Update: Treatments for Non-motor Symptoms of Parkinson's disease – December 2012

Team: Klaus Seppi, Daniel Weintraub, Miguel Coelho, Santiago Perez-Lloret

Ad Hoc: Susan H. Fox, Eva-Maria Hametner, Werner Poewe, Olivier Rascol, Christopher G. Goetz, Cristina Sampaio

The recent MDS EBMR on treatments for non-motor symptoms of PD updated the original comprehensive EBM reviews to end of 2010. We have continued the process and present an update to DEC 2012.

The methodology used was the same as in prior reports. Inclusion criteria included pharmacological, surgical and non-pharmacological therapies, available in at least one country, assessed using level 1, randomized controlled trials (RCTs), where non-motor symptoms were the primary endpoint measured with an established rating scale or well-described outcome. A quality assessment for each article was calculated using predetermined criteria; each drug was assigned 'efficacious, likely efficacious; unlikely efficacious; non-efficacious or insufficient evidence' according to the level of evidence. Safety was assessed and assigned as 'acceptable risk with no specialized monitoring, or with specialized monitoring; unacceptable or insufficient evidence'. The overall implications for clinical practice were then assessed and classed as 'clinically useful, possibly useful, investigational, unlikely useful or not useful'. Each intervention was considered for the following indications:

For the treatment of the non-motor symptoms, 6 new studies[1-6] qualified for review and the updates, according to indication presented in Tables 1 - 7 attached. Interventions where new studies have been published are indicated in ***bold italics*****.** Changes in conclusions are indicated in *italics* and are highlighted as yellow. We did not consider two further explanatory trials with multiple non-primary endpoints for this update[7, 8].

In our definitions, efficacy recommendations are conclusions based on the RCTs

available for a PD-specific indication. Implications for clinical practice are based on overall efficacy and safety conclusions. In several instances for the treatment of the non-motor symptoms, e.g. in depression, efficacy conclusions based on RCTs in PD remain inconclusive for agents with proven efficacy in the same condition outside of PD. We have 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 possible useful also for PD patients. For this update, we have limited this for the treatment of neuropsychiatric symptoms, while future updates will cover all non-motors symptoms.

DRUGS TO TREAT DEPRESSION AND DEPRESSIVE SYMPTOMS IN PD

Two new studies were published for the treatment of depression PD fulfilling the inclusion criteria for review.

- **Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurol 2012;78(16):1229-36.**
- **Dobkin RD, Menza M, Allen LA, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am J Psychiatry 2011;168(10):1066-74.**

SSRI:

Paroxetine (one new study, conclusion: *insufficient evidence*)

Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurol 2012;78(16):1229-36. This 12-week double-blind RCT randomized both paroxetine (n=42) and venlafaxine XR (n=34) vs. placebo (n=39) in 115 patients with PD and depression (56% of placebo arm, 69% of paroxetine arm and 65% of venlafaxine XR arm had major depression)[1]. Maximum daily dosages were 40 mg for paroxetine and 225 mg for venlafaxine XR. Primary endpoint was HAM-D-17 reduction relative to placebo. Inclusion criterion for depression was depressive disorder (DSM IV: i.e., major depressive disorder, dysthymic disorder, minor depressive disorder) or operationally defined subsyndromal depression (presence of ≥ 2 depressive symptoms at threshold or subthreshold levels on the SCID for DSM-IV, at least one of which had to include depressed mood or anhedonia) and score of > 12 on the HAM-D-17. There was a significant HAM-D-17 (primary outcome) reduction relative to placebo for both active treatment arms [paroxetine: 6.2 (97.5%CI 2.2-10.3, p=0.0007); venlafaxine XR: 4.2 (97.5%CI 0.1-8.4, p=0.02)] with no significant difference between active treatment arms (p=0.28). **QS 86%**

Efficacy conclusion: There are conflicting level-1 data for the treatment of depression in PD available. Menza et al (2009)[9] conducted a double-blind randomized placebo controlled comparison study of nortriptyline and paroxetine CR

for the treatment of depression in PD, including 52 PD patients with a DSM-IV diagnosis of major depressive episode or dysthymia. Nortryptiline, but not paroxetine, was superior to placebo in both primary endpoints (change from baseline in HDRS-17 scores and percentage of responders defined as ≥ 50% reduction in HDRS-17 score). Although results appeared negative in this latter RCT, low sample size with the risk of low power (ß-error) and short-study duration of 8 weeks prevented any conclusion on efficacy, which was insufficient evidence for efficacy in the EBMR 2011[10]. Due to the conflicting data of these two high-quality RCTs on the efficacy of paroxetine for depression in PD, there is no change in the conclusions, which remain insufficient evidence for efficacy.

