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Pharmacological treatment of central neuropathic pain: consensus of the Brazilian Academy of Neurology

Tratamento farmacológico da dor neuropática central: consenso da Academia Brasileira de Neurologia

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ABSTRACT

Background: Central neuropathic pain (CNP) is often refractory to available therapeutic strategies and there are few evidence-based treatment options. Many patients with neuropathic pain are not diagnosed or treated properly. Thus, consensus-based recommendations, adapted to the available drugs in the country, are necessary to guide clinical decisions. **Objective:** To develop recommendations for the treatment of CNP in Brazil. **Methods:** Systematic review, meta-analysis, and specialists opinions considering efficacy, adverse events profile, cost, and drug availability in public health. **Results:** Forty-four studies on CNP treatment were found, 20 were included in the qualitative analysis, and 15 in the quantitative analysis. Medications were classified as first-, second-, and third-line treatment based on systematic review, meta-analysis, and expert opinion. As first-line treatment, gabapentin, duloxetine, and tricyclic antidepressants were included. As second-line, venlafaxine, pregabalin for CND secondary to spinal cord injury, lamotrigine for CNP after stroke, and, in association with first-line drugs, weak opioids, in particular tramadol. For refractory patients, strong opioids (methadone and oxycodone), cannabidiol/delta-9-tetrahydrocannabinol, were classified as third-line of treatment, in combination with first or second-line drugs and, for central nervous system (CNS) in multiple sclerosis, dronabinol. **Conclusions:** Studies that address the treatment of CNS are scarce and heterogeneous, and a significant part of the recommendations is based on experts opinions. The CNP approach must be individualized, taking into account the availability of medication, the profile of adverse effects, including addiction risk, and patients' comorbidities.

Keywords: Pain; Pain management; Neuropathic pain; Drug therapy; Consensus.

RESUMO

Introdução: A dor neuropática central (DNC) é frequentemente refratária às estratégias terapêuticas disponíveis e há poucas opções de tratamento baseado em evidência. Muitos pacientes com dor neuropática não são diagnosticados ou tratados adequadamente. Desse modo, recomendações baseadas em consenso, adaptadas à disponibilidade de medicamentos no país, são necessárias para guiar decisões

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clínicas. **Objetivo:** Desenvolver recomendações para o tratamento da DNC no Brasil. **Métodos:** Revisão sistemática, metanálise e discussão dos resultados entre especialistas e pesquisadores da área, considerando eficácia, perfil de eventos adversos, custo e disponibilidade do fármaco na saúde pública. **Resultados:** Foram encontrados 44 estudos sobre tratamento da DNC, dos quais 20 foram incluídos na análise qualitativa e 15, na quantitativa. Classificaram-se as medicações em primeira, segunda e terceira linhas de tratamento, baseando-se em revisão sistemática, meta-análise e opinião de especialistas. Como primeira linha, foram incluídos gabapentina, duloxetina e antidepressivos tricíclicos. Como segunda, venlafaxina, pregabalina para DNC secundária à lesão medular, lamotrigina para DNC pós-acidente vascular cerebral e, em associação aos fármacos de primeira linha, opioides fracos, em particular tramadol. Para os pacientes refratários, opioides fortes (metadona e oxicodona) e canabidiol/delta-9-tetrahidrocanabinol foram classificados como terceira linha de tratamento, em associação com drogas de primeira ou segunda linha, e, para DNC na esclerose múltipla, dronabinol. **Conclusões:** Os estudos que abordam o tratamento da DNC são escassos e heterogêneos, e parte significativa das recomendações é baseada em opiniões de especialistas. A abordagem da DNC deve ser individualizada, levando em conta a disponibilidade de medicação, o perfil de efeitos adversos, incluindo risco de dependência e as comorbidades do paciente.

Palavras-chave: Dor; manejo da dor; dor neuropática central; tratamento farmacológico; consenso.

INTRODUCTION

Chronic pain is defined as pain in one or more anatomical regions that persists or recurs for longer than three months and is associated with significant emotional distress or functional disability[1]. It affects from 19 to 41% of the general population living in developing countries[2]. Neuropathic pain (NP) is defined as pain arising from lesion or disease to the somatosensory pathways[3]. Chronic pain with neuropathic characteristics affects from 6.9 to 10% of the worldwide general population[4], and it is present in 10 to 14.5% of the Brazilian population[5].

Central neuropathic pain (CNP) refers to neuropathic pain that results from a lesion or disease of the central somatosensory nervous system. The prevalence of CNP has been less frequently assessed in the general population, but it is estimated to affect a significant proportion of patients with different neurological diseases, such as 18% of stroke survivors who have somatosensory deficits[6], and 59% of those affected by spinal cord injury[7], and at least 30% of multiple sclerosis patients[8]. Despite its high prevalence, the heavy functional burden, and impact on the patients' quality of life, CNP is often misdiagnosed or neglected, even by specialists[9].

