

AN OBSERVATIONAL STUDY ON THE PRESCRIPTION PATTERNS OF DRUGS IN NEUROPATHIC PAIN AND ADHERENCE TO NeuPSIG GUIDELINES IN CANCER PALLIATIVE CARE

*SADASIVA RAO GALABA,¹ BEERAM POORNA SIVANI,² JANDHYALA VYSHNAVI,³ KARASANI HARINI,⁴ NAIDU CHANDU PRIYA

*Assistant Professor & HOD, Dept. of Pharmacy Practice, Hindu College of Pharmacy, Guntur, A.P., India
^{1,2,3,4}VI/VI PHARM-D Hindu College of Pharmacy, Guntur, A.P., India

ABSTRACT:

AIM: To evaluate the prescription patterns of drugs in the pharmacological management of Cancer-Related Neuropathic pain (CRNP) and assess the adherence to NeuPSIG (Neuropathic Pain in Special Interest Group) guidelines.

MATERIALS AND METHODS: The severity of pain in cancer patients was assessed using VAS scale and neuropathic pain in cancer palliative care patients was assessed using DN4 criteria. The adherence of prescriptions was analysed by NeuPSIG guidelines.

In this study, 100 patients were included and the study was carried over a period of six months. Prescriptions were analyzed whether medication prescribed was according to the NeuPSIG guidelines. The patients in the study were diagnosed with breast cancer, lung cancer, pancreatic cancer, head and neck cancers, colo-rectal cancer, vaginal cancer and ovarian cancer. All the relevant data as collected by interviewing the patients and assessing their medical records.

RESULTS: Both the first line drugs namely Gabapentin, Pregabalin, Duloxetine, Tricyclic anti depressants and second line drugs Tramadol and Acetaminophen were equally prescribed in the study without the consideration of the severity of the pain.

CONCLUSION: On assessing the prescriptions, it was observed that 51% of the prescriptions were completely adhered to the guidelines, 49% with partial adherence and none with poor adherence.

Key words: CRNP, NeuPSIG, DN4, Neuropathic pain, Cancer

INTRODUCTION:

The Neuropathic Pain Special Interest Group (NeuPSIG) defines neuropathic pain as "pain originating as a direct result of a lesion or disease affecting the sensory-motor system."^[1] The precise global prevalence of neuropathic pain is unknown, however studies have estimated that it is in between 1.5 and 8%.^[3] IN cancer, one of the most prevalent symptom is pain. This pain can be nociceptive (musculoskeletal, cutaneous, or visceral), neuropathic, or mixed in many cases. About 19 percent of cancer patients experience cancer-related neuropathic pain (CRNP) as a result of the disease or its treatment.^[2] CRNP prevalence in India spans from 11.8% to 25.13%, as per surveys.^[4,5] In cancer patients, determining the nature and source of pain is difficult. Hence, in order to assess the neuropathic pain in cancer patients we have opted DN4 criteria, which contains ten yes or no type questionnaire based on the symptoms like shooting, stabbing, electric shock-like sensations, burning, tingling, numbness, prickling, itching, and a pins-and-needles feeling.^[3]

In comparison to nociceptive cancer pain, neuropathic cancer pain is associated with decreased physical, cognitive, and social functioning, as well as a greater requirement for pain medicines.^[6] Unrelieved neuropathic Pain remains a significant health concern for cancer patients. This Neuropathic pain is characterised by chronicity, severity, and resistance to over-the-counter medications. Despite the fact that pain is commonly experienced by cancer patients, it is often undertreated^[2,7] due to patients' unwillingness to disclose discomfort or to seek pain medication in addition to cancer treatment.^[8,9] Some of the treatment barriers for cancer-related pain include: Patient obstacles, Professional roadblocks, Systemic barriers and limited pain management understanding among oncologists might sometimes lead to undertreatment.^[10] Thus, CRNP management is difficult. Several pharmacological treatment options are available for the management of neuropathic pain. However, many analgesics are ineffective at treating the neuropathic pain in cancer patients. Hence it is crucial to provide effective pain treatment. Thus, evidence-based guidelines are to be followed 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 meta-analysis.^[18]

NEUPSIGquestionarie:

It contains SIX YES/NO type questions regarding:'

1. Whether the drugs were prescribed according to guidelines.
2. Whether the prescription contained drugs not mentioned in the guidelines.
3. Whether appropriated dose.
4. Whether appropriated frequency.
5. Whether appropriated duration.
6. Whether appropriated dosage.

