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Review

COMBINATION THERAPY FOR NEUROPATHIC PAIN. A SYSTEMATIC REVIEW

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Abstract: Pharmacological treatment is poorly effective for neuropathic pain (NP). A progressive decrease in the estimated effect of NP drugs has been reported, giving rise to an increase in multimodal analgesic approach. We performed a systematic review to assess whether there is more and better-quality evidence available since the last review. We evaluated the efficacy, tolerability and safety of double-blind randomized controlled trials involving only adult participants comparing combination therapy (CT: ≥ 2 drugs) to placebo and/or at least one other comparator with NP indication. The primary outcome was the proportion of participants reporting ≥ 50% pain reduction from baseline. Secondary outcome was the proportion of drop-outs due to treatment-emergent-adverse-events. After removing duplicates, 2323 citations were screened. 164 articles were assessed for eligibility, from which 16 were included for qualitative analysis. From the latter, only 5 lasted for at least 12 weeks and only 6 complied with required data for complete analysis, but not for meta-analysis. CT has been adopted for years without robust evidence. Efforts to achieve better quality evidence have not improved over the years. In this regard, guidelines for NP should attempt to make recommendations on CT research, prioritizing which combinations to analyze.

Keywords: Neuropathic Pain, Combination Therapy, Pharmacotherapy, Randomized Control Trial,

1. Introduction

Neuropathic pain (NP) occurs as a direct consequence of an injury or disease that affects the somatosensory system [1]. The prevalence of NP in the population varies between 6.9% and 10% depending on the tool used for its diagnosis [2], and it negatively affects quality of life, and it negatively affects quality of life, impacting on daily activities, such as sleeping and walking, and on family and social interactions. [3]. Patients with uncontrolled pain keep suffering heavy individual and societal burdens, where they can come to believe that chronic pain is inevitable and untreatable. Especially those who are not responding to standard measures. A considerable number of patients do not achieve sufficient pain relief or improvement in their quality of life with currently available drugs [4]. Pharmacological therapy remains an important component of NP management [5,6]. However, it has been more than a decade since the market-release of the last drug indicated for NP treatment, according to international guidelines. Clinical guidelines recommend starting treatment with monotherapy and place combination treatment (CT) in a second tier, for those patients who do not respond to monotherapy or switching [7,8].

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Treatment of NP is effective in less than 50% of patients and is also associated with significant adverse drug effects [9]. In addition, decreases in the effect of drugs for NP have been reported across all drug classes, with a progressive increase in Number Needed to Treat (NNT) values on randomized control trials (RCTs) [10]. This results in a decrease in the estimated effect of such drugs, although stabilization has been shown around 2010. The reason for this increase in NNT numbers is not well known. Most probably, it is due to a combination of different causes. For instance, new requirements have been published by regulatory agencies like the Federal Drug Agency (FDA) or the European Medical Agency (EMA) [11-13], raising the bar when it comes to complexity of trial design, demanding larger sample sizes, longer study duration, better reporting of randomization and blinding, intention-to-treat (ITT) analysis, and more complete efficacy report (i.e., the use of 30% or 50% pain reduction as outcome measures) were all significantly associated with reduced effect size) [10,14]. Also, there are factors contributing to higher levels of placebo response in NP RCTs [15].

Due to these two factors, the use among clinicians of drug combinations is becoming more and more frequent [16-19]. The rationale for this combined drug therapy is supported by two theories. The first one states that symptoms are better treated based on phenotypic profiles and, thus, on those drugs whose mechanisms of action respond to the fundamentals of phenotypic expression [20]. Since NP perceived by patients is usually described with different negative and positive symptoms, and since different sensory profiles have been detected on the same patients [21,22], it is reasonable to think that CT could be beneficial for those patients. The second theory seeks for synergies in effect whilst reducing side effects. Targeting more than one mechanism simultaneously by using drug combinations can potentially be a better approach than targeting a single mechanism with a single drug [23,24]. Synergistic interactions between different analgesics may allow for lower doses of individual drugs which may provide a better safety/tolerability profile.

The fact is that it is increasingly common to see the use of CT among clinicians, and it is more and more frequent to see recommendations on drug combinations by different scientific societies [16-19]. However, doubts continue to arise regarding which drug combination is effective or which drugs to combine. For instance, some guidelines recommend adding an agent from another class if pain control is inadequate [25]. Others state that there is insufficient data to make any CT recommendations [17,26], or that the evidence for combinations is inconclusive [8], with some recent weak recommendations on certain combinations [8,16]. The last Cochrane review carried out in 2012 already indicated that it was somewhat surprising that they were able to identify only 107 relevant citations, and only 21 were high-quality NP RCTs that evaluated CT [27]. Previously, in 2005, Gilron et al made another review [28], with a 7-year gap from one review to another.

Given that the estimated effect of RCTs for NP has been changing, apparently until 2010, when the effect size tended to stabilize [10], the last review for NP CT was done in 2012 (7 years after the previous one), and that it is still not clear among clinicians when to give drug combinations and which ones to combine, we thought it was time for another review. Hence, we performed a systematic review from 2012 onwards aiming to assess whether there is more evidence available regarding NP CT, and to assess its quality. We reviewed the literature and made some recommendations in this regard. This review discusses the different approaches, guidelines and recent available evidence, and it proposes some guide-points concluded from the actual evidence.

2. Materials and Methods

We evaluated the efficacy, tolerability and safety of various drug combinations for the treatment of NP. For that purpose, we identified only RCTs of various drug combinations for NP from different databases. We also made hand searches for citations of other reviews and trial registries. The most recent search was performed on April 30th, 2021.

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2.1 Criteria for study selection.

We applied the following criteria for selecting studies for the qualitative analysis:

2.2 Types of studies

We sought for double-blind, RCTs for the treatment of NP which compared combinations of two or more drugs to placebo and/or at least one other comparator with NP indication.

2.3 Participants

We included only studies involving adult participants of 18 years and older with a diagnosis of NP.

2.4 Interventions

We included interventions involving a combination of two or more different drugs. We did not include any studies performed with non-pharmacological treatments (even if they were interventional), such as diets (including vitamin supplements) or physical measures.

2.5 Outcomes

2.5.1 Primary outcomes

The primary outcome we looked for was the proportion of participants reporting ≥ 50% pain reduction from baseline. When 50% pain reduction was not reported, we looked for a decrease of a ≥ 30% pain from baseline.

2.5.2 Secondary outcomes

We looked for i) the proportion of drop-outs due to treatment-emergent adverse effects, and ii) proportion of participants reporting each specific adverse effect (i.e., sedation, dizziness) of ≥ moderate severity.

