National Essential Medicine List
Tertiary Medication Review Process
Component: N03AX (α2δ calcium channel ligands)

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: August 2019
Medicine (INN): α2δ calcium channel ligands
Medicine (ATC): N03AX12 and N03AX16
Indication (ICD10 code): G62/M79.2
Patient population: Patients with peripheral neuropathy refractory or intolerant to standard of care (e.g. amitriptyline; or carbamazepine)
Prevalence of condition: 5 to 2 400 per 10 000 population in different community studies[1]
Level of Care: Tertiary
Prescriber Level: Specialist
Current standard of Care: Amitriptyline and/or carbamazepine
Efficacy estimates:

- Diabetic peripheral neuropathy: gabapentin and amitriptyline not shown to be significantly different with regard to pain scores. Mean difference in pain intensity scores favored amitriptyline by 0.091 unit (05% CI, -0.074 to 0.256; p = 0.26).[2]
- Post-herpetic neuralgia: gabapentin and nortriptyline shown to be equally efficacious, reduction in pain scores 42.8% and 47.6% respectively.[3]
- Drug-induced Peripheral Neuropathy there was significant decrease in pain score in pregabalin group as compared to the other groups; amitriptyline group (p = 0.003), gabapentin group (p = 0.042), and placebo group (p = 0.024).[4]

Motivator/reviewer name(s): Tertiary Committee

2. **Name of author(s)/motivator(s):** Tertiary Committee, lead reviewer: Prof Schellack.

3. **Author affiliation and conflict of interest details:** Professor and Acting Head of the Division for Clinical Pharmacy in the School of Pharmacy, Sefako Makgatho Health Sciences University.
No conflicts of interest pertaining to this review.

4. **Introduction/ Background**

Neuropathic pain is a difficult to manage condition that often does not respond to conventional analgesics. Amitriptyline, a tricyclic antidepressant (TCAs), is recommended on the South African Essential Medicines List (EML) as first-line treatment for the management of neuropathic pain, with carbamazepine recommended as an alternative or add on in cases of intolerance or sub-optimal responses.

There is however no alternative agent for patients' who are refractory, intolerant or have sub-optimal responses to either amitriptyline or carbamazepine; or their combination.

The World Health Organisation (WHO) Model List of Essential Medicines recommends amitriptyline as a first-line treatment option together with other TCAs and serotonin and norepinephrine reuptake inhibitor (SNRIs).[1-5] However, the combined use of TCAs and SNRIs are contraindicated, preventing the combinations of these drugs in patients who did not respond adequately to monotherapy (WHO). [5-10]

Gabapentin and pregabalin are both α2δ calcium channel ligands. They can be used as monotherapy or in combination with other classes of medications. The combination therapy has proven to be effective in the management of neuropathic pain. The combinations also have complementary actions and has the potential to enhance efficacy and reduce side effects (through lower dosing of the individual agents). [10-13]

Thus, the ability to use α2δ calcium channel ligands together with the other classes of evidence-based pharmacological therapies, provides clinicians with the scope at tertiary level to manage these resistant patients.[1-13]

5. **Purpose/Objective i.e. PICO question**

-P *(patient/population): Neuropathic pain in patients that are refractory or intolerant to amitriptyline/carbamazepine*
-I *(intervention): Gabapentin/pregabalin*
-C *(comparator): Amitriptyline/Carbamazepine*
-O *(outcome): mean daily pain at maximum tolerated dose*

6. **Methods:**
   a. **Data sources** Pubmed, Google Scholar, Cochrane Library
   b. **Search strategy**
      Studies pertaining to peripheral neuropathy, with gabapentin AND/OR pregabalin as both α2δ calcium channel ligands, refractory to amitriptyline, neuralgia. The primary outcomes had to relate to either gabapentin use, in refractory to treatment in neuralgia, combination therapy for the treatment of neuropathies, treatment failure of first line therapy (amitriptyline/carbamazepine) as it pertains to the treatment of peripheral neuropathy.
      The following search terms were used: gabapentin, pregabalin, amitriptyline, neuralgia, neuropathy, combination therapy in neuralgia, α2δ calcium channel ligands, chemotherapy induced neuropathy, and HIV induced neuropathy with studies limited to English language.

   c. **Excluded studies:**
      Review articles and retrospective papers were excluded.

   d. **Evidence synthesis**
      When comparing head to head for efficacy, the evidence relied mainly on three head-to-head randomized clinical trials (RCTs) comparing α2δ calcium channel ligands to tricyclic antidepressants (also included in Chou et.al meta-analysis).[2,3,5] However, one of these trials, clearly identified as “an open-label pilot study,” as blinding was an issue.[5] Bias for gabapentin might have been influenced in the only trial that showed a better (85 %) response to gabapentin vs tricyclics. However, this review focused on RCTs where α2δ calcium channel

ligands as second- or third-line agents or in combination therapy for patients with neuropathy refractory or intolerant to first line agents.

