Original Article

Prescription Pattern of Drugs Used for Neuropathic Pain and Adherence to NeuPSIG Guidelines in Cancer

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Abstract

Objective: The objective of the present research was to evaluate the prescription pattern of the drugs used in the pharmacological treatment of cancer-related neuropathic pain (CRNP) and to assess the adherence of the physicians to the Neuropathic Pain Special Interest Group (NeuPSIG) Guidelines. **Materials and Methods:** This was a cross-sectional, observational study where patients who presented to the pain and palliative care outpatient clinic of the tertiary care hospital with CRNP were prospectively recruited. Participants were screened for neuropathic pain using DN4 questionnaire. Demographic details, diagnosis, medication details, and adherence to NeuPSIG guidelines were assessed using a validated questionnaire. **Results:** Of 300 patients screened, 64% were male and 36% were female, with a mean age of 48.26 ± 13.05 years. The predominant symptoms found were pin-and-needle sensation (99%) followed by tingling sensation (98.66%). The most common diagnosis was head-and-neck cancers (37.3%) followed by bone cancers (17.3%) and lung cancers (15.3%). Among the first-line drugs recommended in NeuPSIG for CRNP, pregabalin (78.7%) was the most common drug prescribed followed by amitriptyline (67%). The most common co-prescribed drugs were acid suppressants drugs (50.7%). Tapentadol, which is not part of the NeuPSIG guidelines, was prescribed on 51 occasions for neuropathic pain. Underdosing was observed in 272 prescriptions. Only 12 prescriptions completely adhered, while 275 had partial, and 13 prescriptions had poor adherence to NeuPSIG guidelines. **Conclusion:** The most commonly used drugs in the treatment of CRNP were pregabalin and amitriptyline. Most physician partially or did not adhere to the NeuPSIG guideline in the management of CRNP.

Keywords: Cancer, neuropathic pain, neuropathic pain special interest group, pregabalin

Introduction

Neuropathic pain is defined by Neuropathic Pain Special Interest Group (NeuPSIG) as ''pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[1] The exact global prevalence of neuropathic pain is unknown, but studies have estimated it to be between 1.5% and 8%.[2] Unrelieved neuropathic pain continues to be a substantial health problem in patients with cancer. Approximately 19% of people with cancer have cancer-related neuropathic pain (CRNP), as a result of either the disease or its treatment.[3] Identifying the type and source of pain in patients with cancer is complex. Sources of cancer pain vary from direct tumor invasion of bone, nerves, ligaments, etc., metastasis of the disease, neuropathy secondary to tumor antigens, or chemotherapy-induced neuropathy.[4] Cancer-related pain can either be nociceptive (musculoskeletal, cutaneous, or visceral) or neuropathic or mixed type in many cases. The prevalence of cancer patients with mixed pain, which included neuropathic type was estimated to be 39.1%.[3] Studies conducted in India have shown a varied prevalence of CRNP from 11.8% to 25.13%.[5,6]

Establishing the nature of the pain in patients with cancer is key in providing effective pain relief because particular analgesic does not effectively manage both neuropathic and nociceptive pain. Cancer patients experiencing neuropathic type of pain usually describe the symptoms as shooting, stabbing, like an

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electric shock, burning, tingling, numb, prickling, itching, and a sensation of pins and needles. Neuropathic cancer pain is associated with poor physical, cognitive and social functioning, and greater requirements for pain medications than nociceptive cancer pain.[7]

In general, neuropathic pain is chronic, severe, and resistant to over-the-counter analgesics. CRNP has long been suggested to reduce opioid responsiveness and has been claimed to be a major prognostic factor for poor pain control. Thus, the management of CRNP is challenging. Although pain is frequently experienced by patients with cancer, it can remain undertreated,[3,8] as a result of patient's reluctance to report pain or to take treatment for pain relief in addition to cancer treatment.[9,10] Undertreatment can also be caused by limited pain management-related knowledge among oncologists.[9,10]

Several pharmacological treatment options are available for the management of neuropathic pain. However, there is considerable variation in how the treatment should be initiated and the method of titration of dose of drugs to achieve therapeutic level. One more dimension is that a number of commonly used medications are not licensed for treating neuropathic pain, which may limit their use or if used in clinical practice may be off label. Hence, there is a need that physician follow evidence-based guidelines for managing neuropathic pain. Revised and updated clinical guideline for pharmacological treatment of neuropathic pain recommended by NeuPSIG in 2015 was based on a systematic review and metaanalysis. The recommendations were updated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[1] After reviewing the trial outcome for commonly used neuropathic pain medication, and based on GRADE, the study authors created a treatment algorithm supporting the use of:

- Tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin as the first-line therapy
- Lidocaine patches, capsaicin high-concentration patches, and tramadol as the second-line therapy, and
- Strong opioids and botulinum toxin A as the third-line therapy.