2.6 Search methods

We searched the following databases, timelines and restrictions:

- PubMed® with publication dates limited to those from 01/01/2012 to 03/03/2021 for the words "neuropathic pain" AND "combination". Only English language. Search done on 03/03/2021
- Google Scholar for the words "neuropathic pain" and "combination therapy" from 2012 to 2021 (no specific data limit available), only for English pages. Search done on 03/15/2021.
- Web Of Science on "All Databases" except for Zoological limited from 2012 to 2021. Filters were applied to exclude Review Articles, Case Report, Editorial Material, Books, Meeting, and Letters and corrections. Search was done only for English language published articles. Search was done on 04/30/2021.
- SCOPUS with the following selection "neuropathic pain" and combination on: title, abstract or keywords. Limited for publication year >2011, document type "articles" and only English language. Search was done on 04/30/2021.
  We further searched the clinical trials.gov on 03/03/2021
- Finally, we also checked relevant citations on other reviews and meta-analyses published between 2012 and 2021.

2.7 Data collection and analysis

2.7.1 Data extraction

From each selected study, by the aforementioned criteria, we extracted the following data:

- Proportion of participants with 50% pain relief (primary outcome).
- Proportion of participants with 30% pain relief (whenever 50% was not reported or even if reported, too).
- Proportion of drop-outs due to treatment-emergent-adverse-events (secondary outcome).

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- Proportion of dropouts by any reason (secondary outcome).
- Proportion of participants reporting each specific adverse effect (i.e., sedation, dizziness) of ≥ moderate severity.
- Study drug(s): name(s), doses, route of administration and treatment duration.

2.7.2 Risk of bias.

We searched for the following types of bias in all the studies included for qualitative analysis: Random sequence generation and allocation concealment (selection bias), Blinding, Incomplete outcome data, Selective reporting, Other potential sources of bias. We graded all selected studies for quality as per the Cochrane's 'Risk of Bias' tool [29].

2.7.3 Measures of effect.

We looked for the comparison effect between the CT study drugs and its comparator or if both single drugs were used as comparator, and the difference between them and placebo

2.7.4 Unit of analysis.

If we found studies involving more than one active treatment group, we would divide the control treatment group among the active arms for comparison reasons.

2.7.5 Missing data.

We analyzed data based on ITT. We considered in the ITT population all randomized patients who received assigned treatments that provided at least 50% of the required outcome data.

2.7.6 Heterogeneity

For the purpose of avoiding heterogeneity, we did not combine any study that did not have similar conditions for analysis.

2.7.7 Groups and subgroups.

We looked for any subgroup which could make a different combination of study results (i.e., phenotyping). Finally, for the discussion, even if grouping was not possible, we would categorize studies according to CT of drug classes (i.e., opioids, antidepressants, anticonvulsants, etc.…).

2.7.8 Sensitivity analysis.

We intended to perform a sensitivity analysis to assess the impact of a given study considered to be an outlier (regarding study quality, duration, dosages used or pain measurement scales) on the final meta-analysis results. Nonetheless, since we could not perform a meta-analysis for the reasons mentioned elsewhere within this article, a sensitivity analysis also could not be carried out.

3. Results

3.1 Description of Studies

The steps taken during this research are summarized on Figure 1. We identified a total of 3808 citations, including the records from the databases and additional records from other sources, finishing the search on April 30th, 2021. We screened all citations by title and, when not directly excluded, by abstract. After removing duplicate citations, we ended up with 2323 individual citations to screen. After thorough screening we assessed a total of 164 articles for eligibility, out of which 16 were included for qualitative analysis. 6 complied with required data for complete analysis. None of them could be added up or combined for quantitative analysis. Hence, no meta-analysis could be done.

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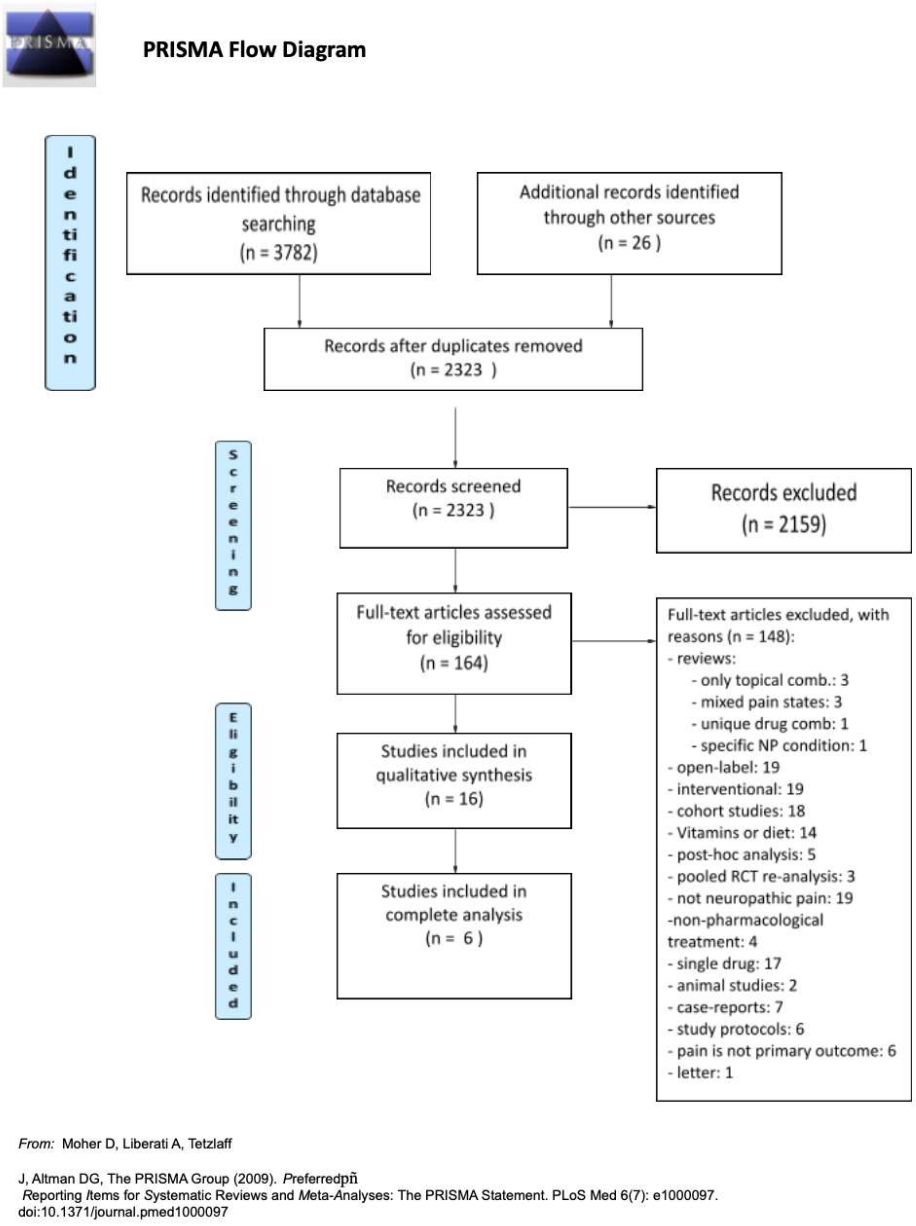

Figure 1. Prisma Flow Diagram.

