A Randomized, Open Label, Exploratory Trial Comparing Efficacy of Amantadine and Ropinirole in Restless Legs Syndrome

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Abstract

Objective Amantadine has both anti-glutamatergic and dopaminergic action and may improve restless legs syndrome (RLS). We compared the efficacy and adverse-effect profile of amantadine and ropinirole in RLS.

Methods In this randomized, open-label, 12-week flexible-dose exploratory study, RLS patients with international RLS study group severity scale score (IRLSS) > 10 were randomized to receive either amantadine(100-300mg/day) or ropinirole (0.5-2-mg/day). Drug dose was increased until week-6 if IRLSS failed to improve by $\geq 10\%$ of previous visit score. IRLSS change from baseline at week-12 was the primary outcome. Secondary outcomes included change in RLS-related quality of life (RLS-QOL) and insomnia severity index (ISI), along with clinical-global-impression of change/improvement (CGI-I), and proportion of patients with adverse-effects and resulting discontinuation.

Results Twenty-four patients received amantadine and 22 received ropinirole. Both groups had a significant effect for visit*treatment arm (F $(2.19,68.15) = 4.35; P = 0.01$). With a similar baseline IRLSS, both intention-to-treat (ITT) and per-protocol analyses revealed comparable IRLSS until week-8, with ropinirole appearing superior from week-10 to week-12 (week-12 IRLSS, amantadine vs ropinirole:17.0 ± 5.7 vs 9.0 ± 4.4; $P < 0.001$). ITT analysis at week-12 showed comparable proportion of responders ($\geq 10\%$ IRLSS reduction) in both groups ($P = 0.10$). Both drugs improved sleep and QOL, but week-12 scores favoured ropinirole [(ISI:14.4 ± 5.7 vs 9.4 ± 4.5; $P = 0.001$) ;(RLS-QOL:70.4 ± 17.9 vs 86.5 ± 9.8; $P = 0.005$)]. CGI-I at week-12 favoured ropinirole (Mann-Whitney U $= 35.50$, S. E $= 23.05; P = 0.01$). Four patients in amantadine and

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► N-Methyl-D-Aspartic acid
► Insomnia

two in ropinirole group developed adverse effects, with resulting discontinuation in two patients on amantadine.

Conclusions The present study reports equivalent reduction in RLS symptoms with both amantadine and ropinirole until week-8, with the latter being superior from week-10 onwards. Ropinirole was better tolerated.

Introduction

Restless legs syndrome (RLS) is a common neurological disorder characterized by an urge to move legs accompanied by abnormal sensations deep inside the muscles, occurring at rest, especially in evening, and alleviated by movement of the affected limb(s).[1] RLS may affect all ages. Its prevalence ranges from 5–15% in general population, with females being more commonly affected.[2,3] As compared to West, the prevalence is lower in Indian population (2-3%).[4,5] Although unclear, the pathophysiology of RLS appears to include a disruption in dopaminergic neurotransmission in patients having genetic predisposition to RLS, apparently precipitated in the presence of environmental and co-morbid disorders.[6] Functional deficiency of dopamine in basal ganglia and iron deficiency in central nervous system are thought to play a role in its pathophysiology.[7] In addition, hypersensitivity of cortico-striatal glutamatergic pathways and higher basal glutamate levels in thalamic neurons have also been reported in patients with RLS.[8]

Several pharmacological and non-pharmacological treatments have been studied for RLS. First-line pharmacological treatments of RLS include dopaminergic agents including ropinirole, pramipexole, rotigotine and alpha 2 delta ($\alpha2\delta$) ligands such as gabapentin enacarbil and pregabalin.[9] Although dopamine agonists and $\alpha2\delta$ ligands have proven efficacy in RLS, at least in short term, they may have bothersome adverse-effects viz., impulsivity, weight gain and depression.[7] In addition, appearance of augmentation with dopaminergic agents further compounds the problem, which has been reported in one-fifth of RLS patients and occurs in 8% patients per year.[10] These issues warrant exploration of pharmacological agents that are at least equi-efficacious and safer for RLS management.

Amantadine, a weak N-Methyl-D-Aspartic acid (NMDA) antagonist which increases release of dopamine and prevents its reuptake, has proven safety and efficacy in Parkinson's disease.[11] In addition, its anti-glutamatergic effect may also negatively modulate the cortico-striatal hypersensitivity and heightened glutamate activity in thalamus.[12] It is also not known to have adverse-effects associated with other dopaminergic medications described above. Because of these properties, it may improve RLS without having major adverse effects. However, to date only one open label study is available which shows that it may improve RLS.[13]

We hypothesized that amantadine would have efficacy equivalent to ropinirole, but a safer adverse effect profile compared to ropinirole. Hence, this comparative exploratory study was planned to compare efficacy and adverse effect profile of amantadine and ropinirole among patients having RLS.

Material and Methods

This randomized, open-label, 12-week flexible dose, exploratory trial was registered (Trial ID REF/2019/04/025566, CTRI/2020/11/029296) and approval from institutional ethics committee was obtained. Considering the large placebo response among patients with RLS,[14] an equivalence margin of $< 35\%$ difference in response rate during the course of trial was defined for accepting two drugs to be equal (available at https://www.sealedenvelope.com/power/binary-equivalence/).[15] Clinically significant response rate ($\geq$ 10% decrease in IRLS score) in treatment groups was assumed to be 90%. Fifteen patients were required in each group to give a power of 90% and alpha value of 5% for equivalence trial. A sample size of 15 completed patients in each group (30 in total) was found appropriate for this study, with an allocation ratio of 1:1.[16,17] The expected dropout rate was 10-15% in each arm. However, polysomnography had to be removed from the trial in view of sleep laboratory being closed due to coronavirus disease-19 (COVID-19) pandemic.

