

A Prospective, Randomized, Open-Label Study Comparing the Efficacy and Safety of Clonazepam versus Nortriptyline on Quality of Life in 40+ Years old Women Presenting with Restless Leg Syndrome

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ABSTRACT

Introduction: Restless legs syndrome (RLS) is a neurological disorder characterized by an urge to move the legs usually accompanied by unpleasant leg sensations. RLS also impacts health related quality of life (QOL) in patients suffering from it. Further, it affects women more than men. Although a voluminous literature of studies is available evaluating the role of benzodiazepines (clonazepam and antidepressant (nortriptyline) in the treatment of RLS, but to the best of our knowledge, no comparative study is available comparing both of these drugs for efficacy and safety for the treatment of RLS QoL among 40 + years old women. **Materials and Methods:** A prospective, randomized, open label comparative study was conducted in Postgraduate Department of Pharmacology in collaboration with the Department of General Medicine, Government Medical College, Jammu, a tertiary care teaching hospital for 1 year. **Conclusion:** Clonazepam proved to be significantly better in improving RLSQoL score. Difference between respective baselines of both groups was statistically insignificant.

KEYWORDS: Clonazepam, Nortriptyline, Plus forty women, Quality of Life, Restless Leg Syndrome

Restless legs syndrome (RLS) is a neurological disorder characterized by an urge to move the legs usually accompanied by unpleasant leg sensations. The symptoms predominantly occur in the evening and at night. Inactivity and rest worsens the symptoms while patients experience relief by movement. The International RLS Study Group has described 4 mandatory clinical features to establish the diagnosis of RLS, namely (i) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (ii) these symptoms begin or worsen during periods of rest or inactivity such as lying or sitting; (iii) are partially or totally relieved by movement; and (iv) symptoms are worse in the evening or night-time.

RLS also impacts health-related quality of life (QOL) in patients suffering from it. Further, it affects women more than men.^[1-3]

Further RLS sufferers report negative influences on mood, energy, and daily activities and are shown to have more daytime fatigue, work difficulties, and driving

impairment.^[4,5] RLS sufferers may be less productive at their work.^[6] Among elders, severe RLS has been associated with poorer social function, daily function, sleep quality, and emotional well-being.^[7]

Similarly, numerous epidemiological and population-based studies exist establishing a relationship between anxiety disorders and RLS.^[8,9] Thereby, suggesting a role of benzodiazepines and anti-depressants in the successful and conclusive treatment of RLS.^[10]

The RLS affects women more in comparison to men and has a very strong linkage with depression, anxiety, and sleep disorders. Further, the antidepressants have

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been well established as adjuvant therapy for the control of pain in various disorders such as fibromyalgia, neuropathic pain, LBA, headache, and rheumatological disorders.^[11]

The dopamine agonists (levodopa, ropinirole, and pramipexole) are considered as the first line therapy for the treatment of moderate-to-severe RLS. Other treatment options available for RLS as per different studies are iron supplementation, opioids (tramadol and methadone), antiepileptic agents (gabapentin, carbamazepine, lamotrigine, valproate, and pregabalin), antidepressants, and benzodiazepines.^[12,13]

Although a voluminous literature of studies is available evaluating the role of benzodiazepines (clonazepam)^[14,15] and antidepressant (nortriptyline)^[16-18] in the treatment of RLS, but to the best of our knowledge, no comparative study is available comparing both of these drugs for efficacy and safety for the treatment of RLS QoL among 40 + years old women.

Hence, the current prospective, randomized, open label study comparing the efficacy and safety of clonazepam versus nortriptyline in RLS QOL in 40 + years old women was undertaken for 1 year. We hope that the outcome of the proposed study will be of immense value for the treating clinician in instituting the more effective and safe therapy in RLS.

A prospective, randomized, open-label comparative study was conducted in Postgraduate Department of Pharmacology in collaboration with the Department of General Medicine, Government Medical College, Jammu, a tertiary care teaching hospital for 1 year.

The study protocol was approved by Institutional Ethics Committee. A written informed consent was obtained from the patients fulfilling inclusion, exclusion criteria after explaining nature and purpose of the study. All principles of bioethics were followed.

Inclusion criteria

- Women with any menstrual status
- Age more than 40 years and < 65 years.
- Legitimate consent
- Any uncomplicated comorbid condition.