There is a paucity of guidelines and consensus to support the CNP management, which may lead not only to uncontrolled pain, but also to undesired side-effects due to inadequate prescription. Pharmacological treatment for CNP is generally accepted as the first treatment. However, despite the significant advances in pharmacotherapy in recent decades, complete relief from NP is rare[10]. The results of monotherapy approaches remain unsatisfactory[11], leading to the frequent association of drugs that are often not supported by evidence or recommendations. Furthermore, there are limitations of cost and access to several medications for NP treatment, including those classified as first-line therapy, and, especially, for the newest and most expensive drugs, in the Brazilian public health care system (*Sistema Único de Saúde* – SUS).

The response of non-pharmacological interventions to CNP such as neuromodulation approaches, despite newer recommendations, suffer from similar limitations, such as restricted evidence of efficacy in this type of pain, as well as cost-related issues[12].

With this in mind, and pressed by the need to propose pharmacological interventions that make sense in view of the current evidence, providing lower risks of side-effects and which are available for the general population, a consensus recommendation was conducted based on a systematic review and meta-analysis of the literature and also based on the opinion of experts when the evidence was conflicting or controversial. This consensus was headed by the Scientific Department on Pain of the Brazilian Academy of Neurology as part of its quadrennial mission.

METHODS

This study followed the Appraisal of Guidelines Research & Evaluation (AGREE) reporting checklist for the development of consensus papers[13]. Details on the methods can be found in supplementary material.

RESULTS AND DISCUSSION

Systematic review of the literature and formulation of the first recommendation

The initial search in the literature retrieved 219 studies, 33 of which were selected for full reading. Manual search identified 11 more, resulting in 44 studies (Figure 1). After full reading of those studies, only 20 were included in the qualitative analysis and 15 in the quantitative synthesis. The studies by Finnerup et al. (2002)[14], Jungehulsing et al. (2013)[15], Drewes et al. (1994)[16], and Vestergaard et al. (2001)[17] were excluded from quantitative synthesis because they did not present means and standard deviations as central and dispersion measures, making it imprecise to include them in the meta-analysis[18]. The study by Leijon et al. (1989)[19] was also excluded from the quantitative synthesis as, in addition to having presented mean and standard deviations as central

