



**International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)**
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

**A PROSPECTIVE STUDY ON DRUG UTILIZATION PATTERN AND THEIR EFFECT
ON QUALITY OF LIFE ON PATIENT OF PERIPHERAL NEUROPATHIC PAIN**

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Received 9th June 2020; Revised 10th July 2020; Accepted 7th Aug. 2020; Available online 1st April 2021

<https://doi.org/10.31032/IJBPAS/2021/10.4.5448>

ABSTRACT

Background: Peripheral Neuropathy (PN) is an ailment of nervous system and its incidence is increasing day by day in Indian subcontinent, mainly due to increase in lifestyle disorders like diabetes mellitus, liver disorders, hypothyroidism, kidney disorders, cancer, autoimmune conditions etc.

Object: A prospective study on prescribing pattern of drugs and its effect on quality of life in patients of peripheral neuropathy in a teaching hospital.

Methods: It was a prospective observational study which was carried out for a period of six months conducted in multispecialty tertiary care teaching hospital. All demographic profile of the patient (age and gender), etiology of peripheral neuropathy, drug prescriptions pattern (name of the drugs with individual drugs, mono or polytherapy) and clinical data of patients were collected and documented in a suitably designed case report form. The Quality of Life (QoL) was evaluated in patients with PN by different neuropathic pain and depression assessment scale. Results were analysed statistically.

Results: Based on the study criteria, 110 patients were selected and enrolled for the study. Maximum number of patients of peripheral neuropathic pain (PNP) resides in the age group of 56–65 years (46%) & more common in females (55%) as compared with male. The most common PNP patients were encountered with diabetic neuropathy (60%). Out of 110 patients, 31 patients (28.18%) were suffering from co-morbid concurrent illness like hypertension followed by renal & hypothyroidism disease. The prescription pattern showed the majority of patients were using neuropathic pain agents (48%) (as monotherapy and combination therapy) followed by patient received prescription with neurotonic and vasoactive agents in combination. Neuropathic pain agents as monotherapy *i.e.* pregabalin (26%) was the highly prescribed drug followed by

combination therapy, *i.e.* pregabalin with multivitamin (38%), and pregabalin with nortriptylline (20%) were the most popular prescribed combinations. In triple drug combination therapy, pregabalin, amitriptylline with multivitamin was the most common prescribed combination. QoL (symptomatic pain as well disability and anxiety) improvements were significantly observed by dual combination of pregabalin with nortriptylline at 6th week when compared with other combination or alone prescription pattern.

Conclusion: It can be concluded that, among all the neuropathic pain agents, the pregabalin with nortriptylline was frequently and highly prescribed drug over other combinations to control the symptomatic pain in neuropathy and moreover highly efficient therapy to improve quality of life.

Keywords: Peripheral neuropathy, Prescribing pattern and Utilization of drug

INTRODUCTION

Peripheral neuropathy is a disorder of peripheral nerves that occurs when these nerves malfunction result of injury to nerve fibres due to various aetiologies including toxic, traumatic, ischemic, metabolic, infectious or compressive damage [1]. It is characterized by the damage to sensory, motor and autonomic nerves. This will damage or disrupts the nerve's normal functioning by affecting the transmission of nerve impulses from central nervous system to the spinal cord [2]. People with peripheral neuropathy are at increased risk of neuronal damage of central as well as peripheral nervous system. The two most common conditions contributing to peripheral neuropathy are diabetes and malignancy [3]. Neuropathic pain (NP) is a common condition characterised by subjective negative and positive symptoms that range from numbness to debilitating pain. Negative symptoms are described as diminished sensations due to loss of sensory function. Positive symptoms are typically altered or painful sensations such as tingling, prickling, or pain described as shooting, stabbing, burning, or having an

electric shock sensation [4]. Associated complications with peripheral neuropathy are: abnormal sweating, loss or decline in urinary bladder control, hypotension, bradycardia/tachycardia, diarrhoea and constipation. Peripheral neuropathy can be classified according to the number of nerves that are damaged and the type of damage to the nerves [5]. Recent studies have pointed out the increasing appearance of neuropathy due to diabetes in Indian patients, which is affecting the quality of life significantly [3]. The epidemiological patterns of peripheral neuropathy are very wide and complex because peripheral neuropathy has varied types of etiology and pathogenesis [6]. The term peripheral neuropathy includes mononeuropathy, polyneuropathy and neuropathies due to comorbid illness [7]. A recent systemic review of NP epidemiological study across the world suggests that the prevalence between 6.9% to 10% in the general population [8].

