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The safety of medications used to treat peripheral neuropathic pain, part 2 (opioids, cannabinoids and other drugs): review of double-blind, placebo-controlled, randomized clinical trials

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1 **The safety of medications used to treat peripheral neuropathic pain,**
2 **part 2 (opioids, cannabinoids and other drugs): review of double-blind,**
3 **placebo-controlled, randomized clinical trials**

4
5 **Introduction**

6 Peripheral neuropathic pain is a highly disabling condition for patients and a
7 challenge for physicians. Although many drugs have been assessed in scientific
8 studies, few have demonstrated clear clinical efficacy against neuropathic pain.
9 Moreover, the paucity of data regarding their safety raises the question of the
10 benefit-risk ratio when used in patients experiencing peripheral neuropathies.

11
12 **Areas covered**

13 We conducted a review of double-blind, placebo-controlled, randomized clinical
14 trials to assess the safety of medications used to treat peripheral neuropathic pain.
15 This second review was focused on opioids, cannabinoids, and other medications.
16 The aim was to provide an overview of the treatment-emergent adverse events
17 (TEAEs) ($\geq 10\%$) and the serious adverse effects described in clinical trials.

18
19 **Expert opinion**

20 Opioids and cannabinoids had significantly more TEAEs than placebos. Locally
21 administered analgesics, such as capsaicin, lidocaine, botulinum toxin A seemed
22 to have the most acceptable safety with only local adverse effects. The results for
23 NMDA antagonists were inconclusive since no safety report was available. Less
24 than half of the studies included presented a good description of adverse effects
25 that included a statistical comparison versus a placebo group. Major
26 methodological improvements must be made to ameliorate the assessment of
27 medication safety in future clinical trials.

28
29 **Keywords:** drug-related side effects and adverse reactions; neuropathic pain;
30 randomized controlled trials; peripheral nervous system diseases

31

1 **Article highlights box**

- 2 - Double-blind, placebo-controlled, randomized clinical trials are reviewed.
- 3 - We specifically focus on the adverse effects of opioids, cannabinoids, NMDA
- 4 antagonists, topical analgesics and botulinum toxin A medications used to treat
- 5 peripheral neuropathic pain.
- 6 - Adverse drug reactions are under-reported in most clinical trials.
- 7 - We recommend that a detailed safety assessment of medications should be
- 8 mandatory for clinical trials on peripheral neuropathic pain.

9

10

1 **1. Introduction**

2 Regarding the management of neuropathic pain, the Neuropathic Pain Special Interest
3 Group (NeuPSIG) of the International Association for the Study of Pain (IASP),
4 presented strong recommendations for gabapentin, gabapentin-extended
5 release/enacarbil, pregabalin, serotonin and noradrenaline reuptake inhibitors (SNRIs),
6 duloxetine/venlafaxine, and tricyclic antidepressants (TCAs), as first-line therapies, and
7 weak recommendations for 8% capsaicin and lidocaine patches, tramadol, botulinum
8 toxin-A (subcutaneous), and strong opioids, which were recommended as second- or
9 third-line therapies [1]. The NeuPSIG highlighted the safety and tolerability of these
10 medications, which were low to moderate for TCAs, tramadol, and strong opioids;
11 moderate for the SNRIs duloxetine and venlafaxine; moderate to high for pregabalin,
12 gabapentin, gabapentin extended release/enacarbil and capsaicin 8% patches; and high
13 for lidocaine patches and botulinum toxin-A (subcutaneous) [1]. Consequently, most of
14 the recommended medications for the treatment of neuropathic pain had moderate
15 safety and tolerability, underlining that in addition to the difficulty of identifying
16 effective treatments for neuropathic pain, the safety of these treatments gives rise for
17 concern [1]. Moreover, the American Society of Clinical Oncology's (ASCO)
18 recommendations for the prevention and the management of chemotherapy-induced
19 peripheral neuropathy (CIPN) suggested that no agent could be recommended for the
20 prevention of CIPN, and included only a moderate recommendation for duloxetine
21 regarding its treatment [2]. The authors of these recommendations also underlined the
22 paucity of data available on adverse effects in clinical trials [2].

23 An initial review on the safety of antidepressant and antiepileptic medications in
24 the treatment of peripheral neuropathic pain, based on double blind randomized clinical
25 trials, showed that the most detailed description of the safety profile of any of these

1 drugs concerned duloxetine [3]. Among the studies included, the most commonly
2 reported adverse effects were dizziness, drowsiness, nausea, and constipation. But only
3 20.0% of the studies included provided a good description of adverse effects including a
4 statistical comparison *versus* a placebo group [3], reflecting the lack of robust safety
5 data in clinical trials mentioned by the NEUPSIG and the ASCO [1,2].

6 The aim of this second review was to assess the safety profile of opioids,
7 cannabinoids and other medications used to treat peripheral neuropathic pain.

8

9 **2. Methods**

10 **2.1. Protocol**

11 The protocol of this review was not registered. The safety of medications used to treat
12 peripheral neuropathic pain was assessed based on results from clinical trials assessing
13 medications compared with a placebo, and a randomized double-blind design.

14

15 **2.2. Eligibility criteria**

16 A bibliographic search was performed to extract original articles on clinical trials
17 assessing opioids or cannabinoids or other medications (except antidepressants and
18 antiepileptics) for the treatment of peripheral neuropathic pain.

19 The inclusion criteria were established to meet the following PICOS items:
20 patients without limit of age, patients with peripheral neuropathic pain, treated by
21 opioids or cannabinoids or other medications (single therapy and chronic treatment for
22 at least 1 week, except for botulinum toxin injection, ketamine infusion and capsaicin
23 application, and follow-up of at least 1 week), compared with a placebo, and a
24 randomized double-blind design. No specific outcome was defined for the inclusion

1 criteria, whatever the description of treatment-related adverse events was. Studies were
2 included and analyzed only if the full-text was available and in English.

3 The exclusion criteria specified restrictions on publication types (exclusion of
4 reviews/meta-analyses, letters to the editor, study protocols, and case reports/case
5 series), therapeutic assessments (exclusion of pathophysiology and epidemiology
6 studies in the fields of neurology, oncology, endocrinology, infectious disease,
7 rheumatology, preclinical studies), and medication assessments (exclusion of massage,
8 acupuncture, electrostimulation, and physical activity, meditation, and cognitive
9 strategies). Studies were excluded if they were focused on central pain or pain other
10 than peripheral neuropathic pain or unknown origin. Studies assessing pharmacokinetic
11 parameters, drugs in development (drug identified only by a code), drug combinations,
12 phase 1 trials, and healthy volunteer trials were excluded. Finally, medications assessed
13 in 3 or less publications were excluded.

14

15 **2.3. Information sources and search**

16 A bibliographic search of the PUBMED database (www.ncbi.nlm.nih.gov/pubmed) was
17 performed. Two data extractions were carried out in the same time frame (01/01/2000-
18 13/02/2019). The first data extraction, focused on peripheral neuropathy, was performed
19 with the following keywords “peripheral neuropathy” and PUBMED filters: clinical
20 trials, human, and English. The second data extraction, focused on neuropathic pain,
21 was performed with the following keywords sequence (((“neuropathic pain”) AND
22 randomized) AND controlled) NOT mice[Title]) NOT rats[Title] and PUBMED filters
23 for “English” and “excluding review”. All duplicate publications were removed
24 between the first and the second extraction. The literature analysis was limited to the
25 publications extracted from PUBMED.

1 **2.4. Study selection**

2 All PUBMED study identification numbers (PMID) were extracted from PUBMED and
3 collated in Zotero software (Roy Rosenzweig Center for History and New Media) to
4 create a Zotero bibliographic database including the following details for each
5 publication: authors, title, journal, year, and abstract. This Zotero bibliographic database
6 was thereafter extracted to Excel software (Microsoft) for analysis. An initial
7 publication selection based on title and abstract was performed by authors NK and DB.
8 After this first study selection, all the authors performed a second study selection based
9 on the full-text of the publication and in accordance with the inclusion/exclusion
10 criteria. If a discrepancy with respect to the inclusion/exclusion criteria was noted for a
11 publication, consensus between the authors was sought on whether to include or
12 withdraw the publication.

13

14 **2.5. Data collection process and data items**

15 The full-texts of the selected studies were analyzed and the following items were
16 collected: authors' names, study design, drug/comparator, drug dose, number of
17 patients, duration of treatment, type of peripheral neuropathy, description or not of
18 treatment-emergent adverse events (TEAEs), list of TEAEs in study drug arm ($\geq 10\%$
19 of patients), statistical comparison of TEAEs between groups, serious adverse events
20 (SAEs) related to the study drug, dropout rate due to TEAEs in study drug arm, drug
21 efficacy and PMID.

