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Investigational Pregabalin Effect on Sleep in Patients with Neuropathic Pain and Sleep Maintenance Disturbance: A Multicentric Study

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Abstract

Objective: *Our goal is to research how Pregabalin affects sleep maintenance in a group of neuropathic pain patients.* ***Method and Material****: A cross-sectional study including a sample of 600 patients was carried out. Patients with a neuropathic pain diagnosis were selected from three hospitals in Gandhinagar. After a medical professional diagnosed the patients with neuropathic pain, they were given a detailed description of the study's approach and asked for their informed consent. Subjects who are open to participating in the study and meet the inclusion and exclusion requirements. The demographic baseline evaluation and PSQI score were completed during Visit-01. After Visit-01, patients began receiving Pregabalin. After approximately 30 days from the date of enrolment, the patient was being monitored. The PSQI score was evaluated 30 days later. The Independent Ethics Committee (IEC) approved the PSQI Questioner and Informed Consent form after reviewing them. SPSS was used to statistically analyze the data ($p < 0.05$).* ***Results:*** *To evaluate variations in the distribution of "sleep disturbances vs. Sleep maintenance" (PSQI), we looked at the PSQI by time point. By using two-tailed paired t-tests, PSQI were compared for baseline and intervention conditions. Pregabalin treatment pre- and post-treatment were shown to differ significantly.* ***Discussion:*** *Sleep disturbances are prevalent characteristics of neuropathic pain that are well-known and well-documented. Patients with Neuropathic Pain had statistically significant improvements in sleep maintenance in the current investigation.* ***Conclusion:*** *The data presented here show that Pregabalin improves sleep quality in patients being treated for neuropathic pain.*

Keywords: *Neuropathic Pain, Sleep Quality, Pittsburgh Sleep Quality Index, Pregabalin*

1. Introduction

Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system". The two types of neuropathic pain are peripheral neuropathic pain from lesions of the peripheral nervous system and central neuropathic pain from lesions of the central nervous system. The therapy of neuropathic pain can be challenging, and like with all pain, it should be approached from a biopsychosocial perspective. There are a number of pharmacological therapies approaches that can be used as part of an all-encompassing plan to improve patients' quality of life and performance [1]. This syndrome is often defined in terms of its etiology or anatomic localization, which is the result of various different pathogenic factors. The conditions and pathophysiological states that determine the onset of neuropathic pain include viral neuropathies like post-herpetic neuralgia, HIV, and leprosy, autoimmune diseases that affect the central nervous system like multiple sclerosis and Guillain-Barre syndrome, chemotherapy-induced peripheral neuropathies, and damage to the nervous system as a result of trauma [2].

Among the symptoms and signs associated with the presence of neuropathic pain are allodynia (pain brought on by a stimulus that does not usually cause pain), hyperalgesia (an increase in the perception of pain brought on by a stimulus that causes pain), and paraesthesia (a condition that determines the perception of abnormal sensations like needle bites, tingling, itching, reduced, or even loss of

sensitivity). Patients with neuropathic pain frequently experience spontaneous pain that doesn't need to be stimulated. The quality of life and mental health of patients are severely compromised by this medical condition [3].

Pregabalin and gabapentin are approved by the Food and Drug Administration (FDA) to treat neuropathic pain. They bind to the Ca^{2+} voltage-dependent channel's 2-subunit due to their structural similarity to the neurotransmitter gamma-aminobutyric acid, restricting Ca2+ input to the cells [4].

The rising list of conditions that are known to be triggered by sleep disruption has made it evident that insufficient sleep has a convoluted relationship with general health. It is now known that a number of neurological, physiological, psychological, and behavioural factors interact with disturbed sleep in a bidirectional manner [5-8]. A reliable, validated subjective assessment as well as an objective polysomnographic (PSG) examination are both crucial in current medical practice because of the important role that sleep plays in general health. Although they are completely different diagnostic techniques, they work well together since subjective tools can pick up on behavioural and psychological trails that PSG cannot. Self-rating questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI), are essential for evaluating sleep health in both clinical and research contexts [9 & 10]. The advantages of these surveys are low cost, high patient compliance, and ease of administration. Perhaps more importantly, because such surveys are self-explanatory and do not require supervision, they reduce the demand on the time of medical specialists [5]. Given the important diagnostic function that rating scale surveys serve, their validity and reliability must be established beyond a reasonable doubt. An essential part of this quality assurance is the psychometric validation of the questionnaires' dimensionality, or if the items are all related and indicative of factors impacting sleep quality [9]. The dimensionality data from the PSQI, one of the most well-liked self-rating sleep quality measures, is examined rigorously in this research [11].

