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Original Article

PATTERNS OF PRESCRIPTION AND ADR MONITORING OF DRUGS IN THE MANAGEMENT OF NEUROPATHIC PAIN IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Objective: Neuropathic pain arises from demage, or the pathological changes in the peripheral or central nervous system. The pain is difficult to treat as standard treatment with conventional analgesics doesn`t typically provide effective relief of pain.

Methods: It was a one year study of utilization and analysis of prescriptions for PNDs (Painful neuropathic disorders). The parameters evaluated were demographic profile of the patient (age and gender), type and etiology of PNDs, drug data (name of the group of drugs with individual drugs, mono or polytherapy, number of drugs per prescription, formulation) and associated adverse drug reactions(ADR) with the prescribed drug.

Results: Maximum number of patients of PNDs resides in the age group of 18 – 35 yrs (41.2%) & more common in females. The most common PND encountered was painful diabetic neuropathy (43.9%) followed by cervical and lumbar radiculopathy, post herpetic neuralgia. 2942 drugs were prescribed in 1020 prescriptions out of which, 96.8% were oral and 3.2% were topical formulations. Most frequently prescribed group of drug was tricyclic antidepressant (27.3%) followed by anticonvulsants (25.3%). Polypharmacy was seen 89.7% as compared to monotherapy (10.3%). Only 132 ADRs of various types were seen. The most common organ system affected was central nervous system followed by gastro intestinal systems. The most common drugs implicated for ADRs were TCAs (24.4%), anticonvulsants (16.6%), and Pregabeline (9.8%). There were no fatal adverse events. Mild to moderate ADRs included constipation, nausea, vomiting, drowsiness, dryness of mouth.

Conclusions: The choice of drug depends on etiology of neuropathic pain, drug efficacy and availability and also on ADR profile.

Keywords: PNDs, Polypharmacy, TCAs, Anticonvulsants, Pregabaline, ADRs.

INTRODUCTION

Neuropathic pain is a type of pain which is either arising as a direct consequence of a lesion (dysfunction of either the peripheral nerves or, less commonly, the central nervous system) or a disease affecting the somatosensory system [1 – 3].

The nervous system is broadly classified into central and peripheral nervous system, and lesions of various etiologies affecting either system can lead to neuropathic pain. The common neuropathic conditions affecting the peripheral nervous system include peripheral diabetic neuropathic pain (PDPN), post-herpetic neuralgia (PHN), AIDS polyneuropathy, cervical or lumbar radiculopathy, mechanical compression such as entrapment syndromes (e. g. Carpal tunnel syndrome), Hansen's neuropathy, phantom limb pain after amputation, trigeminal neuralgia and traumatic nerve injury etc. Central causes for neuropathic pain include spinal cord injury (SCI), multiple sclerosis (MS) and stroke leading to central post-stroke pain (CPSP).

PNDs are difficult to treat, and often require treatment with antiepileptic drugs (AEDs) and/or tricyclic antidepressants (TCAs) instead of addition of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids (agents that are used to treat nociceptive pain). Guidelines for the treatment of painful neuropathies that was recommended previously was a stepwise approach with TCAs and/or AEDs used initially, followed by other agents (e. g., duloxetine, opioids) if required. If the pain persists due to inadequate control with drugs, they are recommended to attend pain clinics and/or psychological support [4]. Currently, the different categories of drugs that are recommended for management of painful neuropathies are TCAs, selected AEDs (i. e., Gabapentin, Pregabalin, Carbamazepine), serotonin-norepinephrine reuptake inhibitor (SNRI), antidepressants (i. e., duloxetine, Venlafaxine), and topical Lidocaine (Lignocaine) as first- and/or second-line therapy for pharmacological management; Tramadol and other Opioids are now recommended as second- and/or third-line therapy [5,6]. Patients' quality of life (both physical and emotional functioning) is mostly affected by painful neuropathic disorders (PNDs) [7 – 11] which is in turn responsible for substantial social stigma to the patient [11 – 16]. It is being a major challenge for the clinician to treat PNDs as it is a type of pain which is refractory in nature to the existing treatments. In randomized clinical trials (RCTs) it has been seen that no more than half of patients experience clinically meaningful pain relief with the available therapy, which is almost always partial but not complete relief [7]. Sometimes it is seen that patients frequently experience adverse effects to the drugs prescribed and due to this there is unsatisfactory patient compliance & require proper vigilance to avoid or minimize this.

