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NEUROPATHIC PAIN SYMPTOMS OF POST HERPETIC NEURALGIA PATIENTS WITH CYP2D6 POLYMORPHISM UNDERGOING TRAMADOL TREATMENT

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ABSTRACT: Main aim of this study was to find out relation of CYP2D6 polymorphism with tramadol action in post herpetic neuralgia (PHN) patients. This non- responders versus responders study mainly includes 246 patients (age group 20-80 years) of PHN, assigned into two groups depending upon their response to tramadol treatment at the end of 2nd week of drug therapy. On the basis of *CYP2D6* polymorphism, an allodynia and pins and needles significant interactions were found with *CYP2D6*2* allele between time, group and metabolizers while with**4* and **10* alleles no interaction observed. Finally, results not showing role of *CYP2D6* polymorphism in the development of neuropathic symptoms in PHN patients

INTRODUCTION: Post-herpetic neuralgia (PHN) is the most common complication of herpes zoster which is caused by *vericella zoster virus* commonly affecting the elderly population and most challenging to treat.[1-3] Time durations for measuring the pain of PHN differing from 3-6 months after the appearance of skin lesions [4-6]. Main feature of neuropathic pain is impaired sensation along with sensory dysfunction which was responsible in experiencing hypo- or hyper-anesthesia. [7, 8]

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Pain perception to harmful stimuli (hyperalgesia) or allodynia are accompanied by burning or electric shock type pain, paroxysms and dysaesthesia. Neuropathic symptoms such as hypoesthesia, hyperalgesia, allodynia and voluntary pain, often develop in early stages [9-11]. These symptoms of painful neuropathy are highly unpleasant for the individuals and affect their quality of life .[12, 13]

Tramadol is an analgesic drug which is used in the treatment of neuropathic pain having poor agonistic activity towards μ –opioid receptors.[14] It is metabolized by O-desmethylation and N-methylation in liver. O-desmethylation reaction is catalyzed by Phase I CYP enzyme. It mainly involves pain inhibition by blocking release of serotonin or noradrenaline in the brainstem.[15] Its antinociceptive effects are altered by *CYP2D6* activity.[16] The analgesic activity in experimental

pain is reduced in PMs which later confirmed in pain patients.[17-19] *CYP2D6* genetic polymorphism plays a minor role in its pharmacokinetics, [19] and pharmacodynamics.[20] Higher incidence of adverse effect is found in PMs than UMs.[21]

Age, sex, drug interaction, disease, genetic factors are mainly influence the efficacy of a drug and their adverse drug reactions. Single nucleotide polymorphism (SNP) was associated with increased or decreased pain also instead of modified effects of pain management. With the help of SNPs, we may distinguish the interindividual response of particular drug which helps in deciding the optimum effective dose of the drug. The property to distinguish the population into responders and non-responders makes easy way to target the specific population who required drug more effectively. In humans, pain perception and processing is therefore more likely to genetically control which helps in modulating analgesic therapy.[22]

Studying drug metabolism polymorphically in a population highlights the proportion of individuals differentially enable to metabolize certain drugs and therefore each react adversely or differentially to drugs.[23] Genetic polymorphism in *CYP2D6* family contributes to inter-individual variations in enzyme activity.[24] According to activity of the enzymes, *CYP2D6* metabolizers are categorized into four groups.

The extensive metabolizers (EMs) show normal metabolic activity with two active alleles or one active and one partial active allele. Intermediate metabolizers (IMs) having one active allele and one inactive allele or two partial alleles requiring lower drug doses, whereas poor metabolizers (PMs) with no active *CYP2D6* alleles or one partial allele are highly responsible for drug induced side effects due to lack of drug elimination. Ultrarapid metabolizers (UMs) with one or more extra allele or one partial allele may require some large dose because of its high drug metabolism activity.

Different *CYP2D6* genotype in patients receiving tramadol may respond differently in terms of pain. It is play important role in finding out pharmacokinetics/pharmacodynamics of tramadol in predicting adverse effects. Thus *CYP2D6* polymorphism play important role in determining the therapeutic efficacy and dose adversity of administered drugs.[25]

Clinical research attract more attention on increasing problem of pain persistence and understanding the possible reason to treat the disease underlying pain but still there is no gold standard therapeutic approach or treatment to manage this difficult to treat pain.[26, 27] Depending on the allele response, allelic variants will show normal, decreased or no *CYP2D6* role in the treatment of neuropathetic pain with different drugs may provide an idea about efficacious treatment response from clinical experience. Hence, the aim of this study was to find the association of *CYP2D6* gene polymorphism with neuropathic pain symptoms undergoing tramadol treated PHN patients.

MATERIAL AND METHODS:

Study design:

The study was a prospective, non-responders versus responders in the treatment of PHN and consisted of oral administration of tramadol (short acting) for 4 weeks with day 0 (baseline) considered as a baseline. A total of 270 patients were initially enrolled for the treatment of which 15 patients did not fit the inclusion criteria and 9 patients did not receive tramadol therapy, according to the study design.

This prospective study included 246 patients (age group 20-80 years) of PHN patients reported with less than 50% pain relief were categorized as “non-responders” (72 males and 51 females), and patients reported with 50% pain relief with 14 days of tramadol were categorized as “responders” (76 males, and 47 females).

The present study was carried out with the help of pain clinic, Department of Anesthesiology, 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 (University of Delhi) & Guru Teg Bahadur Hospital, New Delhi- 110095, India

during the period January 2009 to January 2012. Prior approval of Institutional Ethics Committee – Human Research was received and patients consent was taken in written printed Performa. The oral tramadol treatments were given for 4 weeks and their improvements were recorded from day 0 (Inclusion of visit) to day 28 (The day before the end of visit). PHN patients were rated their pain intensity on 11 point numerical rating scale(NRS) which ranges from 0 for no pain and 10 as worst pain over previous 24 hours.

The dose of tramadol was increased from one tablet per day to 4 tablets per day based on response and acceptability. Dose incriminations were performed as follows: 48 hrs gap of between step 1 (one tablet =50 mg per day) and 2 (two tablets = 100 mg per day), and minimum of 72 h between step 2 and 3 (three tablets= 150 mg per day) or between step 3 and 4 (four tablets = 200mg per day) with patients aged the maximum 70 years. However patients exceeded 70 yrs were considered for 72 hrs time intervals between step 1 and step 2 and5 days between step 2 and 3.