2. Materials And Methods

Method:

A Parallel, Comparative and descriptive study with a quantitative technique of 600 Patients sample were conducted. Patients who had been diagnosed with neuropathic pain and were either male or female and older than 18 were eligible for the trial. Patients chosen from three different Gandhinagar hospitals. The patient's inability to sleep for more than three nights per week for at least one month prior to the screening interview indicates a history of sleep disturbances. The patient must adhere to a routine that includes being awake during the day and sleeping at night with varying bedtimes [12]. During the screening session, the subjective evaluation of the sleep admission criteria was assessed using the PSQI Sleep Questionnaire. Those study participants who are willing to take part. A patient will be rejected if they have a history of any sleep disorder. Any sickness that does not prevent the evaluation of sleep or neuropathy symptoms may be present in the patient. Severe medical conditions that, in the view of the researcher, prevent the patient from taking part in clinical research; the use of any medications that might affect sleep-wake function [13]. Those who have a history of hypersensitivity or allergy to Pregabalin or any of its components. Those who choose not to take part. Prescriptions with awkward wording.

After a medical professional diagnosed the patients with neuropathic pain, they were given a detailed description of the study's approach and asked for their informed consent. Subjects who fit the inclusion and exclusion criteria and are willing to participate in the study. During Visit-1, baseline demographic and PSQI score evaluations were conducted. Patients started receiving Pregabalin after Visit-01. The patient was being followed up on four weeks after the date of enrollment. The PSQI score was tested after four weeks [12 & 14].

Materials:

The PSQI is the most widely used tool for assessing sleep health in both clinical and non-clinical populations. The sleep survey may also be the one that has been translated the most, with [15]. The Pittsburgh Sleep Quality Index (PSQI), a 19-item self-report questionnaire, was developed to evaluate sleep quality and disturbances over the course of a month. Participants are questioned about their regular bedtime, average time to fall asleep, average time to get up, and average amount of actual sleep in the initial PSQI questions. The final 15 Likert-style questions are concerned with subjective sleep quality and how frequently sleep interruptions occurred over the preceding month. Each object is assigned a difficulty rating between 0 and 3, with 3 representing the most difficulty. The 19 items are divided into seven component scores, or subscales: subjective sleep quality (6), sleep latency (2 and 5a), sleep duration (4), habitual sleep efficiency (1 and 4), sleep disturbances (5b to 5j), use of sleep medications

(7), and daytime dysfunction (8 and 9). The range of possible scores for each component is from 0, which denotes no problems to 3, which denotes serious difficulties. Additionally, a total score is generated by adding the values of the seven components, and it ranges from 0 to 21, with lower scores denoting lower sleep quality. The distinction between poor sleepers and outstanding sleepers has been made using a cut-off of > 5 on the total score. Scores below five indicate sound sleepers, while scores above five indicate snorers [6].

Ethical Consideration:

The local ethics committee granted approval for the study's recruitment of participants utilizing an informed consent form and the PSQI Questionnaires, in accordance with the Helsinki Declaration [16 & 17]. The Independent Ethics Committee (IEC), which has been authorized by the Drug Controller General of India (DCGI), provided ethical approval [18].

Statistical Analysis:

All data will be entered into the SPSS program for additional analysis [19]. Based on commonly used rating criteria, the PSQI component and overall scores were calculated. It will be deemed noteworthy if $p<0.05$. Descriptive statistics are reported as Percentages, Frequency, and Means with standard deviations for continuous parametric variables. If there was a significant variation in PSQI score between the two visits, it was determined using Analysis of Variance (ANOVA) and paired *t-tests* [20].

