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Is Pramipexole Safe and Effective in Reducing Depressive Symptoms in Patients with Mild to Moderate Parkinson’s Disease and Depression?

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Is Pramipexole Safe and Effective in Reducing Depressive Symptoms in Patients with Mild to Moderate Parkinson’s Disease and Depression?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

**Objective:** The objective of this selective EBM review is to determine whether or not pramipexole (Mirapex) is a safe and effective drug to treat depression in patients with mild to moderate Parkinson’s Disease (PD).

**Study Design:** Review of three English language primary randomized controlled trials and one randomized prospective, observational study published between 2003-2010.

**Data Sources:** Three randomized controlled trials and one randomized prospective, observational study comparing the efficacy of pramipexole to placebo, sertraline (an SSRI) and other dopamine agonists (pergolide) in the treatment of PD related depression symptoms were found using PubMed.

**Outcome(s) Measured:** Each of the four clinical trials assessed the improvement of depression in PD patients. In addition, they noted how the improvement in mood would impact patient's quality of life. Prior to the study, all patients received an evaluation of the severity of their depressive symptoms in order to get a baseline level; this allowed researchers to note patient's percent change from baseline. This was done through objective evaluation, as well as self-reported questionnaires. Patients were evaluated for disease severity, quality of life, motor functioning, psychopathology, activities of daily living and depression severity.

**Results:** Three randomized-controlled trials and one randomized prospective, observational study were included in this review. Results from each study reveals that pramipexole is a safe and effective drug to treat depression in mild to moderate PD patients. Pramipexole was found to be more effective than placebo, similar in efficacy to pergolide and sertraline, but with less adverse reactions than sertraline. The patients’ quality of life also improved due to the reduction in motor symptoms that pramipexole is currently FDA approved to treat.

**Conclusion:** The four clinical trials included in this review have shown that pramipexole is a safe and effective treatment for depression in PD patients. Pramipexole is currently not approved for use to treat depression in PD and although initial studies are promising, further evaluation is necessary. In addition the FDA is currently investigating an association between pramipexole and increased risk of heart failure.

**Key Words:** pramipexole; Parkinson’s; depression
INTRODUCTION

Parkinson’s Disease (PD) is a neuropsychiatric disorder. While the classic presentation of PD is defined by progressive motor symptoms including rigidity, bradykinesia and resting tremor, there is also a high prevalence of psychopathological and other non-motor symptoms. The most common psychopathologic co-morbid condition affecting those with PD is depression.\(^1\) The prevalence rate of major depressive disorder in PD is 17% and the rate of clinically significant depressive symptoms has been reported to be as high as 35 - 45%.\(^1\) The precise relationship of depression to the underlying brain disease still remains to be clarified.\(^2\) It is thought that the degeneration of dopaminergic neurons in the substantia nigra in PD leads to dysfunction in not only the motor centers of the basal ganglia, but also of the dopamine driven pleasure centers of the limbic system.\(^3\) This ultimately leads to anhedonia, the most prominent symptom of PD related depression.\(^1\)

While little data are yet available on the cost effectiveness of pramipexole (Mirapex) when compared with baseline treatment, depression accounts for approximately 40% of variability in quality of life scores independent from motor symptoms and has been shown to lead to a more rapid decline in the health of PD patients resulting in more frequent and costly hospital stays.\(^1,3,4\) Already PD patients, on average, account for 1.45 times more (95% CI 1.42, 1.48) hospital admissions per year when compared with a group of similar peers without PD.\(^5\)

The standard treatment of PD is usually levodopa/carbidopa, combined with adjunctive medications including COMT inhibitors, MAOB-inhibitors and dopamine agonists. Classically PD patients with depressive symptoms have been treated with selective serotonin reuptake inhibitors (SSRI), specifically sertraline, or the tricyclic antidepressants (TCA) desipramine,
imipramine or nortriptyline. In cases of treatment resistant or psychotic depression, Electroconvulsive Therapy (ECT) is currently the treatment of choice.

Pramipexole has been shown by Goldberg et al, an independent randomized, double blind study, to be more well tolerated and significantly more effective than placebo in improving depressive symptoms in patients with treatment refractory bipolar disorder when used as an add-on therapy of mood stabilizers. Open label trials have suggested that D2/D3 dopamine receptor agonists, such as pramipexole, might also be effective in reducing depression in PD patients. Pramipexole has a preference for D3 vs. D2 receptors in the prefrontal and orbito-frontal cortical areas of the brain, which are integral to the etiology of depression. Also, the addition of pramipexole to standard PD treatment allows for levodopa dosages to be decreased without compromising treatment outcomes. Prolonged treatment with high doses of levodopa has long been associated with the development of dyskinesias and motor fluctuations that greatly decrease the quality of life for those affected.

