ABSTRACT

Introduction: Peripheral neuropathic pain (PNP) arises either acutely or in the chronic phase of a lesion or disease of the peripheral nervous system and is associated with a notable disease burden. The management of PNP is often challenging. The aim of this systematic review was to evaluate current evidence, derived from randomized controlled trials (RCTs) that have assessed pharmacological interventions for the treatment of PNP due to polyneuropathy (PN).

Methods: A systematic search of the PubMed database led to the identification of 538 papers, of which 457 were excluded due to not meeting the eligibility criteria, and two articles were identified through screening of the reference lists of the 81 eligible studies. Ultimately, 83 papers were included in this systematic review.

Results: The best available evidence for the management of painful diabetic polyneuropathy (DPN) is for amitriptyline, duloxetine, gabapentin, pregabalin and venlafaxine as monotherapies and oxycodone as add-on therapy (level II of evidence). Tramadol appears to be effective when used as a monotherapy and add-on therapy in patients with PN of various etiologies (level II of evidence). Weaker evidence (level III) is available on the effectiveness of several other agents discussed in this review for the management of PNP due to PN.

Discussion: Response to treatment may be affected by the underlying pathophysiological mechanisms that are involved in the pathogenesis of the PN and, therefore, it is very important to thoroughly investigate patients presenting with PNP to determine the causes of this neuropathy. Future RCTs should be conducted to shed more light on the use of pharmacological approaches in patients with other forms of PNP and to design specific treatment algorithms.
Keywords: Management; Peripheral neuropathic pain; Pharmacological; Polyneuropathy

Key Summary Points

There is a plethora of pharmacological interventions available for the management of peripheral neuropathic pain.

Amitriptyline, duloxetine, gabapentin, pregabalin and venlafaxine as monotherapies and oxycodone as add-on therapy are effective in reducing the overall pain intensity in patients with diabetic polyneuropathy (PN) (level II evidence).

Tramadol appears to be effective when used as a monotherapy and add-on therapy in patients with PN of various etiologies (level II of evidence).

Response to treatment may be affected by the underlying pathophysiological mechanisms that are involved in the pathogenesis of the neuropathy.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13055918.

INTRODUCTION

The term peripheral neuropathy refers to disorders of the peripheral nervous system and includes mononeuropathies, such as carpal tunnel syndrome, and polyneuropathy (PN), which can be symmetrical or asymmetrical [1]. Many aetiological factors have been implicated in the development of PN, with the most common being diabetes mellitus, cancer, drug toxicity, vitamin deficiencies, excessive alcohol consumption, increased oxidative stress, gluten sensitivity and genetics [2–9].

Peripheral neuropathic pain (PNP) is very prevalent, affecting up to two-thirds of patients with PN, independently of the aetiology [10–12]. It is one of the most—if not the most—burdensome of neuropathic symptoms, leading to an overall poor quality of life, regardless of disease severity [13, 14]. PNP is challenging to control, and often patients require various combinations of medications, with or without adjuvant non-pharmacological interventions, to achieve satisfactory pain management [15, 16].

The aim of this systematic review was to evaluate currently available evidence, derived from randomized controlled trials (RCTs) about pharmacological interventions for the treatment of PNP due to PN.

METHODS

Protocol Registration

This review was registered in PROSPERO, an international prospective register of systematic reviews, under registration number CRD42020179750.

Literature Search Strategy

A systematic literature search of the PubMed database was performed on 12 April 2020 using three medical subject heading (MeSH) terms. Term A was “pain” OR “painful”; term B was “neuropathy” OR “polyneuropathy”; term C was “randomised” OR “randomized”. The filter “clinical trial” was applied. We also searched at https://www.clinicaltrials.gov/, a resource provided by the U.S. National Library of Medicine for unpublished trials, using the same MeSH terms as above, but applying the filters “with results” AND “completed”. The reference lists of articles that met the eligibility criteria were further screened to identify additional studies that may fall within the scope of this review.
Inclusion and Exclusion Criteria and Screening process

Studies eligible to be included in this review had to meet the following inclusion criteria: (1) human subjects were involved; (2) the full article was written in English; (3) the trials were pharmacological RCTs; (4) the studies were of adequate methodological quality (as described below).