A lot of studies have been published regarding the etiology, pathophysiology, and treatment of neuropathic pain; relatively little has been reported about the pattern of prescription, clinical characteristics and demographic profile and adverse effects of drugs used in the treatment of patients with PNDs in clinical practice, including their levels of use of pain-related pharmacotherapy and healthcare services.

Aims and objective

To study the pattern of utilization of drugs for the management of PNDs & their related ADR profile.

MATERIALS AND METHODS

The study was conducted in the Neurology as well as Paediatric OPD in collaboration with the Department of Pharmacology, Department of Dermatology in IMS & SUM Hospital, S 'O' A University, Bhubaneswar, Odisha. It was undertaken for one year from APRIL 2013 to MARCH 2014. Permission from the institutional ethics committee was obtained. Consent was obtained from the patient or their guardians. The current study was designed as a cross sectional, unicentric drug utilization study and analysis of the prescriptions for PNDs. The subjects who had willingly participated were enrolled on the basis of inclusion and exclusion criteria. All prescriptions issued

during this period were recorded on case record forms. Our study was conducted on 1020 patients. All patients with PNDs irrespective of age & sex were included in the study. The criteria for including a subject in the study were that he/she has been diagnosed to have PNDs by a Consultant Neurologist or a paediatrician with a clinical history, examination and relevant investigations and consented to take part in this study. ADRs were recorded as self reporting method using ADR reporting form by CDSCO.

Parameters for evaluation

Demographic profile of the patient (age and gender), type and etiology of PNDs,

Drug data (name of the group of drugs with individual drugs, mono or polytherapy, number of drugs per prescription, formulation) and associated adverse drug reactions with the prescribed drug were recorded during this study period.

RESULTS

Demographic profile of the patients suffering from PNDs enrolled in our study is depicted in table 1. The age ranged from 12 to 83 years with maximum percentage in the age group of 18-35(41.2%).

PNDs were more common in females. Out of a total of 1020 patients, 37.1% were males and 62.9% were females (Table 1).

Table 1: Demographic profile of patients of Painful neuropathic disorders (n= 1020):

Characteristic		Number of Patients with %
Age (years)	<18yr	8(0.7)
	18-35	421(41.2)
	36-50	204(20)
	51-65	263(25.7)
	66 - 80	118(11.5)
	≥ 81	6(0.5)
Sex	Male	378(37.1)
	Female	642(62.9)

The most common PNDs encountered was painful diabetic neuropathy (43.9%) followed by cervical and lumbar radiculopathy (10.9 %), post herpetic neuralgia (8.6%) and nerve impingement syndromes (6.6%). (Table 2)

Table 2: Distribution of painful neuropathic disorders (n = 1020)

Painful neuropathic disorder	Number of Patients with %
Diabetic neuropathy	448(43.9)
Post-herpetic neuralgia	88(8.6)
Phantom limb pain	6((0.5)
Cervical or lumbar radiculopathy	112(10.9)
Neuropathic postoperative pain	65(6.3)
Trigeminal neuralgia and atypical facial pain	64(6.2)
Nerve impingement syndromes	68(6.6)
Alcoholic polyneuropathy	22(2.1)
AIDS polyneuropathy	8(0.7)
Post-traumatic neuralgia (such as nerve root compression, post-thoracotomy)	6(0.5)
Spinal cord injury (SCI)	18(1.7)
Multiple sclerosis (MS)	4(0.3)
Stroke leading to central post-stroke pain (CPSP)	64(6.2)
Hansen neuropathy	27(2.6)
Neuropathic pain, unspecified	20(1.9)

The various oral formulations prescribed were TCAs (Amitriptyline, Imipramine, Nortriptyline, Desipramine), SNRIs (Duloxetine Venlafaxine), Anticonvulsants (Carbamazepine, Gabapentin, Pregabalin, Lamotrigine, Oxcarbazepine, Topiramte, Valproate), Opioids (Tramadol, Morphine) and various topical formulations were Topical lidocaine, Topical capsaicin as listed in the table 3.