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 application of capsaicin 0.05% and /or doxepin 3.33% cream. The dose schedules were four times a day after two weeks on the dermatomes. The efficacy was judged by means neuropathic pain symptoms inventory (NPSI) scores at baseline, day 3, 7, 14 and 28 while continuing study medication.

Inclusion criteria:

The study participants included women and men (20-80 years) of Indo-Aryan ethnicity and had PHN defined as pain continue more than 3 months after healing of a zoster virus skin rash. Eligible criteria of the patients, if their pain was at least 4 on the 11 NRS which includes three of the constituent symptoms of neuropathic pain namely shooting pain, paresthesia, severe burning and allodynia during the base-week preceding randomization. All patients of PHN were having sharp, shooting pain that is unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs). Patients taking NSAIDs were instructed to stop these drugs three days prior to the commencement of treatment with tramadol.

Exclusion criteria:

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

Pain Measurement Scores:

Oral tramadol efficacy was measured by mean NPSI scores on outpatient department (OPD) at pain clinic department visit days i.e. 0 day, 3,7,14 and end on day 28.

Neuropathic Pain Symptom Inventory (NPSI) Scores:

This study included eight parameters [i.e. Burning pain, squeezing pain, pressure pain, electric shock pain, stabbing pain, tingling pain, pins and needles pain, and allodynia (pain provoked by light touch)]. Each of the parameters mean NPSI scores were recorded on scheduled visits: inclusion visit, on day 0, follow-up visits on day 3,7,14, and end visit on day 28, on an 11-point numeric rating scale anchored by 0: No pain (symptom) and 10: Worst (symptom) imaginable pain. [28]

Genotyping:

Five ml of blood was taken out from each PHN patient and collected in EDTA coated vials. DNA was extracted using commercially available DNA

extraction kit (Hi- Media Mini preparation kit, Hi-Media Laboratories Pvt. Ltd. Mumbai, India). Primer sequences of CYP2D6 alleles and PCR-RFLP was done by digesting PCR product with their respective restriction enzymes **(Table 1)**.

TABLE 1: PRIMER SEQUENCES OF CYP2D6 ALLELES AND PCR-RFLP DETECTION METHOD USING THEIR RESPECTIVE ENZYMES

Sr. No.	CYP2D6 alleles	Primer Sequences	Detection Method
1	*2	5'GCTGGGGCCTGAGACTT'3 5'GGCTATCACCAGGTGCTGGTGCT3'	PCR-RFLP using *Hhal*
2	*4	5' TGCCGCCTTCGCCAACCACT3' 5'TCGCCCTGCAGAGACTCCTC3'	PCR-RFLP using *BstNI*
3	*10	5'GTGCTGAGAGTGTCCTGCC3' 5' CACCCACCATCCATGTTTGC3'	PCR-RFLP using *HphI*

Statistical analysis:

The unpaired't' test was used to measure all mean difference between the groups at day 14 time point. One factor repeated measure ANOVA was use to compare means within the group individually at different time intervals with Bonferroni adjustment (α =0.05). Three factor repeated measure ANOVA was applied by taking time as a repeated factors and group and metabolizers as a fix factor. We report multivariate (Wilks' Lambda test) analysis since the Mauchly's test of Sphericity was found to be significant in all neuropathic parameters.

RESULTS:

Total 246 patients of PHN (148 males and 98 females) were selected who fulfilled the inclusion/exclusion criteria

Patient's Characteristics:

The non-responders (n=123) and responders (n=123) of PHN patients were statistically comparable with age and gender ratio. In non-responders mean age was (males 53.94±13.24; females 52.45±11.35) and in responders mean age were (males 53.50±12.72; females 50.17±10.79). The total mean age (in years) of patients in non-responders was 53.33±12.47 and in responders was 52.23±12.08. The total mean weight (in kg) in non-responders was 56.28±10.47 and in responders was 51.23±11.45. The mean duration of disease (in months) of patients in non-responders was 4.79±3.48 and in responders was 4.23±4.47. The gender ratio (M: F) in non-responders and responders was 72:51 and 76:47 respectively.

NPSI scale scores with respect to clinical evaluation:

Within group comparison, there was a statistically significant difference ($p<0.001$) at different time intervals in context of NPSI symptomatic parameters' scores (burning, squeezing, stabbing, pressure, electric shock type, pins & needles, tingling, and allodynia)**.** However, between the groups at day 28, the symptomatic parameters' scores - pressure, electric shock, squeezing and allodynia were non-significant ($p>0.05$). Considering the trend of the NPSI symptomatology of PHN patients over a period of 28 days, we observed high improvement in responders as compared to non-responders **(Fig. 1).**

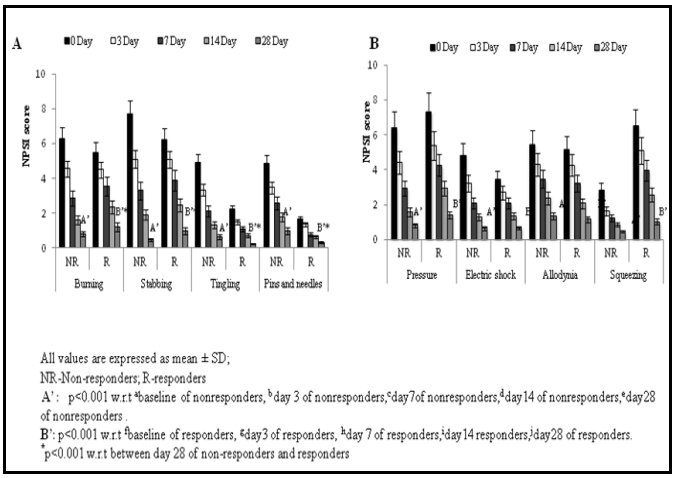

FIG.1: NEUROPATHIC PAIN SYMPTOMS INVENTORY (NPSI) SCORES FOR EACH INDIVIDUAL SYMPTOMATIC PARAMETER IN BOTH THE GROUP

Burning type of pain with respect to *CYP2D6* polymorphism:

All PHN patients experienced the burning type of pain. It was statistically significant at each time interval i,e 3, 7, 14 and 28 days with respect to baseline in both non responders and responder groups whereas it was insignificant at baseline

between the groups. In *2 allele non-responders having UMs (n=3), EMs (n=46), IMs (n=25) and PMs (n=28) patients and responders having UMs (n=3), EMs (n=54), IMs (n=35) and PMs (n=10) patients, respectively.

