ORIGINAL ARTICLE

Neuropathic pain and sleep disturbances with special reference to patients with postherpetic neuralgia

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DOI No: 10.5958/0974-0155.2014.01113.9 *Indian J Sleep Med 2014; 9.3, 119-127*

Abstract

Objective: The impacts of postherpetic neuralgia (PHN) on patients' quality of sleep and global perceived effects (GPEs) are poorly documented. Our main aim of the study was to determine the improvement of sleep and GPE after 4 weeks of tramadol (50–200 mg) treatment with rescue analgesia in the form of topical cream containing 3.33% doxepin and 0.05% capsaicin in patients with PHN in relationship with CYP2D6 polymorphism.

Methods: This study mainly comprised 246 patients with PHN including 123 nonresponders and 123 responders undergoing tramadol treatment. The sleep interference was assessed on 0–10 scale using Daily Sleep Interference Scale. The subjects' overall impression (global evaluation) of the study medication was recorded by subjects' answering the question. All samples were analyzed for CYP2D6*4 and CYP2D6*10 polymorphism using polymerase chain reaction–restriction fragment length polymorphism method.

Results: Clinically significant ($p<0.001$) results were obtained in both the groups when compared with baseline between the Numerical Rating Scale (NRS) sleep scores and GPE scores whereas no associations were found between NRS sleep scores and GPE scores when compared with CYP2D6*4 and *10 polymorphisms ($p > 0.05$).

Conclusions: Treatment with tramadol 50–200 mg/day was found to be significantly associated with reduced sleep interference and improved GPEs of patients with PHN. CYP2D6 (*4 and

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*10) polymorphisms with respect to NRS sleep and GPE may not be a sleep and GPE predictor for patients with PHN.

Keywords: Sleep scores, Global perceived effect, Tramadol, CYP2D6, Postherpetic neuralgia

Introduction

Postherpetic neuralgia (PHN) is the most common sequelae of herpes zoster (HZ) affecting the elderly population[1]. Investigators estimated that the prevalence of PHN ranges from 500,000 to 1 million. HZ and PHN can be associated with severe psychosocial dysfunction, including impaired sleep, decreased appetite, and diminished libido that affects patient's quality of life (QOL)[2,3]. It is a major cause of sleep disturbance that leads to increased pain[4–6]. Nearly 65% people with chronic pain reported sleep disturbance[7]. These patients mainly complain about delayed onset of sleep, frequent awakenings, decreased sleep duration, daytime fatigue, and nonrestorative sleep[8].

Tramadol hydrochloride is a centrally acting opioid analgesic agent that acts as a weak m-opioid receptor agonist, primarily via the O-desmethyl metabolite M1, and is used for the treatment of moderate-to-severe pain. The commercially available tramadol is a racemic mixture of two enantiomers, that is, (+) tramadol and (-) tramadol. The (+) enantiomer is four times more potent than (-) enantiomer in terms of m-opioid receptor binding and serotonin reuptake inhibition, whereas (-) enantiomer is responsible for inhibition of noradrenaline reuptake, thereby enhancing inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of the racemate[9]. Tramadol exhibits monoaminergic activity that inhibits the noradrenaline and serotonin reuptake by blocking nociceptive receptors, thus enhancing the inhibition of pain transmission in the spinal cord. Tramadol is metabolized by O-demethylation and N-demethylation in the liver to O-demethyltramadol (M1), the main analgesic metabolite, and N-demethyltramadol (M2) [10]. The O-demethylation reaction is catalyzed by phase I enzyme cytochrome P450 (CYP) 2D6, whereas N-demethylation is catalyzed by CYP2B6 and CYP3A4. M1 metabolite has a high affinity toward m-opioid receptors and a longer mean elimination half-life (~9 h) as compared to the parent drug, which has very low affinity for m-opioid receptors and short mean elimination half-life of nearly 6 h[11].

The management of neuropathic pain (NP) is challenging because the response to most drugs remains unpredictable despite attempts to develop a more rationale therapeutic approach[12–14]. Tramadol hydrochloride is a centrally acting opioid analgesic agent used for the treatment of moderate-to-severe pain such as acute pain[15], chronic NP[16], painful diabetic neuropathy[17,18], polyneuropathy[16], fibromyalgia[19], and PHN[20–23]. But it has developed lots of drug-induced adverse side effects such as somnolence, dizziness, local site reaction, headache, hypotension, nausea, and vomiting[22–25]. It improves pain impact on sleep but has discrepant effects on QOL[21,22,26]

CYP2D6 is an important drug-metabolizing enzyme involved in the metabolism of many therapeutic agents, such as antidepressants, b-adrenergic antagonists, antiarrhythmics, and opioids[27]. These polymorphisms result in differences of up to 30- to 40-fold in substrate drug clearance, leading to drug concentrations of the therapeutic range in treating patients. Consequently, such differences in *CYP2D6* activity would lead not only to severe adverse effects in clinical therapy[28] but also to nonresponse to medications. Several studies found that patients with decreased *CYP2D6* enzyme activity had a diminished response to tramadol analgesia[29,30]. In our previous report, no role was found between Numerical Rating Scale (NRS) sleep scores and global perceived effect (GPE) scores when compared with *CYP2D6**2 polymorphism, 4-week treatment of tramadol-receiving PHN patients[22].