Table 3: Neuropathic pain medications

Medication class/group	Dose (mg/d)
Tricyclic antidepressants	25 – 150
(amitriptyline,imipramine,nortriptyline,desipramine)	
SNRIs Duloxetine	60 – 120
Venlafaxine	150 – 225
Anticonvulsants	200 – 1200
Carbamazepine	
Gabapentin	1200 – 3600
Pregabalin	150 – 600
Lamotrigine	200 – 400
Oxcarbazepine	600 – 1800
Topiramte	200 – 400
Valproate	1000
Opioids	200 – 400
Tramadol	
Morphine	15 – 300
Miscellaneous	1 – 3 patches per day applied for 12 hours
Topical lidocaine	
Topical capsaicin	0.025% applied four times a day.

A total number of 2942 drugs (Table 4) were prescribed in 1020 prescriptions and the average number of drugs per prescription was found to be 2.88. Out of 2942 drugs prescribed (Table 4), 2848 (96.8%) were oral and 94 (3.2%) were topical formulations. Out of 2848 oral prescriptions, tricyclic antidepressant group of drugs 780 (27.3%) was the most frequently prescribed, as compared to anticonvulsants 721 (25.3%). The number of fixed dose combination prescribed was 1022.

Table 4: Analysis of prescriptions

Number of prescriptions	1020
Total no. of drugs prescribed	2942
Total no. of drugs prescribed through oral route	2848(96.8%)
Total no. of drugs prescribed through topical route	94 (3.2%)
Average no. of drugs prescribed per prescription	2.88
Number of fixed dose combinations	1022(35.8%)

Amitriptyline 522(66.9%) was the most frequently prescribed antidepressant followed by Nortriptyline 156(20%) and Imipramine 63(8.07%). Amongst the anticonvulsants, the most frequently prescribed drug is Pregabalin 464(64.3) followed by Gabapentin 130(18.03). Out of SNRIs, the most frequently prescribed drug is Duloxetine 315(60.5) followed by Desvenlafaxine 160(30.7%). Amongst all opioids the most frequently prescribed drug is Tramadol 407(88.8) followed by Morphine.(table 5&6)

Table 5: Groups of drugs used for the management of neuropathic pain(n=2848)

Types of anti neuropathic drugs	Number of drugs used	Percentage
Tricyclic anti-depressants	780	27.3
SNRIs	520	18.2
Anti-convulsants	721	25.3
Opioids	458	16.08
Miscellaneous	369	12.9

Table 6: Commonly used drugs in the management of neuropathic pain in descending order (n=2848)

Group of anti neuropathic drugs	Name of the drug	Number of drugs prescribed(n=2848)
Tricyclic anti-depressants (n=780)(27.3%)	Amitriptyline	522(66.9)
	Imipramine	63(8.07)
	Nortriptyline	156(20.0)
	Desipramine	39(5.0)
SNRIs (n=520)(18.2%)	Duloxetine	315(60.5)
	Venlafaxine	45(8.6)
	Desvenlafaxine	160(30.7)
Anti-convulsants (n=721)(25.3%)	Carbamazepine	52(7.2)
	Gabapentin	130(18.03)
	Pregabalin	464(64.3)
	Lamotrigine	6(0.83)
	Oxcarbazepine	42(5.8)
	Topiramte	4(0.5)
	Valproate	23(3.1)
Opioids (n=458)(16.08%)	Tramadol	407(88.8)
	Morphine	51(11.2)
Miscellaneous (n=369)(12.9%)	Topical lidocaine	72
	Topical capsaicin	22