NP can have significant negative impact a patient's quality of life. Patients suffering from

chronic NP have higher degrees of anxiety and depression scores, as well as sleep disturbances, compared with patients with non-neuropathic chronic pain, and patients without chronic pain [9-10]. A study in which described that the presence of NP was associated with worse health and function [11]. The treatment of neuropathic pain differs based upon the severity of pain experienced by the patient [12]. There are no standard guidelines for the treatment of peripheral neuropathy. Also, there are no agencies that regulate the management of peripheral neuropathy. Medical practitioners prescribe the medications for peripheral neuropathy on the basis of symptoms and clinical manifestations of peripheral neuropathy [13]. Antidepressants remain the first-line agent in the treatment of neuropathic pain in many centres. Medications such as tricyclic antidepressants, i.e. amitriptyline and nortriptylline, have been found to help in relieving the pain by inhibition of serotonin and norepinephrine. This action on nervous system but they have considerable safety and tolerability issues which need to be kept in mind while treating neuropathic pain [14]. The anticonvulsants drugs includes carbamazepine, gabapentin, pregabalin, topiramate, lamotrigine are another class of drugs which have been used in the in the treatment of neuropathic pain [15]. Over-the-counter pain medications, such as nonsteroidal anti-inflammatory drugs, can relieve mild symptoms. Medications

containing opioids, such as tramadol or oxycodone can give if other treatment option fails. Capsaicin cream, which contains a substance found in hot peppers, can cause improvements in peripheral neuropathy symptoms [16]. Systemic local anaesthetic agents are also used, for example lidocaine patch [17]. Management of PN requires long term use of drugs with doubtful efficacy and safety issues. Selection of medication for the management of neuropathy is challenging, with individualization of doses, attention to potential adverse effects and drug interactions, quality of life before and after medication so as to ensure patient compliance [18]. Hence this study was aimed to assess the drug utilization and prescribing patterns by medical practitioners in peripheral neuropathy patients and its effect on their quality of life along with comparison of different treatment methodologies with respect to their efficacy.

METHODS

A prospective observational study was carried out to find the prescribing patterns of drugs and its effect to improve quality of life in patients of peripheral neuropathy with comorbidities. After obtaining the ethical approval from the Institutional Ethics Committee (IEC No-856), the study was initiated. This study was carried out at department of medicine, MM Institute of Medical Sciences Hospital, Mullana (Ambala), Haryana. Duration of the study was six month commencing from December 2017 to May

2018. In this present study, sample size consist (N=110) of Peripheral Neuropathy patients (inpatients/outpatients), that were observed in hospital.

Inclusion Criteria - All old and new patients from the medicine department of age more than 18 years and both sexes (male & female) were included in the study. The patient should be diagnosed with neuropathy and concomitant illness and having LANSS score above 11.

Exclusion Criteria - The neuropathy cases of paediatric population, pregnant and lactating women, psychiatric patient, TB patient and patient who have numerical pain rating scale (less than 2) were excluded from the study.

Study procedure -The patients attending the medicine outpatient department (O.P.D.) for complaints of peripheral pain were screened for peripheral neuropathy and other diseases known to be causing peripheral neuropathy. Once the diagnosis of peripheral neuropathy was confirmed by the clinician, the patients were questioned for their willingness to participate in the study. The patients were explained about the nature of the study and the need of their follow up visit at 6th week, and to stay in contact throughout the study period. They were also informed about their right to withdraw from the study at any stage. Patients were enrolled in the study after receiving the informed consent.

Study of Patient's Demographic profile: After obtaining the informed consent of the enrolled patients, details of their demographic

profile viz. name, age, sex, address, body weight, were recorded in case record form. Other included parameters like type of disease responsible for PN, co-morbidity, medications prescribed (name of drug, dosage, the class of drug, dosage form of drug, route of administration, frequency of administration, duration of therapy, and other adjuvant drugs prescribed etc.), smoking habits and duration of pain, present complaints, investigations undertaken, history of present medication(s) including their dose, frequency and duration, which were all noted down in the case record form designed for the study.