Safety conclusions related to SSRI (Conclusions: acceptable risk without specialized monitoring): [10] There were no safety concerns identified in the above reviewed study. Although not reported in studies on the treatment of depression in PD, SSRIs may, however, worsen PD tremor in some 4% to 5% of patients and occasionally parkinsonism[11, 12]. Furthermore, there are concerns about the induction of the serotonin syndrome when used in conjunction with the MAO-B inhibitors selegiline and rasagiline. This somewhat loosely defined condition involves hyperpyrexia, tremor, agitation, and other mental status changes and has been found to occur in severe form in 0.24% of PD cases exposed to SSRIs in the presence of the MAO-B inhibitor selegiline in one large survey[13]. 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), with the incidence varying from 0.5% to 32%[14].

Newer Antidepressants

Venlafaxine (one new study, conclusion: *efficacious*)

Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurol 2012;78(16):1229-36. See above (paroxetine)[1].

Efficacy conclusion: Based on this high-quality study in the lack of further level-1 studies, venlafaxine can be rated *efficacious* for the treatment of depression in PD.

Safety conclusions related to Venlafaxine (Conclusions: acceptable risk without specialized monitoring): There were no safety concerns identified in the above reviewed study. Venlafaxine has similar adverse effects compared to SSRI[15], including the development of a potentially life-threatening serotonin syndrome, particularly with concomitant use of serotonergic drugs (including SSRIs and triptans) and with drugs that impair metabolism of serotonin (including MAOIs) as well as hyponatremia[16].

Non-pharmacological interventions

Cognitive-behavioral therapy (one new study, conclusion: *likely efficacious*)

Dobkin RD, Menza M, Allen LA, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am J Psychiatry 2011;168(10):1066-74. This single-blinded (related to assessment of outcomes) randomized controlled trial (duration: 10 weeks treatment with a 4 weeks post-treatment evaluation) explored individually administered cognitive-behavioral therapy (CBT; n=36) vs. clinical monitoring alone (no treatment; n=36) in 80 patients with PD and depression (according to DSM-IV, 81% with major depression, antidepressant use in 54% of the patients in both group)[2]. Primary endpoint was HAM-D-17 reduction. Stable antidepressant and antiparkinsonian medication was required during the trial. There were significant HAM-D reductions in CBT relative to clinical monitoring alone ($p<0.0001$: mean change from baseline 7.35 from 20.9 for CBT vs. 0.05 from 19.4 for clinical monitoring alone) at week 10 with maintained improvement at week 14. **QS 88%**

Efficacy conclusion: This is the first RCT on cognitive-behavioral therapy for the treatment of depression in PD. Based on this high-quality study in the lack of further level-1 studies, cognitive behavioral therapy can be rated as *likely efficacious* for the treatment of depression in PD. All studies in this field however suffer an unavoidable risk of bias because double-blinding is not possible. Therefore, replication of these efficacy results is required.

Safety conclusions: Safety was not assessed in this study. Generally, reporting of adverse events in CBT trials is limited[17, 18]. Indeed, there is a lack of adverse event monitoring to serious adverse events such as suicide attempts, completed suicides, and psychiatric hospitalizations in most behavioral health clinical trials[18]. Temporary increases in anxiety during behavioral health clinical trials are often considered as a normal part of therapy and are therefore not documented as possible adverse events[18]. Therefore, there is insufficient evidence on the safety of CBT in PD patients with depression.

Treatment of depression in PD summary and practice implications

The recommendations for the treatment of depression in PD are summarized in Table 1.