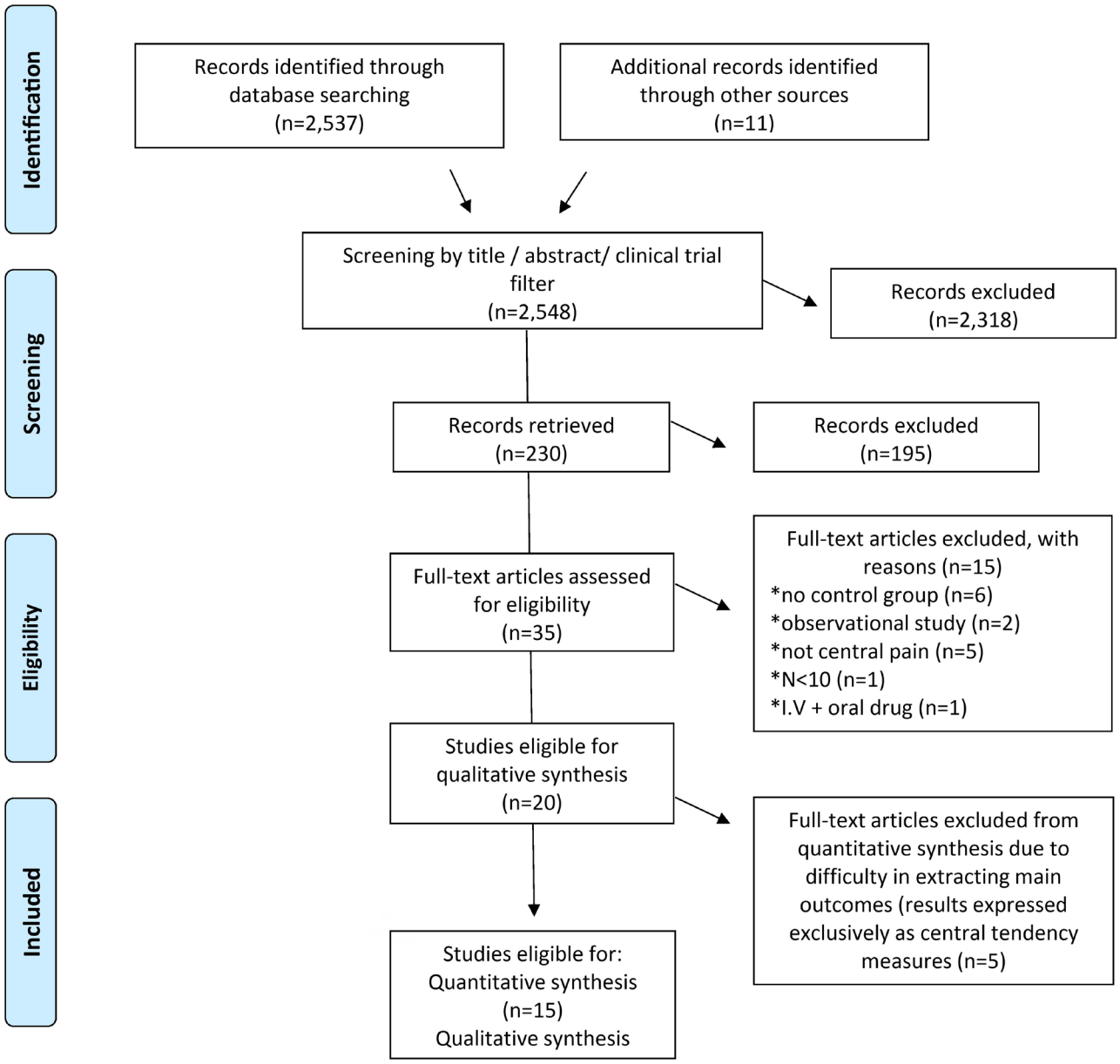

Figure 1. Flowchart of the literature search in Medline (via Pubmed).

tendency and dispersion measures, the statistical analysis was performed with non-parametric tests, making these measures inappropriate. The 20 studies included pharmacological agents employed in the treatment of central pain in multiple sclerosis[20,21,22,23,24,25,26,27,28], spinal cord injury[16,22,27,29,30], stroke[15,20-22,31], and brachial plexus injury with avulsion[32]. They used as pharmacological agents pregabalin[20,21,22,31], gabapentin[29], duloxetine[26,27,30], amitriptyline[19], combinations of cannabidiol/delta-9-tetrahydrocannabinol (CBD/THC)[14,24,32,33], lamotrigine[14,15,24], levetiracetam[15], carbamazepine[19], dronabinol[28], and valproate[16].

Fifteen studies were excluded for not having a control group[34,35,36,37,38,39], for being observational instead of randomized controlled trials (RCT)[38,40], for including individuals with pain other than CNP[41,42,43,44,45], for having less than 10 participants in the treatment arm[46], and for using oral and intravenous drugs in association[47].

The quantitative synthesis showed that pharmacological treatment with the above-described drugs significantly decreased pain intensity (Supplementary Figure S1). However, there was a great heterogeneity among the studies (I^2=93%), making this statement inconsistent. Then, a separate meta-analysis was run by grouping different drugs in the treatment of CNP. A second general quantitative synthesis was performed including studies in which all or all-but-one GRADE items were considered as low-risk of bias (n=8). This second analysis showed an overall efficacy (large effect size - 0.85[0.49-1.22]) for the use of pharmacological agents to

treat CNP (Supplementary Figure S2), this time with higher homogeneity (I^2=24%). This second analysis included six positive studies using pregabalin[21,22], and duloxetine[30] to treat spinal cord injury (SCI)-CNP, and formulations of CBD/THC[33,37] and duloxetine[26] to treat multiple sclerosis-related CNP, as well as two studies using lamotrigine[23] and levetiracetam[24], and dronabinol[28] to treat MS-CNP, and one study using pregabalin to treat central poststroke pain (CPSP)[31].

The classification of studies according to the European Federation of Neurological Societies (EFNS) criteria was the next step in the definition of the final recommendations of this guideline (Table 1). This table also contains the

Table 1. Main results from selected studies.

Studies	Drug/condition	Line of treatment according to the consensus	Results (+/-)	EFNS Classification	Level of Recommendation	Adverse effects	Availability in SUS / Mean cost per month
Levendoglu et al 2004	Gabapentin/SCI	first-line	+	II	C (Possibly effective)	++	Available (Formulary for high cost medicines) / $$$
Vranken et al., 2011	Duloxetine/ CPSP, SCI	first-line	-	II	C (Possibly effective)	++	Not available / $$
Vollmer et al., 2013	Duloxetine/MS		+	I			
Brown et al., 2015	Duloxetine/ MS		+	II			
Leijon et al., 1989	Amitriptyline/ CPSP	first-line	+	II	C (Possibly effective)	+++	Available / $
Siddal et al., 2006	Pregabalin/ SCI	second-line	+	II	C (Possibly effective)	++	Not available / $$$
Cardenas et al., 2013	Pregabalin/SCI		+	I			
Vranken et al., 2008	Pregabalin/ CPSP, SCI		+	II			
Kim et al., 2011	Pregabalin/ CPSP		-	I			
Vestergaard et al., 2001	Lamotrigine/ CPSP	second-line	+	II	B (Possibly ineffective)	++	Not available / $$
Breuer et al., 2007	Lamotrigine/MS		-	II			
Finnerup et al., 2002	Lamotrigine/SCI		-	II			
Svendsen et al., 2004	THC (Dronabinol)/MS	Third-line	+	II	B (Probably effective)*	+++	Not available / $$$$
Berman et al., 2004	CBD/THC/BPI		+	II			
Rog et al., 2005	CBD/THC/MS		+	I			
Langford et al., 2013	CBD/THC/MS		-	II			
Schimrigk et al., 2017	THC (Dronabinol)/MS		-	II			
Falah et al., 2011	Levetiracetam/ MS	Non-favorable	-	II	B (Probably ineffective)	+++	Not available / $$$
Jungehulsing et al., 2012	Levetiracetam/ CPSP	Non-favorable	-	II			
Leijon et al., 1989	Carbamazepine/ CPSP	Favorable in selected patients	-	II	C (Possibly ineffective)	+++	Available / $

Continue...