3.1.1 Study selection

We identified 16 studies which fulfilled the inclusion criteria for this review: RCTs, double-blind, comparing combinations of two or more drugs to placebo and/or at least one other comparator for the treatment of NP [30-45]. Of them, only six provided data on the primary outcome (proportion of participants reporting ≥ 50% or ≥ 30% pain reduction from baseline), either by direct reporting or by deduction through study figures or graphs (Data from such studies can be seen on Table 1). 1243 participants for the study drugs vs 928 for the control groups: one RCT evaluated the combination of cannabinoids delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray and the existing treatment regimen for central neuropathic pain (CNP) in patients with multiple sclerosis [43], a different drug combination (opioid plus pregabalin (PGB) plus duloxetine (DXT) was tested in one RCT in NP in cancer patients [32,40], one tested a combination of DXT and

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PGB against both of them on monotherapy in painful diabetic neuropathy (PDN) [42] and another compared a drug combination of dextromethorphan and quinidine against placebo, again in PDN [45], and capsaicin 8% dermal patch (CP8) in combination with systemic NP medications was evaluated in another RCT in postherpetic neuralgia (PHN) [44]. Likewise, these studies also provided data on the secondary outcomes: i) proportion of participants dropping out of the study due to treatment-emergent adverse effects, and ii) proportion of participants reporting each specific adverse effect (i.e., sedation, dizziness) of ≥ moderate severity.

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Table 1. Data of selected studies

	Pain condition	RCT	Treatment duration (weeks)	**Combination**	target ceiling dose or MTD per day	route	sample size RD [CS]	Control	target ceiling dose or MTD per day	route	sample size RD [CS]
Langford, 2013 [43]	Central neuropathic pain in patients with multiple sclerosis	DB; PARALLEL	14	**THC / CBD + concomitant analgesic medication**	32.4 / 30 mg	oromucosal (spay) + oral	167 [141]	placebo		oromucosal (spray) + oral	172 [156]
Shaibani, 2012 [45]	Diabetic neuropathic pain	DB; PARALLEL	13	**DMQ**	90/60 mg 60/60 mg	oral oral	131 [79] 125 [74]	placebo		oral	123 [89]
Irving, 2012 [44]	Postherpetic neuralgia	DB; PARALLEL	12	**Capsaicin + concomitant neuropathic medication**	640 µg/cm^2	topical (skin) + oral	597 [544]	placebo		topical (skin) + oral	530 [480]
Tesfaye, 2013 [42]	Diabetic neuropathic pain in non-responders' patients to duloxetine or pregabalin	DB; PARALLEL	8	**Duloxetine + Pregabalin**	60 + 300 mg	oral	170 [141]	Duloxetine Pregabalin	120 mg 600 mg	oral oral	74 [?] 99 [?]
Holbech, 2015 [38]	Painful polyneuropathy	DB; CROSSOVER	5	**Imipramine + Pregabalin**	75 + 300 mg	oral	18 [15] - 16 [15] - 15 [12] - 16 [14]	Placebo Imipramine Pregabalin	 75 mg 300 mg;	oral oral oral	19 [18] - 16 [15] - 15 [13] - 12 [11] 18 [17] - 17 [14] - 14 [14] - 12 [12] 18 [15] - 16 [14] - 14 [14] - 13 [13]
Matsuoka, 2019 [32]	Neuropathic pain in cancer patients' non-responders to opioid-pregabalin	DB; PARALLEL	1,5 (10 days)	**Duloxetine + Opioid-Pregabalin**	40 mg + ?-300 mg	oral	35 [34]	placebo + Opioid- pregabalin	?- 300 mg	oral	35 [33]

MTD: maximum tolerated dose; RD [CS]: randomized [completed study]; DB: double-blind; THC/CBD: tetrahydrocannabinol / cannabidiol; DMQ: Dextromethorphan+Quinidine; ?: data not available.

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3.1.2 Study design

Among selected RCTs, twelve studies [30, 32-33, 34-36, 39-40, 42-45] used a parallel design and four [31, 37-38,41] used a cross-over design. None of the cross-over trials conducted analyses involving only first period data, likely due to inadequate statistical power.

Among the six RCTs which provided data on the primary outcome, three compared the combination of interest to placebo alone [43-45], one compared a combination of 2 drugs against monotherapy of each and placebo [38], another one compared CT only against high-dose monotherapy of each, with no placebo control [42], and the last one compared the combination of three painkiller drugs to the combination of only two of these painkiller drugs in cancer patients with NP [32]. It is noteworthy that only three of them had a treatment period of at least 12 weeks, excluding titration period [43-45].

3.1.3 Outcomes

5 studies reported the number of patients with ≥ 50% pain reduction [38,42-45], and on the other one it could be deduced from figures [32]. They also reported the number of patients ≥ 30% pain reduction, except for 2 of them [38,43]. One study described the proportion of patients reporting ≥ 50% pain reduction and ≥ 30% pain reduction, but it was done on a secondary analysis with a percentage of the overall of all treatment groups on a 3-branch crossover study. The specified number of participants could not be calculated from this percentage and the diagram of participants included and withdrawn from the study [37]. Other outcomes like adverse effects, pain relief of patient global impression of change are shown on table on supplementary material (table S1).

According to the guideline on the clinical development of medicinal products intended for the treatment of pain [46], a sustained therapeutic effect in chronic pain should in general be demonstrated in pivotal efficacy trials with a treatment period of at least 12 weeks [47]. Five out of 16 selected RCTs provided data on a period of at least 12 weeks [30,34,43-45], all with a parallel design.

3.1.4 Pain conditions

PDN was explored in three studies [30,42,45], PHN in one study [44], neuropathic cancer pain (N-CP) in three studies [32-33,40]; lumbar spinal stenosis (spinal cord injury (SCI) pain) or low back pain in two studies [35-36]; CNP in two studies [39,43], other different neuropathic conditions were evaluated in four RCTs [34,37-38,41] and one in long-standing NP [31].