While the recommendations for practice implications in the EBMR in 2011 were based solely on evidence available from RCTs performed in patients with PD depression, the current recommendations refer to evidence for the efficacy of antidepressants in treating depression outside of PD as a further criterion for practical implications for their clinical use in PD.

There is still *insufficient evidence* for all SSRIs reviewed. Safety conclusions are that all SSRIs reviewed have an *acceptable risk*. Practice implications have been changed since the EBMR 2011. Although studies on the efficacy of citalopram, paroxetine and sertraline for the treatment of PD depression revealed conflicting data for efficacy[10] and although there were no placebo arms in the studies on fluoxetine for the treatment of PD depression, the practice implications for SSRIs is suggested to be *possibly useful* due to the established efficacy and license of SSRIs in depression outside PD.

Venlafaxine is *efficacious* for the treatment of depressive symptoms in PD. Safety conclusions are that venlafaxine has an *acceptable risk without specialized monitoring*. The practice implications are that venlafaxine is *clinically useful* for the treatment of depressive symptoms in PD.

Although there is *insufficient evidence* for transcranial magnetic stimulation to be rated for the treatment of depression in PD, it provided significant benefits on measures of depression in patients with PD and depression[10]. Moreover, there is not only expanding evidence that rTMS is efficacious for the treatment of depression in the general population[19, 20], but it was also approved by the Food and Drug Administration (FDA) in 2008[19] classifying rTMS systems for the treatment of Major Depressive Disorder into class II (special controls). The FDA however also 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 has not been established such as in movement disorders[21]. Therefore, the practice implication is suggested to be *possibly useful*.

Cognitive-behavioral therapy is *likely efficacious* and there is *insufficient evidence* for its safety in PD patients with depression. The practice implications are that it is *possibly useful* for the treatment of depression in PD.

DRUGS TO TREAT DEMENTIA IN PD

One new study was published for the treatment of dementia PD fulfilling the inclusion criteria for review. We did not consider one further explanatory trials with multiple non-primary endpoints for this update[8].

New studies:

- **Dubois B, Tolosa E, Katzenschlager R, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord. 2012;27(10):1230-8.**

Acetylcholinesterase inhibitors

Donepezil (one new study, conclusion: *insufficient evidence*)

Dubois B, Tolosa E, Katzenschlager R, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord. 2012;27(10):1230-8. This 24-week double-blind RCT randomized 550 patients with PDD to donepezil 5mg, donepezil 10mg or placebo[5]. The predefined co-primary end points were ADAS-cog mean changes from baseline to week 24 and CIBIC+ scores at week 24. The study was negative on the co-primary endpoints. There were non-significant ADAS-cog mean changes from baseline to week 24 (mean difference from placebo: donepezil 5mg: -1.45, 95%CI: -2.90–0.00, p=0.05; donepezil 10mg: -1.45, 95%CI: -3.04–0.15, p=0.076). On the other hand CIBIC+ scores were significant better versus placebo for donepezil 10mg (p=0.04), but not for donepezil 5mg (p=0.113) (mean change score at week 24: donepezil 5mg 3.7±1.12; donepezil 10mg 3.6±1.29; placebo 3.9±1.27). Donepezil demonstrated also significant effects on other outcomes including cognition, executive function, and global status. Referring ADAS-cog analysis (one of the co-primary endpoints), there was a significant treatment-by-country interaction as showed by the preplanned primary analysis for ADAS-cog using an ANCOVA model with equal weighting to countries, resulting in no overall statistically significant treatment effect for the individual donepezil doses on the ADAS-cog. But there were highly significant treatment

benefits for both donepezil arms using post hoc ADAS-cog analysis conducted based on the model without the treatment-by-country interaction term in ANCOVA. Higher rates of parkinsonian AEs (donepezil 5mg 10.8%; donepezil 10mg 10.4%; placebo 6.9%) as well as tremor (donepezil 5mg 7.2%; donepezil 10mg 7.1%; placebo 2.9%) were noted in donepezil-treated patients, but the difference was not significant, without apparent dose dependency and no impact on the UPDRS motor scale. **QS: 82%**

Efficacy conclusion: Based on this new study, which was negative on the co-primary endpoints, there is insufficient evidence to conclude on the efficacy of donepezil for the treatment of dementia in PD.