3. Results and Discussion

The 600 patients were enrolled of Pregabalin & Standard of Care (Gabapentin) for study respectively out of that 241 (80.3%) and 240 (80.0%) Male & 59 (19.7 %) and 60 (20.0 %) Female and Age range between 31 to 70 years [(31-40 Years 21 (7.0 %) & 29 (9.7 %), 41-50 Years 151 (50.3%) & 132 (44.0 %), 51-60 Years 108 (36.0 %) & 120 (40.0 %), 61-70 Years 20 (6.7 %) & 19 (6.3 %)] patients who experienced Neuropathic Pain is shown in Table 01 and Graphs 01 & 02.

Pregabalin & Standard of Care (Gabapentin) Treated patient's Clinical variables were presented by relapse status of sleep quality based on PSQI Seven Components & Global scores for Pre-treatment and Post- Treatment of Neuropathic Drug in Table 02 & 03.

There were statistically Mean ± SD differences in Pre-treatment and Post- treatment sleep-related variables between those Patients treated with Pregabalin & Standard of Care (Gabapentin), with their statistically significant differences between Pre & Post Treatment to Neuropathic Pain Patients.

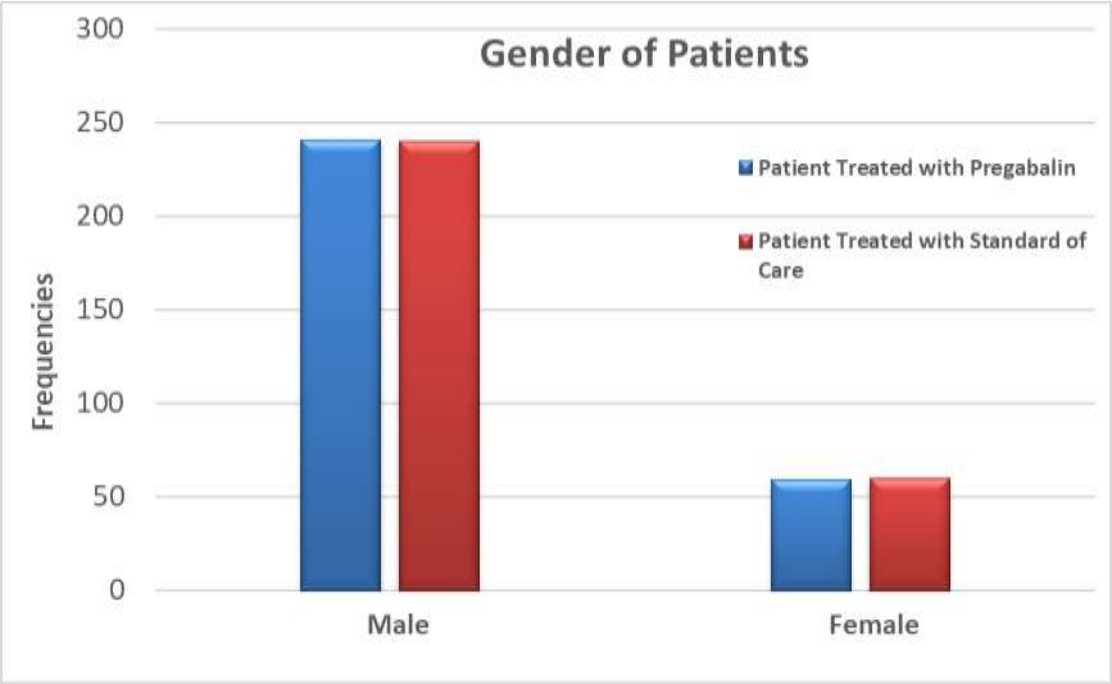
Tables 02 and 03, as well as Graphs 03, 04, 05, and 06, show statistically significant improvements in the PSQI's Subjective Sleep Quality, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleep Medication & Daytime Dysfunction, and PSQI Global score at the post-intervention phase, indicating a significant improvement in Neuropathic Pain Patients' sleep quality.