Table 1. Continuation.

Studies	Drug/condition	Line of treatment according to the consensus	Results (+/-)	EFNS Classification	Level of Recommendation	Adverse effects	Availability in SUS / Mean cost per month
Chiou-Tan et al., 1996	Mexiletine/SCI	Non-favorable	-	II	C (Possibly ineffective)		
Drewes et al., 1994	Valproate/SCI	Non-favorable	-	II	C (Possibly ineffective)		

EFNS: European Federation of Neurological Societies; SCI: Spinal Cord Injury; CPSP: Central post-stroke Pain; MS: Multiple Sclerosis; BPI: Brachial Plexus Injury (with avulsion); CBD: Canabidiol; THC: Delta-9-Tetrahydrocannabinol . *One should consider this recommendation with caution, as formulations and doses are quite different between studies. The initial level A recommendation was downgraded to level B because of this heterogeneity. Drugs without research evidence:Venlafaxin and Opioids. $: low cost, $$: medium cost, $$$: high cost, $$$$: very high cost; + low adverse effects; ++ low/medium adverse effects; +++ high adverse effects.

final recommendations based on the ratings of 12 specialists from the Brazilian Academy of Neurology, who voluntarily responded to the query to vote in the second round of the study. An agreement above 90% was obtained for the recommendations. These ratings took into account the results of the quantitative synthesis, the EFNS level of recommendation, the availability of the drugs in the Brazilian public health system, their cost, side-effect profile, and historical national clinical experience with each drug. Drugs were eventually classified as of first-, second- and third-line according to all these factors.

Consensus recommendation

First-line therapy

Duloxetine

The use of duloxetine to treat CNP associated with multiple sclerosis was based on two studies. In a low-quality, class I, positive study, Vollmer et al. used doses of 60 mg (30 mg for one week, followed by 60 mg for five weeks) followed by a 12 week-open-label extension phase (30-120 mg/day)[27]. Outcomes included daily changes in pain intensity, pain impact on daily activities, quality of life, anxiety/depression, fatigue, and patients' global impression of improvement. Results showed only a small decrease, although statistically significant, in pain intensity at week six, accompanied by significant discontinuation of the intervention due to adverse events.

Brown et al. used duloxetine to treat CNP in multiple sclerosis patients, in a high-quality, positive, class II study[26]. Participants were treated with 30 mg/day for one week, followed by 60 mg/day for five weeks, and 30 mg/day for one week, completing seven weeks of intervention. The average daily pain was reduced by 39% in the active group compared to 10% in the placebo group. Adverse events included nausea, dizziness, fatigue, constipation, and urinary retention. Vranken et al. also used duloxetine (60 and 120mg/day) in patients with CNP caused by spinal cord or stroke in a high-quality, class II, positive study[30]. They have found that duloxetine did not affect the mean pain score and pressure pain thresholds after eight weeks, but alleviated dynamic and cold allodynia. Also, they observed improvement for the bodily pain domain of the Short Form Health Survey 36 (SF-36), but no significant effect on the disability Index and the EQ-5D (instrument for describing and valuing health, based on a descriptive system that defines health in terms of five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression). Duloxetine was generally well tolerated, although dizziness, decreased intellectual performance, and somnolence could be noted.

Duloxetine had a level C of recommendation (possibly effective) to treat CNP because of two positive studies in the treatment of multilpe sclerosis (MS)-related CNP, and one negative study in the treatment of SCI and poststroke CNP. However, the studies used in this recommendation were very homogeneous (I^2=0%), and effect size was moderate (0.73[0.39-1.06]) (Supplementary Figure S3), making the quantitative synthesis very consistent. Hence, the consensus panel upgraded the level of recommendation to B (probably effective) for the use of duloxetine in the treatment of CNP. In accordance with this recommendation, duloxetine had a lower number needed to treat (NNT) (6.4) than gabapentinoids in a recent guideline for neuropathic pain in general[48].

Gabapentin

Gabapentin was used to treat CNP in spinal cord injury in a class II, low-quality, positive study[29]. Paraplegic patients with pain were treated for four weeks with stable doses of up to 3,600mg/day, after a four weeks period of titration. The treatment was efficient in reducing >50% pain intensity, frequency, and almost all neuropathic pain descriptors assessed (hot, sharp, unpleasantness, deep pain, and surface pain), also improving quality of life, assessed by non-standard instruments (Lattinen test). Considering the total number of adverse effects, which included weakness, edema, vertigo,

sedation, headache, and itching, it was significantly higher in patients treated with gabapentin when compared to the placebo group.

