH. Even when nonpharmacological methods[153 57, 153, 154] are performed properly, many patients still require pharmacological treatment to improve symptomatic OH.[153] Droxidopa is “clinically useful” for the short-term treatment of OH, while no data from RCTs in PD are available for longer treatment times. Although there is insufficient evidence for the efficacy of fludrocortisone and midodrine for the treatment of OH in PD, it is considered to be “possibly useful” because of its proven efficacy outside of PD with some signals of efficacy detected in the PD trials.[4] More recently, the norepinephrine transporter blocker atomoxetine has been shown to increase standing blood pressure and reduce the burden of OH symptoms compared to placebo in mixed cohorts of patients with neurogenic OH.[153]

Before attempting any treatment for lower urinary tract symptoms, urinary tract infections should be ruled out. Solifenacin, a type 3 muscarinic receptor antagonist, is considered “possibly useful” in PD, while there are no level I data available in PD patients for other muscarinic receptor antagonists or the selective β3-adrenoceptor agonist mirabegron.

Management of ED in men with PD should first exclude alternative underlying causes such as drug side effects, depression, prostate disorders, or diabetes. When drug treatment is indicated for ED in men with PD, the oral phosphodiesterase-5 (PDE-5) inhibitor sildenafil is “clinically useful”. Other PDE-5 inhibitors have not been tested in PD with RCTs. Open-label reports have claimed efficacy of the dopamine agonist s.c. apomorphine for ED in patients with PD,[155] and although RCTs with sublingual apomorphine have shown efficacy in non-parkinsonian patients with ED, RCTs for apomorphine for the treatment of ED in PD are lacking.

Regarding gastrointestinal dysfunction, the EBM review covers anorexia, nausea, and vomiting associated with dopaminergic therapy such as levodopa and/or dopamine agonist treatment, as well as constipation.[4, 95] The dopamine D2 receptor blocking agent domperidone remains “possibly useful” in this indication, although safety conclusions have been changed to “acceptable risk with specialized monitoring” because domperidone may cause potentially life-threatening ECG changes.[96] An alternative could be the use of trimethobenzamide, another dopamine D2 receptor blocker, which seems to reduce nausea/vomiting during the first 8 weeks of apomorphine therapy.[56] There is a lack of level I evidence to conclude on the efficacy of serotonin 5-HT(3) antagonistic antiemetic drugs in reducing nausea/vomiting associated with dopaminergic therapy.[156] Chronic constipation is usually difficult to treat[4, 157] and lifestyle measures, such as increasing fiber and fluid intake, should always be recommended. The use of probiotics and prebiotic fibers are “clinically

useful" for the treatment of constipation in PD. Laxatives are another cornerstone of pharmacological treatment. Polyethylene glycol, also known as Macrogol, an osmotic agent that causes water to be retained with the stools, has been rated as "possibly useful" in PD. Lubiprostone, an intestinal chloride secretagogue, which has also been rated "possibly useful" in PD, should be reserved for unresponsive patients.

Due to the multiple causative factors involved, the treatment of PD-related sleep problems and daytime somnolence is usually complex. Careful history taking—often including information from a spouse or caregiver—is essential in identifying the most likely and relevant underlying causes. Treatment options include optimizing PD therapies to improve nocturnal symptom control or to reduce daytime somnolence, treatment of NMS like nocturia, depression or mental dysfunction, and counseling about sleep hygiene, as well as the addition of sleep or wakefulness promoting drugs. Rotigotine is "possibly useful" for the treatment of insomnia in PD, as are eszopiclone and melatonin. Suspicion of co-morbid sleep-disordered breathing requires polysomnographic verification to decide on the need for CPAP therapy, which is "possibly useful" in improving sleep and daytime sleepiness in patients with PD and OSA. Before initiating pharmacotherapy for RBD, potential aggravators should be identified and, if possible, removed. In PD, the most common of these are TCAs and SSRIs.[158, 159] Treatment options of RBD include clonazepam or melatonin, or a combination of these, although there are no RCTs available for the treatment of RBD in PD.[159] A small controlled crossover trial reported a decreased number of RBD episodes as monitored by diaries of bed partners with rivastigmine patch compared to placebo,[51] but this study was not included in this review as it did not fulfill the inclusion criteria. New onset EDS or sudden onset of sleep following changes in dopaminergic drug type and dose should raise a suspicion of drug-induced EDS leading to trials of dose reduction or other medication changes. If EDS appears to be caused by insomnia due to PD or co-morbid conditions like sleep apnea or depression, these should be treated accordingly. If this is not feasible, the addition of a wake-promoting drug like modafinil may be considered, which is "possibly useful". Often, treating EDS in PD will involve combinations of these measures.