Ultra rapid metabolizers (UMs) were absent in group having *10 alleles. Since the Mauchly's Test of Sphericity was found to be significant, utilized by multivariate test (for repeated measures) for Wilks's Lambda test interaction between time, group and metabolizers was found to be insignificant with *2 (p= 0. 107), *4 (p= 0. 106), and *10 (P=0. 727) alleles. Interaction between group and metabolizers was found to be insignificant with *2 (p= 0.242), *4 (p= 0.830), and *10 (p=0.702) alleles. However, between non-responders and responders a significant change in pain intensity was observed across time in all alleles (p<0.001) **(Fig.2).**

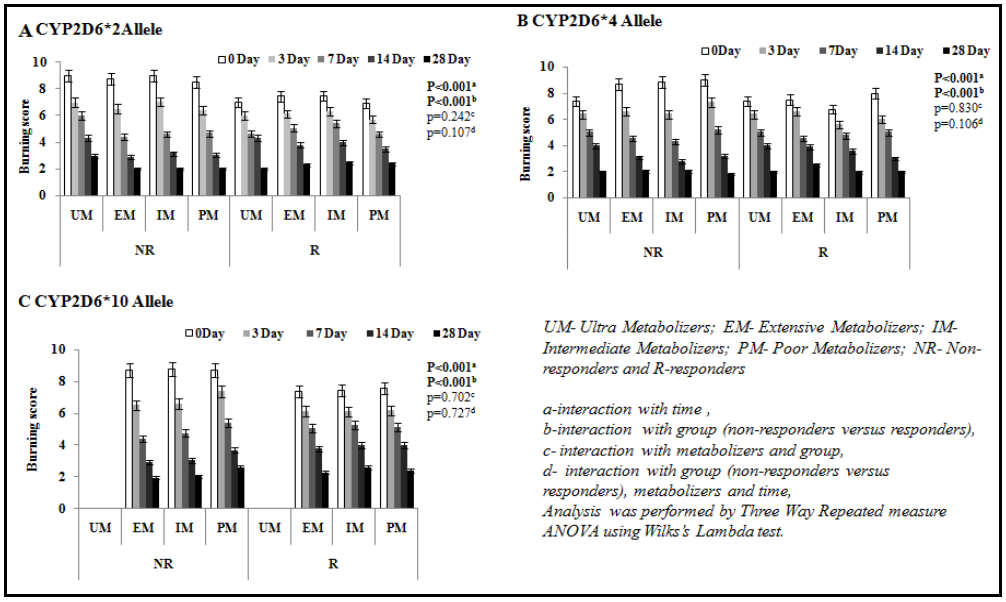

FIG.2: BURNING TYPE OF PAIN AND CYP2D6 POLYMORPHISM

Squeezing type of pain with respect to *CYP2D6* polymorphism:

A total of 61 non-responders and 41 responders reported having a squeezing type of pain. Interaction with time and groups (non-responders and responders) were found to be significant with time in all alleles (p<0.001) as analyzed by multivariate analysis for special Wilk's lambda test. Insignificant results were found between time, groups and metabolizers with *2 (p= 0.714), *4 (p= 0.208), and *10 (p=0. 636) alleles. Similarly interaction between time and metabolizers was found to be insignificant (**Table 2)**.

TABLE 2: SQUEEZING TYPE OF PAIN AND *CYP2D6* POLYMORPHISM

NPSI scale	Group	Metabolizers	0 Day (Baseline)	3 Day	7 Day	14 Day	28 Day	p value
Squeezing type of pain and *CYP2D62 allele**								
Squeezing	Non- responders	UM(n=4)	3.50± 4.123	2.50± 3.000	1.50± 2.474	1.00 ±1.414	0.25± .500	**p=0.001[a]** **p=0.020[b]** p=0.897[c] p=0.714[d]
		EM(n=38)	3.36± 3.988	2.34 ±2.856	1.55 ±2.026	0.93 ±1.412	0.75± 1.643	
		IM(n=10)	3.47 ±3.848	2.43 2.763	1.57± 1.888	0.90 ±1.296	0.33± .661	
		PM(n=9)	4.94 ±3.921	3.61± 3.041	2.55 ±2.538	1.52± 1.661	0.88 ±1.083	
		Total (n=61)	3.81 ±3.951	2.71 ±2.905	1.82± 2.162	1.08 ±1.463	0.67 ±1.297	
	Responders	UM(n=3)	3.00 ±5.196	1.67± 2.887	1.33 ±2.309	1.00 ±1.732	0.33 ±.577	
		EM(n=23)	1.91 ±3.116	1.51 ±2.519	1.18 ±2.007	0.74 ±1.326	0.31 ±.66	
		IM(n=8)	1.85 ±3.054	1.46 ±2.440	1.10± 1.868	0.68 ±1.213	0.27± .672	
		PM(n=7)	1.79 ±3.017	1.50 ±2.565	1.21 ±2.045	0.93 ±1.592	0.36 ±.745	
		Total (n=41)	1.90 ±3.098	1.50± 2.474	1.16 ±1.948	0.75 ±1.316	0.30 ±.664	
Squeezing type of pain and *CYP2D64 allele**								
Squeezing	Non- responders	UM(n=0)	-	-	-	-	-	**p=0.001[a]** **p=0.001[b]** p=0.363[c]
		EM(n=40)	3.47 ±3.912	2.42 ±2.797	1.70 ±2.171	1.03±1.495	0.57±1.219	
		IM(n=14)	4.03 ±3.950	2.91 ±2.948	1.79 ±2.071	1.00 ±1.303	0.82±1.547	
		PM(n=7)	5.91 ±3.910	4.36 ±3.202	2.91 ±2.300	1.82 ±1.662	0.91±1.044	

