TITLE: Pharmacological Management of Depression in Parkinson’s Disease: Evidence for Antidepressant of Choice

DATE: 29 January 2009

CONTEXT AND POLICY ISSUES:

Parkinson’s disease (PD) is a chronic, progressive neurodegenerative disease characterized by resting tremor, rigidity, bradykinesia (slowness of movement), postural instability, and gait disturbance. Although PD is predominantly a movement disorder, other impairments including depression are prevalent and complicate the course of the illness. The mean frequency of depression among PD patients is approximately 35%. However, prevalence rates vary widely across studies ranging from 2.7% to over 90%. This variation is mainly due to differences in the diagnostic scales and criteria used to detect and diagnose depression and differences in the study populations assessed. Depression has been shown to contribute to the decline of both cognitive and motor function in patients with PD, profoundly affecting the patient’s quality of life. Several rating scales have been used to assess depression in PD including the Beck Depression Inventory (BDI), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Hamilton Depression Rating Scale (HAM-D). However, none have been developed specifically for PD. The symptoms of depression overlap with the motor features of PD, making detection of depression difficult. The lack of specialized screening tools means that depression remains undiagnosed and untreated in a high percentage of patients. Furthermore, many antidepressant users remain depressed, suggesting that even when delivered, treatment is often inadequate or ineffective.

Several different antidepressant drug classes including tricyclic antidepressants (e.g., amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (SSRIs) (e.g. escitalopram, citalopram, sertraline), and serotonin norephinephrine reuptake inhibitors (e.g. venlafaxine, duloxetine) are available for the treatment of depression. A recent Veterans Affairs database study found that 63% of PD patients with depression were taking SSRIs, while only 7% were

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taking TCAs.\textsuperscript{15} In general, TCAs can cause undesirable side effects such as dry mouth, blurred vision, confusion, orthostatic hypotension, urinary retention, and constipation.\textsuperscript{10} The elderly are particularly susceptible to memory impairment, confusion, and hallucinations.\textsuperscript{16} Hence, many clinicians start with a SSRI as the likelihood of adverse events is lower with SSRIs than with TCAs. However, there is evidence from several case reports that the use of SSRIs may aggravate motor symptoms of PD.\textsuperscript{17-19}

In light of the high prevalence of depression in patients with PD, an assessment of the comparative clinical effectiveness and safety of different antidepressant classes is necessary to help guide treatment. This report reviews the current evidence for different antidepressants when used in patients with PD. Current guidelines outlining recommendations for the management of depression in this population are also presented.

**RESEARCH QUESTION:**

Is there evidence that one antidepressant is best to use for the management of depression in patients with Parkinson’s disease?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and December 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type. These searches were supplemented by hand searching the bibliographies of selected papers to include relevant information not originally retrieved in the literature search.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and evidence-based guidelines.

**SUMMARY OF FINDINGS:**

**Health technology assessments**

No literature identified

**Systematic reviews and meta-analyses**

Two systematic reviews and meta-analyses\textsuperscript{20,21} and one systematic review\textsuperscript{22} evaluating pharmacological therapy for the management of depression in PD were retrieved. Details of these studies are presented in table 1. The effect size statistic used in the meta-analyses was Cohen’s effect size (d) which represents the standardized mean difference between treatment and control groups measured in standard deviation units. By expressing effect size in standard deviation units, the authors were able to make a direct comparison across all studies despite differences in the depression scales used in the trials.