Efficacy assessment of drugs by improved

Quality of Life: In this study patients were carefully examined for the level of pain and anxiety (Quality of life) in peripheral neuropathy by the physician. The efficacy assessment of drugs used in PN was done by using various questioner form, during the 1st visit (at the time of enrolment) and on 6th week of follow up visit.

Data was collected using the following forms:

- LANSS: Leeds Assessment of Neuropathic Symptoms and Signs [19].
- NPSI: Neuropathic Pain Symptom Inventory [20]
- NPS: Numerical Pain Scale [21]
- NPIQoL: Neuropathic Pain Impact on Quality-of-Life Questionnaire [22]
- SDS: Sheehan Disability Scale [23]
- HADS: Hospital Anxiety and Depression Scale [24]

STATISTICAL METHODS

The data was analyzed by using Microsoft excel and Statistical software SSPs to compare the effect of drug utilization in reference to the diagnosis. Analysis involves percentage and descriptive statistics like mean and frequency distribution.

RESULTS:

The study was carried out to assess the use of drug and prescribing pattern by medical practitioner in peripheral neuropathy patients with or without co-morbidity. In this prospective study analysis, a total of 110 peripheral neuropathy patients were selected on the basis of LANSS criteria (not less than 11). Hence the results are based on 110 patients included in this study.

The demographic data of study indicates that the female (55%) population were found to be more predominantly having peripheral neuropathy as compared to male (45%) population. In this study most of the patients were in the age-group of 56-65 years (46%) with the mean age (range 36–75 years) being 49.5 ± 2.70 years, followed by number of patients between 46-55 years of age (34%). Least number of patients were in age group between 36-45 years of age (12%) followed by age 66-75 years of age (8%). Among all, the majority (63.63%) of the patient were from rural areas of Haryana.

This study emphasis on the exact count of neuropathic patients with respective comorbid illness. In the study, the most of patients

suffered from diabetes (60%) for a mean duration of 5 ± 0.52 years as co-morbidities with peripheral neuropathy followed by the patients of diabetes with hypertension and other coronary heart disease (28.18%). Least number of patients were suffered by diabetes with Chronic Kidney Disease (9%) and hypothyroidism (4%). Majority of patients received neuropathic pain agent as monotherapy and neuropathic pain agent with neurotonic and vasoactive agents as combination therapy (**Table 1**).

Analysis of Prescriptions - A total number of 189 drugs were prescribed in 110 prescriptions and the average number of drugs per prescription was found to be 1.71. Out of 110 prescriptions, anti-convulsants (Pregabalin) 92.72% was the most frequently prescribed as compared to tricyclic antidepressant group of drugs (24.5%).

During this study, the medications predominantly prescribed under different categories. The 1st category is neuropathic pain agent (48%), the medications prescribed under this category were pregabalin (26%), pregabalin with nortriptylline (20%), pregabalin with amitriptylline (2%). In the 2nd category, neurotonic agents (8%) were given in the form of multivitamins (Cyanocobolamin + Pyridoxine+Thiamine). Under 3rd category, the neuropathic pain agent with neurotonic, medications prescribed in this category were pregabalin with multivitamins (38%), and pregabalin, amitriptylline with multivitamins

(2%). The 4th category of medication in which neuropathic pain agent prescribed with vasoactive agent, the medications prescribed under this category were pregabalin with pentoxyphylline (2%). The last category of medication in which physician prescribed neuropathic pain agent, vasoactive agent and neurotonic, medications prescribed were pregabalin, pentoxyphylline with multivitamins (2%) shown in **Table 2, Figure 1**.

Symptomatic Improvement - In this study, the efficacy of prescribed drugs was analysed by symptomatic improvement in pain after six weeks, that was attributed by numerical pain scale (36.24%), followed by neuropathic pain symptom inventory (19.64%) and neuropathic pain impact on quality of life questionnaire (18.50%). The percentage of improvement in quality of life was assessed by hospital depression scale (31.11%), hospital

anxiety scale (23.79%), sheehan disability scale (22.32%) (**Figure 2**).