		Total (n=61)	3.84 ±3.952	2.73 ±2.906	1.84 ±2.164	1.09 ±1.466	0.67±1.301	p=0.208[d]
		UM(n=0)	-	-	-	-	-	
		EM(n=28)	1.60 ±3.006	1.23 ±2.349	0.96±1.869	0.60 ±1.232	0.25±0.657	
	Responders	IM(n=9)	2.76 ±3.345	2.29 ±2.795	1.76 ±2.143	1.19 ±1.504	0.43 ±.676	
		PM(n=4)	2.50 ±3.536	1.50 ±2.121	1.50 ±2.121	1.00 ±1.414	0.50 ± .707	
		Total (n=41)	1.90 ± 3.098	1.50 ± 2.474	1.16 ±1.948	0.75 ±1.316	0.30 ±.664	
		Squeezing type of pain and *CYP2D610 allele**						
		UM(n=0)	-	-	-	-	-	
		EM(n=40)	3.83± 3.904	2.75±..905	1.83 ±2.120	1.10 ±1.488	0.63± 1.209	
	Non- responders	IM(n=10)	4.03 ±4.156	2.70± 2.891	1.80 ±2.140	1.03 ±1.351	0.50 ±0.777	p=0.001[a]
		PM(n=11)	3.17 ±4.019	2.42 ±3.175	1.83 ±2.657	1.08± 1.676	1.33 ±2.425	p=0.001[b]
Squeezing		Total (n=61)	3.81 ±3.951	2.71± 2.905	1.82 ±2.162	1.08 ±1.463	0.67 ±1.297	p=0.543[c]
		UM(n=0)	-	-	-	-	-	p=0.636[d]
		EM(n=27)	1.86 ±3.097	1.44± 2.435	1.12 ±1.946	0.70 ±1.270	0.28± 0.642	
	Responders	IM(n=9)	1.77 ±3.126	1.43± 2.582	1.13± 1.995	0.83 ±1.510	0.33± 0.758	
		PM(n=5)	3.40± 3.209	2.80± 2.683	2.00 ±1.871	1.00± 1.000	0.40 ±0.548	
		Total (n=41)	1.90 ±3.098	1.50± 2.474	1.16 ±1.948	0.75 ±1.316	0.30± 0.664	

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders ;a-interaction with time ;b-interaction with group (non-responders versus responders);c- interaction with metabolizers and group ;d- interaction with group (non-responders versus responders), metabolizers and time; Analysis was performed by Three Way Repeated measure ANOVA using Wilks's Lambda test.

Stabbing type of pain with respect to *CYP2D6* polymorphism:

Out of 246 patients, 58 patients in non-responders and 25 patients in responders group experienced stabbing type of pain. In *2 both groups and *4 allele, only in responders, three UMs were observed whereas PMs were absent in responders in *4 allele (**Table 3)**. In stabbing type of pain, insignificant interaction was found between time, group and metabolizers with *2 (P= 0.524), *4 (P= 0.903), and *10 (P= 0.299) alleles. Similarly, no significant association was found with the groups and time. Pain recovery was found in both the groups it was independent of time and metabolizers.

TABLE 3: STABBING TYPE OF PAIN AND *CYP2D6* POLYMORPHISM

NPSI scale	Group	Metabolizers	0 Day (Baseline)	3 Day	7 Day	14 Day	28 Day	p value
			Stabbing type of pain and *CYP2D62 allele**					
		UM(n=3)	7.00±1.00	5.33±0.57	3.00±0.00	1.00±0.00	0.00±0.00	
		EM(n=26)	7.46±1.45	5.00±2.11	3.81±1.37	2.31±1.08	0.81±0.834	
	Non-responders	IM(n=14)	8.00±1.71	5.00±2.32	3.83±1.31	2.67±1.03	1.50±0.55	**p<0.001[a]**
		PM(n=15)	8.00±1.73	6.50±2.12	5.00±1.41	4.00±1.41	1.50±0.54	**p<0.001[b]**
Stabbing		Total (n=58)	7.71±1.57	5.09±2.03	3.88±1.30	2.48±1.16	1.00±0.82	p=0.463[c]
		UM(n=3)	5.00±0.00	4.00±0.00	2.37±0.57	0.33±0.57	0.00±0.00	p=0.524[d]
		EM(n=16)	6.31±1.10	5.00±1.32	3.31±1.76	1.92±1.44	0.54±0.71	
	Responders	IM(n=6)	6.00±1.27	5.00±1.09	3.29±1.82	2.14±1.03	0.57±0.51	
		PM(n=2)	7.00±1.41	5.41±1.91	3.40±1.64	1.93±1.34	0.33±0.72	
		Total (n=25)	6.24±1.33	5.08±1.32	3.29±1.68	1.90±1.32	0.47±0.66	
			Stabbing type of pain and *CYP2D64 allele**					
		UM(n=0)	-	-	-	-	-	
		EM(n=37)	7.70±1.47	5.27±2.03	4.00±1.52	2.71±1.38	1.29±0.91	
	Non-responders	IM(n=15)	7.93±1.66	5.20±1.65	3.75±1.03	2.25±0.71	0.62±0.52	**p<0.001[a]**
		PM(n=6)	7.17±2.04	3.67±2.58	2.33±1.97	1.67±1.37	0.33±0.50	**p<0.001[b]**
Stabbing		Total (n=58)	7.711±1.56	5.09±2.03	3.88±1.30	2.48±1.15	1.00±0.82	p=0.837[c]
		UM(n=3)	5.67±1.15	4.67±1.15	3.29±1.68	2.00±1.00	0.67±0.57	p=0.903[d]
		EM(n=14)	6.50±1.40	5.29±1.54	3.43±1.69	1.95±1.26	0.49±0.69	
	Responders	IM(n=8)	6.00±1.31	4.88±0.99	3.33±1.49	1.87±1.51	0.47±0.64	
		PM(n=0)	-	-	-	-	-	
		Total (n=25)	6.24±1.33	4.88±1.32	3.29±1.68	1.90±1.32	0.47±0.65	
			Stabbing type of pain and *CYP2D610 allele**					
		UM(n=0)	-	-	-	-	-	
		EM(n=43)	7.72±1.57	5.41±1.41	4.18±1.43	2.59±1.32	1.00±0.34	**p<0.001[a]**
	Non-responders	IM(n=9)	7.56±1.59	4.89±2.26	3.25±0.71	2.25±0.71	1.00±0.54	**p<0.001[b]**
Stabbing		PM(n=6)	7.83±1.72	5.83±1.47	3.67±1.51	1.83±1.60	0.33±0.82	p=0.667[c]
		Total (n=58)	7.71±1.57	5.09±2.02	3.88±1.30	2.48±1.15	1.00±0.81	p=0.299[d]
		UM(n=0)	-	-	-	-	-	
	Responders	EM(n=17)	6.65±1.27	5.02±2.06	3.30±1.70	1.98±1.28	0.51±0.63	