No reports are available that establish the clinical utility of *CYP2D6**4 and *10 genotyping in determining treatment choice or dose in relation to tramadol therapy in patients with PHN in the Indian population. In this study, we investigated the clinical utility of NRS sleep scores and GPE scores with respect to *CYP2D6* *4 and *10 in patients of PHN treated with tramadol.

Material and Methods

Study design

This study was a prospective, nonresponders versus responders for 4 weeks treatment of PHN and consisted of oral administration of tramadol (short acting) .In this study day 0 (baseline) considered as a baseline. A total of 270 patients were initially enrolled for the treatment, of which 15 did not fit the inclusion criteria and 9 did not receive tramadol therapy, according to the study design. Patients of PHN were divided into two groups depending on their response to tramadol therapy based on NRS. The intensity of pain including both resting and movement-associated pain was measured over the past 24 h on an 11-point NRS score ranging from 0 as no pain to 10 as worst possible pain on every visit. The NRS scoring was entered directly into the case record form for each patient[31].

This prospective study included 246 patients of PHN (age group 20–80 years). The patients reported with less than 50% pain relief were categorized as "nonresponders" (72 men and 51 women), and those reported with 50% pain relief with 14-day treatment of tramadol were categorized as "responders" (76 men and 47 women). This study was carried out with the help of Pain Clinic, Department of Anesthesiology, and Department of Dermatology, and all molecular biology analysis were carried out in Environmental Biochemistry and Molecular Biology Laboratory, Department of Biochemistry and Department of Pharmacology at University College of Medical Sciences, and Guru Teg Bahadur (GTB) Hospital, New Delhi, India, from January 2009 to January 2012. The study was approved by the Institutional Human Ethics Committee (Human Research) at University College of Medical Science and GTB Hospital, New Delhi. Written informed consent was obtained from all patients and blood samples were drawn for genetic (*CYP2D6* polymorphisms) analysis.

Inclusion criteria

The study participants included men and women aged between 20 and 80 years who reported chronic PHN pain, which was defined as the persistence of pain for more than 1 month after the onset of the initial eruption of zoster. For the purpose of the study, PHN pain was diagnosed when patient presented with pain (NRS $\geq$ 4 at baseline), which includes three of the constituent symptoms of NP, namely severe burning, shooting pain, and paresthesia and precipitation of pain on touch of pledget of cotton (allodynia).

Exclusion criteria

Patients who presented with symptoms or history of depression; immune system depression; seizures; illicit drug abuse or central nervous system depressant drug abuse; severe hepatic, renal, cardiac, or respiratory pathology; and hypersensitivity to tramadol or to opioids were excluded from the study. Patients likely to receive any treatment known to interfere with the studied drug or with the study design (neurological surgery, anesthetic blocks, local treatments of pain, antidepressants, anticonvulsants, anti-vitamin K, enzymatic inducers) were also excluded. Those with any history of diabetes mellitus, HIV, malignancy, hematological or liver disease, psychiatric illness, alcohol abuse, or those receiving corticosteroids and immunosuppressive drugs were not included. In addition, patients having white blood count of <2500 mm^3, neutrophil count of <1500 mm^3, or platelet count of <100 ′ 10^3 mm^3 were also excluded. Pregnant or breast-feeding women and women who were at risk of becoming pregnant during the study period were not included.

Treatment phase

The symptomatic treatment of PHN with tramadol consisted of 4-week treatment phase with 0 day considered as a baseline. At 0 day, patients rated the intensity of their PHN pain over the previous 24 h using an 11-point NRS (0, no pain; 10, worst possible pain). The duration of treatment was 4 weeks from day 0 (inclusion visit) to day 28 (the day before the last visit).

Dose design

The daily dose was increased (but not decreased) depending on therapeutic response and on treatment acceptability, from one tablet (50 mg) per day to two tablets (100 mg) per day. Dose was increased by steps in accordance with the following schedule: at least 48 h between step 1 (one tablet = 50 mg) and step 2 (two tablets = 100 mg); at least 72 h between step 2 and step 3 (three tablets = 150 mg) or between step 3 and step 4 (four tablets = 200 mg) in patients aged at the maximum 70 years; at least 72 h between step 1 and step 2; and at

least 120 h between step 2 and step 3 in patients aged more than 70 years. The duration of oral tramadol treatment was 4 weeks from day 0 (inclusion visit) to day 28 (the day before the last visit); inclusion and exclusion criteria already discussed in our published paper [18–20]. In the event of unsatisfactory pain relief, rescue analgesia was given to the patients who were not responding to oral medication, in the form of topical cream comprising capsaicin 0.05% and doxepin 3.33%.

