

Ropinirole Augmentation for Depression
A Randomized Controlled Trial Pilot Study

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Gershon AA, Amiaz R, Shem-David H, Grunhaus L. A Randomized Control Trial Pilot Study of Ropinirole Augmentation for Depression. *J Clin Psychopharmacol.* 2019 Jan/Feb;39(1):78-81. doi: 10.1097/JCP.0000000000000984.

Background & Overview			
Background & Rationale	<ul style="list-style-type: none"> Ropinirole is a dopamine agonist that has higher specificity to D3 than to D2 and D4 receptors, and is used to treat Parkinsonism and Restless leg Syndrome. Evidence from animal and human studies suggests a role of dopaminergic pathways in the treatment of depression. Because Pramipexole was shown to have some promise as an antidepressant in several randomized control trials (RCTs), augmentation with Ropinirole, which is known to share similar receptor activity to that of Pramipexole was reported in preliminary clinical reports to improve depressive symptoms in cases of unipolar and bipolar patients. Hence the authors of this study decided to conduct a double blinded RCT of ropinirole augmentation in treating depression. 		
Study Objective	The purpose of this study was to examine the role and effectiveness of ropinirole as an add-on therapy in treating depressed patients.		
Methods			
Study Design & Setting	<ul style="list-style-type: none"> This study was a double-blind, randomized, placebo-controlled trial of add-on ropinirole in depressed patients recruited from outpatient psychiatric clinics and inpatient psychiatric wards of the Sheba Medical Center and Jerusalem Mental Health Center. Patients' randomization to ropinirole and placebo arms was stratified based on diagnosis (unipolar vs bipolar depression). Patients were assessed weekly by a study physician. Depressive symptoms were rated using the HAM-D as the primary outcome measure. Patients were treated and evaluated for a period of 8-weeks. 		
Study Selection	<table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top; width: 50%;"> Key Inclusion Criteria: <ul style="list-style-type: none"> Met DSM-4 criteria for MDD, BP1, BP2 21- item HAM-D \geq 16 4 weeks or more on therapeutic doses of any AD BP patients taking mood stabilizers </td> <td style="vertical-align: top; width: 50%;"> Major Exclusion Criteria: <ul style="list-style-type: none"> Current alcohol/substance abuse Actively suicidal Past/Current Psychotic symptoms Taking other mood-altering drugs History of rapid cycling bipolar disorder History of neurological/medical illness likely to affect mood (stroke, dementia, Parkinsonism) Patients with mixed, hypomanic/manic episode Pregnant </td> </tr> </table>	Key Inclusion Criteria: <ul style="list-style-type: none"> Met DSM-4 criteria for MDD, BP1, BP2 21- item HAM-D \geq 16 4 weeks or more on therapeutic doses of any AD BP patients taking mood stabilizers 	Major Exclusion Criteria: <ul style="list-style-type: none"> Current alcohol/substance abuse Actively suicidal Past/Current Psychotic symptoms Taking other mood-altering drugs History of rapid cycling bipolar disorder History of neurological/medical illness likely to affect mood (stroke, dementia, Parkinsonism) Patients with mixed, hypomanic/manic episode Pregnant
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Treatment Arms	<ul style="list-style-type: none"> Ropinirole starting dose of 0.5mg BID titrated every 3 days to Max dose of 2mg BID (N=17) <ul style="list-style-type: none"> Unipolar (N=11); Bipolar (N=6)¹ Placebo starting dose of 0.5mg BID titrated every 3 days to Max dose of 2mg BID (N=15) <ul style="list-style-type: none"> Unipolar (N=10; Bipolar (N=5)¹ 		
Outcome Measures	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> Change in HAM-D score from baseline at the end of the 7-week study period, as well as changes in hypersomnia and hyperphagia effects mentioned in the MADRS. <ul style="list-style-type: none"> Treatment response was defined as \geq 50% decrease from baseline in the total scores of both scales. <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> Variance in the Clinical Global Impression Scale and Improvement (CGI-S/CGI-I) and Visual Analog Scale (VAS) 		
Statistical Analysis	<ul style="list-style-type: none"> Group differences in demographic and clinical characteristics were analyzed using t-tests analysis (P = 0.06; was not statistically significant). Rating scale results from the ropinirole and placebo groups were compared using repeated-measures analysis of variance. 		