3.1.5 Excluded studies

For the purpose of this review, we did not include any other intervention that was not on drug CT for NP. Thus, all studies, independently if they were RCTs or not, that used other comparators such as diet, vitamins, non-medical therapy (i.e., physical therapy), any kind of interventional therapy (i.e., neuraxial, nerve blocks, etc..) were not included for analysis. We also excluded studies that compared CT for NP but were not RCT (i.e., observational analysis, cohort studies, retrospective analysis, open label, etc..). Post-hoc analysis of other RCTs were excluded too.

Of the 16 selected RCTs which fulfilled the inclusion criteria of this review, 10 were excluded because they did not provide data on the primary outcome [30-31,33-37,39,41,45]. Data on the non-selected studies is shown on table 2. Therefore, this review will focus only on six studies [32,40,42-45], from which only three RCTs provided data on a period of at least 12 weeks [43-45].

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Table 2. Data of non-selected studies

Name	Pain condition	RCT	Treatment duration (weeks)	**Combination**	target ceiling dose or MTD per day	route	sample size RD [CS]	Control	target ceiling dose or MTD per day	route	sample size RD [CS]
Singh, 2021 [30]	Diabetic neuropathic pain	DB; PARALLEL	24 (6 months)	**epalrestat + pregabalin**	100 + 150 mg	oral	50? [?]	Pregabalin	150 mg	Oral	50? [?]
				epalrestat + duloxetine	100 + 60 mg	oral	50? [?]	duloxetine	60 mg	oral	50? [?]
Rigo, 2017 [34]	Neuropathic pain in patients' poorly responsive to neuropathic medication	DB; PARALLEL	13 (3 months)	**methadone + Ketamine**	9 + 90 mg	oral	14 [13]	methadone	9 mg	oral	14 [13]
								ketamine	90 mg	oral	14 [11]
Turcotte, 2015 [39]	Central Neuropathic pain in patients with multiple sclerosis and treated with gabapentin	DB; PARALLEL	9	**nabilone + gabapentin**	2 + 1800 mg	oral	8 [7]	placebo + gabapentin	1800 mg	oral oral	7 [7]
Kim, 2016 [35]	Lumbar spinal stenosis	DB; DD; PARALLEL	8	**limaprost + pregabalin**	15 µg + 225 mg	oral	61 [43]	limaprost pregabalin	15 µg 225 mg	oral oral	61 [40] 60 [43]
Baron, 2014 [36]	Low back pain (with neuropathic component) in patients treated with tapentadol PR	DB; PARALLEL	8	**tapentadol PR + pregabalin**	300 + 300 mg	oral	159 [133]	tapentadol PR	500 mg	oral	154 [126]
Gilron, 2015 [37]	Neuropathic pain	DB; CROSSOVER	6 (period)	**nortriptyline + morphine**	100 + 100 mg	oral	15 [13] -11 [9] - 18 [15]	nortriptyline	100 mg	oral	13 [13] -16 [14] - 16 [16]
								morphine	100 mg	oral	17 [14] -14 [10] - 16 [14]
Pickering, 2020 [31]	Neuropathic pain (long-standing refractory)	DB; CROSSOVER	5 (period)	**ketamine + magnesium**	0.5 mg/kg + 3g	i.v.	20 [20]	placebo ketamine	0.5 mg/kg	i.v. i.v.	20 [20] 20 [20]
Harrison, 2013 [41]	HIV associated polyneuropathy	DB; CROSSOVER	4 (period)	**duloxetine + methadone**	60 + 30 mg	oral	4 [3] -3 [3]? - 3 [3] -4 [3]?	placebo		oral	4 [4]? -4 [3]? - 2 [2]? -4 [3]
								duloxetine	60 mg	oral	4 [4] -3 [3]? - 3 [2] -4 [4]?
								methadone	30 mg	oral	4 [4] - 4 [2] - 2 [2]? -3 [3]?

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Garassino, 2013 [40]	Neuropathic pain in cancer patients	PARALLEL	2	**Pregabalin ↑ + Oxycodone fix** **Pregabalin fix + Oxycodone ↑**	300+20 mg 50+20 mg?	oral oral	38 [32] 37 [35]				
Dou, 2017 [33]	Neuropathic pain in cancer patients treated with morphine	DB; CROSSOVER	2 (period)	**pregabalin + morphine PR**	300 + ≥180 mg	oral	20 [?] - 20 [?]	placebo + morphine PR	+ ≥ 180 mg	oral	20 [?] - 20 [?]

MTD: maximum tolerated dose; RD [CS]: randomized [completed study]; DB: double-blind; DD: double dummy; DMQ: Dextromethorphan / Quinidine; PR: prolonged or sustained release; ?: data not available.

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3.2 Risk of bias

Risk of bias is shown in table 3. Judgements about each risk of bias item presented as percentages across studies can be found in supplemental material (Figures S1 and S2).

Table 3. Risk of Bias

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall Bias
Langford, 2013 [43]	+	+	+	+	?	?
Irving, 2012 [44]	+	+	+	?	?	?
Shaibani, 2012 [45]	+	+	+	+	+	+
Tesfaye, 2013 [42]	+	+	+	+	?	-
Holbech, 2015 [38]	+	+	+	+	?	-
Matsuoka, 2019 [32]	+	+	+	+	?	-
Singh, 2021 [30]	?	-	-	+	?	-
Rigo, 2017 [34]	+	+	+	+	?	-
Kim, 2016 [35]	+	+	+	+	?	-
Baron, 2014 [36]	?	+	+	+	?	-
Gilron,2015 [37]	+	+	+	+	?	-
Pickering, 2020 [31]	+	+	+	+	?	-
Turcotte, 2015 [39]	+	-	+	+	+	-
Harrison, 2013 [41]	+	-	+	+	?	-
Dou, 2017 [33]	+	+	+	+	?	-
Garassino, 2013 [40]	?	-	+	?	?	-

3.2.1 Random sequence generation and allocation concealment (selection bias)

Four of the six studies reported the method used to generate a random sequence and to keep the allocation concealed [32,38,42,44]. The other 2 appropriately reported one or the other item [43,45]

3.2.2 Blinding

Only one study [40] was not blinded. Among the other studies, although all of them claim to be blinded, 5 out of 15 studies [30,35,36,41,45] did not describe the blinding procedure.

3.2.3 Incomplete outcome data

We qualified attrition bias as 'low risk' for studies where the dropout rate was below 20%. We qualified studies with higher dropout rate but including ITT analysis as 'unclear' or 'high risk of bias'. All 6 studies provided information about trial dropouts.

3.2.4 Selective reporting

Although 4 out of 6 selected studies [32,38,42,43] indicated pre-trial registration on a clinical trial registry, all 6 of them reported at least one of the outcomes that were considered to be clinically relevant.