The exclusion criteria were: (1) article made no reference to PN; (2) article was not an original study (i.e. review articles, letters, medical hypotheses, etc.); (3) pain relief was not the primary aim of the study; (4) trials with less than ten patients per treatment arm; (5) withdrawal trials; (6) duplicate articles or papers from the same research teams describing the same patient population; (7) non-pharmacological trials.

All article abstracts were screened three times in a blinded fashion. Those found to meet any of the exclusion criteria were removed and any differences of opinion were discussed in a face-to-face meeting during which the abstracts were re-reviewed. All papers deemed eligible were screened again as a full article by at least three reviewers, and conflicts were settled as previously noted.

Quality Assessment of Included Studies

All studies were initially screened for bias using the Jadad scoring system [17]. Trials with Jadad score < 4 were excluded. Studies with a Jadad score ≥ 4 were further assessed using the Cochrane Collaboration risk of bias assessment tool [18]. See Electronic Supplementary Material for more detailed information.

Data Collection Process

Following identification of the eligible papers, all relevant data were extracted from each study in a structured coding scheme using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). The information collected included population size, gender and age distribution, the type of PN, the means used to diagnose PNP, treatment strategies, the duration of the RCT, patient response to treatment, the manner used to assess the effectiveness of the treatment, the side effects associated with the treatment and the follow-up period of the patients, where applicable. When there was uncertainty regarding how the data should be interpreted or utilized, at least three authors discussed the study in question to reach consensus.

Data Synthesis

This study used aggregate data where possible, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [19].

Clinical Recommendations

To determine the grading of evidence we used the classification proposed by the American Society of Interventional Pain Physicians (ASIPP), where applicable [20].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants performed by any of the authors. Therefore, ethics review was not required.

RESULTS

Study Characteristics

Our search strategy identified a total of 538 articles, of which 457 articles were excluded during the eligibility assessment. Two papers were identified through screening of the reference lists of the included papers. Ultimately, a total of 83 studies, published between 1997 and 2019, were included in the present review [21–103]. The selection process is shown in Fig. 1 (PRISMA chart).
Anticonvulsants

Compared to placebo, gabapentin monotherapy has been found to be effective and well-tolerated for the management of pain and sleep interference in patients with diabetic PN (DPN) \( (n = 165) \) [21] and human immunodeficiency virus (HIV)-related PN (HIVPN) \( (n = 26) \) [22]. However, Rao et al. showed a lack of benefit when gabapentin was used as a monotherapy to treat painful chemotherapy-induced peripheral neuropathy (CIPN) [23]. The prodrug of gabapentin, gabapentin enacarbil, was not effective in treating painful DPN in 420 subjects [24]. In a double-blind, cross-over RCT, Morello et al. compared gabapentin to amitriptyline, both as monotherapies, in 25 subjects with painful DPN [25] and found that both were equally effective in managing the pain. Gilron et al. showed that a combination of gabapentin and nortriptyline is significantly more effective in pain management than gabapentin or nortriptyline alone [26]. In a double-blind placebo-controlled RCT, Sandercock et al. reported that adjuvant prolonged-released gabapentin was significantly more effective than placebo in the management of pain in subjects \( (n = 147) \) with painful DPN [27].

Pregabalin is the most tested drug for the management of painful PN as a monotherapy. The beneficial effect of pregabalin used to treat painful DPN has been demonstrated at higher doses of 300–600 mg daily [28–32]. However, other studies have shown that when pregabalin was used to treat painful DPN at moderate doses of 150–300 mg daily, pain reduction at the endpoint did not differ significantly between the pregabalin and placebo groups [33–35]. Improvements in secondary outcomes, however, such as sleep, may suggest a utility of pregabalin in the overall management of DPN. In a double-blind, cross-over RCT of the pain-relieving effect of pregabalin and amitriptyline in patients with painful DPN \( (n = 51) \), but with no signs of depression, Bansal et al. reported that both agents tested as monotherapies were safe and effective [36], with fewer side effects observed with pregabalin. Holbech et al. demonstrated that pregabalin was superior to placebo in subjects with PNP [37]. In 2013, Tesfaye et al. investigated the efficacy of pregabal 300 mg and duloxetine 60 mg as
monotherapies or in combination in 804 patients with DPN [38]. Although the combination therapy did not reach a significant level of efficacy compared to the respective monotherapies, the combination therapy was considered to be effective, safe and well tolerated. In 2016, González-Duarte et al. demonstrated the potential role of pregabalin as a monotherapy for the treatment of prediabetic small-fibre neuropathic pain in 45 subjects when compared to placebo [39].