Randomised controlled trials

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Morello CM 1999[2]	Prospective, Randomised, Double blinded, double-dummy, crossover study	25	Diabetic peripheral neuropathy with stable glycaemic control	Gabapentin 900 – 1800mg/day Or Amitriptyline 25-75mg/day (1-week washout)	Pain relief (pain scale, and global pain score)	Mean difference in pain intensity scores favored amitriptyline by 0.091 unit (05% CI, -0.074 to 0.256; p = 0.26) no significant difference Global pain score data, pain relief in 52% of patients on gabapentin, and 67% of patients on amitriptyline (p=0.35)	• Small study introduces probability of type II β error. • Only patients with well controlled diabetes mellitus included.
Chandra K, et. al. 2006[3]	Randomised, double-blind, parallel-group trial	70	Adults with post-herpetic neuralgia	Gabapentin Versus Nortriptyline	Change in pain score from baseline to end of study (Likert scale)	Pain scores changed in both groups, 47.6% in nortriptyline group and 42.8% in gabapentin group	
Mishra S, et.al. 2012[4]	Prospective randomized double-blind placebo-controlled study	120	Patients with cancer experiencing severe neuropathic cancer pain	Amitriptyline, or gabapentin, or pregabalin or placebo	Pain scores (visual analogue scale)	Significant decrease in pain score in group pregabalin group as compared to the other groups; amitriptyline group (P = .003), gabapentin group (P = .042), and placebo group (P = .024)	All patients in placebo group needed morphine rescue

e. Evidence quality: Morrello et.al. and Chandra et.al. trials were not adequately powered to detect differences between the active treatment arms. Neither trial included a placebo comparison to ensure assay sensitivity.[3,4] However the trials could detect statistically significant differences in pain when gabapentin is used in combination with an adjunct therapy e.g. nortriptyline or morphine for refractory neuralgia.

Meta-analysis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Chou R, et. al. 2009[6]	Meta-analysis	18 Studies: • 3 head to head trials (n=120) • 6 placebo-controlled trials (Gabapentin) (median n=112) • 9 placebo-controlled trials TCAs (median n=26)	Adults with diabetic neuropathy and/or postherpetic neuralgia	Amitriptyline, gabapentin, placebo	Achieving pain relief	Head to head trial: no difference between gabapentin and amitriptyline in achieving pain relief (RR=0.99, 95% CI 0.76-1.29) Adjusted indirect analysis: gabapentin less successful in achieving pain relief compared to TCAs (RR=0.41, 95% CI 0.23-0.74, p=0.008).	• Composite dichotomous measure for pain relief used • Clinical diversity found in trials such as type of neuropathic pain and doses of drug

Meta-analysis

In the meta-analysis above; Chou and colleagues have also over-represented the response rate to gabapentin in one of the trials. They report that 17 of 19 patients treated with gabapentin achieved a good analgesic response, but the published report of this trial indicates that there were 19 gabapentin-treated patients in the first crossover period.[7] There were a total of 40 gabapentin-treated patients, so the true response rate to gabapentin in the trial was 17/40 (43% rather than 90%).

Unpublished data

It appears there is unpublished head to head data with the use α2δ calcium channel ligands and amitriptyline in patients with neuropathy:[8]

- A multi-center double-blind randomized controlled trial evaluating gabapentin in patients (325 patients), with painful diabetic neuropathy is known to have remained unpublished. In this trial the highest dosage studied (2400 mg/day) failed to show a better analgesic response for gabapentin (30%) than for placebo (25%, $P > 0.05$).[9] Another unpublished double-blind parallel group randomized controlled trial comparing amitriptyline to pregabalin and to placebo in 254 patients with painful diabetic neuropathy showed a higher response rate for amitriptyline (47%) than for pregabalin (40%) or placebo (30%, $P < 0.05$ for placebo comparison with amitriptyline but $P > 0.05$ for placebo comparison with pregabalin; no comparison between amitriptyline and pregabalin is provided).[10]

