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Published in:
Current Drug Safety

DOI (link to publication from Publisher):
10.2174/1574886315666200731173113

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

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Current Drug Safety, 2020, *15*, 000-000

REVIEW ARTICLE

Diabetic Peripheral Neuropathy: Diagnosis and Treatment

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ARTICLE HISTORY

Received: April 01, 2020
Revised: June 04, 2020
Accepted: June 16, 2020

DOI:
10.2174/1574886315666200731173113

Abstract: ***Background*:** Diabetic peripheral neuropathy (DPN) is traditionally divided into large and small fibre neuropathy (SFN). Damage to the large fibres can be detected using nerve conduction studies (NCS) and often results in a significant reduction in sensitivity and loss of protective sensation, while damage to the small fibres is hard to reliably detect and can be either asymptomatic, associated with insensitivity to noxious stimuli, or often manifests itself as intractable neuropathic pain.

***Objective*:** To describe the recent advances in both detection, grading, and treatment of DPN as well as the accompanying neuropathic pain.

***Methods*:** A review of relevant, peer-reviewed, English literature from MEDLINE, EMBASE and Cochrane Library between January 1st 1967 and January 1st 2020 was used.

***Results*:** We identified more than three hundred studies on methods for detecting and grading DPN, and more than eighty randomised-controlled trials for treating painful diabetic neuropathy.

***Conclusion*:** NCS remains the method of choice for detecting LFN in people with diabetes, while a gold standard for the detection of SFN is yet to be internationally accepted. In the recent years, several methods with huge potential for detecting and grading this condition have become available including skin biopsies and corneal confocal microscopy, which in the future could represent reliable endpoints for clinical studies. While several newer methods for detecting SFN have been developed, no new drugs have been accepted for treating neuropathic pain in people with diabetes. Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors and anticonvulsants remain first line treatment, while newer agents targeting the proposed pathophysiology of DPN are being developed.

Keywords: Peripheral, neuropathy, diagnosis, treatment, diabetic.

1. INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes, involving as much as 50% of all people with diabetes [1,2]. It is most commonly classified into injury to small-diameter, thinly myelinated (Aδ) and unmyelinated (C) nerve fibres responsible for e.g. pain and temperature sensation and injury to myelinated, large-diameter (Aα and Aβ) nerve fibres responsible for perception, vibration and proprioception. Despite the frequent occurrence, screening for DPN is often neglected leading to a considerable diagnostic delay and insufficient preventative measures. The reasons are many, but most important are the lack of quick and reliable screening methods alongside the lack of neuropathy-specific preventative pharmacological treatment. Current clinical practise is therefore limited to enhanced glycaemic control and cardiovascular prevention, while the examination of neuropathy often only includes screening for severe large fibre damage and loss of protective sensation (LOPS) with either 10-gram monofilament or by testing vibration sensation with either tuning fork or biothesiometry. Over the last decades, the interest in small fibre neuropathy has increased mostly due to a growing agreement that it is detectable years in advance of large fibre damage [3-8]. Unfortunately, early detection of small fibre neuropathy has proven a diagnostic challenge, as clinicians and researchers currently lack an agreement on a standard gold method. However, several promising candidates have emerged over the latest years.

Painful diabetic neuropathy (PDN) is often a debilitating manifestation of DPN occurring in more than 20% of people with peripheral neuropathy [9]. Although many of the patients experience spontaneous improvement, the condition has shown to significantly influence the quality of life and incurs severely increased health care costs. Over the last

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1574-8863/20 $65.00+.00

decades, our understanding of this condition has gradually improved, although the exact underlying pathophysiological mechanisms are not yet fully elucidated. Therefore, treating the condition remains a challenge, and although several pharmacological options are currently available, they are often non-specific and poorly tolerated or have an insufficient effect.

In the following review, we describe the recent advances in the detection and grading of DPN, as well as the current possibilities and consensus regarding the prevention and pharmacological treatment of accompanying neuropathic pain.

2. SEARCH STRATEGY

All data for this review was collected from electronic literature searches of MEDLINE, EMBASE and the Cochrane Library. All searches were performed from January 1, 1967 to January 1, 2020 and were comprised of relevant terms like drug names or names of diagnostic methods in combination with different versions of "*diabetes*" or "*painful diabetic neuropathy*". Literature restrictions were English language and publication in a peer-reviewed journal. We also identified the most recent reviews relevant for the specific method or drug, and manually screened the reference lists for eligible studies. No limitations regarding drug dosage or treatment duration were applied. For pharmacological treatment, we primarily searched for randomised-controlled trials (RCTs), but larger observational trials were also studied.