Exclusion criteria

- Pregnancy
- Lactation
- Anemia
- Complicated comorbid conditions
- Primary psychiatric disorder
- Allergy and intolerance to research drugs
- History of any substance dependence or abuse
- Neurological disorders

- Hypotensive akathisia
- Peripheral vascular disease/vascular claudication
- Chronic pain syndrome (lumbar and cervical)
- Sleep-related disorders
- Patients having arthritis, fibromyalgia, and varicose veins
- Patients who are on clonazepam or nortriptyline for the past 4 weeks or more.

Treatment arms

Both the treatment arms were allowed to continue with the prescribed medicine for uncomplicated comorbid conditions.

- Group 1 received Tablet Clonazepam 0.5 mg bedtime orally daily
- Group 2 received Tablet Nortriptyline 25 mg bedtime orally daily.

The dose selected for both the drugs was based on the most common clinically used dose for the respective drugs. This was also based on the dose used by various authors in their studies.^[19,20]

The primary endpoints efficacy evaluation was carried out at 0, 4, and 8 weeks. The assessment was carried out by QOL by using Restless Legs Quality of Life Scale (RLSQoL) and were compared.

Restless legs quality of life scale

QOL was seen by scale RLSQoL. It is a prevalidated and pretested scale. It assesses the impact of RLS on daily life, emotional well being, social life, and work life.^[21]

Validation of restless legs quality of life

Abetz *et al.*, 2005^[21] in their study tried to validate RLSQoL scale score and it was found that RLSQoL summary scale score (range: 0–100) demonstrated acceptable internal consistency reliability (Cronbach's alpha = 0.92) and test-retest reliability (intraclass correlation coefficient = 0.84). All items indicated acceptable item-convergent validity. The RLSQoL distinguished between groups with mild, moderate, and severe symptoms ($F = 52.22$, $P < 0.0001$). It demonstrated preliminary responsiveness to changes in RLS status over 2 weeks (effect size: improvement, 0.25; deterioration, -0.32), indicating moderate scale changes consistent with the small clinical change over this time.

All patients completed their follow up except one in the Nortriptyline group who was lost to follow up for unknown reasons.

Mean RLSQoL score in clonazepam group was 59.85 ± 17 at 0 week, 63.57 ± 16.06 at 4 weeks, and 66.85 ± 15.32 at 8 weeks and the difference was

statistically significant ($P < 0.001$). In Nortriptyline group the mean score was 59.62 ± 15.22 at 0 week, 63.36 ± 14.56 at 4 weeks, and 67.10 ± 13.95 at 8 weeks and the difference was statistically insignificant at 4 weeks and statistically significant at 8 weeks ($P < 0.01$). Clonazepam proved to be significantly better in improving RLSQoL score. Difference between respective baselines of both groups was statistically insignificant [Table 1 and Figure 1].

Mean percentage change of RLSQoL score was 6.21% at 4 weeks, 11.41% at 8 weeks in clonazepam group, and 6.27% at 4 weeks, and 12.54% at 8 weeks in nortriptyline group. Nortriptyline showed relatively more improvement numerically in comparison to clonazepam group [Table 2 and Figure 2].

DISCUSSION

In our study, clonazepam showed statistically better improvement on QOL. Nortriptyline recorded its beneficial effect on mood at 8 wks.

Effect of antidepressants on physical day-to-day activity and overall QOL is generally comparable within and between different classes of antidepressants. However, very limited studies could be cited in the review.

The results of the present study are in agreement with various studies.^[18,22,23]

Shi *et al.*, 2004^[22] in their double-blind, placebo-controlled randomized trial on patients with bipolar depression concluded that antidepressants alone or in combination with olanzapine improved QOL.

The results of the current study are in agreement with the study of Liu WQ *et al.*, 2014^[18] where amitriptyline was compared with nortriptyline in the management of pain due to peripheral neuropathy and recorded improvement in sleep efficacy, mood, anxiety, global physical improvement score, disability and overall QOL score, besides being effective in pain amelioration.

Similarly, it was concluded by Zhang *et al.*, 2016^[23] that antidepressants alone or in combination can effectively improve social function, QOL and health of an individual with mild depression whereas combined therapy is better than monotherapy, although our study population was nondepressive.

However, we failed to cite studies purely on nortriptyline having an effect on QOL, but we assume that the effect recorded in the current study may be due to direct or indirect improvement in sleep, mood and day-to-day activity in patients of RLS.