Daily Sleep Interference (NRS sleep) scores

Patients with PHN were depressed, worried, withdrawn, and unable to sleep because of pain [severe burning, throbbing, tingling, stabbing piercing, shooting pain, paresthesia and precipitation of pain on touch of pledget of cotton (allodynia)]. All these contribute to inability of a person to perform daily activities. The most frequent sleep complaints include delayed onset of sleep, frequent awakenings, decreased sleep duration, daytime fatigue, and nonrestorative sleep.

This measure was used to assess the degree to which pain interfered with sleep during the preceding 24-h period on an 11-point Daily Sleep Interference rating scale (0, did not interfere with sleep; 10, completely interfered with sleep). It was included in the daily card on each visit day, that is, at baseline, day 3, day 7, day 14, and day 28[32].

Global perceived effect scores

The GPE consists of an evaluation by the clinician of the patient's overall change since the beginning of the study, rated on the four-point scale visit at baseline, day 7, day 14, and day 28[33].

Genotyping

Blood (5 mL) was drawn from each patient and collected in EDTA-coated vials. DNA was extracted using commercially available DNA extraction kit (Mini preparation kit; HiMedia Laboratories, Mumbai, India). The polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method was performed by digesting PCR products (*CYP2D6**4 and *CYP2D6**10) with their respective restriction enzymes, which determines the polymorphic site depending on the presence or absence of its recognition sequences (Table 1). The patients were categorized into ultrarapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs) based on genetic analysis (PCR-RFLP method) [22,23,34,35].

Table 1: Primer sequences of CYP2D6 alleles and PCR-RFLP detection method using their respective enzymes.

S. No.	CYP2D6 alleles	Primer sequences	Detection method
1	*4	5 –TGCCGCCTTCGCCAACCACT-3 5 -TCGCCCTGCAGAGACTCCTC-3	PCR-RFLP using *Bst*NI
2	*10	5 -GTGCTGAGAGTGTCCTGCC-3 5 –CACCCACCATCCATGTTTGC -3	PCR-RFLP using *Hph*I

Statistical analysis

The descriptive statistics were expressed as mean ± SD. The unpaired test was used to compare all mean difference between two groups at day 14. One-way repeated-measures analysis of variance (ANOVA) was used to compare the means within the group at different time intervals with Bonferroni adjustment ($\acute{a} = 0.05$) in the both the groups separately. Three-way repeated-measures ANOVA was applied taking time as a repeated factor and group and metabolizer as fix factors. We report multivariate (Wilks' lambda test) analysis because the Mauchly's test of Sphericity was found to be significant in NRS sleep and GPE. p-Values of <0.05 were considered to be significant.

Results

Patient data

Both the groups (123 nonresponders and 123 responders) of patients with PHN compared with respect to sex, age, weight, duration of disease, and gender ratio were found to be nonsignificant ($p > 0.05$). The total gender mean of nonresponders was 53.33 ± 12.47 (males 53.94 ± 13.24; females 52.45 ± 11.35) and total mean of responders was 52.23 ± 12.08 (males 53.50 ± 12.72; females 50.17 ± 10.79.33). The mean age (in years) of patients in the nonresponder group was 53.33 ± 12.47 and of those in the responder group was 52.23 ± 12.08. The mean weight (in kg) of patients in the nonresponder group was 56.28 ± 10.95 and of those in the responder group was 51.23 ± 11.45. The mean duration of disease (in months) of patients in the nonresponder group was 4.79 ± 3.48 and of those in the responder group was 4.23 ± 4.47. The gender ratios (male/female) in the nonresponder and responder groups were 72:51 and 76:47, respectively.

Numerical Rating Scale sleep scores

Statistically insignificant difference ($p > 0.05$) was observed at baseline in mean NRS sleep score of patients with PHN in both the groups. However, statistically significant difference (p<0.001) was observed in the NRS sleep scores on days 3, 7, 14, and 28 in the patients in the responder group as compared to those in the nonresponder group. A statistically significant improvement ($p < 0.001$) was also observed in the NRS sleep scores on days 3, 7, 14, and 28 as compared to baseline in both the groups (Table 2).