Gabapentin reached a level C of recommendation (probably effective) in the treatment of CNP. This was based on only one positive class II study, with a high effect size (4.30[3.74-4.86], P<0.001) (Supplementary Figure S4), independent of its low quality. Other guidelines present gabapentin as a first-line drug in the treatment of neuropathic pain in general[48]. However, similar to pregabalin, gabapentin's NNT for the treatment of NP, in general, is very high (7.2). As this drug may also be a reasonable option for CNP, future studies should improve in quality, sample size, and diversity of CNP syndromes, in order to investigate its specific efficacy.

Amitriptyline (and other tricyclics antidepressants)

Leijon et al. (1989) compared amitriptyline *vs.* carbamazepine and placebo interventions in periods of four weeks, in a low-quality, class II, positive study[19]. Using final doses of 75 mg/day for amitriptyline, they found statistical significance between groups for average pain intensity in central poststroke pain. Outcome measures included the assessment of pain intensity and depression. Amitriptyline produced a small decrease in pain intensity, an effect related to the plasma concentration of the drug, with good tolerance to the final dose.

Amitriptyline was attributed a level C (possibly effective) in the treatment of CNP because of one positive study in the treatment of post-stroke CNP. This study was not included in quantitative synthesis, as although they reported mean and standard deviations as statistical measures, their analysis of significance was based on non-parametric tests, making means obsolete measures (Supplementary Figure S5). However, as this drug is widely available in Brazil, at low cost and generally considered a first-line medication in the treatment of neuropathic pain in general[48,49], the consensus panel opted to maintain it as a first-line medication in the control of CNP. The use of pregabalin, gabapentin, duloxetine and amitriptyline as first-line drugs in the treatment of CNP is in accordance with other guidelines for NP in general[48,49,50]. However, it should be mentioned that CNP is more refractory than peripheral NP[51], making the development of new clinical trials investigating their effectiveness in larger samples necessary, with different doses, and together with other pharmacological and non-pharmacological approaches.

Second-line therapy

Pregabalin

The use of pregabalin for the treatment of CNP in spinal cord injury was based on three positive[20,21,22] and one negative[31] studies. The first was a low-quality, positive study[20], which had more than 25 individuals per study arm, but was downgraded to class II due to problems in blinding and attrition bias. They used 150, 300, or 600 mg/day of the drug, twice a day, for 12 weeks. Results showed a dose-dependent effect, with the medium dose of 460mg/day being more effective than the placebo in controlling pain. Active intervention was associated with decreased The short-form McGill Pain Questionnaire (SF-MPQ) scores, sleep problems, and anxiety. Patients' impression of change was greater in the active group. Adverse events were seen in 75% of the participants in the placebo group and 96% in the active group, being severe in 12% of the placebo and in 19% of the active group. Somnolence and dizziness were the most frequent adverse events, and euphoria was also reported, though only in the active group. The second report was a high-quality, positive, class II study[22], which used 150 to 600mg of the drug, depending on the participants' responses to the intervention during four weeks. The intervention was effective for pain relief, measured through the Pain Disability Index, and the results were slightly positive for quality of life through EQ-5D and in the bodily of the SF-36. Pregabalin, in a flexible-dose regime, produced clinically significant reductions in pain intensity, as well as improvements in health status. The most frequently reported adverse events were central nervous system-related (dizziness, decreased intellectual performance, and somnolence) and nausea. The incidence of these adverse events (mild or moderate in intensity), however, did not differ significantly between treatment groups.

The third report was a high-quality, positive, class I study[21], which used a maximum of 600 mg/day, for 12 weeks. Results showed a significant decrease in pain intensity, with almost 50% of the pregabalin group *vs.* 31.4% in the control group, achieving >30% of pain intensity relief. Positive differences were also seen in sleep quality and depression, but not in anxiety. The fourth study was the largest, with 219 participants allocated to the active or placebo groups. This negative high-quality class I study used doses of 150 to 600 mg/day for 12 weeks to treat CPSP. Results were negative for pain relief, but positive for improving sleep, anxiety, and global impression of change. However, adverse events were more frequent in the active group.

Based on the level of evidence alone, (presence of one class I and two class II positive, and one class I negative studies), the drug received a recommendation level B (probably beneficial). However, this recommendation was not supported by quantitative synthesis, as although the overall effect size was positive (0.89[0.23-1.56], P<0.01) (Supplementary Figure S6), the heterogeneity of the studies was high (I^2=85%). Hence, based on the imprecision of the effect size[52], the level of recommendation for the use of pregabalin in the treatment of CNP was downgraded to level C (possibly effective) by the consensus panel. This is in accordance with recent guidelines for the treatment of NP in general[53], but points toward an urgent need to improve the quality of studies in the area. The NNT of pregabalin in the treatment of peripheral and CNP was recently estimated between 7.7 (6.5-9.4)and more than 9

including the most recent studies[48,53]. These are high values, and would probably be higher in cases of CNP exclusively.