Based on two new studies,[24, 29] for the first time level I evidence is available for the management of pain in PD, a key unmet need. Although both studies failed to show efficacy for the primary endpoint, there were signals in secondary and *post hoc* analyses (see supplementary table). Central, musculoskeletal and nocturnal pain may respond to oxycodone–PR although the risks of using an opiate in PD should be considered and patients monitored closely; therefore, the use of oxycodone PR is "possibly useful" for the treatment of pain in PD. In patients with non-motor fluctuations dominated by pain, rotigotine

transdermal patch could be considered, although practice implications are “investigational”. There is a need for level I evidence to determine if strategies of more continuous dopaminergic stimulation including intrajejunal levodopa infusion and subcutaneous apomorphine infusion[160] or DBS,[161] can diminish pain in PD, especially if associated with motor or non-motor fluctuations. There is also a lack of level I evidence on whether other pharmacological approaches, such as the use of antidepressants (tricyclic agents and serotonin-norepinephrine reuptake inhibitors) and anticonvulsants (gabapentin and pregabalin),[162] can reduce pain in patients with PD.

Fatigue is an important specific NMS of PD and can be distinct from EDS as well as depressive state.[163] Management of fatigue is complex and there are only a few studies providing a good quality evidence base. At the current time, therefore, rasagiline (1mg)[22] is “possibly useful” for the management of fatigue in PD when other secondary causes of fatigue have been excluded while the role of acupuncture, methylphenidate and modafinil is “investigational”.

While treatment of motor symptoms as an indication is standard in PD trial methodology, targeting the NMS burden as an indication has rarely been performed in PD despite NMS burden being a key driver of quality of life in PD.[164-166] There are validated screening tools to address NMS in PD in the clinic setting. These include the NMS questionnaire (NMSQuest), the NMS scale (NMSS), and part 1 (Non-Motor Aspects of Experiences of Daily Living; nM-EDL) of the MDS-UPDRS.[4] Having been employed as a secondary outcome in the ADAGIO study, the latter has been shown to be sensitive to change in very early PD.[167] The NMSS has been widely used in several international clinical trials involving intrajejunal levodopa infusion, apomorphine infusion, rotigotine transdermal patch, and DBS as primary or secondary endpoints and has been shown to be sensitive to change across motor disease stages in PD.[28, 160, 168] However, as the NMS of PD include a multitude of clinical systems derived from complex multi-neurotransmitter dysfunction involving not just the dopaminergic pathways, but also cholinergic, noradrenergic and serotonergic pathways in the brain,[165] it is unlikely that NMS as holistic endpoints are feasible. In future, clinical trials in PD should attempt to include a holistic NMS outcome in addition to validated motor and cognitive outcome measures to ensure non-motor benefits are not overlooked.

In summary, while RCTs in PD have increasingly involved NMS since the previous update of the MDS EBM Review, many non-motor areas still lack an adequate evidence base of high-

quality studies. The MDS is committed to an ongoing process of updating EBM reviews and to making them current and useful to clinicians. Systematic reviews have become a cornerstone of evidence-based healthcare, but approximately half are out of date after five years.[169] In addition, the methodology that has been standard for years has limitations (e.g., with respect to the lack of strict definitions for implications for clinical practice). Therefore, the MDS is considering changes in methodology, including new assessment tools for grading the evidence,[170, 171] as well as more frequent updates, in order to provide clinicians and investigators with an up-to-date evidence base for their treatment decision-making.