Apart from the studies with diabetic or prediabetic subjects, pregabalin has been tested in patients with painful HIVPN as a monotherapy (n = 377) [40] or as an add-on (n = 302) [41]; however, it was not superior to placebo in this study. In a double-blind placebo-controlled RCT (n = 323), Raskin et al. demonstrated that topiramate monotherapy provided pain relief more effectively than placebo in patients with moderate to severe painful DPN [42]. However, this finding was not confirmed in a larger study conducted by Thienel et al. [43].

Lacosamide is a safe and well-tolerated agent which has been demonstrated to be effective in managing pain due to DPN either as a monotherapy [44, 45]) or as an add-on [46]. De Greef et al. showed that it is also effective in the management of pain in pure small-fibre neuropathy when used as an add-on analgesic [47].

In the initial trials Lamotrigine, as monotherapy, has initially shown a potential for the management of painful DPN [48, 49]. However, its beneficial effect was not confirmed in two larger double-blind placebo-controlled RCTs when used as an add-on for managing painful DPN [50] or when used as a monotherapy for treating painful CIPN [51]. When used as an add-on treatment lamotrigine was effective for the management of painful HIVPN [52].

Evidence on the use of sodium valproate in the management of PNP is also conflicting. Two studies reported that this drug has a potential for managing pain in subjects with painful DPN, compared to placebo, either as monotherapy [53] or in combination with glyceryl-trinitrate spray [54]. However, these results were not confirmed in another study [55].

In 2006, Beydoun et al. showed that, compared to placebo, oxcarbazepine improves pain scores when given as monotherapy in patients with painful DPN, but the benefit was not statistically significant compared to placebo [56].

Levetiracetam [57], perampanel [58] and some experimental anticonvulsants, namely ABT-639 [59] and PF-05089771 [60], have been found to be of no value for the treatment of PNP.

**Antidepressants**

_Serotonin-Norepinephrine Reuptake Inhibitors_

In their RCT, Rowbotham et al. showed that venlafaxine at high doses (150–225 mg daily) was effective in treating painful DPN when compared to low-dose venlafaxine (75 mg daily) and placebo [61]. In other studies comparing venlafaxine to other antineuralgics, venlafaxine monotherapy was found to be superior to carbamazepine [62], equally effective to imipramine [63] and inferior to pregabalin [64] for the treatment of PNP.

_Duloxetine_ is a safe and well-tolerated agent that has been used effectively to treat pain in DPN, in comparison to placebo, when used as a monotherapy [65–67] and painful CIPN, when used as an add-on treatment [68]. Compared to other antineuralgics, duloxetine monotherapy is equally effective to gabapentin for the treatment of pain due to DPN but shows better tolerability [69]. Similarly, duloxetine is equally effective to pregabalin for the treatment of pain due to DPN [38, 70].

_Tricyclic and Tetracyclic Antidepressants_

Tricyclic (TCAs) and tetracyclic antidepressants (TeCAs) have been tested in a few studies, but evidence for their effectiveness is somewhat contradictory. In a double-blind crossover placebo-controlled RCT, Vrethem et al. showed that amitriptyline and maprotiline, when used as monotherapies, are superior to placebo for pain management in patients with diabetic and nondiabetic PN [71]. Results from small RCTs show that amitriptyline [25, 36] and nortriptyline [26] are effective in the management of painful DPN. However, when administered in subjects with HIVPN neither amitriptyline nor mexiletine monotherapy provided statistically significant improvement in pain relief compared to placebo [72, 73].
In 2015, Holbech et al. demonstrated the superiority of imipramine as a monotherapy or in combination with pregabalin, in comparison to pregabalin alone or placebo, in subjects with PNP [37].

**Selective Serotonin Reuptake Inhibitors**

Escitalopram as monotherapy appears to produce a weak to moderate pain relief compared to placebo in depressive and non-depressive patients with painful PN of various etiologies [74].