This paper evaluated three randomized controlled trials and one randomized prospective, observational study comparing the efficacy of pramipexole to placebo, sertraline (an SSRI) and other dopamine agonists (pergolide) in the treatment of PD related depression symptoms.

OBJECTIVES

The objective of this selective EBM review is to determine whether or not pramipexole is safe and effective in reducing depressive symptoms in patients with mild to moderate Parkinson’s Disease and depression.

METHODS

All four clinical trials utilized for this review were selected because their population included both male and female patients with mild to moderate PD who were at least 18 years old.
and currently on stable levodopa therapy without symptoms of dementia or severe depression.
The intervention used for these PD patients was the administration of pramipexole titrated to an
optimized therapeutic dose. Barone et al (2010) compared the administration of pramipexole to a
visually matched placebo; Rektorova et al compared pramipexole to another dopamine receptor
agonist, pergolide; Barone et al (2006) compared pramipexole to the SSRI sertraline.1,2,4

Outcomes measured in each study were all patient oriented evidence that matters
(POEMs) and included both self reported and observer rated disease severity measurements,
quality of life, motor functioning, psychopathology, activities of daily living (ADLs) and
depression severity measurements. 3 Three of the studies included are randomized controlled
trials, one of which was double blind and placebo controlled while the other two were open label
but randomized and semi-blind (performed by an independent blinded observer). The fourth
study included is a prospective, observational, open study.

Information obtained for this review was found on PubMed using the following key
words: pramipexole; Parkinson’s; depression. All articles were published in the English language
in peer-reviewed journals between the years 2003 – 2010.

All of the articles were selected based on their relevance and importance of outcomes to
the patient. The three trials included in this review were chosen because they met the following
inclusion criteria: randomized-controlled trials, at least semi-blinded, published after 1996 and
patient oriented evidence that matters (POEM). Other studies were excluded based on the
following criteria: not randomized-controlled trials, disease-oriented evidence (DOE), did not
include the selected patient population, did not exclude patients with dementia, severe PD,
history of psychosis/suicidal ideation, pts currently taking dopamine agonists.
Table 1: Demographics and Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># of pts</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barone (^1)</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>296</td>
<td>&gt;30 yo</td>
<td>-M or F -Idiopathic PD -HoehYahr stage 1-3 -Clinically relevant Depression &gt;5 on GDS-15</td>
<td>-Motor fluctuations -Score of &lt; 24 on MMSE -Suicidal depression or psychotherapy -Malignant melanoma</td>
<td>30</td>
<td>Randomized to receive PPX or placebo</td>
</tr>
<tr>
<td>Barone (^2), 2006</td>
<td>National multicenter parallel group randomized study</td>
<td>67</td>
<td>64.8 ± 8.3</td>
<td>-HAM-D score &gt;16 -Stable treatment w. L-dopa -No history of motor fluctuations -HoehnYahr stage 1.5-4</td>
<td>-Treatment with dopamine agonists -Treatment with antidepressants -Hx of psychosis or suicide attempts -Cardiovascular disease</td>
<td>8</td>
<td>Randomized to receive PPX or Sertraline</td>
</tr>
<tr>
<td>Lemke, 2006</td>
<td>Prospective, Observational Study</td>
<td>657</td>
<td>67.7±9.2</td>
<td>-Clinical Dx of PD -Hoehn-Yahr stage 2-3 -Psychotic symptoms -Moderate to severe dementia -CI for PPX</td>
<td></td>
<td>23</td>
<td>PPX added to L-Dopa regimen</td>
</tr>
<tr>
<td>Rektorova, 2003</td>
<td>Randomized controlled Trial</td>
<td>41</td>
<td>59±7.7 PPX 63.5±7.5 Pergolide</td>
<td>-Idiopathic PD -Mild to moderate depression -Stable treatment with L-dopa</td>
<td>-Hypersensitivity to study medications -Renal or Cardiovascular failure -Pregnancy -Treatment with neuroleptics -Presence of dementia -Severe depression -Current Tx with dopamine agonists -Presence of other psychiatric illness</td>
<td>22</td>
<td>Randomized to receive PPX or Pergolide</td>
</tr>
</tbody>
</table>

The statistics used in the studies were 95% confidence intervals (CI), Chi squared (\(X^2\)), two sided ANCOVA, mean change from baseline, t-test or non-parametric Wilcoxon test and Odds Ratio (OR) analyses all converted to p-values.
OUTCOMES MEASURED