Results																																			
Baseline Characteristics	<ul style="list-style-type: none"> The placebo and treatment groups were similar in terms of demographics, as well as in their initial baseline scores on HAM-D, MADRS, CGI-S, and VAS scales (Table 1). All patients received AD; BP patients received mood stabilizers. AD and mood stabilizers were evenly distributed between both placebo and treatment groups. 																																		
Outcomes	<p>TABLE 1. Participant Demographics and Clinical Characteristics</p> <table border="1"> <thead> <tr> <th>Total (n = 32)</th> <th>Placebo (n = 15)</th> <th>Ropinirole (n = 17)</th> </tr> </thead> <tbody> <tr> <td>Age, mean ± SD, y</td> <td>51.3 ± 13</td> <td>52.2 ± 16</td> </tr> <tr> <td>n (female)</td> <td>15 (6)</td> <td>17 (9)</td> </tr> <tr> <td>Unipolar depression</td> <td>10</td> <td>11</td> </tr> <tr> <td>Bipolar depression</td> <td>5</td> <td>6</td> </tr> <tr> <td>HAM-D bl, mean ± SD</td> <td>21.9 ± 4</td> <td>21.8 ± 4</td> </tr> <tr> <td>HAM-D (change from bl)</td> <td>-5.45 ± 6.7</td> <td>-5.52 ± 6.5</td> </tr> <tr> <td>MADRS, mean ± SD</td> <td>32.1 ± 6</td> <td>30.0 ± 6</td> </tr> <tr> <td>MADRS (change from bl), mean ± SD</td> <td>-8.06 ± 11.7</td> <td>-7.53 ± 9.70</td> </tr> <tr> <td>CGI-S bl, mean ± SD</td> <td>5.5 ± 1</td> <td>5.2 ± 1</td> </tr> <tr> <td>VAS bl, mean ± SD</td> <td>4.8 ± 2</td> <td>5.6 ± 3</td> </tr> </tbody> </table> <p>bl indicates baseline; Change from bl, score at the end of study – score at baseline.</p>	Total (n = 32)	Placebo (n = 15)	Ropinirole (n = 17)	Age, mean ± SD, y	51.3 ± 13	52.2 ± 16	n (female)	15 (6)	17 (9)	Unipolar depression	10	11	Bipolar depression	5	6	HAM-D bl, mean ± SD	21.9 ± 4	21.8 ± 4	HAM-D (change from bl)	-5.45 ± 6.7	-5.52 ± 6.5	MADRS, mean ± SD	32.1 ± 6	30.0 ± 6	MADRS (change from bl), mean ± SD	-8.06 ± 11.7	-7.53 ± 9.70	CGI-S bl, mean ± SD	5.5 ± 1	5.2 ± 1	VAS bl, mean ± SD	4.8 ± 2	5.6 ± 3	<ul style="list-style-type: none"> A significant reduction in both HAM-D ($F_{7,24} = 3.03, P = 0.020$) and MADRS ($F_{2,24} = 2.92, P = 0.023$) scores was seen with time effect of 8-week period in depression rates of all patients. However, no time x group interaction term was observed in HAM-D ($P = 0.90$) or MADRS ($P = 0.88$) scales. Similar results were obtained in the CGI-S which improved with time ($F_{2,24} = 3.18, P = 0.016$), but no time x group interaction term was found in CGI-S. VAS scores throughout the 8-week period ($P = 0.34$) were also recorded. No significant differences were found in terms of percent change in both the HAM-D and MADRS, CGI-S and VAS depression scales across the placebo and ropinirole groups as well as in unipolar and bipolar groups (data is not shown).
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Authors' Conclusions																																			
<p>“These results differ from previous studies and are unexpected in light of theoretical considerations. This may indicate that there are differences in the pharmacological activity between ropinirole and other dopaminergic agents such as pramipexole.”</p>																																			
Discussion																																			
Weaknesses	<ul style="list-style-type: none"> The study was limited by sample size Admission of only non responders to conventional treatment (most patients had failed ≥ 1 AD) Study included participants with treatment resistant depression (TRD), which responds poorly to conventional therapy. Sample included many BP patients; BP depression is known to be much more difficult to treat with AD The maximum dosing used was 4mg/d and was based on previous open studies which supported the use of low doses for depression; doses as high as 36mg/d have been given safely in other reports. <ul style="list-style-type: none"> Ropinirole is usually given TID for treatment of parkinsonism, however this study used BID dosing regimen in order to encourage adherence and decrease side effects. Low doses or dosing regimen could have contributed to treatment failure. 																																		
Strengths	<ul style="list-style-type: none"> Broadly included Bipolar depressive patients to capture more patients. Study actually published non-significant or negative results. 																																		
Clinical Implications/Evaluation																																			
<ul style="list-style-type: none"> Further randomized, double blind, placebo-controlled studies with larger sample sizes are required to assess the effects of selective dopaminergic neurotransmission as well as the role of ropinirole in the treatment of depression. Longer treatment periods such as 12 weeks with titration schedules that have higher doses may be required in future studies, as was seen in the following study: <i>Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicenter, randomized, placebo-controlled study.</i>² 																																			

References

- Gershon AA, Amiaz R, Shem-David H, Grunhaus L. Ropinirole Augmentation for Depression: A Randomized Controlled Trial Pilot Study. *J Clin Psychopharmacol.* 2019;39(1):78-81.
- Benes H, Mattern W, Peglau I, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. *J Neurol.* 2011;258(6):1046-1054.