The Mean ± SD of PSQI Global score were improved after treatment with Pregabalin & Standard of Care (Gabapentin) is shown in Table 04. Significantly improvement in Global score of PSQI was demonstrate that the sleep quality was better after Treatment of Pregabalin in Neuropathic Pain Patients as Compare to Standard of Care (Gabapentin).

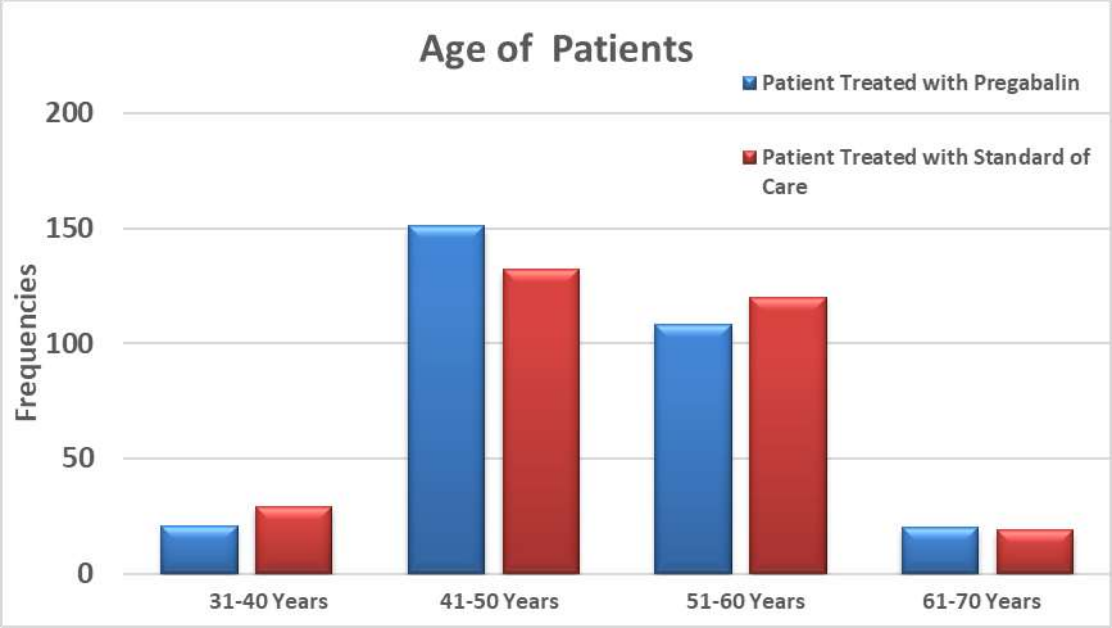
Table 01. Comparison of Participant Demography and Treatment of Pregabalin or STD with different Clinical Variables.

Demographic Details		**Pregabalin (*n* = *300*)**		**STD (*n*= *300*)**	
		f	**%**	**f**	**%**
Gender	Male	241	80.3	240	80.0
	Female	59	19.7	60	20.0
Age	31-40 Years	21	7.0	29	9.7
	41-50 Years	151	50.3	132	44.0
	51-60 Years	108	36.0	120	40.0
	61-70 Years	20	6.7	19	6.3

***n*= Sample size, f= Frequencies, %= Percentage, STD= Standard Drug, Mean ± SD = Mean± Standard Deviation,**



Graph: 01. Gender Frequencies of participant used for study data evaluation.