22

23 **2.6. Risk of bias in individual studies and across studies**

24 No risk of bias was assessed across the studies included. However, the quality of the
25 safety assessment was considered and discussed in the overall analysis of the studies.

1

2 **2.7. Summary measures and synthesis of results**

3 The analyzed items were collected and presented in synthetic and harmonized tables by
4 pharmacological classes and international non-proprietary names. All the cited adverse
5 effects and statistical analyses (p-values) were derived from the studies included.

6

7 **3. Results**

8 Among the 2,148 publications identified, 50 publications describing double-blind,
9 placebo-controlled, randomized clinical trials of opioids (13 publications), lidocaine (9
10 publications), cannabinoids (8 publications), capsaicin (7 publications), botulinum toxin
11 (5 publications), ketamine (4 publications), and memantine (4 publications) medications
12 were included and analyzed in this review (Figure 1).

13

14 **3.1. Opioids**

15 Opioids, derived from *Papaver somniferum*, commonly known as the opium poppy,
16 have been known and used for thousands of years [4]. Opioids bind to specific opioid
17 receptors in the nervous system and other tissues. There are three principal classes of
18 opioid receptors, μ , κ , δ (mu, kappa, and delta). They are found principally in the central
19 and peripheral nervous system and the gastrointestinal tract. These receptors mediate
20 both the psychoactive and the somatic effects of opioids. These drugs currently remain a
21 reference for the management of moderate to severe acute pain, while they sometimes
22 remain controversial for the management of chronic pain [5]. Nevertheless, events over
23 the last few decades and the recent opioid crisis in North America and most developed
24 countries [6–8], have highlighted their many therapeutic limitations and adverse effects.
25 Concerns about long-term adverse effects, such as physical dependency, and prescribed

1 opioid use disorder, can limit their use in patients with chronic non-cancer related pain
2 [9–12]. The main opioids used clinically to treat neuropathic pain are morphine,
3 tramadol, oxycodone, tapentadol and fentanyl. According to NeuPSIG
4 recommendations, these opioids are recommended as second to third line therapies to
5 treat neuropathic pain [13] since their benefit-risk ratio is less than optimal due to their
6 many adverse effects and their contrasting efficacy for treating neuropathic pain [14].

7 Based on highly evidence-based clinical studies (randomized, double-blind, and
8 placebo-controlled), we selected thirteen clinical studies, between 2000 and today, for
9 our analysis of opioid-induced adverse effects in the treatment of peripheral neuropathic
10 pain (Table 1). These studies included a total of 1582 patients: four of them evaluated
11 tapentadol [15–18], one fentanyl [19], two oxycodone [20,21], two tramadol [22,23],
12 one buprenorphine [24], two methadone [25,26] and one morphine [27] (Table 1).

13

14 *3.1.1. Tapentadol (Table 1)*

15 In 828 patients with neuropathic pain, the efficacy and safety of tapentadol were
16 evaluated after 4-12 weeks of treatment, with doses ranging from 50 to 500 mg daily
17 [15–18]. The doses used in these studies were in accordance with the recommendations
18 (100 to 250 mg orally twice a day). The results obtained showed that 70.9 to 86.7% of
19 patients who received tapentadol had TEAEs, including mainly nausea, drowsiness,
20 constipation, and vomiting. The drop-out rate due to TEAEs and the frequency of
21 occurrence of SAEs ranged from 0.0 to 11.4% and from 4.8 to 5.1%, respectively. None
22 of the TEAEs were statistically compared to a placebo in terms of frequency of
23 occurrence. Concerning analgesic efficacy, the studies showed a modest effect of
24 tapentadol compared to a placebo in peripheral neuropathic pain [15–18].

25

1 3.1.2. *Tramadol (Table 1)*

2 The two studies evaluating tramadol were conducted with 100 patients with cancer or
3 cancer treatment related peripheral neuropathic pain [22,23]. The tramadol doses used
4 ranged from 1-1.5 mg/kg every 6 hours for 45 days or 200-400 mg/day for 4 weeks
5 [22,23]. Only the study of Arbaiza et al. showed an average of 67.0% of patients
6 receiving tramadol who reported an adverse effect, and the drop-out rate due to adverse
7 effects was 17.0% [23]. Among the adverse effects described in these two studies, the
8 majority were reported as nausea, dizziness, vomiting, constipation, fatigue, and sleep
9 disorders. SAEs were reported by from 1.6% to 17.0% of patients. None of these studies
10 carried out a statistical comparison of the frequency of adverse effects with the placebo
11 group. Concerning the efficacy of tramadol, these two studies were positive for
12 peripheral neuropathic pain [22,23].

13

14 3.1.3. *Fentanyl (Table 1)*

15 The study by Simpson et al. evaluated fentanyl in 79 patients with neuropathic pain over
16 a 3-week period, compared to a placebo [19]. The dose varied from 100 to 800 µg per
17 dose. The doses used in this study were in accordance with the recommendations (100-
18 800 µg, 4 breakthrough episodes per day at intervals of at least 2 hours). In this study,
19 63.0% of patients reported TEAEs, mainly nausea, dizziness and drowsiness. Among
20 these TEAEs, 1.0% were reported as serious and 11.7% of patients discontinued the
21 trial because of TEAEs. The frequency of these TEAEs was not statistically compared
22 with a placebo [19]. The main TEAEs observed were identical to those indicated in the
23 SPC.

24

1 3.1.4. Oxycodone (Table 1)

2 The studies, involving 318 patients, evaluated the analgesic effect of oxycodone in
3 patients with diabetic neuropathic pain [20,21]. These studies evaluated daily doses of
4 oxycodone ranging from 10 to 60 mg/day for 6 weeks. The doses used were in
5 accordance with the recommendations. TEAEs were reported only in the study of
6 Gimbel et al. and 96.0% of patients declared TEAEs, mainly constipation, nausea,
7 dizziness, drowsiness, pruritus, dry mouth, and vomiting [21]. The SAE rate in this
8 study was 4.9% and the drop-out rate was 5.2%. No statistical comparison with a
9 placebo was made in this study [21]. The main TEAEs observed were consistent with
10 those of SPC. Oxycodone significantly reduced peripheral neuropathic pain in these 2
11 studies [20,21].

12
13 3.1.5. Morphine (Table 1)

14 A study evaluating slow-release (SR) oral morphine was conducted on a total of 38
15 patients with peripheral neuropathic pain and complex regional pain syndrome I [27].
16 The dose evaluated was 90 mg/day over 1 week. The recommended doses in clinical
17 practice are 10-15 mg of morphine every 4 h or as needed (after 1-2 weeks conversion
18 to long-acting opioids or transdermal applications, use short-acting drug as needed and
19 as tolerated). The results of this study showed that 90.0% of patients reported a TEAE,
20 mainly nausea, vomiting, itching and headache. No statistical comparison with a
21 placebo was made in this study. The analgesic efficacy of morphine in peripheral
22 neuropathic pain was demonstrated in this study [27].

23
24
25

1 *3.1.6. Methadone (Table 1)*

2 Two studies evaluated methadone on a total of 33 patients with various peripheral
3 neuropathic pains [25,26]. The dose evaluated was 10-20 or 30 mg daily over 4 weeks
4 or 40 days, and conformed with the doses recommended in clinical practice. The results
5 showed that patients reported several TEAEs, mainly nausea, dizziness and drowsiness
6 [25,26]. Only the study of Harrison et al. demonstrated that 40.0% of patients elicited
7 TEAEs [25]. No statistical comparison with placebo was made in these studies. The
8 analgesic efficacy of methadone in peripheral neuropathic pain was not demonstrated in
9 these two studies [25,26].

10

11 *3.1.7. Buprenorphine (Table 1)*

12 The only study evaluating buprenorphine was conducted by Simpson et al. on a total of
13 186 patients with diabetic neuropathic pain [24]. The dose evaluated was 10-40 µg / h
14 using transdermal patches over 12 weeks. The recommended doses in clinical practice
15 are 5-40 µg / h. The results showed that 93.6% of patients reported an adverse effect,
16 mainly nausea and constipation. No statistical comparison with a placebo was made in
17 this study. The analgesic efficacy of buprenorphine in peripheral neuropathic pain was
18 not demonstrated in this study (intent-to-treat analysis), mainly explained by the
19 occurrence of TEAEs and related drop-outs [24].