7. **Alternative agents:** amitriptyline, carbamazepine
8. **Safety Concern**

   A population based study[22] has identified possible association between antiepileptic's (including gabapentinoids) and suicidal behavior. It is recommended that closer observation and caution must be taken in the following risk populations: those with an underlying psychiatric disorders, young individuals (< 24 years), and those abusing substances including cannabis.
9. **Costs**

Drug	Dose	Strengths	Units in a package	Price per pack	Price per tablet	Cost/month	
Amitriptyline	Initially 25mg at night.	25mg	28	R4.16	R0.15	At 25 mg/day:	R4.16
	Increase dose at two weekly intervals to a maximum of 75mg at night.					At 75 mg/day:	R12.48
Carbamazepine	initially 100 mg twice daily	200mg	56	R18.44	R0.33	At 200 mg/day	R9.22
	Usual maintenance: 600 mg/day					At 600 mg/day	R27.66
	Increased over by 100mg/week to maximum of 1200mg					At 1200 mg/day	R55.32
Pregabalin	Initially 75 mg 12 hourly	75mg	56	R69.99	R1.25	At 150 mg/day	R69.99
	Maintenance 150 mg 12 hourly					At 300 mg/day	R139.98
Gabapentin	Initially 300mg per day, increasing dose with 300mg per day until 900mg (8 hourly) is reached.	100mg	100	R45.50	R0.46	At 900 mg/day	R114.66
	Usual dose: 900 mg/day						
	Usual dose maximum: 1800 mg/day					At 1800 mg/day	R229.32
	Maximum 3600 mg/day					At 3600 mg/day	R458.64

10. **Summary:**

Patients with peripheral neuropathy typically do not respond to traditional analgesics (paracetamol, NSAIDs) or weak opioids. Furthermore, many patients do not achieve satisfactory pain relief with tricyclic antidepressants and/or carbamazepine; or do not tolerate effective doses due tof adverse effects. The following deductions were made from the evidence:

a. Head-to-head trials favour TCAs, however there does not seem to be enough studies to conduct a meaningful meta-analysis. Indirect meta-analysis favours tricyclics through a broad range of sensitivity analyses, and inclusion of the unpublished trial data may tilt the balance further in favour of tricyclics. More head-to-head RCTS are needed. Until there are adequately powered and designed head-to-head double-blind RCTs, the best relative ranking of efficacy seems to come from the indirect meta-analyses.

b. For combination therapy – In patients who show a partial response to either gabapentin/pregabalin or nortriptyline with diabetic polyneuropathy or postherpetic neuralgia, combined gabapentin/pregabalin and a TCA seems to be more efficacious than either drug given alone.

c. The difference in responses shown by different antiepileptic drugs depends on the aetiology of the underlying mechanisms in neuropathic pain.

d. It is worth noting that gabapentin/pregabalin was no better than placebo in two studies of HIV-neuropathy and that carbamazepine is likely to have interactions with antiretroviral agents. Thus amitriptyline would be the primary treatment option in these patients.

e. Combination of the α2δ calcium channel ligands for drug-induced neuropathy, has shown superiority.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [x] Not confident [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [x] No [ ]</td><td>List the members of the group.
• Gabapentin
• Pregabalin</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)/month
maintenance therapy</th></tr><tr><td>Amitriptyline</td><td>R12.48</td></tr><tr><td>Carbamazepine</td><td>R27.66</td></tr><tr><td>Pregabalin</td><td>R139.98</td></tr><tr><td>Gabapentin</td><td>R229.32</td></tr></table></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [ ] Uncertain [X]</td><td></td></tr>
</table>

FEASIBILITY	Is the implementation of this recommendation feasible? Yes [X] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	**X**

Tertiary Recommendations

It is recommended that α2δ Calcium channel ligands be included on the Essential Medicines List as an option in patient who may be refractory or resistant to standard of care (amitriptyline or carbamazepine). These agents may be used in combination with other therapies, should monotherapy fail. Refer to figure 1: treatment protocol.

These agents may be used in the following settings:

1. The use of combination therapy with a α2δ calcium channel ligands with a tricyclic antidepressant.
2. As single stand-alone therapy for refractory neuropathic pain not responding to a tricyclic antidepressant at maximum dose.
3. As third-line treatment for painful diabetic peripheral neuropathy post-herpetic neuropathy.
4. For drug-induced painful neuropathy in patients refractory or intolerant to amitriptyline and/or carbamazepine.