All patients, > 18 and < 60 years age, visiting Sleep Disorders Clinic and Movement Disorders Clinic from February 2020 to February 2021 were screened for RLS using International RLS study group criteria,[1] by two authors (RG and NK) experienced in diagnosis and management of RLS. RLS diagnosis was based on face-to-face interview along with clinical examination. Patients symptomatic for at least 6 months at the time of screening, with RLS symptoms occurring ≥ 15 nights per month, were requested to participate. However, patients were excluded if they were meeting any of the following criteria- patients using non-pharmacological measures for management of RLS (e.g., sequential compression devices), having symptomatic neuropathies or current diagnosis of clinically relevant concomitant conditions that may confound clinical assessments of RLS and/or severe enough to disturb sleep; Pregnant women; had neurodegenerative diseases that interfered with interview; using medications that were likely to influence sleep architecture or interacting with dopaminergic system e.g., dopaminergic agents, sedatives, hypnotics, antipsychotics, cannabis, opioids, opiates; had low Glomerular filtration rate (calculated by formula- eGFR < 60ml/min/1.73m^2 body surface area); Hemoglobin < 10gm/dl; and if they had known hypersensitivity to any components of the trial medication or similar drugs.

Eligible patients were explained the rationale of the study. Consecutive patients providing written informed consent and having IRLS score >10, with/without any medication for treatment of RLS, were included. Patients on any medication for RLS symptoms were given a wash-out period of 4 weeks. Severity of RLS at the time of starting the trial medication was considered as the baseline IRLS score.

The primary end point was change in IRLS score from baseline following initiation of therapy at week 12. The secondary endpoints included change in RLS related quality of life, severity of insomnia and overall clinical impression of change/improvement from baseline at week 12. In addition, adverse events related to the therapies were recorded.

Assessments

International RLS study group severity rating scale (IRLS) [18,19] was used to assess severity of RLS; quality of life among RLS patients was assessed using RLS Quality of Life (RLS-QOL) scale,[20,21] and Insomnia severity index (ISI)[22,23] was used to assess the presence and/or severity of insomnia symptoms. Clinical global impression-Improvement/change (CGI-I) scale[24] was used to assess global improvement. Permission was obtained from the relevant agencies for using these questionnaires. While IRLS score was assessed every two weeks (week 0, 2, 4, 6, 8,10, and 12), ISI and RLS-QOL were assessed at baseline and end of week 12. CGI-I scale was used to assess the improvement in clinical condition at week 12.

Assessment of patients was done in outpatient department at baseline and at week 12 visit. For other visits, patients were given the flexibility to contact treating team either through tele-medicine services or physically in the outpatient department. However, they were encouraged to attend the outpatient services whenever possible.

International RLS Study Group Rating Scale (IRLS)

Developed by International RLS Study group (IRLSSG) in 2003, IRLS assess and quantify the RLS symptoms during past one week. It is a 10-item scale, and each item is scored on a 4 point Likert's scale (0 = absence of the symptom, 4 = very severe symptom). This scale classifies severity of RLS on a score ranging between 0-40 and indicates the frequency and severity of RLS symptoms and their impact on sleep, mood, and activities of daily living. Score up to 10 are considered mild, between 11 to 20 as moderate, 21 to 30 as severe, and 31 to 40 as very severe RLS.[19] Validated Hindi version of IRLS having high internal consistency (Cronbach's Alpha 0.86) was used in this study.[18]

Insomnia Severity Index (ISI)

It's a patient reported measure which assesses presence and/or severity of insomnia during past seven days. Score ranges between 0-28. Score below 7 is considered clinically insignificant insomnia, 8-14- mild, 15-21 moderate and 22-28 as severe insomnia.[23] It's validated Hindi version was used (Cronbach's Alpha of 0.91).[22]

RLS Quality of Life (RLS-QOL)

RLS-QoL is an 18-item scale to assess the impact of RLS on daily life in several domains ranging from professional, emotional, and social. Higher score of RLS-QoL indicate a better quality of life. It has a high internal consistency (Cronbach's alpha 0.92) and acceptable test-retest reliability (interclass correlation coefficient 0.84).[21] For Hindi speaking patients, a validated Hindi questionnaire was used (Cronbach's alpha 0.85).[20]

Clinical Global Impression-Improvement/change (CGI) Scale

CGI offers a brief and practical measurement tool which can be easily administered by a clinician.[24] It is a three-item clinician-rated scale, that measures illness severity (CGI-S), global improvement or change (CGI-I) and therapeutic response. In this study, CGI-I part of the scale was used, which has scores ranging from 1 (very much improved) through to 7 (very much worse).

Adverse Effects

At each visit, patients were asked regarding any problem, other than those related to RLS, after starting the new drugs in the trial, since the last visit. Proportion of patients developing adverse effects and resulting discontinuation were assessed.

Intervention

Patients were randomly assigned to receive amantadine (100-300 mg PO flexible dose) and ropinirole (0.5-2mg PO flexible dose), once daily, 1-3 hours before bedtime. Simple randomization was done using a computer-generated randomization list. This list was kept securely with the author (PD) who was not involved in the clinical assessment of patients, and he assigned the patients to one of the treatment arms. Assignment to groups was disclosed for one patient at a time.

Amantadine was started at the dose of 100 mg per day. Dose was increased by 100mg every two weeks up to a maximum of 300 mg per day, if the IRLS score failed to improve by at least 10% of the previous visit score. Patients in ropinirole arm were started with 0.5 mg per day with followed by an increase of 0.5mg every two weeks until the maximum daily dose of 2 mg, if the IRLS score failed to improve by at least 10% of previous visit score. If there was inability to tolerate a higher dose, it was reduced to the previous level. Dose adjustments were allowed only for the first six weeks and thereafter the patients were maintained on a stable does for the next six weeks.