3.2.5 Other potential source of bias

We assessed the 'other bias' item as high risk in studies where the follow-up was shorter than twelve weeks [32,38,42] and/or the study had fewer than 50 participants per arm or period of treatment in parallel or cross-over studies, respectively [32,38].

3.3 Effect of interventions

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When combining THC/CBD oromucosal spray as an add-on with a pre-existing regimen, there was no difference against placebo, mostly due to a similar (high) number of placebo responders [43].

For a 12-week period, CP8 as an add-on therapy reduced NP on PHN, regardless of concomitant systemic NP medication use [44]. We could not differentiate between concomitant medications. No data in this regard was given.

A combination of dextromethorphan and quinidine was effective, with an acceptable safety profile, for treatment of PDN pain [45].

A combination of PGB+DXT showed no significant difference in pain reduction, when compared to either PGB or DXT at high dose monotherapy [42].

A combination of moderate doses of the tricyclic antidepressant (ATC) imipramine and PGB could be considered as an alternative to high-dosage monotherapy [38].

Adding DXT to an opioid-PGB therapy might have clinical benefit in alleviating refractory N-CP. [32]. However, this effect was only for a 10-day therapy. There is no information for a longer period of treatment.

4. Discussion

In this review we have tried to identify new RCTs which could bring new evidence on CT for NP, after the last Cochrane's review in 2012 [27]. After a thorough data search from various databases, we could only find 16 RCTs, of which only 5 directly reported the primary outcome and in one RCT it was deductible from the figures. In addition, out of the 16, only 5 RCTs reported pain outcomes after 12 weeks [30,34,43-45], also as required by standards. We did not perform a quantitative analysis (meta-analysis) due to the small number of trials included and due to the heterogeneity among drug types and combinations used, which makes it impossible to accomplish a meta-analysis. Nevertheless, we have tried to approach the literature in the most similar approach.

4.1 Main results.

We can presume that there is no effect on adding THC/CBD to pre-existing treatment for NP, that there is no difference between a PGB-DXT combination against either of them on high-dose monotherapy. However, a combination of an ATC like imipramine and PGB may be an alternative to high dose monotherapy. Likewise adding DXT to a previous opioid-PGB therapy may be beneficial too, and topical CP8 for peripheral NP is effective for reducing NP regardless of the concomitant therapy. Different unusual combinations like dextromethorphan and quinidine may be another useful treatment option.

For the secondary outcomes, all the selected studies had safety reports where they differentiated adverse effects, drop-outs by treatment-emergent adverse effects (except one of them for the latter [32]. However, data on prescribed rescue medication was either not available [42], or not analyzed [42-44]. Other pain ratings or sleep interference were evaluated in some studies. Patient global impression of change (PGIC) was evaluated on 3 [42-44], and brief pain inventory (BPI) was evaluated also on 3 [32,42-43]. Sleep interference was evaluated on 4 of them [32,42-43,45]. On the other hand, NP symptoms or sensory testing was reported only in one study [38], whereas data about it was unclear on other 2 of them [42-43].

4.2 Quality of evidence.

In this systematic review, before obtaining results, we initially intended to make a meta-analysis. At first, we doubted if we should include for the quantitative analysis those studies already included in the last review. As the NNT has been changing, stabilizing around the year 2010 [10], we thought that it would be wise to do a separate one, and only after that try combining all studies. However, after the screening and selection we found out that a meta-analysis would not be possible, not only within the selected studies for the period of this review, but even if we tried to combine them with others already reviewed. Thus, the quality of evidence has not increased after all these years. Nevertheless,

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some good-quality studies have demonstrated superior efficacy of two-drug combinations against placebo and against monotherapy.

10 studies had very small treatment groups [31-35,37-41]. Small numbers' impact on effect cannot be really calculated and it can overestimate treatment effects [48]. Half of the studies did not report the primary outcome (i.e., ≥ 50% or ≥ 30% pain reduction from baseline), more than half did not report a comparison period of experimental treatment versus comparator for 12 weeks or longer, and there is 1 study [45] with a comparison period of 12 weeks or longer that did not report the primary outcome. It is noteworthy that there already was a recommendation in 2012 that a sustained therapeutic effect in chronic pain should be demonstrated in pivotal efficacy trials with a treatment period of at least 12 weeks [47].

As we did not find several available studies with good quality of evidence for any one specific combination, it precluded the conduction of any quantitative analysis, even if we added the previous systematic review [27]. So, we cannot make any recommendations on any specific drug combination for neuropathic pain over another.

4.3 Data from the other unselected studies and articles assessed for eligibility.

As we could not afford to perform a quantitative analysis from the selected studies, we went one step back and looked for evidence on the other 12 studies, and open-label or observational studies published in this period, which were assessed for eligibility but not included for the qualitative synthesis. Even though the conclusions we can take from those studies are not enough to make strong recommendations, they may be useful to show a path for further studies.

4.3.1 Cannabinoids in combination

One of the results of this review is that adding THC/CBD to pre-existing treatment for NP did not show any benefits for these patients [43]. On the other hand, a recent review only on nabiximol (THC/CBD) for NP found that it was superior to placebo, but with a small effect size [49]. This small effect size alone may be the reason why it is not useful in combination. There may be a difference if the CT is with THC alone. Nabilone, a synthetic THC analogous, added to gabapentin (GBP) could be beneficial [39], but, again, the results were found with a very small number of participants, and the study was performed only for 9 weeks. There have also been findings indicating that GBP synergistically enhances THC [50]. Thus, THC, but not a combination THC/CBD, may represent a potential adjuvant for NP medications.

4.3.2 Topical treatments in combination

Evidence on other topical treatments in CT is also controversial. Apart from the RCT selected in this review, where CP8 demonstrated to reduce NP as an add-on therapy [44], we also found 3 other not-selected studies on a lidocaine 5% plaster [51-53], one retrospective analysis on transdermal buprenorphine [54], and a very recent study protocol of a study combining clonidine and pentoxifylline [55]. One of the Lidocaine 5% plaster studies [51] and the transdermal buprenorphine study not only were retrospective, but also had a low number of participants, with different pain conditions and several concomitant therapies. Therefore, they were not suited for drawing any conclusions. Another retrospective study using a Lidocaine 5% plaster as an off-label add-on therapy for different localized NP syndromes and conducted with 130 patients found that only 79 were still on plaster after 3 months (44 after a year) [52]. Nevertheless, out of the 130, 66 reported >30% pain relief, from which 39 reported > 50%. Despite being retrospective, this study suggests that lidocaine 5% plaster as add-on therapy could have the same effect as the CP8. Furthermore, an RCT for lidocaine 5% plaster against placebo did pinpoint some findings on this behalf [53]. Randomization was stratified by concomitant treatment status, and no significant differences were found among the study groups, even though the treatment arm experienced better pain relief. Subgroup analysis showed that the add-on therapy

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group behaved almost like the placebo group. Hence, results on available literature for the lidocaine 5% plaster are heterogeneous and inconsistent and should be clarified on a proper RCT for CT.