The review of the literature using PubMed search engine using the search terms "Neuropathic Pain and Audit" showed 42 studies, and none had done conducted a complete audit of drugs used for CRNP, and there were no studies showing the adherence of physicians to this revised guideline.

Therefore, a study was conducted to evaluate the prescribing pattern of drugs and adherence of the physicians to the newer NeuPSIG guideline for neuropathic pain.

Materials and Methods

It was a cross-sectional, observational study conducted in a pain clinic and palliative care outpatient department (OPD) of a tertiary care hospital. The total duration of the study was 2 years (November 2016–2018) which included screening, recruitment of participants, and data analysis. Sample size calculation for prescription audit was done according to the WHO which recommends at least 100 cases/facility. As in our study, we have recruited 300 eligible patients attending the general pain and palliative care outpatient clinics.[11]

Before initiating the study, the investigator obtained approval from the Institutional Ethics Committee (IEC) (IEC/0217/1790/001). Subsequently, written informed consent was obtained before the recruitment of the participant. Cancer patients aged above 18 years and below 80 years experiencing neuropathic pain and screened using DN4 neuropathic pain diagnostic questionnaire with score ≥4 were included in the study. Patients with an established diagnosis of neurogenic pain associated with localized peripheral neuropathies (e.g., postherpetic neuralgia, diabetic neuropathy, and postsurgical/traumatic neuropathic pain) were excluded from the study.

Sociodemographic details were recorded. Body mass index (BMI) was recorded to find a proportion of participants with cancer cachexia (BMI <20).[12] The baseline pain score of the participants was recorded using the Visual Analogue Scale (VAS), and the participants were divided into three groups according to the severity of pain. The pain score of 1–3 was defined as mild, 4–6 as moderate, and pain score of 7 and above as severe pain. The prescription was reviewed for the profile of drugs, and its details with the diagnosis and completeness of prescription were determined. Drugs were checked for their availability in the hospital formulary. Prescribing indicators were assessed as per the WHO guidelines. The International Classification of Diseases-11 published by the WHO in 2018 was used to classify the participants according to the diagnosis and type of cancer. The completeness of the prescription was decided based on the rational prescribing principle, which encompasses the name of drug, dose, dosage form, frequency, and duration of treatment, and if anyone of these was absent, it meant incomplete prescription.

Prescriptions were analyzed whether medication prescribed was according to the NeuPSIG guidelines. Adherence of physician to the NeuPSIG guidelines were analyzed based on the validated questionnaire. It contained six Yes/No type questions regarding whether the drugs were prescribed according to guidelines, whether the prescription contained drugs not mentioned in the guidelines, and whether appropriated dose, dosage, frequency, and duration was mentioned. The total score for the questionnaire was 6, complete adherence to guidelines was considered when the score was 6, while partial and poor adherence for score between 3–5 and ≤2, respectively.

Statistical analysis plan

Demographic data that was continuous (age) were expressed as mean ± standard deviation (SD). Categorical data (gender) were expressed as percentage. Continuous variables were presented as mean ± SD. The individual scores obtained on the VAS were summated as median and range. Drug details and adherence to guidelines were analyzed using the descriptive statistics in the SPSS software version 21 by IBM, New York, USA.

Results

Demographic profile of study participant

A total of 300 cancer patients experiencing neuropathic pain were recruited in the study. The mean age of participants was 48.26 ± 13.05 years (mean ± SD). One hundred and ninety-three participants were male, whereas 107 were female. Seventy-three percent of the participants were literate. Forty-five percent of the participants had BMI <20, whereas 55% had BMI >20.

Screening of participants

The participants were screened for neuropathic pain using DN4 questionnaire. The participants with DN4 score of equal or more than 4 were diagnostic of neuropathic pain. The most common symptom found on screening was pin-and-needle sensation (99%) followed by tingling sensation (98.66%), electric shock sensation (96.33%), burning sensation (86.66%), numbness (68.33%), itching (38.33%), hypoesthesia to touch (32%), hypoesthesia to prick (28%), and painful cold (13.33%). The least common symptom found was brushing sensation (11.33%). Fifty-seven percent of participants were experiencing moderate pain, i.e., pain score of 4–6, while 112 (37.3%) participants had severe pain, and 17 (5.7%) participants had mild pain as per VAS.