Safety conclusions related to Acetylcholinesterase Inhibitors (Conclusions: acceptable risk without specialized monitoring): [10] There were no safety concerns identified in the above reviewed study, which showed a higher incidence of nausea (donepezil 5mg 17.4%; donepezil 10mg 20.9%; placebo 6.9%) and vomiting (donepezil 5mg 8.2%; donepezil 10mg 4.9%; placebo 1.2%) in the donepezil-treated groups. The RCTs using donepezil for dementia in PD were consistent in showing good tolerability of donepezil without significant worsening of UPDRS motor scores, [5] [10] although the above reviewed study showed higher rates of parkinsonian AEs as well as tremor in donepezil-treated patients. [5] Nausea and vomiting were the most common side effects observed with rivastigmine, affecting between 17% and 29% of patients[22]. Although there were no statistically significant differences in UPDRS motor scores between rivastigmine and placebo-treated patients, more patients on rivastigmine reported tremor as an AE[22]. Worsening of tremor occurred in some patients treated with galantamine[23]. Standard medical monitoring for cholinergic effects can include blood pressure or electrocardiograph (ECG) monitoring. Therefore acetylcholinesterase inhibitors are considered to pose an acceptable risk without specialized monitoring.

Treatment of dementia in PD summary and practice implications

The recommendations for the treatment of depression in PD are summarized in Table 4.

While the recommendations for practice implications in the EBMR in 2011 were based solely on evidence available from RCTs performed in patients with PD depression, the current recommendations refer to evidence for the efficacy of antidementive drugs in treating dementia outside of PD as a further criterion for practical implications for their clinical use in PD.

There is still *insufficient evidence* for the acetylcholinesterase inhibitors donepezil and galantamine as well as for memantine for the treatment of dementia in PD. Safety conclusions are that these drugs have an *acceptable risk without specialized monitoring*. Practice implications have been changed since the EBMR 2011. Due to the established efficacy and license of donepezil, galantamine and memantine in dementia outside PD dementia, the practice implications for donepezil, galantamine and memantine are suggested to be *possibly useful*.

Recommendations for rivastigmine for the treatment of dementia in PD did not change. Rivastigmine is *efficacious* for the treatment of dementia in PD. Safety conclusions are that rivastigmine has an *acceptable risk without specialized monitoring*. The practice implications are that rivastigmine is *clinically useful* for the treatment of dementia in PD.

DRUGS TO TREAT DISORDERS OF SLEEP AND WAKEFULNESS IN PD

New studies:

- **Postuma RB, Lang AE, Munhoz RP et al. Caffeine for treatment of Parkinson disease: a randomized controlled trial. Neurology. 2012 Aug 14;79(7):651-8.**

Caffeine (one new study, conclusion: *insufficient evidence*)

Postuma RB, Lang AE, Munhoz RP et al. Caffeine for treatment of Parkinson disease: a randomized controlled trial. Neurology. 2012 Aug 14;79(7):651-8. This randomized double-blind placebo controlled study allocated 61 patients with PD and excessive daytime sleepiness (EDS) (Epworth sleepiness scale score, ESS ≥10) to caffeine 200 mg daily for 3 weeks, followed by 400 mg for another 3 weeks (n=30) or matching placebo (n=31)[6]. The primary endpoint was the ESS. Secondary outcomes included motor severity (UPDRS), global clinical measure of change (CGIC, Clinical Global Impression of Change), sleep markers, fatigue, depression, and quality of life. On the primary intention-to-treat (ITT) analysis, caffeine resulted in a reduction in ESS score (-1.71 points; 95% CI -3.57, 0.13), which was however not significant. Somnolence improved significantly on the CGIC (ITT: +0.64; 95% CI 0.16, 1.13) and in the per-protocol analysis of the ESS (-1.97; 95% CI -3.87, -0.05). Moreover, caffeine reduced the total UPDRS score (-4.69 points; 95% CI -7.7, -1.6) and the objective motor component UPDRS-III (-3.15 points; 95% CI -5.50, -0.83). Adverse events were comparable in caffeine and placebo groups. **QS 95%**

Efficacy conclusion: Based on this study, there is insufficient evidence to conclude on the efficacy of caffeine for the treatment of EDS in PD.