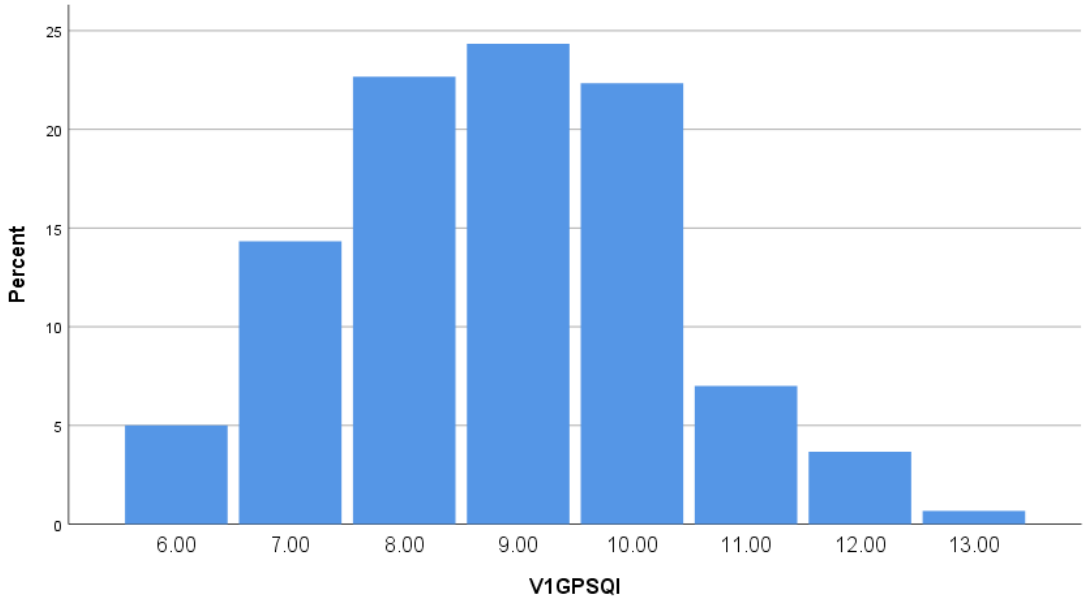


Graph: 02. Age Frequencies of participant used for study data evaluation.

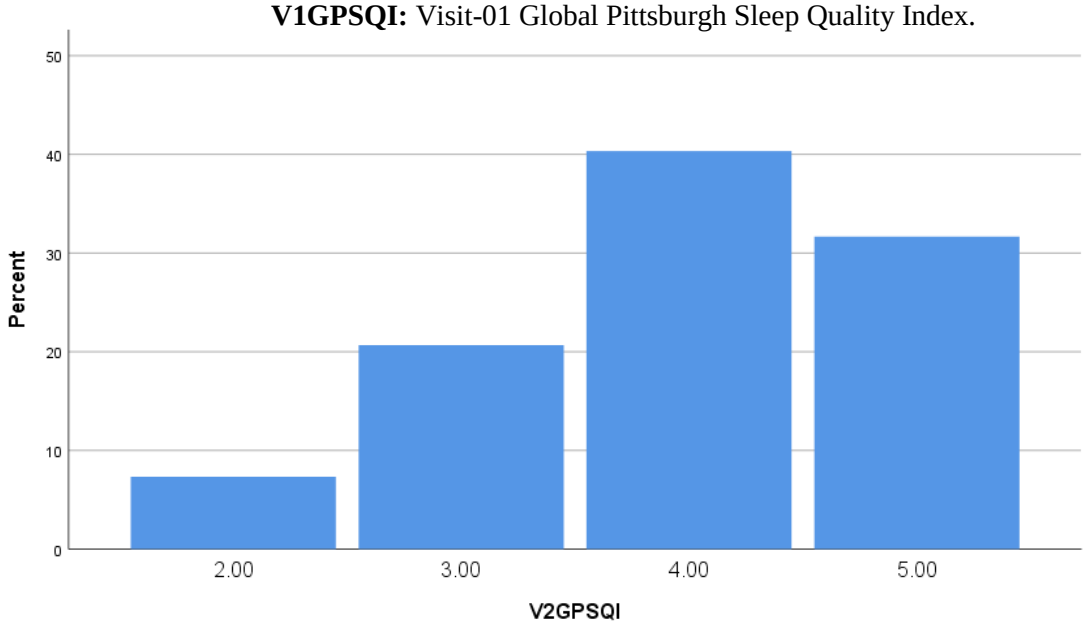
Table: 02. Comparison of the mean values of Pittsburgh Sleep Quality Index (PSQI): Components Vs Pre & Post Treatment of Pregabalin with different Clinical Variables.