Efficacy Analysis Assessment- The improvement in neuropathic pain symptoms after six weeks with dual therapy (pregabalin and nortriptylline) was more predominantly shown in neuropathic pain symptoms inventory (27.14%), numerical pain scale (41.38%), and neuropathic pain impact on quality of life questionnaire (24.61%) followed by triple therapy than single therapy (**Table 3**).

Assessment of QoL - The improvement in QoL assessed by disability and depression scale after six weeks with dual therapy of pregabalin and nortriptylline was more predominantly shown in sheehan disability scale (29.28%), hospital anxiety (29.78%) and depression Scale (36.06%) followed by pregabalin with multivitamin as shown in **Table 4**.

Table 1: Demographic data of Patients

Gender (Sex)	Number of Patients
Male	50 (45%)
Female	60 (55%)
Total Patients	110
Age	-----
36 Years to 45 Years	13 (12%)
46 Year to 55 Year	37 (34%)
56 Year to 65 Year	51 (46%)
66 Year to 75 Year	9 (8%)
Age (mean \pm SD)	49.5 \pm 2.70
Area	-----
Rural	70 (63.63%)
Urban	40 (36.36 %)
Comorbid illness	
Diabetic	66 (60%)
Diabetic with Cardiac Disease	31 (28.18%)
Diabetic with CKD	9 (8.18%)
Hypothyroidism	4 (3.63%)
Therapy	
Monotherapy	38 (34.54%)
Combination therapy	72 (65.45%)

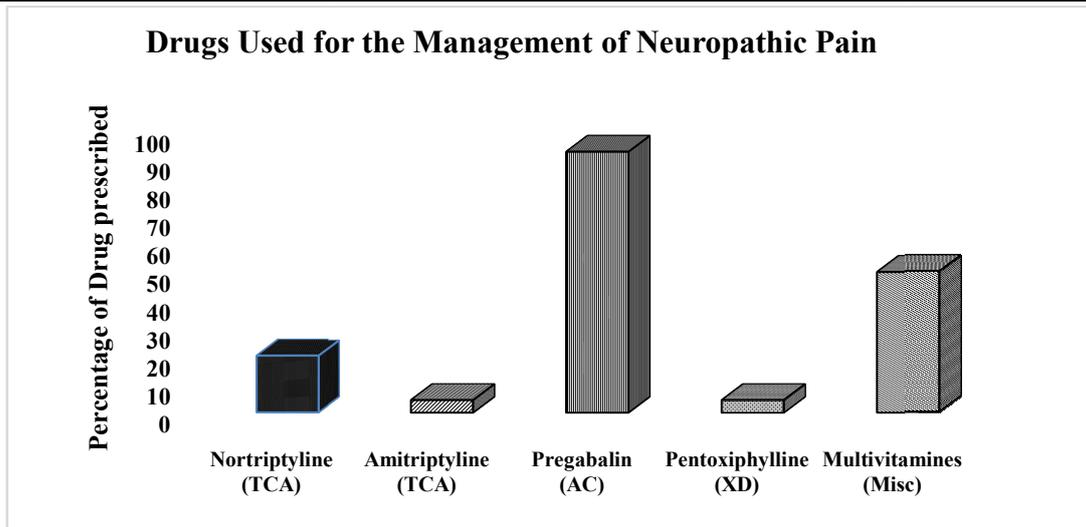


Figure 1: Groups of drugs used for the management of neuropathic pain(n=189)
 TC-Tricyclic anti-depressants; AC-Anti-convulsants; XD-Xanthine Derivative, Misc-Miscellaneous

Table2: Category of Medication Prescribed pattern for Peripheral Neuropathy

Medications	Percentage of Patients
NEUROPATHIC PAIN AGENT	
Pregabalin(Mono Therapy)	26%
Pregabalin with Nortriptyline(Dual Therapy)	20%
Pregabalin with Amitriptyline(Dual Therapy)	2%
NEUROTONIC	
*Multivitamin(Mono Therapy)	8%
NEUROPATHIC PAIN AGENT with NEUROTONIC	
Pregabalin with *Multivitamin(Dual Therapy)	38%
Pregabalin and Amitriptyline with *Multivitamin(Triple Therapy)	2%
NEUROPATHIC PAIN AGENT with VASOACTIVE AGENT	
Pregabalin with Pentoxiphylline(Dual Therapy)	2%
NEUROPATHIC PAIN AGENT + VASOACTIVE AGENT + NEUROTONIC	
Pregabalin with Pentoxiphylline and *Multivitamin(Triple Therapy)	2%

