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## ORIGINAL ARTICLE

# Investigational Gabapentinoid Effect on Sleep in Patients with Neuropathic Pain and Sleep Maintenance Disturbance

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**ABSTRACT**
*Our goal is to research how Gabapentinoid (Pregabalin or Gabapentin) affects sleep maintenance in a group of neuropathic pain patients. A cross sectional study with a 600- patients sample was conducted. Patients from three hospitals in Gandhinagar who had been diagnosed with neuropathic pain were chosen. Following a doctor's diagnosis of neuropathic pain, the patients received a thorough explanation of the study's methodology, and their informed consent was obtained. 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 Gabapentinoid (Pregabalin or Gabapentin). 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 ($p < 0.05$). To evaluate variations in the distribution of "sleep disturbances vs. Sleep maintenance", we looked at the PSQI by time point. By using paired t-tests, PSQI were compared for baseline and intervention conditions. Gabapentinoid treatment pre- and post-treatment were shown to differ significantly. 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. The data presented here show that Gabapentinoid improves sleep quality in patients being treated for neuropathic pain.*
***Keywords:*** *Neuropathic Pain, Pittsburgh Sleep Quality Index, Gabapentinoid.*

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## INTRODUCTION

"Neuropathy Pain initiated or caused by a primary lesion or dysfunction in the nervous system" is how neuropathic pain is characterized. Peripheral neuropathic pain resulting from lesions of the peripheral nervous system and central pain following lesions of the central nervous system are the two categories of neuropathic pain. Neuropathic pain management can be difficult, and like with all pain, it should be treated from a biopsychosocial point of view. As part of a comprehensive strategy to enhance patients' quality of life and function, there are various alternatives for pharmacological treatment [1]. The etiology or anatomic localisation of this syndrome, which is the outcome of numerous different pathogenic causes, is typically used to define it. Neuropathies caused by viral infections, such as post-herpetic neuralgia, HIV, and leprosy, autoimmune conditions that affect the central nervous system, such as multiple sclerosis and Guillain-Barre syndrome, chemotherapy-induced peripheral neuropathies, and damage to the nervous system as a result of trauma are the conditions and pathophysiological states that determine the onset of neuropathic pain [2].

Allodynia (pain caused by a stimulus that does not typically cause pain), hyperalgesia (an increase in the perception of pain generated by a stimulus that causes pain), and paresthesia (a condition that determines the perception of anomalous sensations similar to needle bites, tingling, itching, reduced, or even loss of sensitivity) are among the signs and symptoms linked to the presence of neuropathic pain. The pain that neuropathic pain patients experience frequently manifests spontaneously, without the

requirement for a stimulation. This medical disease seriously impairs patients' quality of life and compromises their mental health [3]. The Food and Drug Administration (FDA) has authorized the use of gabapentin and Gabapentinoid to treat neuropathic pain. Due to their structural resemblance to the neurotransmitter gamma-aminobutyric acid, they bind to the Ca2+ voltage-dependent channel's 2-subunit, limiting Ca2+ input to the cells [4]. 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 behavioural components interact in a bidirectional manner with disrupted sleep [5-8]. The crucial role that sleeps plays in general health has thus highlighted the necessity for objective polysomnographic (PSG) assessment as well as trustworthy, validated subjective instruments in modern medical practice. Although they are quite distinct diagnostic methods, they are complementary in that subjective tools can detect psychological and behavioural aspects that PSG cannot detect. In both clinical and research contexts, self-rating questionnaires like the Pittsburgh Sleep Quality Index (PSQI) are crucial for assessing sleep health [9, 10]. These questionnaires have the benefits of being affordable, having high patient compliance, and being simple to administer. Perhaps more significantly, they lessen the demand on the time of medical specialists because such surveys are self-explanatory and do not require supervision5. The reliability and validity of rating scale surveys must be proven beyond a reasonable doubt given the significant diagnostic role they play. The psychometric validation of the questionnaires' dimensionality, or whether the items are all connected and reflective of elements affecting sleep quality, is a crucial component of this quality assurance [9]. This paper critically evaluates the PSQI 's dimensionality evidence, one of the most popular self-rating sleep quality tools [10, 11].

