An Exploratory Retrospective Evaluation of Ropinirole-Associated Psychotic Symptoms in an Outpatient Population Treated for Restless Legs Syndrome or Parkinson’s Disease

Steven C Stoner, Megan M Dahmen, Mignon Makos, Jessica W Lea, Lora J Carver, and Rafia S Rasu

Traditional pharmacologic treatment approaches for the management of Parkinson’s disease (PD) include the use of the dopamine precursor levodopa, as well as other direct and indirect dopamine agonists, monoamine oxidase inhibitors (MAOIs), catechol-O-methyltransferase (COMT) inhibitors, and anticholinergics.1,2 The treatment for restless leg syndrome (RLS) also often includes the use of dopamine agonists. When treating either PD or RLS in psychiatric patients, there is an inherent concern that dopaminergic agents used to treat and manage neurologic symptoms may contribute to the development or exacerbation of preexisting psychiatric features. Dopamine agonists are used in PD and RLS based on the idea that action on dopamine receptors will provide relief of neurologic symptoms through agonistic activity on striatal dopamine receptors. One theoretical benefit of dopamine agonists that are selective for the D3 receptor (eg, ropinirole) is the ability to circumvent excessive stimulation of D2 receptors in the mesolimbic regions of the brain.

Data are limited regarding the stimulation of targeted individual dopamine receptors and subsequent differences in the rates or prevalence of psychosis, although case reports suggest the potential for development of psychosis and mania with ropinirole.3,5 There is also little in...

BACKGROUND: Traditional treatment approaches for the management of restless legs syndrome (RLS) and Parkinson’s disease (PD) include the use of medications that either directly or indirectly increase dopamine levels. In turn, a potential adverse event that could be expected is the development or exacerbation of psychiatric-related symptoms.

OBJECTIVE: To evaluate and describe the incidence of psychosis and associated behavioral features in patients taking ropinirole for RLS or PD.

METHODS: Patients were identified from a computerized database search of outpatients being treated with ropinirole for 1 of 2 medical conditions: PD or RLS. Data were collected in a retrospective manner from 95 patients who were tracked over the course of their therapy to determine whether psychosis or associated behavioral symptoms developed as a result and whether an intervention was needed to adjust ropinirole dosing or if additional medications had to be added to control features associated with psychosis.

RESULTS: A total of 284 patients being treated for RLS or PD were identified; of this group, 95 patients were identified as being treated for PD or RLS with ropinirole. Of the 95 patients being treated with ropinirole, 13 developed psychotic features that required therapeutic intervention with either the use of an antipsychotic or dose adjustment of ropinirole. PD patients included in this study were numerically more likely to develop psychotic features compared with RLS patients; however, the difference was not statistically significant (p = 0.122). The results do suggest that this risk is increased when ropinirole is used as part of a dual therapy approach with dopamine agonists in the treatment of either PD or RLS (p = 0.003).

DISCUSSION: Dopamine agonists have long been used as preferred treatment in the management of PD and RLS. When treating either PD or RLS in the psychiatric population, the concern arises that increased activity at dopamine receptors may induce or exacerbate psychiatric features. A potential clinical concern with the use of ropinirole is the potential for patients to develop psychiatric features, although there are few data available to demonstrate whether stimulation of targeted individual dopamine receptors is linked to the development or exacerbation of psychotic features. It is also undetermined whether concurrent antipsychotic treatment provides any protective benefit against psychosis, especially in patients already being treated for psychotic symptoms.

CONCLUSIONS: Our findings suggest that ropinirole may play a role in inducing or exacerbating psychosis and its associated features, although a number of confounding variables prevent the determination of a clear association and suggest that further investigation is warranted in controlled clinical trials.

KEY WORDS: dopamine, Parkinson’s disease, psychosis, restless legs syndrome, ropinirole.


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formation to identify whether concurrent antipsychotic treatment provides a protective benefit against development of psychosis, particularly in patients already being treated for psychotic symptoms. Early studies of ropinirole in patients with PD found an estimated 5% prevalence rate of hallucinations in patients not concurrently being treated with levodopa, although more recent studies suggest rates of up to 17%.6-8 Early trials found that when ropinirole was combined with levodopa, the rate of reported hallucinations nearly doubled. The results of one study conflict with these results and suggest a low incidence of hallucinations, confusion, and psychosis with the combination of ropinirole and levodopa.9 In part, this finding may be the result of the study design, which allowed for reduction of the levodopa dosage in response to clinical benefits observed with dual therapy.