*Multivitamin: Cyanocobolamin + Pyridoxine + Thiamine

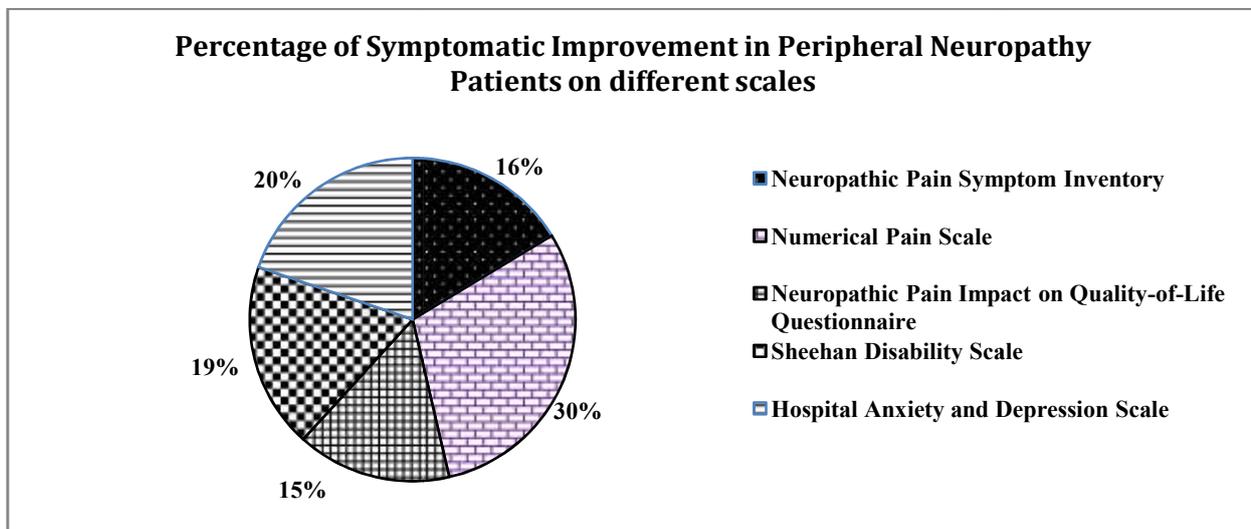


Figure 2: Percentage of symptomatic improvement in peripheral neuropathy patients on the different scales after 6 weeks

Table 3: Percentage of symptomatic pain improvement in peripheral neuropathy patients on different Pain scales by different therapeutic treatment

Therapy	Medications	NPSI	NPS	NPIQoL
Mono Therapy	Pregabalin	23.28%	36.76%	19.28%
	Multivitamin	07.72%	11.42%	05.24%
Dual Therapy	Pregabalin with Nortriptylline	27.14%	41.38%	24.61%
	Pregabalin with Amitriptylline	20.12%	17.11%	12.33%
	Pregabalin with Pentoxiphylline	15.40%	33.33%	13.57%
	Pregabalin with Multivitamin	24.33%	29.32%	23.69%
Triple Therapy	Pregabalin and Nortriptylline with Multivitamin	26.67%	50.45%	21.74%
	Pregabalin and Pentoxiphylline with Multivitamin	17.5%	35%	13.57%

Table 4: Percentage of QoL improvement in peripheral neuropathy patients on disability and Depression scale by different therapeutic treatment

Therapy	Medications	Sheehan Disability Scale	Hospital Anxiety and Depression Scale	
Mono Therapy	Pregabalin	20.28%	26.22%	33.59%
	Multivitamin	12.87%	01.51%	3.92%
Dual Therapy	Pregabalin with Nortriptylline	29.17%	29.78%	36.06%
	Pregabalin with Amitriptylline	26.03%	16.67%	21.43%
	Pregabalin with Pentoxiphylline	22.5%	17.69%	23.53%
	Pregabalin with Multivitamin	23.92%	27.49%	35.93%
Triple Therapy	Pregabalin and Nortriptylline with Multivitamin	20.45%	18.33%	33.33%
	Pregabalin and Pentoxiphylline with Multivitamin	19.23%	17.90%	25.65%