Weak opioids (in particular tramadol)

Tramadol, a weak mu-agonist which centrally acts in serotonin and noradrenaline reuptake inhibition, is a second-line therapy for NP according to current guidelines[3,54]. However, according to a recent systematic review, there is not enough data of adequate quality to provide convincing evidence that tramadol is effective in relieving NP[54,55]. Besides, along with all other opioid drugs, it has barely been studied specifically in CNP patients. A single positive controlled study evaluated tramadol in CNP due to SCI[55]; none were performed in CPSP and MS-CNP patients.

Lamotrigine

The use of lamotrigine in the control of CNP was investigated in three studies. In the first study, Vestergaard et al. used 25, 50, 100, or 200mg lamotrigine to treat poststroke CNP, a high-quality, class II, positive study[17]. Patients were treated for eight weeks, followed by a two-week washout period. The active group showed a small decrease in median pain intensity with the 200mg dose only. Effects were also seen in the physical pain item of the Global Pain Rating, and in the acetone drop test, highlighting the potential use of this drug in the control of cold allodynia present in CNP. The adverse effects of the drug were similar to those of placebo. This study was not included in quantitative synthesis, as they reported only the median as a central tendency measure.

In the second study, Finnerup et al. (2002), in a high-quality, class II, negative RCT study using lamotrigine (maximum 400mg for 9 weeks) in spinal cord injury CNP, have found no reduction in pain intensity, spasticity, sleep interference, and quality of life in 42 patients [14]. However, they observed that, for patients with incomplete spinal cord injury, there were significant reductions in at or below-level pain, tactile, pressure, and warm threshold, compared with complete spinal cord lesion. Lamotrigine was generally well tolerated, being necessary for only one patient to be withdrawn due to a rash. In the third study, Breuer et al. used increasing doses of lamotrigine, up to 400mg/day to treat multiple sclerosis-related CNP in a high-quality, class II, negative study[23]. Patients were treated for eight weeks, and the results showed no effects on none of the outcome measures, directed to assess pain intensity and its impact on daily life (mean pain - 0.80 [-1.55 - 3.15, P=0.5] (Supplementary Figure S7), neuropathic pain characteristics or quality of life. In this study, adverse effects were more frequent in the active group. As only the study of Breuer et al.[23] could be included in the quantitative synthesis, it was not possible to pool all three studies in the meta-analysis. The consensus panel attributed a level B of recommendation (possibly ineffective) to the use of lamotrigine to treat post-stroke, spinal cord injury, and multiple sclerosis-related CNP. However, analysis of individual included studies shows that it may help in the control of some characteristics of CNP, such as painful spasms, paroxysms, and the presence of the Lhermitte's sign-related pain.

Venlafaxine

The use of venlafaxine in the treatment of CNP was not investigated in any of the included studies. Analgesic effects are due to central noradrenergic effects, obtained with higher doses of venlafaxine (150-225mg/day)[12,48], being titrated from 37.5mg up and in some cases being used 300 mg/day. Advent or worsening of high blood pressure must be monitored during treatment[56]. Hence, according to the specialists' opinions, it may be considered as a second-line option or an alternative for duloxetine. CNP specific investigations are suggested. Also, venlafaxine is a good option to treat commonly CNP-related anxiety and depressive disorders.

Third-line therapy

Strong opioids (methadone, morphine, oxycodone, buprenorphine, fentanyl)

Most studies with opioids in NP evaluated post-herpetic neuralgia and other painful peripheral neuropathies from different etiologies. As already mentioned above, no controlled study has evaluated the use of strong opioids in the treatment of CNP. A recent systematic review on the efficacy, tolerability, and safety of opioids in non-cancer NP ponders that opioids may have a short-term substantial pain relief in highly selected patients in some NP syndromes[57]. Despite the lack of good quality evidence, strong opioids — especially methadone and morphine, affordable and accessible in the Brazilian health system — have been used for CNP in patients refractory to treatment as an add-on therapy to first-line medications in referred pain centers in Brazil. There is an obvious need for quality-controlled studies to clarify the role of strong opioids in the treatment of CNP.

Cannabinoids

The use of specific cannabinoid combinations (delta-9-tetrahydrocannabinol (THC)/Cannabidiol (CBD) for the treatment of CNP was based on three positive and two negative studies. Rog et al. developed a high-quality class I study using CBD/THC to treat MS-related CNP[37]. The drug was administered at doses of eight (21.6mg THC: 20mg CBD) to 48 (129.6mg THC: 120mg CBD) sprays daily, for five weeks. There was a reduction of 41.5% in the pain numeric rating scale (NRS), and 32.0% in the neuropathic pain scale (NPS) in the active group, with a reduction of 22.1% in the NRS, and 17.6% in the NPS in the sham group. There was also improvement in sleep in the active group, but no influence on anxiety and depression scale or disability. The placebo group improved in neurophysiological testing. Adverse events were identified in 88.2% of patients in the active group and 68.8% in the placebo group and were mainly with central characteristics in