Patients who were lost to follow up or developed serious adverse effects (not relieved with time or dose reduction) and those non-compliant to therapy were discontinued. For each dropout, a new patient was included so as to complete 15 patients in each arm. Adverse events from treatment were monitored throughout the trial.

Statistical Analysis

The analysis was done using Statistical Package for Social Sciences (SPSS) v 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Mac, Version 28.0.1.0 (142) Armonk, NY: IBM Corp.) Analysis was done using two methods - per protocol

and intention to treat (ITT) using last observation carried forward method for imputation. Patients completing follow-up and assessments at least up to 6 week following initiation of the therapy were included in ITT analysis. Descriptive statistics was calculated. Normality of data was tested using Shapiro-wilk test. Chi Square test was used to compare categorical variables across groups. To compare continuous variables across groups that were normally distributed, paired t test and independent sample t test were applied. Man-Whitney U test was done to compare continuous variables not having normal distribution (CGI-I).

A mixed ANOVA with Bonferroni correction was used to compare improvement in IRLS score over the study period. Age, duration of illness, family history of illness and serum ferritin at baseline were taken as co-variates. While comparing the change in RLS severity across seven timepoints of measurements, test of sphericity could not be met in the sample; hence Greenhouse-Geiser corrected degrees of freedom were used while interpreting the results. Levene's test depicted a homogenous variance.

Results

A total of 77 patients fulfilling the diagnostic criteria for RLS were screened for inclusion in the trial, out of which 31 were excluded and 46 underwent randomization. Thirty-seven patients completed week 6 follow-up, 19 in the amantadine and 18 in the ropinirole group and were included in ITT analysis (►Figure 1). Data obtained in this study were normally distributed except for CGI-I. (►Supplementary Table S1). Trial ended after 15 patients in each group

completed the week 12 follow-up and these patients were included in per-protocol analysis.

Baseline characteristics of patients in amantadine and ropinirole groups were comparable, irrespective of ITT or per-protocol analysis (►Table 1). The most common words used to describe the RLS symptoms were pain (43.5%, 20), restlessness (23.9%, 11), unpleasant sensation (15.2%, 7), stiffness (10.9%, 5), and insect-crawling like sensation (8.7%, 4). Twenty-nine (63.04%) patients never received any drug for their RLS symptoms. Patients already on medication for RLS were comparable in between both arms (►Supplementary Table S2). While ropinirole was used by three patients in the past, none had taken amantadine.

After 6 weeks of treatment, patients in ITT analysis were either on amantadine monotherapy (mean [SD] = 210.52 [65.78] mg per day; range 100–300 mg per day) or ropinirole (mean [SD] = 0.97 [0.46] mg per day; range 0.5–2 mg per day).

As per ITT analysis at 12 weeks, proportion of responders ($\geq$ 10% reduction in IRLS score) in both the groups was comparable (P = 0.10) (►Figure 2). A mixed ANOVA was applied to compare the change in IRLS score across visits between the two treatment groups (►Figure 3; ►Supplementary Table S3; ►Supplementary Table S4). Mauchly's test of sphericity was violated in both ITT and per-protocol analysis. Hence, Greenhouse-Geisser values were considered. On ITT analysis, a significant effect for visit*treatment arm ($F_{(2.19, 68.15)} = 4.35$; P = 0.01) was observed. A significant effect of "treatment arm," ($F_{(1, 31)} = 10.12$; P = 0.003) and "duration of illness," ($F_{(1, 31)} = 5.28$; P = 0.02) was observed in "between the patients"
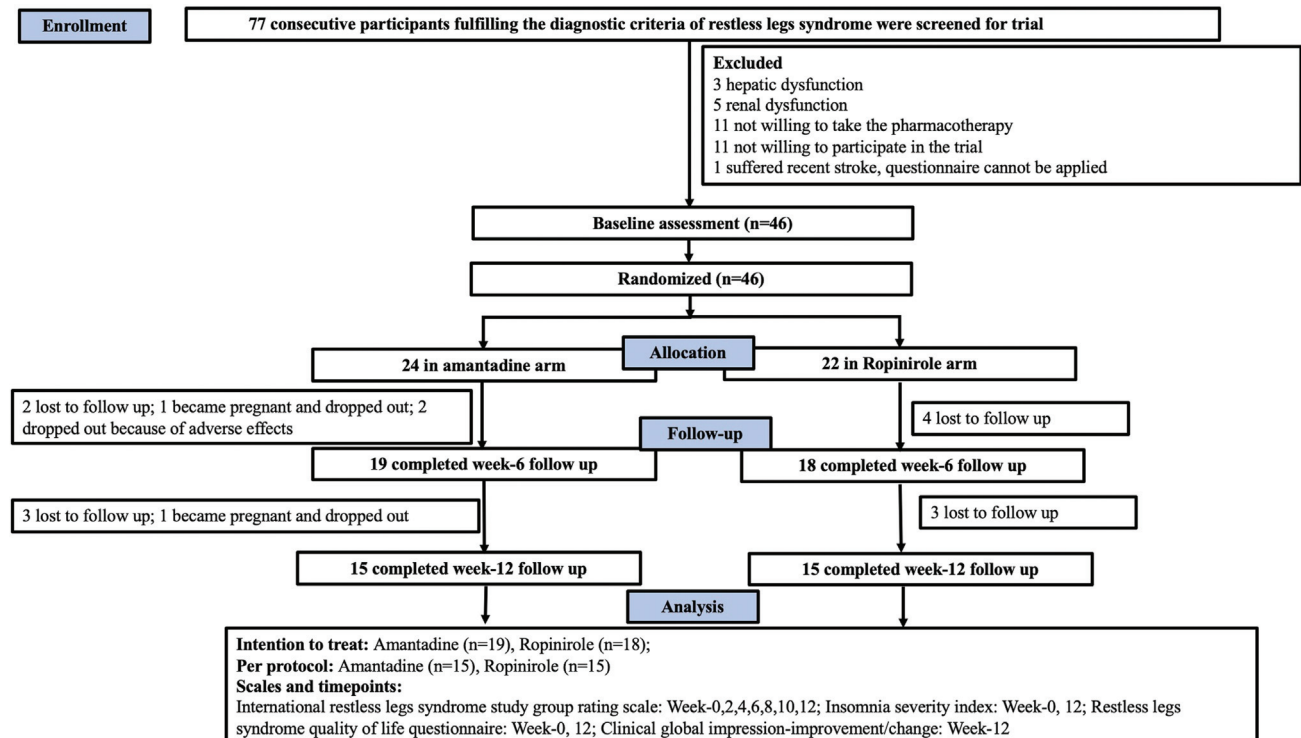