4.3.3 Gabapentinoids and opioids combinations

Findings on the association of gabapentinoids with opioids are inconclusive, and perhaps we could say that they might speak against the CT. One RCT with a small number of participants and carried out for only 14 days showed that adding PGB to morphine in N-CP was useful to reduce morphine dosage [33]. This morphine dose reduction was also suggested in a retrospective analysis [56]. However, efficacy was the same between the CT and morphine alone. An open-label study with morphine and PGB against both in monotherapy under different NP conditions showed that CT was similar to morphine and superior to PGB in monotherapy [57], although this study, in addition to being open-labeled, had a very high drop-out rate on both monotherapy arms. A similar finding was reported on an 8-week non-inferiority RCT where tapentadol alone showed no difference when compared to a combination of tapentadol plus PGB [36]. There was no comparison on PGB alone, nor placebo. Unfortunately, even though this RCT showed a decrease in mean changes in pain intensity on both arms, the primary outcome for selection on this review was not shown, and neither could we deduce it from figures nor tables. On the contrary, 2 open-label observational studies that added PGB to pre-existing treatment [58,59], and another that added oxycodone/naloxone to patients already taking gabapentinoids [60], reported a decrease in pain. Neither of them was an actual RCT (i.e., no placebo, no randomization). As a result, we can say that there seems to be little to no difference in efficacy when combining gabapentinoids with opioids, whereas it may be a useful leverage for opioid dose reduction.

4.3.4 Antidepressants and opioids combinations

Literature on antidepressants and opioids is limited too, but results are more consistent towards a benefit for CT. In fact, combining antidepressants, be they tricyclic or otherwise, with opioids is a more frequent combination than combining antiepileptics with opioids [61]. Whilst DXT and methadone reduce cancer-related pain when compared to each drug alone (monotherapy) [62], adding DXT to an opioid-PGB therapy might have clinical benefit in alleviating refractory N-CP [32], and there has also been reported a superior efficacy of a nortriptyline–morphine combination over each of these drugs in monotherapy [37]. Another RCT with a DXT-methadone combination could not be completed due to recruitment and retention issues [41]. Even though there is little evidence, quality seems better for CT with antidepressants plus opioids than the one with gabapentinoids plus opioids.

4.3.5 Gabapentinoids and antidepressants in combination

Another very frequently found combination is the one between gabapentinoids and antidepressants [61,63]. In fact, combinations of PGB/GBP and DXT/TCAs have been previously recommended to be considered as an alternative to increasing dosages in monotherapy for patients unresponsive to monotherapy with moderate dosages [8]. The American Academy of Neurology (AAN) guidelines have recommended adding venlafaxine to GBP in patients with inadequate pain relief on GBP monotherapy [64]. Recent evidence is contradictory, and recommendations may need to be reconsidered. A RCT selected in this review demonstrated superiority for CT with PGB and imipramine. [38]. This RCT, though, had a low number of patients per arm, and the test lasted only for 5 weeks. The period was too short to show persistence of effect. Even so, PGB and imipramine in moderate doses was significantly superior to either drug in moderate dose monotherapy. In another cohort study, PGB superadded to a pre-existing amitriptyline regimen helped to reduce pain [65]. But, although authors claim it to be a randomized placebo-controlled study, blinding and randomization allocation was not described properly. However, there

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are other recent contradictory results. In a post-hoc analysis of another previous non-inferiority trial for DXT against PGB, patients treated with DXT plus GBP showed greater pain reduction than PGB monotherapy, but not to DXT monotherapy, which was even more effective in patients who previously did not take any type of antidepressant [66]. And one of the other selected RCTs, the COMBO-DN Study, did not find any statistically significant difference between the combination of DXT with PGB and high-dose monotherapy of either of them [42]. This RCT had some biases that made results difficult to interpret. It only lasted 8 weeks in the comparison period, there was no comparison for CT against low doses monotherapy, and it had a high drop-out rate for several reasons: 109 out of 804 (13,5%) of initial participants were drop-outs due to adverse effects, 10 due to lack of efficacy, 42 due to patient decision, 64 for other reasons (it is noteworthy that 12 of them were withdrawn in spite of presenting a "satisfactory response", just before the completion of the trial, whereas this issue, far from being odd, also appears in another selected study [44]), whereas only 290 completed the study out of 804 initially randomized. Also, in another cohort study, a combination of anticonvulsant and antidepressant was not associated with improved pain control at 6 months compared to individual therapy [67]. After considering these heterogeneous results, we are not sure recent evidence is strong enough to support recommendation on combining antidepressants with gabapentinoids. If there is a need to do such combinations, evidence shows it may be better to combine gabapentinoids with tricyclics.

Nevertheless, it remains a matter of enlightenment whether PGB should be added to the treatment of refractory, uncontrolled pain, with a broad pharmacological profile. This has also been reported, with a relevant improvement of pain and treatment satisfaction, in two big observational studies [58,68], and neither TCAs nor opioids were found to be predictive factors for adverse events associated with PGB [69]. However, a re-analysis with pooled data from several RCTs showed that the therapeutic response to PGB was unaffected by concurrent NP medications, whereas the appearance of adverse events was unaffected too [70].

4.3.6 Other combinations

Finally, there have been some interesting studies on other CTs, such as the combination of limaprost (prostaglandin E1 analog) with PGB, which did not provide additional relief in symptoms when compared to monotherapy with each of these drugs [35]. It was not better either when a combination of methadone and the N-methyl-D-aspartate (NMDA) antagonist ketamine was tried out against methadone or ketamine alone [34], although the number of participants was low (14 on each arm). Either way, in a recent RCT, both ketamine alone, and in combination with magnesium were found to not provide pain relief [31], despite a short 5-week duration study period. DXT and PGB, again in monotherapy, were compared, also recently, against a combination of either one with epalrestat (an aldose reductase inhibitor approved in some countries for the improvement of subjective neuropathy symptoms associated with diabetic peripheral neuropathy) [30]. It demonstrated that PGB and Epalrestat therapy had a better effect on NP reduction than DXT and Epalrestat on a 3 and 6-month period, but we could not figure out if there was significant difference against monotherapy. Neither could we find information on the number of responders nor drop-outs. The other RCT included for qualitative analysis, but not for complete analysis due to not meeting with the requirements, compared two dose levels on a combination of dextromethorphan and quinidine [45]. There was a comparison against placebo, but not against monotherapy. Nevertheless, these drugs, in combination, are not within those recommended by clinical guidelines. So, recommendations in this regard must be cautious.