Safety conclusions (Conclusions: acceptable risk without specialized monitoring): There were no safety concerns identified in the above reviewed study on caffeine for the treatment of EDS in PD.

Treatment of Excessive Daytime Sleepiness in PD—Summary and Practice Implications

The recommendations for the treatment of EDS in PD are summarized in Table 6.

There is insufficient evidence to conclude on the efficacy of caffeine for the treatment of EDS in PD. Safety conclusions are that caffeine has an acceptable risk without specialized monitoring. Practice implications are that caffeine is investigational for the treatment of EDS in PD.

Treatment of Insomnia in PD—Summary and Practice Implications

The recommendations for the treatment of excessive daytime sleepiness in PD are summarized in Table 6.

There is *insufficient evidence* to conclude on the efficacy of melatonin for the treatment of insomnia in PD. Safety conclusions are that melatonin has an *acceptable risk without specialized monitoring*[10]. However, 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 suggested to be *possibly useful*.

DRUGS TO TREAT AUTONOMIC DYSFUNCTION IN PD

DRUGS TO TREAT SIALORRHEA IN PD:

New studies:

- **Chinnapongse R, Gullo K, Nemeth P, et al. Safety and efficacy of botulinum toxin type B for treatment of sialorrhea in Parkinson's disease: a prospective double-blind trial. Mov Disord. 2012;27(2):219-26.**

Botulinum toxin type B (BoNT-B) (one new study, conclusion: *efficacious*)

Chinnapongse R, Gullo K, Nemeth P, et al. Safety and efficacy of botulinum toxin type B for treatment of sialorrhea in Parkinson's disease: a prospective double-blind trial. Mov Disord. 2012;27(2):219-26. This was a high quality RCT[4] (duration 20 weeks) on three different dosages of BoNT-B (1.500U, n=13 - 2.500U, n=10 - 3.500U, n=12; blinding was maintained within each cohort but not across cohorts because of increasing volumes were required with increasing dose) vs. placebo (n=12) for the treatment of sialorrhea in 49 patients with PD with safety/tolerability as primary endpoint and efficacy as secondary outcome including several drooling measures (i.e. rating scales and unstimulated salivary flow rates) with the DFSS as main secondary outcome measure. Overall BoNT-B appears safe and all three BoNT-B improved significantly in most of the efficacy outcomes including the DFSS. **QS: 81%**

Efficacy conclusion: Based on this study, there is no change on the efficacy conclusion of BoNT-B for the treatment of sialorrhea in PD, which can be considered efficacious for BoNT-B.

Safety conclusions Related to Botulinum Toxin A and B (Conclusions: acceptable risk with specialized monitoring): There were no new safety concerns identified in the above reviewed study on BoNT-B for the treatment of sialorrhea in PD. Consistently reported side effects of BoNT-A and BoNT-B were dry mouth and

transient swallowing difficulties including rarely severe dysphagia. Therefore BoNT-A and BoNT-B are considered to pose an acceptable risk with specialized monitoring of the training of the application of BoNT-A and BoNT-B, as they should be given by well-trained physicians with accession to specialized monitoring techniques. [10]

Treatment of sialorrhea in PD—Summary and Practice Implications

Recommendations for the treatment of sialorrhea in PD did not change since the EBMR 2011 [10] and are summarized in table 7.