Note: *That α2δ calcium channel ligands should not be approved for HIV-associated painful neuropathy as the available evidence shows that it is not superior to placebo.*

Rationale:

In patients with refractory pain compared with alone therapy a better response to pain was achieved with the use of combination therapy.

Level of Evidence: I and II

NEMLC Recommendation – Meeting 30 January 2020

NEMLC **did not accept the inclusion of gabapentin and pregabalin** onto the Essential Medicines List for the management of refractory or resistant neuropathic pain, or patient intolerant to standard therapy. NEMLC recommended that this agent should be managed as a named-patient basis, with motivations being managed by Provincial Pharmaceutical and Therapeutics Committees.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	X

VEN status:

Vital	Essential	Necessary
	X	

References

[1] Trivendi S, Pandit A, Das SK. Epidemiology of peripheral neuropathy: An Indian Perspective. Ann Indian Acad Neurol. 2017, 20 (3): 173-184.

[2] Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med. 1999; 15916:1931–7.

[3] Chandra K, Shafiq N, Pandhi P, Gupta S, Malhotra S. Gabapentin versus nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial—the GONIP trial. Int J Clin Pharm Ther. 2006;44:358–63.

[4] Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhya 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 May;29(3):177-82. doi: 10.1177/1049909111412539. Epub 2011 Jul 10.

[5] Dallocchio C, Buffa C, Mazzarella P, Chiroli S. Gabapentin vs amitriptyline in painful diabetic neuropathy: an open label pilot study. J Pain Symptom Manage. 2000, 20:280-285.

[5]Chou R, Carson S, Chan BKS. Gabapentin versus tricyclic antidepressants for diabetic neuropathy and post-herpetic neuralgia: discrepancies between direct and indirect meta-analyses of randomized controlled trials. J Gen Intern Med. 2009;24:178–88.

[6]Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentinin the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry. 1999;662:251–2.

[7]Steinman MA, Bero LA, Chren MM, Landefield CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. Ann Intern Med. 2006; 145:284–93.

[8]Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther. 2003; 251:81–104.

[9]Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentinin the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry. 1999;662:251–2.

[10] Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet. 2009; 374: 1252–61

[11] Finnerup NB, Sindrup SH, Jensen TS (2010) The evidence for pharmacological treatment of neuropathic pain. Pain 150: 573–581.

[12] Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, et al. (2007) Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 132: 237–251.

[13] Tan T, Barry P, Reken S, Baker M, Guideline Development Group (2010) Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. BMJ 340: c1079.

[14] Smyth K, Affandi JS, McArthur JC, Bowtell-Harris C, Mijch AM, et al. Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia 1993–2006. HIV Med. 2007;8:367–373. [PubMed] [Google Scholar]

[15]Lipkin WI, Parry G, Kiprov D, Abrams D. Inflammatory neuropathy in homosexual men with lymphadenopathy. Neurology. 1985;35:1479–1483. [PubMed] [Google Scholar]

[16]Barohn R, Gronseth G, Leforce B, McVey A, McGuire A, et al. Peripheral nerve involvement in a large cohort of human immunodeficiency virus-infected individuals. Arch Neurol. 1993;50:167–171. [PubMed] [Google Scholar]

[17]Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, et al. (2004) A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. J Neurol 251: 1260–1266.

[18]La Spina I, Porazzi D, Maggiolo F, Bottura P, Suter F. Gabapentin in painful HIV-related neuropathy: a report of 19 patients, preliminary observations. Eur J Neurol. 2001;8:71–75. [PubMed] [Google Scholar]