Frisina et al. conducted a systematic review and meta-analysis to determine the safety and efficacy of antidepressants for depression in PD.\textsuperscript{20} Although selegiline is now used to treat the motor symptoms of PD, the drug was initially introduced as an antidepressant and was included in the analysis. Studies assessing levodopa and dopamine agonists were excluded due to insufficient evidence for antidepressant effects. A total of 12 placebo-controlled RCTs (n=1444)
were included in the meta-analysis. Results showed that antidepressants significantly reduce depression in PD when compared to placebo (d=0.10; p<0.05). When analyzed according to antidepressant drug class, TCAs produced a small but significant treatment effect (d=0.37; p=0.04). SSRIs and selegiline produced negligible non-significant treatment effects (d=0.05 and d=0.08, respectively). Comparing the mean weighted effect sizes for different antidepressant classes showed significant differences when TCAs and SSRIs were compared (p<0.01) and when TCAs and selegiline were compared (p<0.01). Regarding adverse effects, results showed that TCAs produced a small but significant negative effect size (d=-0.27) with an odds of developing an adverse event 3 times greater than placebo. Psychological complications were the most significant adverse effect, but cardiac abnormalities did not differ from the placebo group. SSRIs produced a non-significant effect size (d=-0.03) with an odds of developing an adverse event 1.83 times greater than placebo. It is important to note that motor outcomes were not assessed in any of the included studies. A negligible but significant effect size was reported for adverse effects in patients receiving selegiline (d=-0.05), but the odds of developing an adverse events was 1.63 greater with selegiline than placebo. Although the mean effect sizes were negative and statistically significant for motor, cardiac, and pain-discomfort side effects in patients receiving selegiline, their odds ratios were relatively small (2.12, 2.22, 1.83, respectively). Side effect data showed significant differences when TCAs and SSRIs were compared (p<0.05) but not when TCAs and selegiline (p>0.30) or when SSRIs and selegiline were compared (p<0.50). These findings indicate that TCAs have a modest treatment effect on depression with a minimal side effect profile. SSRIs appear more tolerable than TCAs but their efficacy for depression in PD remains to be established. Results for selegiline did not demonstrate sufficient efficacy or safety to be recommended for use for depression in PD.

Weintraub et al. conducted a systematic review and meta-analysis to determine the effect sizes for both antidepressant treatment and placebo for depression in PD. Safety was not assessed in this report. Studies assessing levodopa and dopamine agonists were excluded due to insufficient evidence for antidepressant effects. A total of 27 studies (n=772) met the inclusion criteria, 11 of which were placebo-controlled studies. Of the 11 placebo-controlled studies, six reported no statistically significant difference between active and placebo treatment. A total of 11 (n=309) studies met the inclusion criteria for meta-analysis. Two of the studies were placebo-controlled and the active and placebo treatment arms of these studies were analyzed separately. The remaining nine studies were open-label. A large effect size for depression was reported in both the antidepressant (d=0.93) and placebo control group (d=1.18). However, the researchers did not observe a significant between-group difference (p=0.44). The authors reported that age and type of depression significantly affected treatment response. Increasing age was associated with a better response to treatment and studies that enrolled a variety of depression diagnoses (i.e. missed depression samples) showed less treatment effect than did those that restricted enrollment to patients with major depression. Overall, these findings suggest that antidepressant treatment has a non-specific effect on depression in PD. This result may be confounded by effect size data for the placebo group being derived from only two studies that possibly contained sampling error. Moreover, the researchers excluded the TCAs from their analysis which may have further limited their ability to detect a significant treatment effect between the antidepressant and placebo groups. Overall, these results suggest that the use of antidepressants for the management of depression in PD may not be effective.

Ghazi-Noori et al. conducted a systematic review to assess the safety and efficacy of antidepressant therapies in PD. A total of three RCTs (n=106) with significant methodological limitations were included in the review. Results showed that nortriptyline improved depressive symptoms relative to placebo in the first half of a crossover trial with no deterioration in parkinsonian symptoms, but statistical significance was not calculated. The second trial showed that citalopram provided no additional benefit over placebo in the treatment of depressive
symptoms. A third trial reported that fluvoxamine and amitryptiline showed similar efficacy. Confusion and visual hallucinations were infrequently reported in people taking fluvoxamine and amitryptiline but no other major adverse events were reported. The authors concluded that there is insufficient evidence for the effectiveness and safety of antidepressants in the treatment of depression in PD to allow recommendations for their use.