Outcomes measured were based on observer rated scales or self-reported questionnaires. Disease severity was measured using the Hoehn-Yahr Scale, which ranges from 0-5 (Stage 1 = unilateral symptoms, Stage 5 = restricted to wheelchair or bed if unsupported). Trained observers rated PD motor and non-motor symptom (psychopathology, depression and ADLs) severity using the Short-Parkinson’s-Evaluation-Scale (SPES) (range 0-98 with higher values representing more severe symptoms). Anhedonia was assessed with the patient reported Snaith-Hamilton Pleasure Scale (SHAPS-D) (range 0-14, cut-off score for anhedonia ≥ 3, higher values represent increasing severity). The presence and severity of clinically relevant depression was evaluated by trained observers using the 15 item Geriatric-Depression-Scale (GDS-15) (higher values represent increasing severity), the Montgomery-Asberg Depression Rating Scale (MADRS) (higher values represent increasing severity), the Hamilton Depression Rating Scale (HAM-D) and the Beck depression Inventory (BDI). Depressive symptoms were also assessed using the patient reported Zung subjective Self-Rating Depression Scale. The neurological examination consisted of an evaluation of motor symptoms, depression and activities of daily living based on the Unified Parkinson’s Disease Rating Scale (UPDRS) (UPDRS I: item 3 depression; UPDRS II: activities of daily living; UPDRS III: motor examination; UPDRS IV: complications of therapy).

RESULTS

Lemke et al was a prospective, observational open study designed to evaluate the safety and effectiveness of pramipexole as an add-on therapy to levodopa to treat anhedonia and depression in PD patients. Based on SHAPS-D scores, the frequency of anhedonia decreased significantly from 45.7% at baseline to 25.5% at the end of the study ($X^2 = 94.45$, $p < 0.001$).
The decrease in mild depression, as measured by SPES depression scores, from 46.6% to 37.6% ($\chi^2 = 214.73, p<0.001$) was also statistically significant. Anhedonia and depression scores were significantly correlated ($p<0.001$). Drop-outs due to adverse effects occurred in only 3.5% of subjects. The limiting factor of this study is that 86% of patients included received co-medication in the form of classic antidepressant medications including SSRIs and TCAs. As a result other variables may have affected the outcomes of the study.

Barone et al (2010) investigated the efficacy and safety of pramipexole versus placebo in a randomized, double blind placebo controlled trial. The primary endpoint was a change in BDI total score along with a secondary path analysis to differentiate between direct effects of pramipexole on depression and indirect improvement from a reduction in motor symptoms. The adjusted mean change from baseline in BDI scores among subjects not receiving any other antidepressant medication was -6.2 for pramipexole and -3.7 for placebo (difference -2.5, 95% CI -4.1 to -0.8; $p = 0.004$). The adjusted mean change from baseline in GDS-15 scores was -2.5 for pramipexole and -1.7 for placebo (difference -0.8, 95% CI -1.5 to -0.1; $p = 0.035$). Based on the results of a path analysis of the total effect of treatment with pramipexole (path coefficient -1.87), 80% (-1.49) of the effect of treatment was caused by direct effect on depressive symptoms and only 20% (-0.38) was caused by pramipexole’s effects on motor function. 12 subjects in the pramipexole group (8%) and 6 in the placebo group (4%) had severe adverse events. The number needed to harm (NNH) was 25 for severe adverse events. Meaning that for every 25 people treated with pramipexole, one will have a severe adverse event.

Table 2: BDI Responders

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Number needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18%</td>
<td>27%</td>
<td>0.5</td>
<td>0.09</td>
<td>12</td>
</tr>
</tbody>
</table>
Table 3: Comparison between PPX and Placebo: Mean change from baseline