Authors' roles
1) Research project: A. Conception, B. Organization, C. Execution;
2) Manuscript: A. Writing of the first draft, B. Review and Critique

Klaus Seppi (1) A,B,C (2) A, B

Lana Chahine (1) A,B,C (2) B

K. Ray Chaudhuri (1) A,B,C (2) B

Miguel Coelho (1) A,B,C (2) B

Beatrice Heim (1) A,B,C (2) B

Eva-Maria Hametner (1) A,B,C (2) B

Atbin Djamshidian-Tehrani (1) A,B,C (2) B

Regina Katzenschlager (1) A,B,C (2) B

Shen-Yang Lim (1) A,B,C (2) B

Santiago Perez Lloret (1) A,B,C (2) B

Cristina Sampaio (1) A,B,C (2) B

Susan H. Fox (1) A,B,C (2) B

Daniel Weintraub (1) A,B,C (2) B

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Daniel Weintraub

Tables

Table 1: Indications of non-motor symptoms covered by this review

- Neuropsychiatric symptoms:
  - Depression and depressive symptoms
  - Anxiety and anxiety symptoms
  - Apathy
  - Psychosis
  - Impulse control and related disorders
  - Dementia
  - Cognitive impairment (other than dementia; mainly mild cognitive impairment [MCI])
- Autonomic dysfunction
  - Drooling
  - Orthostatic hypotension
  - Urinary dysfunction
  - Erectile dysfunction
  - Gastrointestinal dysfunction
  - Excessive sweating
- Disorders of sleep and wakefulness
  - Sleep fragmentation and insomnia
  - Rapid eye movement sleep behavior disorder (RBD)
  - Excessive daytime sleepiness (EDS)
- Others
  - Pain
  - Fatigue
  - Olfactory dysfunction
  - Ophthalmologic dysfunction
  - Non-motor symptoms (as an indication)

Table 2: Interventions to treat depression including depressive symptoms in PD

INTERVENTION		EFFICACY	PRACTICE IMPLICATIONS	SAFETY
DRUG CLASS	**DRUG**			
DOPAMINE AGONISTS	Pramipexole	Efficacious	Clinically useful	Acceptable risk without specialized monitoring
	Pergolide	Insufficient evidence	Not useful	Acceptable risk with specialized monitoring
	Rotigotine	*Unlikely efficacious*	*Investigational*	Acceptable risk without specialized monitoring
MAO-B inhibitors	***Rasagiline***	*Insufficient evidence*	*Investigational*	Acceptable risk without specialized monitoring
	Selegeline	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Moclobemide	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring [1]

TRICYCLIC ANTIDEPRESSANTS (TCA)	Nortriptyline	Likely efficacious	Possibly useful	Acceptable risk without specialized monitoring [3]
	Desipramine	Likely efficacious	Possibly useful	Acceptable risk without specialized monitoring [3]
	Amitriptyline	Insufficient evidence	*Possibly useful* [2]	Acceptable risk without specialized monitoring [3]
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)/ SELECTIVE SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS	Citalopram	Insufficient evidence	*Possibly useful* [4]	Acceptable risk without specialized monitoring [5]
	Sertraline	Insufficient evidence	*Possibly useful* [4]	Acceptable risk without specialized monitoring [5]
	Paroxetine	insufficient evidence	*Possibly useful* [4]	Acceptable risk without specialized monitoring [5]
	Fluoxetine	Insufficient evidence	*Possibly useful* [2]	Acceptable risk without specialized monitoring [5]
	Venlafaxine	*Efficacious*	*Clinically useful*	Acceptable risk without specialized monitoring [5]

OTHER ANTIDEPRESSANTS	Atomoxetine	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Nefazodone	Insufficient evidence	Not useful	Unacceptable risk
ALTERNATIVE THERAPIES	Ω-3 fatty acids	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
NON-PHARMACOLOGICAL INTERVENTIONS	***rTMS***	*Insufficient evidence*	*Possibly useful (short-term)*	Acceptable risk without specialized monitoring[6]
	CBT	*Likely efficacious*	*Possibly useful*	*Insufficient evidence* [7]

[1] Combined treatment with either TCAs or SSRIs carries an unacceptable risk.