Table 1: Systematic reviews and meta-analyses for antidepressants in PD

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<thead>
<tr>
<th>AUTHOR, YEAR</th>
<th>STUDY DESIGN</th>
<th>MAIN RESULTS AND LIMITATIONS</th>
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<tbody>
<tr>
<td>Frisina et al., 2006&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Inclusion criteria: Placebo-controlled RCTs published between 1965 and January 2005 studying antidepressants in patients with PD</td>
<td>Overall mean weighted effect size: d=0.10 (r=0.06; p&lt;0.05)</td>
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<tr>
<td></td>
<td>Included studies: 12 Placebo-controlled RCTs (n=1444) Mean duration: Not reported</td>
<td>Mean weighted effect size by antidepressant class:</td>
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<td></td>
<td>Study Medications:</td>
<td>TCA: d=0.37 (r=0.20; p=0.04)</td>
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<td>TCAs vs. Placebo</td>
<td>SSRI: d=0.05 (r=0.02; p=0.44)</td>
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<td>Nortriptyline, Amitriptyline, Desipramine (3 studies, n=88)</td>
<td>Selegiline: d=0.08 (r=0.01; p=0.08)</td>
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<td>SSRIs vs. Placebo</td>
<td>TCA vs. SSRI: p&lt;0.01</td>
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<td>Sertraline, Citalopram (2 studies, n=32)</td>
<td>TCA vs. Selegiline: p&lt;0.01</td>
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<td>MAOI vs. Placebo</td>
<td>Overall effect size for adverse events: d= -0.27 (r= -0.04; p=0.13; OR 2.18)</td>
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<td></td>
<td>Selegiline (7 studies, n=1324)</td>
<td>Mean weighted effect size by antidepressant class for adverse effects:</td>
</tr>
<tr>
<td>Weintraub et al., 2005&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Inclusion criteria: Studies published between January 1965 and December 2003 assessing antidepressants in patients with PD To be included in the meta-analysis studies also had to use a standardized rating scale of depression severity.</td>
<td>TCA: d= -0.27 (r= -0.14; p&lt;0.01; OR 3.07)</td>
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<tr>
<td></td>
<td>Studies included in meta-analysis: 2 placebo-controlled RCTs (n=49) 9 open-label studies (n=260) Mean duration: 11.9 weeks</td>
<td>SSRI: d= -0.03 (r= -0.01; p=0.42; OR 1.83)</td>
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<td></td>
<td>Selegiline: d= -0.05 (r= -0.03; p&lt;0.01; OR 1.63)</td>
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<td>TCA vs. SSRI: p&lt;0.05</td>
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<td></td>
<td></td>
<td>TCA vs. Selegiline: p&lt;0.30</td>
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<td></td>
<td></td>
<td>SSRI vs. Selegiline: p&lt;0.50</td>
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<td></td>
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<td>Limitations: Limited studies were included evaluating TCAs and SSRIs. Included trials were of small sample size.</td>
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Pharmacological Management of Depression in Parkinson’s Disease
### Health Technology Inquiry Service (HTIS)

<table>
<thead>
<tr>
<th>AUTHOR, YEAR</th>
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<th>MAIN RESULTS AND LIMITATIONS</th>
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</table>
| Ghazi-Noori *et al.*, 2003[^22] | **Inclusion criteria:** RCTs published before February 2001 studying antidepressants in patients with PD  
**Included studies:** 3 RCTs (n=106)  
Duration range: 16-52 weeks (duration not reported in one trial  
**Study Medications:**  
TCAs vs. Placebo  
Nortriptyline (1 study, n=22)  
SSRIs vs. Placebo  
Citalopram (1 study, n=18)  
TCA vs. SSRI  
Fluvoxamine vs. Amitriptyline (1 study, n=47) | **Limitations:** Insufficient data on the effectiveness and safety of antidepressant therapies in PD.  
The included trials included small sample sizes and were of short duration. Included studies lacked details on methods of randomization and allocation concealment. |

**RCT=Randomized controlled trial, PD= Parkinson’s disease, SSRI=Selective serotonin reuptake inhibitor, TCA=Tricyclic antidepressant, MAOI=Monoamine oxidase inhibitor, r=Correlation coefficient, OR=Odds ratio**

#### Randomized controlled trials

Four RCTs evaluating pharmacological therapy for the management of depression in PD were retrieved.[^23-^26] Details of these trials are presented in table 2.

Menza *et al.* performed the largest published double-blind placebo-controlled RCT to date comparing a controlled release (CR) formulation of paroxetine, nortriptyline, and placebo in 52 PD patients with depression.[^23] Baseline characteristics did not differ among groups except that majority of the individuals randomly assigned to receive nortriptyline were women (65%) and majority of the individuals randomly assigned to receive paroxetine CR were men (72%). Fifty patients had major depression, two had major depression with dysthymia, and two only had dysthymia. The mean age was 62.8 years and the mean duration of PD was 6.6 years. Doses were escalated up to three times, based on efficacy and tolerability. The average dose of medication was 28.4 mg for paroxetine CR, 48.5 mg for nortriptyline, and 2.7 pills for placebo. The authors chose a primary outcome of a change in the HAM-D score and the percentage of responders (defined as a 50% reduction in HAM-D score) following eight weeks of treatment. An intention-to-treat study design was employed with the last observation carried forward (LOCF) for all subjects. Results showed that nortriptyline was superior to placebo for a change in HAM-D score (p<0.002), while paroxetine CR was not (p<0.165). However, the differences between nortriptyline and paroxetine CR for change in HAM-D score at eight weeks were not significant.
Nortriptyline produced significantly more responders when compared with paroxetine CR (p=0.034). Nortriptyline was also superior to paroxetine CR or placebo for various secondary outcomes including improvement in sleep and alleviation of anxiety. Quality of life scores did not differ among groups. There was a significantly higher average number of side effects (including orthostatic hypotension, fatigue) in the paroxetine CR group compared with placebo (p=0.0281) but no differences between nortriptyline and placebo. However, dropout rates were similar in the two treatment arms indicating that paroxetine CR and nortriptyline were well tolerated at the doses given. There were no significant effects of nortriptyline on cardiac conduction.