<table>
<thead>
<tr>
<th></th>
<th>PPX (n=139)</th>
<th>Placebo (n=148)</th>
<th>Treatment group comparison</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS</td>
<td>-2.5</td>
<td>-1.7</td>
<td>-0.8</td>
<td>-1.5 to -0.1</td>
<td>0.035</td>
</tr>
<tr>
<td>UPDRS part II</td>
<td>-2.4</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.9 to -0.4</td>
<td>0.003</td>
</tr>
<tr>
<td>UPDRS part III</td>
<td>-4.4</td>
<td>-2.2</td>
<td>-2.2</td>
<td>-3.7 to -0.7</td>
<td>0.003</td>
</tr>
<tr>
<td>SHAPS-D</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>-1 to 0.0</td>
<td>0.52</td>
</tr>
<tr>
<td>BDI</td>
<td>-6.2</td>
<td>-3.7</td>
<td>-2.5</td>
<td>-4.1 to -0.8</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Rektorova et al compared pramipexole against another dopamine receptor agonist, pergolide. The two drugs differ in their chemical composition. Pramipexole is a non-ergoline preparation, while pergolide is an ergoline preparation. As a result, they act differently on dopamine receptors. A statistically significant decrease in all UPDRS scores was observed in both the pramipexole and pergolide groups at the 1% significance level. The average Self-rated subjective Zung scores decreased similarly in both groups at the 1% significance level. In terms of objective MADRS scores a statistically significant decrease was seen only in the pramipexole group at the 5% significance level. This difference was still observed after the effect of motor improvement (measured by UPDRS III) was controlled for (p =0.036).

Table 4: Mean change from baseline, pramipexole vs. pergolide

<table>
<thead>
<tr>
<th></th>
<th>UPDRS II</th>
<th>UPDRS III</th>
<th>UPDRS IV</th>
<th>Zung</th>
<th>MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>pramipexole</td>
<td>-7.6</td>
<td>-16</td>
<td>-2.5</td>
<td>-10.5</td>
<td>-5.83</td>
</tr>
<tr>
<td>pergolide</td>
<td>-8.3</td>
<td>-18.0</td>
<td>-2.2</td>
<td>-17.0</td>
<td>-1.19</td>
</tr>
</tbody>
</table>

The rate of MADRS responders (defined as a decrease of >50%) was 44% in the pramipexole group and 18.7% in the pergolide group. The Number Needed to Treat (NNT) was four. In both groups there was a statistically significant decrease in the daily levodopa dosage: 22% in the pramipexole group and -28% in the pergolide group. No statistical significant difference was noted between the two groups. Both groups were similar in regard to total number of adverse effects, except for sleep disturbance, which was seen in 4 patients (22%) in the
pramipexole group and 10 patients (62.5%) in the pergolide group. The NNH for all adverse effects was 17.

Table 5: Treatment effect for MADRS responders

<table>
<thead>
<tr>
<th>Control Event Rate (CER)</th>
<th>Experimental Event Rate (EER)</th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Number needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.7%</td>
<td>44%</td>
<td>1.35</td>
<td>0.253</td>
<td>4</td>
</tr>
</tbody>
</table>

Barone et al (2006) studied the safety and effectiveness of pramipexole when compared to an SSRI, sertraline, which is currently commonly used to treat depression in PD patients. The overall HAM-D score, which evaluated total effect of each drug on depression symptoms, decreased significantly in both groups. The overall difference was -9.03 ± 7.28 for sertraline and -10.76 ± 5.74 for pramipexole. Analysis with the Student’s T-test showed that both changes were highly significant (p<0.001). The rate of complete recovery in the pramipexole group (final HAM-D score ≤ 8) was 60.6%, significantly higher (p=0.006) than 27.3% in the sertraline group. Based on Chi squared analysis, the rate of HAM-D responders (defined by a decrease of ≥ 50%) was not significantly different between the two groups (p=0.08). Depressive symptoms in both groups decreased significantly in terms of the self reported Zung scores, from 48.1±7.4 at baseline to 35.5±10.5 for pramipexole and 49.8±7.7 to 39.3±8.8 for sertraline (both p < 0.0001, Wilcoxon test). Ancova analysis showed that the difference between groups was not significant (F = 0.56; p = 0.4586). The UPDRS II and III scores decreased in both groups. In both cases, the change was statistically significant only for the pramipexole group (p<0.05, Wilcoxon test).

Table 6: mean change from baseline of UPDRS scores

<table>
<thead>
<tr>
<th></th>
<th>Pramipexole</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS II</td>
<td>-2.8±3.5</td>
<td>-1.8±4.3</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>-5.7±8.5</td>
<td>-0.9±7.2</td>
</tr>
</tbody>
</table>
11 patients in the study reported adverse reactions, all of which were mild or moderate. Three (9.1%) from the pramipexole group reported dyskinesias, nausea, abdominal pain or hypothyroidism and eight (24.2%) from the sertraline group reported vertigo, nausea, anxiety, abdominal pain, asthenia, palpitations, influenza or tremor. No patients withdrew from the pramipexole group, but five withdrew from sertraline. The NNH was 7.

