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

SUBHRANSU SEKHAR JENA1, MONALISA JENA2*, NIBEDITA PATRO3, SWATI MISHRA2, MAITREYEYEE PANDA3, MRUTUNJAY DASH4

1Department of Neurology, IMS & SUM Hospital, SOA University, Bhubaneswar, Odisha, 2Department of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, Odisha, 3Department of Dermatology, IMS & SUM Hospital, SOA University, Bhubaneswar, Odisha, 4Department of Paediatrics, IMS & SUM Hospital, SOA University, Bhubaneswar, Odisha.

Received: 22 Aug 2014 Revised and Accepted: 20 Sep 2014

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 antiinconvulsants (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 gastrointestinal systems.

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, Pregabalin, 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 diabetic peripheral neuropathy (DPN), 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).

| 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)

| Painful neuropathic disorder | Number of Patients with % |
|-----------------------------|---------------------------|
| Diabetic neuropathy         | 448(43.9)                 |
| Post-herpetic neuralgia     | 288(28.6)                 |
| 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(0.4)                    |
| 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.

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

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.
Amongst the anticonvulsants, the most frequently prescribed drug is Pregabalin 464 (64.3%) followed by Gabapentin 130 (18.03%). Out of SNRIs, the ADRs (57.5%; n=132) were probable category & 56 were in the commonest ADR noted. Dermatological ADRs were commonly seen with topical preparations. Pregabalin 13 (9.8%). Drowsiness, dizziness, Nausea was the prescribed drug is Tramadol 407 (88.8) followed by Morphine. (Table 5&6).

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).

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).

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).

Amotriptyline 522 (66.9%) was the most frequently prescribed antidepressant followed by Nortriptyline 150 (20%) and Imipramine 63 (8.07%). Amongst all opioids the most frequently prescribed drug is Duloxetine 315 (60.5%) followed by Desvenlafaxine 160 (30.7%). Amongst all antidepressants the most frequently prescribed drug is Amitriptyline 522 (66.9%) was the most frequently prescribed antidepressant followed by Nortriptyline 156 (20%) and Imipramine 63 (8.07%).

| 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                  | 16.06      |
| 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) |
| SNRIs (n=520) (18.2%) | Imipramine | 638 (14.7) |
| Anti-convulsants (n=721) (25.3%) | Nortriptyline | 156 (21.3) |
| Opioids (n=458) (16.08%) | Desvenlafaxine | 458 (18.3) |
| Miscellaneous (n=369) (12.9%) | Tramadol | 369 (13.1) |

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.

Table 7: Type of prescription (n=1020)

| Type of prescription | No. of prescription (%) |
|----------------------|-------------------------|
| Monotherapy          | 106 (10.5)              |
| Polytherapy          | 914 (89.7)              |

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

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 (38.08)                        |
| Anti-convulsants           | 36 (47.52)                        |
| SNRIs                      | 21 (27.72)                        |
| Opioids                    | 13 (17.16)                        |
| Miscellaneous              | 18 (23.76)                        |
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: Adverse drug reaction profile of drugs used in the management of PNDs:

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

The most common PND encountered during the 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 deficit. Its treatment. There is also some peculiar neuropathies which is having similarities between epilepsy and neuropathic pain (in 1885) by Charcot-Marie-Tooth disease, and the effects of cancer processes and treatment. There is 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 10.3% prescriptions with monotherapy. Combination therapy showed 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].

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 patches and tricyclic antidepressants in post-herpetic neuralgia and duloxetine, gabapentin, pregabalin, tricyclic antidepressants and venlafaxine in painful diabetic neuropathy [33].

The data in this study is informative and may help in improving the quality of pain management. However, it is important to keep in mind that this is a cross-sectional study and further research is needed to confirm these findings. The incidence of use of opioids is slightly increased due to availability of tramadol as a first-line treatment in phantom limb pain [33].

Out of SNRIs, the most frequently prescribed drug is Duloxetine (61.50%) followed by Desvenlafaxine (30.70%). 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 was 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].

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 is 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].

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) by Charcot-Marie-Tooth disease, and the effects of cancer processes and treatment. There is also some peculiar neuropathies which is having similarities between epilepsy and neuropathic pain (in 1885) by Charcot-Marie-Tooth disease, and the effects of cancer processes and treatment.

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 was 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].