4.4 Implications for clinical practice

The burden of NP seems to be related to the complexity of neuropathic symptoms, poor outcomes and difficult treatment decisions. Importantly, quality of life is impaired

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in patients with NP owing to increased drug prescriptions and visits to healthcare providers [71]. Published guidelines up until now recommend starting treatment with monotherapy [7-8,25-26]. If the first treatment is ineffective, the recommendation most frequently given is to switch drugs for another first line treatment. However, there are some controversies as to what to do in case of poor efficacy. After achieving the maximum tolerated dose, in clinical practice, for the management of NP, a second, and even a third drug in combination regimens are frequently added [5-6,19]

There is little evidence regarding CT. Despite the different treatment options available for NP, many patients do not experience clinically significant pain relief. In addition, they often experience adverse effects that make them unable to tolerate treatment. [72]. Thus, clinicians often resort to concurrent administration of more than one pharmacological agent [58,73]. It has been demonstrated that combinations of analgesics used simultaneously in acute pain provide additive pain relief [74-75], and combination analgesics are among the most effective drugs in acute pain [76]. Given the evidence that a considerable number of patients with NP receive two or more drugs [61,63], we were only able to identify 16 recent relevant citations for this review and only 6 high-quality NP RCTs that evaluated the strategy of CT. It is even more surprising that, almost 10 years after the last review was published [27], these problems have not been addressed and clinicians still need to rely on low-quality evidence and empirical knowledge when it comes to prescribing CT for NP.

Nevertheless, with the current recent evidence, we have made an effort to suggest a flow diagram for those in need to start CT. This proposal is based on the results of this review and is only intended to serve as a guide point. It is not our aim with this review to make any recommendations. The flowchart begins for a patient who is already on antidepressants or on opioids, as concurrent medication (Figure 2). The option for those who are already on gabapentinoids or on duloxetine is not shown. Evidence in this regard is inconclusive and controversial.

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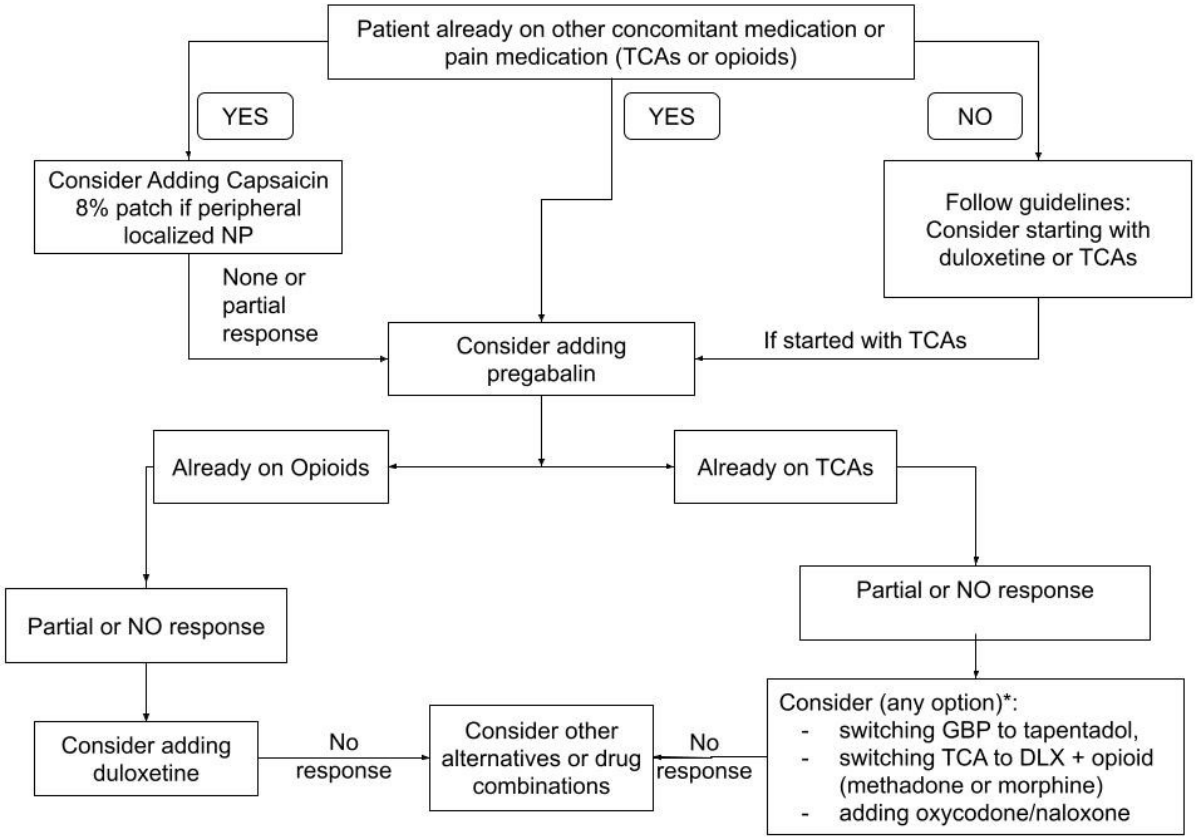

Figure 2. Guide point flowchart for a strategy for Combination Therapy for Neuropathic Pain. This flowchart is a strategy proposal to perform combination therapy for neuropathic pain that begins with a patient already on opioids or tricyclic antidepressants. The option for those who are already on gabapentinoids or on duloxetine is not shown. Evidence in this regard is inconclusive and controversial. This flowchart is a proposal drawn from the recent current evidence on this review. Clinicians should consider that it may (and should) change as new evidence is brought to light. * = evidence on opioid combination therapy is controversial and inconclusive. Frome recent evidence these seem to be the best available options. TCAs = Tricyclic antidepressants, NP = Neuropathic Pain, DLX = duloxetine

4.5 Implications for research

In order to properly identify specific CT, which provide superior efficacy and/or safety, we recommend that future NP studies of two-drug combinations include comparisons with placebo and both single-agent components. When designing the study protocol, before calculating the sample size, researchers should consider that pain RCTs have a higher placebo response [15], and that there have been claims about an increase in dropout numbers [38,41-42]. Besides, a crossover trial will take longer than a parallel one, increasing the chance of more dropouts.

In addition, we encourage NP guidelines to include recommendations of which NP CT to study, so that better evidence can be reached, and meta-analysis can be made afterwards. Reports of widespread clinical NP CT benefits provide an urge for additional future investigations. In this matter, demonstration of CT benefits by several studies in animals could also provide a rationale in this and other directions [77-86].