Devos et al. conducted a similar double-blind, placebo-controlled study comparing desipramine with citalopram in 48 PD patients with major depression. The authors stated that at baseline, the three groups did not differ significantly, but details on the demographic and clinical characteristics of each group were not presented. The primary endpoint was a change in the MADRS score at day 14 and day 30 relative to baseline. After 14 days, patients receiving desipramine showed a significant improvement in depressive symptoms compared with placebo (p=0.003) and citalopram (p=0.005) as measured using the MADRS. After 30 days, patients receiving desipramine or citalopram showed significant improvements in depressive symptoms when compared with placebo (p=0.03 and p=0.002, respectively) but both drugs produced similar reductions in the MADRS (statistical significance not calculated). Patients receiving desipramine or citalopram showed an equivalent improvement in anxiety compared with the placebo group after 30 days of treatment. Mild adverse events (including dry mouth and constipation) were twice as frequent in the desipramine group as in the other groups. Two patients in the citalopram group discontinued therapy due to a worsening of bradykinesia (n=1) and erectile dysfunction (n=1). One patient in the desipramine discontinued therapy due to orthostatic hypotension.

Barone et al. conducted an open-label RCT comparing pramipexole (a dopamine agonist) with sertraline. A total of 67 patients with major depression but no motor complications (such fluctuations of dyskinesia which may influence depressive symptoms) were included. Demographic characteristics including age and gender were similar between the two treatment groups. The mean age of participants was 66.5 years. The groups were also homogenous at baseline for PD severity and for depression severity. The primary outcome measure was a change in the HAM-D score after 12 weeks of treatment following a 2 week screening period. Doses of pramipexole were titrated to achieve optimal efficacy. The HAM-D score decreased significantly in both groups after 14 weeks (p<0.001 for both groups) but the difference between the two groups was not significant (p=0.055). However, the proportion of patients who recovered (defined as a final HAM-D score of eight or less) was significantly higher in the pramipexole group (p=0.006). Despite the absence of motor complications, the pramipexole recipients showed an improvement in motor function. However, no statistical correlation was found between motor improvement and relief of depressive symptoms, suggesting that pramipexole might exert an antidepressant effect independent of its effect on motor symptoms. Pramipexole was well tolerated as no patients withdrew as a result of adverse effects. However, five patients in the sertraline group withdrew as a result of nausea (n=2), vertigo (n=1), anxiety (n=1), and abdominal pain (n=1).

Antonini et al. conducted a single-blind RCT studying the effect of treatment with sertraline or amitriptyline in 31 patients with PD-related depression. The authors stated that there were no statistically significant differences between the two groups with respect to baseline and clinical characteristics but only information for patients that completed the study were presented. The average age of participants was 70.15 years and the duration of PD was 7.4 years. Both drugs significantly reduced the HAM-D score after three months of treatment (p<0.01 for both groups),
although the responder rate (defined as a reduction in HAM-D score of 50% or greater) was higher for sertraline than for amitriptyline (statistical significance not calculated). Sertraline showed significant improvements in the mobility, activities of daily living, emotional, and stigma sub-scores of the Parkinson’s Disease questionnaire (PDQ-39). However, no change was noted in these PDQ-39 sub-scores for patients in the amitriptyline arm. Neither group had a significant change in motor function. Four patients in the sertraline group discontinued treatment due to nausea (n=2), confusion (n=1), or hypotension (n=1). Four patients in the amitriptyline group discontinued treatment due to confusion and visual hallucinations (n=2), sleepiness (n=1), headache and tachycardia (n=1).