2.1. Detecting Peripheral Neuropathy in People with Diabetes

Early detection and monitoring of DPN are recommended in most clinical guidelines, including consensus statements from the Toronto Diabetic Neuropathy Expert Group [10] and the American Diabetes Association [11]. Assessment of DPN can be carried out using symptom questionnaires, composite neurological scores, quantitative sensory testing (QST) or nerve conduction studies (NCS), which are all validated methods. Unfortunately, these methods have continuously failed as robust endpoints in clinical trials, as they lack the sensitivity to detect minor changes happening over the course of a study period [12–16]. Therefore, more time-consuming and equipment-heavy methods have emerged over recent years, aiming to provide researchers with more reliable clinical endpoints for future studies (Tables **1** and **2**).

Table 1. Advantages and disadvantages of different methods for assessing diabetic peripheral neuropathy.

Method	Detects	Advantage	Disadvantage
Composite neurological scores	Large and small fibre neuropathy	Non-invasive, simple, quick, easy to perform, does not require special equipment	Not sensitive, not reproducible, not good for grading
Quantitative sensory testing	Large and small fibre neuropathy	Non-invasive, quantifiable, relatively easy to perform	Largely subjective, low-moderate reproducibility, time-consuming, requires specialised equipment
Nerve conduction studies	Large fibre neuropathy	Non-invasive, sensitive, objective, quantifiable, considered gold standard	Requires specialized equipment, moderate inter-rater reproducibility
Skin biopsies (IENFD)	Small fibre neuropathy	Quantifiable, sensitive, good reproducibility, considered gold standard	Invasive, costly, requires specialized equipment and personal, associated with risk of wounds and infection at biopsy site, describes only morphology and not function
Corneal confocal microscopy (*in vivo*)	Small fibre neuropathy	Non-invasive, quick, sensitive, quantifiable, decent reproducibility	Requires specialized equipment and personal, not disease-specific

Table 2. Most commonly used agents for treatment of PDN and their most common side effects

Agent	Dosage	Common Side Effects
Tricyclic antidepressants (TCA)		
Amitriptyline	10-100 mg daily	Dry mouth, urinary retention, sedation, vertigo, constipation, weight gain, arrhythmias
Desipramine	10-150 mg daily	Dry mouth, urinary retention, sedation, vertigo, constipation, weight gain, arrhythmias
Serotonin-norepinephrine reuptake inhibitors (SNRI)		
Duloxetine (FDA approved)	60-120 mg daily	Nausea, somnolence, hyperhidrosis, anorexia, vomiting, constipation, fatigue, dry mouth
Venlafaxine	75-225 mg daily	Nausea, somnolence, ECG changes

Agent	Dosage	Common Side Effects
Calcium channel modulators		
Pregabalin (FDA approved)	150-600 mg daily	Somnolence, dizziness, peripheral edema, weight gain
Gabapentin	900-3,600 mg daily	Dizziness, somnolence, diarrhea, fatigue, GI upset, peripheral edema
Opioids		
Oxycodone	5-120 mg daily	Constipation, somnolence, dizziness, nausea, vomiting, itchiness
Tramadol	50-200 mg daily	Nausea, sedation, constipation, headache, dry mouth, urinary retention, confusion, tremor, seizures
Tapentalol (FDA approved)	50-250 mg daily	Nausea, dizziness, somnolence, constipation, vomiting, headache

Over the latest decades, a large number of composite neurological scores have been developed and validated in DPN. The most widely used ones include the Michigan Neuropathy Screening Instrument (MNSI) [17], the Neuropathy Disability Score (NDS) [18,19] and the modified Toronto Clinical Neuropathy Score (mTCNS) [20]. Common for all of these composite scores is the fact that they mostly excel in identifying or denying the presence of DPN, although neuropathy grading based on the total score has been widely used in the literature (i.e. NDS < 3, NDS 3-6 or NDS > 6). Other validated composite neurological scores include the Clinical Neurological Examination (CNE) [21,22], the Diabetic Neuropathy Examination (DNE) [23], the Neuropathy Symptom Profile (NSP) [24], the Diabetic Neuropathy Symptom Score (DNS) [25], the Neuropathy impairment Score (NIS) [26], the Neuropathy impairment Score in the Lower Limbs (NIS-LL) [27,28], the Neuropathy Symptom Score (NSS) [18,19], the Toronto Clinical Scoring System (TCSS) [29], the Michigan Diabetic Neuropathy Score (MDNS) [17], the Neuropathy Symptom and Change Score (NSC) [30], the Neuropathy Total Symptom Score 6 (NTSS-6) [31], the Total Neuropathy Score (TNS) [32] and the Total Symptom Score (TSS) [33].