In contrast to findings in PD trials, the reported incidence of hallucinations from early ropinirole RLS studies was dramatically less, with hallucinations reported at a rate of less than 1% of patients in both short- and long-term trials.10-12 These findings are of particular interest when considering possible dose relationships and implementation of single-agent versus dual therapy. Attention should be given to the dosage of drugs being used, recognizing that doses of ropinirole in patients with RLS are typically lower than those used in patients with PD.

The pathophysiology of each disease state may also be an important variable when examining the prevalence of psychotic symptoms and adverse events in each patient group. One common link between the disorders is that the regulation of dopamine plays a critical role in response rates and adverse events. PD is a degenerative disorder of the central nervous system caused by neuronal impairment and dysfunctional dopamine activity in the substantia nigra and corpus striatum. Alterations in dopaminergic function contribute to the classical presentation of PD characterized by rigidity, tremor, masked facies, drooling, and shuffled gait. RLS is also a neurologic disorder that is, in part, the consequence of reduced dopamine levels and diminished dopamine activity. The clinical presentation of RLS differs from that of PD in that patients report unpleasant feelings in the legs followed by the urge to move in an effort to relieve the discomfort.

One common treatment approach for both PD and RLS is based on increasing dopamine activity. This can be accomplished through the use of the combination of levodopa/carbidopa, although the potential for developing dyskinesias and other motor symptoms within a few years of starting these agents has led practitioners to consider alternative treatment modalities as first-line drugs. Dopamine agonists have been shown to be effective treatments and are categorized as ergolinic (ergot; eg, bromocriptine, cabergoline) and nonergolinic (nonergot; eg, ropinirole, pramipexole, rotigotine). The ergot and non-ergot derivatives differ not only in chemical structure, but also in receptor affinity, half-life, and duration of action.13

As stated previously, other alternative treatments for PD include MAO-B inhibitors (eg, selegiline, rasagiline), anti-cholinergics (eg, benztropine), amantadine, and COMT inhibitors (eg, entacapone, tolcapone). Additional treatments for RLS include the use of benzodiazepines, anticonvulsants, and opioids.

The development of psychotic features can be a major limitation for the effective treatment of PD. The presence of psychotic features can be a part of the physiologic progression of PD and is estimated to occur naturally in 20–40% of patients with PD, usually in the latter stages of the disease process.14-16 The most common psychotic features occur in the form of paranoid ideations and visual hallucinations, although other symptoms may present.

A second mechanism for psychosis-related symptoms in PD patients is the overstimulation or activation of the D2 receptor from drugs, which may contribute to the development of hallucinations, delusions, agitation, and paranoid ideations. Although other dopamine receptors have been identified and studied, there have not been any trials that definitively describe the clinical implications of stimulating the D1, D3, and D4 receptor sites and possible correlation with development or exacerbation of psychosis. It is hypothesized that ropinirole is less likely to amplify or initiate the development of psychotic features due to its high selective affinity for the D3 receptor compared with the D2 receptor.17-19 In vitro studies have shown that ropinirole is 10–20 times more selective for the D3 receptor than for the D2 receptor.18-20 This activity more closely resembles endogenous dopamine than does the activity of nonselective treatments, as dopamine is estimated to be 17 times more selective for the D3 receptor.21 This theoretically implies that ropinirole should reduce the risk of psychotic symptoms compared with nonselective dopamine agonists during the treatment of PD or RLS. Additionally, increased activity at the D3 receptor has been associated with improvement of depressed mood, amotivation, and bradykinetic movement.21 Dependent upon disease state, the dosing ranges vary for symptomatic treatment of PD, starting at 0.75 mg/day and increasing to 24 mg/day, while RLS treatment starts at 0.25 mg/day and may be increased to 4 mg/day. Safety data compiled from clinical trials in both PD and RLS patients conclude that hallucinations and other psychiatric features are more often associated with doses of ropinirole that are larger than those commonly used in the management of RLS.