The total score of the questionnaire was 6

- complete adherence -6
- Partial adherence 3-5
- Poor adherence ≤ 2

The recommendations were updated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).^[1] The authors developed a therapy strategy based on GRADE after examining the trial results for commonly used neuropathic pain medications. They are: As first-line therapy, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, pregabalin, and gabapentin are used, as Second-line treatments include lidocaine patches, capsaicin high-concentration patches, and tramadol; as Third-line treatments include strong opioids and botulinum toxin A as they have weak GRADE rating for use due to safety concerns of Opioids or lack of evidence in the use of Botulinum toxin A. Patients requiring larger dosages of strong opioids need to be closely monitored.^[14,15]

For patients who are refractory to modest dosages of additional monotherapy, a combination of pregabalin or gabapentin with duloxetine or tricyclic antidepressants may be a better option than increasing solo doses.^[13,14]

Though there are a set of guidelines for treatment of neuropathic pain in cancer patients, the effective outcome from the patients was not achieved from the patients and one of the major barrier for poor outcome is improper prescribing patterns.^[22] Hence, this study was done to assess the drug prescribing patterns and physician adherence to the revised NeuPSIG guideline for neuropathic pain.

OBJECTIVE: The primary objective of the study is to evaluate various patterns of drugs prescribed to manage the neuropathic pain in cancer patients during the course of chemotherapy. The Secondary objective is to check the rate of adherence of prescriptions to NeuPSIG guidelines.

METHODOLOGY

STUDY SITE: The study was conducted in a tertiary care hospital in Guntur, Andhra Pradesh for a period of six months.

STUDY DESIGN: This is an observational study where patients who presented to the pain and palliative care department of the hospital with CRNP were prospectively recruited. Participants were screened for neuropathic pain using DN4 questionnaire. Demographics details, diagnosis, medication details, and adherence to NeuPSIG guidelines were assessed using a validated questionnaires.

STUDY CRITERIA:

INCLUSION CRITERIA: Age >18 years. Experiencing neuropathic pain and screened using DN4 neuropathic pain diagnostic questionnaire with score ≥ 4 were included in the study.

EXCLUSION CRITERIA: Age greater than 80 years. Patients with an established diagnosis of neurogenic pain associated with localized peripheral neuropathies (eg: Post herpetic neuralgia, diabetic neuropathy, and post surgical/traumatic neuropathic pain)

MATERIALS AND METHODS:

- Those subjects whose inclusion criteria is satisfied will be enrolled into the study.
- Relevant data such as demographic details like age, gender, past & present medical history and medication history, pain regimen including drug name, brand name, dose, route, frequency, duration of therapy will be collected from medical records of the patients and by patient interview when ever required and are recorded, documented.
- Prescriptions were analyzed whether medication prescribed was according to the NeuPSIG guidelines. Adherence of physician to the NeuPSIG guidelines were analysed based on the validated questionnaire.
- Those subjects whose inclusion criteria is satisfied will be enrolled into the study.
- Relevant data such as demographic details like age, gender, past & present medical history and medication history, pain regimen including drug name, brand name, dose, route, frequency, duration of therapy will be collected from medical records of the patients and by patient interview when ever required and are recorded, documented.
- Prescriptions were analyzed whether medication prescribed was according to the NeuPSIG guidelines. Adherence of physician to the NeuPSIG guidelines were analysed based on the validated questionnaire

SOURCES OF DATA:

All the relevant and necessary data was collected from

1. Treatment charts, pharmacy records.
2. Interviewing the patient and patient care takers.
3. Interviewing nurse, Physician.
4. Follow up for 15 days, 1 month and 2 months period.

STATISTICAL ANALYSIS: All the raw data was collected, entered in Excel sheet 2007 in windows 10 version, the statistical analysis was done in SPSS 16.0 Software by an appropriate statistical methods.