QST has for many years been considered the gold standard in neuropathy research and especially so in neuropathic pain research. This method is painless, non-invasive and aim to diagnose both small and large fibre damage as well as both gain and loss of sensory function. Throughout the years, several protocols have been developed, including the protocol from the German Research Network on Neuropathic Pain [34], which holds a large database of standardized material from healthy controls and which have recently been validated all over Europe [35]. However, labour intensity, relatively poor sensitivity, low reproducibility and disease-specific sensitivity remain important concerns, limiting the use of QST as a reliable endpoint in clinical trials [36,37]. Recently, international consortiums focused around neuropathic pain have performed subgrouping of people with PDN and other neuropathic conditions based on QST data, increasing diagnostic accuracy and potentially paving the way for the use of the method in more symptom specific trials [38].

Conventional NCS are currently considered the gold standard test for detecting large fibre neuropathy in people with diabetes [39]. This test is objective, non-invasive and reasonably quick, but requires specialized equipment and only detects changes in the largest nerve fibres. Furthermore, NCS have previously show poor inter-rater reproducibility, due to varying conditions including electrode placement, room temperature and examination routines, which presents a huge challenge in multicentre trials [40,41]. A positive NCS is not required for a definite diagnosis of DPN, but is useful to distinguish the condition from other neuropathies in case of an atypical presentation. Classic findings in people with DPN include reduced amplitude of compound muscle action potential, prolonged F-wave latency, slower conduction velocity and altered H-reflex [42].

Skin biopsy is a novel technique developed to evaluate intra-epidermal nerve fibre density (IENFD) in the most superficial layers of the skin [43,44]. The technique is used to detect small fibre damage, and is widely considered the new gold standard [45,46]. The examination is invasive and requires specialized laboratories and stains, but excels due to the fact that it is objective, reproducible and not confounded by height and weight, although age and gender-specific decline has been reported [47–49]. Inter-observer reliability is generally considered high using this method [50–52], although some smaller studies have shown significant differences [53]. Normative reference values for IENFD at the distal leg adjusted for sex and age are available for the most widely used techniques (bright-field microscopy and immunofluorescence) [49,54], which also seems to have acceptable agreement [55]. Currently, one of the most important concerns regarding the broad usage of skin biopsies in large multicentre trials, is the fact that only a limited number of studies have examined the intra-person variability in unhealthy subjects where IENFD might potentially vary significantly from site to site [56]. A further concern is that the IENFD only relates to morphological changes of the nerve fibres, while the functionality remains inaccessible. However, axonal swellings visualized by specialized stains in skin biopsies, have recently been proposed as pre-degenerative changes that might predict loss of intra epidermal nerve fi-

bres, although their actual role is yet to be fully determined [57,58].

Corneal confocal microscopy (CCM) is a promising new ophthalmic imaging technique proposed as a new surrogate endpoint for small fibre neuropathy [59,60]. The method exploits the fact that Bowman's layer, located between the superficial epithelium and the stroma in the cornea of the eye, can be visualized using this technique, giving insight into the area with the largest density of nerve endings found in the body [60]. The method is rapid, non-invasive and reproducible, and have high inter-observer correlation [61–63]. CCM has previously shown small fibre repair following pancreatic transplantation in people with type 1 diabetes (T1DM) [64,65], and was recently assessed in a large multicentre trial displaying promising results [66]. Three methodological measurements of CCM have been developed over the course of the last decades, but recently only the latest addition, the laser scanning confocal microscopy, have seen use in clinical studies as it offers higher resolution and clearer visualization of the cornea [67]. The measurements that can be assessed by CCM include corneal nerve fibre density (CNFD), corneal nerve fibre length (CNFL), corneal nerve branch density (CNBD) and corneal nerve fibre tortuosity (CNFT), although CNFT recently has fallen out of favour due to inconsistent results. CCM was previously compared with IENFD measured by skin biopsies [68,69], and was recently proposed as a method for distinguishing ordinary DPN from PDN [70]. While most studies support the use of CCM in DPN, some larger studies failed to distinguish people with and without neuropathy [71]. Critics of the technique argue that CCM is too unspecific for evaluating DPN, as a long list of different diseases has been associated with the reduction of CNFL, CNFD and CNBD [72]. Internationally generated normative values now also exist for CCM, which enhances its use in clinical trials [73].

