## Tables

Interventions where new studies have been published are indicated in ***bold italics***. Changes in conclusions are indicated in *italics* and are highlighted in yellow.

Any interventions, where RCTs in PD are not available, are not included in the tables.

With the exception of one low-quality safety study, which lasted 76 weeks,[1] all of the studies included in this review had a maximum duration of 6 months. Therefore, these recommendations do not refer to the long-term management of a given non-motor symptom in PD.

**Table 1: 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 with specialized monitoring |
| | Pergolide | Insufficient evidence | Not useful | |
| | ***Rotigotine*** | *Unlikely efficacious* | *Investigational* | |
| **MAO-B inhibitors** | ***Rasagiline*** | *Insufficient evidence* | *Investigational* | Acceptable risk with specialized monitoring [C] |
| | Selegeline | Insufficient evidence | Investigational | |
| | Moclobemide | Insufficient evidence | Investigational | |
| **TRICYCLIC ANTIDEPRESSANTS (TCA)** | Nortriptyline | Likely efficacious | Possibly useful | |
| | Desipramine | Likely efficacious | Possibly useful | |
| | Amitriptyline | Insufficient evidence | *Possibly useful* [2] | |

| | | | | |
|---|---|---|---|---|
| **SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)/ SELECTIVE SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS** | Citalopram | Insufficient evidence | *Possibly useful* [1] | Acceptable risk |
| | Sertraline | Insufficient evidence | *Possibly useful* [1] | |
| | ***Paroxetine*** | insufficient evidence | *Possibly useful* [1] | |
| | Fluoxetine | Insufficient evidence | *Possibly useful* [2] | |
| | ***Venlafaxine*** | *Efficacious* | *Clinically useful* | |
| **OTHER ANTIDEPRESSANTS** | Atomoxetine | Insufficient evidence | Investigational | |
| | Nefazodone | Insufficient evidence | Not useful | Unacceptable risk |
| **ALTERNATIVE THERAPIES** | Ω-3 fatty acids | Insufficient evidence | Investigational | |
| **NON-PHARMACOLOGICAL INTERVENTIONS** | ***rTMS*** | *Insufficient evidence* | *Possibly useful (short-term)* | |
| | ***CBT*** | *Likely efficacious* | *Possibly useful* | *Insufficient evidence* |

*Unless otherwise specified safety conclusions are ”acceptable risk without specialized monitoring”.

[1] 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.

[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.

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

[D] Combined treatment with either TCAs or SSRIs is unacceptable.

**Table 2: Interventions to treat apathy in PD**

| INTERVENTION | | EFFICACY | PRACTICE | SAFETY* |
|---|---|---|---|---|
| **DRUG CLASS** | **DRUG** | | | |
| **DOPAMINE AGONISTS** | ***Piribedil*** [1] | *Likely efficacious* | *Possibly useful* | |
| | ***Rotigotine*** | *Unlikely efficacious* | *Investigational* | |
| **ACETYLCHOLINESTERASE INHIBITORS** | ***Rivastigmine*** | *Efficacious* | *Possibly useful* | |
| | | | | |

*Unless otherwise specified safety conclusions are ”Acceptable risk without specialized monitoring”.

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

**Table 3: Interventions to treat medication-related impulse dyscontrol and abnormal repetitive behaviors in PD**

| INTERVENTION | | EFFICACY | PRACTICE | SAFETY* |
|---|---|---|---|---|
| **DRUG CLASS** | **DRUG** | | | |
| **NMDA ANTAGONISTS** | **Amantadine** [1] | Insufficient evidence | Investigational | |
| **ANTI-OPIOIDS** | ***Naltrexone*** [2] | *Insufficient evidence* | *Investigational* | *Insufficient evidence* |
| **NON-PHARMACOLOGICAL INTERVENTIONS** | ***CBT*** [2] | *Likely efficacious* | *Possibly useful* | *Insufficient evidence* |
| | | | | |

*Unless otherwise specified safety conclusions are ”Acceptable risk without specialized monitoring”.

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

**Table 4: Interventions to treat dementia in PD**

| DRUG CLASS | DRUG | EFFICACY | PRACTICE IMPLICATIONS | SAFETY* |
|---|---|---|---|---|
| **ACETYLCHOLINESTERASE INHIBITORS** | ***Donepezil*** | Insufficient evidence | *Possibly useful*[1] | |
| | Rivastigmine | Efficacious | Clinically useful | |
| | Galantamine | Insufficient evidence | *Possibly useful*[2] | |
| **NMDA ANTAGONISTS** | **MEMANTINE** | Insufficient evidence | *Investigational* | |

*Unless otherwise specified safety conclusions are ”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.

**Table 5: Drugs to treat non-dementia cognitive impairment in PD**

| INTERVENTION | | EFFICACY | PRACTICE | SAFETY* |
|---|---|---|---|---|
| **DRUG CLASS** | **DRUG** | | | |
| **ACETYLCHOLINESTERASE INHIBITORS** | ***Rivastigmine*** | *Insufficient evidence* | *Investigational* | |
| **MAO-B INHIBITORS** | ***Rasagiline*** | *Insufficient evidence* | *Investigational* | |
| **NON-PHARMACOLOGICAL INTERVENTIONS** | ***t-DCS*** | *Insufficient evidence* | *Investigational* | *Insufficient evidence* |
| | ***Cognitive rehabilitation*** | *Insufficient evidence* | *Investigational* | *Insufficient evidence* |

*Unless otherwise specified safety conclusions are ”Acceptable risk without specialized monitoring”.