Fig. 1 CONSORT flowchart for screening, inclusion, and dropout.

Table 1 Baseline demographic and clinical parameters of patients included in the trial.

Sl. No.	Parameters	Intention to treat			Per protocol		
		Amantadine arm (n = 19)	Ropinirole arm (n = 18)	P-value	Amantadine arm (n = 15)	Ropinirole arm (n = 15)	P-value
1	Age in years: mean (SD)	40.3 (12.4)	40.6 (11.6)	0.94	41.4 (13.2)	40.1 (12.0)	0.77
2	Gender (Female): n (%)	13 (68.4%)	12 (66.7%)	0.90	10 (66.7%)	10 (66.7%)	1.00
3	Disease duration in years: mean (SD)	3.4 (2.2)	4.6 (3.1)	0.18	3.6 (2.4)	4.8 (3.4)	0.29
4	Delay in Diagnosis in years: mean (SD)	3.2 (2.1)	4.2 (3.0)	0.26	3.5 (2.3)	4.4 (3.2)	0.39
5	Chronic persistent RLS: n (%)	13 (68.4%)	13 (72.2%)	0.80	10 (66.7%)	11 (73.3%)	0.690
6	Associated restless Arms: n (%)	9 (47.4%)	6 (33.3%)	0.38	7 (46.7%)	5 (33.5%)	0.456
7	Family history of RLS: n (%)	8 (42.1%)	5 (27.8%)	0.36	8 (53.3%)	3 (20.0%)	0.066
8	Associated comorbidities						
A	Hypertension: n (%)	5 (26.3%)	2 (11.1%)	0.23	3 (20.0%)	1 (6.7%)	0.283
B	Diabetes mellitus: n (%)	3 (15.8%)	2 (11.1%)	0.67	3 (20.0%)	1 (6.7%)	0.283
C	Migraine: n (%)	6 (31.6%)	7 (38.9%)	0.64	5 (33.3%)	7 (46.7%)	0.456
D	Hypothyroid: n (%)	3 (15.8%)	2 (11.1%)	0.67	2 (13.3%)	1 (6.7%)	0.543
9	RLS and sleep scores						
A	IRLS score at baseline: mean (SD)	23.4 (5.1)	22.4 (7.8)	0.63	23.8 (5.4)	24 (7.3)	0.93
B	RLS-QOL at baseline: mean (SD)	59.6 (17.8)	58.8 (23.6)	0.90	58.1 (19.5)	55.90 (23.8)	0.77
C	ISI at baseline: mean (SD)	18.7 (5.0)	19.5 (6.5)	0.69	19.4 (5.3)	20.9 (5.0)	0.42
10	Severity of RLS						
A	Moderate RLS	5 (26.3%)	8 (44.4%)	0.08	3 (20.0%)	5 (33.3%)	0.15
B	Severe RLS	13 (68.4%)	6 (33.3%)		11 (73.3%)	6 (40.0%)	
C	Very severe RLS	1 (5.3%)	4 (22.2%)		1 (6.7%)	4 (26.7%)	
11	Hemoglobin (gm%): mean (SD)	11.4 (1.7)	11.8 (1.7)	0.27	11.7 (1.8)	11.9 (1.9)	0.74
12	Serum Iron (mcg%)*: mean (SD)	75.8 (31.3)	67.7 (29.6)	0.21	75.2 (32.1)	68.7 (32.0)	0.58
13	Serum ferritin (ng/ml)*: mean (SD)	126.9 (57.4)	135.9 (65.9)	0.33	122.5 (52.8)	142.7 (68.4)	0.37

Abbreviations: IRLS score: International restless legs syndrome severity score; ISI: insomnia severity index; RLS-QOL: RLS quality of life scale; RLS: restless legs syndrome; SD: standard deviation.
Chi-Square test was used to compare categorical variables across groups. Continuous variables across groups were normally distributed and compared using independent sample t test.
*None of the patients in either group had low serum iron or ferritin levels requiring an iron supplement.

comparison. However, no effect was observed for visit*age, visit*duration of illness, visit*family history, and visit*ferritin.

Similar results were obtained using per-protocol analysis (►Figure 3; ►Supplementary Table S3; ►Supplementary Table S5) where a significant mean effect for visit*treatment arm, (F(2.36, 56.69) = 5.25; P = 0.005) in "within the patients" comparison and for "treatment arm," (F (1, 24) = 5.80; P = 0.02) and "duration of illness," (F (1, 24) = 4.50; P = 0.04) in "between the patients" comparisons was observed. However, no effect was observed of visit*age, visit*duration of illness, visit*family history, and visit*ferritin.