**Opioids**

A few double-blind placebo-controlled RCTs have reported that tramadol is effective in the management of PNP, either as monotherapy [75] or in a combination with paracetamol [76] or acetaminophen [77], with few and transient side effects.

Controlled-release oxycodone has been shown to improve moderate to severe pain due to DPN, compared to placebo, when used as an add-on treatment [78, 79]. However, in a double-blind placebo-controlled phase II RCT, the beneficial effect of oxycodone/naloxone when used as adjuvant to pregabalin in opioid-naïve patients suffering from PNP was not confirmed [80].

In a double-blind placebo-controlled RCT, Shaibani et al. demonstrated that dextromethorphan/quinidine, when used as a monotherapy, provides a significant reduction in pain due to DPN. At high doses, however, there is a risk for serious adverse effects, such as hypertensive crises and cardiac arrhythmias [81].

In 2015, the effectiveness of adjuvant use of cebranopadol compared to placebo and pregabalin was tested in a double-blind RCT in subjects with DPN; the authors found that this opioid was statistically effective in pain relief when administered at a dose of 600 µg daily [82].

**Cannabinoids**

Adjuvant treatment with delta-9-tetrahydrocannabinol has shown a potential for the management of painful HIVPN, but current evidence is based only on small placebo-controlled studies [83, 84].

**Topical Treatments**

Capsaicin has been used either as a patch or a lotion in different concentrations. Studies have demonstrated that the application of a capsaicin 8% patch is effective in the management of pain due to HIVPN [85] and DPN [86]. However, other studies on capsaicin lotion did not achieve a statistically significant pain reduction in subjects with pain due to DPN [87, 88].

Ketamine/amitriptyline cream has been found to be of no therapeutic value compared to placebo for alleviating painful DPN [89] or CIPN [90].

The application of glyceryl-trinitrate spray [91] and isosorbide dinitrate spray [92] has been reported to provide a statistically significant, but short-lasting, analgesic effect and improvement in burning sensation, when used in patients with painful DPN.

Topical clonidine as add-on, although safe, did not reach statistical significance for the management of painful DPN [93].

**Monoclonal Antibodies**

In a double-blind placebo-controlled RCT on the pain-relieving effect of tanezumab as a monotherapy in patients with painful DPN, Bramson et al. showed that tanezumab achieved a statistically significant reduction of pain, with mild and transient side effects but not any change in the sensory function of small and large fibres [94].

**Botulinum Toxin Type A**

In a small double-blind, cross-over placebo-controlled RCT, Yuan et al. investigated the efficacy of intradermal botulinum toxin type A injections at the dorsum of the foot as add-on for the management of PNP due to diabetes, and reported a significant reduction in pain intensity [95].
| Drug                                      | Monotherapy or add-on | Type of polyneuropathy | Effectiveness* |
|-------------------------------------------|-----------------------|------------------------|----------------|
| Amitriptyline                             | Monotherapy           | DPN                    | Effective (level II) |
|                                           | Monotherapy           | HIVPN                  | Ineffective     |
| Acetyl L-carnitine (ALCAR)                | Unclear               | HIVPN                  | Ineffective     |
| Botulinum toxin type A                    | Add-on                | DPN                    | Effective (level III) |
| Capsaicin 8% patch                        | Add-on                | DPN                    | Effective (level III) |
|                                           | Add-on                | HIVPN                  | Effective (level III) |
| Capsaicin 0.075% lotion                   | Add-on                | DPN                    | Ineffective     |
| Capsaicin 0.025% gel                      | Add-on                | DPN                    | Ineffective     |
| Cebranopadol                              | Add-on                | DPN                    | Effective (level III) |
| *Citralius colocynth* (topical application)| Unclear               | DPN                    | Effective (level III) |
| Clonidine (topical application)           | Add-on                | DPN                    | Ineffective     |
| Delta-9-tetrahydrocannabinol              | Add-on                | HIVPN                  | Effective (level III) |
| Dextromethorphan/quinidine                | Monotherapy           | DPN                    | Effective (level III) |
| Duloxetine                                | Monotherapy           | DPN                    | Effective (level III) |
|                                           | Add-on                | CIPN                   | Effective (level III) |
| Escitalopram                              | Monotherapy           | Various etiologies     | Effective (level III) |
| Gabapentin                                | Monotherapy           | DPN                    | Effective (level II) |
|                                           | Monotherapy           | HIVPN                  | Effective (level III) |
|                                           | Monotherapy           | CIPN                   | Ineffective     |
| Glyceryl trinitrate spray                 | Unclear               | DPN                    | Effective       |
| Imipramine                                | Monotherapy           | Various etiologies     | Effective (level III) |
| Isosorbide dinitrate spray                | Monotherapy           | DPN                    | Effective (level III) |
| Ketamine/amitriptyline cream              | Unclear               | DPN                    | Ineffective     |
|                                           | Add-on                | CIPN                   | Ineffective     |
| Lacosamide                                | Monotherapy or add on | DPN                    | Effective (level III) |
|                                           | Add-on                | SFN                    | Effective (level III) |
| Lamotrigine                               | Monotherapy           | CIPN                   | Ineffective     |
|                                           | Monotherapy or add on | DPN                    | Contradictory results |
|                                           | Add-on                | HIVPN                  | Effective (level III) |
| Levetiracetam                             | Monotherapy           | Various etiologies     | Ineffective     |
| Maprotiline                               | Monotherapy           | DPN                    | Effective (level III) |
Herbal Therapies