the active group. Berman et al. used a cannabinoid-based approach (CBD/THC) to treat pain in brachial plexus injury in a low-quality, class II, negative study[32]. The treatment consisted of THC 21.6mg, THC 21.6 mg/CBD 20 mg or placebo, four to eight times a day, for seven to 24 days. The results were significant, but not clinically relevant in decreasing pain intensity, and improving sleep. Adverse events were small, present only in one participant in each group. Svendsen et al. showed in a high-quality, class II, positive study that dronabinol (cannabinoid), 2.5-5 mg, twice a day, for three weeks was effective in the control of CNP in multiple sclerosis[33]. The intervention decreased more than 50% of pain intensity in almost half of the participants in the active group (42-50%, depending on the order of crossover administration), compared to 8 to 25% in the placebo group. Improvement in radiating pain, pressure pain threshold, and mental health (SF-36) were seen in the active group. High adverse events were observed in the first week, being mainly central and musculoskeletal complaints, and were found in 96% of the participants in the active group, against 46% in the control group. Langford et al. published a low-quality, class II, negative study using THC/CBD oro-mucosal spray for 14 weeks in combination in CNP in 339 patients with multiple sclerosis in an RCT and found differences in pain NRS and sleep quality without difference between the respondents in phase I of the study[57]. Patients experienced no severe adverse events involving dizziness, fatigue, somnolence, vertigo, and nausea. Schimrigk et al.[28] published a low-quality class II study using dronabinol to treat MS CNP, for 16 weeks. Dronabinol was not superior to placebo in decreasing pain intensity, and the presence of adverse effects was higher in the active group.

The consensus panel recommended against the use of cannabinoids as monotherapy for the treatment of CNP, based on two positive and two negative studies. Cannabis-based drugs were considered as a third-line treatment, as an add-on drug or an alternative for opioids in selected refractory patients. This recommendation is in accordance with the quantitative synthesis, as the overall effect size was not significant (0.63 [-0.04 - 1.30], P=0.07) (Supplementary Figure S8), and with high heterogeneity (I^2=74%). Also, among the four studies included, formulations and doses were quite heterogeneous, and the quality of the studies was low in two of them. This recommendation is in line with a recent review that failed to show beneficial effects in the treatment of neuropathic pain in general[58]. Furthermore, at the present moment, cannabis-based drugs are not fully available in the Brazilian public health system and are actually very high-cost medications, which is likely to change in the years to come.

Combination of first-, second- and third-line drugs

A minority of CNP patients have full control of pain with a single drug. Monotherapy often leads to a limited analgesic effect and dose-related side effects. In clinical practice, the combination of drugs has been frequently used by specialists in order to obtain a minimum satisfactory control of pain, of comorbidities commonly associated with CNP such as depression, anxiety, and sleep disorders, and to help patients improve functionality and quality of life. The combination of drugs may potentiate analgesic effects due to synergistic properties and possibly allow the use of lower doses and minimize the occurrence of adverse effects. However, studies that evaluated the combination of drugs in chronic pain are scarce, mostly evaluated peripheral neuropathic pain, and none was performed in CNP. A systematic review on combined pharmacotherapy in NP pointed out that good quality studies have demonstrated superior efficacy of different two-drug combinations, but it could not recommend the use of any specific combination of drugs due to the limited trial sizes and duration[59]. Gabapentinoids have been commonly used in association with other drugs for the treatment of NP patients. The absence of drug interactions and hepatic metabolism favors its combination with other drugs such as the serotonin-norepinephrine reuptake inhibitors (SNRI), for instance. However, safety concerns have been brought about the combination of gabapentinoids and opioids. Gomes et al. described an increased risk for opioid-related death due to respiratory depression in patients taking gabapentinoids[60].

Drugs classically used for neuropathic pain in general or CNP in particular, in Brazil, and potentially able to benefit some patients

Carbamazepine

Leijon et al., in a low quality, class II, negative study, compared carbamazepine *vs.* placebo intervention in periods of four weeks, using final doses of 800mg/day, and found no statistical significance between groups for mean pain intensity in central poststroke pain[19]. Outcome measures included the assessment of pain intensity and depression. Carbamazepine was not effective and produced several adverse effects, generating high dropout rates during the segment study. Carbamazepine has been classically used to treat trigeminal neuralgia. In CNP, despite the paucity of studies, it can also be useful to treat shock-like, paroxysmal NP, especially in SCI (*e.g.* Lhermitte's sign), even at low doses. In addition, carbamazepine is an affordable and widely available drug in Brazil, even in SUS. Further studies are needed to establish a role for carbamazepine in patients in specific subsets of CNP.

Summary of classification of selected studies

Based on these results and taking into account the positive or negative effects of the drugs, specialists' opinions, balancing their adverse effects, cost, and availability in SUS, Table 1, Figure 2 and Box 1 summarize the results of the consensus panel according to the use of drugs to treat CNP in Brazil.