Improvement in IRLS appeared within first 2 week with both the drugs. The IRLS score showed a progressive improvement over the 12-week period in patients on ropinir-

ole, but it stabilized after week 6 in the amantadine group. ►Figure 3 shows that the confidence intervals of mean IRLS scores in both groups are overlapping until visit 5 i.e., week 8 follow-up. Thereafter, compared to the amantadine group, patients in the ropinirole group had a significantly lower IRLS score from week 10 to week 12 in both ITT and per-protocol analyses (►Figure 3; ►Supplementary Table S3). Sleep disturbance and RLS related quality of life were comparable at the baseline between two groups, however, it improved significantly in both groups by week 12, with greater improvement in ropinirole arm (►Table 2). CGI-I at week 12 favoured ropinirole (Mann-Whitney U = 35.50, S. E = 23.05; P = 0.01).

Adverse effects were reported by two patients (9.1%) in ropinirole group, and four (16.7%) in amantadine group. Two of these four patients in the amantadine group chose to
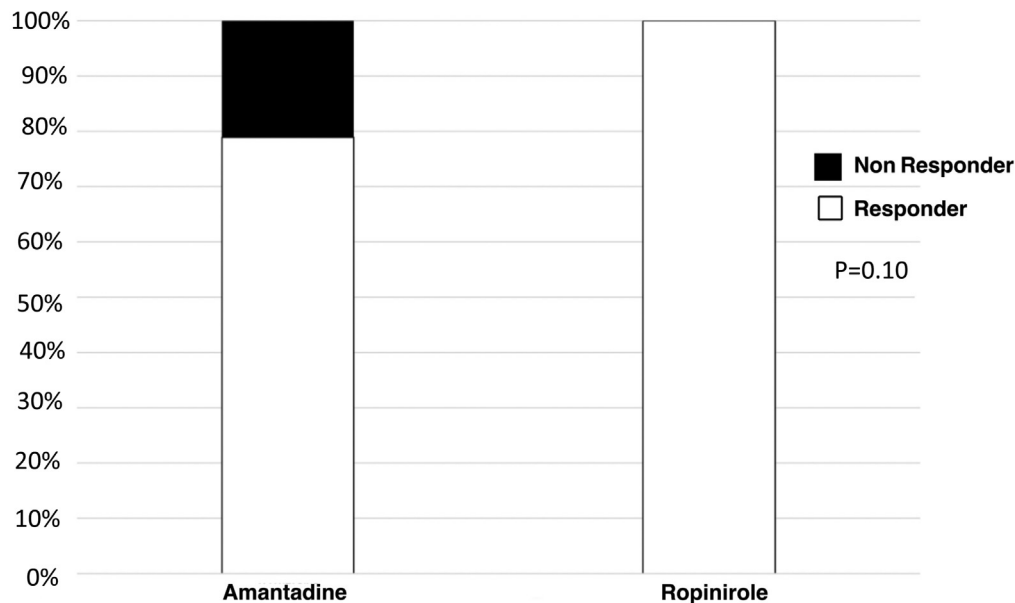
Fig. 2 Proportion of patients having international restless legs syndrome study group severity score reduction ≥ 10% from baseline at 12 weeks.

discontinue amantadine before week 6. One had blurring of vision, and the other developed recurrent vomiting and blurring of vision. The other two patients had constipation and dizziness respectively, however, these adverse effects were mild and resolved over time. In ropinirole arm, diarrhoea and perioral paraesthesia were reported by two patients, however, they were mild and transient.
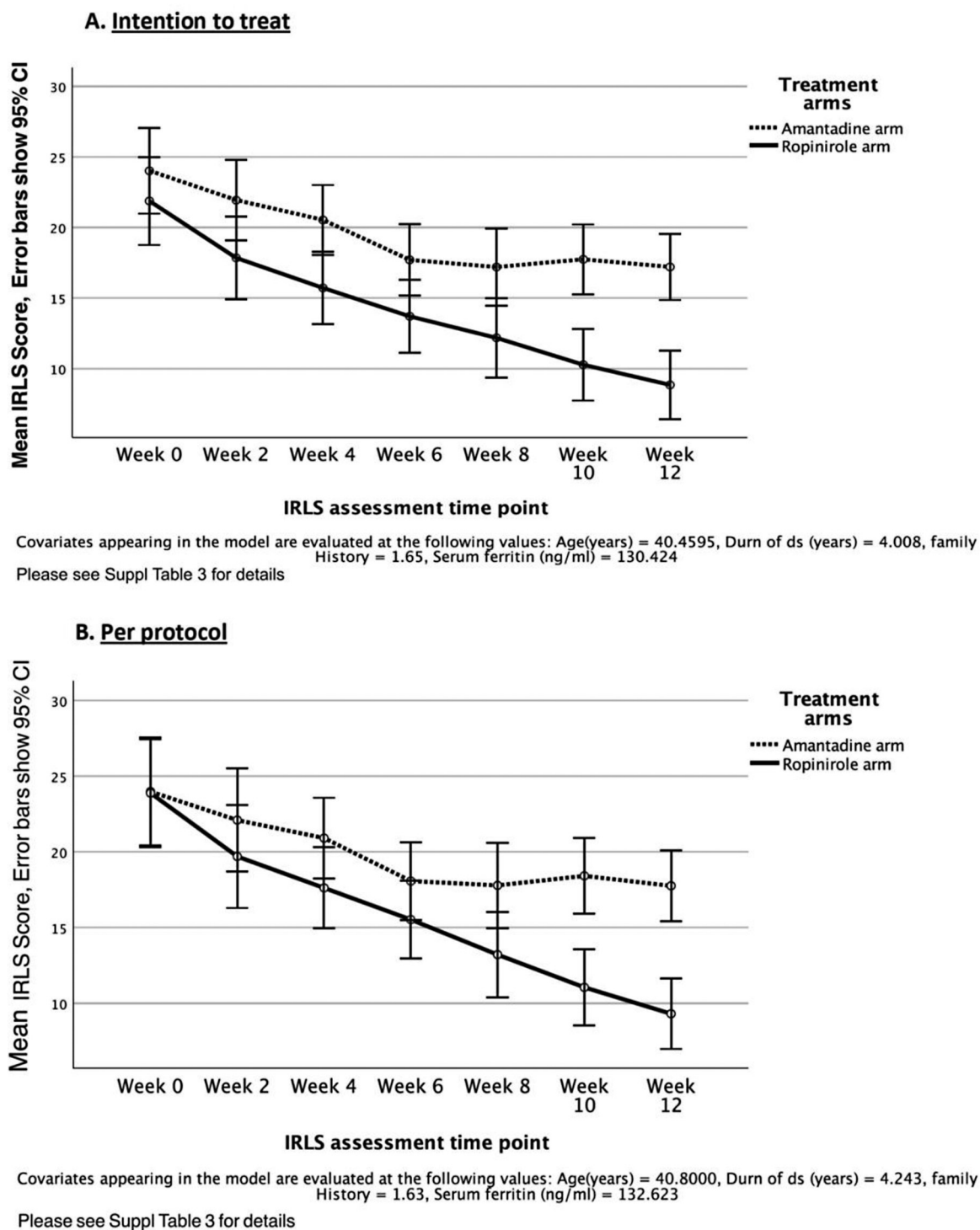
Discussion