Diagnosis of participants

The most common diagnosis of the participant experiencing neuropathic pain was head-and-neck cancers (37.3% cases), followed by bone- and soft-tissue sarcomas (17.3% cases), and lung cancers (15.3% cases) and neoplasm of the breast in 8.66%.

Drug use indicators

A total of 909 pain medications and 267 comedications (total of 1176 drugs) were prescribed in the 300 prescriptions. The total number of drugs per prescription was 4 ± 1 (mean ± SD). Pain medication prescribed per prescription was 3 ± 1 (mean ± SD), whereas co-medication per prescription was found to be 1 ± 1 (mean ± SD). Of 909 pain medication, 355 (35.87%) were prescribed by their generic name, whereas 554 (64.12%) were prescribed by their brand names.

The results of prescribing indicators as per the WHO are summarized in Table 1.

Table 1: Results of prescribing indicators

Prescribing indicator	Results
Average number of drugs per encounter, mean±SD	4±1
Percentage of drugs prescribed by generic name (%)	35.87
Percentage of encounters with an antibiotic prescribed	None
Percentage of encounters with an injection prescribed	None
Percentage of drugs prescribed from essential drugs list or hospital formulary	All drugs (1176) were available in hospital formulary

SD: Standard deviation

The pain medication prescribed was divided into three categories according to NeuPSIG guidelines.

1 First-line drugs: the most common first-line drug prescribed in the management of neuropathic pain was pregabalin which was prescribed in 236 of 300 prescriptions (78.7%). This was followed by amitriptyline (tricyclic antidepressant) (67%), gabapentin (3.33%), and duloxetine (serotonin and norepinephrine reuptake inhibitors [SNRI]) were found only two prescriptions
2 Second-line drugs: Of the second-line agents mentioned in NeuPSIG guidelines, tramadol was the only drug prescribed in 36.67% cases
3 Third-line drugs: Strong opioids (108 prescriptions had morphine, 8 prescriptions had fentanyl patch, and 2 prescriptions contained buprenorphine patch) were seen in 39.33% cases for the management of neuropathic pain.

The most common nonsteroidal anti-inflammatory drugs (NSAIDs) prescribed were etoricoxib (81 prescriptions) and paracetamol (80 prescriptions), whereas diclofenac was prescribed in 19 prescriptions. The most common comedication prescribed along with the pain medication in the treatment of neuropathic pain was acid-suppressing drugs (50.7%) followed by laxatives (28%) and anti-emetics (6.4%). We found that 39 (36%) prescriptions did not contain a prophylactic co-prescribed laxative when morphine was given (108 prescriptions). The antiemetics prescribed were ondansetron (12 prescriptions) and domperidone (7 prescriptions).

Completeness of the prescriptions

Of the 300 prescriptions analyzed, 146 (48.7%) were found to be complete, whereas 154 (51.3%) prescriptions were incomplete. One hundred and twenty-eight of the 300 (42.7%) prescriptions did not mention the dosage form of drugs; 30 of the 300 (10%) prescriptions did not mention the duration of the prescribed drugs; 22 of 300 (7.4%) did not mention the dose of drugs prescribed, whereas the frequency of administration of drugs was missing from only 2 of the 300 prescriptions.

Adherence of the physician to the guidelines

A validated questionnaire was used to check the adherence of the physicians to NeuPSIG guidelines in prescribing the pain medication for the management of neuropathic pain. At least one drug was prescribed according to the guideline in 295 out of 300 prescriptions (98.34%). Nearly 18.67% of prescriptions contained drugs which are not mentioned in the guidelines. Only 6.34% prescriptions had appropriate dose mentioned according to the guidelines. Dosage was mentioned in 56% prescriptions, whereas frequency and duration were mentioned in 97.6% and 87.33% prescriptions, respectively. The most common dosage error by physician while prescribing brand of pregabalin was prescribed as tablet, whereas it was available in capsule form. Fifty-six prescriptions contained drugs which are not mentioned in NeuPSIG guidelines, of which tapentadol was prescribed to 51 participants. Tramadol fixed-dose

combination (FDC) was prescribed to three participants, whereas carbamazepine and flupertine were prescribed to one participant each.

Underdosing of pregabalin and amitriptyline when prescribed together was seen in 98 of 300 prescriptions (32.67%). Even when the prescription contained individual drugs, they were under-dosed; pregabalin in 77 (25.67%) and amitriptyline in 52 (17.34%) prescriptions, respectively. We found the doses used in our study for pregabalin, amitriptyline, and gabapentin were 75 mg once a day, 10 mg once a day, and 300 mg once a day, respectively. Morphine was underdosed in 34 prescriptions where it was prescribed as TDS dose (32 prescriptions) and BD dose (2 prescriptions).