The drugs under miscellaneous groups are NSAIDs, Baclofen, Clonidine, Paroxetine, Citalopram, Bupropion, Polypharmacy was seen in 914 (89.7%) prescriptions as compared to 106(10.3%) prescriptions with monotherapy (table 7)

Table 7: Type of prescription (n=1020)

Type of prescription	No. of prescription (%)
Monotherapy	106(10.3)
Polytherapy	914(89.7)

In our study group 116 patients developed 132 ADRs of various types. (Table 8). Some patients developed more than one ADR. In most of the ADRs, the organ system affected was central nervous system followed by gastro intestinal systems. The most common drugs implicated for ADRs were TCAs [Most common Amitriptyline; 32(24.4%)], Anticonvulsants [(Carbamazepine; 22 (16.6%)], and Pregabalin 13 (9.8%). Drowsiness, dizziness, Nausea was the commonest ADR noted. Dermatological ADRs were commonly seen with topical preparations**.** Causality assessment revealed that 76 ADRs (57.5%; n=132) were probable category & 56 were in the category of possible ADRs according to WHO-UMC criteria. Not a single case of 'certain' category was noted as rechallenge was not attempted by the physician, once a drug was withdrawn.

There were no fatal adverse events; however two cases of orthostatic hypotension with Amitriptyline necessitating hospitalization. Mild to moderate ADRs included constipation, nausea, vomiting, drowsiness, dryness of mouth and were treated by dose adjustment and/or relevant medications to treat the symptoms. There was discontinuation of Amitriptyline for weight gain, urinary retention & orthostatic hypotension (one case for each), lidocaine patch for swelling under patch (2 cases).

Table 8: Drugs for PNDs responsible for ADRs noted:

Name of the group of drugs	% of ADRs (total no of ADRs = 132)
Tricyclic anti-depressants	44(58.08)
Anti-convulsants	36(47.52)
SNRIs	21(27.72)
Opioids	13(17.16)
Miscellaneous	18(23.76)

DISCUSSION

Combination therapy is preferred over monotherapy in case of PND management because the combination therapy target different pain mechanisms which may be due to its additive or synergistic effects; but the evidence, supporting this is less developed [17]. Previous studies only focused on monotherapy rather than sequential or parallel combinations. There is also less studies published regarding the peripheral neuropathic pain in comparison to central neuropathic pain.

In our study maximum percentage of PNDs were seen in the age group of 18-35(41.2%) and more common in females (62.9%). It was described in some studies that the incidence of post herpetic neuralgia, painful diabetic neuropathy, phantom limb pain increased with age & also depend on severity of the underlying condition [19, 20]. Phantom limb pain was more common in men than women, while post-herpetic neuralgia was more common in women [18].

Table 9: Adverse drug reaction profile of drugs used in the management of PNDs:

Types of Drugs	ADRs
Tricyclic anti-depressants	Drowsiness, Confusion, Dry mouth, Orthostatic hypotension, Weight gain, Urinary symptoms
SNRIs	Nausea, Dizziness, Dry mouth
Anti-convulsants	Nausea, Dizziness, Drowsiness
Opioids	Constipation, Dizziness, Drowsiness
Miscellaneous	Skin reactions (such as redness or swelling under patch, erythema)

The most common PND encountered during our study period was painful diabetic neuropathy (43.9%) followed by cervical and lumbar radiculopathy (10.9 %), post herpetic neuralgia (8.6%) and nerve impingement syndromes (6.6%) which is contrasting to the study of Hall GC et al which showed that post-herpetic neuralgia was the most common cause of PNDs followed by trigeminal neuralgia & painful diabetic neuropathy [21].

Chronic neuropathic pain is a common late complication of leprosy. Its diagnosis is made when patient complaints of pain after completion of MDT and in the absence of any reaction or new nerve impairment. It presents as continuous burning type of pain with glove and stocking distribution [22, 23].