This study showed that in middle-aged patients having moderate to severe RLS, a 12-week therapy with either amantadine or ropinirole reduces the severity of RLS symptoms. For both the drugs, the improvement in IRLS score appeared within first 2 week. While the improvement in IRLS score continued through the 12-week period in ropinirole group, it stabilized after week 6 in patients on amantadine. As compared to amantadine group, patients in ropinirole group had a significantly lower IRLS score from week 10 to week 12. Results remained unaffected by either method of analysis, ITT as well as per protocol. In addition, an improvement in sleep and quality of life was observed with both drugs, with a greater improvement in the ropinirole group. CGI-I at week 12 favoured ropinirole. A higher proportion of patients in the amantadine group developed adverse effects.

Ropinirole, a non-ergot dopaminergic agonist, has US Food and Drug Administration (FDA) approval for use in RLS.[25] Based on several randomized controlled trials, a task force commissioned by the International Parkinson and Movement Disorder Society (2017), has reported ropinirole (0.78–4.6 mg/ day) to be efficacious in RLS.[9] Results of the present study are in concordance with earlier findings. However, previous trials of ropinirole included European and American population which might be genetically different from the Indian population studied in the present trial.[26–29] Additionally, patients in these studies were older,

had longer duration of illness compared to present study, and studies adopted different methodologies making direct comparison difficult.[26–33] In addition to its comparison with placebo,[26,34] ropinirole has been compared with other drugs including gabapentin[35] and bupropion,[36] but never with amantadine.

To date only one single-arm prospective open-label study, involving 21 patients, reported improvement in RLS symptoms with amantadine, used in a flexible dose of 100 - 300 mg/day.[13] While the mean dose of amantadine[13] was 227 mg/day in the previous study, it was 210.52 mg/day in present study. A number of factors could be responsible for difference in doses viz., older age of patients (average age 70 ± 9 years compared to 40.3 ± 12.4 years in the present study), longer duration of illness (average duration 18 ± 17 years compared to 3.4 ± 2.2 years in the present study), non-improvement with the management of RLS (57% in previous trial compared to 36.9% in present study), presence of peripheral polyneuropathy (38% in previous trial compared to none in present study), and timed dose escalation (every 3-5 days) compared to escalation based on change in IRLS score in present study.[13]

Present study differs from that by Evidente et al.[13] in several ways other than mentioned above- first, RLS severity in the present trial was assessed using a validated questionnaire, absence of concomitant medications, scheduled assessment points during the study, which add to the reliability of the results. However, the present study shows benefit from the amantadine for 3 months, while Evidente et al[13] reported persistent benefit for up to 13 months (mean, 3.6 ± 4.5 months) in nearly half of their 21 patients without augmentation and rebound. Duration of present study is too short to comment on augmentation. The adverse effects encountered in present study have been previously reported.[11,27] Ropinirole was better tolerated than amantadine throughout the study period.

A. Intention to treat

Covariates appearing in the model are evaluated at the following values: Age(years) = 40.4595, Durn of ds (years) = 4.008, family History = 1.65, Serum ferritin (ng/ml) = 130.424
Please see Suppl Table 3 for details

B. Per protocol

Covariates appearing in the model are evaluated at the following values: Age(years) = 40.8000, Durn of ds (years) = 4.243, family History = 1.63, Serum ferritin (ng/ml) = 132.623
Please see Suppl Table 3 for details

Fig. 3 Graphical representation of effect of amantadine and ropinirole on International restless legs syndrome study group rating scale (IRLS) score at different timepoints in amantadine and ropinirole arm using (A) intention to treat and (B) per-protocol analysis. Please refer to ►**Supplementary Table S3** for details regarding IRLS score at different timepoints.