DRUGS TO TREAT CONSTIPATION IN PD:

New studies:

- **Ondo WG, Kenney C, Sullivan K, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology. 2012;78(21):1650-4.**

Lubiprostone (one new study, conclusion: *likely efficacious*)

Ondo WG, Kenney C, Sullivan K, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology. 2012;78(21):1650-4. In this 4-week double-blind RCT[3] patients were randomized either on lubiprostone (n=25; a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum) or placebo (n=27) for constipation in PD using different outcome measures including diary of bowel movements (no clear defined primary outcome measure). There were significant increased stools per day by diary in lubiprostone, which was titrated up to 48 µg/day, versus placebo (lubiprostone: from 0.75±0.80 to 0.97±0.88, placebo: from 0.84±0.76 to 0.83±0.76; p=0.001),a significant improved visual analog scale score in lubiprostone versus placebo (lubiprostone: from 51.4±8.5 to 71.2, placebo: from 50.7± 5.9 to 56.8±13.0;

p=0.001) and a significant improved constipation questionnaire in lubiprostone versus placebo (p=0.033). Moreover, analysis of the CGIC revealed that significantly more patients had a favorable outcome in the lubiprostone group than in the placebo group (p=0.001). Indeed, much or very much improved constipation was observed in 64% of lubiprostone treated patients versus 19% of the placebo treated patients. (Quality score: 71%)

Efficacy conclusion: Based on this study, lubiprostone can be rated likely efficacious for the treatment of constipation in PD.

Safety conclusions related to lubiprostone (Conclusion: insufficient evidence): Lubiprostone is approved to treat Chronic Idiopathic Constipation in adults (24µg b.i.d.) and Irritable Bowel Syndrome with Constipation in women 18 years of age and older (8µg b.i.d.). Typical AEs of lubiprostone include nausea with consecutive discontinuation in up to 9% ot the patients on it, diarrhea with consecutive discontinuation in up to 2% of the patients on it and dyspnea in up to 2.5% of the patients treated with it. Lubiprostone has been approved only in 2006 (not available in most of European countries)[24]. Overall there is a lack of safety data in PD patients and geriatric patient[25]. Therefore, there is insufficient evidence on the safety of lubiprostone in PD patients with constipation.

Treatment of constipation in PD—Summary and Practice Implications

The recommendations for the treatment of sialorrhea in PD are summarized in Table 7.

Lubiprostone is likely efficacious, there is insufficient evidence for its safety in PD patients with constipation and the practice implications are that it is investigational for the treatment of constipation in PD.

Other recommendations for the treatment of constipation in PD did not change since the EBMR 2011 and are summarized in table 7.

Tables

TABLE 1: DRUGS TO TREAT DEPRESSION INCLUDING DEPRESSIVE SYMPTOMS IN PD

DRUG CLASS	DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
DOPAMINE AGONISTS	Pramipexole	Efficacious	Clinically useful	
	Pergolide	Insufficient evidence	Not useful	Acceptable risk with specialized monitoring
TRICYCLIC ANTIDEPRESSANTS (TCA)	Nortriptyline	Likely efficacious	Possibly useful	
	Desipramine	Likely efficacious	Possibly useful	
	Amitriptyline	Insufficient evidence	*Possibly useful* [2]	
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	Citalopram	Insufficient evidence	*Possibly useful* [1]	
	Sertraline	Insufficient evidence	*Possibly useful* [1]	
	Paroxetine	insufficient evidence	*Possibly useful* [1]	
	Fluoxetine	Insufficient evidence	*Possibly useful* [2]	
NEWER ANTIDEPRESSANTS	Atomoxetine	Insufficient evidence	Investigational	
	Nefazodone	Insufficient evidence	Not useful	Unacceptable risk

	Venlafaxine	*efficacious*	*clinically useful*	
ALTERNATIVE THERAPIES	Ω-3 fatty acids	Insufficient evidence	Investigational	
NON-PHARMACOLOGICAL INTERVENTIONS	rTMS	Insufficient evidence	*possibly useful* [3]	
	ECT	Insufficient evidence	Investigational	Insufficient evidence
	CBT	*Likely efficacious*	*possibly useful*	*Insufficient evidence*

Note; In all tables, where no safety findings are indicated, outcome conclusion was 'Acceptable risk without specialized monitoring'.

