Pharmacological Management in Diabetic Peripheral Neuropathy

Subjects: Pharmacology & Pharmacy | Anesthesiology | Medicine, General & Internal

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Diabetic peripheral neuropathy is a common complication of longstanding diabetes mellitus. These neuropathies can present in various forms, and with the increasing prevalence of diabetes mellitus, a subsequent increase in peripheral neuropathy cases has been noted. Peripheral neuropathy has a significant societal and economic burden, with patients requiring concomitant medication and often experiencing a decline in their quality of life. There is currently a wide variety of pharmacological interventions, including serotonin norepinephrine reuptake inhibitors, gapentanoids, sodium channel blockers, and tricyclic antidepressants.

diabetic peripheral neuropathy diabetes neuropathic pain GLP-1

1. Introduction

The management of diabetic peripheral neuropathy (DPN) is a complicated subject with cultural and patient-specific nuances. A summary of the included systematic reviews, meta-analysis, and studies is shown in **Table 1**.

Table 1. Table of mentioned systematic reviews, meta-analyses and important studies.

Name/Reference	Type	Year	RCTs/Studies	Patients	Treatment/Intervention/Measurement	Outcomes
Lunn et al. [1]	SR	2014	18	6407	Duloxetine: 60, 120 mg/day	Primary: Short-term improvement in pain Secondary: Long-term improvement in pain, improvement in quality of life score, patient-reported pain, adverse effects during treatment
Yuan-Chun Ko et al. [2]	SR and MA	2021	3	290	Duloxetine: 20–80 mg/day Gabapentin: 300–1200 mg/day	Primary: VAS (Visual Analogue

Name/Reference	Type	Year	RCTs/Studies	Patients	Treatment/Intervention/Measurement	Outcomes
						Scale) Secondary: Sleep Interference Score, Clinical Global Impression of Change, Patient Global Impression of Change, DN Symptom Score, DN Examination Score, Neuropathic Disability score
Chung-Sheng Wu et al. [3]	SR and MA	2023	7	2205	Duloxetine: 20–120 mg/day	Pain improvement, patient-reported health performance and quality of life
Andreas Limpas et al. [4]	SR	2021	83	/	Anticonvulsants, SNRIs, TCAs, opioids, topical treatment, cannabinoids, monoclonal antibodies, botulinum toxin, other	/
Floortje van Nooten et al. [5]	SR and MA	2017	24	5870	Capsaicin 8%	At least 30% pain reduction, at least 50% pain reduction, tolerability
Aaron Vinik et al. [6]	R, DB, Comparator-Controlled Study	2014	/	452	Mirogabalin: 5–30 mg/day	Primary: ADPS (Average Daily Pain Score) change from baseline Secondary: Characterizing dose response, incidence of responders, comparing effects of mirogabalin to pregabalin,

Name/Reference	Type	Year	RCTs/Studies	Patients	Treatment/Intervention/Measurement	Outcomes
						assessing time to meaningful pain relief
Masayuki Baba et al. [7]	RA, DB, PC Study	2019	/	834	Mirogabalin: 15–30 mg/day	Efficacy, safety, and tolerability
Titas Buksnys et al. [8]	SR and MA	2020	43	/	Lidocaine medicated plaster 700 mg	Efficacy, adverse effects
Moisset et al. [9]	SR	2020	131	/	TCAs, SNRIs, antiepileptics, opioids, topical agents, cannabinoids, ketamine, other	Comprehensive assessment of all therapies for neuropathic pain treatment
Farag Hussein et al. [10]	SR and MA	2022	36	11,930	Duloxetine: 60 and 120 mg/day Pregabalin: 150–600 mg/day Milnacipran: 100 and 200 mg/day Amitriptyline	Comparative effectiveness and acceptability of medication for pain, sleep, depression, fatigue, and quality of life
Nanna Finnerup et al. [11]	SR and MA	2015	229	/	TCAs, SNRIs, antiepileptics, opioids, oromucosal cannabinoids, topical lidocaine, capsaicin patches, other	Individual and combined number needed to treat and number needed to harm values
Solomon Tesfaye et al. [12]	R, DB, Multicenter, Crossover Trial	2022	/	130		Primary: Difference in 7-day average NRS (Numerical Rating Scale) daily pain Secondary: HADS (Hospital Anxiety and Depression Scale), proportion of patients achieving 30% and 50% pain reduction from baseline, ISI