RESULTS:

FIGURE 1: AGE DISTRIBUTION OF THE PATIENTS FROM THE STUDY:

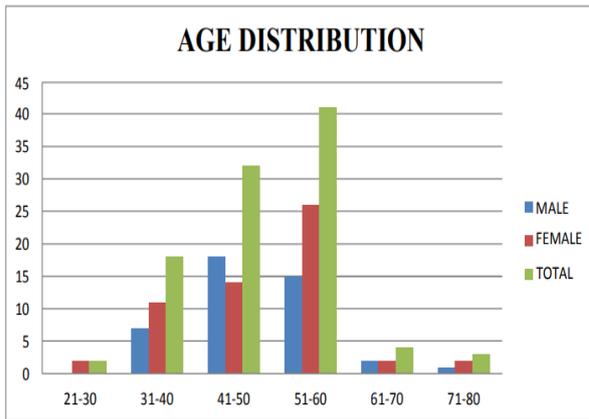


FIGURE 2: GENDER DIFFERENTIATION

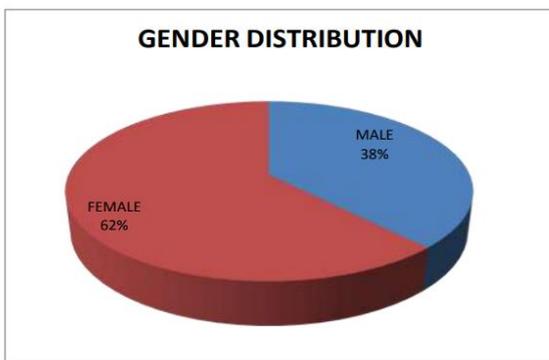


Figure 3: CO-MORBIDITIES:

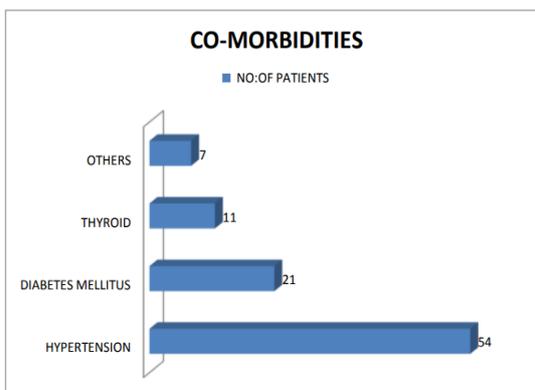


FIGURE 4: BMI CATEGORIZATION

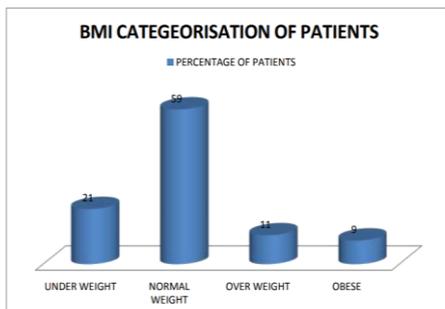


Figure 5: Social History

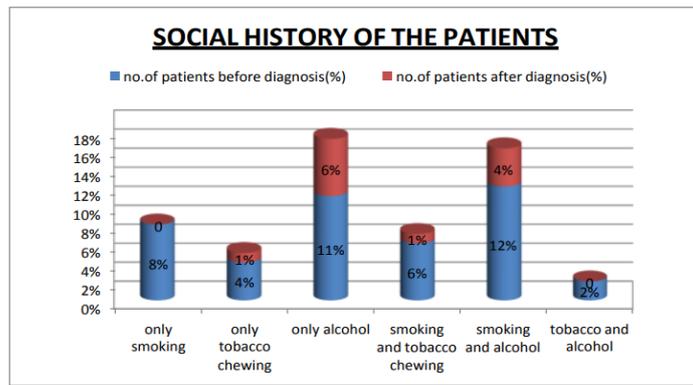


Figure: 6 Diagnosis Of The Patients From The Study.