20

21 **3.2. Cannabinoids**

22 Like opioids, cannabinoids have been known and used since antiquity, both for medical
23 and recreational purposes. They are mainly composed of the phytocannabinoid
24 tetrahydrocannabinol (THC) and cannabidiol (CBD) is another major constituent of the
25 plant [28]. Synthetic cannabinoids are manufactured artificially and newer compounds

1 are no longer related to natural cannabinoids or are based on the structure of the
2 endogenous cannabinoids [29]. Cannabinoids produce their physiological and
3 behavioral effects mainly via two types of cannabinoid receptors, termed CB1 and CB2
4 [30]. Currently, the use of cannabinoids to treat neuropathic pain, and more broadly
5 chronic pain, remains controversial and their medical use remains limited to a few
6 countries in the world, mainly in cancer support care. Among the studies selected in this
7 review, 8 studies, involving a total of 537 patients, evaluated tetrahydrocannabinol
8 (THC) / cannabidiol (CBD) [31–34], nabilone [35], Cannabis cigarette [36,37] and CT-
9 3 1',1'dimethylheptyl- Δ 8-tetrahydrocannabinol-11-oic acid [38] (Table 2).

10

11 3.2.1. *Tetrahydrocannabinol (THC) / cannabidiol (CBD) (Table 2)*

12 Four studies with 222 patients treated with inhaled THC/CBD(2-12 inhalations/day;
13 27 mg/ml / 25 mg/ml, spray of 100 μ L; 2.7 mg / 2.5 mg, 11 inhalations/day) were
14 conducted over 4 weeks until 15 weeks [34,31–33]. They showed that the main TEAEs
15 observed were fatigue (15-43.8%), dizziness (28.6-37.5%), nausea (17-37.5%) and dry
16 mouth (17.5-31.3%). However, none of these TEAEs were statistically compared to a
17 placebo. The drop-out rate due to TEAEs was about 18 and 19% in 2 [34,31] of the 4
18 studies. THC/CBD association was effective (primary endpoint) in two studies [31,34]
19 and not in the two other studies [32,33].

20

21 3.2.2. *Nabilone (Table 2)*

22 Only one study tested nabilone 1-4 mg/day versus placebo in a monocentric setting with
23 few patients (13 patients treated with nabilone) [35]. The overall TEAE was about 54%
24 but not compared to a placebo group. The drop-out rate for TEAEs corresponded to the
25 rate of SAEs in this study, i.e. 5.4%. In the selected study, nabilone was effective [35].

1

2 *3.2.3. Cannabis cigarette (Table 2)*

3 Two studies evaluated the effect of cannabis cigarettes (1-8% Δ -9-THC and 3.56% Δ -9-
4 THC) several times a day in 41 patients versus a placebo group over 7 weeks and 12
5 days [36,37]. In the first study, the main TEAE was tachycardia (46%) and not
6 compared to placebo groups, with a drop-out rate of 12.5% [36]. In the second study,
7 the main TEAEs were anxiety, sedation, disorientation, confusion and euphoria. No
8 proportion of TEAEs was provided in the study, but these TEAEs were significantly
9 greater than those of the placebo group. About 4.0% of patients treated with cannabis
10 cigarettes developed SAEs, but no patient dropped-out due to TEAEs [37]. Cannabis
11 cigarettes were effective (primary endpoint) in the two selected studies [36,37].

12

13 *3.2.4. CT-3 1',1'dimethylheptyl- Δ 8-tetrahydrocannabinol-11-oic acid (Table 2)*

14 Only one study assessed CT-3 1',1'dimethylheptyl- Δ 8-tetrahydrocannabinol-11-oic acid
15 administered by capsule at 40-80 mg/day in 10 patients versus a placebo for 1 week
16 [38]. There are no details on TEAEs but overall TEAEs were reported to be
17 significantly higher than those of the placebo group. SAEs were reported in 10.0% of
18 patients as was the dropout rate [38]. In the selected study, CT-3 1',1'dimethylheptyl-
19 Δ 8-tetrahydrocannabinol-11-oic acid was effective (primary endpoint) [38].

20

21 **3.3. NMDA antagonists**

22 N-Methyl-D-Aspartic Acid (NMDA) antagonists act, as their name suggests, by
23 blocking NMDA receptors (NMDARs). NMDARs are ionotropic receptors, activated in
24 physiological condition by glutamate and glycine, and are essential for normal brain
25 function including memory and synaptic plasticity. They are the only glutamate

1 receptors to be specifically activated by the pharmacological agonist NMDA. The
2 activation of NMDARs has been associated with neuropathic pain and result from
3 increased spinal neuron sensitization, leading to a heightened level of pain. NMDA
4 antagonists may reduce pain by reducing central sensitization. Moreover, NMDA
5 antagonists may reduce opioid tolerance. Several NMDAR antagonists are available,
6 mainly ketamine, memantine, and dextromethorphan used for pain management. These
7 antagonists are important modulators of chronic pain and have been shown to be useful
8 in preventive analgesia by reducing acute postoperative pain, analgesic consumption, or
9 both when added to more conventional means of providing analgesia, such as opioids
10 and nonsteroidal anti-inflammatory drugs, in the perioperative period. The severity and
11 frequency of adverse effects depend on affinity for the NMDAR [39]. This review
12 reports 8 studies including a total of 456 patients which evaluated ketamine [40–43] and
13 memantine [44–47] (Table 3).

14

15 *3.3.1. Ketamine (Table 3)*

16 Ketamine is used in high doses as a general anesthetic, and in low doses as an analgesic.
17 Ketamine is a phenylpiperidine, the racemic form of which is used clinically. It
18 comprises similar amounts of two stereoisomers that have different pharmacological
19 properties: the S(+) ketamine is four times more potent than the R(-) isomer, and is
20 associated with faster awakening and a decrease in hallucinatory phenomena [48,49].

21 Three studies were conducted on a total of 250 patients to evaluate the efficacy
22 of the perioperative administration of S(+) ketamine [42] and R(-) ketamine (143 treated
23 patients) [40,41] on neuropathic pain after thoracotomy. Ketamine was injected locally
24 before incision and infused via the epidural [40] or intravenous [40–42] route during
25 and after the surgical procedure with different doses, ranging from 0.5 to 1 mg/kg for

1 induction and 0.1 to 1 mg/kg for maintenance infusion during surgery. Patients were
2 followed up to 6 months post-surgery. The results of these studies showed that patients
3 receiving ketamine reported adverse effects in 12.1-51.1% of cases. The main adverse
4 effects related to ketamine were nightmares/psychotomimetic effects, pruritus,
5 hypotension and dry mouth sensation. Patients who had received epidural ketamine
6 experienced more cognitive and visual effects such as nightmares and diplopia than
7 when administrated by the intravenous route, but there was no statistical difference. The
8 TEAEs were statistically compared to a placebo but there was no difference in terms of
9 frequency of occurrence. Moreover, the rate of drop-outs due to adverse effects was null
10 in these studies.

11 An additional study included a total of 47 patients and 22 patients receiving
12 ketamine in 1% cream form with 3 applications / day, compared to a placebo for 3
13 weeks to relieve various peripheral neuropathic pains [43]. In this study patients
14 reported TEAEs in 30% of cases only in the ketamine group. The drop-out rate due to
15 TAEs for this study was 9.1%. Finally, there were no statistical comparisons of TEAEs
16 with a placebo in terms of frequency of occurrence in any of the studies.

17 Concerning analgesic efficacy, the studies showed no significant effect
18 compared to placebo groups. The doses used in these studies were in accordance with
19 the recommendations (0.5 to 2 mg/kg for the first induction and 0.1 to 1 mg/h/kg for
20 maintenance infusion during surgery) [50]. The main adverse effects reported (>10%)
21 were also reported as very frequent (>10%) and/or frequent (1-10%) in the summary of
22 product characteristics (SPC). Nevertheless, some adverse effects indicated as very
23 frequent and/or frequent in SPC did not appear in the studies analyzed, such as
24 increased respiratory rate, erythema and morbilliform rash.

25

1 3.3.2. *Memantine (Table 3)*

2 Since the development of chronic neuropathic pain involves central sensitization and
3 NMDA receptor activation, well-tolerated uncompetitive NMDA receptor antagonists
4 such as memantine hydrochloride (NAMENDA) are of interest to clinicians. Memantine
5 is an amantadine derivative first synthesized in 1968 and approved in 2000 by the Food
6 and Drug Administration for the treatment of moderate to severe dementia in
7 Alzheimer's disease. Memantine is a low-affinity uncompetitive NMDA-receptor
8 antagonist which dissociates rapidly from the NMDA receptor channel after
9 inactivation, thereby causing minimal interference with normal physiological
10 transmission mediated by NMDA receptors. In addition to its rapid blocking /
11 unblocking kinetics, it is associated with high bioavailability and no cytochrome P-450
12 inhibition or CYP induction. The most common adverse reactions (incidence $\geq 5\%$ and
13 higher than placebo) caused by memantine are dizziness, headache, confusion and
14 constipation. There is no described contraindication for memantine but it is
15 recommended to reduce the dose in patients with renal and hepatic impairment. Despite
16 its potential, a recent meta-analysis concluded that the use of memantine for chronic
17 pain is limited and uncertain [51]. In view of this, it was useful to consider the safety of
18 memantine in the management of neuropathic pain.