## MATERIAL AND METHODS

### Participants and Procedure:

A descriptive cross-sectional study using a quantitative technique with a 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]. The PSQI Sleep Questionnaire will be used to evaluate the subjective assessment of the sleep admission criteria during the screening session. Participants in the study who are willing to participate. If a patient had a history of any sleep issue, they would be disqualified. Patients may have any illness that would not interfere with the evaluation of sleep or neuropathy symptoms. Severe medical diseases that, in the investigator's opinion, preclude the patient from participating in the clinical research; the use of any drugs that may interfere with sleep-wake function [13, 25, 26]. Those who have a history of allergy or hypersensitivity to Gabapentinoid or any of its ingredients. Those who do not want to participate. Prescriptions that are worded poorly. Following a doctor's diagnosis of neuropathic pain, the patients received a thorough explanation of the study's methodology, and their informed consent was obtained. Individuals who fit the inclusion and exclusion criteria and are willing to participate in the study. During Visit-1, baseline demographic and PSQI score measurements were completed. After Visit-01, patients began receiving Gabapentinoid. After four weeks from the date of enrolment, the patient was being followed up. After four weeks, the PSQI score was evaluated [12, 13, 14].

### Material:

The most popular measure for evaluating sleep health in both clinical and non-clinical groups is the PSQI. It may also be the sleep questionnaire that has been translated the most [15]. A 19-item self-report questionnaire called the Pittsburgh Sleep Quality Index (PSQI) was created to assess sleep quality and disruptions over the course of a month. The initial PSQI questions ask participants about their typical bedtime, average time to fall asleep, average time to get up, and average amount of actual sleep. The remaining 15 Likert-type questions focus on subjective sleep quality and the frequency of sleep disruptions over the previous month. Each object is given a difficulty rating from 0 to 3, with 0 denoting no difficulty and 3 denoting extreme difficulty. Seven component scores, or subscales, are created from the 19 items: subjective sleep quality (item 6), sleep latency (items 2 and 5a), sleep duration (item 4), habitual sleep efficiency (items 1 and 4), sleep disturbances (items 5b to 5j), use of sleep medications (item 7), and daytime dysfunction (items 8 and 9). Scores for each component vary from 0, which indicates no issue, to 3, which indicates significant challenges. Additionally, the sum of the seven component values results in a final score that runs from 0 to 21, with lower scores indicating poorer sleep

quality. A cut-off of > 5 on the overall score has been used to separate bad sleepers from excellent sleepers. Scores under 5 denote sound sleepers, whereas scores over 5 denote snorers [6].

**Ethical Consideration:**

According to the declaration of Helsinki, the local ethics committee approved the recruitment of participants for the study using an informed consent form and the PSQI Questionnaire [16, 17]. The Aartham Independent Ethics Committee (IEC), which has been authorized by the Drug Controller General of India (DCGI), provided ethical approval [18].

**Statistical Analysis:**

All data were entered into the SPSS program for additional analysis [19]. The PSQI component and overall scores were computed based on accepted scoring guidelines. $p<0.05$ was considered significant. For continuous parametric variables, descriptive statistics were presented as percentages, frequencies, and means with standard deviations. Paired t-tests were used to determine whether there was a significant difference in PSQI score between the two visits [20].

**RESULT**

The 600 patients were enrolled of Gabapentinoid (Pregabalin & 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 Figure 01 & 02. Gabapentinoid (Pregabalin & 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 Gabapentinoid (Pregabalin & Gabapentin), with their statistically significant differences between Pre & Post Treatment to Neuropathic Pain Patients. Table 02 & 03 and Figure 03, 04, 05 & 06 demonstrates statistically significant improvements in PSQI components of Subjective Sleep Quality sleep latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use Of Sleep Medication & Daytime Dysfunction and PSQI Global score at the post-intervention phase, which indicates significant improvement in Neuropathic Pain Patients sleep quality. The Mean ± SD of PSQI Global score were improved after treatment with Gabapentinoid (Pregabalin & Gabapentin) is shown in Table 04. Significantly improvement in Global score of PSQI was demonstrate that the sleep quality was better after Treatment of Gabapentinoid in Neuropathic Pain Patients.