	IM(n=8)	5.37±1.06	4.38±0.74	3.00±1.08	1.56±1.42	0.33±0.71
	PM(n=0)	-	-	-	-	-
	Total (n=25)	6.24±1.33	5.00±1.32	3.29±1.66	1.90±1.32	0.47±0.65

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders ;a-interaction with time ;b-interaction with group (non-responders versus responders);c- interaction with metabolizers and group ;d- interaction with group (non-responders versus responders), metabolizers and time; Analysis was performed b Three Way Repeated measure ANOVA using Wilks's Lambda test.

Pressure type of pain with respect to *CYP2D6* polymorphism:

Out of 246 patients, pressure type of pain was experienced by 67 patients in non-responders and 27 patients from responder group. The multivariate analysis (for repeated measures) Wilks's Lambda test interaction between time, group and metabolizers were found to be insignificant with *2 (P= 0.767), *4 (P= 0.857), and *10 (P=0.942) alleles. Interaction between group and metabolizers were found to be insignificant with *2 (P= 0.963), *4 (P= 0.538), and *10 (P=0. 464) alleles. In the non-responders and responders significant change in pain intensity was observed across time in *2, *4 and *10 alleles (p<0.001) **(Table 4).**

TABLE 4: PRESSURE TYPE OF PAIN AND *CYP2D6* POLYMORPHISM

NPSI scale	Group	Metabolizers	0 Day (Baseline)	3 Day	7 Day	14 Day	28 Day	p value
Pressure type of pain and *CYP2D62 allele**								
Pressure	Non- responders	UM(n=2)	6.50±2.12	5.00±1.41	3.50±0.71	2.00±1.37	1.00±1.41	**p<0.001[a]** **p<0.001[b]** p=0.963[c] p=0.767[d]
		EM(n=33)	6.42±1.54	4.91±2.55	3.91±2.02	2.55±1.57	1.27±1.01	
		IM(n=14)	7.58±1.45	5.58±2.11	4.42±1.95	3.00±1.34	1.33±1.16	
		PM(n=18)	7.50±1.92	6.00±1.88	4.75±1.50	3.75±1.50	2.00±0.82	
		Total (n=67)	7.33±1.54	5.37±1.96	4.26±1.65	2.93±1.46	1.41±1.05	
	Responders	UM(n=0)	-	-	-	-	-	
		EM(n=11)	7.00±1.79	4.58±1.66	3.03±1.51	1.61±1.22	0.88±0.78	
		IM(n=12)	6.36±1.24	3.86±1.37	2.43±1.95	1.67±1.28	0.79±1.05	
		PM(n=4)	6.28±1.93	4.50±1.88	3.11±1.81	1.67±1.28	0.72±0.96	
		Total (n=27)	6.37±1.61	4.42±1.80	2.94±1.67	1.58±1.28	0.82±0.88	
Pressure type of pain and *CYP2D64 allele**								
Pressure	Non- responders	UM(n=0)	-	-	-	-	-	**p<0.001[a]** **p<0.001[b]** p=0.538[c] p=0.857[d]
		EM(n=44)	7.55±1.46	5.45±2.16	4.30±1.78	2.95±1.61	1.50±1.15	
		IM(n=21)	7.00±1.15	5.25±2.16	4.25±0.96	3.00±0.82	1.25±0.50	
		PM(n=2)	8.00±0.00	6.00±2.83	3.50±3.53	2.50±2.12	1.00±1.41	
		Total (n=67)	7.33±1.54	5.37±1.96	4.26±1.65	2.93±1.46	1.41±1.05	
	Responders	UM(n=3)	6.33±2.51	5.00±2.00	4.00±2.00	2.67±1.52	1.00±1.00	
		EM(n=20)	6.36±1.58	4.57±1.44	2.98±1.49	1.55±1.27	0.84±0.86	
		IM(n=4)	6.24±1.70	3.95±2.31	2.81±1.94	1.57±1.28	0.76±0.94	
		PM(n=0)	-	-	-	-	-	
		Total (n=27)	6.37±1.61	4.69±1.89	2.94±1.67	1.58±1.28	0.82±0.89	
Pressure type of pain and *CYP2D610 allele**								
Pressure	Non- responders	UM(n=0)	-	-	-	-	-	**p<0.001[a]** **p<0.021[b]** p=0.464[c] p=0.942[d]
		EM(n=48)	7.45±1.50	5.45±2.11	4.32±1.76	2.86±1.55	1.36±1.09	
		IM(n=10)	8.00±2.82	5.50±2.12	4.50±2.12	3.50±2.12	2.00±1.41	
		PM(n=9)	6.13±2.29	5.00±2.13	3.78±0.57	3.00±0.00	1.50±1.45	
		Total (n=67)	7.33±1.54	5.37±1.96	4.26±1.65	2.93±1.46	1.41±1.05	
	Responders	UM(n=0)	-	-	-	-	-	
		EM(n=18)	6.21±1.45	4.21±1.73	2.77±1.57	1.49±1.22	0.79±0.77	
		IM(n=7)	6.94±1.61	4.69±1.85	3.00±1.59	1.38±0.96	0.56±0.73	
		PM(n=2)	6.00±0.00	4.67±0.57	3.67±2.25	2.50±1.85	1.33±0.58	
		Total (n=27)	6.37±1.61	4.42±1.80	2.94±1.67	1.58±1.28	0.82±0.89	

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders ;a-interaction with time ;b-interaction with group (non-responders versus responders);c- interaction with metabolizers and group ;d- interaction with group (non-responders versus responders), metabolizers and time; Analysis was performed by Three Way Repeated measure ANOVA using Wilks's Lambda test.