19 In the present review, we identified 4 double-blind, placebo-controlled,
20 randomized clinical trials that included a total of 112 patients and 71 patients receiving
21 oral memantine (from 10 to 40 mg daily) or a placebo for a treatment duration from 4 to
22 16 weeks [44–47]. Three of the 4 studies reported no positive therapeutic effects of
23 memantine on neuropathic pain [44–46]. Only one study reported TEAEs in more than
24 10% of the patients corresponding to dizziness, headache, nausea and drop-foot [47].

1 Given the small sample sizes, the short period of observation (from 4 to 16
2 weeks) and the disparity of doses used (10 to 40 mg), the conclusions drawn from these
3 studies were limited and underlined the necessity for largescale clinical trials to
4 investigate such adverse effects.

5 **3.4. Capsaicin**

6 Capsaicin (6-nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methyl- (6E)), a
7 natural alkaloid, extracted from the *Solanaceae* plant family (red chili peppers),
8 selectively binds to the transient receptor potential vanilloid 1 (TRPV1), a ligand-gated,
9 nonselective cation channel, predominantly expressed in unmyelinated C nerve fibers).
10 Opening the ion channel leads to depolarization and the production of action potentials,
11 which are usually perceived as itching, pricking or burning sensations. Repeated
12 applications or high concentrations give rise to a long-lasting effect, which has been
13 termed 'defunctionalization' of nociceptor fibers. Defunctionalization is due to a number
14 of effects that include temporary loss of membrane potential, inability to transport
15 neurotrophic factors leading to phenotype alteration, and the reversible retraction of
16 epidermal and dermal nerve fiber terminals [52]. Contrary to other natural irritants,
17 capsaicin induces an initial pain response, followed by a lasting refractory state,
18 traditionally referred to as desensitization in which the previously excited neurons are
19 unresponsive not only to a repeated capsaicin challenge but also to various unrelated
20 stimuli [53].

21 Low-concentration (<1%) capsaicin creams might function as counterirritants. A
22 Cochrane review from 2012 concluded there were insufficient data to draw any
23 conclusions about the efficacy of low-concentration capsaicin cream in the treatment of
24 neuropathic pain [54]. A high-concentration (8%) patch was developed to increase the
25 amount of capsaicin delivered to the skin, and improve tolerability. Rapid delivery is

1 thought to improve tolerability because cutaneous nociceptors are 'defunctionalized'
2 quickly, and single application avoids both noncompliance and contamination of the
3 home environment with particles of dried capsaicin cream [55]. Its clinical use is
4 approved for peripheral neuropathic pain of diverse etiology in the European Union, and
5 for the treatment of post-herpetic neuralgia in the USA. A Cochrane review of ten clinical
6 studies with high-concentration topical capsaicin involving 2903 patients with post-
7 herpetic neuralgia, painful human immunodeficiency virus (HIV)-neuropathy and
8 peripheral diabetic neuropathy, found moderate or more substantial levels of pain relief
9 than control treatment [55].

10 The seven trials included in our analysis comprised a total of 580 patients (Table
11 4). Capsaicin was tested in diabetic neuropathic patients in three of them as a 0.025%
12 (in 33 patients [56]) or 0.075% (in 21 patients [57]) lotion or as a 8% patch (in 186
13 patients [58]) versus a placebo for 8 to 12 weeks. One trial assessed capsaicin in low
14 concentration (0.625% or 1.25%) patches versus a placebo or a 0.075% lotion in 5
15 diabetic neuropathic patients and 55 post herpetic neuropathic patients for 6 weeks [59].
16 Another trial assessed a 0.025 liposomal capsaicin lotion in 14 post herpetic neuropathic
17 patients for 6 weeks [60]. Yet another trial assessed a 0.1 mg dose capsaicin injection in
18 30 Morton's neuroma patients versus placebo (28 patients) [61]. A 0.075% capsaicin
19 lotion was also assessed in 26 HIV-associated peripheral neuropathic patients versus
20 placebo for 4 weeks [62]. The number of positive studies (analgesic efficacy of
21 capsaicin compared to placebo) was only 3 (43%). These positive effects were modest
22 and obtained for the 0.1 mg dose in Morton's patients and the high dose (8%) capsaicin
23 patch in diabetic subjects. Lower dose capsaicin patches gave inconsistent results in
24 Moon et al.'s trial since only the lower (0.625% concentration) resulted in a positive
25 effect, while the higher concentration patch (1.25%) failed to have a significant

1 analgesic effect [59]. TEAEs, mainly skin reaction at the administration site, were
2 observed in 46.6% to 87.5% of patients (among the six studies that evaluated overall
3 frequency), who reported at least one TEAE associated with capsaicin (of which 0.0%
4 to 2.2 were considered serious), leading to dropouts in 2.2 to 33.3% of cases. The main
5 TEAEs observed were burning sensation (3-41.7%) and erythema (1.1-11.1%) (Table
6 4). It was observed that the safety assessment of capsaicin was not performed in one
7 study.

8 Data obtained for low concentration capsaicin are in line with recent conclusions
9 made on the safety of these capsaicin preparations [54]. Hence, local skin irritation,
10 often mild and transient but possibly leading to withdrawal, was common, while
11 systemic adverse effects were rare when low concentration capsaicin lotions were
12 tested. Interestingly, liposomal topical capsaicin was tested in a small number of post-
13 herpetic patients [60] to increase the therapeutic index. This delivery system was
14 designed to deliver the medication to its target with fewer adverse effects.

15 Unfortunately, safety data are scarce. Further studies are thus needed with this type of
16 formulation. In Morton's neuroma subjects, a single dose of capsaicin injected locally
17 resulted in a significant decrease in pain, while the overall adverse effect profile of all
18 causalities and treatment-related characteristics was similar in both the capsaicin and
19 control groups. Given that this was an exploratory study, there is more to learn
20 regarding dosing, the control of procedure pain, and effect durability. Data obtained
21 with high concentration capsaicin were also in line with conclusions made recently
22 regarding the safety of these capsaicin preparations [55]. Hence, one 30-minute
23 capsaicin 8% patch treatment provides modest improvements in pain and sleep quality
24 versus a placebo in patients with painful diabetic peripheral neuropathy, whereas, apart
25 from application site reactions, TEAEs were similar between groups. This result is of

1 importance in this particular condition. Hence, the clinical characteristics of painful
2 diabetic peripheral neuropathy which involve distal extremities in hands/feet have been
3 postulated as being unsuitable for the application of patch preparations with high
4 concentrations [63].

5 **3.5. Lidocaine**

6 Lidocaine is an amide-type local anesthetic agent that acts by stabilizing neuronal
7 membranes. Lidocaine is a voltage-gated sodium channel inhibitor, which acts by
8 blocking the abnormal functioning of Nav1.7 and Nav1.8 sodium channels in the
9 dermal nociceptors of A delta and C fibers, thereby reducing the number of ectopic
10 discharges [64]. Other effects on keratinocytes and immune cells, or the activation of
11 irritant receptors (TRPV1 and TRPA1), may also contribute to the analgesic effect of
12 topical lidocaine [65]. Long-term use may cause a loss of epidermal nerve fibers [66].
13 Lidocaine is mainly used as a 5% lidocaine patch and has demonstrated efficacy in a
14 variety of neuropathic pain conditions and in long-term treatment. It has an excellent
15 safety profile, does not require dose titration, and can easily be applied by the patient
16 [64]. However, these results must be mitigated by the results of the overview of
17 Cochrane Reviews of topical analgesics for acute and chronic pain in adults. They
18 showed very low quality but the findings were typically limited to single studies or
19 comparisons with sparse data [67].

20 Nine studies assessing lidocaine in peripheral neuropathic pain were included in
21 a review enrolling a total of 760 patients and 492 patients treated with lidocaine [68–76]
22 (Table 4). As can be seen three studies focused on various peripheral neuropathic pains
23 [69,70,73], two on postoperative neuropathic pain [68,72], two on post-herpetic
24 neuropathic pain [71,76], one on HIV-associated neuropathy [74], and one on focal
25 peripheral neuropathic pain syndromes [75]. Six studies mentioned the use of a 5%

1 lidocaine patch applied 12-24 hours per day for 1 to 12 weeks [68,70–72,75,76], two
2 studies with a 5% topical gel with one to two applications per day for 1 to 2 weeks
3 [73,74], and one with a 3 mg/kg lidocaine intravenous infusion once per week for 4
4 weeks [69]. One study did not report TEAEs [74], one study reported no TEAEs \geq 10%
5 [76], and one study did not report the frequency of overall TEAEs [72]. In other studies,
6 overall TEAEs for topical lidocaine ranged between 13.6% and 52% of lidocaine treated
7 patients. Only one study assessed the statistical significance of the overall TEAEs of
8 topical lidocaine, and found no difference compared to the placebo group [73]. The
9 main TEAEs for topical lidocaine were local reactions ranging from 11.6 to 21.9%.
10 Only one study assessed the statistical significance of these TEAEs and found no
11 difference in comparison to the placebo group [72]. The study assessing lidocaine
12 infusion reported a 14.3% frequency of overall TEAEs with no significance in
13 comparison to the placebo group [69]. No SAEs were reported in the 6 studies
14 mentioning it [68–70,73–75]. Drop-out rates due to TEAEs were reported in 7 studies
15 and ranged between 0 and 7.0% [68–71,73–75].