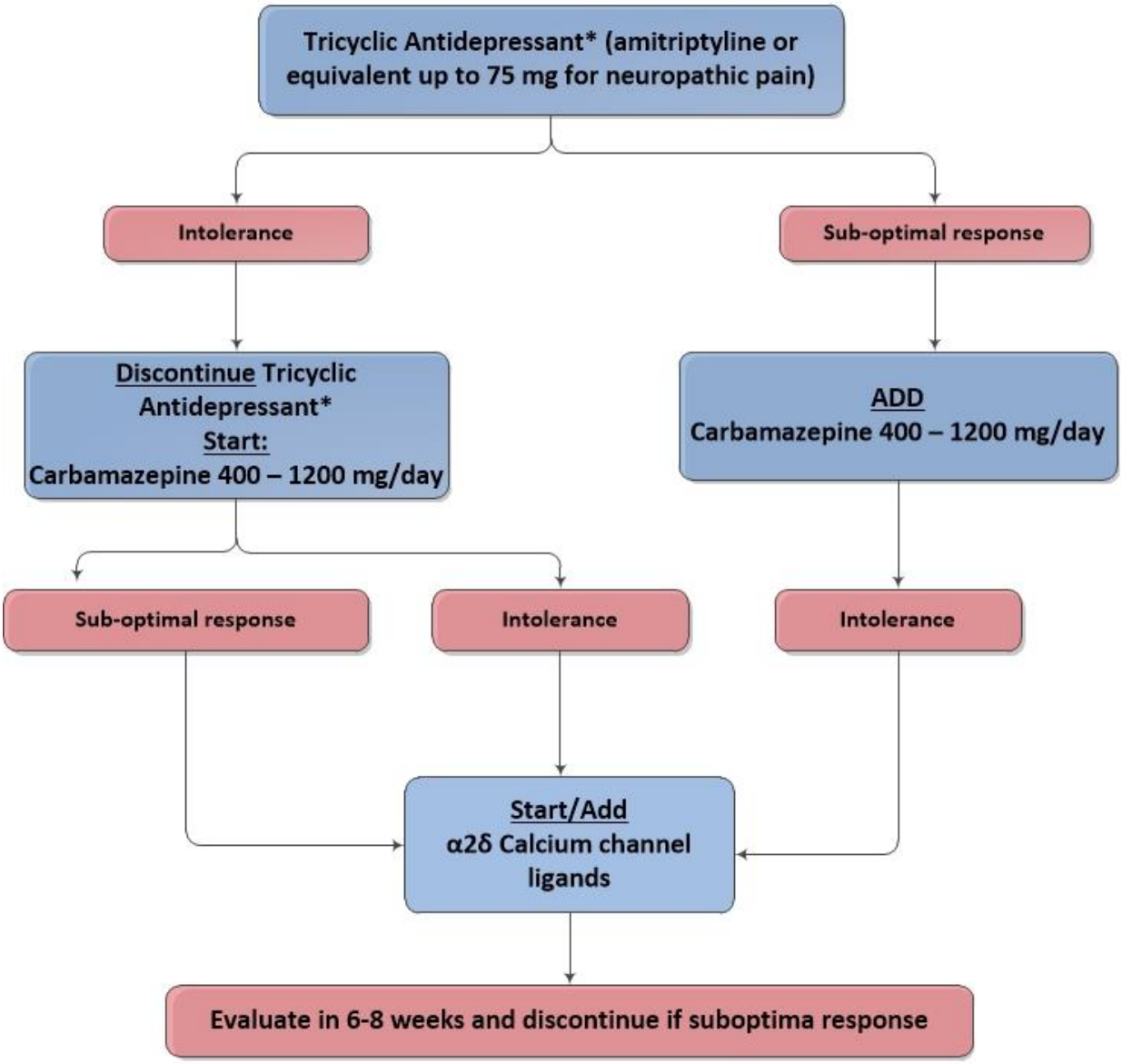
[19]Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, et al. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology. 2010;74:413–420. [PMC free article] [PubMed] [Google Scholar]

[20] Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, Warner DO, Novotny P, Kutteh LA, Wong GY. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3) Cancer. 2007;110:2110–2118. doi:10.1002/cncr.23008. [PubMed] [Google Scholar]

[21]Aghili M, Zare M, Mousavi N, Ghalehtaki R, Sotoudeh S, Kalaghchi B, Akrami S, Esmati E Breast J. Efficacy of gabapentin for the prevention of paclitaxel induced peripheral neuropathy: A randomized placebo controlled clinical trial. 2019;25(2):226. Epub 2019

[22] Molero Y, Larsson H, D'Onofrio BMD, Sharp DJ, Fazel S. Associations between gabapentiods and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents and violent crime: population based cohort study in Sweden. BMJ, 2019, 365:1214.

Figure 1: Neuropathic pain – Treatment protocol



- *Opioid should not be used in combination with Tricyclic Antidepressant
- The doses of medicines whenever used in the protocol need to be titrated slowly upwards, over several weeks to ensure efficacy and reduce side effects