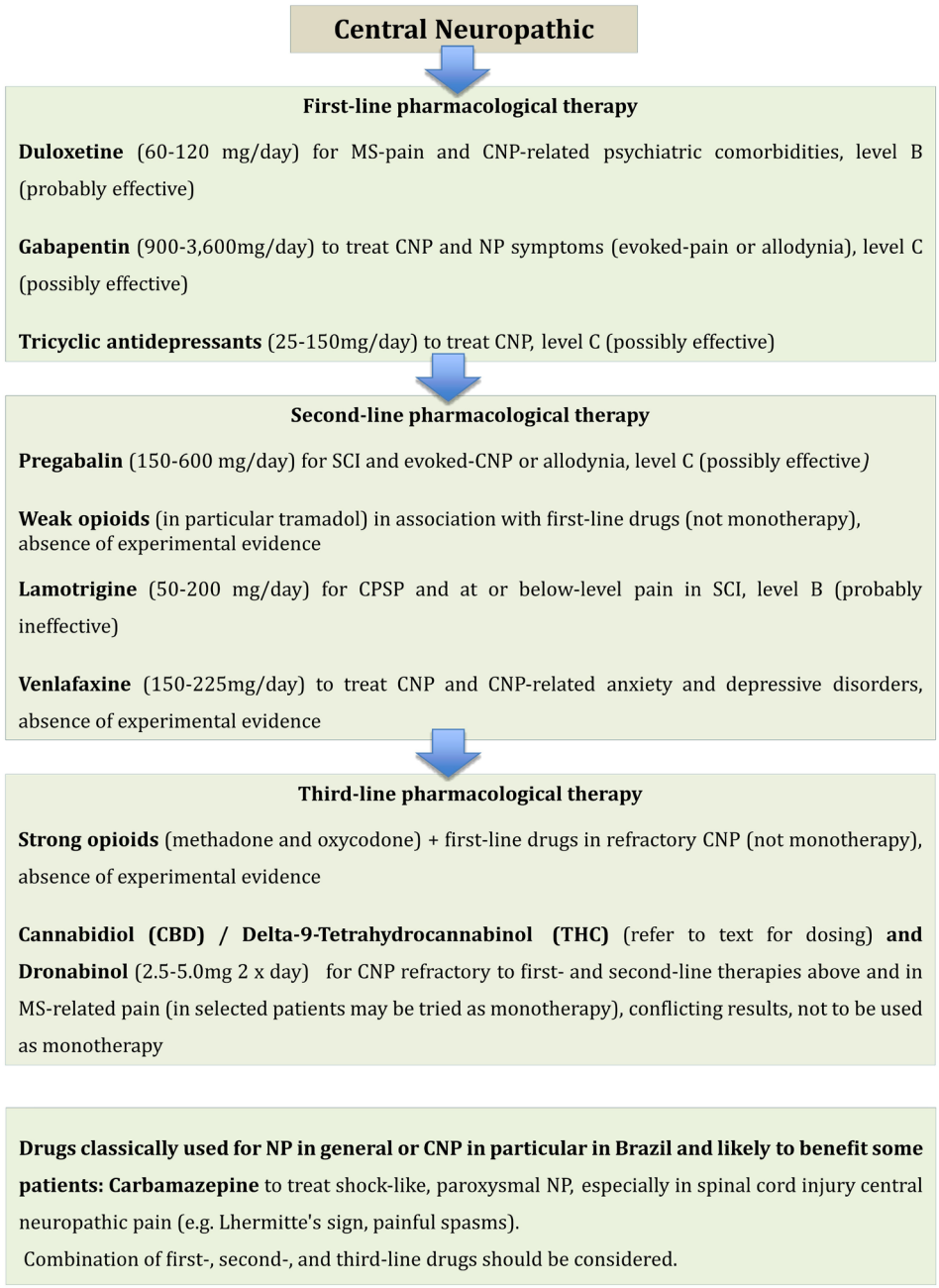

Figure 2. Central Neuropathic Pain guideline.

Special issues in prescribing drugs for CNP

Is pain in central nervous system (CNS) diseases always central neuropathic?

CNP happens after lesion or dysfunction of the CNS and is associated with signs of central hyperexcitability, loss of sensation, spontaneous and/or abnormally evoked pain, and other characteristics of maladaptive plasticity — plasticity leading to decreased function in the CNS[61]. However, as signs and symptoms are very remarkable, little attention is put on other possible sources of pain, including nociceptive and nociplastic pain. Other sources of pain in patients with CNP include spasticity and spasms related pain[62,63], musculoskeletal pain secondary to joint, muscle or myofascial dysfunction[63,64], fatigue[65], migraine and tension-type headache[66], treatment pain[67,68], peripheral neuropathy[69], and central sensitization or nociplastic pain[70]. Importantly, a recent study found that seven out of eight patients with post-stroke CNP were relieved by a peripheral nerve block, suggesting that peripheral components may have an important role in CNP[71]. Hence, a thorough evaluation of pain sources should contribute to the understanding of the true role of central and peripheral mechanisms associated with CNP.

UPDATING PROCEDURE

The consensus will meet every five years to update the recommendations. At that time the initial panel of experts will be invited to participate, as well as other representatives of Brazilian associations involved in the management of CNP. The procedure to update the recommendations will follow the guidelines in force to report such studies.

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