Table 2: Mean NRS sleep score in both the groups at various time intervals

S. No.	Group	Baseline	Day 3	Day 7	Day 14	Day 28	*p*-Value
1	Nonresponders(n = 123)	8.22 ± 1.14[b,c,d,e]	6.34 ± 1.01[a,c,d,e]	4.69 ± 1.06[a,b,d,e]	3.41 ± 1.05[a,b,c,e]	2.11 ± 1.05[a,b,c,d,*]	**<0.001**
2	Responders (n = 123)	6.71 ± 1.35[g,h,i,j]	5.44 ± 1.57[f,h,i,j]	4.20 ± 1.62[f,g,i,j]	2.77 ± 1.41[f,g,h,j]	1.54 ± 1.11[f,g,h,i,*]	**<0.001**
	***p*-Value**					**<0.001**	

Global perceived effect scores

At baseline, both the groups were statistically insignificant with respect to each other in terms of GPE. The patients in the responder group experienced a significant improvement in GPE as compared to patients in the nonresponder group at various time intervals (days 7, 14, and 28; $p < 0.001$). Patients in both the groups experienced a statistically significant improvement in GPE on days 7, 14, and 28 as compared to respective baselines ($p < 0.001$; Table 3).

Table 3: Global perceived effect score in both the groups at various time intervals

S. No.	Group	Baseline	Day 7	Day 14	Day 28	*p*-Value
1	Nonresponders (n = 123)	1.14 ± 1.23[b,c,d]	1.60 ± 1.99 [a,c,d]	2.21 ± 1.57 [a,b,d]	3.11 ± 1.48[a,b,c,*]	**<0.001**
2	Responders (n = 123)	1.27 ± 1.18[f,g,h]	2.27 ± 1.41[e,g,h]	3.19 ± 1.62[e,f,h]	4.43 ± 1.57[e,f,g,*]	**<0.001**
	p-Value				**<0.001**	

All the values are expressed as mean ± SD; $p < 0.001$ w.r.t. [a]baseline of nonresponders, [b]day 7 of nonresponders, [c]day 14 of nonresponders, [d]day 28 of nonresponders, [e]baseline of responders, [f]day 7 of responders, [g]day 14 of responders, [h]day 28 of responders. [*]$p < 0.001$ w.r.t. between day 14 of nonresponders and responders.

Numerical Rating Scale sleep scores with respect to CYP2D6 polymorphism

NRS sleep scores are useful for clinically assessing how intensely patients were feeling pain during sleep and for monitoring the effectiveness of treatment at different time intervals. Here NRS sleep score has been compared with different metabolizers of *CYP2D6**4 and *10 polymorphism with a different time interval from baseline to the end of treatment. Three-factor repeated-measure ANOVA was applied to find out the interaction between time, group, and metabolizers. In *4 allele, no significant ($p = 0.121$) association was found between groups. The NRS sleep score with metabolizers was found to be ($p = 0.370$) insignificant and that with groups and metabolizers was also found to be insignificant ($p = 0.088$). In *10 allele, the interaction between time and group was found to be significant ($p < 0.001$), which showed improvement sleep scores change with time. No significant association was found between improvement sleep score and metabolizers ($p = 0.919$) and the same between group and metabolizers ($p = 0.465$; Table 4).