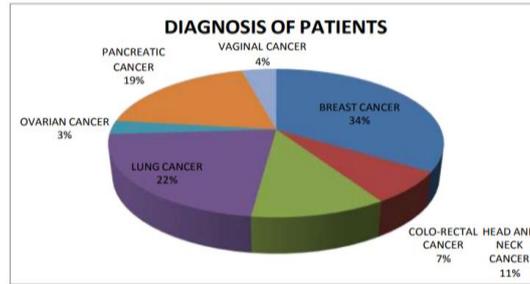


Figure7: Assessing Pain Using Vas (Visual Analogue Scale).

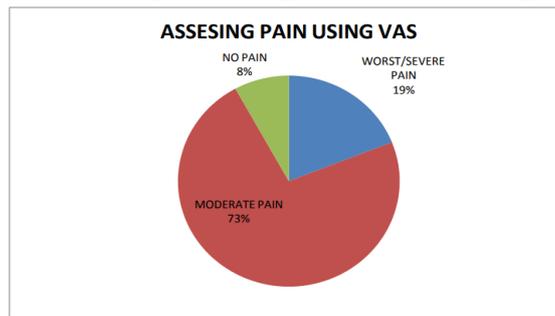


Figure 8: Assessing Neuropatic Pain Using DN4 Questionnaire.

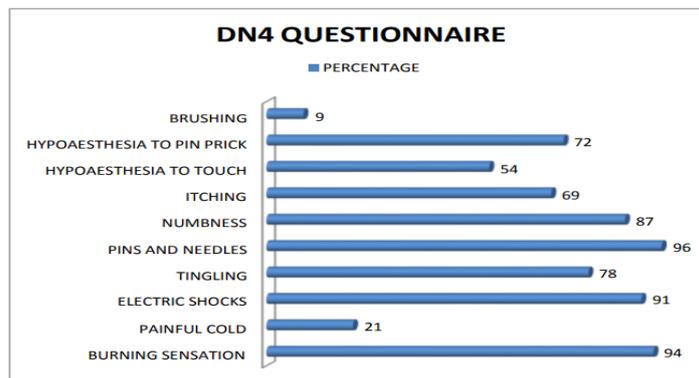


Figure 9 Assessing Pain Patterns

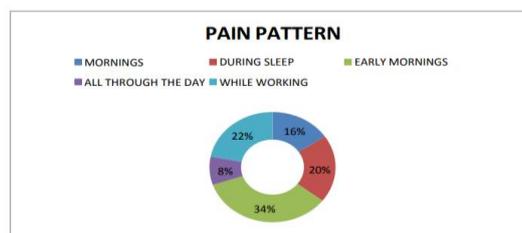


Table 5.1 Quality Of Life:

Percentage affecting	General activity	Mood	Normal work	Relation ship	Sleep	Enjoyment of life
0-10%	5	4	12	21	7	11
11-20%	10	8	10	19	8	15
21-30%	13	17	8	18	6	14
31-40%	14	14	16	14	8	16
41-50%	12	11	19	6	10	13
51-60%	18	17	15	5	14	9
61-70%	13	13	4	9	17	10
71-80%	8	9	7	6	19	8
81-90%	5	6	5	2	8	3
91-100%	2	1	4	0	3	1

TABLE 5.2: ADHERENCE TO GUIDELINES.

S.NO	Questionnaire	YES	% of yes	NO	% of no
1.	Whether drugs are prescribed according to guidelines	88	88%	12	12%
2.	Whether the prescription contained drugs not mentioned in the guidelines	1	1%	99	99%
3.	Whether appropriate dose of drugs is mentioned in the prescription	86	86%	14	14%
4.	Whether appropriate frequency of drugs mentioned in the prescription	84	84%	16	16%
5.	Whether appropriate duration of drug regimen mentioned in the prescription	71	71%	29	29%
6.	Whether appropriate dosage form of drug mentioned in the prescription	86	86%	14	14%

Table 5.3 CATEGORISING THE ADHERENCE OF PRESCRIPTIONS TO THE GUIDELINES.