**Table 01. Comparison of Participant Demography and Treatment of Gabapentinoid (Pregabalin & Gabapentin) with different Clinical Variables.**

| Demographic Details | | Pregabalin (*n = 300*) | | Gabapentin (*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** | | | | | |

 

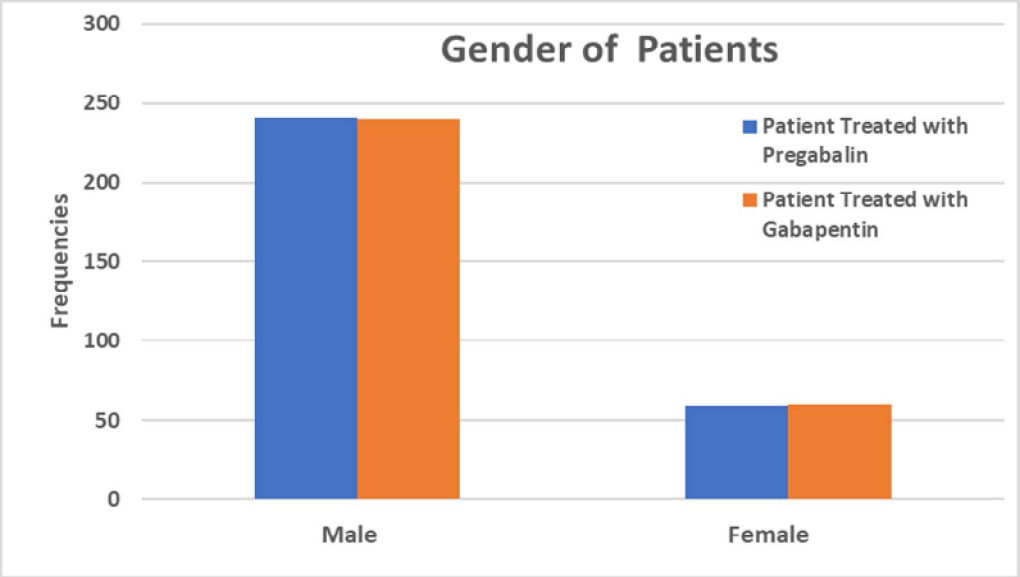


**Figure: 01. Gender Frequencies of participant used for study data evaluation.**

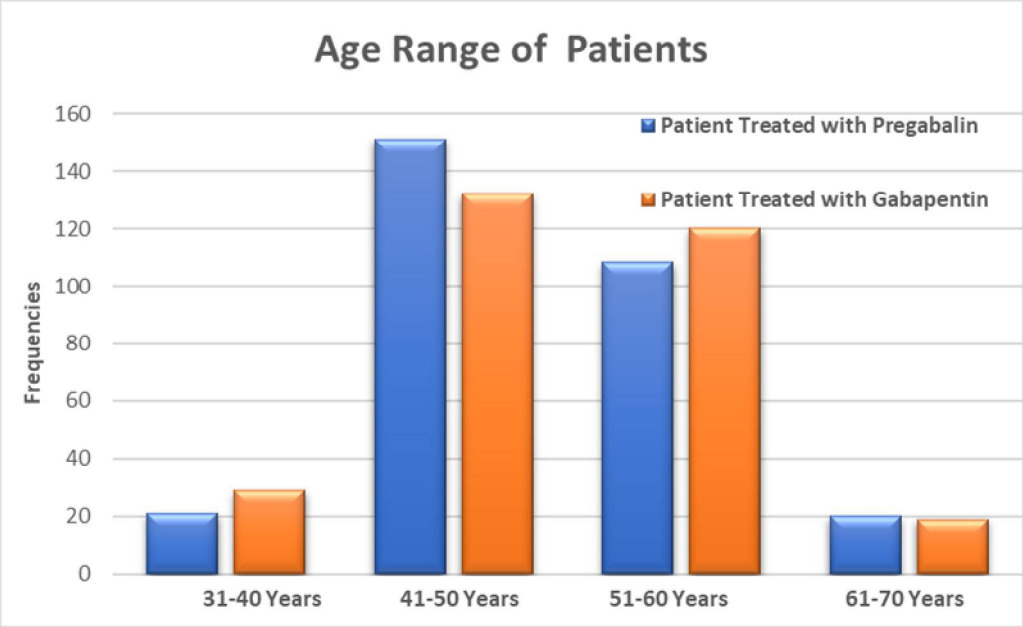


**Figure: 02. Age Frequencies of participant used for study data evaluation.**

**Table: 02. Comparison of the Pittsburgh Sleep Quality Index (PSQI) mean values: Components vs. Pregabalin Treatment and Post-treatment with Various Clinical Variables.**

| PSQI Components | Pregabalin (*n = 300*) Mean ± SD | | *t-Test* | *P-Value* |
|---|---|---|---|---|
| | 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. Since there is no standard error of the difference, it is not possible to determine the correlation or t.