16 Among the studies included, seven studies found positive results on peripheral
17 neuropathic pain [68–71,73,75,76] and two negative results [72,74].

18

19 **3.6. *Botulinum toxin (BoNT)***

20 BoNT is protein group produced by *Clostridium botulinum* bacteria. Botulinum toxin A
21 (BoNT-A) and B (BoNT-B) are the most commonly used drugs. BoNT-A is currently
22 approved for several indications such as dystonia or seizures, and cosmetic treatments
23 [77]. BoNT-A enters the nerve ending, blocks exocytosis and acetylcholine secretion,
24 resulting in blocking muscle innervation at the neuromuscular junction and inducing
25 flaccid paralysis [77]. BoNT-A also reduces neuropathic pain. BoNT-A inhibits the

1 secretion of pain mediators (substance P, glutamate, and calcitonin gene related protein
2 (CGRP)) from the nerve endings and dorsal root ganglions (DRG), reduces local
3 inflammation around the nerve endings, deactivates sodium channels, and exhibits
4 axonal transport (for review see: Park and Park, 2017 [77]).

5 Among the publications selected, five publications assessing BoNT-A presented
6 results from double blind placebo controlled trials, three of them with parallel groups
7 [78–80] and the remaining two with a cross-over design [81,82] (Table 4). In these
8 studies, a total of 177 patients were included for the treatment of various peripheral
9 neuropathic and diabetic neuropathic pains, and 109 patients received one intradermal
10 injection of BoNT-A (50-190 U) [78,80–82] or two intradermal injections of BoNT-A
11 (until a maximum of 300 U) [79]. The follow-up of these patients was 3 weeks for one
12 study [80], 12 weeks for two studies [81,82], and 24 weeks for the two other studies
13 [78,79]. All the studies concluded on significant and positive results of BoNT-A
14 relating to peripheral neuropathic pain [78–82]. One study did not provide safety data
15 on TEAEs [81]. The safety data available in the remaining studies mentioned very few
16 TEAEs, no TEAEs or less than 10% [80,82], and pain at the injection site which was,
17 however, not significant in comparison to the placebo groups [78,79]. No SAEs were
18 recorded in two studies [79,82] and unknown in the three others [78,80,81]. No patient
19 dropped out of the studies due to TEAEs.

20 The safety profile of BoNT-A was assessed in four meta-analyses for trigeminal
21 neuralgia [83], painful temporomandibular disorders [84], upper limb spasticity after
22 stroke and traumatic brain injury [85], and overactive bladder [86]. None of these meta-
23 analyses found significant adverse effects related to BoNT-A injections between BoNT-
24 A and placebo groups [83–86].

1 In conclusion, BoNT-A has a good safety profile relating to peripheral
2 neuropathic pain with few or no TEAEs reported in the studies selected.

3 4 5 6 **4. Conclusion**

7 Among the studies included, 12.0% (6) of them did not provide any information on
8 TEAEs, 34.0% (17) on SAEs, and 16.0% (8) on drop-out rates. Adverse events were
9 reported as secondary outcomes for 64% (32) of studies, as sporadic observations for
10 34% (17) of them. For one study (2%), there was no information on adverse events.

11 Among the studies detailing TEAEs, 36.4% (16) studies did not provide information on
12 the overall rate of TEAEs, and 47.7% (21) did not assess the statistical significance of
13 TEAE frequency in comparison with the placebo group.

14 Moreover, peripheral neuropathic pain, defined by the IASP as “pain caused by
15 a lesion or disease of the peripheral somatosensory nervous system”, refers to a broad
16 range of clinical conditions that can be categorized as degenerative, traumatic,
17 infectious, metabolic, or toxic [87]. Regarding the trials included in this review, a clear
18 disequilibrium can be observed regarding the number of trials performed on patients
19 suffering from peripheral neuropathy of metabolic origin (28% of studies focusing
20 specifically on diabetic neuropathy), of traumatic origin (12% of studies focusing
21 specifically on postoperative neuropathic pain) and of infectious origin (14% of studies
22 focusing specifically on HIV patients and 6% on post-herpetic neuropathy) in
23 comparison to other etiological origins. Moreover, 30% of studies included populations
24 of patients with peripheral neuropathic pain of various origins, making it difficult to
25 assess safety (and efficacy) for a specific type of peripheral neuropathy. Only one study

1 included patients with CIPN, whereas this peripheral neuropathy is highly prevalent
2 among cancer patients and cancer survivors [88].

3 The safety of opioids was statistically assessed in only two publications. One
4 publication for tramadol showed a significantly higher overall frequency of TEAEs
5 (67%) than a placebo [23]. One publication relating to oxycodone showed significantly
6 higher frequencies of constipation (42.0%), drowsiness (40.0%), nausea (36.0%),
7 dizziness (32.0%), pruritus (24.0%), vomiting (21.0%), and dry mouth (16.0%) than a
8 placebo [21]. In the light of the results of all the studies, the benefit-risk ratio of opioids
9 seems far from satisfactory for treating neuropathic pain. Since the analgesic efficacy of
10 opioids on neuropathic pain is subject to considerable uncertainty, [14] with a range of
11 TEAE frequency from 40.0 to 96.0% (SAEs: 0.0 to 17.0%), opioids do not seem to be
12 favored for the treatment of peripheral neuropathic pain, not to mention the effects of
13 long-term tolerance, dependence and substance use disorder, which were not evaluated
14 in the studies selected. This observation is in line with the results of the various recent
15 meta-analyses [14,89–92].

16 Concerning prescribed opioid use disorder, the non-medical use of, and
17 dependence on, pharmaceutical drugs has been described as a major health problem. An
18 estimated 26 to 36 million people were using opioids in 2010, with around half of them
19 using pharmaceutical opioids [93]. There are an estimated 15.6 million opioid
20 dependent people worldwide, and the global consumption of opioids is considered to be
21 increasing [94]. Prescribed opioid use disorder is a chronic relapsing condition with
22 significant cost to human life [95].

23 There are few or no studies that have actually compared the risks of opioid use
24 disorder between these different drugs. Nevertheless, Cepeda *et al.* [96], in a cohort
25 study using two claims databases, concluded that patients treated with tapentadol

1 immediate release have a lower risk of receiving an abuse diagnosis and developing a
2 prescribed opioid use disorder than with oxycodone immediate release. Moreover, in
3 spite of providing an overall low rate of adverse events, tramadol was shown to have
4 considerable dependence and abuse potential. Given the contribution of the μ -*opioid*
5 peptide receptor component to dependence and abuse, and considering the more
6 pronounced noradrenaline reuptake inhibition component of tapentadol, the analgesic
7 efficacy of tramadol is comparable to that of other strong opioids, but with considerably
8 fewer opioid adverse effects and less abuse potential. Its minimal serotonergic effect,
9 along with evidence of enhanced gastrointestinal tolerability and no negative effects on
10 neurogenesis, makes it a promising alternative for the treatment of chronic and
11 neuropathic pain. Moreover, unlike tramadol and oxycodone, tapentadol does not
12 depend on the CYP450 system to produce a more active metabolite [97]

13 The safety of cannabinoids was statistically assessed in only two publications
14 with significantly more TEAEs (without the frequency and details of these TEAEs) than
15 placebo in one publication [38], and significantly more central nervous adverse effects
16 such as anxiety, sedation, disorientation, confusion and dizziness (without frequency
17 details) in another publication [37]. This is consistent with results presented by Aviram
18 and Samuelly-Leichtag in their meta-analysis on the efficacy and safety of cannabis
19 based medicines for pain management [98]. The main and significant TEAEs were:
20 central nervous system-related adverse effects (risk ratio models 2.84 [2.16, 3.73], $p <$
21 0.001, cannabis based medicines vs placebo) and the most prevalent were dizziness and
22 drowsiness; gastrointestinal-related adverse effects (risk ratio models 1.86 [1.43, 2.43],
23 $p = 0.001$, cannabis based medicines vs placebo) and the most prevalent were nausea
24 and vomiting; psychological-related adverse effects (risk ratio models 3.07 [1.79, 5.26],
25 $p < 0.001$, cannabis based medicines vs placebo); hearing related adverse effects (risk

1 ratio models 3.25 [1.58, 6.67], $p = 0.001$, cannabis based medicines vs placebo) of
2 which the most prevalent was tinnitus [98].