[1] Although RCTs for PD depression reveal conflicting data for efficacy, the practice implication is suggested to be 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 suggested to be possibly useful due to proven antidepressant efficacy and license outside of PD

[3] Although there is insufficient evidence for transcranial magnetic stimulation to be rated for the treatment of depression in PD, it provided significant benefits on measures of depression in patients with PD and depression. Moreover, there is expanding evidence that rTMS is efficacious for the treatment of depression in the general population. Therefore, the practice implication is suggested to be possibly useful.

TABLE 2: DRUGS TO TREAT FATIGUE IN PD

DRUG	EFFICACY	PRACTICE	SAFETY
METHYLPHENIDATE	Insufficient	Investigational	Insufficient evidence
MODAFINIL	Insufficient	Investigational	Insufficient evidence

Note; In all tables, where no safety findings are indicated, outcome conclusion was 'Acceptable risk without specialized monitoring'.

TABLE 3: DRUGS TO TREAT PATHOLOGICAL GAMBLING IN PD

DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
AMANTADINE	Insufficient	Investigational	

Note; In all tables, where no safety findings are indicated, outcome conclusion was 'Acceptable risk without specialized monitoring'.

TABLE 4: DRUGS 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]	
	MEMANTINE	Insufficient evidence	*Possibly useful*[3]	

Note; In all tables, where no safety findings are indicated, outcome conclusion was 'Acceptable risk without specialized monitoring'.

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

[3] Although RCTs to treat dementia in PD with memantine reveal conflicting data for efficacy, the practice implication is suggested to be possibly useful due to the proven antidementive efficacy and license outside of PD.

TABLE 5: DRUGS TO TREAT PSYCHOSIS IN PD

DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
CLOZAPINE	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
OLANZAPINE	Unlikely efficacious	Not useful	Unacceptable risk
QUETIAPINE	Insufficient evidence	Investigational	

Note; In all tables, where no safety findings are indicated, outcome conclusion was 'Acceptable risk without specialized monitoring'.

TABLE 6: DRUGS TO TREAT DISORDERS OF SLEEP AND WAKEFULNESS IN PD

DISORDERS OF SLEEP AND WAKEFULNESS	DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
INSOMNIA	Controlled-release formulation of levodopa/carbidopa	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring
	Pergolide	Insufficient evidence	Not useful	
	Eszopiclone	Insufficient evidence	Investigational	
	Melatonin	Insufficient evidence	*possibly useful* [1]	
EXCESSIVE DAYTIME SOMNOLENCE AND THE SUDDEN ONSET OF SLEEP	Modafinil	Insufficient evidence	Investigational	Insufficient evidence
	Caffeine	Insufficient evidence	Investigational	

Note; In all tables, where no safety findings are indicated, outcome conclusion was 'Acceptable risk without specialized monitoring'.

[1] 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 suggested to be possibly useful.

TABLE 7: DRUGS TO TREAT AUTONOMIC DYSFUNCTION IN PD

	DRUG	EFFICACY	PRACTICE IMPLICATIONS	SAFETY
ORTHOSTATIC HYPOTENSION	Fludrocortisone	Insufficient evidence	Investigational	Insufficient evidence
	Domperidone	Insufficient evidence	Investigational	Insufficient evidence
	Midodrin	Insufficient evidence	Investigational	Insufficient evidence
	Dihydroergotamine	Insufficient evidence	Investigational	Insufficient evidence
	Etilefrine hydrochloride	Insufficient evidence	Investigational	Insufficient evidence
	Indomethacine	Insufficient evidence	Investigational	Insufficient evidence
	Yohimbine	Insufficient evidence	Investigational	Insufficient evidence
	L-threo-3.4-dihydroxy-phenylserine	Insufficient evidence	Investigational	Insufficient evidence
SEXUAL DYSFUNCTION	Sildenafil	Insufficient evidence	Investigational	Insufficient evidence
CONSTIPATION	Macrogol	Likely efficacious	Possibly useful	
	Lubiprostone	*Likely efficacious*	*Investigational*	*Insufficient evidence*
ANOREXIA,	Domperiodone	Likely efficacious	Possibly useful	