Table 4: Numerical rating scale sleep and *CYP2D6* polymorphism

NPSI scale	Group	Metabolizers	Day 0 (baseline)	Day 3	Day 7	Day 14	Day 28	*p*-Value
*Numerical Rating Scale: sleep and CYP2D6*4 allele*								
NRS sleep	NR	UM (n = 0)	-	-	-	-	-	**0.001[a]; 0.121[b]; 0.370[c]; 0.088[d]**
		EM (n = 77)	8.19 ± 1.064	6.36 ± 1.012	4.65 ± 1.023	3.39 ± 0.975	2.06 ± 1.092	
		IM (n = 35)	8.44 ± 1.330	6.41 ± 1.019	4.74 ± 1.189	3.24 ± 1.257	2.12 ± 1.008	
		PM (n = 11)	7.64 ± 0.924	5.91 ± 0.944	4.82 ± 1.079	4.00 ± 0.775	2.36 ± 1.027	
		Total (n = 123)	8.21 ± 1.144	6.34 ± 1.009	4.69 ± 1.069	3.40 ± 1.058	2.11 ± 1.059	
	R	UM (n = 8)	6.50 ± 1.414	5.25 ± 1.282	4.00 ± 1.195	2.38 ± 1.408	1.50 ± 1.195	
		EM (n = 92)	6.38 ± 1.274	5.40 ± 1.590	4.22 ± 1.656	2.78 ± 1.381	1.57 ± 1.062	
		IM (n = 21)	6.81 ± 1.365	5.43 ± 1.326	4.19 ± 1.537	2.86 ± 1.424	1.38 ± 1.203	
		PM (n = 2)	5.50 ± 0.707	3.50 ± 0.707	2.00 ± 0.000	1.00 ± 0.000	0.50 ± 0.707	
		Total (n = 123)	6.45 ± 1.294	5.37 ± 1.527	4.16 ± 1.611	2.74 ± 1.390	1.51 ± 1.089	
*Numerical Rating Scale: sleep and CYP2D6*10 allele*								
NRS sleep	NR	UM (n = 0)	-	-	-	-	-	**0.001[a]; 0.001[b]; 0.919[c]; 0.465[d]**
		EM (n = 81)	8.14 ± 1.202	6.25 ± 1.019	4.57 ± 1.024	3.30 ± 1.018	2.02 ± 1.060	
		IM (n = 30)	8.33 ± 1.093	6.43 ± 1.040	4.97 ± 1.098	3.57 ± 1.073	2.17 ± 1.085	
		PM (n = 12)	8.50 ± 0.798	6.75 ± 0.754	4.83 ± 1.193	3.75 ± 1.215	2.58 ± 0.900	
		Total (n = 123)	8.22 ± 1.142	6.34 ± 1.007	4.69 ± 1.065	3.41 ± 1.055	2.11 ± 1.057	
	R	UM (n = 0)	-	-	-	-	-	
		EM (n = 88)	6.45 ± 1.338	5.32 ± 1.520	4.14 ± 1.641	2.72 ± 1.389	1.47 ± 1.082	
		IM (n = 30)	6.30 ± 1.179	5.30 ± 1.557	4.03 ± 1.497	2.67 ± 1.422	1.57 ± 1.165	
		PM (n = 5)	7.20 ± 1.095	6.60 ± 1.140	5.40 ± 1.517	3.60 ± 1.140	2.00 ± 0.707	
		Total (n = 123)	6.45 ± 1.294	5.37 ± 1.527	4.16 ± 1.611	2.74 ± 1.390	1.51 ± 1.089	

Global perceived effect scores with respect to CYP2D6 polymorphism

A global rating of change can be used to separate stable patients from improved patients in the dimension of physical impairment. In *4 allele, the interaction between time and group was found to be significant ($p < 0.001$), which showed that GPE score changes with time. Insignificant interaction was found between time and metabolizers ($p = 0.941$) in *4 genotype; similar results were observed between time, group, and metabolizers ($p = 0.227$) in *10 allele. UMs were absent in both the groups. The interaction between groups was found to be significant ($p < 0.001$), which showed GPE scores change with time. Significant interaction was found with metabolizers ($p = 0.110$) and that with time, metabolizers, and groups ($p = 0.744$; Table 5).

Table 5: Numerical Rating Scale: GPE and *CYP2D6* polymorphism

Scale	Group	Metabolizers	Day 0 (baseline)	Day 7	Day 14	Day 28	*p*-Value
*Numerical Rating Scale: GPE and CYP2D6*4 allele*							
GPE	NR	UM ($n = 0$)	-	-	-	-	**0.015**[a]; 0.941[b]; 0.227[c]; 0.227[d]
		EM ($n = 77$)	1.48 ± 0.641	1.73 ± 0.700	2.01 ± 0.698	2.45 ± 0.882	
		IM ($n = 35$)	1.50 ± 0.564	1.65 ± 0.544	1.97 ± 0.627	2.50 ± 0.707	
		PM ($n = 11$)	1.45 ± 0.522	1.64 ± 0.505	2.00 ± 0.632	2.73 ± 0.786	
		Total ($n = 123$)	1.48 ± 0.606	1.70 ± 0.641	2.00 ± 0.668	2.49 ± 0.826	
	R	UM ($n = 8$)	2.62 ± 1.061	3.25 ± 0.886	3.38 ± 0.744	3.75 ± 0.463	
		EM ($n = 92$)	2.50 ± 0.978	2.90 ± 0.757	3.10 ± 0.680	3.61 ± 0.534	
		IM ($n = 21$)	2.52 ± 0.928	2.95 ± 0.740	2.95 ± 0.740	3.43 ± 0.507	
		PM ($n = 2$)	2.50 ± 2.121	3.00 ± 1.414	3.00 ± 1.414	3.00 ± 1.414	
		Total ($n = 123$)	2.51 ± 0.978	2.93 ± 0.765	3.09 ± 0.701	3.58 ± 0.543	
*Numerical Rating Scale: GPE and CYP2D6*10 allele*							
GPE	NR	UM (n=0)	-	-	-	-	**0.001**[a]; 0.110[b]; 0.744[c]; 0.744[d]
		EM (n=81)	1.44 ± 0.570	1.63 ± 0.641	1.95 ± 0.650	2.43 ± 0.851	
		IM (n=30)	1.63 ± 0.718	1.87 ± 0.681	2.17 ± 0.699	2.60 ± 0.724	
		PM (n=12)	1.33 ± 0.492	1.67 ± 0.492	1.92 ± 0.669	2.58 ± 0.900	
		Total (n=123)	1.48 ± 0.605	1.69 ± 0.642	2.00 ± 0.665	2.49 ± 0.823	
	R	UM (n=0)	-	-	-	-	
		EM (n=88)	2.50 ± 0.971	2.89 ± 0.780	3.06 ± 0.701	3.55 ± 0.545	
		IM (n=30)	2.63 ± 1.033	3.07 ± 0.740	3.20 ± 0.714	3.67 ± 0.479	
		PM (n=5)	2.00 ± 0.707	3.00 ± 0.707	3.00 ± 0.707	3.60 ± 0.894	
		Total (n=123)	2.51 ± 0.978	2.93 ± 0.765	3.09 ± 0.701	3.58 ± 0.543	