We hypothesized that amantadine would bring greater improvement in RLS compared to ropinirole as amantadine had two pronged action, anti-glutamate as well as dopaminergic facilitation,[12] compared to ropinirole which is traditionally believed to activate only the post-synaptic dopamine D2 receptors.[37] However, this study showed while both were found to be efficacious in reducing RLS severity as well as improving sleep and quality of life, ropinirole was significantly superior to amantadine. As compared to amantadine group, patients in ropinirole group had a significantly lower IRLS score from week 10 to week 12. Recent advancement in pathophysiology of RLS have shown that it is a state of

Table 2 Comparison of sleep and quality of life within and across groups (Per protocol analysis).

	Scores and timelines	Amantadine arm (n = 15)	Ropinirole arm (n = 15)	P** value	Cohen's d (95% CI)
1	**ISI score:** mean (SD)				
	At week 0	19.4 (5.3)	20.9 (5.0)	0.42	–
	At week 12	14.4 (5.7)	9.4 (4.5)	**0.01**	0.98 (0.21 to 1.73)
	P-value*	**0.004**	**<0.001**		
	Cohen's d (95% CI)	0.88 (0.27 to 1.47)	2.62 (1.53 to 3.7)		
2	**RLS-QOL score:** mean (SD)				
	At week 0	58.1 (19.5)	55.9 (23.8)	0.77	–
	At 12 weeks	70.4 (17.9)	86.5 (9.8)	**0.005**	-1.11 (-1.87 to -0.33)
	P-value*	**0.009**	**< 0.001**		
	Cohen's d (95% CI)	-0.784 (-1.35 to -0.19)	-1.57 (-2.33 to -0.79)		

Abbreviations: CI: Confidence interval; ISI: Insomnia severity index, RLS-QOL: Restless Legs Syndrome - Quality of life score.
P*: Paired sample test.
P**: Independent sample test.

presynaptic dopamine excess, with increased synthesis and release of dopamine that contribute to akathisia, and hyper-glutamatergic along with hyper-adenosinergic state leading to arousal part.[8] In addition, work on animal models of RLS suggested a possible anti-glutamatergic role of ropinirole, in addition to its dopaminergic modulation action.[38] The weak anti-glutamatergic effect of amantadine, related to its low-affinity and non-competitive NMDA-receptor antagonism,[12] appears a plausible reason for earlier plateau in its effect.

In addition to RLS, amantadine also improved insomnia. This may be ascribed to the anticholinergic effect of amantadine. Improvement in quality-of-life scores may be because of its antidepressant, mood-elevating, attention-improving, anti-fatigue, and sexual function improving properties.[39] Amantadine has also been shown to facilitate the action of dopaminergic agents.[12] This raises a possibility of its role as an adjuvant to the mainstream dopamine therapy among partial responders that should be investigated in future.

Like any other scientific investigation, present study also has some limitations. First, sample size was small and study period was short. Second, although randomized, our study was open label. Third, as compared to other reported studies, patients were younger and had a shorter disease duration. Fourth, there was no placebo arm in this study. Lastly, dose of amantadine could have been increased further. Future studies using higher doses of amantadine or using it in combination with dopamine agonists may advance our understanding of its use in RLS.

Conclusions

The present study reports equivalent improvement in RLS symptoms in middle-aged patients having moderate to severe RLS using either amantadine or ropinirole for 8 weeks. However, from week 10 to week 12, ropinirole appeared superior in efficacy for reducing the RLS symptoms. Ropinirole was better tolerated than amantadine throughout the study. Though amantadine shows an efficacy similar to ropinirole in reducing RLS symptoms in short-term, yet its tolerability remains a concern.

References

1 Allen RP, Picchietti DL, Garcia-Borreguero D, et al; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med 2014; 15(08):860–873. Doi: 10.1016/j.sleep.2014.03.025

2 Koo BB. Restless Leg Syndrome Across the Globe: Epidemiology of the Restless Legs Syndrome/Willis-Ekbom Disease. Sleep Med Clin 2015;10(03):189–205, xi. Doi: 10.1016/j.jsmc.2015.05.004

3 Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 2004;164(02):196–202. Doi: 10.1001/archinte.164.2.196

4 Gupta R, Ulfberg J, Allen RP, Goel D. High prevalence of restless legs syndrome/Willis Ekbom Disease (RLS/WED) among people living at high altitude in the Indian Himalaya. Sleep Med 2017;35(35):7–11. Doi: 10.1016/j.sleep.2017.02.031

5 Rangarajan S, Rangarajan S, D'Souza GA. Restless legs syndrome in an Indian urban population. Sleep Med 2007;9(01):88–93. Doi: 10.1016/j.sleep.2006.11.004

6 Guo S, Huang J, Jiang H, et al. Restless legs syndrome: From pathophysiology to clinical diagnosis and management. Front Aging Neurosci 2017;9(JUN):171. Doi: 10.3389/fnagi.2017.00171

7 Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013;14(07):675–684. Doi: 10.1016/j.sleep.2013.05.016

8   Ferré S, García-Borreguero D, Allen RP, Earley CJ. New Insights into the Neurobiology of Restless Legs Syndrome. Neuroscientist 2019;25(02):113–125. Doi: 10.1177/1073858418791763

9   Winkelmann J, Allen RP, Högl B, et al. Treatment of restless legs syndrome: Evidence-based review and implications for clinical practice (Revised 2017)§. Mov Disord 2018;33(07):1077–1091. Doi: 10.1002/mds.27260

10 Allen RP, Ondo WG, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Med 2011;12(05):431–439. Doi: 10.1016/j.sleep.2011.03.003

11 Crosby N, Deane K, Clarke C. Amantadine in Parkinson ' s disease. (Review). Cochrane Database Syst Rev 2009;22(01):1–23. Doi: 10.1002/14651858.CD003468.www.cochranelibrary.com