Despite the theory, this has not been addressed as the primary outcome measure in any published clinical trials. This naturalistic, retrospective study will provide information about patients who have been given ropinirole for up to 2 years to help determine whether there is a significant

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risk of developing new or worsening psychotic features during treatment.

Methods

OBJECTIVE

The primary objective of this retrospective study was to evaluate and describe the incidence of psychosis in patients taking ropinirole for RLS or PD and to describe the clinical interventions taken if symptoms of psychosis were reported either as new symptoms or the exacerbation of preexisting symptoms. Any patients being treated for symptoms of psychosis, depression, or a mood disorder with antipsychotic medication prior to the initiation of ropinirole were specifically analyzed as a subset to examine this effect.

STUDY DESIGN

The primary endpoint of this study was to determine whether patients developed new symptoms of psychosis or experienced a worsening of other mental health disorders while being treated with ropinirole. In the event there was a documented change in mental status, the type of clinical intervention was described and placed into one of the following categories:

1. lowering of ropinirole dose due to documentation of symptoms of psychosis;
2. discontinuation of ropinirole due to development of symptoms of psychosis;
3. inpatient admission of patient for psychiatric treatment;
4. initiation of antipsychotic treatment;
5. increased frequency or initiation of outpatient psychiatric treatment;
6. change in current antipsychotic dosing (preexisting condition); or
7. physician documentation of increased symptoms of psychosis with no intervention. Given the retrospective nature of the study, all interventions were made as part of usual and standard care.

Additional collection of data included basic demographics of age; race; sex; concurrent medications; Axis I, II, and III diagnosis; documentation of adherence; and length and history of treatment for RLS or PD.

Patients were included if they were prescribed ropinirole for PD or RLS as an outpatient. Patients were excluded if they were under the age of 18 years, if they were using ropinirole for an indication other than PD or RLS, or if the dosing was outside that of the recommended package labeling.

Statistical analysis included basic statistics on demographic information, while \( \chi^2 \) or Fisher’s exact tests were conducted as appropriate to determine associations between RLS and PD with mental illness for the development of psychosis. Statistics were conducted with STATA Data Analysis and Statistical Software, version 9.1 (Stata Corp LP, College Station, TX).

Results

Patients were first identified through a database review of all patients treated in the outpatient neurology clinic for either RLS or PD. This search identified 284 potential patients for inclusion in the study. After the initial patient group was identified, medical records were reviewed to determine whether ropinirole had ever been prescribed as a part of their treatment. From this search, 95 patients were identified as being treated for PD (n = 59), RLS (n = 35), or both (n = 1). The average age ± SD of the included patients was 69.78 ± 13.16 years. Males (n = 52) made up
the majority of the study population versus females (n = 43).

Of these 95 patients, 42 were diagnosed with and being treated for an Axis I psychiatric disorder. Some patients had multiple diagnoses, with the most frequent reported as depression (n = 33), followed by anxiety disorder (n = 13), psychosis not otherwise specified (NOS) (n = 2), bipolar I (n = 2), and schizophrenia (n = 1). While there were 42 patients with clearly documented Axis I diagnoses, there was a total of 68 patients receiving psychotropic medication including antidepressants, antipsychotics, anxiolytics, and mood stabilizers for mood.

In all, of the 95 patients who received treatment with ropinirole, 13 (13.7%) developed or experienced a worsening of psychotic or clinically associated symptoms (ie, hallucinations, delusions, paranoia, agitation, mood changes) that required intervention. With the development of these new or worsening symptoms, 2 primary types of interventions were observed: reduction of the dose of ropinirole and the introduction or dose increase of antipsychotic medication. The average daily dose of ropinirole at which a dose reduction was made was 2.86 mg/day, while the average daily dose of ropinirole at which an antipsychotic was introduced or increased was 1.19 mg/day (Table 1). There were 4 patients diagnosed or treated for schizophrenia or psychosis at the time of ropinirole initiation, although only 2 of these 4 required an intervention.

Statistical analysis showed that the diagnosis of RLS or PD was not a significant positive predictor of developing new or worsening psychotic features (p = 0.122) (Table 2). A total of 11 patients with the primary diagnosis of PD and 2 patients with RLS developed an increase in psychotic features following the initiation of ropinirole. The average age of the PD patients who developed psychotic features was 78.54 ± 8.71 years and the average age of the RLS patients was 68.5 ± 20.51 years.