Discussion

In the management of PHN, so far there is no single appropriate therapy or intervention approach. With most forms of NP, the treatment response is best described as inconsistent. In this study, with the use of tramadol therapy approach in patients with PHN, a significant ($p<0.001$) improvement was observed in NRS sleep scores in patients of the responder group. Patients with PHN were observed to have reduced pain, such as severe burning, throbbing, tingling, stabbing piercing, and shooting pain, and improved the quality of sleep, reduced frequented awaking, and increased sleep duration. NRS sleep scores were found to have insignificant interactions ($p > 0.05$) (time, metabolizers, and group) with *CYP2D6* *4 and *10 polymorphisms. It also confirmed the previous published work reported that orally administered tramadol (50–200 mg) over 4 weeks is safe for patients with PHN[21,22]. In addition, clinically, statistically significant ($p < 0.001$) results were obtained in both the groups when compared with baseline in the NRS sleep whereas no association was found between NRS sleep when compared with *CYP2D6**2 polymorphism ($p > 0.05$)[22].

Tramadol extended-release (ER) treatment was associated with significant improvements in pain-related sleep disturbances in both studies. In the study, involving the 246 patients, tramadol ER treatment was associated with statistically significant means improvements from a baseline average over 12 weeks of the study in pain-related sleep disturbances when compared with placebo treatment using Chronic Pain Sleep Inventory[36]. Specifically, improvements were seen in trouble falling asleep due to pain being awakened by pain during the night, being awakened by pain in the morning, and overall sleep quality. The pain-related sleep improvements were seen using tramadol because there was a significant reduction in pain-related sleep disturbances in patients with chronic osteoarthritis pain[37].

Several NP trials of tricyclic antidepressants, anticonvulsants, and opioids that included secondary outcome measures of QOL and mood have been reported[38-40]. Results from such clinical trials showed that the effects of analgesic treatment on QOL and/or mood vary widely. As expected, most trials that failed to show analgesia also failed to show improvements in QOL[41-43]. Several of the first-line medications had consistently improved the sleep, and opioids[44,45] had produced statistically significant improvement in sleep relative to placebo.

QOL especially sleep and mood is frequently impaired in patients with NP[26,46]. The quality of NP treatment appears to be poor, with few patients receiving recommended medications in efficacious dosages. The effective treatment of pain-related sleep disturbances should be considered a key component of the overall approach to managing chronic pain[7]. Because greater pain intensity has been associated with decreased sleep

satisfaction, less total sleep time, delayed onset of sleep, and more awakenings due to pain[47], effective pain control should improve sleep in patients with chronic pain.

In this study, a concomitant improvement ($p < 0.001$) in GPE was observed among patients in both the groups over a treatment period of 28 days. The tramadol-treated patients had optimum pain relief as evidenced by the significant rise of GPE ($p < 0.001$) at day 14 and day 28 after the start of multimodal therapy. Although there was an improvement in GPE scores in nonresponders, the degree of improvement was much higher ($p < 0.001$) in responders. Moreover, responders had an early onset of pain relief as compared to nonresponders. To our knowledge, based on the genetic model of the *CYP2D6* polymorphism, in present literature, it is difficult to find GPE correlating with *CYP2D6* genotypes of patients with PHN. Our results also showed that there was no significant interaction between *CYP2D6**4 and *10 polymorphism among the GPE. Our previous report also suggested that tramadol-treated (50–200 mg) patients had optimum pain relief as evidenced by a greater global improvement on GPE scores ($p < 0.001$) on days 14 and 28 multimodal therapy[21,22]. In addition, there was no significant interaction between *CYP2D6**2 polymorphism among the GPE[22]. Norrbrink and Lundeberg[48] have observed a significant difference in global life satisfaction between the tramadol and the placebo groups. The median values seem to indicate that the tramadol-treated group ratings were stable over time and that difference between the groups were due to changes in the placebo group ratings. No effect on these parameters was reported in two other studies with tramadol[17,20].