[2] Although RCTs did not contain a placebo arm, the practice implication is ""possibly useful" due to proven antidepressant efficacy and license outside of PD.

[3] Typical antimuscarinic adverse events (AEs) have to be considered, such as dry mouth, constipation, urinary retention, and hyperhidrosis. Moreover, concomitant treatment of PD patients with TCAs can contribute to psychosis, sedation, and daytime sleepiness, as well as to cognitive dysfunction or delirium when used in patients with PD dementia.[4] The risk of mortality has to be considered if overdosing occurs. TCAs should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, cardiovascular disorders and cognitive dysfunction

[4] Although RCTs for PD depression report conflicting data for efficacy, the practice implication is "possibly useful" due to proven antidepressant efficacy and license outside of PD.

[5] There are concerns about the induction of the serotonin syndrome when used in conjunction with the MAO-B inhibitors selegiline and rasagiline.[4] Hyponatremia may be associated with SSRI use, especially in elderly people with low body weight and concomitant use of diuretics, thought to be secondary to the development of the syndrome of inappropriate antidiuretic hormone (SIADH).[4] Due to the risk of QTc prolongation, regular electrocardiograph (ECG) monitoring is recommended with citalopram when prescribed at a dose >20 mg/day in elderly patients.

[6]

[6] The FDA notes that labeling should include precautions for the use of rTMS devices in the treatment of patients with depressive or related conditions where safety and efficacy have not been established such as in movement disorders.[172]

[7] In general, reporting of AEs in CBT trials is limited;[83, 84] in most behavioral health clinical trials there is a lack of monitoring of AEs, including serious AEs such as suicide attempts, completed suicides, and psychiatric hospitalizations.[84] Temporary increases in anxiety during behavioral health clinical trials are often considered a normal part of therapy and are therefore not documented as possible AEs.[84]

Table 3: Interventions to treat apathy in PD

INTERVENTION		EFFICACY	PRACTICE	SAFETY
DRUG CLASS	**DRUG**			
DOPAMINE AGONISTS	***Piribedil*** [1]	*Likely efficacious*	*Possibly useful*	acceptable risk without specialized monitoring
	Rotigotine	*Unlikely efficacious*	*Investigational*	acceptable risk without specialized monitoring
ACETYLCHOLINESTERASE INHIBITORS	***Rivastigmine***	*Efficacious*	*Possibly useful*	acceptable risk without specialized monitoring [2]

[1] Recommendations apply only for PD patients following STN stimulation

[2] Worsening of tremor may occur in some patients treated with cholinesterase inhibitors. Medical monitoring for cholinergic effects could include blood pressure or ECG monitoring but acetylcholinesterase inhibitors are considered to pose an acceptable risk even without specialized monitoring.[4]

Table 4: Interventions to treat impulse control and related disorders in PD

INTERVENTION		EFFICACY	PRACTICE	SAFETY
DRUG CLASS	**DRUG**			
NMDA ANTAGONISTS	**Amantadine** [1]	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
ANTI-OPIOIDS	***Naltrexone*** [2]	*Insufficient evidence*	*Investigational*	*Insufficient evidence*
NON-PHARMACOLOGICAL INTERVENTIONS	***CBT*** [2]	*Likely efficacious*	*Possibly useful*	*Insufficient evidence* [3]

[1] Recommendations apply for PD patients with pathological gambling
[2] Recommendations apply for PD patients with ICDs
[3] See table 2