Table 2: Summary of RCTs Comparing Antidepressants in PD

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<tr>
<th>AUTHOR, YEAR</th>
<th>STUDY DESIGN INTERVENTIONS</th>
<th>MAIN RESULTS</th>
<th>CONCLUSIONS AND LIMITATIONS</th>
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<tbody>
<tr>
<td>Menza et al., 2008</td>
<td>Design: Double-blind, placebo-controlled RCT Duration: 8 weeks</td>
<td>Baseline HAM-D Score: Paroxetine CR: 18.82 ± 5.60 Nortriptyline: 21.12 ± 5.64 Placebo: 19.29 ± 5.64</td>
<td>Paroxetine CR is not superior to placebo for the treatment of depression in patients with PD and may be inferior to nortriptyline.</td>
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<td></td>
<td>Inclusion criteria: PD patients aged 35 to 80 with a diagnosis of major depression or dysthymia</td>
<td>Mean change in HAM-D Score at 8 weeks: Paroxetine CR: -6.37 Nortriptyline: -10.28 Placebo: -3.48</td>
<td>Limitations: Small sample size, short duration, high dropout rate (35%), unclear allocation concealment</td>
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<td>Interventions: Paroxetine CR 12.5-37.5 mg daily (n=18) vs. Nortriptyline 25-75 mg daily (n=17) or Placebo 1-3 pills daily (n=17)</td>
<td>Paroxetine CR vs. Placebo: p&lt;0.165 Nortriptyline vs. Placebo: p&lt;0.002 Nortriptyline vs. Paroxetine CR: p&lt;0.079</td>
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<td>HAM-D Score Reduced by 50% at 8 weeks (%): Paroxetine CR: 11 Nortriptyline: 53 Placebo: 24</td>
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<td>Nortriptyline vs. Paroxetine CR: p=0.034</td>
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<td>Dropout rate (%): Paroxetine CR: 39 Nortriptyline: 29 Placebo: 35</td>
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| Devos et al., 2008<sup>24</sup> | Design: Double-blind, placebo-controlled RCT  
Duration: 30 days  
Inclusion criteria: Non-demented PD patients under 80 years old suffering from major depression  
Interventions:  
Citalopram 20 mg daily (<i>n</i>=15)  
vs.  
Desipramine 75mg daily (<i>n</i>=17)  
or  
Placebo 3 tablets daily (<i>n</i>=16) | Baseline MADRS Score:  
(Quartile range):  
Citalopram: 25 (24,28)  
Desipramine: 29 (27,34)  
Placebo: 27 (24,32)  
Change in MADRS Score at 14 days:  
Citalopram: -6  
Desipramine: -16  
Placebo: -8  
Citalopram vs. Placebo:  
p=NS  
Desipramine vs. Placebo:  
p=0.003  
Citalopram vs. Desipramine:  
p=0.005  
Change in MADRS Score at 30 days:  
Citalopram: -14  
Desipramine: -20  
Placebo: -9  
Citalopram vs. Placebo:  
p=0.03  
Desipramine vs. Placebo:  
p=0.002  
Citalopram vs. Desipramine  
(<i>p</i> value not reported) | Desipramine could be useful for rapidly alleviating depression in PD but both desipramine and citalopram appear to have equivalent efficacy after 1 month of treatment.  
Limitations: Small sample size, short duration, unclear allocation concealment, fixed dosing, baseline characteristics not presented. |
### Barone et al., 2006

**Design:**
Open-label RCT
Duration: 14 weeks

**Inclusion criteria:**
PD patients with major depression but no motor complications (no history of fluctuations and/or dyskinesia)

**Interventions:**
- Pramipexole 1.5-4.5 mg daily (n=33)
- Sertraline 50 mg daily (n=34)

**Main Results:**
- **Baseline HAM-D Score:**
  - Pramipexole: 19.7 ± 3.5
  - Sertraline: 21.33 ± 4.4
- **Mean change in HAM-D Score at 14 weeks:**
  - Pramipexole: -10.76 ± 5.74 (p<0.001)
  - Sertraline: -9.03 ± 7.28 (p<0.001)
- **Pramipexole vs. Sertraline:**
  - p=0.055
- **HAM-D Score ≤ 8 at 14 weeks (%):**
  - Pramipexole: 60.6
  - Sertraline: 27.3 (p=0.006)

**Conclusions and Limitations:**
Dopamine agonists may be an alternative to antidepressants for the management of depression in PD.

Limitations:
- No placebo control,
- Small sample size,
- Short duration,
- Non-blinded,
- Fixed sertraline dose.