The results of the current study also become clinically relevant because RLS has an impact on health-related

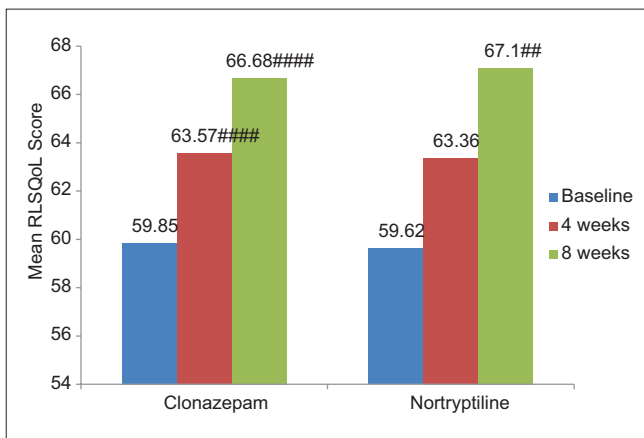


Figure 1: Comparative Effect of Clonazepam versus nortriptyline on Mean Restless Leg Syndrome Quality of Life Score

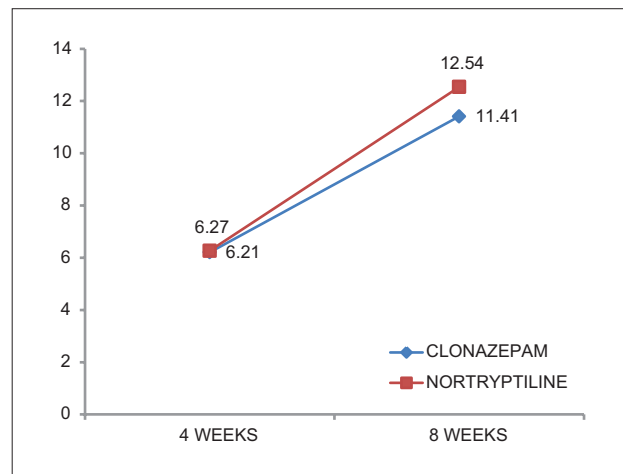


Figure 2: Mean Difference (% change) observed with clonazepam versus nortriptyline on Mean Restless Leg Syndrome Quality of Life Score

Table 1: Comparative effect of clonazepam versus nortriptyline on mean Restless Leg Syndrome Quality of Life Score

Duration	Mean±SD		t	P	Statistical significance
	Clonazepam	Nortriptyline			
Baseline	59.85±17.0 (n=60)	59.62±15.22 (n=60)	0.07	0.937	NS
4 weeks	63.57±16.06#### (n=60)	63.36±14.56 (n=59)	1.40	0.162	NS
8 weeks	66.68±15.32##### (n=60)	67.10±13.95## (n=59)	0.15	0.876	NS

The data is shown as mean±SD. Paired *t* test in comparison to respective baselines # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$, #### $P < 0.001$. Comparison between the groups at baseline, 4 weeks and 8 weeks with student unpaired *t* test * $P < 0.05$, $P < 0.01$, $P < 0.001$. NS: Not significant, SD: Standard deviation

Table 2: Mean difference (percentage change) observed with clonazepam versus nortriptyline on mean Restless Leg Syndrome Quality of Life Score

Duration	Mean±SD	
	Clonazepam (n=60) (%)	Nortriptyline (n=59) (%)
4 weeks	3.72±0.94 (6.21)	3.74±0.66 (6.27)
8 weeks	6.83±1.68 (11.41)	7.48±1.25 (12.54)

SD: Standard deviation

QOL in the affected patients. It affects women more than men.^[1-3]

Further, it is assumed that if longer duration study is done in future nortriptyline may show a better profile on overall QOL contrary to the finding recorded in the current study.

In our study, clonazepam and nortriptyline have shown comparable results on QOL with clonazepam showing statistically better improvement on QoL starting at 4 weeks. This may be directly or indirectly by improving sleep, mood, or day-to-day activity in patients of RLS.

The effect on day-to-day activity by nortriptyline and clonazepam came out to be statistically comparable in our study with nortriptyline showing numerically better effect.

The symptoms of RLS are less noticeable during the daytime, but more prevalent at night. Therefore, the disorder can induce low QOL, insomnia, and impairment of daytime activity. The recommended treatment guidelines for the general population established by Medical Advisory Board of the RLS foundation include dopamine agonists, levodopa, gabapentin, benzodiazepines, and opioid. Thus, improvement on QOL and day-to-day activity by clonazepam may be indirectly by improvement in sleep, mood, and RLS symptoms.

Giddiness (44.4%) was the most common ADR in clonazepam group followed by increased sleep (33.3%), constipation (11.1%), and gastritis (11.1%) whereas in nortriptyline group increased sleep and palpitations (33.3%) were followed by giddiness (25%) and gastritis (8.3%).

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Conflicts of interest

There are no conflicts of interest.

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