Table 7: Treatment Benefits: HAM-D Recovery

<table>
<thead>
<tr>
<th>Control Event Rate (CER)</th>
<th>Experimental Event Rate (EER)</th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Number needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.3%</td>
<td>60.6%</td>
<td>1.22</td>
<td>0.33</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 8: Risk of Adverse Reactions

<table>
<thead>
<tr>
<th>Control Event Rate (CER)</th>
<th>Experimental Event Rate (EER)</th>
<th>Relative risk increase (RRI)</th>
<th>Absolute risk increase (ARI)</th>
<th>Number needed to harm (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.2%</td>
<td>9.1%</td>
<td>0.624</td>
<td>0.151</td>
<td>7</td>
</tr>
</tbody>
</table>

DISCUSSION

Throughout all the trials, pramipexole proved to be an effective drug to treat depression in mild to moderate PD patients. In Lemke et al, both the severity and the frequency of depression as well as anhedonia and motor deficits were reduced significantly following treatment with pramipexole. This study also showed excellent applicability in that 95.3% of patients offered the SHAPS-D completed the questionnaire. This study, however, was limited by its open study design and the fact that it utilized multiple study sites. As a result a selection bias cannot be excluded.

The study by Barone et al (2010) also showed a substantially higher overall improvement in depressive symptoms in the pramipexole group over placebo as shown by both the GDS-15 and BDI scores. All of the results were modest, possibly due to the mild to moderate initial
severity of depressive symptoms. Still, there was an overall correlation between the improvement in depression and an increase in quality of life in the pramipexole group.¹ This study was enhanced by the exclusion of patients with motor fluctuations.

Rektorova, et al found that the efficacy of pramipexole was similar to that of pergolide when evaluated using Zung scores, but greater than pergolide when evaluated via MADRS, even when the effect of motor symptoms was controlled for by data analysis. It is important to note that only the MADRS and HAM-D are used to diagnose depressive disorder in PD, and as such, may be considered to be a more reliable instrument than the Zung scale for evaluating depression.² When considering the safety of pramipexole versus pergolide there were similar overall numbers of adverse reactions, but significantly more sleep disturbances in the pergolide group. A possible limitation of this study is that there was a statistically insignificant difference between the baseline values of MADRS scores (15.11 for pramipexole, 11.25 for pergolide).² It is possible that the milder initial symptoms in the pergolide group may have added bias by limiting the potential size of treatment effect. Another limitation is the small number of patients included in the study, which may affect generalisability.

Barone et al (2006) found that, based on HAM-D scales, both pramipexole and sertaline, were significantly effective in reducing depressive symptoms in PD patients (p <0.001).⁴ Pramipexole was, however, significantly more effective in inducing HAM-D recovery (final score ≤8) than sertraline. Data analysis also showed that there was no significant correlation between improvement in motor function and improvement in mood. This suggests that pramipexole exerted a direct antidepressant effect on study subjects. In terms of safety, pramipexole proved to be superior to sertraline in terms of the number of adverse events reported by subjects. Sertraline along with other SSRIs have also been associated with producing a
reversible parkinsonism in elderly patients taking this class of drugs. In patients who already experience rigidity, bradykinesia and resting tremor these effects are even more unacceptable.

Pramipexole is currently approved for the treatment of idiopathic PD and moderate to severe Restless Leg Syndrome. It is also used off label for the treatment of resistant bipolar depression in addition to mood stabilizers. There is currently an ongoing safety review in progress by the FDA regarding the significant risk of heart failure in patients taking pramipexole (RR: 1.86; 95% CI: 1.21-2.85). Pramipexole has also been associated with orthostatic hypotension, dyskinesias and impulse control problems. Therefore, blood pressure and behavioral monitoring is recommended. The cost of a 30 day supply of pramipexole is approximately $240 and is covered by most insurance companies and Medicare.

Pramipexole and all the other drugs studied in the articles included in this review are already FDA approved and commercially available for use in the United States. Also, none of the dosages of pramipexole administered in the studies exceeded the approved dose range. Thus, no new safety risks were anticipated.

CONCLUSION

Pramipexole, a non-ergoline D2/D3 dopamine receptor agonist, was proven to be a safe and effective treatment for depression in patients with mild to moderate PD. It is similar in efficacy, if not slightly more effective, than pergolide. In addition, pramipexole, at doses already utilized for control of motor symptoms, may provide a bonus antidepressant effect without the risks normally associated with anti-depressant medications. Pramipexole is not currently FDA approved for the treatment of depression in PD. All of the studies included in this review agree that further evaluation of pramipexole use as an antidepressant in PD patients is warranted.
References


8. Lexi-Comp Online, Pramipexole (Lexi Drugs), Hudson, Ohio: Lexi-Comp, Inc.; December 02, 2012.