Electric shock type pain with respect to *CYP2D6* polymorphism:

Out of 246 PHN patients, 102 in non-responders and 90 patients of responders group had electric shock type of pain. Mauchly's Test of Sphericity was found to be significant. In the multivariate test (repeated measures) it was found that there was insignificant interaction between time, groups and metabolizers with **2* and **4* and **10* alleles (**Table 5).**

TABLE 5: ELECTRIC SHOCK TYPE PAIN AND *CYP2D6* POLYMORPHISM

NPSI scale	Group	Metabolizers	0 Day (Baseline)	3 Day	7 Day	14 Day	28 Day	P value
Electric shock type pain and *CYP2D62 allele**								
Electric shock	Non-responders	UM(n=4)	6.50±2.38	4.75±2.06	3.50±1.73	2.00±1.14	0.75±0.50	**p<0.001[a]** **p=0.003[b]** P=0.985[c] P=0.937[d]
		EM(n=45)	6.78±1.58	4.56±1.05	2.82±1.23	1.67±1.18	0.80±0.75	
		IM(n=26)	6.65±1.57	4.58±1.23	3.19±1.23	1.88±1.27	0.88±0.99	
		PM(n=27)	6.48±1.82	4.56±1.69	3.04±1.69	2.04±1.16	1.00±0.83	
		Total n=102)	6.66±1.65	4.57±1.31	3.00±1.37	1.83±1.20	0.87±0.82	
	Responders	UM(n=3)	6.00±1.00	5.00±1.00	3.67±0.57	2.33±1.15	1.00±0.00	
		EM(n=51)	5.82±1.39	4.82±1.27	3.86±1.13	2.61±1.08	1.27± 1.00	
		IM(n=29)	5.52±0.98	4.48±0.82	3.48±0.82	2.28±0.88	1.14±0.95	
		PM(n=7)	5.71±1.11	4.57±1.13	3.57±0.97	2.43±0.78	1.14±0.69	
		Total(n=90)	5.72±1.23	4.70±1.12	3.71±1.02	2.48±0.99	1.21±0.94	
Electric shock type pain and *CYP2D64 allele**								
Electric shock	Non-responders	UM(n=0)	-	-	-	-	-	**p<0.001[a]** P=0.308[b] p=0.881[c] p=0.250[d]
		EM(n=67)	6.55±1.63	4.84±1.15	3.84±1.08	2.56±1.08	1.32±1.02	
		IM(n=27)	7.07±1.73	4.74±1.34	3.40±0.73	2.33±0.62	0.96±085	
		PM(n=8)	6.13±1.46	4.75±1.83	3.75±1.67	2.75±1.16	1.38±0.00	
		Total(n=102)	6.66±1.65	4.57±1.31	3.71±1.01	2.48±0.99	1.38±0.74	
	Responders	UM(n=6)	5.17±0.75	4.33±0.81	3.17±0.41	2.00±0.63	1.00±0.00	
		EM(n=68)	5.85±1.27	4.48±1.24	2.88±1.25	1.73±1.13	0.78±0.81	
		IM(n=15)	5.27±1.10	4.27±1.03	3.07±1.56	1.81±1.30	0.87±0.52	
		PM(n=1)	7.00±0.00	4.00±0.00	3.00±0.00	2.00±0.00	0.00±.0.00	
		Total (n=90)	5.72±1.23	4.70±1.12	3.00±1.37	1.83±1.20	0.00±0.00	
Electric shock type pain and *CYP2D610 allele**								
Electric shock	Non-responders	UM(n=0)	-	-	-	-	-	**p<0.001[a]** **p<0.001[b]** p=0.547[c] p=0.552[d]
		EM(n=65)	6.45±1.71	4.48±1.22	2.92±1.30	1.75±1.16	0.82±0.76	
		IM(n=29)	7.03±1.42	4.62±1.29	3.00±1.41	1.79±1.21	0.83±0.75	
		PM(n=8)	7.00±1.85	5.12±2.03	3.62±1.84	2.62±1.41	1.50±1.30	
		Total n=102)	6.66±1.51	4.57±1.32	3.00±1.37	1.83±1.20	0.87±0.82	
	Responders	UM(n=0)	-	-	-	-	-	
		EM(n=68)	5.72±1.18	4.66±1.03	3.71±0.91	2.46±0.99	1.25±0.95	
		IM(n=18)	5.89±1.41	5.06±1.34	3.83±1.38	2.61±1.03	1.11±0.96	
		PM(n=4)	5.00±1.41	3.75±1.25	3.25±0.95	2.25±0.95	1.00±0.81	
		Total (n=90)	5.72±1.23	4.70±1.12	3.71±1.02	2.48±0.99	1.21±0.94	

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders;a-interaction with time;b-interaction with group (non-responders versus responders);c-interaction with metabolizers and group;d- interaction with group (non-responders versus responders), metabolizers and time;Analysis was performed by Three Way Repeated measure ANOVA using Wilks's Lambda test

Tingling type of pain with respect to *CYP2D6* polymorphism:

Tingling type of pain was observed in 89 patients of non-responders and 45 patients of responder group. Insignificant interaction between time, groups and metabolizers with *CYP2D6* polymorphism was observed (**Fig.3)**.

Pins and needles type of pain with respect to *CYP2D6* polymorphism:

Pins and needles type of pain was found in considerable higher number of patients in non-responders (n=107) and responders (n=92). In **2* allele, interaction between time, metabolizers and group were found to be significant (p=0. 003). It was also observed that changes in pain intensity with respect to time were dependent on metabolizers. Similarly, interaction with group and metabolizers were found nearer to significant (p=0.076). In patients with *4 and *10 alleles insignificant interaction was found with respect to time, group and metabolizers (**Fig. 4).**

Allodynia type of pain with respect to *CYP2D6* polymorphism

Out of 246 PHN patients, 116 non-responders and 75 responders' allodynia type of pain. With **2*

allele, interaction between time, metabolizers and group were found to be significant (P=0. 029). It was also observed that, changes in pain intensity with respect to time were dependent on metabolizers and groups (non-responders and responders). The interaction with time and the group was not significant (p>0.001) showing allodynia type of pain score across the time, was not dependent upon group in **2* and **4* alleles. No significant association was found between time, metabolizers and groups (**Table 6).**