Paediatric neuropathic pain related studies are minimal due to the fact that the most common neuropathic pain conditions seen in adults are rare in children. For example, among children having diabetes are do not progress to the point at which neuropathy is considered as a risk. Incidence of postherpetic neuralgia, trigeminal neuralgia, radiculopathies, and complications of stroke are rare in children & adolescent populations. But in comparison to adult neuropathies, there is some peculiar neuropathies are there which is having specificity toward paediatric populations such as complex regional pain syndromes (CRPSs), phantom limb pain, spinal cord injury, trauma and postoperative neuropathic pain, autoimmune and degenerative neuropathies (e. g. Guillain-Barre syndrome, Charcot-Marie-Tooth disease), and the effects of cancer disease processes and treatment. There is also some rare neuropathic pain syndromes are seen which are relatively unique to the pediatric population, including toxic and metabolic neuropathies (eg, lead, mercury, alcohol, and infection), hereditary neurodegenerative disorders (e. g. Fabry disease), mitochondrial disorders, and primary erythromelalgia [24].

A total number of 2942 drugs were prescribed among which 96.8% were oral and 3.2% were topical formulations and the average number of drugs per prescription was found to be 2.88. Tricyclic antidepressant was most commonly prescribed group of drugs (27.3%) followed by anticonvulsants (25.3%). TCAs have long been used as most commonly prescribed drug in all types of neuropathic pain [25]. Analgesic actions may be attributable to noradrenaline and serotonin reuptake blockade (presumably enhancing descending inhibition), NMDA-receptor antagonism and sodium-channel blockade [26]. Amitriptyline (66.9%) was the most frequently prescribed antidepressant followed by Nortriptyline 156(20%) and Imipramine 63(8.07%) which is in contrast to a study showing secondary amine tricyclic antidepressants (Nortriptyline and Desipramine) are better tolerated than tertiary amine tricyclic antidepressants (Amitriptyline, Imipramine, Clomipramine) so more prescribed [27]. Amongst the anticonvulsants, the most frequently prescribed drug is Pregabalin (64.3) followed by Gabapentin (18.03). Till now it was seen that in various previous studies, carbamazepine remains the most frequently used anticonvulsant for neuropathic pain [28]. It has long been appreciated that there a similarities between epilepsy and neuropathic pain (in 1885 Trousseau described trigeminal neuralgia as "epileptiform neuralgia [29] and that drugs that are effective in reducing seizure frequency may also have an analgesic effect in neuropathic pain [30, 31].Gabapentin was also frequently prescribed as a first-line treatment in the painful diabetic neuropathy and in post-herpetic neuralgia, with the use of both gabapentin and Pregabalin increasing over the study period. This demonstrates a maintained shift from predominant use of opioid and non-opioid analgesics in the late 1990's to use of tricyclic antidepressants and antiepileptics, with initiation of these therapies now evident in primary, rather than secondary, care. Antiepileptic prescribing has moved from carbamazepine to gabapentin and Pregabalin, both of which are now used more frequently in phantom limb pain.

Out of SNRIs, the most frequently prescribed drug is Duloxetine (60.5%) followed by Desvenlafaxine (30.7%). They have a better side effect profile and may therefore be more suitable for elderly patients or those with cardiac disease [25] and these drugs may soon replace the use of tricyclic antidepressants Amongst all opioids the most frequently prescribed drug is Tramadol (88.8) followed by Morphine. Opioids can be considered as a first-line approach in selected clinical circumstances, such as intractable pain, episodic exacerbations of severe pain, acute neuropathic pain, and neuropathic cancer pain [32]. The incidence of use of opioids is slightly increased due to availability of tramadol as a first-line treatment in phantom limb pain [33].