Name/Reference	Type	Year	RCTs/Studies	Patients	Treatment/Intervention/Measurement	Outcomes
						(Insomnia Severity Index), NPSI (Neuropathic Pain Symptom Inventory), other
Zin Zin Htike et al. [13]	SR and Mixed-Treatment Comparison Analysis	2017	34	14,464	Glucagon-like peptide-1 receptor agonist (GLP-1ARs): albiglutide, dulaglutide, exenatide, liraglutide, others	Glycemic control, body weight, blood pressure and lipid profile, gastrointestinal and other side effects
Donna Shu-Han Lin et al. [14]	Retrospective Cohort	2022	/	101,440	Glucagon-like peptide-1 receptor agonist (GLP-1ARs); Sodium-glucose cotransporter 2 inhibitors (SGLT2is)	Primary: Major adverse limb events (MALE) Secondary: Major adverse cardiac events (MACE), death from any cause, hospitalization due to heart failure
Tuan Dinh Le et al. [15]	Cross-sectional	2022	/	473	GLP-1 serum levels	Prevalence of DPN and its risk factors, relation between DPN and fasting GLP-1 levels
Steven Marso et al. [16]	R, DB Trial	2016	/	9340 [19]	Liraglutide 1.8 mg/day	Fist occurrence of death from cardiovascular causes, non-fatal MI, or non-fatal stroke, microvascular outcomes (renal and retinal), neoplasms, pancreatitis

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placebo. Patients were pooled from the trials across multiple doses: 20 mg, 40 mg, 60 mg, or 120 mg per day. The review found that the relative rate of greater than 50% improvement in pain was 1.53 (95% CI). The paper further specified that the 20 mg-treated patients did not have a statistically significant change, but there was a paucity of data as only one trial had a 20 mg arm [1].

The statistical review carried out by the AAN in the writing of their guidelines found that duloxetine is moderately effective with moderate confidence, while desvenlafaxine was also found to be moderately effective with lower confidence [20].

Name/Reference	Type	Year	RCTs/Studies	Patients	Treatment/Intervention/Measurement	Outcomes
Steven Marso et al. [17]	R, DB Trial	2016	/	3297	Semaglutide 0.5 or 1.0 mg/week [2]	Fist occurrence of death from cardiovascular causes, non-fatal MI, or non-fatal stroke, microvascular outcomes (renal and retinal)
Tushar Issar et al. [18]	Cross-sectional	2021	/	90	GLP-1RA, DPP-4i, SGLT-2i	Improvement in nerve excitability

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side effect reports, further confirming its safety [3]. A recent systematic review found comparable results, proposing duloxetine as a preferential drug in comparison to gabapentin, due to the same levels of efficacy but better duloxetine tolerance [4].

SA—systematic analysis; MA—meta-analysis; R—randomized; DB—double-blind; PC—placebo-controlled.

It is worth noting that a 2017 meta-analysis comparing local capsaicin use to oral pain relief medication showed promising results. The study analyzed 25 randomized controlled trials, suggesting that a capsaicin 8% patch provides pain relief similar to that of oral duloxetine, while also being an adequate substitute for pregabalin and gabapentin. Moreover, the study suggests that the patches may have a better side-effect profile compared to oral medication, in part due to the method of administration [5].