Only 12 prescriptions (4%) completely adhered, whereas 275 prescriptions (91.66%) adhered partially to the NeuPSIG guideline in prescribing the medication for the management of neuropathic pain. Thirteen prescriptions (4.33%) showed low adherence of physician to the guideline.

Discussion

The sociodemographic profile and cancer typologies in the study were similar to the study conducted by Mishra *et al*.[13] and Jain *et al*.[6] In this study, neuropathic pain was most commonly associated with oral cancer (44%) in males. The prevalence of oral cancer is high in India, accounting for about 30% of all types of cancer. Furthermore, males face twice the risk of developing oral cancer as compared to females due to excessive consumption of tobacco and smoking.[14]

There are several tools available for differentiating neuropathic pain from other types of pain. Screening tools, which combine self-reporting with physical examination, are more accurate than those using self-reporting alone. DN4 questionnaire has a higher sensitivity (83%) and specificity (90%) than the other tools used for screening. Furthermore, other validated tools available for neuropathic pain are cumbersome to use in clinical settings.[15] We used DN4 questionnaire to screen the cancer patients for neuropathic pain as it is easy to use and score in clinical setting which incorporates questions of both self-reporting and physical examination. The symptom screening conducted using DN4 questionnaire in this study was comparable to the study conducted by Lecomte *et al*.[16] However, the percentage of symptoms was higher in our study. Intensity of the mean pain scores measured through VAS was similar to the study conducted by Birtle *et al*.[17] Change in pain scores due to intervention could not be analyzed, as it was a cross-sectional observational study.

More than half the prescriptions were found to be incomplete in terms of dose, dosage form, frequency, and duration, of which error in dosage forms contributed the most. This can be attributed to the lack of awareness among the physicians regarding the dosage forms available in hospital formulary. However, this error can be resolved by regular updates of the formulations available. We found that close to two-third of the pain medications were prescribed by their brand name. In the Indian scenario, many of the drugs are not available in generic form as a result of which patients end up being prescribed branded drugs. This significantly increases the cost of therapy. At the study site, branded drugs were available at a subsidized rate. Physicians often face the confusion of having to choose from a long list of available brands. For example, among the first-line drugs, pregabalin alone is available in the form of 120 different brands. It is marketed in the form of both tablets and capsules in doses varying from 25 mg to 300 mg, with prices ranging from Rs. 50 to Rs. 1800.[18] Generic prescribing encourages the availability of medicines at an affordable price and avoids any potential confusion with similar brand names.[19]

The study showed pregabalin followed by amitriptyline and gabapentin to be the most commonly prescribed first line similar to a study conducted in India by Kamble *et al*.[20] Of these three drugs, pregabalin and amitriptyline were preferred over gabapentin. Despite a similar mechanism of action, pregabalin has a higher analgesic potency compared to gabapentin owing to its greater binding affinity for the alpha-2/delta-1 subunit as well as higher bioavailability. These distinct pharmacokinetic advantages of pregabalin over gabapentin might have been the reason why it was favored by the physicians. However, there were few prescriptions with gabapentin as well, which may be due to its time-tested efficacy in neuropathic pain.[21]

Among SNRI, duloxetine and venlafaxine have been studied to a greater extent and have demonstrated a combined number needed to treat (NNT) value of about 6.4 and number needed to harm (NNH) of 11.8. Among tricyclic antidepressants (TCAs), amitriptyline has been widely studied and has shown a combined number NNT value of about 3.6 and NNH of 13.4.[1] In this study, amitriptyline was prescribed in almost two-third of the patients, whereas duloxetine (SNRI) was prescribed only to two patients. Although a larger proportion of patients were prescribed TCA as compared to SNRI, it should be borne in mind that TCAs are not free from side effects and can provoke sedation, dizziness, dry mouth, and constipation.[22] This can be especially troublesome in elderly patients where cancer prevalence is more. SNRI is preferred in patients with prostate hypertrophy, glaucoma, or cardiac conduction disturbances where TCAs should be used with caution.[23]