Table 5: Interventions to treat dementia in PD

DRUG CLASS	DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
ACETYLCHOLINESTERASE INHIBITORS	***Donepezil***	Insufficient evidence	*Possibly useful*[1]	Acceptable risk without specialized monitoring [3]
	Rivastigmine	Efficacious	Clinically useful	Acceptable risk without specialized monitoring [3]
	Galantamine	Insufficient evidence	*Possibly useful*[2]	Acceptable risk without specialized monitoring [3]
NMDA ANTAGONISTS	**MEMANTINE**	Insufficient evidence	*Investigational*	Acceptable risk without specialized monitoring

[1] Refers to donepezil 10mg; although RCTs to treat dementia in PD with donepezil report conflicting data for efficacy, the practice implication for donepezil is "possibly useful" due to the proven antidementive efficacy and license outside of PD.

[2] Although there is "insufficient evidence" for galantamine to be rated for the treatment of dementia in PD, the practice implication is "possibly useful" due to the proven antidementive efficacy and license outside of PD. Moreover, there were positive signals in favor for galantamine in the trial performed for PD dementia.

[3] See table 1

Table 6: Drugs to treat non-dementia cognitive impairment in PD

INTERVENTION		EFFICACY	PRACTICE	SAFETY
DRUG CLASS	**DRUG**			
ACETYLCHOLINESTERASE INHIBITORS	***Rivastigmine***	*Insufficient evidence*	*Investigational*	Acceptable risk without specialized monitoring [1]
MAO-B INHIBITORS	***Rasagiline***	*Insufficient evidence*	*Investigational*	Acceptable risk without specialized monitoring
NON-PHARMACOLOGICAL INTERVENTIONS	***t-DCS***	*Insufficient evidence*	*Investigational*	*Insufficient evidence*
	Cognitive rehabilitation	*Insufficient evidence*	*Investigational*	*Insufficient evidence*

[1] See table 3

Table 7: Interventions to treat psychosis in PD

DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY *
CLOZAPINE	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
OLANZAPINE	*Not efficacious*	*Not useful*	Unacceptable risk
QUETIAPINE	Insufficient evidence	Possibly useful [1]	Acceptable risk without specialized monitoring
PIMAVANSERIN	*Efficacious*	*Possibly useful* [2]	*Insufficient evidence* [3]

* The FDA mandates that antipsychotic drug manufacturers add black box warnings to labels and prescribing information because of the link found between antipsychotics and an increased mortality risk in elderly dementia patients.

[1] Although there is insufficient evidence for quetiapine to be rated for the treatment of psychosis in PD, the practice implication is "possibly useful". There are no high-quality RCTs available for the treatment of quetiapine for psychosis in PD and quetiapine was similarly efficacious to clozapine in the clozapine-controlled trials.

[2] Based on information of a *World Report* in the *Lancet*, where it has been stated that pimavanserin succeeded only after three previous trials had failed to demonstrate a benefit.[88]

[3] Due to lack of safety data regarding durability beyond 6 weeks and because the FDA is currently conducting an evaluation of available information about pimavanserin after the publication of reports of post-marketing adverse events.[88] There were more serious AEs in the pimavanserin arm (7.9%) compared to the placebo arm (3.5%), but without a unifying pattern and as such it is difficult to interpret these as drug-related.[27]

Table 8: Drugs to treat disorders of sleep and wakefulness in PD

DISORDERS OF SLEEP AND WAKEFULNESS	DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
DRUG CLASS	**DRUG**			
INSOMNIA				
LEVODOPA	Controlled-release formulation of levodopa/carbidopa	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
DOPAMINE AGONISTS	Pergolide	Insufficient evidence	Not useful	Acceptable risk with specialized monitoring
	Piribedil	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Rotigotine	Likely efficacious	Possibly useful	Acceptable risk without specialized monitoring
HYPNOTICS	Eszopiclone	Insufficient evidence	*Possibly useful*[1]	Acceptable risk without specialized monitoring[1]
MELATONIN	3-5mg	Insufficient evidence	*Possibly useful* [2]	Acceptable risk without specialized monitoring
	50mg	Insufficient evidence	Investigational	Insufficient evidence
NON-PHARMACOLOGICAL	Continuous positive airway pressure	*Likely efficacious*	*Possibly useful*	Acceptable risk without specialized