2.2. Gabapentinoids

Gabapentinoids are a class of drugs that include gabapentin and pregabalin. The mechanism of action of gabapentinoids is thought to involve modulation of the activity of voltage-gated calcium channels. Specifically, gabapentinoids bind to the alpha2-delta subunit of these channels, which reduces calcium influx into neurons and thereby decreases the release of excitatory neurotransmitters such as glutamate and substance P [21]. This effect may account for their anticonvulsant properties as well as their ability to reduce neuropathic pain. Additionally, gabapentinoids have been shown to increase the synthesis and release of GABA, the primary inhibitory neurotransmitter in the central nervous system. This effect may also contribute to their anticonvulsant properties and may explain why they are effective in treating anxiety disorders [21].

The efficacy of pregabalin, which is FDA-approved for the treatment of painful diabetic neuropathy, has been shown to be high for both the management of pain of common comorbidities that arise due to DPN, such as sleep interference [22]. Gabapentin has also been shown to have a pain-reducing effect, with one multicenter RCT showing a mean relief of 39% after 8 weeks [23].

Mirogabalin (DS-5565) is a new gabapentinoid recently brought onto the market in Japan. The drug has the same mechanism of action as other gabapentinoid medications, but has increased potency at the alpha2-delta subunit, as compared to pregabalin [24]. The following clinical trials indicate efficacy in the treatment of DPN.

A randomized double-blind trial specifically looking at patients with DPN showed that doses of mirogabalin between 15 and 30 mg/day led to significant reductions in pain when compared to a placebo at the 5-week mark [6]. The trial

also had a single arm with patients randomized to 300 mg of pregabalin, and found no significant improvement in pain for patients.

Another randomized, double-blind trial was conducted with 834 patients, all of whom had DPN. Patients were randomized to either a placebo group or a group who received a mirogabalin dose between 15 and 30 mg/day. In all groups, the average daily pain score did decrease over the course of the 14-week trial, but the final results only showed a statistically significant decrease for the group randomized to the 30 mg/day dose [7].

So far, all clinical trials involving mirogabalin have been performed in East Asian countries, and the medication is approved for usage in Japan. At this time, there is no indication if mirogabalin will undergo clinical trial for DPN elsewhere.

2.3. Sodium Channel Blockers

Sodium channel blockers are a class of drugs that target the voltage-gated sodium channels found in neurons and cardiac cells. These channels are responsible for generating and propagating action potentials, which are essential for the transmission of signals in the nervous and cardiovascular systems. Sodium channel blockers work by binding to the channel pore and preventing the influx of sodium ions, which results in the inhibition of action potential generation and propagation. Sodium channel blockers that are currently used in the treatment of pain are drugs that are also used as anesthetics, class 1 antiarrhythmics, anti-convulsants (such as oxcarbazepine), and tricyclic antidepressants [25].

Sodium channel inhibition can be selective or non-selective, depending on the specific drug and the type of sodium channel being targeted. For example, some drugs, such as lidocaine, selectively block channels that are in an activated or inactivated state.

On the other hand, drugs such as tetrodotoxin (TTX) selectively inhibit specific isoforms of sodium channels. This discovery led to the categorization of nine known isoforms of sodium channels into two groups, TTX-sensitive and TTX-resistant. Isoforms $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.4$, $Na_V1.6$, and $Na_V1.7$ are TTX-sensitive, with their predominant location being on the central and peripheral neurons, with the exception of $Na_V1.4$ being mostly found in skeletal muscle. The remaining three isoforms are TTX-resistant and expressed in cardiac muscle ($Na_V1.5$) and the dorsal root ganglion neurons ($Na_V1.8$ and $Na_V1.9$) [26]. This range in sensitivity amongst the sodium channels is due to a difference in the amino acid sequence that makes the binding site for TTX, leaving some of them resistant to this sodium channel inhibitor [27].

While in some clinical applications, broad-spectrum blockade is favorable, only certain sodium channels have been implicated in nociceptive pathways and, therefore, are preferable to selectively inhibit to avoid systemic side effects [25].

A $Na_V1.7$ isoform of the sodium channel has been the target of extensive research in previous years due to the fact that a loss of function mutation of the gene that encodes this isoform results in total body insensitivity to pain. This

discovery lead researchers to believe that a selective inhibition of this channel might prove beneficial in pain treatment in various pathological states [28][29].