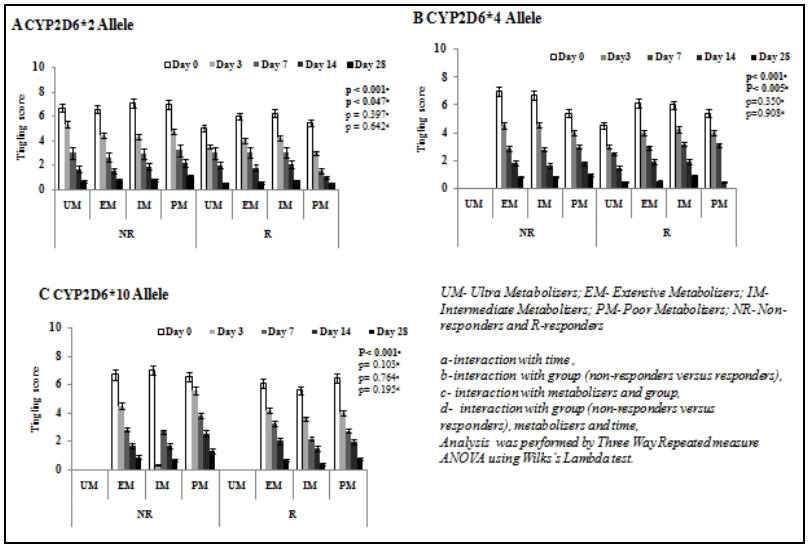

FIG.3: TINGLING TYPE OF PAIN AND CYP2D6 POLYMORPHISM

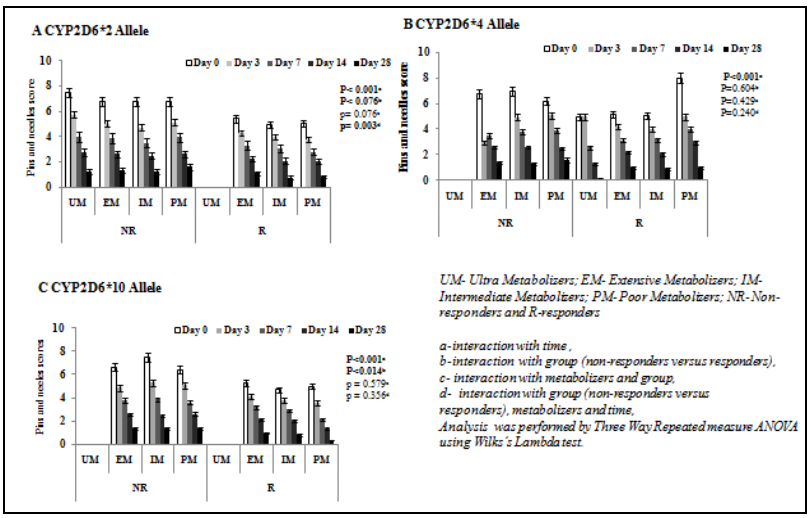

FIG.4: TINGLING TYPE OF PAIN AND CYP2D6 POLYMORPHISM

TABLE 6: ALLODYNIA TYPE OF PAIN AND *CYP2D6* POLYMORPHISM

Allodynia type of pain and *CYP2D6**2 allele								
NPSI scale	**Group**	**Metabolizers**	**0 Day (Baseline)**	**3 Day**	**7 Day**	**14 Day**	**28 Day**	**p-value**
Allodynia	Non-responders	UM(n=3)	7.50±0.70	5.00±1.73	4.00±1.73	2.67±1.15	1.67±0.57	
		EM(n=57)	7.59±1.63	5.95±1.32	4.82±1.40	3.32±1.19	1.84±1.18	
		IM(n=31)	7.50±1.60	5.90±1.29	4.90±1.61	3.55±1.46	1.95±1.23	
		PM(n=25)	7.36±1.60	6.04±1.37	4.60±1.50	3.31±2.10	1.88±0.93	**p<0.001[a]**
		Total (n=116)	7.45±1.64	5.93±1.33	4.75±1.47	3.27±1.23	1.87±1.10	p=0.887[b]
	Responders	UM(n=2)	4.67±2.08	3.81±0.00	2.50±0.70	2.00±1.41	1.50±0.69	p=0.338[c]
		EM(n=40)	5.86±1.36	4.91±1.53	3.65±1.54	2.37±1.43	1.16±1.12	**p=0.029[d]**
		IM(n=20)	6.06±1.18	5.17±1.36	4.14±1.19	2.57±1.26	1.29±0.95	
		PM(n=13)	6.08±2.13	5.54±2.14	4.38±2.02	2.81±1.09	1.69±1.60	
		Total (n=75)	5.98±1.42	5.07±1.55	3.90±1.50	2.54±1.51	1.69±1.60	

Allodynia type of pain and *CYP2D64 allele**								
Allodynia	Non-responders	UM(n=5)	5.40±0.54	4.60±0.89	3.80±0.48	2.60±0.55	1.20±0.45	
		EM(n=84)	7.62±1.49	5.98±1.42	4.70±1.48	3.13±1.26	1.78±1.14	
		IM(n=21)	7.43±1.72	5.86±1.41	4.79±1.57	3.41±1.09	1.97±1.19	
		PM(n=6)	6.88±1.73	5.75±1.03	4.88±1.24	3.62±1.29	2.12±0.68	**p<0.001[a]**
		Total (n=116)	7.44±1.64	5.92±1.34	4.75±1.48	3.26±1.23	1.87±1.10	p=0.437[b]
	Responders	UM(n=0)	-	-	-	-	-	p=0.761[c]
		EM(n=54)	7.43±1.72	5.30±1.62	4.11±1.56	2.74±1.59	1.40±1.19	p=0.687[d]
		IM(n=19)	5.12±0.99	4.18±0.88	2.94±1.03	1.65±0.78	0.71±0.69	
		PM(n=2)	5.00±0.00	4.00±0.00	3.00±0.00	1.00±0.00	0.00±0.00	
		Total (n=75)	5.98±1.42	5.07±1.55	3.90±1.50	2.54±1.51	1.27±1.13	
Allodynia type of pain and *CYP2D610 allele**								
Allodynia	Non-responders	UM(n=0)	-	-	-	-	-	
		EM(n=74)	7.46±1.43	5.98±1.24	4.86±1.35	3.30±1.14	1.90±1.08	
		IM(n=30)	7.80±1.64	6.05±1.23	4.75±1.62	3.50±1.35	1.95±1.15	
		PM(n=12)	6.56±2.65	5.33±2.06	4.00±1.87	2.56±1.42	1.44±1.13	**p<0.001[a]**
		Total (n=116)	7.45±1.64	5.93±1.33	4.75±1.47	3.27±1.23	1.87±1.10	**p=0.005[b]**
	Responders	UM(n=0)	-	-	-	-	-	p=0.765[c]
		EM(n=45)	6.11±1.40	5.17±1.56	3.95±1.56	2.65±1.55	1.39±1.20	p=0.738[d]
		IM(n=26)	5.75±1.45	4.86±1.51	3.82±1.44	2.32±1.46	1.00±0.94	
		PM(n=4)	5.25±1.50	4.75±1.89	3.50±1.00	2.00±0.82	1.00±0.82	
		Total (n=75)	5.98±1.42	5.07±1.55	3.90±1.50	2.88±1.43	1.27±1.13	