3 The safety of ketamine infusion was statistically assessed in three publications.
4 No information was provide on overall TEAEs, but the TEAEs were detailed and not
5 significantly different from a placebo [40–42]. The safety of topical ketamine was
6 assessed in only one publication and no TEAEs $\geq 10\%$ were reported [43].

7 Very little information was available for memantine, since only one publication
8 reported the frequency of occurrence of TEAEs but without statistical comparison to the
9 placebo group [47].

10 The safety of topical capsaicin was statistically assessed in three publications,
11 but none of them reported the overall frequency of TEAEs [56,57,60]. However, two of
12 these studies reported significantly more local skin reactions (14.7% - 50%) with topical
13 capsaicin than placebo [56,57].

14 The safety of topical lidocaine was statistically assessed in three publications
15 with overall TEAEs (14.3% - 21.9%) [69,73], and local skin reactions (21.0%) [72]
16 without significance in comparison to placebo

17 Safety of local injection of BoNT-A was statistically assessed in only two
18 publications and reported non-significant pain at the injection site compared to placebo
19 [78,79].

20 So, given the paucity of safety details on the selected publication, no conclusion
21 can be clearly drawn on the safety profiles of the medications analyzed.

22

23 **5. Expert opinion**

24 Based on the selected publication, locally administered analgesics, such as capsaicin,
25 lidocaine, and BoNT-A, seem to have the most acceptable safety with only local

1 TEAEs, which is in accordance with the results of the NeuPSIG [1]. Importantly,
2 topical treatment are strictly limited to some peripheral neuropathic pain with presumed
3 local pain generator [1]. Capsaicin 8% patches and lidocaine patches are recommended
4 in second-line therapy for peripheral neuropathic pain [1]. BoNT-A is recommended in
5 third-line therapy and for specialist use [1]. Opioids and cannabinoids had significantly
6 more TEAEs than placebo. Tramadol is recommended as second-line therapy and
7 strong opioids as third-line therapy [1]. Tapentadol is not classified by the NeuPSIG
8 because of inconclusive results [1]. However, the prescription and use of opioids in the
9 context of the opioid crisis is still an unresolved issue associated with misuse, overdose
10 and death [99], and which have not been assessed in the selected publication. NeuPSIG
11 provides a weak recommendation against the use of cannabinoids for peripheral
12 neuropathic pain, mainly because of negative results, potential misuse, abuse, diversion
13 and long term mental health risks, particularly in susceptible individuals [1]. In this
14 review, the results obtained on NMDA antagonists were inconclusive because of a lack
15 of TEAE reported in the selected studies. NMDA antagonists are not classified by the
16 NeuPSIG, also because of inconclusive results [1].

17 As mentioned in our first review on antidepressant and antiepileptic medications
18 [3], the majority of the adverse effects related to medications used to treat peripheral
19 neuropathic pain are not life threatening, but they can significantly alter the quality of life
20 of patients, and be an obstacle to treatment adherence [3].

21 The main weakness of this review is related to the fact that many of the clinical
22 trials included in this review failed to sufficiently describe the safety of the drugs
23 evaluated. Although double-blind, placebo-controlled, randomized clinical trials were
24 included in this review, more than half of them did not provide a statistical analysis of
25 TEAE frequency. Consequently, caution must be taken when assessing the frequency of

1 TEAEs in these studies. Moreover, their authors did not mention if the observed adverse
2 events were related to the medications evaluated, which may have contributed to an
3 overestimation of reported TEAEs. Many issues have been raised regarding the
4 assessment and reporting of drug safety during randomized clinical trials [100];
5 however, no gold standard of evidence for safety assessment has been defined.
6 Randomized clinical trials have a limited statistical power for TEAE assessment as
7 sample sizes are designed with the main objective of efficacy. In addition, the lack of
8 adequate ascertainment and classification of TEAEs leads to inconsistencies in their
9 reporting. The hyper-selection of patients through restrictive inclusion and exclusion
10 criteria leads to limited generalizability [100].

11 We encourage the publication of clinical trials in accordance with CONSORT
12 guidelines [101]; furthermore, authors should incorporate in their manuscript a table
13 describing all the observed adverse events, including the relationship between the
14 adverse events and treatments, serious TEAEs, the dropout rate related to TEAEs, and
15 the statistical significance of these TEAEs versus placebo. Since, major reasons for
16 early withdrawal in clinical trials of treatments for chronic pain include perceived lack
17 of efficacy and adverse events, careful consideration of the trial objectives should
18 determine the definition of the trial estimand, which in turn should inform methods used
19 to accommodate missing data in the statistical analysis [102].

20

21 The management of peripheral neuropathic pain is a largely unmet medical need
22 [1]. Pain physicians and patients are still waiting for pharmacological innovations that
23 will improve the safety of pain medications.

24

25

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1 **Figure 1: Flow diagram of publication selection**

2

Authors' names	Study design	Drug/comparator dose/day (patient number) Route	Duration	Pathology	List of TEAEs (≥ 10% of patient) * different from placebo ^{ns} not statistically different from placebo # no statistical comparison to placebo	SAEs related to study drug (%)	Dropout due to TEAEs (%)	Reference (PMID)
Simpson <i>et al.</i> 2016	Parallel-group Multicenter	Buprenorphine patch 10-40 µg/h weekly (93) Placebo (93)	12 weeks	Diabetic neuropathy	All (93.6) # Nausea (43.0) # Constipation (31.2) #	4.3	30.1	27311495
Simpson <i>et al.</i> 2007	Crossover-group Multicenter	Fentanyl, 9 breakthrough pain, buccal tablet 100-800 µg (79) Placebo (79)	3 weeks	Various peripheral neuropathic pain	All (63.0) # Dizziness (13.0) # Nausea (13.0) # Drowsiness (10.0) #	1.0	11.7	17617282
Harrison <i>et al.</i> 2013	Crossover-group Multicenter	Methadone 30 mg/day (15) Placebo (15)	4 weeks	HIV-associated neuropathy	All (40.0) #	0.0	0.0	23565581
Morley <i>et al.</i> 2003	Crossover-group Multicenter	Methadone 10 mg/day (18) Methadone 20 mg/day (18) Placebo (18)	40 days	Various peripheral neuropathic pain	<i>Methadone 10 mg</i> All (UK) Nausea (36.8) # Dizziness (31.6) # Headache (26.3) # Vomiting (21.1) # Drowsiness (10.5) # Pruritus (10.5) # Constipation (10.5) # Diarrhea (10.5) # Sweating (10.5) # <i>Methadone 20 mg</i> All (UK) Nausea (47.1) # Dizziness (17.6) # Drowsiness (17.6) # Constipation (17.6) # Sweating (17.6) # Pruritus (11.7) # Diarrhea (11.7) #	0.0	22.2	14594148
Harke <i>et al.</i> 2001	Parallel group Monocenter	Morphine SR 90 mg/day (21) Placebo (17)	8 days	Neuropathic pain Complex regional pain syndrome I	All (90) # Headache (10) # Sweating (10) # Nausea (25) # Vomiting (15) #	UK	4.7	11159256
Jensen <i>et al.</i> 2006	Parallel-group Multicenter	Oxycodone CR 10-60 mg/day (82) Placebo (77)	6 weeks	Diabetic neuropathy	No safety assessment	No safety assessment	8.5	16340598
Gimbel <i>et al.</i> 2003	Parallel-group Multicenter	Oxycodone CR 10-60 mg/day (82) Placebo (77)	6 weeks	Diabetic neuropathy	All (96.0) # Constipation (42.0) * Drowsiness (40.0) * Nausea (36.0) * Dizziness (32.0) * Pruritus (24.0) * Vomiting (21.0) * Dry mouth (16.0) *	4.9	5.2	12654955