St. John’s wort as monotherapy for the management of PNP [96], DA-9801 as monotherapy for the management of DPN [97] and topical application of nutmeg extract oil as add-on treatment of pain due to DPN [98] have been found to have no analgesic effect. To the contrary, application of a topical formulation of *Citrullus colocynthis* appears to significantly improve pain in patients with DPN [99].

Other Treatments

Acetyl l-carnitine [100], prosaptide [101], mexiletine [102] and the non-peptide NK1-receptor antagonist TKA-731 [103] have been studied in small RCTs for their respective analgesic effect in PNP; no analgesic effect was found.

A summary of the effectiveness of each drug mentioned in this review for managing pain due to PN is provided in Table 1.
DISCUSSION

Our systematic review underscores the plethora of different pharmacological interventions that are available for the management of PNP. The majority of the RCTs studied populations of patients suffering from DPN, followed in decreasing number by populations of patients with HIVPN and CIPN, respectively. The results from these studies allows for specific recommendations to be made based on the cause of PNP.

Using the ASIPP criteria, the currently best available evidence for the management of painful DPN is on amitriptyline, duloxetine, gabapentin, pregabalin and venlafaxine as monotherapies and oxycodone as add-on therapy (level II of evidence). Weaker evidence for the management of painful DPN exists for dextromethorphan/quinidine, isosorbide dinitrate spray amitriptyline, maprotiline, lacosamide and tanezumab monotherapies and botulinum toxin type A, capsaicin 8% patch, cebranopadol and lacosamide add-on therapies (level III of evidence).

With regards to HIVPN, the currently best available evidence exists for gabapentin as monotherapy and capsaicin 8% patch, delta-9-tetrahydrocannabinol and lamotrigine as add-on therapies (level III of evidence). Interestingly, there is evidence that neither pregabalin nor amitriptyline are effective for the management of pain due to HIVPN.

With regards to CIPN, the currently best available evidence is on duloxetine as an add-on therapy (level III of evidence).

These observations highlight the possibility that response to treatment may be affected by the underlying pathophysiological mechanisms that are involved in the pathogenesis of the PN. Consequently, it is very important to thoroughly examine patients presenting with PNP to determine the exact causes of the PN.

Our results should be interpreted with some caution given the limitations of our study design. Firstly, we only searched for publications in PubMed and clinicaltrials.gov; therefore, it is possible that some studies that were only indexed in other databases were missed.

Moreover, there was a great deal of heterogeneity in terms of the manner in which PN was diagnosed. In the majority of studies PN was diagnosed on the basis of symptoms and/or clinical examination, with only a few studies including an electrophysiological evaluation, which is important to determine the type and the severity of PN [104].

Future RCTs need to be conducted to shed more light on the use of pharmacological approaches in patients with other forms of PNP, but also to make a face-to-face comparison of the available effective treatments with the aim to design specific treatment algorithms.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants performed by any of the authors. Therefore, ethics review was not required.

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