INTERVENTIONS	(CPAP) [3]			monitoring
EXCESSIVE DAYTIME SOMNOLENCE AND SUDDEN ONSET OF SLEEP				
DRUG CLASS	**DRUG**			
PSYCHOACTIVE DRUGS	Modafinil	Insufficient evidence	*Possibly useful* [4]	Insufficient evidence[5]
	Caffeine	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
NON-PHARMACOLOGICAL INTERVENTIONS	Continuous positive airway pressure (CPAP) [3]	*Likely efficacious*	*Possibly useful*	Acceptable risk without specialized monitoring

[1] Although there is insufficient evidence for eszopiclone to be rated for the treatment of insomnia in PD, it can improve global and sleep outcomes for insomnia disorder, and it can be associated with associated with infrequent but serious harms such as fractures, and major injury.[91] Therefore, the practice implication is suggested to be possibly useful.

[2] Although there is insufficient evidence for melatonin to be rated for the treatment of insomnia in PD, it provided significant benefits on measures of insomnia compared to placebo in patients with PD and insomnia. Moreover, melatonin has not only been approved in the EU for patients aged 55 or over suffering from primary insomnia, but is available over-the-counter in the United States since the mid-1990s. Therefore, the practice implication is "possibly useful".

[3] Recommendations apply for PD patients with obstructive sleep apnea

[4] Modafinil provided significant benefits on measures of excessive daytime somnolence compared to placebo in patients with PD and excessive daytime somnolence[4] and a recent meta-analysis of three trials evaluating modafinil, which were also included in the previous review,[4] showed a significant reduction in sleepiness, as assessed by the Epworth Sleepiness Scale.[92]

[5] Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience. Estimates of the incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years. Psychiatric AEs have been reported in patients treated with modafinil with many, but not all, patients having had a prior psychiatric history; postmarketing AEs associated with the use of modafinil have included mania, delusions, hallucinations, suicidal ideation, and aggression, some resulting in hospitalization.[4]

Table 9: Interventions to treat autonomic dysfunction in PD

	DRUG/ INTERVENTION	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
ORTHOSTATIC HYPOTENSION	Fludrocortisone	Insufficient evidence	*Possibly useful* [1]	Insufficient evidence
	Midodrine	Insufficient evidence	*Possibly useful* [2]	Insufficient evidence
	Domperidone	Insufficient evidence	Investigational	*Acceptable risk with specialized monitoring* [3]
	Yohimbine	Non efficacious	Investigational	Insufficient evidence
	Droxidopa [4]	*Efficacious (short-term)*	*Possibly useful*	*Acceptable risk without specialized monitoring (short-term)* [5]
SEXUAL DYSFUNCTION	***Sildenafil***	*Efficacious*	*Clinically useful*	Acceptable risk without specialized monitoring
CONSTIPATION	Macrogol	Likely efficacious	Possibly useful	Acceptable risk without specialized monitoring
	Lubiprostone	*Likely efficacious*	*Possibly useful*	Acceptable risk without specialized monitoring
	Probiotics and prebiotic fiber	*Efficacious*	*Clinically useful*	Acceptable risk without specialized monitoring
	Abdominal massages	*Insufficient evidence*	*Investigational*	*Insufficient evidence*
ANOREXIA, NAUSEA AND VOMITING ASSOCIATED WITH LEVODOPA	Domperiodone	Likely efficacious	Possibly useful	*Acceptable risk with specialized monitoring*[3]

AND/OR DOPAMINE AGONIST TREATMENT				
DROOLING	Ipratropium Bromide Spray	Insufficient evidence	Investigational	Insufficient evidence
	Glycopyrrolate	Efficacious	Possibly useful	Insufficient evidence
	Botulinum Toxin B	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
	Botulinum Toxin A	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
URINARY FREQUENCY, URGENCY, AND/OR URGE INCONTINENCE	***Solifenacin***[6]	*Insufficient evidence*	*Possibly useful* [7]	Acceptable risk without specialized monitoring [8]

[1] Although there is insufficient evidence for fludrocortisone to be rated for the treatment of OH in PD, it provided some significant benefits in one RCT.[4] Therefore, the practice implication is "possibly useful".