12 Rascol O, Fabbri M, Poewe W. Amantadine in the treatment of Parkinson's disease and other movement disorders. Lancet Neurol 2021;20(12):1048–1056. Doi: 10.1016/s1474-4422(21)00249-0

13 Evidente VGH, Adler CH, Caviness JN, Hentz JG, Gwinn-Hardy K. Amantadine is beneficial in restless legs syndrome. Mov Disord 2000;15(02):324–327. Doi: 10.1002/1531-8257(200003)15:2<324:AID-MDS1020>3.0.CO;2-4

14 Fulda S, Wetter TC. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. Brain 2008;131(Pt 4):902–917. Doi: 10.1093/brain/awm244

15 Sealed Envelope Ltd. Power calculator for binary outcome equivalence trial. [Online].Available from: [Accessed Tue Dec 07 2021] . https://www.sealedenvelope.com/power/binary-equivalence/

16 Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat 2005;4(04):287–291. Doi: 10.1002/pst.185

17 Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008;31(02):180–191. Doi: 10.1002/nur.20247

18 Gupta R, Lahan V, Goel D. Translation and validation of international restless leg syndrome study group rating scale in hindi language. Ann Indian Acad Neurol 2011;14(04):257–261. Doi: 10.4103/0972-2327.91939

19 Walters AS, LeBrocq C, Dhar A, et al; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4(02):121–132. Doi: 10.1016/S1389-9457(02)00258-7

20 Vishwakarma K, Lahan V, Gupta R, et al. Translation and validation of restless leg syndrome quality of life questionnaire in Hindi language. Neurol India 2012;60(05):476–480. Doi: 10.4103/0028-3886.103188

21 Abetz L, Vallow SM, Kirsch J, Allen RP, Washburn T, Earley CJ. Validation of the Restless Legs Syndrome Quality of Life questionnaire. Value Health 2005;8(02):157–167. Doi: 10.1111/j.1524-4733.2005.03010.x

22 Lahan V, Gupta R. Translation and validation of the insomnia severity index in hindi language. Indian J Psychol Med 2011;33(02):172–176. Doi: 10.4103/0253-7176.92060

23 Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(04):297–307. Doi: 10.1016/S1389-9457(00)00065-4

24 Guy W. ECDEU assessment manual for psychopharmacology. US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.

25 Aurora RN, Kristo DA, Bista SR, et al. Update to the AASM Clinical Practice Guideline: "The treatment of restless legs syndrome and periodic limb movement disorder in adults-an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses". Sleep 2012;35(08):1037. Doi: 10.5665/sleep.1986

26 Bliwise DL, Freeman A, Ingram CD, Rye DB, Chakravorty S, Watts RL. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. Sleep Med 2005;6(02):141–147. Doi: 10.1016/j.sleep.2004.12.002

27 Trenkwalder C, Garcia-Borreguero D, Montagna P, et al; Therapy with Ropiunirole; Efficacy and Tolerability in RLS 1 Study Group. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry 2004;75(01):92–97

28 Kushida CA, Geyer J, Tolson JM, Asgharian A. Patient- and physician-rated measures demonstrate the effectiveness of ropinirole in the treatment of restless legs syndrome. Clin Neuropharmacol 2008;31(05):281–286. Doi: 10.1097/WNF.0B013E31815A3EEC

29 Giorgi L, Asgharian A, Hunter B, Kingdom U. Ropinirole in Patients With Restless Legs Syndrome and Baseline IRLS Total Scores ≥ 24: Ef fi cacy and Tolerability in a Study Followed by a 40-Week Open-Label Extension. Clin Ther 2013;35(09):1321–1336. Doi: 10.1016/j.clinthera.2013.06.016

30 Montplaisir J, Karrasch J, Haan J, Volc D. Ropinirole is effective in the long-term management of restless legs syndrome: a randomized controlled trial. Mov Disord 2006;21(10):1627–1635. Doi: 10.1002/mds.21050

31 Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep 2004;27(05):907–914. Doi: 10.1093/sleep/27.5.907

32 Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi KTREAT RLS 2 (Therapy with Ropinirole: Efficacy And Tolerability in RLS 2) Study Group. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord 2004;19(12):1414–1423. Doi: 10.1002/mds.20257

33 Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SYTREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc 2006;81(01):17–27. Doi: 10.4065/81.1.17

34 Adler CH, Hauser RA, Sethi K, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. Neurology 2004;62(08):1405–1407. Doi: 10.1212/01.WNL.0000120672.94060.F1

35 Happe S, Sauter C, Klösch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology 2003;48(02):82–86. Doi: 10.1159/000072882

36 Vishwakarma K, Kalra J, Gupta R, Sharma M, Sharma T. A double-blind, randomized, controlled trial to compare the efficacy and tolerability of fixed doses of ropinirole, bupropion, and iron in treatment of restless legs syndrome (Willis-Ekbom disease). Ann Indian Acad Neurol 2016;19(04):472–477. Doi: 10.4103/0972-2327.194424

37 Rewane A, Nagalli S. Ropinirole. 2021 Jul 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. PMID: 32119419.

38 Yepes G, Guitart X, Rea W, et al. Targeting hypersensitive cortico-striatal terminals in restless legs syndrome. Ann Neurol 2017;82(06):951–960. Doi: 10.1002/ana.25104

39 Raupp-Barcaro IF, Vital MA, Galduróz JC, Andreatini R. Potential antidepressant effect of amantadine: a review of preclinical studies and clinical trials. Br J Psychiatry 2018;40(04):449–458. Doi: 10.1590/1516-4446-2017-2393