Adherence	Number of prescriptions	Percentage
Complete adherence	51	51%
Partial adherence	49	49%
Poor adherence	0	0%

DISCUSSION:

The current study was to assess the prescription patterns of drugs used in treatment of neuropathic pain and adherence to NeuPSIG guidelines in cancer palliative care patients. Initially 117 patients were enrolled in the study among them, 17 were excluded since they do not meet the required DN4 criteria and the final sample size was 100 patients. These patients were assessed for the severity of pain using VAS and the neuropathic pain was assessed with the help of DN4 criteria. Questionnaire regarding the range of effect and interference of pain in their quality of life were framed accordingly and the response from the patients was collected. The results of the study shows that most of the patients fall under the age group of 41-50years followed by 51-60years, 31-40years, 61-70years respectively and the gender distribution shows females majorly by 56% followed by males with 44%. The co-morbid status implicates that most of the patients were hypertensive followed by diabetes mellitus, thyroid disorders and very few with other conditions like PCOS and COPD. The BMI categorisation implicates that most of the patients were of normal weight (59%) and 25% with underweight, 11% with overweight and least 9% were obese. BMI plays a major role because cancer cachexia is the major affect seen in cancer patients. The social history of the patients illustrates that 8% have the habit of smoking, 4% with the habit of tobacco chewing, 11% with alcohol consumption, 6% with both smoking and tobacco chewing, 12% with smoking and alcohol consumption, 2% with tobacco and alcohol consumption.

The diagnostic criteria illustrates that most of the patients from the study were diagnosed with breast cancer followed by lung cancer, pancreatic cancer, head and neck cancers, colo-rectal cancer, vaginal cancer, ovarian cancer respectively and the chemotherapeutic regimens for these types of cancers are epirubicin and cyclophosphamide combination, adriamycin and cyclophosphamide combination, paclitaxel or docetaxel alone for breast cancer; CAPOX (capecitabine + oxaliplatin), FOLFOX (5-fluoro uracil+leucovorin+oxaliplatin) for colo-rectal cancers; pemetrexed and carboplatin combination for adeno carcinomas lung cancer; paclitaxel and carboplatin for squamous cell carcinomas lung cancer, head and neck cancers, ovarian cancer and vaginal cancer; gemcitabine and oxaliplatin combination; gemcitabine and carboplatin combination; leucovorin, 5fluorouracil, oxaliplatin, irinotecan combination for pancreatic cancer. The severity of the pain was assessed using VAS and the results illustrates that most patients suffer with moderate pain followed by worst/severe pain and then moderate pain respectively.

The neuropathic pain was assessed using the DN4 criteria. This contains 10 yes or no type questionnaires and the responses of the patients were burning sensation by 94% patients, painful old by 21% patients, electric shock by 91%, tingling by 78%, pins and needles by 96%, numbness by 87%, itching by 69%, hypoesthesia to touch by 54%, hypoesthesia to pin prick by 72% and finally brushing by 9% patients. The pain patterns of the patients interprets that most of the patients observed pain in early mornings followed by pain while working, at nights during sleep, in the mornings and then all through the day respectively. Various parameters were considered to assess the quality of life of patients and the patients response

enumerates that their general activity was interrupted by the pain to the range of 20- 70%, normal work upto 50%, relationship status of 40%, sleep of 40-80% and enjoyment of life to the range of 50%. These results interpret that the pain interferes the quality of life almost to the range of 50% on an average. It was also illustrated from the results that the prescription patterns of the drugs prescribed to the patients were mostly the oral dosage forms of gabapentin, pregabalin, tricyclic antidepressants (duloxetine, amitriptyline) alone or gabapentin in combination with tricyclic antidepressants which are first line drugs, a second line drug Tramadol and third line drugs namely buprenorphine in the form of transdermal patches, morphine as injectables.