PSQI Components	Pregabalin (*n = 300*)		*t-Test*	*P-Value*
	Mean ± SD			
	Pre-Treatment Visit-01	Post-Treatment Visit-02		
Subjective Sleep Quality	1.56 ± 0.61	0.76 ± 0.47	19.05	0.00
Sleep Latency	1.86 ± 0.35	0.92 ± 0.44	28.73	0.00
Sleep Duration	0.60 ± 0.64	0.01 ± 0.11	15.48	0.00
Habitual Sleep Efficiency	0.00[a] ± 0.00	0.00[a] ± 0.00	0.00	0.00
Sleep Disturbances	1.91 ± 0.46	0.99 ± 0.11	33.56	0.00
Use Of Sleep Medication	1.00 ± 0.61	0.40 ± 0.49	13.23	0.00
Daytime Dysfunction	1.89 ± 0.46	0.88 ± 0. .40	27.99	0.00
Global Score	8.84 ± 1.47	3.96 ± 0.90	50.14	0.00

n= Sample size, Mean ± SD= Mean± Standard Deviation, *t- Test* = Paired t-Test, *P-Value <0.05*.a. The correlation and t-cannot be computed because the standard error of the difference is 0.



Graph: 03. Percentage (%) of Participant before Treatment of Pregabalin – Global Scoring 6-21 Represent as Bad /Poor Sleep.
V1GPSQI: Visit-01 Global Pittsburgh Sleep Quality Index.



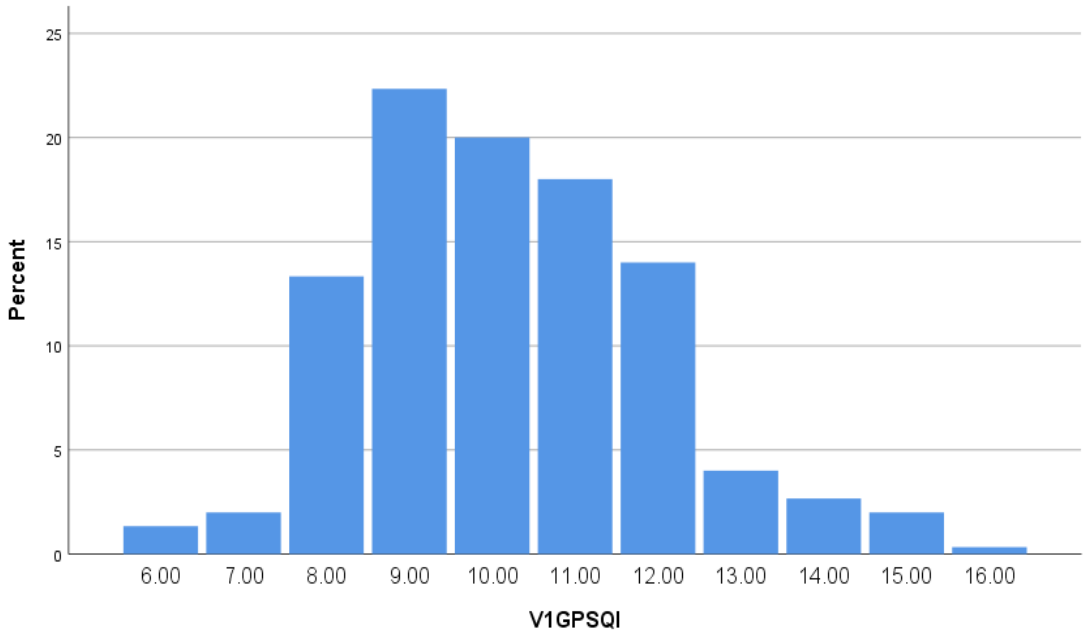
Graph: 04. Percentage (%) of Participants after Treatment of Pregabalin - Global Scoring 0-5 Represent as Good Sleep.
V2GPSQI: Visit-02 Global Pittsburgh Sleep Quality Index.

Table: 03. Comparison of the mean values of Pittsburgh Sleep Quality Index (PSQI): Components Vs Pre & Post Treatment of Standard Drug with different Clinical Variables.