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders;a-interaction with time; b-interaction with group (non-responders versus responders);c- interaction with metabolizers and group; d- interaction with group (non-responders versus responders), metabolizers and time; Analysis was performed by Three Way Repeated measure ANOVA using Wilks's Lambda test.

DISCUSSION: Among north Indians investigation of interactions between pain mechanisms, *CYP2D6* polymorphism and clinical outcomes of pain scores have not been reported in PHN patients undergoing tramadol treatment in previous observations. According to the currently available literature, difficulties arise while finding out the interaction between *CYP2D6* polymorphism with clinical outcomes at different time points in PHN patients.

In our earlier studies, tramadol (50mg -200mg) treated PHN patients experienced maximum pain relief as evidenced by a highly significant ($p<0.001$) reduction in NRS scores at day 14 and day 28. It also confirmed that tramadol treatment for 4 week is safe in PHN patients [22, 29]. The treatment of tramadol efficacy in other forms of neuropathic pain has been observed in double-blind placebo-controlled studies.[26, 27, 28]

In the present study statistically insignificant results were observed at baseline in all NPSI scores in both the groups whereas after 28 days tramadol treatment. The magnitude of improvement in NPSI scores at day 3, 7, 14 and 28 was much higher ($p<0.001$) in responders as compared to non-responders. In our previous observations in small numbers of patients were found that same type of results. [22, 31]

In this study, performance of pain evaluation on the basis of *CYP2D6* polymorphism shows significant interaction in allodynia and pins and needles with *CYP2D6**2 allele between time, group and metabolizers while with other alleles we did not find significant interaction. Stabbing, pressure, tingling, electric shock type of pains did not find any association between the *CYP2D6* polymorphism. In our previous study, reported relationship of the *CYP2D6**4 polymorphism with the clinical pain scores, inter individual variations in *CYP2D6* activity was observed along with the adverse drug effects in PHN patients receiving tramadol. The NPSI scores obtained from 158 patients (78 non responders and 80 responders) who were treated with tramadol, some parameters i. e burning, squeezing, tingling and pins and needles were significantly associated with the *CYP2D6*4* polymorphism ($p<0.05$). However, other parameters (stabbing, pressure, electric shock type pain and allodynia) were non-significant with the *CYP2D6**4 polymorphism ($p>0.05$). [22] In our previous study, assessment of *CYP2D6*10* metabolic status may not help to identify PHN patients at risk for no response to drug therapy [32].

Genetic research on pain mechanisms and clinical pain therapy is still restricted to specific pain reliever or clinical settings. Presently, pain therapy cannot be appropriately individual to the patient's genotype. Considering codeine, failure of treatment can be predictable, whereas the side effects in UMs can only be estimated at the expense of combining *CYP2D6* genotyping with phenotyping.[33] Prodromal symptoms and intensity of the rash [34, 35] have been identified as predictors of neuropathic pain (NP) or chronic neuropathic pain (CNP). The management of patients with CNP is not clearly understood and response to existing treatments is often inadequate. Even with well-established NP medications, effectiveness are unpredictable, dosing can be complicated, delayed analgesia and side effects are common. Evidence-based consensus treatment recommendations exist [36] and suggest that drugs have differential effects on the quality of NP i.e., Burning, deep, paroxysmal.[13, 37-38]

Although predictors of response to some drugs (e.g., opioids, lidocaine plasters) were identified in post hoc analyses [39-40], no randomized controlled trial has yet been designed to detect predictive factors of the response based on baseline phenotypic profile. Nonetheless, the amount of research performed into identifying predictive factors for NP or the persistence of NP remains limited. Specifically, pain coping was reported to be predictive of developing phantom limb pain, forms of allodynia, and PHN [41-43].

Pain catastrophizing was reported as a predictor for chronic PHN [44], and depression and trait anxiety were both found to be predictors for chronic herpes zoster pain. Continued high pain intensity was found to be a predictor for chronic herpes zoster pain.[45] The latter also proved to be the case for PHN patients.[46-48.] In addition, the literature provides support for variables which were not among the most important predictors of CNP identified;: hypoesthesia [43,49], hyperalgesia [50], age [46-47,51-54], prodromal symptoms [50], numbness [54], different measures of pain intensity such NRS [53], severity of cutaneous manifestation,[48] and DNIC.[56]

The genetics of pain plays an important research tool in describing the role of molecular analysis in human nociception and analgesia.[57] The heredity of common pain and analgesia are challenging to target genetic – based personalized medicine measurement. In most of the clinical settings, common genetic factors can not clearly describe individual analgesic response.[58-59]

CONCLUSION: In PHN patients receiving tramadol treatment *CYP2D6* polymorphism may not be a predictor of treatment in patients with neuropathic symptoms. In the future, with the help of multimodal therapy and some more advanced methodologies, *CYP2D6* gene polymorphism can produce useful information related personalized-genome data and develop new opportunities for early diagnosis, prevention and management of neuropathic pain.

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