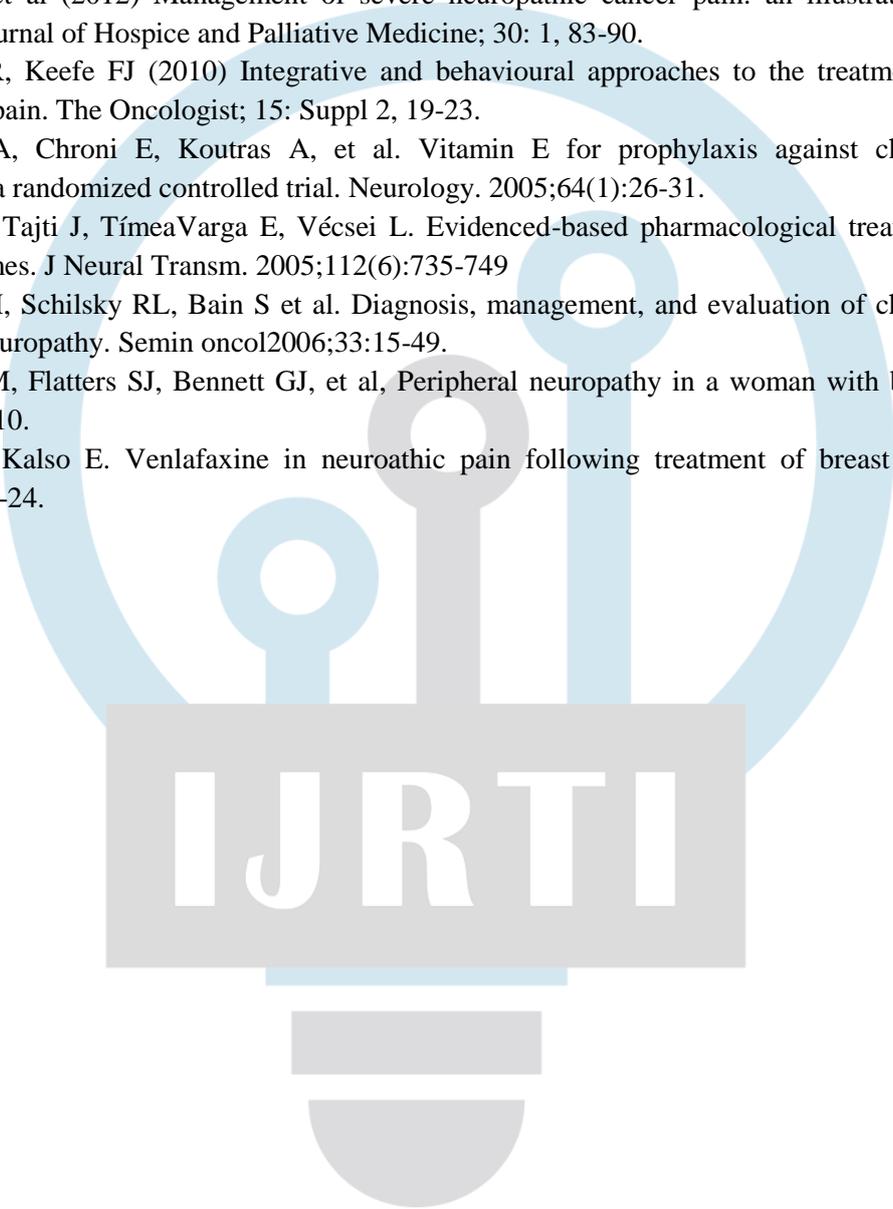
Among the prescriptions, second line drugs tramadol was equally prescribed. This may be due to the involvement of third party payers or due to its cost effectiveness. The adherence of the prescriptions to NeuPSIG guidelines were assessed by using six yes or no questionnaire and the analysis of prescriptions analyse that 88% of the drugs were prescribed according to the guidelines. In 86% of prescriptions the drugs were prescribed along with the doses. In 84% of prescriptions frequency of drugs was mentioned, 71% of prescriptions contain the duration of therapy to be used, and in 86% of prescription the dosage form of the drug was mentioned. Thus, it is analysed that 51% of the prescriptions shows complete adherence, 41% with partial adherence and none with poor adherence.

CONCLUSION: Both the first line drugs namely gabapentin, pregabalin, duloxetine and tricyclic anti-depressants and second line drugs agents tramadol and acetaminophen were equally prescribed in the study without the consideration of the severity of the pain. This might be due to the interference of the third party payer and due to cost effectiveness of second line agents. On assessing the prescriptions, it was observed that 51% of the prescriptions were completely adhered to the guidelines, 49% with partial adherence and none with poor adherence. Thus, the prescriptions of the patients with CINP by the physicians were adhered to NeuPSIG guidelines in cancer palliative care patients.