Depression, which was the most common concurrent Axis I disorder, also was not shown to be a positive predictor of developing new or worsening psychotic features (p = 0.537) (Table 3). Additionally, the presence of any concurrent Axis I disorder showed no statistical significance with development of new or worsening psychotic features (p = 0.552) (Table 4).

In addition to the previously mentioned 4 patients who were already being treated with an antipsychotic medication at the time of starting ropinirole, there were 2 patients who started an antipsychotic after receiving treatment with ropinirole. In both cases the symptoms of psychosis were considered to be of new onset.

During the course of ropinirole treatment, 11 patients developed symptoms of psychosis that resulted in the ropinirole dose being lowered or discontinued. Two of these patients had also received the intervention of an antipsychotic being introduced. All 13 patients for whom an intervention was made were also receiving concurrent dopamine agonists, which was found to be significant (p = 0.003; Table 5).

### Table 1. Patients Developing Psychotic Features

<table>
<thead>
<tr>
<th>Pt</th>
<th>Disease</th>
<th>Axis I Diagnosis</th>
<th>Ropinirole Dose (mg/day)</th>
<th>When Reduced&lt;sup&gt;a&lt;/sup&gt;</th>
<th>When Antipsychotic Introduced&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PD</td>
<td>depression</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PD</td>
<td>depression</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PD</td>
<td>depression</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RLS</td>
<td>depression/anxiety</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PD</td>
<td>none</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RLS</td>
<td>psychosis NOS</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PD</td>
<td>none</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PD</td>
<td>none</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PD</td>
<td>depression</td>
<td>3.75</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>PD</td>
<td>none</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>PD</td>
<td>depression/anxiety</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>PD</td>
<td>schizophrenia</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>PD</td>
<td>none</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOS = not otherwise specified; PD = Parkinson’s disease; RLS = restless legs syndrome.

<sup>a</sup>All patients receiving a second dopamine agonist.

<sup>b</sup>Average dose 2.86 mg/day.

<sup>c</sup>Average dose 1.19 mg/day.

### Table 2. Parkinson's Disease as a Predictor of Associated Psychotic Features

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RLS</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for psychosis</td>
<td>33</td>
<td>49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82</td>
</tr>
<tr>
<td>Positive for psychosis</td>
<td>2</td>
<td>11</td>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>60</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup>One patient diagnosed with both RLS and PD was grouped with the PD cohort based on maintenance dose of 1.5 mg 3 times daily.

<sup>b</sup>Fisher’s exact test (p = 0.122).

### Table 3. Depression as a Predictor of Associated Psychotic Features

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Depression</th>
<th>Nondepression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for psychosis</td>
<td>27</td>
<td>55</td>
<td>82</td>
</tr>
<tr>
<td>Positive for psychosis</td>
<td>6</td>
<td>7</td>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>62</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup>χ² analysis (p = 0.537).
Discussion

This study showed that the use of ropinirole in patients with PD or RLS does have the potential to exacerbate or induce psychotic features, particularly when used in combination with a second dopamine-stimulating medication. Despite the targeted stimulation of dopamine receptors by ropinirole, its use may introduce an increased risk of contributing to the development of psychosis or associated symptoms, requiring a clinical intervention. Previously reported safety data from clinical trials in both PD and RLS patients have concluded that hallucinations and other psychiatric features are more commonly associated with escalated doses of ropinirole; however, our retrospective usual care study did not produce evidence to support this theory. Our findings showed that an intervention of a dose reduction of ropinirole was initiated when the average dose was 2.86 mg, while the average dose of ropinirole when an antipsychotic was introduced or the dose was increased was 1.19 mg. Of the 95 patients studied, 13 needed an intervention and all 13 patients were on dual therapy of dopamine agonists when they presented with psychotic features. Of these patients, 9 received a reduction in their ropinirole dose, 2 received both the initiation of an antipsychotic and a dose reduction of ropinirole, 2 presented with new psychotic features and required the initiation of an antipsychotic, and 2 patients previously treated for psychosis required an increase in the dose of the antipsychotic.