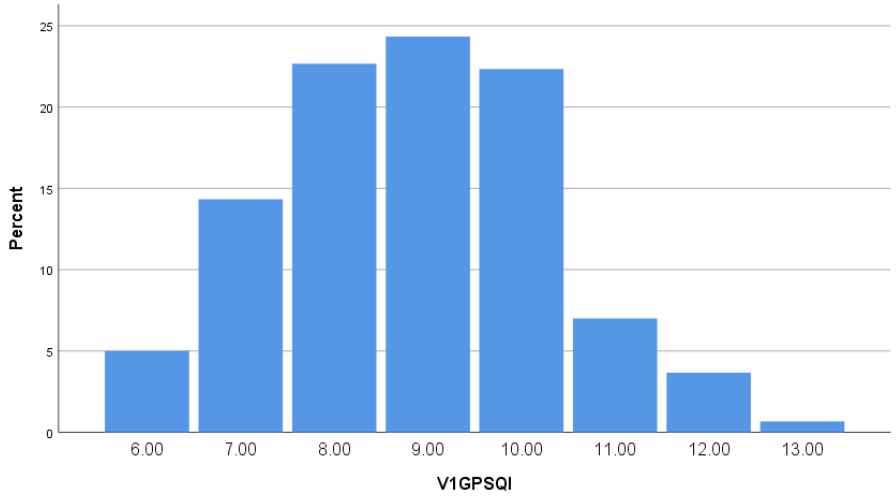


**Figure: 03.** Percentage (%) of Participant before Treatment of Pregabalin - Global Scoring 6-21 Represent as Bad /Poor Sleep. **V1GPSQI:** Visit-01 Global Pittsburgh Sleep Quality Index.

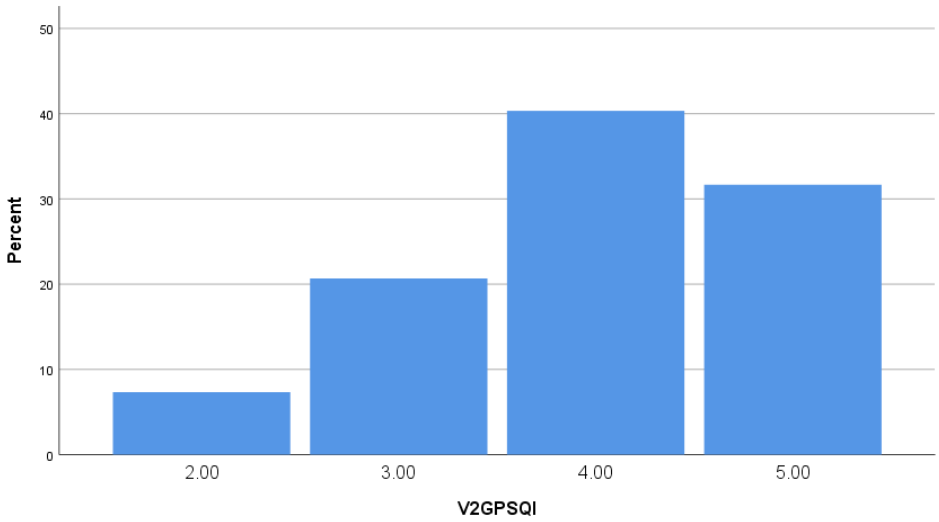


**Figure: 04.** Percentage (%) of Participants after Treatment of Pregabalin - Global Scoring 0-5 Represent as Good Sleep. **V2GPSQI:** Visit-02 Global Pittsburgh Sleep Quality Index.