					Fatigue (15.0) ns Headache (11.0) ns			
Tominaga <i>et al.</i> 2016	Parallel-group Multicenter	Tapentadol ER 50-500 mg/day (60) Placebo (31)	12 weeks	Diabetic neuropathy Post-herpetic neuropathic pain	All (86.7)# Nausea (31.7) # Drowsiness (28.3) # Constipation (26.7) # Vomiting (18.3) # Decreased appetite (15) # Nasopharyngitis (11.7) # Drug withdrawal syndrome (10) #	UK	UK	27224908
Niesters <i>et al.</i> 2014	Parallel-group Monocenter	Tapentadol SR 200-500 mg/day (12) Placebo (12)	4 weeks	Diabetic neuropathy	No safety assessment	No safety assessment	0.0	24713310
Vinik <i>et al.</i> 2014	Parallel-group Multicenter	Tapentadol ER, 200-500 mg/day (166) Placebo (152)	12 weeks	Diabetic neuropathy	All (79.5)# Nausea (21.1)# Vomiting (12.7)#	4.8	11.4	24848284
Schwartz <i>et al.</i> 2011	Parallel-group Multicenter	Tapentadol ER, 200-500 mg/day (199) Placebo (196)	12 weeks	Diabetic neuropathy	All (70.9)# Gastrointestinal disorders (29.1)# Nervous system disorders (18.9)# Psychiatric disorders (16.8)# Respiratory, thoracic and mediastinal disorders (12.2)# Musculoskeletal and connective tissue disorders – pain (14.3)#	5.1	11.2	21162697
Sindrup <i>et al.</i> 2012	Crossover-group Multicenter	Tramadol 200-400 mg/day (64) Placebo (64)	4 weeks	Various peripheral neuropathic pain	All (UK) Nausea (25.0)# Constipation (25.0)# Vomiting (10.7)# Fatigue (26.8)# Decrease appetite (10.7)# Dizziness (16.1)# Headache (12.5)# Sleep disorder (25.0)# Pruritus (12.5)#	1.6	UK	22337471
Arbaiza <i>et al.</i> 2007	Parallel-group Monocenter	Tramadol 1-1.5 mg/kg every 6 hours (18) Placebo (18)	45 days	Cancer- or cancer treatment-related neuropathic pain	All (67.0) * Nausea/constipation (62.0) # Vomiting (39.0) #	17.0	17.0	17177582

Table 1: Summary table of opioids.

Route of administration is not provided when administered orally.

* statistically different from placebo; ns not statistically difference from placebo; # no statistical comparison to placebo; TEAE, treatment-emergent adverse event; SAEs, serious adverse event; UK, unknown; ER, extended-release; CR, controlled-release; SR, sustained-released.

Authors' names	Study design	Drug/comparator dose/day (patient number) Route	Duration	Pathology	List of TEAEs (≥ 10% of patient) * different from placebo ^{ns} not statistically different from placebo # no statistical comparison to placebo	SAEs related to study drug (%)	Dropout due to TEAEs (%)	Reference (PMID)
Lynch <i>et al.</i> 2014	Crossover-group Monocenter	Tetrahydrocannabinol / cannabidiol (Sativex®) 2-12 inhalations/day (16) Placebo (16)	4 weeks	Chemotherapy-induced peripheral neuropathy	All (UK) Fatigue (43.8) # Dizziness (37.5) # Nausea (37.5) # Dry mouth (31.3) # Increased appetite (12.5) # Diarrhea (12.5) # Headache (12.5) # Confusion (12.5) #	0.0	UK	23742737
Serpell <i>et al.</i> 2014	Parallel-group Multicenter	Tetrahydrocannabinol / cannabidiol (27 mg/ml / 25 mg/ml, spray of 100 µL) oromucosal spray maximum of 24 sprays/day (128) Placebo (118)	15 weeks	Peripheral neuropathic pain	All (UK) Dizziness (39.0) # Dysgeusia (11.0) # Nausea (17.0) # Fatigue (15.0) #	0.0	19.0	24420962
Toth <i>et al.</i> 2012	Parallel-group Monocenter	Nabilone 1-4 mg/day (13) Placebo (13)	5 weeks	Diabetic neuropathy	All (54.0) #	5.4	5.4	22921260
Selvarajah <i>et al.</i> 2010	Parallel-group Monocenter	Tetrahydrocannabinol / cannabidiol (27 mg/ml / 25 mg/ml) (15) Placebo (15)	12 weeks	Diabetic neuropathy	No safety assessment	No safety assessment	6.0	19808912
Ellis <i>et al.</i> 2009	Parallel-group Monocenter	Cannabis cigarette (1-8% Δ-9-THC) administered in 4 days smoking sessions separated by intervals of 90–120 min (16) Placebo (18)	7 weeks	HIV-associated neuropathy	All (UK) Increases in heart rate (46.0) #	UK	12.5	18688212
Nurmikko <i>et al.</i> 2007	Parallel-group Multicenter	Tetrahydrocannabinol / cannabidiol (2.7 mg / 2.5 mg) mean of 11 sprays/day (63) Placebo (62)	5 weeks	HIV-associated neuropathy	All (91%) # Dizziness (28.6) # Nausea (22.2) # Fatigue (20.6) # Dry mouth (17.5) # Vomiting (12.7) #	1.6	18.0	17997224
Abrams <i>et al.</i> 2007	Parallel-group Monocenter	Cannabis cigarette (3.56% Δ-9-THC) 3/day for 5 days (25) Placebo (25)	12 days	HIV-associated neuropathy	All(UK) Anxiety (UK) * Sedation (UK) * Disorientation (UK) * Confusion (UK) * Dizziness (UK) *	4.0	0.0	17296917
Karst <i>et al.</i> 2003	Crossover-group Multicenter	CT-3 1',1'dimethylheptyl-Δ8-tetrahydrocannabinol-11-oic acid (capsule) 40-80 mg/day (10) Placebo (11)	1 week	Various peripheral neuropathic pain	All (UK) * No details on TEAEs frequencies	10.0	10.0	14519710

Table 2: Summary table of cannabinoids.

Route of administration is not provided when administered orally.

* statistically different from placebo; ns not statistically different from placebo; # no statistical comparison to placebo; TEAE, treatment-emergent adverse event; SAEs, serious adverse event; UK, unknown.

Authors' names	Study design	Drug/comparator dose/day (patient number) Route	Duration	Pathology	List of TEAEs (≥ 10% of patient) * different from placebo ^{ns} not statistically different from placebo [#] no statistical comparison to placebo	SAEs related to study drug (%)	Dropout due to TEAEs (%)	Reference (PMID)
Ketamine								
Tena <i>et al.</i> 2014	Parallel-group Monocenter	Ketamine 0.5 mg/kg preincisional + 0.25 mg/kg/h for 48h epidural infusion (36) Ketamine 0.5 mg/kg preincisional + 0.25 mg/kg/h for 48h iv infusion (33) Placebo (35)	6 months	Postoperative neuropathic pain	All (UK) <i>Ketamine epidural group</i> Nightmares/psychotomimetic effects (25) ^{ns} Diplopia (16.7) ^{ns} <i>Ketamine iv group</i> Nightmares/psychotomimetic effects (12.1) ^{ns}	0.0	0.0	24281290
Mendola <i>et al.</i> 2012	Parallel-group Monocenter	Ketamine 0.1 mg/kg/h for 60h iv infusion (32) Placebo (30)	6 months	Postoperative neuropathic pain	All (UK) Pruritus (37) ^{ns} Hypotension (37) ^{ns} Vomiting (31) ^{ns} Nausea (25) ^{ns}	0.0	0.0	22441361
Dualé <i>et al.</i> 2009	Parallel-group Monocenter	Ketamine 1 mg/kg preincisional + 1 mg/kg/h during surgery + 1 mg/kg during 24h iv infusion (42) Placebo (44)	4 months	Postoperative neuropathic pain	All (UK) Dry mouth sensation (51.1) ^{ns} Bradypnea (21.1) ^{ns}	0.0	0.0	18783971
Lynch <i>et al.</i> 2005	Parallel-group Monocenter	1% ketamine 4 ml 3 applications/day (22) Placebo (25)	3 weeks	Various peripheral neuropathic pain	All (30.0) ^{ns} No TEAE ≥ 10%	0.0	9.1	15983466
Memantine								
Morel <i>et al.</i> 2016	Parallel-group Monocenter	Memantine 20 mg/day (20) Placebo (20)	4 weeks	Postoperative neuropathic pain	No TEAE ≥ 10%	0.0	0.0	27050431
Schifitto <i>et al.</i> 2006	Parallel-group Multicenter	Memantine 30 mg/day (24) Placebo (21)	16 weeks	HIV-associated neuropathy	All (UK)	UK	UK	16966223
Wiech <i>et al.</i> 2004	Crossover-group Monocenter	Memantine 30 mg/day (8) Placebo (8)	4 weeks	Phantom Limb Pain	All (UK) Nausea (UK) ^{ns} Fatigue (UK) ^{ns} Dizziness (UK) ^{ns} Headache (UK) ^{ns} Agitation (UK) ^{ns}	UK	UK	14742379
Nikolajsen <i>et al.</i> 2000	Crossover-group Monocenter	Memantine 20 mg/day (19) Placebo (19)	5 weeks	Post-traumatic peripheral neuropathic pain	All (34.5) # Dizziness (15.8) # Headache (10.5) #	5.3	UK	11004057

Table 3: Summary table of NMDA antagonists (ketamine and memantine).

Route of administration is not provided when administered orally.