DISCUSSION

The present study is a prospective observational study, being undertaken to assess the effect of various drugs used in the management of peripheral neuropathy pain at medicine O.P.D. of tertiary care hospital. One hundred twenty patients satisfying the inclusion criteria were included into this study at initial visit, but 10 dropped out due to unexplained causes and rest 110 completed the study. Hence, analysis of demographic data and the efficacy analysis was done for all patients (n=110) included in this study. After analysis of the demographic profile of the PN patients it was observed that most of them belonged to the age group of 56-65 years (46%), with the mean age being 49.5±2.70 years. This is similar data with other studies

i.e. BIRDEM study, conducted at Dhaka in 2006 in which the mean age of DN patients was 50.8 ±10.6 years and females were significantly younger than males [25]. In our study majority of the patients were females (55%) and only 45% were males. Literature review reveals that PN has a gender predilection with females suffering more than males [26]. The maximum patients recruited in our study suffered from diabetes, for a mean duration of 5±0.52 years as co-morbidities with peripheral neuropathy followed by the patients of diabetes with hypertension, diabetes with CKD, and hypothyroidism.

Many medications are available for the treatment of neuropathic pain like tricyclic antidepressants, gabapentin, pregabalin, carbamazepine, oxcarbazepine, phenytoin,

lamotrigine, and opioids, but prescription pattern of an individual patient after considering the side effects of drug and depending on patient general health [27]. On analysis of the Drug Utilization Pattern in patients of PN, it was observed that anti-neuropathic pain drugs prescribed were mono therapy and anticonvulsants was the most commonly prescribed class of drugs followed by tricyclic antidepressant. According to different studies till date the first line agent in treatment of PN are antiepileptics and antidepressants and but some clinical trials supported the shift from carbamazepine to gabapentin, or Pregabalin. In the present study, this trend in pharmacotherapy could be due to the recent reports which state that Pregabalin is the most recent anticonvulsant medication approved by FDA for PN treatment, and may be considered as a first line agent [28]. Although, gabapentin was in use for long time, for the treatment of PN before the discovery of pregabalin, but now it is second line of drug due to its adverse effect profile, especially sedation. Similarly nortriptylline, a common antidepressant used with success for treating neuropathic pain but now become a third line agent due to its concomitant adverse anticholinergic side-effects [29]. The dose of Pregabalin prescribed in our study varied through a wide range, from 75 to 300 mg/day depending on patient's symptoms. The European Federation of Neurological Sciences (EFNS) 2010 guidelines recommend

gabapentin, pregabalin, and tricyclic antidepressants are most effective in painful neuropathy [30]. In present study it was seen that anti-convulsants (Pregabalin) combination with tricyclic anti-depressant (Nortriptylline) are more efficacious to improve neuropathic pain and QoL than anti-convulsants alone or in combination with other TCA, SSRIs & SNRIs. The results of the present study clearly suggests that pregabalin with nortriptylline is the most frequently prescribed drug for peripheral neuropathy in our set up, followed by monotherapy of Pregabalin.

CONCLUSION

Drug utilization studies are an important mirror for pattern of use of drugs in community in actual practice. It is a dynamic process, hence is to be undertaken time by time on different places, on different patient population with different socio economic back ground. It is hoped that this paper highlights the current outpatient therapeutic options and demonstrates a rational approach to the management of the patients with neuropathic pain. The present study indicates that females constitute the higher proportion of patients suffering from peripheral neuropathy as compared to males. The study also reveals that the maximally prescribed drug regimen by medical practitioner is dual therapy combination for peripheral neuropathic pain. The maximum improvement in the symptoms of neuropathic pain, quality of life with depression and anxiety was found to be with

dual therapy (pregabalin with nortriptylline). The improvement in work, social and family life found to be improved again with same dual therapy. So pregabalin with nortriptylline combination is superior treatment and it would be first choice of drug combination in the treatment of neuropathic pain.

ACKNOWLEDGEMENTS -The authors would like to thank M.M. Institute of Medical Science and Research and Department of Pharmacy Practice, M.M. College of Pharmacy.

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