In this study, a significant ($p > 0.001$) improvement was observed in NRS sleep and GPE scores of patients in the responder group, but not much improvement of sleep and GPE scores among few patients in the nonresponder group due to poor response needs further exploration into genetic factors and may be due to imbalance in the functional integrity caused by single-nucleotide polymorphism in the genes involved in pharmacokinetics of tramadol. Moreover, further studies to analyze the genetic profile of such patients with PHN need to be carried out, especially with reference to genes/enzymes of the CYP 450 family. Polymorphism in these genes may result in increased/decreased activity, thereby affecting the efficacy of drug action[21]. Therefore, the detection of genetic variations in *CYP2D6* is useful in identifying sleep disturbance is a prevalent complaint among patients with PHN type of pain and thus the improvement of sleep quality is an important goal in pain management.

Conclusion

Patients treated with tramadol had optimum pain relief as evidenced by a significant reduction in NRS sleep scores and also significant rise of GPE ($p < 0.001$) at day 14 and day 28 after the start of this multimodal therapy. Although there was an improvement in NRS sleep and GPE scores in nonresponders, the degree of improvement was much higher ($p < 0.001$) in responders. Moreover, responders had an early onset of pain relief as compared to nonresponders. Thus, sleep disturbances and GPE may serve as a marker for the assessment of response to treatment for chronic NP such as PHN. The *CYP2D6* polymorphism may not be sleep and GPE predictors of treatment outcome of patients with PHN receiving tramadol.

Acknowledgment

We thank patients and their relatives for their support and cooperation. This study was supported by an SRF Fellowship grant (ICMR) provided to Mrs. Namita Vilas Nasare (Grant No. 45/22/09/ PHA-BMS).

References

1. **Gilden DH**. Herpes zoster with post herpetic neuralgia-persisting pain and frustration. *N Engl J Med* 1994;330:932–4.
2. **Lydick E**, Epstein RS, Himmelberger D, White CJ. Herpes zoster and quality of life: A self-limited disease with severe impact. *Neurology* 1995;45:S52–3.
3. **Graff-Radford SB**, Kames LD, Naliboff BD. Measure of psychological adjustment and perception of pain in post herpetic neuralgia and trigeminal neuralgia. *Clin J Pain* 1986;2:55–8.
4. **Drewes AM**. Pain and sleep disturbance with special reference to fibromyalgia and rheumatoid arthritis. *Rheumatology (Oxford)* 1999;38:1035–8.
5. **Kundermann B**, Spernal J, Huber MT, Krieg JC, Lautenbacher S. Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom Med* 2004;66:932–7.
6. **Onen SH**, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res* 2001;10:35–42.