For instance, in non-clinical studies, potentiation of morphine by GBP has been validated in a chronic constriction injury model of NP [77-78]. Likewise, for the combination of GBP and tramadol in a partial sciatic nerve ligation model [79], or peripheral neuropathy induced by paclitaxel [80], and in diabetic neuropathy [81]. Furthermore, no significant drug-to-drug interaction between PGB and tramadol has been already studied in healthy volunteers [87], and, surprisingly, there has been a recent proposal to make a

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compound tablet with tramadol and GBP [88], even though these combinations have not yet been validated in proper RCTs.

Similarly, other combinations have been also tested on animal models. THC (with no CBD) and GBP reduced mechanical and cold allodynia in a chronic constriction injury model, but without diminishing the THC-related side effects [82]. Another pan-cannabinoid receptor agonist, when administered together with morphine, reduced allodynia in a synergistic manner but had only an additive effect on motor incoordination [83]. The same agonist had supra-additive effects on cold allodynia in a post-operative model, combined with a selective noradrenaline reuptake inhibitor [84].

Finally, researchers could also try different combinations. CT with 2 or more classes of antiepileptics is common in clinical practice for epilepsy disorders. This has not been fully explored in NP. In this matter, some results have been found in a nerve ligation model, where carbamazepine and PGB synergistically ameliorated NP at higher doses [85]. In addition, NMDA receptor antagonists, together with GBP, have also provided synergistic effects in alleviation of NP, while reducing side effects, in a SCI model [86].

Moreover, research on phenotypes responding to treatment may give further advice on CT for NP. Even among individuals with seemingly singular neuropathic conditions (e.g., PHN), substantial diversity exists with respect to various clinical manifestations, sensory examination features and presumably underlying pain mechanisms [21-22]. For instance, recently, Benavides et al have found a functional polymorphism that could predict pharmacologic response to combination of nortriptyline and morphine in NP patients [89].

4.6 Potential biases and limitations.

We have tried to scope the results of this review in the most objective way possible. However, we have some difficulties finding data. First, some trials were found after the third, or even the fourth database search. So, even being unlikely, there still exists the possibility of missing RCTs. As we could not afford the fee for making a search on EMBASE, we may have missed information. Also, as the search was already very big, we did not follow on the other websites (controlled-trials.com; clinicalstudyresults.org). Thus, we may have missed a RCT. But we consider that, as the search was done on 4 major databases, with over 2.000 results, after duplicities, with over 1500 duplicated results, the probability of missing a trial was very low, and the amount of work and duplicates would increase even further. Another difficulty we found was in looking for data into the proper publications. Some were very accessible, but others needed to be inferred by tables, figures, or even in the discussion. Thus, even asking a colleague (on acknowledgments) for a second reading, we may have made mistakes with the discernment of extracted data.

We could also have done a thorough meta-analysis including all those RCTs published prior to 2012 [27]. By doing this we could have achieved a quantitative analysis. Chaparro et al did so with only 2 RCTs. But, given the changes in trial methodology and requirements by EMA and FDA, and that the NNT has increased (accompanied by a decrease in effect size) which stabilized around 2010 [10], we thought it would be wise not to include them. Mixing those trials could generate bias and confusion. Maybe we should have been more thorough and include those published after 2010. But it would be wiser to try to make a complete meta-analysis based on individual data, not sizing up from several RCTs, but by shelling individual data of every RCT and, only then, making the complete meta-analysis. This work would have been very time consuming just only for the purpose of retrieving individual data on old records, and we could not afford to do it. We recommend other researchers to follow this path for the purpose of getting better evidence on CT for NP.

Finally, we decided to keep the primary outcome strictly for proportion of participants reporting ≥ 50% pain reduction from baseline (or ≥ 30% when 50% was not reported) and not add other possibilities such as ≥ moderate pain relief or ≥ moderate global improvement for the purpose of obtaining stronger evidence. In fact, the latest review did

have these other options as primary outcome [27]. If we had added these criteria in the primary outcome, we could have gathered more studies. But we feel it is awkward for a study to have measures of pain reduction as a primary outcome and afterwards not reporting the number of participants with that pain reduction on their results. Hence, giving them the same status as others, justifies the fact that it is not necessary to report it. Reporting the number of participants with a pain reduction is important. Reporting the number of participants with reduction on other issues like global improvement or pain relief is useful, but it should not compromise reporting the important one.

4.7 Agreements or disagreements with other studies or reviews.

We totally agree with Eisenberg and Suzan's review. Even though there have been several new trials using various drug combinations for NP, there are still inconsistent results due to methodological problems [24]. We partially agree with the review by Finnerup et al [8]. In the last years there have been no trials on GBP CT. Combination of PGB with TCAs may be an option, whereas its combination with DXT (or other selective serotonin noradrenaline reuptake inhibitors) is yet to be elucidated.

In a review on topical treatments for localized neuropathic pain by Casale et al, there is still insufficient evidence to support systematic use as treatment options. [90]. Now, we think that, after reviewing selected and other recent non-selected studies, CP8 may be used systematically as an add-on therapy.

We do not agree completely with conclusions by Guan et al. for anticonvulsants or antidepressants in which they say CT reduces NP [91]. Even though it was a systematic review and meta-analysis only for NP in cancer patients, only 3 of the 8 selected did have drug combinations as experimental compounds. We found that evidence in this matter remains controversial.

Again, more than 9 years from the last review, we continue to agree with the conclusions of the last systematic review [27]. For this period, the total number of citations may have increased, but the number of high-quality NP RCTs that evaluated the strategy of CT have not. Again, in our review, only one eligible study evaluated a combination of the two most widely used classes of neuropathic pain drugs, i.e., antidepressants and anticonvulsants. And once again, the paucity of recent available studies for each drug class combination studied from last review till now precludes any well-founded conclusions about most combinations. The search strategy for this review was not designed to capture all studies up to date, but only those after 2012, so maybe another review that includes all the studies published to date may come to different conclusions. However, as aforementioned, we designed the review according to changes that may have influenced RCTs. Combining recent and older RCTs may also generate confusion.

5. Conclusions

Neuropathic pain treatment continues to be an unmet medical need, as patients keep reporting inadequate pain relief. Clinicians continue to have problems dealing with how to face pharmacological strategy when first-line treatment fails. CT has been a practice adopted for many years, for which evidence is not solid. Efforts have been made to achieve better quality evidence, but it has not improved over the years. Guidelines for neuropathic pain should attempt to make recommendations on CT research, prioritizing which combinations to try to analyze over others, so that there is a way forward in the search for better evidence.

Supplementary Materials: Table S1: Secondary outcomes and other evaluations, Figure S1: Judgements about each risk of bias item presented as percentages across the 6 selected studies, Figure S2: Judgements about each risk of bias item presented as percentages across the 10 unselected studies.

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