Multiple studies have suggested that a group of molecules called arylsulfonamides could play a significant role in finding a specific inhibitor of the $Na_V1.7$ isoform [30][31]. Moreover, certain sodium channel blockers such as lidocaine have been shown to enhance the inhibitory effect arylsulfonamides have on $Na_V1.7$ channels. [32] Due to the very similar structure of these channels and their abundance in different tissues throughout the body, the search for a specific inhibitor is proving to be difficult, and more extensive research is needed in the field.

Both the AAN and ADA have sodium channel blockers as listed therapy options for the treatment of DPN, with the AAN specifically stating they have a moderate confidence in the data cited in their review [20].

A 2020 systematic review analyzing 43 randomized controlled trials showed that a lidocaine 700 mg medicated plaster was equivalently efficient in peripheral neuropathic pain management compared to pregabalin, yet had a better adverse event profile [8].

2.4. Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are a class of drugs that were among the first antidepressants to be developed and widely used. The mechanism of action of TCAs is complex, but they primarily act by inhibiting the reuptake of the monoamine neurotransmitters, including norepinephrine, serotonin, and dopamine, back into presynaptic neurons. This results in an increased concentration of these neurotransmitters in the synaptic cleft, which enhances neurotransmission and mood stabilization. Additionally, TCAs are known to block various receptors, including histamine, alpha-adrenergic, and muscarinic receptors, which may contribute to their clinical effects and side effects [9].

TCAs are considered second-line to SNRIs when it comes to neuropathic pain [33]. TCAs can be successfully used as monotherapy for neuropathic pain, but their adverse event profile can be more burdensome to patients compared to SNRIs [34]. Moreover, a dose greater than 75 mg daily is not recommended for patients over the age of 65 because of the dose-dependent anticholinergic side effects and an increased risk of falling [35].

Amongst a vast body of literature detailing this point, a newer 2020 systematic review of 18 placebo-controlled trials further confirmed that SNRIs are a preferential treatment for neuropathic pain, leaving TCAs as an alternative option [9].

A 2022 network meta-analysis looking at fibromyalgia treatment further corroborates these statements, showing that even though amitriptyline was associated with improvement in quality of life, fatigue, and pain, to some degree, duloxetine 120 mg (SNRI) was found to be more beneficial [10].

In a recent meta-analysis, 16 out of 18 placebo-controlled trial comparisons were positive for TCA use in chronic neuropathic pain, with the combined number needed to treat being 3.6, further confirming the use of TCAs in these

patients [11].

The 2022 multicenter, crossover OPTION-DM trial studied the efficacy of different combinations of drugs used in the treatment of DPN. Over the course of 50 weeks, all patients enrolled underwent therapy with different treatment pathways, testing both monotherapies and combination therapy if patients did not have adequate pain relief. The study showed that supplementing amitriptyline with pregabalin (amongst other supplementation combinations) resulted in no statistically significant difference in diabetic neuropathy pain management outcome compared to other treatment combinations (including amitriptyline, pregabalin, and duloxetine). Furthermore, the study illustrated that current therapeutics alone are not adequate for a large number of patients, as monotherapy did not provide significant pain relief for about two thirds of trial participants. Although the study did give credibility to the usage of combination therapy, as it was generally more efficacious, the study also showed that a significant number of patients did not reach adequate levels of pain reduction with any combination, showing the need for new therapies [12].

3. Pathogenesis-Based Therapy

3.1. GLP-1

The options available in the treatment of diabetes have recently expanded with glucagon-like peptide-1 (GLP-1) agonists, which operate via the modulation of the incretin hormonal system. This system normally operates via the enteroendocrine system in a periprandial fashion. As a bolus of food is ingested, GLP-1 is released from secretory granules by intestinal L cells both through a neural signaling pathway via gastrin-releasing peptide (GRP) and acetylcholine, and eventually through L-cell direct contact interaction with the bolus of food. GLP-1 itself then can act on the GLP-1 receptor (GLP-1R), which is found on pancreatic islets, as well as throughout the GI tract, the vagus nerve, hypothalamus, and brainstem. Action on the pancreas leads to a stimulation of insulin release, while simultaneously inhibiting glucagon release and slowing gastric emptying. GLP-1 is then degraded by dipeptidyl peptidase-4 (DPP-4), as well as other endopeptidases [36].