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 which 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 is 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

REFERENCES

1. Treede RD, Jensen JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70(18):1630–5.
2. Fields HL, Martin JB. Pain: pathophysiology and management. In Harrison’s Principles of Internal Medicine. 14 editions. Edited by: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL. United States of America: McGraw-Hill Companies; 1997. p. 55-8.
3. Merskey H, Bogduk N. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2 editions. Seattle: IASP Press; 1994.
4. Attal N, Cruccu G, Hanpa M, Jensen TS, Nurmikko T, Sampaio C, et al. ENFS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153-69.
5. O’Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 2009;122S2:S32.
6. Attal N, Finnerup NB. On behalf of the IASP Neuropathic Pain Special Interest Group (NeuPSIG): pharmacological management of neuropathic pain. IASP 2010;18:1-8.
7. Oster G, Harding G, Dukes E, Edelberg J, Cleary PD. Pain, medication use, and health-related quality of life in older persons with post herpetic neuralgia: results from a population-based survey. J Pain 2005;6(6):356-63.
8. Gore M, Brandenburg NA, Hoffman DL, Tai KS, Stacey B. Burden of illness in painful diabetic peripheral neuropathy: the patients’ perspectives. J Pain 2006;7(12):989-900.
9. McDermott AM, Tolle TR, Rowbotham DM, Haeker CP, Dukes EM. The burden of neuropathic pain results of a cross-sectional survey. Eur J Pain 2010;12(6):127-35.
10. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007;68(15):1178-82.
11. O’Connor AB. Neuropathic pain: a review of the quality of life impact, costs, and cost-effectiveness of therapy. Pharmacoconomics 2009;27(2):95-112.
12. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. J Pain 2010;11(2):143-9.
13. Dworkin RH, White R, O’Connor AB, Baser O, Hawkins K. Health care costs of acute and chronic pain associated with a diagnosis of herpes zoster. J Am Geriatr Soc 2007;55(8):1168-75.
14. Dworkin RH, Malone DC, Panerites CJ, Armstrong EP, Pham SV. Impact of postherpetic neuralgia and painful diabetic peripheral neuropathy on health care costs. J Pain 2010:92(2):143-9.
15. van Hoek AJ, Gay N, Melegaro A, Opstelten W, Edmunds WJ. Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. Vaccine 2009;27(9):145-67.
16. Donaldson Sir L. The 2008 report of the Chief Medical Officer: 150 years of the Annual Report of the Chief Medical Officer: on the state of public health 2008. London, England: Department of Health, 2009. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/AnnualReports/DH_096206. Accessed 1.2.2010.
17. Gilron I, Max MB. Combination pharmacotherapy for neuropathic pain: current evidence and future directions. Expert Rev Neurother 2005;5:823-30.
18. Gillian C, Hall, Steve V, et al. Antidepressants - a review for the management of neuropathic pain. J Pain 2007;8(11):592-607.
19. Hietaharju A, Croft R, Alam R, et al. Chronic neuropathic pain in treated leprosy. Lancet 2000;356:1080-81.
20. Gustorf B, Dorner T, Likar R, Grisold W, Lawrence K, Schwarz F, et al. Prevalence of self-reported neuropathic pain and impact on quality of life: a prospective representative survey. Acta Anaesthesiol Scand 2008;52:132-6.
21. Hall GC, Carroll D, McQuay H. Primary care incidence and treatment of four neuropathic pain conditions: a descriptive study, 2002-2005. BMC Fam Pract 2008;9:26.
22. Land C, Koskimen, Suneetha S, et al. Histopathological and clinical findings in leprosy patients with chronic neuropathic pain: a study from Hyderabad, India. Lepr Rev 2007;78:369-80.
23. McQuay H, White R, O’Connor AB, Baser O, Hawkins K. Health care costs of acute and chronic pain associated with a diagnosis of herpes zoster. J Am Geriatr Soc 2007;55(8):1168-75.
24. Meuleman GJ, Anticonvulsants-epilepsy or pain? In Press Ulster Medical Journal.
25. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ 1995;311:1047-52.
31. Kingery WS. A critical review of controlled trials for peripheral neuropathic pain and complex regional pain syndrome. Pain 1997;73:123-39.
32. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237-51.
33. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nummikko T. European federation of neurological societies: efns guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17(9):1113–e88.
34. Gilron I, Bailey JM. Trends in opioid use for chronic neuropathic pain: a survey of patients pursuing enrollment in clinical trials. Can J Anaesth 2003;50:42-7.
35. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352:1324-34.
36. McIntyre RS, Panjwani ZD, Nguyen HT, et al. The hepatic safety profile of duloxetine: a review. Expert Opin Drug Metab Toxicol 2008;4(3):281-5.
37. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004;110(3):697-706.
38. Fava M, Mulroy R, Alpert J, Nerenberg AA, Rosenbaum JF. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. Am J Psychiatry 1997;154(12):1760-2.