The findings from this small retrospective study suggest that ropinirole may play a role in the development of psychotic features during treatment for PD or RLS. Our findings suggest that the risk is lower with ropinirole mono-therapy than when it is combined with another agent with dopamine agonist properties. This conclusion, however, must take into consideration that given the retrospective nature of the study, there are multiple limitations associated with the interpretation of the results. There was not an active comparator group, dosing of ropinirole and other interventions were not controlled and were instead based upon usual care findings, and there was no formal assessment or quantifiable measure other than patient records to document the presence of psychosis and associated symptoms.

Additional limitations of this specific study preclude us from providing information related to other new selective dopamine agonists and their associated prevalence of contributing to the development of psychotic symptoms. This study was an investigator-initiated grant that was supported by the pharmaceutical company that markets ropinirole and the study proposal included only ropinirole. While our study does not specifically address this issue, we note that other newer selective dopamine agonists, such as pramipexole, have been associated with the development of psychotic features.22,23

This study focused on the prevalence or occurrence of psychotic features in patients being treated with ropinirole. The study is limited in that it does not address the overall effectiveness of the described adjustments in dosing from either reducing the dose of ropinirole or adding or increasing the dose of antipsychotic. Future study considerations should include the use of an active comparator for the overall prevalence of psychotic features. This could also include a crossover trial design where patients who develop psychotic features during treatment with one drug could be switched to another. The effectiveness of dopamine agonist dose reductions and the use of antipsychotic medications should also be included so as to provide some frame of reference on which clinicians could base their interventions from an evidence-based medicine perspective.

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References


**Evaluation Retrospectiva Exploratoria de Síntomas Psicóticos Asociados a Ropinirol en Pacientes Ambulatorios Tratados para el Síndrome de la Pierna Inquieta o la Enfermedad de Parkinson**

SC Stoner, MM Dahmen, M Makos, JW Lea, LJ Carver, y RS Rasu
MÉTHODES: Les patients ont été identifiés dans une banque de données pour les patients traités en ambulatoire et qui recevaient du ropinirole pour 1 des 2 problèmes médicaux suivants soit la maladie de Parkinson ou le syndrome des jambes sans repos. Les données ont été recueillies rétrospectivement chez 95 patients qui ont été suivis durant leur traitement pour déterminer la présence d’une psychose ou des troubles de comportement. De plus, les auteurs voulaient évaluer si la posologie du ropinirole avait été modifiée ou si des médicaments avaient été prescrits pour diminuer les effets associés à la psychose.

RÉSULTATS: Un nombre de 284 patients ont été identifiés ayant la maladie de Parkinson ou le syndrome des jambes sans repos. De ce groupe, 95 patients recevaient le ropinirole soit pour la maladie de Parkinson ou le syndrome des jambes sans repos. Un nombre de 13 patients ont développé des problèmes psychotiques qui ont nécessité une intervention thérapeutique soit l’utilisation d’un antipsychotique ou un ajustement de la posologie du ropinirole. Les patients qui souffraient de la maladie de Parkinson étaient plus à risque de développer des problèmes psychotiques que les patients ayant un syndrome des jambes sans repos; cependant, la différence n’était pas statistiquement significative (p = 0.122). Les résultats suggèrent que le risque est augmenté lorsque le ropinirole est prescrit comme traitement jumelé aux autres agonistes dopaminergiques dans le traitement de la maladie de Parkinson ou du syndrome des jambes sans repos (p = 0.003).

DISCUSSION: Les agonistes dopaminergiques sont utilisés comme médicaments de premier choix dans le traitement de la maladie de Parkinson ou du syndrome des jambes sans repos. En traitant ces patients, on peut se demander si l’augmentation de l’activité aux récepteurs dopaminergiques peut induire ou exacerber les problèmes psychotiques. Il n’a cependant pas été clairement déterminé si l’association concomitante d’un antipsychotique apportait un effet protecteur dans l’apparition d’une psychose spécialement chez les patients déjà traités pour des symptômes psychiatriques.

CONCLUSIONS: Les résultats de cette étude suggèrent que le ropinirole pourrait jouer un rôle dans l’apparition ou l’exacerbation de troubles psychotiques chez les patients avec maladie de Parkinson ou présentant avec un syndrome des jambes sans repos. Les auteurs suggèrent que des études cliniques contrôlées soient effectuées afin de préciser ce sujet.