**Table: 03.** Comparison of the Pittsburgh Sleep Quality Index (PSQI) mean values with various clinical variables before and after gabapentin use.

| **PSQI Components** | **Gabapentin (*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, Mean ± SD=** Mean± Standard Deviation, ***t- Test*** = Paired t-Test,
***P-Value*** *<0.05*

a. Since there is no standard error of the difference, it is not possible to determine the correlation or t..

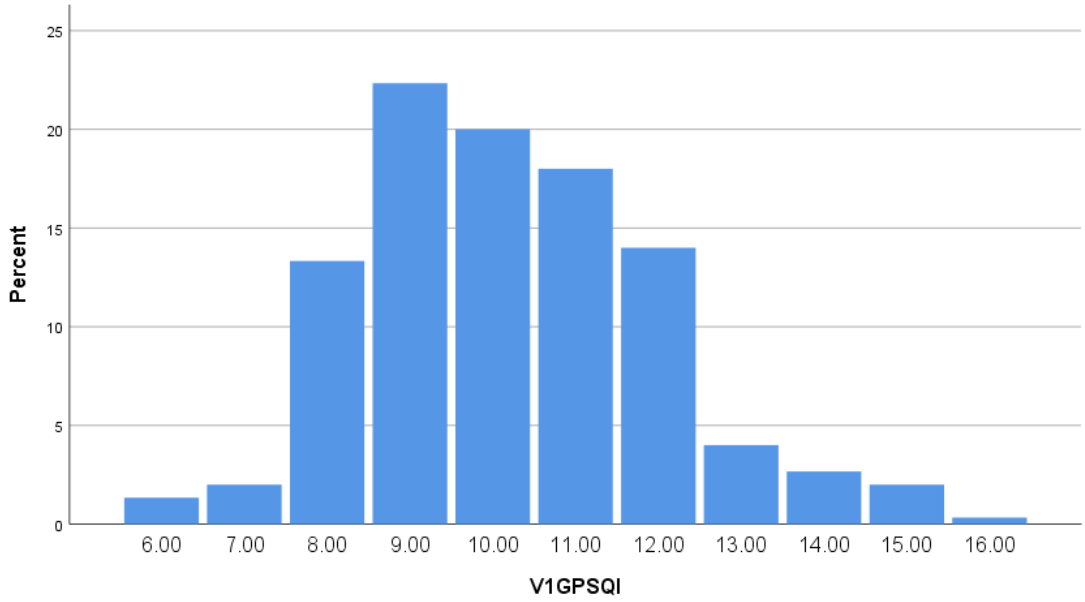


**Figure: 05.** Percentage (%) of Participant before Treatment of Gabapentin - Global Scoring 6-21 Represent as Bad /Poor Sleep. **V1GPSQI:** Visit-01 Global Pittsburgh Sleep Quality Index.

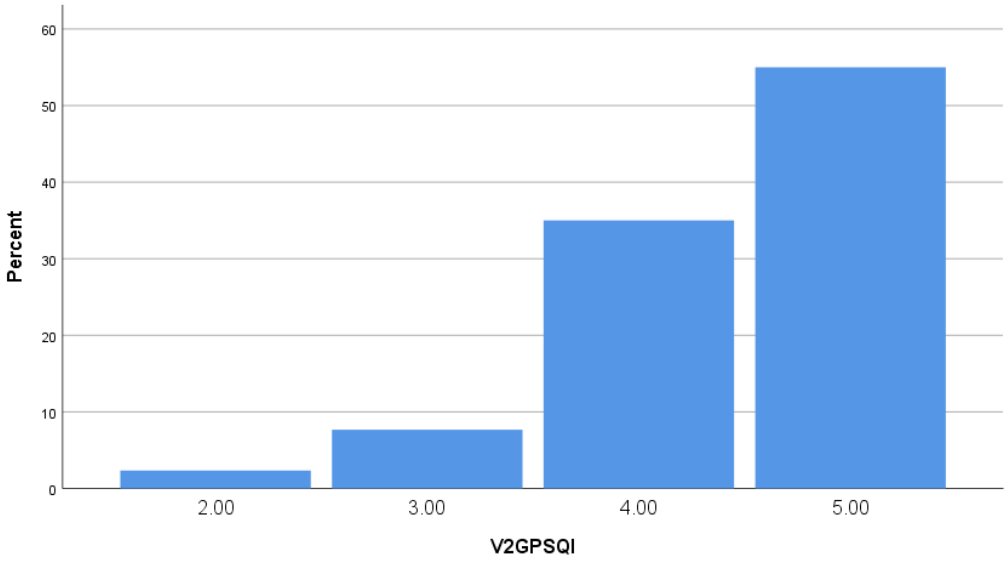


**Figure: 06.** Percentage (%) of Participants after Treatment of Gabapentin – Global Scoring 0-5 Represent as Good Sleep.**V2GPSQI:** Visit-02 Global Pittsburgh Sleep Quality Index.