NAUSEA AND VOMITING ASSOCIATED WITH LEVODOPA AND/OR DOPAMINE AGONIST TREATMENT	Metoclopramide	Insufficient evidence	Not useful	Unacceptable risk
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	Oxybutynin	Insufficient evidence	Investigational	Insufficient evidence
	Tolteradine	Insufficient evidence	Investigational	Insufficient evidence
	Flavoxate	Insufficient evidence	Investigational	Insufficient evidence
	Propiverine	Insufficient evidence	Investigational	Insufficient evidence
	Prazosin	Insufficient evidence	Investigational	Insufficient evidence
	Desmopressin	Insufficient evidence	Investigational	Insufficient evidence

Note; In all tables, where no safety findings are indicated, outcome conclusion was 'Acceptable risk without specialized monitoring'.

References

1. Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology. 2012 Apr;78(16):1229-36.
2. Dobkin RD, Menza M, Allen LA, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am J Psychiatry. 2011 Oct;168(10):1066-74.
3. Ondo WG, Kenney C, Sullivan K, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology. 2012 May;78(21):1650-4.
4. Chinnapongse R, Gullo K, Nemeth P, Zhang Y, Griggs L. Safety and efficacy of botulinum toxin type B for treatment of sialorrhea in Parkinson's disease: a prospective double-blind trial. Mov Disord. 2012 Feb;27(2):219-26.
5. Dubois B, Tolosa E, Katzenschlager R, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord. 2012 Sep;27(10):1230-8.
6. Postuma RB, Lang AE, Munhoz RP, et al. Caffeine for treatment of Parkinson disease: a randomized controlled trial. Neurology. 2012 Aug;79(7):651-8.
7. Ondo WG, Shinawi L, Davidson A, Lai D. Memantine for non-motor features of Parkinson's disease: a double-blind placebo controlled exploratory pilot trial. Parkinsonism Relat Disord. 2011 Mar;17(3):156-9.
8. Hanagasi HA, Gurvit H, Unsalan P, et al. The effects of rasagiline on cognitive deficits in Parkinson's disease patients without dementia: a randomized, double-blind, placebo-controlled, multicenter study. Mov Disord. 2011 Aug;26(10):1851-8.
9. Menza M, Dobkin R, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 2009 Mar;72(10):886-92.
10. 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 Oct;26 Suppl 3:S42-80.
11. Ceravolo R, Nuti A, Piccinni A, et al. Paroxetine in Parkinson's disease: effects on motor and depressive symptoms. Neurology. 2000 Oct;55(8):1216-8.
12. Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry. 1996 Oct;57(10):449-54.
13. Richard IH, Kurlan R, Tanner C, et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. Neurology. 1997 Apr;48(4):1070-7.
14. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. Ann Pharmacother. 2006 Sep;40(9):1618-22.
15. Westenberg HG, Sandner C. Tolerability and safety of fluvoxamine and other antidepressants. Int J Clin Pract. 2006 Apr;60(4):482-91.
16. http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020151s044,020699s071lbl.pdf: FDA; [cited 2014 15th January].
17. Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. BMC Fam Pract. 2012;13:40.
18. Peterson AL, Roache JD, Raj J, Young-McCaughan S, Consortium SS. The need for expanded monitoring of adverse events in behavioral health clinical trials. Contemp Clin Trials. 2013 Jan;34(1):152-4.
19. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry. 2013 Jan;26(1):13-8.
20. Lee JC, Blumberger DM, Fitzgerald PB, Daskalakis ZJ, Levinson AJ. The role of transcranial magnetic stimulation in treatment-resistant depression: a review. Curr Pharm Des. 2012;18(36):5846-52.

21. Administration USFaD. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265269.htm2011 [Nov. 2013].
22. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004 Dec;351(24):2509-18.
23. Litvinenko I, Odinak M, Mogil'naya V, Emelin A. Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). Neurosci Behav Physiol. 2008 Nov;38(9):937-45.
24. FDA. Highliths of prescribing information - Amitiza (lubiprostone) capsules. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021908s005lbl.pdf2006.
25. Gras-Miralles B, Cremonini F. A critical appraisal of lubiprostone in the treatment of chronic constipation in the elderly. Clin Interv Aging. 2013;8:191-200.