7. **Deardorff W**. *Chronic Pain and Insomnia: Breaking the Cycle*, 2007. Available at: http://www.spine-health.com/wellness/sleep/chronic-pain-and-insomnia-breaking-cycle (last accessed on December 19, 2013).
8. **Cohen MJM**, Menefee LA, Doghramji K, Anderson WR, Frank ED. Sleep in chronic pain: Problems and treatments. *Int Rev Psychiatry* 2000;12:115–26.
9. **Raffa RB**, Friderichs E. The basic science aspect of tramadol hydrochloride. *Pain Rev* 1996;3:249–71.
10. **Dayer P**, Desmeules J, Collart L. [Pharmacology of tramadol.] [Article in French] Drugs 1997;53:18–27.
11. **Grond S**, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004;43:879–923.
12. **Dworkin RH**, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007;132:237–51.
13. **Finnerup NB**, Jensen TS. Mechanisms of disease: Mechanism-based classification of neuropathic pain-a critical analysis. *Nat Clin Pract Neurol* 2006;2:107–15.
14. **Baron R**. Mechanisms of disease: neuropathic pain: A clinical perspective. *Nat Clin Pract Neurol* 2006;2:95–106.
15. **Katz J**, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Acute pain in herpes zoster and its impact on health-related quality of life. *Clin Infect Dis* 2004;39:342–8.
16. **Sindrup SH**, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to mechanism of drug action. *Pain* 1999;83:389–400.
17. **Harati Y**, Gooch C, Swenson M, Edelman S, Greene D, Raskin P, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998;50:1842–6.
18. **Harati Y**, Gooch C, Swenson M, Edelman SV, Greene D, Raskin P, et al. Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. *J Diabetes Complications* 2000;14:65–70.
19. **Russell IJ**, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol* 2000;6:250–7.
20. **Boureau F**, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: A randomized, double-blind, placebo-controlled trial. *Pain* 2003;104:323–31.
21. **Saxena AK**, Nasare NV, Jain S, Dhakate G, Ahmed RS, Bhattacharya SN, et al. A randomized, prospective study of efficacy and safety of oral tramadol in the management of post herpetic neuralgia in patients from north India. *Pain Pract* 2013;13:264–75.
22. **Nasare NV**, Banerjee BD, Deshmukh PS, Mediratta PK, Saxena AK, Ahmed RS, et al. *CYP2D6**2 polymorphism as predictor of failed outpatient tramadol therapy in post herpetic neuralgia patients. *Am J Ther* [Epub ahead of print] 2013 Apr 5.
23. **Nasare NV**, Deshmukh PS, Banerjee BD, Mediratta PK, Ahmed RS, Saxena AK, et al. *CYP2D6**4 polymorphism in tramadol treatment and its clinical impact in patients of post herpetic neuralgia. *Personalized Med* 2012;9:371–85.
24. **Follin SL**, Charland SL. Acute pain management: Operative or medical procedures and trauma. *Ann Pharmacother* 1997;31:1068–76.
25. **Lehmann K**, Kratzenberg U, Schroeder-Bark B, Horrichs-Haermeyer G. Postoperative patient-controlled analgesia with tramadol: Analgesic efficacy and minimum effective concentration. Clin J Pain 1990;6:212–20.
26. **O'Connor AB**. Neuropathic pain: Quality of life impact, costs and cost effectiveness of therapy. *Pharmacogenomics* 2009;27:95–112.
27. **Zanger UM**, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: Overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol* 2004;369:23–37.
28. **Kirchheiner J**, Nickchen K, Bauer M, Wong ML, Licinio J, Roots I, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry* 2004;9:442–73.
29. **Poulsen L**, Arendt-Nielsen L, Brøsen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to *CYP2D6*. *Clin Pharmacol Ther* 1996;60:636–44.
30. **Stamer UM**, Lehnen K, Höthker F, Bayerer B, Wolf S, Hoeft A, et al. Impact of *CYP2D6* genotype on postoperative tramadol analgesia. *Pain* 2003;105:231–8.
31. **Hartrick CT**, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: A ratio measure? *Pain Pract* 2003;3:310–6.
32. **Vernon MK**, Brandenburg NA, Alvir JM, Griesing T, Revicki DA. Reliability, Validity, and Responsiveness of the Daily Sleep Interference Scale among Diabetic Peripheral Neuropathy and Postherpetic Neuralgia Patients. *J Pain Symptom Manage* 2008;36:58–68.
33. **Kamper SJ**, Ostelo RW, Knol DL, Maher CG, de Vet HC, Hancock MJ. Global perceived effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol* 2010;63:760–6.
34. **Kirchheiner J**, Keulen JT, Bauer S, Roots I, Brockmöller J. Effects of the *CYP2D6* gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. *J Clin Psychopharmacol* 2008;28:78–83.
35. **Nageswararao D**, Manjula G, Sailaja K, Raghunadharao S, Vishnupriya R. Association of *CYP2D6**4 polymorphism with acute leukemia. *J Cell Tissue Res* 2010;10:2201–5.
36. **Babul N**, Noveck R, Chipman H, Roth SH, Gana T, Albert K. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: A randomized 12-week clinical trial in osteoarthritis of the knee. *J Pain Symptom Manag* 2004; 28:59–71.
37. **Nicholson B**. Benefits of extended-release opioid analgesic formulations in the treatment of chronic pain. *Pain Pract* 2009;9:71–81.
38. **McQuay HJ**, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68:217–27.

39. **Collins SL**, Moore RA, McQuay HJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: A quantitative systematic review. *J Pain Symptom Manage* 2000;20:449–58.

40. **Watson CP**. A new treatment for postherpetic neuralgia. *N Engl J Med* 2000;23:1563–5.

41. **McQuay HJ,** Carroll D, Jadad AR, Glynn CJ, Jack T, Moore RA, et al. Dextromethorphan for the treatment of neuropathic pain: A double-blind randomized controlled crossover trial with integral n-of-1 design. *Pain* 1994;59:127–33.

42. **McCleane GJ**. 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: A randomised, double-blind, placebo controlled trial. *Pain* 1999;83:105–7.

43. **Wallace MS**, Magnuson S, Ridgeway B. Efficacy of oral mexiletine for neuropathic pain with allodynia: A double-blind, placebo-controlled, crossover study. *Reg Anesth Pain Med* 2000;25:459–67.

44. **Rowbotham MC**, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *New Engl J Med* 2003;348:1223–32.

45. **Gimbel JS**, Richards P, Portenoy RK. Controlled release oxycodone for pain in diabetic neuropathy. A randomized controlled trial. *Neurology* 2003;60:927–34.

46. **Jensen MP**, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: Review and implications. *Neurology* 2007;68:1178–82.

47. **Atkinson JH**, Slatter MA, Patterson TL, Grant I, Garfin SR. Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain a controlled study. *Pain* 1991;45:111–21.

48. **Norrbrink C**, Lundeberg T. Tramadol in neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled trial. *Clin J Pain* 2009;25:177–84.