Due to the potential risk of abuse and concerns about recent increase in mortality associated with opioid overdose, strong opioids are now recommended as the third line of therapy by NeuPSIG guidelines.[1] In our study, opioids such as morphine, buprenorphine, and fentanyl were prescribed in 39.33% prescriptions. An increased trend toward prescription of opioids was observed in our study since it was conducted in a tertiary care cancer hospital where majority of the patients presented with mixed nociceptive and neuropathic kind of pain. More than one-third of the prescriptions lacked a prophylactic laxative when morphine was prescribed. A survey conducted in advanced cancer patients revealed that 87% of patients on strong opioids and 74% on weak opioids required the

use of laxatives.[24,25] Although NeuPSIG guidelines do not mention about concurrent prophylactic use of laxatives with opioid analgesics, prescribing laxatives is considered a good practice.[26,27] The most common NSAIDs prescribed were etoricoxib and paracetamol. Although not recommended by NeuPSIG guidelines, physicians may have prescribed them as a Step 1 analgesics or for bone pain present in cancer patients with neuropathic pain.

The tertiary care hospital where the study was conducted had all the drugs available in the formulary. This is a good indicator of the facility versus government setups and municipal run hospitals where all the drugs are not available.[28]

Adherence of physicians to guidelines while prescribing medication was assessed as complementary drug indicators given by the WHO. Fifty-six prescriptions contained drugs that are not recommended by NeuPSIG guidelines for the management of neuropathic pain. These consisted of drugs such as tapentadol, FDC of tramadol with paracetamol, carbamazepine, and flupertine. NeuPSIG guidelines do not recommend tapentadol and combination therapy in the management of neuropathic pain due to inconclusive evidence.[1] However, the authors of the NeuPSIG guidelines recommend further studies to firmly establish the role of tapentadol in the treatment of neuropathic pain. Tramadol plus paracetamol FDC was prescribed to three participants. This is a rational FDC approved by the Drugs Controller General of India in 2003 for the short-term (5 days or less) management of acute pain in adult. Although tramadol monotherapy is approved by NeuPSIG guidelines for the treatment of neuropathic pain, its FDCs are not recommended by the same.[1] Flupirtine, which is a centrally acting nonopioid analgesic used for acute as well as chronic pain, was prescribed to one of the patients.[29] Further inquiry regarding the prescription revealed that it had been prescribed for neuropathic pain, even though it is not recommended.[1] Carbamazepine had been prescribed to a patient with neuropathic pain due to oral cancer when it is only recommended specifically for trigeminal neuralgia and not for other types of neuropathic pain.[1]

Low doses of pregabalin, amitriptyline, and gabapentin for the management of neuropathic pain were found in this study. The standard dose of pregabalin, amitriptyline, and gabapentin mentioned in NeuPSIG guidelines is 300–600 mg in two divided doses, 25–150 mg once a day or in two divided doses, and 1200–3600 mg in three divided doses, respectively.[1] This study revealed the use of pregabalin, amitriptyline, and gabapentin at the doses of 75 mg once a day, 10 mg once a day, and 300 mg once a day, respectively. The higher prevalence of cancer cachexia leading to the inability to tolerate the standard dose was cited as the reason for underdosing by treating physicians. Fearon *et al*. defined cancer cachexia based on weight loss, BMI (BMI <20), and skeletal muscle mass loss.[12] Since this was a cross-sectional study, we were unable to tap weight loss and skeletal muscle mass loss; thus, only BMI was taken into consideration. More than half of the patients in the study had BMI more than 20, which makes the above-cited reason for under-dosing invalid. Kamble *et al*.,[20] in their study, revealed similar findings regarding underdosing and stated low tolerance at standard doses and acceptable efficacy at lower doses. Most of the patients were recruited from general pain OPD, and these prescriptions were prescribed by junior physicians. Unawareness about the recent changes in the NeuPSIG guideline among the junior physicians could be one of the reasons for underdosing.

A study by Liu *et al*.[30] assessed the adherence of treating physicians to the American College of Rheumatology guidelines for managing pain in patients with fibromyalgia. Nonadherence to the treatment guidelines and use of lower-than-recommended doses potentially resulting in poor effectiveness were reported in the study. In our study, only 4% of the prescriptions completely adhered to the guidelines, whereas 91.66% adhered partially. The management of patients following evidence-based guidelines is necessary for achieving maximum effectiveness of treatment. Our study, however, was not targeted to measure the effectiveness in decreasing the pain score with the reported prescription pattern. Efficacy of lower doses of first-line drugs needs to be validated for its use in the management of neuropathic pain. Further trials investigating this parameter may add more value to this finding.

Conclusion

The most commonly used drugs in the treatment of CRNP found in this study are pregabalin and amitriptyline. Most physicians partially or poorly adhered to the NeuPSIG guideline in the management of CRNP.

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Conflicts of interest

There are no conflicts of interest.

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