BIBLIOGRAPHY

1. IASP taxonomy 2012. <http://www.iasp-pain.org/Education/content.aspx?ItemNumber=1698&navItemNumber=576> (accessed June 24, 2014).
2. Langley PC, Van Litsenberg C, Cappelleri JC, Carroll D. The burden associated with neuropathic pain in Western Europe. *J Med Econ* 2013; 16: 85–95.
3. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9: 807–19.
4. Merskey H, Bogduk N. Classification of Chronic pain, Second Edition. Seattle, WA: International Association for the Study of Pain (IASP) Press, 1994:1–240.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines for Adult Cancer Pain (v. 1.2009). Available at http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf, accessed February 19, 2010.
6. Urch CE, Dickenson AH. Neuropathic pain in cancer. *Eur J Cancer* 2008; 44:1091–1096. Torrance N, Ferguson JA, Afolabi E, et al. Neuropathic pain in the community: more under-treated than refractory? *Pain* 2013; 154: 690–99.
7. Turk DC, Okifuji A. Chapter 2: Pain terms and taxonomies of pain. In: Loeser JD, Butler SH, Chapman CR et al, eds. *Bonica's Management of Pain*, Third Edition. Philadelphia: Lippincott Williams & Wilkins, 2001: 17–25.
8. Foley KM, Gelband H, eds. *Improving Palliative Care for Cancer*. Institute of Medicine Report. Washington, DC: National Academies Press, 2001: 1–344.
9. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; 17: 1113–e88.
10. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010; 150: 573–81
11. Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhyay SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care* 2012; 29: 177–82
12. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012; 13: e58–68
13. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol* 2011; 72: 735–44
14. Rice AS. Should cannabinoids be used as analgesics for neuropathic pain?. *Nat Clin Pract Neurol* 2008; 4: 654–55

15. AcharA, ChatterjeeRayTG, NaskarB. Comparative study of clinical efficacy with amitriptyline, pregabalin, and amitriptyline plus pregabalin combination in postherpetic neuralgia. *Indian J Dermatol Venereol Leprol* 2010; 76:63–5
16. Gilron I, Max MB. Combination pharmacotherapy for neuropathic pain: current evidence and future directions. *Expert Rev Neurother* 2005; 5: 823–30
17. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* 2012; 85: S3–14
18. Gilron I et al, (2015) Neuropathic pain: principles of diagnosis and treatment. *Mayo Clinic Proceedings*; 90: 4, 532-545.
19. Connolly I et al (2012) Management of severe neuropathic cancer pain: an illustrated case and review. *American Journal of Hospice and Palliative Medicine*; 30: 1, 83-90.
20. Cassileth BR, Keefe FJ (2010) Integrative and behavioural approaches to the treatment of cancer-related neuropathic pain. *The Oncologist*; 15: Suppl 2, 19-23.
21. Argyriou AA, Chroni E, Koutras A, et al. Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology*. 2005;64(1):26-31.
22. Beniczky S, Tajti J, TímeaVarga E, Vécsei L. Evidenced-based pharmacological treatment of neuropathic pain syndromes. *J Neural Transm*. 2005;112(6):735-749
23. Hausheer FH, Schilsky RL, Bain S et al. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. *Semin oncol*2006;33:15-49.
24. Cianfrocca M, Flatters SJ, Bennett GJ, et al, Peripheral neuropathy in a woman with breast cancer. *J pain*. 2006;7(1):2-10.
25. Tasmuth T, Kalso E. Venlafaxine in neuroathic pain following treatment of breast cancer. *Eur J Pain*. 2002;6(1):17-24.

A large, light blue watermark logo is centered on the page. It features a stylized lightbulb shape with a circular top and a semi-circular base. Inside the circle, there are three vertical lines of varying heights, each ending in a small circle. Below the circle is a grey rectangular box containing the text 'IJRTI' in white, bold, sans-serif capital letters. Below the box is another grey rectangular box, and at the bottom is a grey semi-circle.

IJRTI