**Table 6: 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] | |
| ***PIMAVANSERIN*** | *Efficacious* | *Possibly useful* [2] | *Insufficient evidence* [3] |

*Unless otherwise specified safety conclusions are "Acceptable risk without specialized monitoring". Generally, all atypical antipsychotics must be used with great caution in demented patients with psychosis due to risk of adverse events including falls, cognitive worsening, pneumonia, cardiovascular effects, stroke and death.[2] Indeed, 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. Moreover, the NICE guidelines (NICE 1.5.16) consider quetiapine acceptable for the treatment of hallucinations and delusions in people with PD who have no cognitive impairment.[3]

[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.[4]

[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.[4]

**Table 7: 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 | |
| **DOPAMINE AGONISTS** | Pergolide | Insufficient evidence | Not useful | Acceptable risk with specialized monitoring |
| | Piribedil | Insufficient evidence | Investigational | |
| | Rotigotine | Likely efficacious | Possibly useful | |
| **HYPNOTICS** | Eszopiclone | Insufficient evidence | *Possibly useful*[1] | |
| **MELATONIN** | 3-5mg | Insufficient evidence | *Possibly useful* [2] | |
| | 50mg | Insufficient evidence | Investigational | Insufficient evidence |
| **NON-PHARMACOLOGICAL INTERVENTIONS** | Continuous positive airway pressure (CPAP) [A] | *Likely efficacious* | *Possibly useful* | |
| **EXCESSIVE DAYTIME SOMNOLENCE AND SUDDEN ONSET OF SLEEP** | | | | |
| **DRUG CLASS** | **DRUG** | | | |

| | | | | |
|---|---|---|---|---|
| **PSYCHOACTIVE DRUGS** | Modafinil | Insufficient evidence | *Possibly useful* [3] | Insufficient evidence |
| | Caffeine | Insufficient evidence | Investigational | |
| **NON-PHARMACOLOGICAL INTERVENTIONS** | Continuous positive airway pressure (CPAP) [A] | *Likely efficacious* | *Possibly useful* | |
| | | | | |

*Unless otherwise specified safety conclusions are ”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.[5]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] Although there is insufficient evidence for modafinil to be rated for the treatment of excessive daytime somnolence in PD, it provided significant benefits on measures of excessive daytime somnolence compared to placebo in patients with PD and excessive daytime somnolence. Moreover, a recent meta-analysis of three trials evaluating modafinil showed a significant reduction in sleepiness, as assessed by the Epworth Sleepiness Scale.[6].).

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

**Table 8: 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)* |
| **SEXUAL DYSFUNCTION** | ***Sildenafil*** | *Efficacious* | *Clinically useful* | |
| **CONSTIPATION** | Macrogol | Likely efficacious | Possibly useful | |
| | ***Lubiprostone*** | *Likely efficacious* | *Possibly useful* | |
| | ***Probiotics and prebiotic fiber*** | *Efficacious* | *Clinically useful* | |
| | ***Abdominal massages*** | *Insufficient evidence* | *Investigational* | *Insufficient evidence* |
| **ANOREXIA, NAUSEA AND VOMITING ASSOCIATED WITH LEVODOPA AND/OR DOPAMINE** | Domperiodone | Likely efficacious | Possibly useful | *Acceptable risk with specialized monitoring* [3] |

| | | | | |
|---|---|---|---|---|
| **AGONIST TREATMENT** | | | | |
| **SIALORRHEA** | 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***[5] | *Insufficient evidence* | *Possibly useful* [6] | |

*Unless otherwise specified safety conclusions are ”Acceptable risk without specialized monitoring”.

[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.[7] Moreover, the American Society of Hypertension Writing Group recommend fludrocortisone in the non-hypertensive patient for the pharmacological treatment of OH in general.[8]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.[9] Moreover, the American Society of Hypertension Writing Group recommend midodrine in the hypertensive patient or in patients with history of heart failure for the pharmacological treatment of OH in general.[8] 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..

[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] for the treatment of overactive bladder

[6] 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.

**Table 9: Interventions to treat fatigue in PD**

| INTERVENTION | | EFFICACY | PRACTICE | SAFETY* |
|---|---|---|---|---|
| **DRUG CLASS** | **DRUG** | | | |
| **MAO-B INHIBITORS** | ***Rasagiline*** | *Efficacious* | *Possibly useful* | |
| **PSYCHOACTIVE DRUGS** | **Methylphenidate** | Insufficient evidence | Investigational | Insufficient evidence |
| | **Modafinil** | Insufficient evidence | Investigational | Insufficient evidence |
| **NON-PHARMACOLOGICAL INTERVENTIONS** | ***Acupuncture*** | *Insufficient evidence* | *Investigational* | |

*Unless otherwise specified safety conclusions are ”Acceptable risk without specialized monitoring”.

**Table 10: Interventions to treat pain in PD**

| DRUG | EFFICACY | PRACTICE IMPLICATIONS | SAFETY * |
|---|---|---|---|
| ***ROTIGOTINE*** | *Insufficient evidence* | *investigational* | |
| ***OXYCODONE-NALOXONE PROLONGED RELEASE*** | *Insufficient evidence* | *Possibly useful* [1] | |

*Unless otherwise specified safety conclusions are ”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.

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

| DRUG | EFFICACY | PRACTICE IMPLICATIONS | SAFETY * |
|---|---|---|---|
| ***ROTIGOTINE*** | *Insufficient evidence* | *Investigational* | |

*Unless otherwise specified safety conclusions are "Acceptable risk without specialized monitoring".


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