### Antonini et al., 2006

**Design:**
Single-blind RCT
Duration: 3 months

**Inclusion criteria:**
PD patients with depression with stable motor conditions for at least 3 months

**Interventions:**
- Sertraline 50 mg daily (n=16)
- Amitriptyline 25 mg daily (n=15)

**Main Results:**
- **Baseline HAM-D Score (of completers):**
  - Sertraline: 20.33 ± 3.94
  - Amitriptyline: 19.73 ± 2.76
- **Mean change in HAM-D Score at 3 months:**
  - Sertraline: -12.16 (p<0.001)
  - Amitriptyline: -11.09 (p<0.01)
- **HAM-D Score Reduced by 50% at 3 months (%):**
  - Sertraline: 83.3
  - Amitriptyline: 72.7 (p value not reported)

**Conclusions and Limitations:**
Both sertraline and low-dose amitriptyline improved depressive symptoms in PD, but a significant benefit on quality of life was only observed with sertraline.

Limitations:
- No placebo control,
- Small sample size,
- Short duration,
- Fixed dosing,
- Baseline characteristics of only those that completed trial are presented.

**Abbreviations:**
- RCT=Randomized controlled trial, PD=Parkinson’s disease, SSRI=Selective serotonin reuptake inhibitor, TCA=Tricyclic antidepressant, CR=Controlled release, HAM-D=Hamilton Depression Rating Scale, MADRS=Montgomery-Asberg Depression Rating Scale, NS=Non-significant
Guidelines

Three guidelines addressing the pharmacological management of depression in PD were identified in the search.27-29

In 2006, the American Academy of Neurology (AAN) released a practice parameter presenting recommendations for the pharmacologic treatment of depression in PD. Based on a systematic review of the literature, the AAN concluded that amitriptyline may be effective for the management of depression in PD without dementia (level of evidence C; based on a randomized controlled study in a representative population with masked outcome assessment). However, the authors state that “although the highest level of evidence is for amitriptyline, it is not necessarily the first choice” due to its side effect profile. The AAN found insufficient evidence to support or refute the effectiveness of other antidepressant medications in this setting.

A 2006 guideline produced by a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES) is based on a review of the literature and consensus. Recommendations for the treatment of depression in PD include optimization of antiparkinsonian therapy and the use of TCAs or SSRIs (good practice point based on expert opinion and consensus). The guidelines do not provide clear recommendations for which antidepressant class to use but state that SSRIs are less likely to produce adverse effects. No recommendations are made for other antidepressants including venlafaxine.

The Royal College of Physicians in the United Kingdom issued a national clinical guideline for the management of Parkinson’s disease in 2006.29 Based on a systematic review of the literature, the guidelines state that there is insufficient evidence from RCTs for the efficacy and safety of any antidepressant therapy in PD and management should be tailored to the individual and co-existing therapy (good practice point based on expert opinion and consensus).

Limitations

Results from available systematic reviews indicate that there are very few published RCTs comparing the safety and efficacy of antidepressants for depression in PD. A high placebo response rate has been demonstrated in studies for depression14, but majority of the available RCTs lacked a placebo control, making it difficult to assess whether either drug is effective in this setting. Furthermore, the available RCTs were not sufficiently powered to exclude a clinically important benefit. Many of the existing studies included patients with minor and major depression where treatment effects were not examined separately in these two patient groups. Different rating assessments were used that have not been developed specifically for PD. No RCTs have yet been published evaluating other classes of antidepressants including venlafaxine, duloxetine, bupropion, and mirtazapine. Available guidelines indicate that there is no clear consensus regarding the use of antidepressants for the treatment of depression in patients with PD.

Further randomized, double-blind, placebo-controlled studies of adequate size and duration assessing different antidepressant classes for clinically significant outcomes such as slower progression of cognitive and motor decline in PD are needed to provide clear recommendations for use in clinical practice.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In summary, despite the high frequency of PD associated depression, pharmacological interventions have been poorly studied and the available data are conflicting. To date, the long-term safety and efficacy of antidepressants in the treatment of depression in PD has not been demonstrated. The scarcity of controlled trials and the variability of study methodologies complicate the interpretation and generalizability of the results. There is evidence that TCAs may not be as poorly tolerated, and SSRIs may not be as efficacious as currently perceived. \(^{30}\) Two ongoing placebo-controlled RCTs assessing the effectiveness of venlafaxine versus paroxetine\(^ {31}\) and atomoxetine \(^ {32}\) for the treatment of depression in PD will be of particular interest.

Until further evidence available, the choice of antidepressant should depend on the presence and nature of co-morbid conditions, potential interactions with concomitant medications, patient acceptability, and the adverse effect profile of the antidepressant.

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REFERENCES:


