The safety of medications used to treat peripheral neuropathic pain, part 1 (antidepressants and antiepileptics): review of double-blind, placebo-controlled, randomized clinical trials

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Introduction

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

Areas covered

We conducted a review of double-blind, placebo-controlled, randomized clinical trials to assess the safety of medications used to treat neuropathic pain. This first review was focused on antidepressant and antiepileptic medications. The aim was to provide an overview of the treatment-emergent adverse events (≥10%) and the serious adverse effects described in clinical trials.

Expert opinion

Among antiepileptics and antidepressants, duloxetine appeared to have the most detailed safety for the treatment of peripheral neuropathic pain. Over all studies, the most commonly reported adverse effects were dizziness, drowsiness, nausea, and constipation. Only 20.0% of the included studies (N=90) presented a good description of adverse effects that included a statistical comparison versus a placebo group. Important methodological improvements must be made to improve the assessment of medication safety in future clinical trials.

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

1. Introduction

Sensitive peripheral neuropathy and its most disabling symptoms, neuropathic pain, refers to a lesion or disease of the somatosensory nervous system [1]. Peripheral neuropathy can be classified as a mixture of phenomenological, neurophysiological, pathological, and etiological parameters [2]. The most common form of peripheral neuropathy is chronic axonal length-dependent sensorimotor polyneuropathy. Neuropathic symptoms can be divided into sensory and motor symptoms. The sensory symptoms include tingling, pins/needles, numbness, tightness, burning, pain, and sensory ataxia. Motor symptoms include muscle cramps, stiffness, weakness, and wasting [3]. Peripheral neuropathy may result from various conditions, including traumatisms (e.g., amputation, surgery, nerve compression), diabetes, toxicants (e.g., neurotoxic drugs, lead, alcohol), and infectious agents (e.g., herpes zoster, leprosy) [4].

The prevalence of neuropathic pain in the general population is approximately 6.9%–10% [5–7]. According to IASP (International Association for the Study of Pain), chronic neuropathic pain can be divided in two subgroups, central neuropathic pain and peripheral neuropathic pain [8]. However, in a cohort of Spanish patients with neuropathic pain, only 12.9% had a pure peripheral neuropathic pain. Most patients with peripheral neuropathy do not develop neuropathic pain. In patients suffering from diabetic peripheral neuropathy, 21% of patients presented neuropathic pain symptoms. However, the prevalence of neuropathic pain increased to 60% in those with severe clinical neuropathy [9]. The same results have been found for patients suffering from oxaliplatin-induced peripheral neuropathy [10].

In 2016, the Neuropathic Pain Special Interest Group (NeuPSIG) from the International Association for the Study of Pain (IASP) performed a meta-analysis of randomized, double-blind clinical trials (RCTs) assessing medications for the treatment of neuropathic pain [11]. The NeuPSIG presented strong recommendations for gabapentin,

gabapentin-extended release/enacarbil, pregabalin, serotonin and noradrenaline reuptake inhibitors (SNRIs), duloxetine/venlafaxine, and tricyclic antidepressants (TCAs), which were recommended as first-line therapies, and weak recommendations for 8% capsaicin and lidocaine patches, tramadol, botulinum toxin-A (subcutaneous), and strong opioids, which were recommended as second- or third-line therapies [11]. In addition to these recommendations, the NeuPSIG highlighted the safety and tolerability of these medications, which was low to moderate for TCAs, tramadol, and strong opioids; moderate for the SNRIs duloxetine and venlafaxine; moderate to high for pregabalin, gabapentin, gabapentin extended release/enacarbil and capsaicin 8% patches; and high for lidocaine patches and botulinum toxin-A (subcutaneous) [11]. Consequently, most of the recommended medications for the treatment of neuropathic pain had moderate safety and tolerability, underlining that in addition to the difficulty of identifying effective treatments for neuropathic pain, the safety of these treatments is a concern [11]. It should be noted that chemotherapy-induced peripheral neuropathy (CIPN) is a special case. Indeed, the American Society of Clinical Oncology (ASCO) recommendations for the prevention and the management of CIPN suggested that there was no agent recommended for the prevention of CIPN [12]. For the treatment of CIPN, the available data indicate only a moderate recommendation for duloxetine. Authors of these recommendations also underlined the paucity of data available on adverse events in clinical trials [12].

The aim of this review was to assess the safety profile of medications used to treat peripheral neuropathic pain. This first review was focused on antidepressant and antiepileptic medications.

2. Methods

2.1. Protocol

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

2.2. Eligibility criteria

A bibliographic search was performed to extract original articles on clinical trials assessing antidepressant and antiepileptic medications for the treatment of peripheral neuropathic pain.

The inclusion criteria were established to meet the following PICOS items: patients without limit of age, patients with peripheral neuropathic pain, treated by antidepressant or antiepileptic medications (single therapy and chronic treatment for at least 1 week), compared with a placebo, and a randomized double-blind design. No specific outcome was defined for the inclusion criteria, whatever the description of treatment-related adverse events was. Studies were included and analyzed only if the full-text was available and in English.

The exclusion criteria specified restrictions on publication types (exclusion of reviews/meta-analyses, letters to the editor, study protocols, and case reports/case series), therapeutic assessments (exclusion of pathophysiology and epidemiology studies in the fields of neurology, oncology, endocrinology, infectious disease, rheumatology, preclinical studies), and medication assessments (exclusion of massage, acupuncture, electrostimulation, and physical activity, meditation, and cognitive strategies). Studies were excluded if they were focused on central pain or pain other than peripheral neuropathic pain. Studies assessing pharmacokinetic parameters and drug combinations, Phase 1 trials, and healthy volunteer trials were excluded.

2.3. Information sources and search

A bibliographic search of the PUBMED database (www.ncbi.nlm.nih.gov/pubmed) was performed. Two data extractions have been done on the same time frame (01/01/2000-13/02/2019). The first data extraction, focused on peripheral neuropathy, was performed with the following keywords "peripheral neuropathy" and PUBMED filters: clinical trials, human, and English. The second data extraction, focused on neuropathic pain, was performed with the following keywords sequence ((((("neuropathic pain") AND randomized) AND controlled) NOT mice[Title]) NOT rats[Title] and PUBMED filter for "English" and "excluding review". All duplicate publications were removed between the first and the second extraction. The literature analysis was limited to the publications extracted from PUBMED.

2.4. Study selection

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

2.5. Data collection process and data items

The full-text of the selected studies was analyzed and the following items were collected:

authors' names, study design, drug/comparator, drug dose, number of patients, duration of treatment, type of peripheral neuropathy, description or not of treatment-emergent adverse events (TEAEs), list of TEAEs in study drug arm (≥ 10% of patients), statistical comparison of TEAEs between groups, serious adverse events (SAEs) related to the study drug, dropout rate due to TEAEs in study drug arm, drug efficacy and PMID.

2.6. Risk of bias in individual studies and across studies

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

2.7. Summary measures and synthesis of results

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

3. Results

Among the 2148 identified publications, 92 publications describing double-blind, placebo-controlled, randomized clinical trials of antidepressant and antiepileptic medications were identified. Two full texts were not available and, overall, 90 publications were included and analyzed in this review (Figure 1).

Based on the selected publications, the following medications have been assessed:

● Antiepileptics: gabapentinoids: gabapentin, pregabalin and mirogabalin (Table 1); other antiepileptics: lamotrigine, lacosamide, levetiracetam, valproate, zonisamide, ethosuximide, carisbamate, oxcarbazepine and carbamazepine (Table 2).

● Antidepressants (Table 3): serotonin and noradrenaline reuptake inhibitors (SNRIs): duloxetine, venlafaxine and milnacipran; tricyclic antidepressants (TCAs); escitalopram.

3.1. Antiepileptics

The use of antiepileptic drugs has increased the last decade, mainly because of increased utilization in indications other than epilepsy such as neuropathic pain and psychiatry. Antiepileptic drugs are strongly associated with TEAEs, which may lead to early discontinuation of treatment (and account for almost 25% of all discontinuation of antiepileptic drug treatment) and non-adherence, and impact the quality of life of patients [13,14]. In addition, TEAEs are one of the most common causes of treatment failure [13,15]. Thus, careful safety considerations for each individual patient are crucial for the optimal treatment outcome.

3.1.1. *Gabapentinoids*

Gabapentinoids are a class of drugs that are derivatives of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), which block the α2δ subunit of voltage-gated calcium channels (VGCCs) [16]. Commonly used gabapentinoids include gabapentin, pregabalin, mirogabalin, and gabapentin enacarbil (gabapentin prodrug).

3.1.1.1 Gabapentin. Gabapentin is mainly used for the treatment of partial seizures, neuropathic pain, hot flashes, and restless leg syndrome [17]. Gabapentin, discovered by Parke-Davis in 1975, was patented in 1977 and its medical use was first authorized in the United States in 1993 [18]. Gabapentin, via α2δ calcium channel subunit inhibition [16,19], exerts antiepileptic, analgesic, and anxiolytic effects [19], and it is marketed and genericized under various names (e.g. Neurontin®). The wholesale price of gabapentin the developing

world as of 2015 was approximately US$10.80 per month, and in 2016, it was the 11th most prescribed medication in the United States, with more than 44 million prescriptions [20]. For the treatment of chronic pain, gabapentin is recommended as a first-line medication (among others) for neuropathic pain mainly caused by diabetic neuropathy and postherpetic neuralgia [21]; however, evidence of its efficacy on other types of neuropathic pain remains very limited [22].

The 15 RCTs included in our analysis included 2553 patients: 1604 received oral gabapentin or placebo. The daily dose of gabapentin administered was from 300mg to -3600mg, for a treatment duration from 10 days to 98 days, in patients with various neuropathic pain. The number of positive studies (analgesic efficacy of gabapentin compared to placebo) was only 5 (33.3%), and the effects were mainly modest. This was consistent with the last Cochrane meta-analysis, which demonstrated the limited efficacy of gabapentin on neuropathic pain [22]. Multiple TEAEs were observed, in 46.9% to 82.0% of patients (among the six studies that evaluated the overall frequency) reported at least one TEAE associated with gabapentin (of which 0.0% to 5.0 were considered serious), leading to dropouts in 0.0 to 18.0% of cases. The main TEAEs observed were dizziness (10-37.3]) and drowsiness (10.0-87.5]) (Table 1). In the six studies that reported the SAE occurrence, the gabapentin-related SAEs were gastritis and fainting episodes. It was observed that the safety assessment of gabapentin was not performed in two studies, and that four studies did not assess the frequency of TEAE occurrence (9 SAEs). Among the four studies that compared different doses or dosing regimens, we found no difference in the type (dizziness and drowsiness) and frequency of TEAE occurrence (46.9-82.0%). In addition, 13 studies (87.0%) did not statistically compare the frequencies of appearance of TEAEs with placebo, making it impossible to determine whether the TEAEs observed were indeed related to gabapentin. In the two studies that statistically compared TEAEs with placebo, one showed no difference

and the second showed that only dizziness, drowsiness, and lethargy were more frequent. This was consistent with the summary of product characteristics (SPC) for gabapentin, which described common TEAEs related to gabapentin, including drowsiness and dizziness [17]. Recently, gabapentin was also shown to induce abuse and addiction disorders, affecting 1.1% of the general population and 22.0% of the population in drug abuse treatment centers [23]. Withdrawal syndromes also exist, and occurred following discontinuation of the medication [23]. Finally, the misuse of gabapentin has been recorded for a number of reasons, including self-medication, self-harm, and recreational use [24]. Indeed, the misuse and abuse of gabapentin, known on the streets as "Gabbies," for its euphoric effects is increasing [25].

3.1.1.2 Pregabalin. Pregabalin is used to treat epilepsy, neuropathic pain, fibromyalgia, restless leg syndrome, and generalized anxiety disorder [26,27]. Pregabalin was invented and synthesized in 1990, as an antiepileptic, by Richard Bruce Silverman. Pregabalin and gabapentin had similar affinities for the human recombinant α2δ-1 subunit, although a study showed that pregabalin possessed six-fold higher affinity for the α2δ subunit than gabapentin [28]. Pregabalin is more potent than gabapentin as an analgesic and an antiepileptic [29,30]. Pregabalin, developed as a successor to gabapentin, was first approved in the United States in 2004. Pregabalin is recommended as a first-line medication for the treatment of chronic pain related to diabetic neuropathy, post-herpetic neuralgia, and central neuropathic pain [21], but its use for sciatica and low back pain [31,32], cancer-related pain [33], migraine [34], and prevention of post-surgical chronic pain [35,36] is controversial.

Our analysis included 38 RCTs representing 8739 patients: 4771 received oral pregabalin or placebo. The daily dose of pregabalin administered was from 75mg to 600mg], for a treatment duration from 7 days to 1380 days, in patients with various neuropathic pain. The number of positive studies (analgesic efficacy of pregabalin compared to placebo) was 20

(53%), and the effects were mainly modest. This was consistent with the recent Cochrane meta-analysis, which concluded that *"Evidence shows efficacy of pregabalin in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy; evidence of efficacy in central neuropathic pain is inadequate. Some people will derive substantial benefit with pregabalin; more will have moderate benefit, but many will have no benefit or will discontinue treatment"* [37]. As for gabapentin, multiple TEAEs were observed and their frequencies were similar: 7.0-85.8% of patients (among the 24 studies that evaluated the overall frequency) reported at least one TEAE associated with pregabalin (including 0.0 to10.4% considered serious among the 15 studies that evaluated them), causing from 0.0 to 21.1% of dropouts. Similar to gabapentin in terms of types and frequencies, the main TEAEs observed were dizziness (10.1-46.0%) and drowsiness (10.5-40.0%) (Table 1). In the 15 studies that reported the frequency of occurrence of SAEs, pregabalin-related SAEs were dyspnea and nausea, suicidal thoughts, tremor, and ventricular extrasystoles. The safety assessment was not performed in one study, and six studies did not assess the frequency of AE occurrence (20 for SAEs). Among the seven studies that compared different doses or dosing regimens, there appeared to be a relationship between dose and frequency of occurrence of TEAEs. Daily doses of 150, 300, and 600 mg induced dizziness (11.1% [95% CI: 5.1%–18.1%], 27.6% [95% CI: 16.6%–38.6%], and 37.3% [95% CI: 29.3%–45.3%], respectively) and drowsiness (0.0% [95% CI: 0.0%–7.0%], 17.4% [95% CI: 8.4%–26.4%], and 23.8% [95% CI: 12.8%–34.8%], respectively). Only one study statistically compared the frequencies of TEAE with placebo, making it impossible to determine whether the observed TEAEs were indeed related to pregabalin [38]. In this study, only dizziness occurred more frequently. Overall, the safety profiles observed were consistent with the SPC of pregabalin, which describes common TEAEs related to pregabalin, including drowsiness and dizziness, and SAEs, including an

increased risk of suicide and drug reactions. Finally, pregabalin can induce withdrawal symptoms following abrupt or rapid discontinuation, and recent studies have reported the risk of abuse, misuse, dependence, or overdose following the use of pregabalin [25].

3.1.1.3 Mirogabalin. Mirogabalin was developed by Daiichi Sankyo. As with other gabapentinoids, mirogabalin binds to the α2δ subunit of VGCCs, but with a significantly higher potency than pregabalin. Mirogabalin was approved in 2018 in Japan for the treatment of peripheral neuropathic pain. Clinical development of the drug for fibromyalgia treatment was discontinued in the United States and Europe after the primary endpoint was not met in Phase 3 trials [39].

Only three RCTs evaluated mirogabalin for neuropathic pain treatment, comprising 1,721 patients with diabetic peripheral neuropathic pain: 1,061 received mirogabalin or placebo. The daily dose of mirogabalin was from 5 mg to 30 mg, and the duration was from 35 days to 98 days. All studies were positive for the treatment of diabetic peripheral neuropathy; however, further studies are needed to evaluate its therapeutic effect on other types of neuropathic pain. Only the study of Merante *et al.* evaluated the percentage of subjects reporting at least one TEAEs, with 10.9% for mirogabalin 5 mg, 19.6% for mirogabalin 10 mg, 26.4% for mirogabalin 15 mg, 19.6% for mirogabalin 20 mg, and 28.1% for mirogabalin 30 mg [40]. The commons TEAEs identified by the three studies were dizziness, drowsiness, and headache (< 10% of patients). From 0.0% to 2.9% of SAEs were observed (Table 1). Only one study performed a statistical comparison of the frequencies of appearance of TEAEs between treatment and placebo, making it impossible to determine whether the TEAEs observed were indeed related to mirogabalin. In this study, only drowsiness occurred more frequently. However, the number of studies is too small to show a difference between the different doses in terms of TEAEs frequencies. Finally, concerning the

risk of abuse and misuse, the recent study of Mendell *et al.* concluded that "*This indicates therapeutic doses mirogabalin may have less abuse potential versus diazepam or pregabalin. At supratherapeutic doses (≥ 4× therapeutic dose), mirogabalin had significantly higher Drug Liking E_{max} than placebo, but lower E_{max} than pregabalin. In both studies, therapeutic doses of mirogabalin demonstrated limited evidence of abuse potential.*" [41].

3.1.2. *Other antiepileptics*

3.1.2.1 Lamotrigine. Lamotrigine (Lamictal®, GSK) is a phenyltriazine derivative that is believed to inhibit the release of excitatory neurotransmitters, particularly glutamate and aspartate. It also acts directly on neuronal ion channels, inhibiting several voltage-gated sodium channels [42] N-(Cav2.2), P/Q-(Cav2.1), and R-type (Cav2.3) [43]. Lamotrigine was approved for epilepsy in the United States in 1994 and it is still commonly used. It is indicated for the prevention and management of partial and generalized seizures either alone or in combination with other antiepileptic agents. Lamotrigine is also approved for use as a mood stabilizer in bipolar disorders. It is used off-label for several other conditions, including peripheral neuropathy, neuropathic pain, migraine headaches, and trigeminal neuralgia. However, very slow titration of the drug is required to avoid the development of rash. Lamotrigine is on the World Health Organization's List of Essential Medicines, which comprises the most effective and safest medicines needed in a healthcare system.

The three RCTs included in our analysis included 572 patients: 189 of whom received oral lamotrigine or placebo (Table 2). In all datasets, the maintenance daily dose of study medication in the lamotrigine groups was between 300 and 600 mg, inclusive, for a treatment duration from 10 to 14 weeks in patients with various neuropathic pain. The number of positive studies (analgesic efficacy of lamotrigine compared with placebo) was only 1 (33.3%). The most common TEAEs were rash, infection, diarrhea, nausea, and headache, and

the frequency of dropouts induced by TEAEs was from 6.7% to 24.0%. Only the study of Silver *et al*. evaluated the frequency of total TEAEs, with 71.0% of patients receiving lamotrigine experiencing at least one TEAE (0.0% SAE) [44]. There was no statistical comparison of the incidence of TEAEs between the treatment and placebo in these three studies. In the SPC of lamotrigine, the dose-related TEAEs included dizziness, blurred vision, diplopia, unsteadiness, nausea and vomiting, headache, and tremor. Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome, suicide, and hemophagocytic lymphohistiocytosis were SAEs. The number of studies was too small to show a difference between the different doses in terms of TEAEs frequencies.

3.1.2.2 Lacosamide. Lacosamide, discovered by Harold Kohn, Shridhar Andurkar, and colleagues at the University of Houston in 1996 [45], is indicated as monotherapy and adjunctive therapy for focal seizures and for diabetic neuropathic pain. Lacosamide blocks sodium channels, enhancing slow inactivation, unlike most classic sodium channel blockers, which enhance fast sodium channel inactivation.

In five RCTs, lacosamide (100–600 mg/day) was used for from 7 to 18 weeks in patients with diabetic neuropathy in four multicenter studies and in patients with Nav1.7-related small fiber neuropathy in one single-center study (Table 2). The safety and efficacy analyses from these studies indicated that lacosamide provided a moderate balance between efficacy (four of the five studies showed positive results) and TEAEs both in patients with diabetic neuropathy and with Nav1.7-related small fiber neuropathy. The proportion of patients that experienced TEAEs that were considered by the investigators to be at least possibly related to trial medication was from 58.7% to 89.2% whatever the dose. In these studies, the most frequent TEAEs following lacosamide treatment were dizziness (10.8-41.7%), and nausea (11.3-25.0%). Nevertheless, none of the five studies performed statistical

comparison of the frequencies of TEAE occurrence with the placebo group, making it impossible to determine whether the TEAEs observed were indeed related to lacosamide. SAEs (occurring from 4.2% to 8.3% of patients in the studies they were evaluated in) were considered unrelated or unlikely to be related to trial medication by the investigators. Among the three studies that compared different doses or dosing regimens, no difference in the type (dizziness and nausea) and frequency of TEAEs were reported in the publications. In the SPC of lacosamide, the most common TEAEs described are dizziness, headache, nausea, vomiting, diplopia, fatigue, and sedation, all of which were more common at higher doses.

3.1.2.3 Levetiracetam. Levetiracetam is the (*S*)-enantiomer of the ethyl analog of piracetam. It is a well-tolerated widely used antiepileptic, with almost no important adverse drug interactions [46]. It has been shown that levetiracetam does not directly affect voltage-gated sodium channels or voltage-gated T-type calcium channels [47]; although the drug exhibits a mild selective inhibition of high-voltage-gated N-type calcium channels [48], there is no doubt that the mode of action is very different from other antiepileptics. Presumably, the main effect of levetiracetam is accomplished by binding to the vesicle transmembrane protein called SV2A and subsequently altering the regulation of calcium-dependent exocytosis of neurotransmitters into the synaptic gap [49]. Although levetiracetam is not FDA approved for monotherapy in the United States, it is used widely as a first-line treatment for focal and generalized tonic-clonic seizures and is approved for initial monotherapy in Europe. It is also an excellent adjunctive treatment owing view of its safety and absence of interactions.

Levetiracetam (3000 mg/day, from 4 to 6 weeks in duration) was evaluated in 25 women with post-mastectomy pain syndrome and in 16 patients with painful polyneuropathy (Table 2). No analgesic effect was found in these studies. A higher incidence of fatigue (17.7% and 40.0%) during levetiracetam administration was found. Only the study of Holbech

et al. [50] compared TEAE frequencies with placebo, and no significant difference was found. In the study of Vilholm *et al*. [51], dizziness, headache, and gastric upset were observed in 12.0% of patients. Overall, 6.7%– 7.7% of patients discontinued the studies because of TEAEs. According to SPC of levetiracetam, the most common TEAEs include somnolence, dizziness, and asthenia; irritability, depression, and hostility may also occur, more often in children.

3.1.2.4 Valproate. Valproic acid is an antiepileptic drug that has been shown to alter the activity of the neurotransmitter GABA by potentiating the inhibitory activity of GABA through several mechanisms, including inhibition of GABA degradation, inhibition of GABA transaminobutyratre, increased GABA synthesis, and decreased turnover [52]. Moreover, valproate attenuates N-methyl-D-aspartate-mediated excitation [53] and blocks Na^+ channels, voltage-dependent L type calcium channels, and voltage-gated K^+ channels [54]. Valproate is normally used for the treatment of seizures, manic episodes, and bipolar disorder [55]. Valproate acid (brand name Depakote®, among others) was first made in 1881 by Beverly S. Burton as an analog of valeric acid, which is found naturally in valerian. In 1962, Pierre Eymard serendipitously discovered the antiepileptic properties [56]; it was approved as an antiepileptic drug in 1967 and subsequently became the most widely prescribed antiepileptic drug worldwide [55]. Valproate acid is primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches, and it is included in the World Health Organization's List of Essential Medicines.

Valproate acid at 20 mg/kg/day for 12 weeks was assessed in the presence and absence of glyceryl trinitrate spray in a randomized monocenter clinical trial in 20 patients with diabetic neuropathy versus placebo (21 patients) [57] (Table 2). In this study, a significant subjective improvement in diabetic neuropathic pain in patients receiving glyceryl

trinitrate or sodium valproate, or both drugs in combination was observed in comparison to placebo. Both drugs, which have different mechanisms of action, appear to achieve maximum effect with minimal side effects when administered in combination. Negligible TEAEs (mainly nausea) and no dropouts were observed in groups receiving valproate either alone or in combination with glyceryl trinitrate. In this single study, the frequency of TEAEs was not compared between the study arms, and no information was available on the rate of SAEs. According to SPC of valproate, the common TEAEs include nausea, vomiting, sleepiness, and dry mouth; the SAEs are liver problems, pancreatitis, and an increased suicide risk. If taken during pregnancy, valproic acid is also known to cause serious abnormalities in the child; therefore, it is contraindicated in the case of pregnancy.

3.1.2.5 Zonisamide. Zonisamide is a sulfonamide antiepileptic drug approved in the United States, United Kingdom, Japan, and Australia for the treatment of various forms of epilepsy and Parkinson's disease [58]. Zonisamide was discovered by Uno *et al.* in 1972 and was first marketed by Dainippon Pharmaceutical in 1989. Zonisamide, as with several other antiepileptic drugs, prolongs the inactive phase of voltage-dependent sodium channels, thereby inhibiting the propagation of action potentials [59]. Daily doses of oral zonisamide are usually in the range of 200 to 600 mg.

Zonisamide has been used in a small number (n = 13) of patients with diabetic neuropathy for 12 weeks at the dose of 540 mg/day (Table 2). The study was negative: pain scores were not statistically decreased compared with the placebo group. The tolerability of zonisamide was only fair in this study, as a high number of patients experienced at least one TEAE (91.0%), and one patient (8.3%) experienced the SAE of drug rash. Many TEAEs were observed, including rash, dizziness, irritation, restlessness/insomnia, and respiratory disorders. Nevertheless, the frequencies of occurrence of these TEAEs were not statistically different

from those in the placebo group. The SPC of zonisamide describes typical TEAEs as somnolence, dizziness, and anorexia.

3.1.2.6 Ethosuximide. Ethosuximide is an FDA-approved T-type calcium-channel blocker currently used and for the management of absence seizures in patients over 3 years of age. Ethosuximide was approved for medical use in the United States in 1960, and it is on the World Health Organization's List of Essential Medicines. Numerous recent pre-clinical studies have shown its therapeutic potential for the treatment of neuropathic pain [60].

Only one proof-of-concept, multicenter, RCT has evaluated and compared the efficacy and safety of ethosuximide (administered as an add-on therapy for 6 weeks at doses from 500 to 1500 mg/day) with the efficacy of an inactive control in 114 patients with non-diabetic neuropathic pain (Table 2). In this study, ethosuximide failed to reduce total pain after 6 weeks of treatment, compared with the inactive control. Moreover, tolerance to ethosuximide was poor in comparison to that with the inactive control, with 69.5% of patients experiencing at least one TEAEs, and a dropout rate of 59.3%, mainly due to TEAEs. The most frequent TEAEs were dyspepsia (39%), headache (32%), and dizziness (20%). SAEs related to ethosuximide comprised dermabrasion or self-injurious ideation/suicide attempts and were reported in four patients (6.8%). According to the literature, the overall rate of TEAEs with ethosuximide used in epileptic patients was less than that for most other antiepileptic drugs (26% to 46%); the TEAEs were mainly gastrointestinal and often diminished after 1–2 weeks. Other common TEAEs include drowsiness, lethargy, insomnia, headache, and hiccups [61]. In addition, reports exist of rare idiosyncratic reactions such as Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, and systemic lupus erythematosus [62,63].

3.1.2.7 Carisbamate. Carisbamate is an investigational compound that has been shown to be

effective and well tolerated in patients with refractory focal-onset seizures [64]. The compound may modulate neuronal excitability through the inhibition of voltage-gated sodium channels, thereby reducing action potential discharges [65]. In addition, carisbamate reduces glutamatergic transmission through the inhibition of AMPA and NMDA excitatory post-synaptic potentials [66]. Carisbamate increased the tonic activation of somatodendritic 5-HT_{1A} serotonergic receptors, leading to the inhibition of pyramidal neurons in the hippocampus [67]. Recent data have demonstrated that its neuroprotective and anti-seizure activity likely resulted, in part, from decreased $[Ca^{2+}]_i$ accumulation through the blockade of T-type calcium channels [68].

Carisbamate has been used in three proof-of-concept studies for its efficacy and safety in the treatment of neuropathic pain (Table 2). Studies 1 (postherpetic neuralgia) and 2 (diabetic neuropathy) followed a crossover design, in which patients received carisbamate 400 mg/day or placebo for 4 weeks and then the other treatment for 4 weeks. In study 3 (diabetic neuropathy), patients were randomized (1:1:1:1) to receive either carisbamate 800 mg/day, 1200 mg/day, pregabalin 300 mg/day, or placebo for 15 weeks. The efficacy of carisbamate in neuropathic pain was not demonstrated in these studies. In general, carisbamate was well tolerated (from 15% to 38% of patients with at least TEAEs, according to dose), with no new or unexpected safety concerns in neuropathic pain populations compared with previous epilepsy trials [64,69,70]. In the current studies, only two patients in the carisbamate 800 mg/day group in study 3 had ALT elevations of > 3× ULN; in both patients, these resolved without any sequelae. TEAEs particularly relevant in the diabetic population, such as weight gain, somnolence, and peripheral edema, occurred less frequently with carisbamate than pregabalin. However, some gastrointestinal TEAEs, as well as dizziness, were more frequently reported with carisbamate than with pregabalin; however, none of these studies compared the frequency of TEAEs with placebo. According to the literature, the most

frequently reported TEAEs associated with carisbamate are dizziness, headache, somnolence, and nausea [71].

3.1.2.8 Oxcarbazepine and carbamazepine. Oxcarbazepine, a structural analog of carbamazepine, is used to treat epilepsy. The compound was patented in 1969 and was brought into medical use in 1990. Multiple comparative monotherapy trials for new-onset focal epilepsy have demonstrated that oxcarbazepine was equal in efficacy to phenytoin and immediate-release carbamazepine with possibly superior tolerability [72,73]. Oxcarbazepine is known to cause a nonspecific sodium channel blockade [74] that may also have an effect on calcium and potassium channels [74,75]. Carbamazepine is also used for the treatment of neuropathic pain [76], but main trials assessing carbamazepine efficacy on peripheral neuropathic pain were published before 2000. Only one study assessing carbamazepine, in the treatment of neuropathic pain and complex regional pain syndrome I, has been included in the review but with an unclear description of adverse effects. This study concluded on positive effects of carbamazepine [77].

The efficacy and safety of oxcarbazepine has been evaluated in two multicenter double-blind, placebo-controlled, randomized clinical trials in patients with peripheral neuropathy. Oxcarbazepine was initiated at a dose of 300 mg/day and titrated to a maximum dose of 1800 mg/day in 69 patients with diabetic neuropathy for 16 weeks in study 1 [78], and at 1800–2400 mg for two 6-week treatment periods in patients with peripheral neuropathic pain in study 2 [79]. In both studies, it was found to be efficacious for the relief of neuropathic pain. Most TEAEs were mild to moderate in severity, transient, and in line with the known tolerability profile of oxcarbazepine. The most frequent TEAEs were dizziness, somnolence, and fatigue, with diarrhea and nausea/vomiting also reported. In study 1, SAEs occurred in 10% of oxcarbazepine-treated patients. These TEAEs were considered related to

treatment in two patients (erythema multiforme and asthenia/dizziness/fatigue). None of these studies compared the frequency of TEAEs with placebo. According to the literature, oxcarbazepine may cause drowsiness, headache, and fatigue, and higher doses may cause dizziness, blurred vision, diplopia, nausea, vomiting, and ataxia [46].

3.2. Antidepressants

Antidepressants form a heterogeneous group of molecules that are usually classified according to their chemical structure, psychoactive/sedative properties, and monoaminergic action; that is, by their ability to modulate serotonergic and/or noradrenergic transmission. On this basis, six classes of antidepressants can be distinguished, of which two are recommended for the treatment of peripheral or central neuropathic pain. Indeed, a systematic review and meta-analysis of published and unpublished data, including 229 RCTs, performed by the NeuPSIG, led to the recommendation of, in addition to gabapentinoids, TCAs and SNRIs as first-line treatments [11].

The efficacy of TCAs (e.g. amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, protriptyline, and trimipramine) is similar regardless of the molecule used, although amitriptyline is the most commonly studied. As the number of clinical studies increases, the decrease in estimated drug efficacy, which was first observed in 2013 [11], has been recently confirmed [80]. The number needed to treat (NNT) for TCAs (amitriptyline and nortriptyline) was estimated at 3.6 in 2015; it had increased to 4–5 in 2017 [80], suggesting a decreased efficacy. In addition to the limited efficacy of these recommended treatments, the incidence of TEAEs and treatment interruption due to TEAEs may also contribute to the unsatisfactory management of neuropathic pain. Indeed, in addition to serotonin and noradrenaline, TCAs can interfere with other neurotransmitters, causing many adverse effects.

SNRIs (e.g. duloxetine, venlafaxine, and milnacipran) appear to be more selective than TCAs and cause fewer TEAEs: the efficacy of the SNRIs venlafaxine and duloxetine has been shown with an overall estimated NNT of 6.4 and an NNH of 11.8 [11]. TEAEs include digestive disorders (nausea, abdominal pain, and constipation), dizziness, somnolence, and a risk of high blood pressure. The risk of serotonin syndrome contraindicates the association with monoamine oxidase inhibitors, and the use of other molecules capable of interfering with serotonin is a precautionary measure (especially the association with tramadol). Although TCAs and SNRIs have a moderate and significant level of evidence, respectively, the selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) have an inconclusive level of evidence.

In the present review, we identified 24 double-blind, placebo-controlled, randomized clinical trials that examined the TEAEs related to antidepressants strongly recommended for use in neuropathic pain. The trials included 3998 patients; 15 were of SNRIs (9 with duloxetine, 5 with venlafaxine, and 1 with milnacipran) and 8 were of TCAs (6 with amitriptyline, 1 with nortriptyline, and 1 with imipramine). One publication presented results on escitalopram efficacy on various neuropathic pain conditions.

3.2.1. *Serotonin and noradrenaline reuptake inhibitors (SNRIs)*

3.2.1.1 Duloxetine. Duloxetine (Cymbalta®) was created by researchers at Eli Lilly in the 1990s [81], approved in United States in 2004, and is indicated for the treatment of major depressive disorder, generalized anxiety disorder, diabetic neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. Duloxetine inhibits the reuptake of serotonin and noradrenaline in the central nervous system, and increases dopamine specifically in the prefrontal cortex, via the inhibition of the noradrenaline reuptake transporter, which is believed to mediate reuptake of dopamine and noradrenaline [82]. The analgesic action of duloxetine in the treatment of

diabetic neuropathic pain and central pain syndromes are due to Na^+ ion channel inhibition [83].

In total, 3173 patients were included in the 9 RCTs; 2126 received duloxetine at daily dose from 20 mg to 120 mg for a treatment duration from 4 weeks to 12 weeks. The majority of studies showed positive results (7/9). Except for patient groups treated with 20 or 40 mg daily, the most common TEAEs, i.e., TEAEs that occurred significantly more frequently in the duloxetine (60 or 120 mg/day) group than in the placebo group, were nausea (10.4%–32.1%), constipation/diarrhea (10.6%–19.0%), somnolence (15.0%–28.3%), and dizziness (11.0%–23.0%). Only three studies reported dry mouth (10%–35%), two reported decreased appetite (12.4%–19.0%), and one study reported hyperhidrosis (10.0%) in patients receiving duloxetine 120 mg daily. The occurrence of dropouts due to TEAEs was from 4.3% to19.4% whatever the dose. SAEs occurred in 0.0% to 6.7% of patients treated with duloxetine.

3.2.1.2 Venlafaxine. The SNRI venlafaxine hydrochloride (Effexor®), first introduced by Wyeth in 1993, is indicated for the treatment of major depressive disorder and social anxiety disorder. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine, are potent inhibitors of neuronal serotonin and noradrenaline reuptake, and weak inhibitors of dopamine reuptake. Venlafaxine and O-desmethylvenlafaxine have no significant affinity for muscarinic cholinergic, H1-histaminergic, or α1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and O-desmethylvenlafaxine do not possess monoamine oxidase (MAO) inhibitory activity [84,85].

We identified five RCTs of venlafaxine with a 37.5-150 mg daily dose and a treatment duration from 11 days to 56 days. The etiology of neuropathic pain was various neuropathies.

Among these five studies, only one was positive, and TEAEs were reported in only two studies. The most frequent TEAEs were asthenia/fatigue, sweating, and dry mouth, followed by headache, constipation, and nausea. No significant SAEs related to venlafaxine treatment were reported. The dropout rate due to TEAEs, reported in four of the five studies, was 9/98 (9.2%) treated patients.

3.2.1.3 Milnacipran. Milnacipran hydrochloride (Savella®) is a selective serotonin and noradrenaline dual reuptake inhibitor. Originally developed and manufactured by Pierre Fabre Medicament, it was approved in France in 1997 as an antidepressant and by the FDA in 2009 for the management of fibromyalgia [86]. Only one study, with a 10-week duration, reported the use of milnacipran in neuropathic pain due to radiculopathy. The small number of patients (n = 7) did not permit the evaluation of the significance of TEAEs; however, 28.7% of patients discontinued the study due to TEAEs.

3.2.2. *Tricyclic antidepressants (TCAs)*

Among TCAs, amitriptyline is the most studied. Amitriptyline (sold under the trade name Elavil®) was discovered in 1960 and approved by the FDA in 1961 [87]. It is on the World Health Organization's List of Essential Medicines. Amitriptyline inhibits the neuronal reuptake of serotonin and noradrenaline from synapses in the central nervous system, with strong activity on the serotonin transporter and moderate activity on the norepinephrine transporter [88]. Amitriptyline also modulates several receptors and ion channels, such as the serotonin, α1-adrenergic, H1, H2, muscarinic acetylcholine, sigma-1, NMDA, TrkA, and TrkB receptors, and sodium, L-type calcium, and voltage-gated potassium channels [89–94].

In the present review, we identified eight double-blind, placebo-controlled, randomized clinical trials, six evaluated amitriptyline, one evaluated nortriptyline, and one

evaluating imipramine in various neuropathic pain conditions. One study lasted 12 weeks; the rest were short-controlled studies, lasting between 1 and 5 weeks. TCAs were administered systemically for all studies, with the exception of two controlled trials using topical amitriptyline (2% or 5% gel). Only the study investigating imipramine had positive results. TEAEs, e.g. dry mouth, dizziness, and constipation, were reported only in patients receiving nortriptyline 100 mg daily for 4 weeks. Dropout due to TEAEs occurred in 17% and 3.9% of patients treated with imipramine and nortriptyline, respectively. Amitriptyline led to dropout rates of 10% in one trial (over four p.o. routes) and 4.5% in another trial (over two topical routes).

3.2.3. *Escitalopram*

Escitalopram, a pharmacologically active S-(+)-enantiomer of citalopram, potentiates serotonergic neurotransmission in the central nervous system through selectively binding to the serotonin transporter to inhibit 5-HT reuptake [95]. Escitalopram is mainly indicated in depressive disorders [95]. Indeed, escitalopram, as for other SSRIs, is not recommended for the management of neuropathic pain [11].

Escitalopram (10–20 mg/day for 6 weeks) has been assessed in only one crossover RCT, which included 48 patients with various types of neuropathic pain (Table 3). A clinically relevant efficacy of escitalopram was found for a very small number of patients. However, 51.2% of patients experienced TEAEs, the most frequent of which were digestive disorders (abdominal discomfort and nausea/vomiting), and 10.4% of patients discontinued the study because of TEAEs.

4. Conclusion

Among the selected studies, when a statistical analysis of TEAEs was performed in

comparison to the placebo groups, the rate of any TEAEs ranged from 7.0% to 91.7%, and the highest rate was found for duloxetine (46.5%–89.5%, $p < 0.05$). The most frequently cited TEAEs in the included studies with a statistical analysis were nausea (all 10.4%–43.1%, $p < 0.05$; duloxetine 10.4%–32.1% and venlafaxine 43.1%), drowsiness (all 15.0%–28.3%, $p < 0.05$; duloxetine 15.0%–28.3% and gabapentin, 27.8%), dizziness (all 11.0%–49.0%, $p < 0.05$; duloxetine 11.0%–23.0%; pregabalin 13.7%; gabapentin 37.3%; and nortriptyline 49.0%), constipation (all 10.6%–41.0%, $p < 0.05$; duloxetine 10.6%–18.8%; and nortriptyline, 41%), fatigue (duloxetine 11.0%–12.5%, $p < 0.05$), headache (all 10.5%–25.0%, $p > 0.05$), and dry mouth (all 10.0%–62.0%, $p < 0.05$; duloxetine 10.0%–35.0%; and nortriptyline 62.0%).

Gabapentin and pregabalin have similar safety profiles, with the same types and frequencies of occurrence of TEAEs. In terms of efficacy, pregabalin appeared to be more effective for the treatment of neuropathic pain than gabapentin. The small number of studies and types of peripheral neuropathy evaluated did not allow conclusions to be drawn on the safety of mirogabalin. The first studies appeared promising, with a better efficacy (one study demonstrated a better efficacy than pregabalin) and fewer TEAEs than pregabalin and gabapentin. However, a recent article [39], including three clinical trials, showed that the frequency of TEAEs related to mirogabalin (74.8%) was similar to pregabalin, including dizziness (15.2%), headache (13.5%), and drowsiness (9.6%). Unfortunately, the frequency of occurrence was not compared with the placebo group, and the authors concluded that mirogabalin was ineffective for the treatment of pain related to fibromyalgia. Finally, owing to the limited analgesic efficacy and the high frequency of TEAEs (over 50% of patients for gabapentin and pregabalin), the safety of gabapentinoids for the treatment of neuropathic pain was far from optimal, especially when the risks of addiction and misuse induced by these molecules were accounted for [25]. For other antiepileptics, the small number of studies with

a good assessment of TEAEs made it difficult to draw conclusions on their safety. Nevertheless, the occurrence of TEAEs, ranging from 56.0% to 94.0%, and the relatively low proportion of positive studies (9/17) may suggest concerns regarding the safety for other antiepileptics. It should also be noted that carisbamate appear to stand out, with a TEAE occurrence between 15% and 38% according to the dose and proven efficacy, but this should be taken with caution, as only one study was reviewed.

With respect to antidepressants, the majority of studies (9/24) evaluated duloxetine, making it difficult to conclude on the safety of other antidepressants owing to the small number of studies. Studies on duloxetine have shown moderate tolerance, but this was counterbalanced by a high analgesic efficacy (7 positive studies out of 9). Indeed, the therapeutic effects were more modest, or even absent, with only one positive study out of the five studies of venlafaxine and no positive studies for amitriptyline. As each of the other molecules have been evaluated only in a single study, we could not conclude on their safety. It should be noted that in these studies, only milnacipran and imipramine were demonstrated as effective.

5. Expert opinion

Overall, duloxetine appeared to have the most detailed safety for the treatment of neuropathic pain compared with other antidepressants and with antiepileptics. For all studies, the most commonly reported adverse effects were dizziness, drowsiness, nausea, and constipation. The great majority of these TEAEs were not life-threatening, although TEAEs such as dizziness and drowsiness alter the quality of life of patients [96,97]. These TEAEs may be a contributory factor to the low adherence rate and the under use of pain medications [98,99]. Patients with chronic pain had a low adherence rate to pain medications (e.g., 40% for various types of chronic pain [99], 50%–91% for cancer pain, and 63% for rheumatoid arthritis

[100]). As antidepressants and antiepileptics used in the treatment of peripheral neuropathic pain have equivocal efficacy and safety concerns, the assessment of the benefit-risk ratio would be particularly relevant.

The main weakness of this review is related to the fact that many clinical trials included in this review had a poor description of the safety of the assessed drugs. Although double-blind, placebo-controlled, randomized clinical trials have been included in this review, only 20.0% (18) of studies presented statistical comparisons of TEAEs between groups: 62.2% (56) did not present any statistical comparisons and 17.8% (16) provided insufficient details on TEAE frequencies or no safety data. Only 43.8% (39) of studies reported SAEs and 84.3% (75) reported dropout of patients owing to TEAEs. Consequently, caution must be taken when assessing the frequency of TEAEs in these studies. Frequently, authors did not mention if the observed adverse events were related to the assessed medications, which may have contributed to an overestimation of reported TEAEs in this review. Many issues have been raised regarding the assessment and reporting of drug safety during RCTs [101]; however, no evidentiary gold standard for safety assessment has been defined. RCTs have a limited statistical power for TEAE assessment as sample sizes are designed for the main objective of efficacy. In addition, the lack of adequate ascertainment and classification of TEAEs leads to inconsistencies in the reporting of TEAEs. The hyper-selection of patients through restrictive inclusion and exclusion criteria leads to limited generalizability [101].

We encourage the publication of clinical trials in accordance with CONSORT guidelines [102]; furthermore, authors should incorporate in their manuscript a table describing all the observed adverse events, including the relationship between the adverse events and treatments, serious TEAEs, the dropout rate related to TEAEs, and the statistical significance of these TEAEs versus a placebo.

The management of peripheral neuropathic pain is a largely unmet medical need [11]. Pain physicians and patients are still waiting for pharmacological innovations that will improve the safety of pain medications.

Article highlights box

- Review of double-blind, placebo-controlled, randomized clinical trials
- Specific focus on adverse effects of antidepressant and antiepileptic medications used to treat peripheral neuropathic pain
- Duloxetine presents the most detailed safety for the treatment of peripheral neuropathic pain
- Adverse drug reactions are under-reported in most of the clinical trials
- A detailed safety assessment of antidepressant and antiepileptic medications should be mandatory for clinical trials on peripheral neuropathic pain

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Figure 1: Flow diagram of publication selection

Authors' names	Study design	Drug/comparator and dose (patient number)	Duration	Pathology	List of TEAEs in study drug arm (≥ 10% of patients)	SAEs related to study drug (%)	Dropout due to TEAE in study drug arm (%)	Reference (PMID)
Pregabalin								
Reyad et al. 2019	Parallel-group Monocenter	Pregabalin 75-300 mg/day (100) Placebo (100)	7 days	Post-traumatic neuropathic pain	Any (7.0) ns No TEAE ≥ 10% of patients	UK	UK	30359684
Jiang et al. 2019	Parallel-group Multicenter	Pregabalin 75-150 mg/day (68) Placebo (69)	16 weeks	Radiotherapy-Related Neuropathic Pain	Any (54.7) ns Dizziness (18.8) # Drowsiness (20.3) #	UK	1.5	30457920
Mu et al. 2018	Parallel-group Multicenter	Pregabalin 150-300 mg/day (314) Placebo (309)	11 weeks	Diabetic neuropathy	Any (36.0) # No TEAE ≥ 10% of patients	0.0	3.5	28727270
Markman et al. 2018	Parallel-group Multicenter	Pregabalin 150-600 mg/day (274) Placebo (265)	3 months	Post-traumatic neuropathic pain	Any (50.4) # Dizziness (14.6) #	0.0	4.7	30242745
Wanigasekera et al. 2018	Crossover-group Multicenter	Pregabalin 75-300 mg/day (16) Tramadol 50-400 mg/day (16) Placebo (16)	1 week	Post-traumatic neuropathic pain	No safety	No safety	No safety	29406179
Ciampi de Andrade et al. 2017	Parallel-group Monocenter	Pregabalin 150-600 mg/day (78) Placebo (65)	3 days before to 3 days after each chemotherapy infusion (weeks 1-3-5).	Chemotherapy-induced peripheral neuropathy	Any (31.0) # No sufficient detail on frequencies of patients with TEAEs	UK	UK	28652279
Schlaeger et al. 2017	Parallel-group Monocenter	Pregabalin 150-600 mg/day (11) Placebo (11)	3 months	Sickle cell disease	Any (UK) Sleepiness (18.2) # Dizziness (18.2) # Drowsiness (18.2) #	UK	9.1	28843636
Mathieson et al.	Parallel-group	Pregabalin 150-600 mg/day (180)	8 weeks	Radiculopathy	Any (64.2) *	1,9	0.0	28328324

2017	Multicenter	Placebo (101)			Dizziness (39.6) #			
Fallon et al. 2016	Parallel-group Multicenter	Pregabalin 75-300 mg/day (116) Placebo (117)	4 weeks	Neuropathic cancer pain	No sufficient detail on frequencies of patients with TEAEs	UK	4.3	26644535
Shinde et al. 2016	Parallel-groups Multicenter	Pregabalin 150 mg/day (23) Placebo (23)	12 weeks	CIPN	No sufficient detail on frequencies of patients with TEAEs	UK	UK	26155765
González-Duarte et al. 2016	Crossover-group Monocenter	Pregabalin 75-300 mg (26) Placebo (26)	2 months	Diabetic neuropathy	Any (UK) Dizziness (15.4) #	UK	UK	26670614
Raskin et al. 2016	Crossover-group Multicenter	Pregabalin 150-300 mg/day (154) Placebo (147)	6 weeks	Diabetic neuropathy	Any (54.0) # Dizziness (10.3) #	1.8	6.6	25968451
Huffman et al. 2015	Crossover-group Multicenter	pregabalin 150-300 mg/day (198) Placebo (186)	6 weeks	Diabetic neuropathy	Any (47.5) # No TEAE ≥ 10% of patients	0.0	4.5	25565583
Malik et al. 2015	Parallel-group Monocenter	Pregabalin 150-300 mg/day (10) Placebo (9)	3 weeks	Radiculopathy	No sufficient detail on frequencies of patients with TEAEs	UK	11.1	26478867
Holbech et al. 2015	Crossover-group Multicenter	Pregabalin 300 mg/day (18) Imipramine 75 mg/day (18) Combination therapy (18) Placebo (19)	5 weeks	Various neuropathic pain	No sufficient detail on frequencies of patients with TEAEs	Only for pregabalin UK	Only for pregabalin 11.1	25719617
Vinik et al. 2014	Parallel-group Multicenter	Pregabalin 300 mg/day (56) Mirogabalin 5 mg/day (57) Mirogabalin 10 mg/day (57) Mirogabalin 15 mg/day (57) Mirogabalin 20 mg/day (56) Mirogabalin 30 mg/day (57) Placebo (112)	5 weeks	Diabetic neuropathy	Only for pregabalin group Any (22.0) # No TEAEs ≥ 10% of patients	Only for pregabalin 0.0	Only for pregabalin 4.0	25231896
Simpson et al. 2014	Parallel-group Multicenter	Pregabalin 150-600 mg/day (183) Placebo (192)	12 weeks	HIV-associated neuropathy	Any (68.9) # Headache (13.7) ns	3.8	1.6	24907403

					Dizziness (13.7) *			
Raskin et al. 2014	Parallel-group Multicenter	Pregabalin 150-300 mg/day (147) Placebo (147)	13 weeks	Diabetic neuropathy	Any (UK) No TEAE ≥ 10% of patients	0.0	1.4	23887339
Karmakar et al. 2014	Crossover-group Monocenter	Pregabalin 75-300 mg/day (14) Placebo (14)	14 weeks	Diabetic neuropathy	No sufficient detail on frequencies of patients with TEAEs	UK	UK	25139539
Smith et al. 2014	Parallel-group Multicenter	Carisbamate 800 mg/day (94) Carisbamate 1200 mg/day (98) Pregabalin 300 mg/day (99) Placebo (95)	15 weeks	Diabetic neuropathy	Pregabalin 300 mg/day (3) Any (32.0) # Somnolence (10.0) #	Pregabalin 300 mg/day (3.1)	Pregabalin 300 mg/day (15.0)	23692321
Rauck et al. 2013	Parallel-group Multicenter	Pregabalin 300 mg/day (56) Gabapentin enacarbil 1200 mg/day (56) Gabapentin enacarbil 2400 mg/day (56) Gabapentin enacarbil 3600 mg/day (112) Placebo (112)	12 weeks	Diabetic neuropathy	Only for pregabalin group Any (71.0) # Dizziness (14.0) # Drowsiness (14.0) # Peripheral edema (17.0) #	UK	9.0	23186035
Mishra et al. 2012	Parallel-group Monocenter	Pregabalin 150-600 mg/day (30) Amitriptyline 50-100 mg/day (30) Gabapentin 900-1800 md/day (30) Placebo (30)	4 weeks	Neuropathic cancer pain	No sufficient detail on frequencies of patients with TEAEs	UK	UK	21745832
Jenkins et al. 2012	Crossover-group Multicenter	Pregabalin 300 mg/day (13) Placebo (12)	2 weeks	Post-traumatic neuropathic pain	Any (46.0) # Dizziness (46.0) # Nausea (30.7) # Drowsiness (23.0) #	UK	0.0	22888270
Satoh et al. 2011	Parallel-group Multicenter	Pregabalin 300 mg/day (134) Pregabalin 600 mg/day (45) Placebo (137)	14 weeks	Diabetic neuropathy	Pregabalin 300 mg Any (57.0) # Drowsiness (20.9) #	UK	Pregabalin 300 mg (3.0) Pregabalin 600 mg (17.8)	21166852

					Dizziness (19.4) # Peripheral edema (12.7) # Weight increased (11.2) # Pregabalin 600 mg Any (80.0) # Drowsiness (40.0) # Dizziness (37.8) # Peripheral edema (13.3) # Weight increased (11.1) #			
Gilron et al. 2011	Parallel-group Multicenter	Pregabalin 450-600 mg/day (80) Placebo (77)	5 weeks	Various neuropathic pain	Any (71.4) # No TEAE ≥ 10% of patients	UK	2.5	21178603
Guan et al. 2011	Parallel-group Multicenter	Pregabalin 150-600 mg/day (206) Placebo (102)	10 weeks	Radiculopathy	Any (50.0) # Dizziness (11.2) #	UK	5.3	21444113
Simpson et al. 2010	Parallel-group Multicenter	Pregabalin 150-600 mg/day (151) Placebo (151)	14 weeks	HIV-associated neuropathy	Any (81.5) # Drowsiness (23.2) # Dizziness (19.2) #	UK	6.0	20124207
van Seventer et al. 2010	Parallel-group Multicenter	Pregabalin 150-600 mg/day (127) Placebo (127)	8 weeks	Post-traumatic neuropathic pain	Any (85.8) # Dizziness (43.3) # Drowsiness (15.7) # Headache (11.8) # Fatigue (11.8) # Dry mouth (11.0) #	0.8	19.7	20236172
Baron et al. 2010	Parallel-group Multicenter	Pregabalin 150-600 mg/day (110) Placebo (107)	46 weeks	Radiculopathy	Any (73.6) # Dizziness (30.5) # Drowsiness (12.6) #	0.0	9.9	20493632

Moon et al. 2010	Parallel-group Multicenter	Pregabalin 150-600 mg/day (162) Placebo (78)	10 weeks	Chemotherapy-induced peripheral neuropathy	Any (50.0) # Dizziness (21.0) # Drowsiness (13.6) #	UK	4.9	21353106
Arrezo et al. 2008	Parallel-group Multicenter	Pregabalin 600 mg/day (82) Placebo (85)	12 weeks	Diabetic neuropathy	Any (84.0) # Peripheral edema (36.6) # Dizziness (32.9) # Weight gain (14.6) # Drowsiness (13.4) # Fatigue (9.8) #	0.0	17.1	18796160
Tölle et al. 2008	Parallel-group Multicenter	Pregabalin 150 mg/day (99) Pregabalin 300 mg/day (99) Pregabalin 600 mg/day (101) Placebo (96)	12 weeks	Diabetic neuropathy	Pregabalin 150 mg Any (UK) No TEAE ≥ 10% of patients Pregabalin 300 mg Any (UK) No TEAE ≥ 10% of patients Pregabalin 600 mg Any (UK) Dizziness (13.9) #	UK	Pregabalin 150 mg (5.1) Pregabalin 300 mg (11.1) Pregabalin 600 mg (12.9)	17631400
van Seventer et al. 2006	Parallel-group Multicenter	Pregabalin 150 mg (87) Pregabalin 300 mg (98) Pregabalin 600 mg (90) Placebo (93)	12 weeks	Post-herpetic neuropathic pain	Pregabalin 150 mg Any (UK) Dizziness (16.1) # Pregabalin 300 mg Any (UK)	UK	Pregabalin 150 mg (8.0) Pregabalin 300 mg (15.3) Pregabalin 600 mg (21.1)	16466610

					Dizziness (32.7) # Peripheral edema (14.3) # Drowsiness (11.2) # Pregabalin 600 mg Any (UK) Dizziness (36.7) # Drowsiness (25.6) # Peripheral edema (13.3) # Ataxia (12.2) # Dry mouth (12.2) #			
Richter et al. 2005	Parallel-group Multicenter	Pregabalin 150 mg/day (79) Pregabalin 600 mg/day (82) Placebo (85)	6 weeks	Diabetic neuropathy	Pregabalin 150 mg Any (UK) Dizziness (10.1) # Infection (12.7) # Pregabalin 600 mg Any (UK) Dizziness (37.8) # Drowsiness (22.0) # Peripheral edema (17.1) # Headache (15.9) # Fatigue (12.2) #	Pregabalin 150 mg (0.0) Pregabalin 600 mg (8.5)	Pregabalin 150 mg (2.5) Pregabalin 600 mg (8.5)	15820913
Freynhagen et al. 2005	Parallel-group Multicenter	Pregabalin 150-600 mg/day (141) Pregabalin 600 mg/day (141) Placebo (65)	12 weeks	Various neuropathic pain	Pregabalin 150 - 600 mg Any (55.3) # Dizziness (19.1) #	UK	Pregabalin 150 - 600 mg (17.0)	15911152

					Peripheral edema (15.6) # Weight gain (12.1) # Drowsiness (10.5) # Pregabalin 600 mg Any (68.9) # Dizziness (28.8) # Weight gain (13.6) # Drowsiness (12.9) # Nausea (10.6) #		Pregabalin 600 mg (25.0)	
Sabatowski et al. 2004	Parallel-group Multicenter	Pregabalin 150 mg/day (81) Pregabalin 300 mg/day (76) Placebo (81)	8 weeks	Post-herpetic neuropathic pain	Pregabalin 150 mg Any (UK) Dizziness (12.0) # Drowsiness (15.0) # Peripheral edema (3.0) # Headache (11.0) # Dry mouth (11.0) # Pregabalin 300 mg Any (83.0) # Dizziness (28.0) # Drowsiness (24.0) # Peripheral edema (13.0) # Headache (11.0) # Dry mouth (7.0) #	Pregabalin 150 mg (4.9) Pregabalin 300 mg (1.3)	Pregabalin 150 mg (11.1) Pregabalin 300 mg (15.8)	15082123

Rosenstock et al. 2004	Parallel-group Multicenter	Pregabalin 300 mg/day (76) Placebo (70)	8 weeks	Diabetic neuropathy	Any (62.0) # Dizziness (35.5) # Drowsiness (19.7) # Infection (14.5) # Peripheral edema (10.5) #	UK	11.0	15288403
Lesser et al. 2004	Parallel-group Multicenter	Pregabalin 75 mg/day (77) Pregabalin 300 mg/day (81) Pregabalin 600 mg/day (82) Placebo (97)	5 weeks	Diabetic neuropathy	Pregabalin 75 mg Any (UK) No TEAE ≥ 10% of patients Pregabalin 300 mg Any (UK) Dizziness (27.2) # Drowsiness (23.5) # Pregabalin 600 mg Any (UK) Dizziness (39.0) # Drowsiness (26.8) # Peripheral edema (13.4) #	Pregabalin 75 mg (10.4) Pregabalin 600 mg (4.9)	0.0	15596757
Mirogabalin								
Baba et al. 2019	Parallel-group Multicenter	Mirogabalin 15 mg/day (166) Mirogabalin 20 mg/day (168) Mirogabalin 30 mg/day (166) Placebo (334)	14 weeks	Diabetic neuropathy	Mirogabalin 15 mg Any (UK) No TEAE ≥ 10% of patients Mirogabalin 20 mg	0.0	Mirogabalin 15 mg (2.4) Mirogabalin 20 mg (4.2) Mirogabalin 30 mg (9.7)	30672128

					Any (UK) No TEAE ≥ 10% of patients Mirogabalin 30 mg Any (UK) Drowsiness (14.5) ns			
Merante et al. 2017	Parallel-group Multicenter	Mirogabalin 5 mg/day (55) Mirogabalin 10 mg/day (56) Mirogabalin 15 mg/day (53) Mirogabalin 20 mg/day (56) Mirogabalin 30 mg/day (57) Pregabalin 300 mg/day (50) Placebo (108)	5 weeks	Diabetic neuropathy	Only mirogabalin groups Mirogabalin 5 mg Any (10.9) # No TEAE ≥ 10% of patients Mirogabalin 10 mg Any (19.6) # Dizziness (12.5) # Mirogabalin 15 mg Any (26.4) # Dizziness (11.3) # Mirogabalin 20 mg Any (19.6) # No TEAE ≥ 10% of patients Mirogabalin 30 mg Any (28.1) #	UK	UK	28371941

					Dizziness (15.8) #			
Vinik et al. 2014	Parallel-group Multicenter	Mirogabalin 5 mg/day (57) Mirogabalin 10 mg/day (57) Mirogabalin 15mg/day (57) Mirogabalin 20 mg/day (56) Mirogabalin 30 mg/day (57) Pregabalin 300 mg/day (56) Placebo (112)	5 weeks	Diabetic neuropathy	Only mirogabalin groups Mirogabalin 5 mg Any (UK) Headache (10.9) # Mirogabalin 10 mg Any (UK) Dizziness (12.5) # Mirogabalin 15mg Any (UK) Dizziness (11.3) # Mirogabalin 20 mg Any (UK) No TEAE ≥ 10% of patients Mirogabalin 30 mg Any (UK) Dizziness (15.8) # Drowsiness (12.3) #	All mirogabalin groups (2.9)	All mirogabalin groups (7.2)	25231896
Gabapentin								

Bulilete et al. 2019	Parallel-group Multicenter	Gabapentin 300 - 1800 mg/day (33) Placebo (42)	5 weeks	Post-herpetic neuropathic pain	No sufficient detail on frequencies of patients with TEAEs	0.0	6.1	31166976
Rauck et al. 2013	Parallel-group Multicenter	Gabapentin enacarbil 1200 mg/day (56) Gabapentin enacarbil 2400 mg/day (56) Gabapentin enacarbil 3600 mg/day (112) Pregabalin 300 mg/day (56) Placebo (112)	12 weeks	Diabetic neuropathy	Only for Gabapentin enacarbil group Gabapentin enacarbil 1200 mg Any (73.0) # Dizziness (15.0) # Nausea (11.0) # Muscle spasms (10.0) # Gabapentin enacarbil 2400 mg Any (68.0) # Dizziness (14.0) # Drowsiness (13.0) # Gabapentin enacarbil 3600 mg Any (74.0) # Dizziness (14.0) # Drowsiness (12.0) #	Only for Gabapentin enacarbil (0.0)	Only for Gabapentin enacarbil Gabapentin enacarbil 1200 mg (8.0) Gabapentin enacarbil 2400 mg (21.0) Gabapentin enacarbil 3600 mg (18.0)	23186035
Zhang et al. 2013	Parallel-group Multicenter	Gabapentin enacarbil 1200 mg/day (107) Gabapentin enacarbil 2400 mg/day (82) Gabapentin enacarbil 3600 mg/day (87) Placebo (95)	14 weeks	Post-herpetic neuropathic pain	Gabapentin enacarbil 1200 mg Any (70.0) # Dizziness (17.0) # Drowsiness (10.0) # Headache (10.0) # Gabapentin enacarbil 2400 mg	Gabapentin enacarbil 1200 mg (0.0) Gabapentin enacarbil 2400 mg (0.0) Gabapentin enacarbil 3600 mg (1.1)	Gabapentin enacarbil 1200 mg (6.0) Gabapentin enacarbil 2400 mg (UK) Gabapentin enacarbil 3600 mg (18.0)	23602345

					Any (78.0) # Dizziness (26.0) # Drowsiness (11.0) # Headache (10.0) # Gabapentin enacarbil 3600 mg Any (82.0) # Dizziness (30.0) # Drowsiness (14.0) # Headache (7.0) #			
Sandercock et al. 2012	Parallel-group Multicenter	Gabapentin GR 3000 mg/day (46) Gabapentin GR 1200 mg/day + 1800 mg/day (50) Placebo (51)	4 weeks	Diabetic neuropathy	Gabapentin-GR 3000 mg Any (57.4) # Dizziness (17.0) # Drowsiness (12.8) # Gabapentin GR 1200 + 1800 mg Any (46.9) # Dizziness (12.2) #	UK	Gabapentin GR 3000 mg (8.7) Gabapentin GR 1200 + 1800 mg (6.0)	22497967
Mishra et al. 2012	Parallel-group Monocenter	Amitriptyline 50 - 100 mg/day (30) Gabapentin 900 - 1800 mg/day (30) Pregabalin 150 - 600 mg/day (30) Placebo (30)	4 weeks	Neuropathic cancer pain	No detail on TEAEs frequencies	UK	UK	21745832
Hui et al. 2011	Parallel-group Monocenter	Gabapentin 300 - 900 mg/day (71) Placebo (69)	8 weeks	Carpal tunnel syndrome	No detail on TEAEs frequencies	UK	7.0	21143704
Wallace et al. 2010	Parallel-group Multicenter	Gabapentin ER 1800 mg/day (136)	10 weeks	Post-herpetic neuropathic pain	Gabapentin ER 1800 mg Any (57.0) #	Gabapentin ER 1800 mg (3.0)	Gabapentin ER 1800 mg (12.0)	20818838

		Gabapentin ER 600 mg/day + 1200 mg/day (137) Placebo (134)			Dizziness (10.0) # Gabapentin ER 600 mg + 1200 mg Any (58.0) # Dizziness (15.0) #	Gabapentin ER 600 mg + 1200 mg (5.0)	Gabapentin ER 600 mg + 1200 mg (11.0)	
Amr et al. 2010	Parallel-group Monocenter	Gabapentin 300 mg/day (50) Venlafaxine ER 37.5 mg/day (50) Placebo (50)	10 days	Post-traumatic neuropathic pain	No sufficient detail on frequencies of patients with TEAEs	UK	UK	20473044
Jensen et al. 2009	Parallel-group Monocenter	Gabapentin 1800 mg/day (48) Placebo (48)	4 weeks	Post-herpetic neuropathic pain	No safety	No safety	No safety	19590476
Yelland et al. 2009	Crossover-group, Multicenter	Gabapentin 600 - 1800 mg/day (73) Placebo (73)	2 weeks	Various neuropathic pain	No safety	No safety	No safety	19453961
Gordh et al. 2008	Crossover-group, Multicenter	Gabapentin 600 -2400 mg/day (120) Placebo (120)	5 weeks	Post-traumatic neuropathic pain	Any (UK) Dizziness (32.5) # Fatigue (25.8) # Headache (15.0) # Confusion (13.3) #	UK	5.8	18258368
Rao et al. 2007	Crossover-group, Multicenter	Gabapentin 2700 mg/day (91) Placebo (89)	6 weeks	Chemotherapy-induced peripheral neuropathy	Any (UK) No TEAE ≥ 10% of patients	0.0	0.0	17853395
Van de Vusse et al. 2004	Crossover-group, Monocenter	Gabapentin 600-1800 mg/day (58) Placebo (58)	3 weeks	Complex regional pain syndrome	Any (62.1) # Dizziness (37.3) * Drowsiness (27.8) * Lethargy (20.4) * Nausea (18.5) ns	UK	5.2	15453912
Serpell et al. 2002	Parallel-group Multicenter	Gabapentin 2400 mg/day (153) Placebo (152)	8 weeks	Various neuropathic pain	Any (76.5) # Dizziness (24.2) #	2.6	15.7	12406532

					Drowsiness (14.4) #			
Bone et al. 2002	Crossover-group, Multicenter	Gabapentin 300-2400 mg/day (8) Placebo (6)	6 weeks	Phantom Limb Pain	Any (UK) Drowsiness (87.5) ns Dizziness (25.0) ns Headache (25.0) ns Nausea 12.5) ns	UK	0.0	12373695

Table 1: Summary table for gabapentinoids

TEAE, treatment-emergent adverse event; ER, extended-release; GR, Gastroretentive; SAEs, serious adverse event; UK, unknown.

Route of administration is not provided when administered orally.

* Statistically different from placebo; ns, no statistical difference from placebo; #, no statistical comparison to placebo

Authors' names	Study design	Drug/comparator and dose (patient number)	Duration	Pathology	List of TEAEs in study drug arm (≥ 10% of patients)	SAEs related to study drug (%)	Dropout due to TEAE in study drug arm (%)	Reference (PMID)
Lamotrigine								
Rao et al. 2008	Parallel-group Multicenter	Lamotrigine 300 mg/day (63) Placebo (62)	10 weeks	Chemotherapy-induced peripheral neuropathy	No TEAE ≥ 10% of patients	UK	11.1	18428211
Silver et al. 2007	Parallel-group Multicenter	Lamotrigine 200 - 400 mg/day (111) placebo (109)	14 weeks	Various neuropathic pain	Any (71.0) # Rash (18.0) #	0.0	24.0	17662571
Simpson et al. 2003	Parallel-group Multicenter	Lamotrigine 600 mg/day (150) Placebo (77)	12 weeks	HIV-associated neuropathy	Any (UK) Rash (14.0) # Infection (11.0) # Nausea (11.0) # Diarrhea (11.0) # Headache (11.0) #	0.0	6.7	12743240
Lacosamide								
de Greef BTA et al. 2019	Crossover-group, Monocenter	Lacosamide 400 mg/day (24) Placebo (23)	14 weeks	Small fiber neuropathy	Any (87.5) # Dizziness (41.7) # headache (25) # Nausea (25) # fatigue (20.8) # tremor (20.8) # Drowsiness (16.7) # epigastric pain (16.7) # memory impaired (12.5) #	4.2	0.0	30649227

					pruritus (12.5) #			
Ziegler et al. 2010	Parallel-group Multicenter	Lacosamide 400 mg/day (150) Lacosamide 600 mg/day (133) Placebo (74)	18 weeks	Diabetic neuropathy	Lacosamide 400 mg Any (58.7) # Fatigue (10.0) # Lacosamide 600 mg Any (64.7) # Dizziness (19.5) # Nausea (11.3) #	Lacosamide 400 mg (7.3) Lacosamide 600 mg (8.3)	13.0 (both groups)	20067958
Wymer et al. 2009	Parallel-group Multicenter	Lacosamide200 mg/day (93) Lacosamide 400 mg/day (93) Lacosamide 600 mg/day (93) Placebo (93)	12 weeks	Diabetic neuropathy	Lacosamide 200 mg Any (75.3) # Dizziness (10.8) # Lacosamide 400 mg Any (78.0) # Dizziness (15.4) # Lacosamide 600 mg Any (89.2) # Dizziness (35.5) # Nausea (15.1) # Fatigue (15.1) #	UK	Lacosamide200 mg (8.6) Lacosamide 400 mg (23.1) Lacosamide 600 mg (39.8)	19454870
Shaibani et al. 2009	Parallel-group Multicenter	Lacosamide200 mg/day (141) Lacosamide 400 mg/day (125) Lacosamide 600 mg/day (137) Placebo (65)	12 weeks	Diabetic neuropathy	Lacosamide 200 mg Any (80.1) # No TEAE ≥ 10% of patients	UK	Lacosamide 200 mg (12.1) Lacosamide 400 mg (24.0)	19409861

					Lacosamide 400 mg Any (79.2) # Dizziness (21.6) # Lacosamide 600 mg Any (86.9) # Dizziness (28.5) # Nausea (18.2) # Tremor (14.6) # Headache (13.1) #		Lacosamide 600 mg (42.3)	
Rauck et al. 2007	Parallel-group Multicenter	Lacosamide 100-400 mg/day (60) Placebo (59)	7 weeks	Diabetic neuropathy	Any (87.0) # Dizziness (15.0) # Nausea (12.0) # Back pain (10.0) # Headache (18.0) # Upper respiratory tract symptoms (25.0) #	7.0	8.3	17237664
Levetiracetam								
Holbech et al. 2011	Crossover-group, Multicenter	Levetiracetam 3000 mg/day (21) Placebo (18)	6 weeks	Various neuropathic pain	Any (UK) Fatigue (17.7) ns	0.0	7.7	21183370
Vilholm et al. 2008	Crossover-group, Monocenter	Levetiracetam 3000 mg/day (27) Placebo (27)	4 weeks	Post-traumatic neuropathic pain	Any (56.0) # Fatigue (40.0) # Dizziness (12.0) # Headache (12.0) # Gastric upset (12.0) #	UK	6.7	18565107
Sodium valproate								

Agrawal et al. 2009	Parallel-group Monocenter	Sodium valproate 20 mg/kg/day (20) Placebo (21)	12 weeks	Diabetic neuropathy	Any (UK) Nausea (10.0) #	UK	0.0	19208440
Zonisamide								
Atli et al. 2005	Parallel-group Monocenter	Zonisamide 540 mg/day (13) Placebo (12)	12 weeks	Diabetic neuropathy	Any (91.7) ns Urinary (25.0) ns Cardiovascular (25.0) ns Dermatological (33.3) ns Musculoskeletal (25.0) ns Headache (16.7) ns Dizziness (25.0) ns Drowsiness/sleepiness (16.7) ns Restless/insomnia (25.0) ns Respiratory (33.3) ns Special senses (16.7) ns	8.3	8.3	15972086
Ethosuximide								
Kerckhove et al. 2018	Parallel-group Multicenter	Ethosuximide 250-1500 mg/day (59) Placebo (55)	6 weeks	Various neuropathic pain	Any (69.5) # Headache (32.0) # Dyspepsia (39.0) # Dizziness (20.3) # Insomnia (11.9) # Skin rash (11.9) # Drowsiness (10.2) # Vomiting (10.2) #	6.8	59.3	29577519
Carisbamate								

Smith et al. 2014	Study 1 Crossover-group, Multicenter Study 2: Crossover-group, Multicenter Study 3: Parallel-group Multicenter	Study1 Carisbamate 400 mg/day (84) Placebo (89) Study 2: Carisbamate 400 mg/day (131) Placebo (133) Study 3: Carisbamate 800 mg/day (94) Carisbamate 1200 mg/day (98) Pregabalin 300 mg/day (99) Placebo (95)	Study 1: 8 weeks Study 2: 8 weeks Study 3: 15 weeks	Study 1: Post-herpetic neuropathic pain Study 2: Diabetic neuropathy Study 3: Diabetic neuropathy	Study 1 Any (27) # Dizziness (12) # Headache (12) # Study 2 Any (15) # No TEAE ≥ 10% of patients Study 3 Carisbamate 800 mg/day Any (38) # Dizziness (14) # Headache (13) # Carisbamate 1200 mg/day Any (35) # Dizziness (13) # Somnolence (10) #	Study 1 None Study 2 2 Study 3 Carisbamate 800 mg/day (4) Carisbamate 1200 mg/day (3)	Study 1 1 Study 2 1 Study 3 Carisbamate 800 mg/day (15) Carisbamate 1200 mg/day (14)	23692321
Carbamazepine								
Harke et al. 2001	Crossover-group Monocenter	Carbamazepine 600 to 400 mg/d (22) Placebo (21)	8 days	Neuropathic pain Complex regional pain syndrome I	Any (UK)# Daily description of adverse effects	UK	13.6	11159256
Oxcarbazepine								

Demant et al. 2014	Crossover-group, Monocenter	Oxcarbazepine 1800-2400 mg/day (47) Placebo (50)	6 weeks	Various neuropathic pain	Any (94.0) # Dizziness (67.0) # Tiredness (47.0) # Headache (24.0) # Nausea (36.0) # Vomiting (16.0) # Diplopia (19.0) #	UK	17.7	25139589
Dogra et al. 2005	Parallel-group Multicenter	Oxcarbazepine 300-1800 mg/day (69) Placebo (77)	16 weeks	Diabetic neuropathy	Any (UK) Dizziness (44.9) # Headache (24.6) # Nausea (23.2) # Drowsiness (11.6) # Fatigue (11.6) #	2.9	27.5	16139183

Table 2: Summary table of other antiepileptics

TEAE, treatment-emergent adverse event; SAEs, serious adverse event; UK, unknown;

Route of administration is not provided when administered orally.

* statistically different from placebo ; ns no statistically different from placebo; # no statistically compared to placebo

Authors' names	Study design	Drug/comparator and dose (patient number)	Duration	Pathology	List of TEAEs in study drug arm (≥ 10% of patients)	SAEs related to study drug (%)	Dropout due to TEAE in study drug arm (%)	Reference (PMID)
Duloxetine								
Schukro et al. 2016	Crossover-group, Monocenter	Duloxetine 120 mg/day (31) Placebo (29)	4 weeks	Radiculopathy	Any (65.0) # Sweating (35.0) ns Dry mouth (35.0) * Fatigue (26.0) ns Nausea (19.0) ns Constipation (19.0) ns Loss of appetite (19.0) * Dizziness (16.0) ns	UK	19.35	26517858
Gao et al. 2015	Parallel-group Multicenter	Duloxetine 60 mg qd (203) Placebo (202)	12 weeks	Diabetic neuropathy	Any (46.5) * Nausea (10.4) *	1.5	8.4	25939897
Harrison et al. 2013	Crossover-group, Monocenter	Duloxetine 60 mg/day (15) Methadone 10 mg/day (15) Duloxetine 60 mg/day + Methadone 10 mg/day (15) Placebo (15)	4 weeks	HIV-associated neuropathy	Only for duloxetine group Any (40.0) #	6.7	UK	23565581
Smith et al. 2013	Crossover-group, Multicenter	Duloxetine 60 mg/day (220) Placebo (220)	5 weeks	Chemotherapy-induced peripheral neuropathy	Any (UK)	0.0	8.4	23549581
Yasuda et al. 2011	Parallel-group Multicenter	Duloxetine 40 mg/day (86) Duloxetine 60 mg/day (86) Placebo (167)	12 weeks	Diabetic neuropathy	Duloxetine 40 mg Any (84.7) * Drowsiness (18.8) ns	Duloxetine 40 mg: 3.5	Duloxetine 40 mg : 10.5	24843472

					Nausea (11.8) ns Duloxetine 60 mg Any (84.9) * Drowsiness (24.4) ns Nausea (16.3) ns	Duloxetine 60 mg: 2.3	Duloxetine 60 mg: 14.0	
Ziegler et al. 2007	Parallel-group Multicenter	Duloxetine 60 mg/day (344) Duloxetine 120 mg/day (341) Placebo (339)	12 weeks	Diabetic neuropathy	Duloxetine 60 mg Any (UK) Nausea (24.0) * Drowsiness (15.0) * Dizziness (11.0) * Diarrhea (11.0) * Duloxetine 120 mg Any (UK) Nausea (27.0) * Drowsiness (19.0) * Dizziness (13.0) * Constipation (12.0) * Fatigue (11.0) * Hyperhidrosis (10.0) * Dry mouth (10.0) *	UK	UK	17327338
Wernicke et al. 2006	Parallel-group Multicenter	Duloxetine 60 mg/day (114) Duloxetine 120 mg/day (112) Placebo (108)	12 weeks	Diabetic neuropathy	Duloxetine 60 mg Any (89.5) * Nausea (28.1) * Dizziness (15.8) *	Duloxetine 60 mg: 4.4	Duloxetine 60 mg: 14.9	17060567

					Fatigue (12.3) * Headache (10.5) ns Diarrhoea 13 (11.4) * Duloxetine 120 mg Any (85.7) * Nausea (32.1) * Drowsiness (15.2) * Constipation (18.8) * Headache (13.4) ns Fatigue (12.5) * Dizziness (10.7) ns	Duloxetine 120 mg: 1.8	Duloxetine 120 mg :17.9	
Goldstein et al. 2005	Parallel-group Multicenter	Duloxetine 20 mg/d (115) Duloxetine 60 mg/d (114) Duloxetine 120 mg/d (113) Placebo (115)	12 weeks	Diabetic neuropathy	Duloxetine 20 mg Any (UK) Nausea (13.9) ns Duloxetine 60 mg Any (UK) Nausea (16.7) ns Drowsiness (20.2) * Constipation (14.9) * Duloxetine 120 mg Any (UK) Nausea (27.4) * Drowsiness (28.3) *	Duloxetine 20 mg: 1.7 Duloxetine 60 mg: 0.0 Duloxetine 120 mg: 1.8	Duloxetine 20 mg: 4.3 Duloxetine 60 mg: 13.2 Duloxetine 120 mg: 19.5	15927394

					Dizziness (23.0) * Constipation (10.6) * Dry mouth (15.0) * Decreased appetite (12.4) *			
Raskin et al. 2005	Parallel-group Multicenter	Duloxetine 60 mg/day (116) Duloxetine 120 mg/day (116) Placebo (116)	12 weeks	Diabetic neuropathy	Duloxetine 60 mg Any (61.2) ns Duloxetine 120 mg Any (62.9) *	Duloxetine 60 mg: 3.4 Duloxetine 120 mg: 1.7	Duloxetine 60 mg: 4.3 Duloxetine 120 mg: 12.1	16266355
Venlafaxine								
Zimmermann et al. 2016	Parallel-group Multicenter	Venlafaxine 75 mg/day (25) Placebo (25)	Throughout chemotherapy	Chemotherapy-induced peripheral neuropathy	No sufficient detail on frequencies of patients with TEAEs	0.0	0.0	26248652
Durand et al. 2012	Parallel-group Multicenter	Venlafaxine 75 mg/day (24) Placebo (24)	11 days	Chemotherapy-induced peripheral neuropathy	Any (UK) Nausea (43.1) * Fatigue / Drowsiness (39.2) * Vomiting (19.6) *	0.0	16.7	21427067
Amr et al. 2010	Parallel-group Monocenter	Venlafaxine ER 37.5 mg/day (50) Gabapentin 300 mg/day (50) Placebo (50)	10 days	Post-traumatic neuropathic pain	No sufficient detail on frequencies of patients with TEAEs	UK	UK	20473044
Yucel et al. 2005	Parallel-group Monocenter	Venlafaxine 75 mg/day (19) Venlafaxine 150 mg/day (17) Placebo (19)	8 weeks	Various neuropathic pain	No sufficient detail on frequencies of patients with TEAEs	UK	Venlafaxine 150 mg: 17.6 Venlafaxine 75 mg: 5.3	15979021
Tasmuth et al. 2002	Crossover-group, Monocenter	Venlafaxine 18.75 until 75 mg/day (13) Placebo (13)	4 weeks	Neuropathic cancer pain	Any (UK) Fatigue (69.2) #	UK	6.7	11888224

					Dry mouth (61.5) # Sweating (61.5) # Headache (46.2) # Constipation (30.8) # Nausea (30.8) # Loss of appetite (23.1) # Palpitation (23.1) # Nightmares (15.4) # Difficult to urinate (15.4) #			
Milnacipran								
Marks et al. 2014	Parallel-group Monocenter	Milnacipran 100 - 200 mg (7) Placebo (4)	10 weeks	Radiculopathy	Any (UK) Headache (28.6) # Constipation (28.6) # Nausea (14.3) # Dizziness (14.3) # Elevated blood pressure (14.3) # Palpitations (14.3) # Dyspepsia (14.3) # Urinary hesitancy (14.3) # Drowsiness (14.3) #	UK	28.7	25664215
Amitriptyline								
Vanelderen et al. 2015	Parallel-group Monocenter	Amitriptyline 25mg/day (20) Placebo (20)	2 weeks	Radiculopathy	Any (10.0) # Nausea/vomiting (5.0) # Rash (5.0) #	UK	10.0	25373391

Mishra et al. 2012	Parallel-group Multicenter	Amitriptyline 50-100 mg/day (30) Gabapentin 900-1800 mg/day (30) Pregabalin 150-600 mg/day (30) Placebo (30)	4 weeks	Neuropathic cancer pain	Any (UK) No sufficient detail on frequencies of patients with TEAEs	UK	UK	21745832
Kautio et al. 2009	Parallel-group Monocenter	Amitriptyline 25-100 mg/day (58) Placebo (56)	Throughout chemotherapy	Chemotherapy-induced peripheral neuropathy	Any (UK) Fatigue (19.0) # Dry mouth (UK) Visual disturbances (UK) Constipation (UK)	UK	UK	19596934
Kautio et al. 2008	Parallel-group Monocenter	Amitriptyline 10-50 mg/day (22) Placebo (22)	12 weeks	Chemotherapy-induced peripheral neuropathy	No safety	No safety	No safety	17980550
Ho et al. 2008	Parallel-group Monocenter	Amitriptyline 5% gel (35) Lidocaine 5% gel (35) Placebo (35)	1 week	Various neuropathic pain	Only for Amitriptyline group Any (18.8) # Itching (31.4) #	UK	Only for amitriptyline 0.0	18180637
Lynch et al. 2005	Parallel-group Multicenter	Topical 2% amitriptyline (22) Topical 1% ketamine (22) Topical 2% amitriptyline-1% ketamine (23) Placebo (25)	3 weeks	Various neuropathic pain	Only amitriptyline group Any (26.0) ns No TEAE ≥ 10% of patients	UK	4.5	15983466
Nortriptyline								
Hammack et al. 2002	Crossover-group, Monocenter	Nortriptyline 100 mg/day (51) Placebo (51)	4 weeks	Chemotherapy-induced peripheral neuropathy	Any (UK) Dry mouth (62.0) * Dizziness (49.0) * Constipation (41.0) *	UK	3.9	12098632
Imipramine								

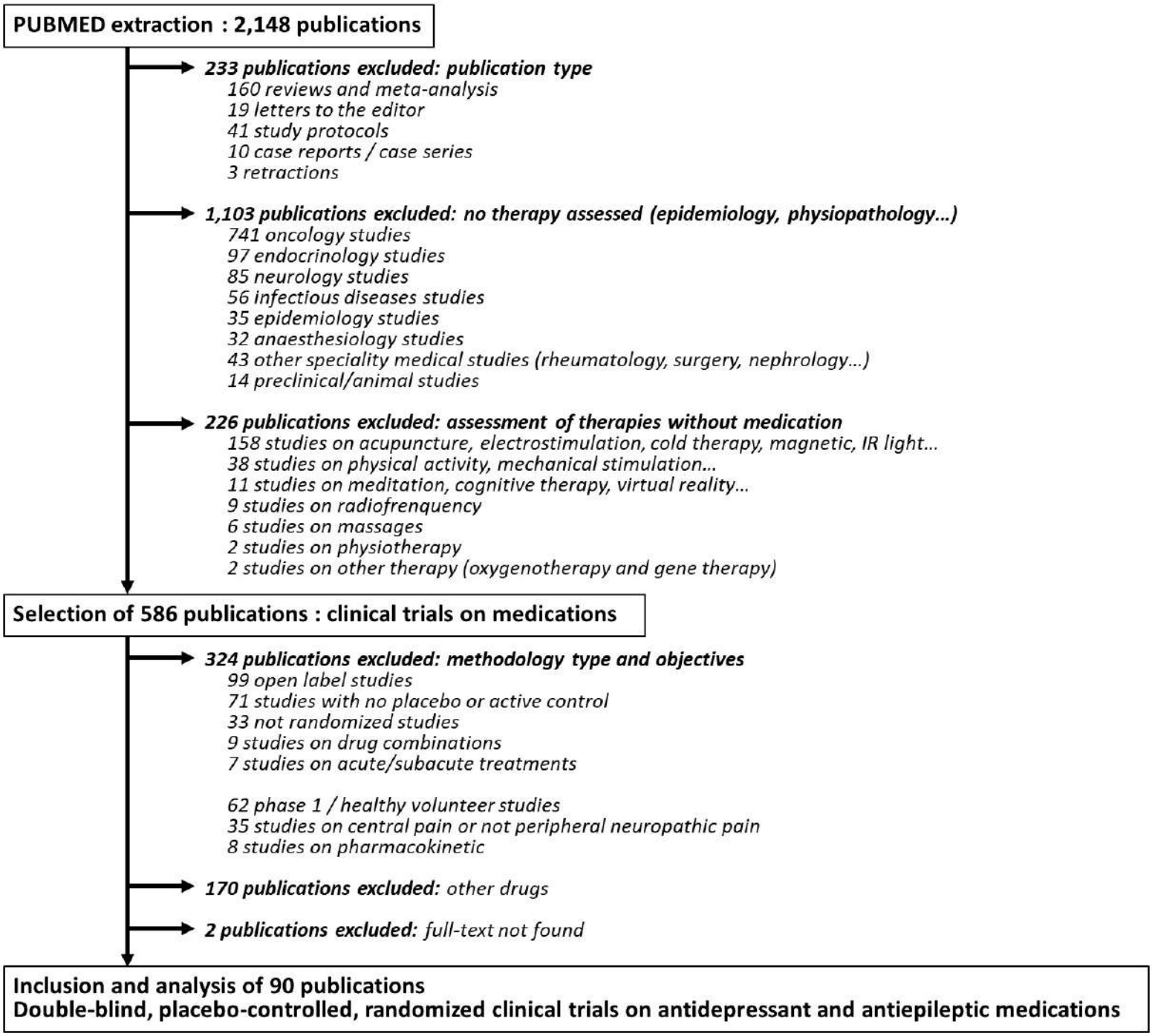
Holbech et al. 2015	Crossover-group, Monocenter	Imipramine 75 mg/day (18) Pregabalin 600 mg (18) Placebo (19)	5 weeks	Various neuropathic pain	Only Imipramine group Any (43.0) # Dry mouth (22.0) # Sweating (20.0) # Dizziness (10.0) #	UK	Only imipramine 17.0	25719617
Escitalopram								
Otto et al. 2008	Crossover-group, Multicenter	Escitalopram 10-20 mg/day (48) Placebo (48)	6 weeks	Various neuropathic pain	Any (51.2) # Abdominal discomfort (14.6) # Nausea/vomiting (14.6) #	UK	10.4	18547727

Table 3: Summary table for antidepressants

TEAE, treatment-emergent adverse event; ER, extended-release; SAEs, serious adverse event; UK, unknown.

Route of administration is not provided when administered orally.

* Statistically different from placebo; ns, no statistical difference from placebo; #, no statistical comparison to placebo


PUBMED extraction : 2,148 publications
233 publications excluded: publication type
160 reviews and meta-analysis
19 letters to the editor
41 study protocols
10 case reports / case series
3 retractions
1,103 publications excluded: no therapy assessed (epidemiology, physiopathology…)
741 oncology studies
97 endocrinology studies
85 neurology studies
56 infectious diseases studies
35 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, IR light…
38 studies on physical activity, mechanical stimulation…
11 studies on meditation, cognitive therapy, virtual reality…
9 studies on radiofrenquency
6 studies on massages
2 studies on physiotherapy
2 studies on other therapy (oxygenotherapy and gene therapy)
Selection of 586 publications : clinical trials on medications
324 publications excluded: methodology type and objectives
99 open label studies
71 studies with no placebo or active control
33 not randomized studies
9 studies on drug combinations
7 studies on acute/subacute treatments
62 phase 1 / healthy volunteer studies
35 studies on central pain or not peripheral neuropathic pain
8 studies on pharmacokinetic
170 publications excluded: other drugs
2 publications excluded: full-text not found
Inclusion and analysis of 90 publications
Double-blind, placebo-controlled, randomized clinical trials on antidepressant and antiepileptic medications