* statistically different from placebo; ^{ns} not statistically different from placebo; # no statistical comparison to placebo; TEAE, treatment-emergent adverse event; SAEs, serious adverse event; UK, unknown.

Authors' names	Study design	Drug/comparator dose/day (patient number) Route	Duration	Pathology	List of TEAEs (≥ 10% of patient) * different from placebo ns not statistically different from placebo # no statistical comparison to placebo	SAEs related to study drug (%)	Dropout due to TEAEs (%)	Reference (PMID)
Capsaicin								
Kulkantrakorn <i>et al.</i> 2019	Crossover-group Multicenter	Capsaicin 0.075% (lotion) 3 applications/day (21) Placebo (21)	8 weeks	Diabetic neuropathy	All (UK) Skin reaction (50.0) * Burning sensation (41.7) * Erythema (11.1) ns	0.0	19.0	30472337
Moon <i>et al.</i> 2017	Parallel-group Multicenter	Capsaicin 0.625% (patch) 1 or more applications for 3 days and 1-day interval (4-day cycle) (16) Capsaicin 1.25% (patch) 1 or more applications for 3 days and 1-day interval (4-day cycle) (14) Capsaicin 0.075% (cream) 3-4 applications/day (16) Placebo (14)	6 weeks	Various peripheral neuropathic pain	Any (46.7) # Constipation (2.2) # Paresthesia (UK)	0.0	2.2	28158151
Simpson <i>et al.</i> 2017	Parallel-group Multicenter	Capsaicin 8% (patch) for 30 min once (186) Placebo (183)	12-weeks	Diabetic neuropathy	All (46.8) # Burning sensation (14) # Pain in extremity (10.8) #	2.2	0.0	27746370
Campbell <i>et al.</i> 2016	Parallel-group Multicenter	Capsaicin 0.1 mg, single dose injection (30) Placebo (28)	3 weeks	Morton's neuroma	All (50.0) # Pain in the foot (16.7) # Nausea (13.3) # Headache (10.0) # Peripheral swelling (10.0) #	0.0	0.0	26963851
Teixeira <i>et al.</i> 2015	Crossover-group Monocenter	Capsaicin 0.025% (liposomal cream) 2-3/day (13) Placebo (13)	6 weeks	Post-herpetic neuropathic pain	All (87.5%) # Discomfort (56.25%) ns	UK	0.0	25807130
Kulkantrakorn <i>et al.</i> 2013	Crossover-group Monocenter	Capsaicin 0.025% (gel) 2 inches of gel 3-4/day (33) Placebo (33)	8 weeks	Diabetic neuropathy	All (50.0) # Skin reaction (14.7) * Hypertension (33.3) ns	UK	15.2	23228119
Paice <i>et al.</i> 2000	Parallel-group Multicenter	Capsaicin 0.075% (cream) 4/day (15) Placebo (11)	4 weeks	HIV-associated neuropathy	No safety assessment	No safety assessment	33.3	10687326
Lidocaine								
Palladini <i>et al.</i> 2019	Parallel-group Multicenter	Lidocaine 5% (patch) 12h/day (180) Placebo (183)	12 weeks	Postoperative neuropathic pain	All (52.0) # Skin reaction (12.8) #	0.0	3.4	30614286
Kim <i>et al.</i> 2018	Parallel-group Monocenter	Lidocaine 1 intravenous infusion / week (3 mg/kg) (22) Placebo (21)	4 weeks	Various peripheral neuropathic pain	All (14.3) ns	0.0	0.0	29381569
Demant <i>et al.</i> 2015	Crossover-group Multicenter	Lidocaine 5% (patch) 12h/day (43) Placebo (43)	4 weeks	Various peripheral neuropathic pain	All (27.9) # Skin reaction (11.6) #	0.0	7.0	26090758
Binder <i>et al.</i> 2009	Parallel-group Multicenter	Lidocaine 5% (patch) up to 3 applications for 12h/day (36) Placebo (35)	2 weeks	Post-herpetic neuropathic pain	All (13.6) #	UK	4.5	19432499
Cheville <i>et al.</i> 2009	Crossover-group Multicenter	Lidocaine 5% (patch) 18h/day (19) Placebo (20)	4 weeks	Postoperative neuropathic pain	All (UK) Rash-desquamation (21.0) ns Worst toxicity (28.0) ns	UK	UK	19142669
Ho <i>et al.</i> 2008	Crossover-group Multicenter	Lidocaine 5% (gel) 3-5 ml twice a day (35) Placebo (35)	1 week	Various peripheral neuropathic pain	All (21.9) ns Itching (14.3) #	0.0	0.0	18180637
Estanislao <i>et al.</i> 2004	Crossover-group Multicenter	Lidocaine (5%, gel) 1/day (32) Placebo (32)	2 weeks	HIV-associated neuropathy	No details on TEAEs frequencies	0.0	6.3	15577414
Meier <i>et al.</i> 2003	Crossover-group Multicenter	Lidocaine (5%, patch) 12h/day (58) Placebo (58)	1 week	Focal peripheral neuropathic pain syndromes	All (34.5) # Rash (17.2) #	0.0	1.7	14581122

Galer <i>et al.</i> 2002	Parallel-group Multicenter	Lidocaine (5%, patch) 1/day (67) Placebo (29)	3 weeks	Post-herpetic neuropathic pain	No TEAE ≥ 10%	UK	UK	12218500
Botulinum toxin								
Ranoux <i>et al.</i> 2008	Parallel-group Monocenter	Botulinum toxin A 20–190 U (intra-dermal injection) once (15) Placebo (14)	24 weeks	Various peripheral neuropathic pain	All (UK) Pain at injection site (86.7) ns	UK	0.0	18546285
Attal <i>et al.</i> 2016	Parallel-group Multicenter	Botulinum toxin A maximum of 300 U (intra-dermal injection) one injection for 12 weeks repeated twice (34) Placebo (34)	24 weeks	Various peripheral neuropathic pain	All (UK) Pain at injection (56.0) ns	0.0	0.0	26947719
Ghasemi <i>et al.</i> 2014	Parallel-group Monocenter	Botulinum toxin A 100 U (intra-dermal injection) once (20) Placebo (20)	3 weeks	Diabetic neuropathy	All (0.0) #	UK	0.0	24778662
Chen <i>et al.</i> 2013	Crossover-group Monocenter	Botulinum toxin A 50 U (intra-dermal injection) once (20) Placebo (20)	12 weeks	Diabetic neuropathy	No safety assessment	UK	0.0	23462284
Yuan <i>et al.</i> 2009	Crossover-group Monocenter	Botulinum toxin A 50 U (intra-dermal injection) once (20) Placebo (20)	12 weeks	Diabetic neuropathy	No TEAE ≥ 10%	0.0	0.0	19246421

Table 4: Summary table of capsaicin, lidocaine and botulinum toxin.

* statistically different from placebo; ns not statistically different from placebo; # no statistical comparison to placebo; TEAE, treatment-emergent adverse event; SAEs, serious adverse event; UK, unknown.

PUBMED extraction : 2,148 publications

→ **236 publications excluded: publication type**

161 reviews and meta-analysis
20 letters to the editor
42 study protocols
10 case reports / case series
3 retractions

→ **1,108 publications excluded: no therapy assessed (epidemiology, physiopathology...)**

742 oncology studies
97 endocrinology studies
87 neurology studies
56 infectious diseases studies
37 epidemiology studies
32 anaesthesiology studies
43 other speciality medical studies (rheumatology, surgery, nephrology...)
14 preclinical/animal studies

→ **226 publications excluded: assessment of therapies without medication**

158 studies on acupuncture, electrostimulation, cold therapy, magnetic...
38 studies on physical activity, mechanical stimulation...
11 studies on meditation, cognitive therapy, virtual reality...
9 studies on radiofrequency
6 studies on massages
2 studies on physiotherapy
2 studies on other therapy (oxygenotherapy and gene therapy)

Selection of 578 publications : clinical trials on medications

→ **353 publications excluded: methodology type and objectives**

75 open label studies
57 studies with no placebo or active control
33 not randomized studies
26 studies on acute/subacute treatments or short term follow-up
16 studies on drug in development
16 studies on drug combinations

63 phase 1 / healthy volunteer studies
58 studies on central pain or not peripheral neuropathic pain
9 studies on pharmacokinetic

→ **3 publications excluded: full-text not found**

→ **86 publications excluded: antidepressants and antiepileptics**

(4 other publications including both antidepressants or antiepileptics and opioids or lidocaine or ketamine were included in the analysis)

→ **86 publications excluded : other drugs (3 or less publications by drug)**

Inclusion and analysis of 50 publications

Double-blind, placebo-controlled, randomized clinical trials on opioids (13), lidocaine (9), cannabinoids (8), capsaicin (7), botulinum toxin (5), ketamine (4) and memantine (4) medications