[2] Although there is insufficient evidence for midodrine to be rated for the treatment of OH in PD, it provided some significant benefits on measures of OH in RCTs in mixed population of patients of which only a subgroup had PD.[95] Therefore, the practice implication is "possibly useful".

[3] Due to the risk of QT prolongation and the association with ventricular tachyarrhythmia /sudden cardiac death in PD patients with preexisting cardiac disease.[96]

[4] Recommendations are for the very short-term treatment of OH in PD, while there is insufficient evidence to conclude on the efficacy and safety of droxidopa for the treatment of OH in PD for the long-term.

[5] A recent systematic review evaluated the cardiovascular safety of droxidopa in patients with symptomatic neurogenic OH who participated in RCTs (short-term RCTs: 1 to 2 weeks, n=444; intermediate RCTs: 8 to 10-weeks, n=222) and long-term open-label studies (n=422).[97] Adjusting for exposure time, cardiovascular AEs rates were 0.30 events/patient-year in the short- and intermediate-term studies, and 0.15 events/patient-year in the long-term open-label studies, and most evident in patients with preexisting cardiac disorders. Moreover, the risk for supine hypertension has to be considered. Indeed, in the post-marketing surveillance, one case with intracranial hemorrhages has been reported.[98]

[6] for the treatment of overactive bladder

[7] There were some significant benefits in the active arm and as such the practice implications for solifenacin for the treatment of overactive bladder is “possibly useful” due to the established efficacy and license of solifenacin in this indication outside PD.

[8] A systematic review including 4,188 subjects (3 952 subjects in placebo-controlled trials; 650 of them randomized to solifenacin) aged 65 or older randomized to antimuscarinic medications for 4 to 12 weeks and 3 026 randomized to placebo, revealed that treatment for overactive bladder using antimuscarinics in adults aged 65 or older resulted in significant increased risk of several AEs compared to placebo including both anticholinergic (e.g., dry mouth, constipation) and non-anticholinergic (e.g., dyspepsia, dizziness, headaches) AEs.[101] Moreover, incidence of urinary tract infections with solifenacin was significantly higher compared to placebo.

Table 10: Interventions to treat fatigue in PD

INTERVENTION		EFFICACY	PRACTICE	SAFETY
DRUG CLASS	**DRUG**			
MAO-B INHIBITORS	***Rasagiline***	*Efficacious*	*Possibly useful*	Acceptable risk without specialized monitoring
PSYCHOACTIVE DRUGS	**Methylphenidate**	Insufficient evidence	Investigational	Insufficient evidence
	Modafinil	Insufficient evidence	Investigational	Insufficient evidence [1]
NON-PHARMACOLOGICAL INTERVENTIONS	***Acupuncture***	*Insufficient evidence*	*Investigational*	Acceptable risk without specialized monitoring

[1] See table 8

Table 11: Interventions to treat pain in PD

DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
ROTIGOTINE	*Insufficient evidence*	*investigational*	Acceptable risk without specialized monitoring
OXYCODONE-NALOXONE PROLONGED RELEASE	*Insufficient evidence*	*Possibly useful* [1]	Acceptable risk without specialized monitoring

[1] There were some significant benefits in the active arm such as the practice implications for oxycodone/naloxone prolonged release for the treatment of pain is “possibly useful” due to the established efficacy and license of oxycodone/naloxone prolonged release in adults with severe chronic pain outside PD. [111, 112]

Table 12: Interventions to treat non-motor symptoms in PD

DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY *
ROTIGOTINE	*Insufficient evidence*	*Investigational*	Acceptable risk without specialized monitoring

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