Therefore, drugs that act to modulate this system either operate by mimicking GLP-1 or delaying endogenous GLP-1 degradation via inhibition of DPP-4. Drugs recently brought to market include semaglutide, lixisenatide, dulaglutide, liraglutide, and exenatide.

Tirzepatide is a GLP-1 agonist that is a modified analog of gastric inhibitory peptide (GIP). It has been demonstrated that tirzepatide has stronger affinity for the GIP receptor than the GLP-1 receptor. This dual mechanism of action still acts to promote insulin secretion, but has different pharmacodynamic properties, which have been shown to be beneficial in terms of improving insulin sensitivity, as well as reducing obesity [37].

Furthermore, retatrutide, a GLP/GIP/glucagon triple agonist, with limited but promising data, is another medication being brought to market [38]. As with the current treatments for DPN, future trials testing the effects of these multi-receptor incretin mimetics on DPN are still needed.

If a provider feels that a patient is a good candidate for GLP-1 agonist treatment, then lab testing and patient history guide the selection of which specific agent is appropriate. Half-lives vary dramatically, with current market formulations lasting between 2.4 h and a week [39]. A review of different GLP-1 agonists found that longer-acting agents are more effective at improving glycemic control.

A meta-analysis of 34 RCTs showed that GLP-1 agonists of all formulations are very effective at lowering HbA1c, with treatments ranging between 0.55% and 1.21%; dulaglutide and liraglutide had the greatest reduction of 1.21% and 1.15% on average, respectively [13].

3.2. SGLT-2 Inhibitors

SGLT-2 inhibitors are another class of medications that have been theorized to have potential efficacy in the treatment of DPN. SGLT-2 inhibitors are used in the treatment of type 2 diabetes and act on the kidney to inhibit the reabsorption of glucose. Although there have been many clinical trials that have involved SGLT-2 inhibitors, the vast majority have not assessed outcomes related to DPN. As previously mentioned in this paper, meta-analyses have not found a correlation between the usage of SGLT-2 inhibitors and distal limb protectiveness. One analysis stated that GLP-1 agonists had a statistically significant reduction in adverse limb events as compared to SGLT-2 inhibitors [14]. This finding needs more supporting evidence, as another meta-analysis found no difference between SGLT-2 inhibitors and GLP-1 agonists when looking at limb amputation as a specific adverse limb outcome [40].

So far, no trials have looked at SGLT-2 inhibitors as a monotherapy for the treatment of DPN in diabetic patients. Looking to the future, there is currently one trial underway (NCT05162690) that looks to test the efficacy of dapagliflozin in DPN.

In animal models, a few studies have shown some promising preliminary data. in one trial, the SGLT-2 inhibitor ipragliflozin was tested on rats to determine the effects on DPN. The rats were diabetic prior to the start of testing, and non-diabetic rats were used as a control. The study found that the conduction velocity of peripheral leg nerves improved after SGLT-2 inhibitor treatment [41].

A study that used streptozotocin to induce diabetes in rats showed that SGLT2 inhibitor therapy may have a role in slowing down the pathogenesis of DPN via reversing risk factors such as oxidative stress, inflammation, and glucotoxicity [42]. Another trial, which used empagliflozin in diabetic rats, found that SGLT2 inhibitor treatment prevented the loss of skin nerve fibers and peripheral hypersensitivity [43].

Although these trials generally do provide insight into the possible efficacy of SGLT-2 inhibitors in limiting DPN, the lack of clinical trials means that conclusions cannot be drawn as to the efficacy of these medications in humans.

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