According to different studies till date the first line agent in treatment of PNDs are antiepileptics and antidepressants and but some clinical trials supported the shift from carbamazepine to gabapentin, or Pregabalin. The European Federation of Neurological Sciences (EFNS) 2010 guidelines recommend gabapentin, pregabalin, lidocaine plasters and tricyclic antidepressants in post-herpetic neuralgia and duloxetine, gabapentin, pregabalin, tricyclic antidepressants and venlafaxine in painful diabetic neuropathy [33].

The number of fixed dose combination prescribed was 1022. Polypharmacy was seen in 89.7%prescriptions as compared to 10.3% prescriptions with monotherapy. Combination therapy show better result at lower doses and with fewer side effects [34]. In a recent study it was seen that morphine with gabapentin combination was superior to treatment with either drug alone [35].

Another study revealed that gabapentin– venlafaxine combination was superior to gabapentin alone [35]. Patients who received more than one therapeutic category usually received a mixture of an opioid and a non-opioid analgesic rather than combinations with demonstrated efficacy in neuropathic pain, such as gabapentin and opioids or Nortriptyline [33].

In our study group 132 ADRs were encountered only in 116 patients of PNDs with various groups of drugs. Some patients developed more than one ADR. The most common organ system affected was central nervous system and Gastro intestinal systems. The most common drugs implicated for ADRs were Amitriptyline (24.4%), Carbamazepine (16.6%), and Pregabalin (9.8%).

In some studies it was seen that tricyclic antidepressants are more efficacious than SSRIs & SNRIs but side effect profile are better in latter; therefore suitable for elderly patients or those with cardiac disease [25]. As systemic side effects are extremely rare with topical treatments, they are safe particularly for elderly patients. The most common side effects seen with TCAs were anticholinergic side effects which can be reduced by starting with low dosages at bedtime and dose titration [25, 32]. The most common adverse effect of duloxetine is nausea, which seems to be reduced by starting with low dose & increasing the dose gradually [36]. SSRIs (e. g.: Venlafaxine) was associated with cardiac conduction abnormalities,[37] and increases in blood pressure and should be tapered due to chance of withdrawal syndrome [38].

Gabapentin and Pregabalin are safer drugs with few adverse drug reactions such as dose-dependent dizziness and sedation, which can

be reduced by low dosage regimen and dose titration [25, 32]. Topical drugs show mild local reactions which is becoming advantageous in elderly PNDs [25, 32].

Constipation, nausea, and sedation are the most common adverse effects of opioids necessitating the low dose treatment & dose titration. However, constipation tends to be a chronic problem for patients taking opioids & should be monitored. The adverse effect profile of tramadol is similar to that of opioids, but tramadol also lowers the seizure threshold

CONCLUSION

Appropriate studies were not published regarding the use of drugs in the management of neuropathic pain specifically in paediatric population even if many agents may be used in treating neuropathic pain. It is the hope of neurologists that the rational use of drugs increases the chance of achieving analgesia in patients suffering from neuropathic pain. No one therapeutic intervention is guaranteed of success.

Future trials are needed to evaluate optimal drug combinations and dose ratios as well as safety, compliance and cost-effectiveness [17].

Desired analgesia may be achieved by the pharmacological management in most of the patients, but not all, patients. In those who fail to respond, in those situations other treatment modalities may be considered, ranging from behavior modification and to the more major invasive medical techniques. The future aspect of the study is that we have the prospect of developing newer additional agents which may or may not prove useful analgesics in neuropathic pain including agents with more specific sodium channel blocking effects, calcium channel blockers and new generation anticonvulsants and capitalize on the major expansion in knowledge generated from the work of the basic scientists.

It is hoped that this paper highlights the current outpatient therapeutic options and demonstrates a rational approach to the management of the patient with neuropathic pain.

Surgical and chemical sympathectomy has been used to treat neuropathic pain.

Important areas for future research include developing a specific diagnostic method for neuropathic pain; identifying associations between symptoms, signs, and pathology to guide mechanism based treatment strategies; comparing combination treatments with monotherapy; and conducting pharmacogenomic studies to guide prescribing.

CONFLICT OF INTERESTS

Declared None

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