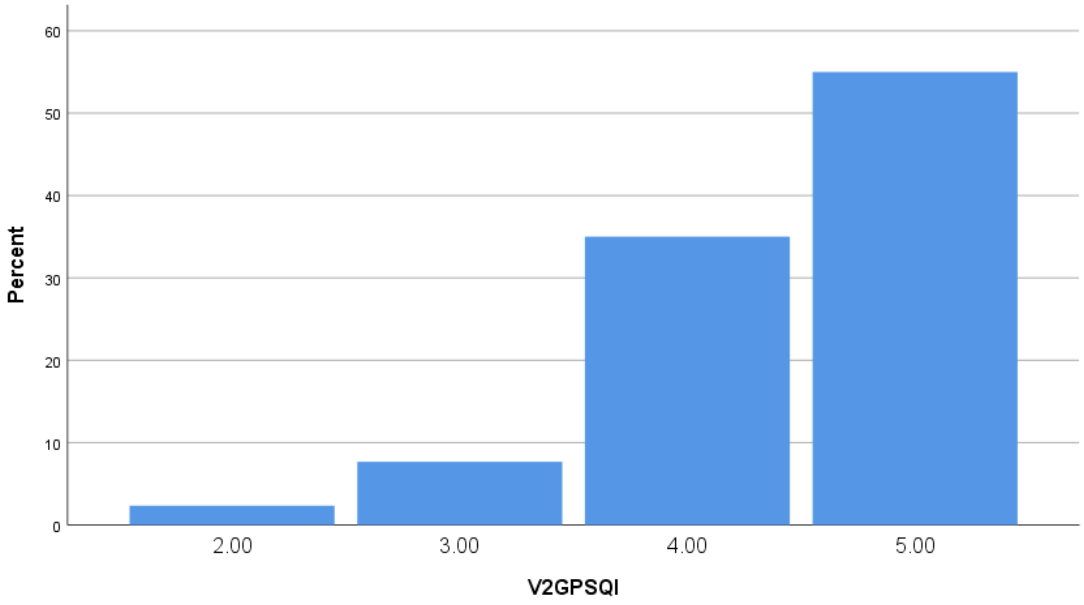
PSQI Components	STD (*n = 300*) Mean ± SD		*t-Test*	*P-Value*
	Pre-Treatment Visit-01	Post-Treatment Visit-02		
Subjective Sleep Quality	1.45 ± 0.55	0.87 ± 0.38	14.41	0.00
Sleep Latency	1.90 ± 0.30	0.91 ± 0.43	31.23	0.00
Sleep Duration	1.11 ± 0.87	0.03 ± 0.17	21.26	0.00

Habitual Sleep Efficiency	0.00[a] ± 0.00	0.00 [a]± 0.00	00.00	0.00
Sleep Disturbances	2.08 ± 0.32	1.00 ±0.10	53.40	0.00
Use Of Sleep Medication	1.51 ± 0.69	0.70 ± 0.45	16.73	0.00
Daytime Dysfunction	2.15 ± 0.49	0.92 ± 0.30	35.60	0.00
Global Score	10.20 ±1.80	4.43 ± 0.73	48.85	0.00

n= Sample size, STD= Standard of Care, Mean ± SD= Mean± Standard Deviation, *t- Test* = Paired t-Test, *P-Value <0.05*.a. The correlation and *t* cannot be computed because the standard error of the difference is 0.



Graph: 05. Percentage (%) of Participant before Treatment of Standard Drug – Global Scoring 6-21 Represent as Bad /Poor Sleep.
V1GPSQI: Visit-01 Global Pittsburgh Sleep Quality Index.



Graph: 06. Percentage (%) of Participants after Treatment of Standard Drug – Global Scoring 0-5 Represent as Good Sleep.
V2GPSQI: Visit-02 Global Pittsburgh Sleep Quality Index.

Table: 04. Comparison of the mean values of Pittsburgh Sleep Quality Index (PSQI): Global Scores Vs Visit-01 & Visit-02 Treatment for Pregabalin & Standard Drug with different Clinical Variables.