**Table: 04.** Pittsburgh Sleep Quality Index (PSQI): Global Scores vs Visit-01 & Visit-02 Treatment for Pregabalin & Gabapentin with Various Clinical Variables means comparison.

| **Visit** | **Mean ± SD** | | ***t-Test*** | ***P-Value*** |
|---|---|---|---|---|
| | **PSQI Global score with treatment of Pregabalin (*n= 300*)** | **PSQI Global score with treatment of Gabapentin (*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, Mean ± SD=** Mean± Standard Deviation, ***t- Test*** = Paired t-Test, ***P-Value*** *<0.05.* | | | | |

## DISCUSSION

A well-known and well-documented common characteristic of neuropathic pain is disturbed sleep [21-23]. The growing list of issues linked to sleep disorder has made it apparent that there is more to inadequate sleep than meets the eye in terms of general health.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 [24-26]. 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 [27, 28].

Thus, the importance of sleep for general health has highlighted the necessity for both valid and trustworthy subjective instruments assessment in contemporary medical practice. While these represent very different diagnostic approaches, for Poor/Bad Sleep or Good Sleep assessed by PSQI. Self-rating questionnaires such as the Pittsburgh Sleep Quality Index (PSQI) have an important role in sleep health assessment in both clinical and research settings 09 & 10. The advantages of these surveys are their ease of administration, high patient compliance, and cost effectiveness. Perhaps more significantly, these self-explanatory and unsupervised questionnaires free up medical specialists' time because they don't need supervision. Rating scale surveys play a significant diagnostic function, hence proving their validity and reliability beyond a reasonable doubt is crucial. A crucial component of sleep is the confirmation of the questionnaires' dimensionality, or whether the items are correlated and representative of the factors affecting sleep quality. Examples of these factors include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction for sleep quality. This review critically appraises the evidence for dimensionality of one of the most widely used self-rating instruments of sleep quality, the PSQI [29, 11].

The beneficial effects of Gabapentinoid (Pregabalin and Gabapentin) on sleep disturbance in maintenance haemodialysis patients with painful peripheral neuropathy. Gabapentinoid has been found to be effective in pain-related sleep disturbance [29]. Gabapentinoid basically exerts its beneficial effects on sleep quality through alleviation of chronic pain. However, accruing evidence showed that Gabapentinoid has some favourable effects on sleep architecture as well [30-32]. Gabapentinoid has also been found to be effective for the treatment of restless legs syndrome and improve sleep architecture and periodic limb movements [33].

Painful Neuropathy is also common and closely interrelated with sleep disturbance. It is clinical importance to determine these prevalent disorders and treat appropriately. Effects of Gabapentinoid on sleep quality have been appreciated in painful neuropathy. This study showing beneficial effects of Gabapentinoid on sleep disturbance in Neuropathic Pain patients. Gabapentinoid was more effective on these derangements.

Due to Gabapentinoid well-known tolerability profile [34], the AE were not reported in this trial. Given the objective increases in sleep duration and statistically significant improvement in PSQI observed in the current study, Gabapentinoid has positive effects on a variety of sleep parameters.

## CONCLUSION

According to the study, Gabapentinoid was helpful in regulating the maintenance of Sleep as measured by the Global PSQI Score. In domains of neuropathic pain, Gabapentinoid was noticeably more effective. Reducing the overall score and the Seven Component Score of the PSQI was more successful with the Gabapentinoid. Gabapentinoid (Pregabalin & Gabapentin) showed well tolerated by patient & more effective on sleep maintenance in Neuropathic Pain patients.

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## COMPETING INTERESTS

The authors claim that there are no conflicting interests.

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