Visit	Mean ± SD		*t-Test*	*P-Value*
	PSQI Global score with treatment of Pregabalin (*n= 300*)	PSQI Global score with treatment of STD (*n = 300*)		
Visit-01	8.84 ± 1.47	10.20 ± 1.80	10.23	0.00
Visit-02	3.96 ± 0.90	4.42 ± 0.73	6.75	0.00
n= Sample size, STD= Standard Drug, Mean ± SD= Mean± Standard Deviation, *t- Test* = Paired t-Test, *P-Value <0.05*				

A well-known and well-documented common characteristic of neuropathic pain is disturbed sleep [21, 22 & 23]. It has become clear that inadequate sleep has a complicated link with general health as a result of the growing number of issues that are known to be brought on by sleep disruption. It has become clear that inadequate sleep has a complicated link with general health as a result of the growing number of issues that are known to be brought on by sleep disruption. It is now understood that a variety of neurological, physiological, psychological, and behavioral variables interact bilaterally with sleep disruption [24–25]. Older persons frequently experience sleep disturbances, with more than 30% of them having poor sleep quality and ongoing problems sleeping. These issues might include difficulty falling asleep quickly, numerous nighttime awakenings, and trouble settling back to sleep after waking. Such sleep abnormalities affect daytime functioning, and are reportedly linked to deteriorating health status, rising all-cause mortality, and decreased quality of life [26 & 27].

The significance of sleep for overall health has so highlighted the demand for trustworthy, verified subjective instruments assessment in contemporary medicine. For Poor/Bad Sleep or Good Sleep as measured by PSQI, these represent completely distinct diagnosis techniques. In both clinical and research contexts, self-rating questionnaires like the Pittsburgh Sleep Quality Index (PSQI) are crucial for assessing sleep health [09 & 10]. These questionnaires have the benefits of being affordable, having high patient compliance, and being simple to administer. Perhaps more significantly, they lessen the time demands placed on medical specialists because such questionnaires are self-explanatory and do not require monitoring. The reliability and validity of rating scale surveys must be proven beyond a reasonable doubt given the significant diagnostic role they play. A crucial aspect of sleep is the confirmation of the questionnaires' dimensionality, or whether the items are related and accurately reflect the factors that affect sleep quality. Examples of this include Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Use of sleeping medications, and Daytime Dysfunction for Sleep Quality. This paper critically evaluates the PSQI, one of the most popular self-rating sleep quality instruments, and its dimensionality data [11].

The advantages of Gabapentin and Pregabalin on insomnia in patients receiving maintenance haemodialysis and suffering from excruciating peripheral neuropathy. Pregabalin has been shown to be beneficial in treating sleep disturbances brought on by pain [28]. In essence, the way that Pregabalin improves sleep quality is through reducing chronic pain. Pregabalin, however, has some positive benefits on sleep architecture as well, according to accumulating research [29, 30 & 31]. Additionally, Pregabalin has been shown to be useful in the management of restless legs syndrome, enhance the quality of sleep, and reduce periodic limb movements [32].

Common and closely related to sleep disturbance is painful neuropathy. The identification of these common diseases and appropriate treatment are of therapeutic importance. Pregabalin effects on sleep quality have been noticed in patients with painful neuropathy. This is the first study demonstrating Pregabalin positive effects on individuals with Neuropathic Pain who have sleep disturbances. On these abnormalities, Pregabalin was more effective than gabapentin.

The adverse events (AE) were not reported in this experiment due to Pregabalin well-known tolerability profile [33]. Pregabalin has beneficial benefits on a number of sleep metrics, as seen by the objective increases in sleep duration and statistically significant improvement in PSQI seen in the current study.

4. Conclusion

The study found that Pregabalin helped to control the maintenance of Sleep as indicated by the Global PSQI Score. Pregabalin was noticeably more effective in areas of neuropathic pain. Pregabalin was

more successful in raising the PSQI's Seven Component Score and overall scoring. Pregabalin showed well tolerated by patient & more effective on sleep maintenance in Neuropathic Pain patients as compared to Gabapentin. Pregabalin effects on patients with neuropathic pain may aid doctors in making a prescription decision.

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Declaration of Conflict:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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