Other modalities for studying DPN include laser Doppler-examinations [74,75], electrochemical skin conductance [76,77], sweat gland activity [78,79], bedside NCS [80] and other electrophysiological examinations like threshold tracking techniques [81,82], although these methods currently remain purely experimental. An exciting new addition to the traditional array of examinations used to study the distal neurons and nerve endings is the introduction of neuropathic itch, which has been proposed to be partially mediated by a subset of cutaneous small fibres (most C fibres) in combination with a reduced descending inhibition from the central nervous system [83]. The current state of the neuropathic itch research evolves around the use of either histamine or cowage, which seems to activate not only C fibres, but also slowly conducting mechanically-insensitive Aδ fibres or mechanically-sensitive Aδ fibres, respectively [84].

2.2. Preventing Neuropathy in People with Diabetes

Although the possibilities of early detection of DPN remain a challenge, the preventative possibilities, when detected are unfortunately even more sparse. As of now, there are no disease-modifying treatments for DPN approved by the US food and Drug Administration (FDA) or the European Medicines Agency (EMA), which is why optimization of glycaemic control to prevent progression remains the clinicians' most important tool. Several large clinical trials have shown beneficial effects of tight glycaemic control in preventing DPN in people with T1DM [85]. The DCCT/EDIC-study was one of the hallmark studies indicating a beneficial effect of intensified glycaemic control even years after terminating the intervention [86]. For people with type 2 diabetes (T2DM) the evidence of beneficial effects of tight glycaemic control in preventing DPN is less convincing. In a small Japanese study the authors found a relatively small beneficial effect [87], but several larger studies including the UKPDS, ACCORD-, ADDITION, Steno 2- and VADT-studies [88–92], all failed to show significant results regarding DPN, although other microvascular complications generally improved. Previous clinical trials in both people with T1DM and T2DM have demonstrated beneficial effects of angiotensin-converting enzyme (ACE)-inhibitors on mainly autonomic neuropathy but also DPN, although larger studies are still needed to confirm the findings [93–95]. Also statins and fibrates have been shown to halt the progression of DPN [96,97], but might rarely induce neuropathy on their own [98].

2.3. Treating Neuropathic Pain in People with Diabetes

Treatment of PDN is generally limited due to the lack of knowledge concerning the pathophysiology of the condition. Both pharmacological and non-pharmacological treatments are therefore, mainly focused around symptomatic treatment attempting to relieve or soothe the symptoms and to improve quality of life. Unfortunately, almost all pharmacological options are vitiated by side effects, with a small therapeutic window between beneficial effect and at times incapacitating side effects. Furthermore, co-morbidities like nephropathy or ischemic heart disease may further limit the availability of many of the pharmacological options, which is why the correct management of the condition often require personalised treatment regimes. Monotherapy with only one analgesic is often insufficient for pain relief, and peripheral analgesics like paracetamol or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are rarely adequate and generally not recommended for chronic pain conditions like PDN, although a small placebo-controlled study of older date has indicated beneficial pain-relief of NSAIDs [99]. Safety and efficacy of therapeutic drugs are often compared using the number needed to treat (NNT)- and number needed to harm (NNH)-principles. Still, although these numbers often form the foundation of clinical guidelines, they may vary slightly due to differences in the criteria employed when defining efficacy and side effects. However, most guidelines and recommendations encourage the use of tricyclic agents (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and γ-aminobutyric (GABA) analogues as first line treatment, often followed by opioids and topical treatment [100,101]. Data on direct comparison of the first line agents are still quite sparse, but a large multicentre-study comparing amitriptyline, duloxetine and pregabalin (OPTION-DM) is currently running in the United Kingdom with results expected in 2020 [102]. Mentionable is also the COMBO-DN study [103], where authors compared duloxetine 120 mg daily or pregabalin 600 mg daily with a combination of duloxetine 60 mg daily and pregabalin 300 mg without finding significant

differences between high dosage monotherapy with either drug and combination therapy.

TCAs are originally antidepressant agents with multimodal actions, including blocking the serotonin and noradrenaline reuptake and inhibiting the anticholinergic receptor. Some agents from this class might also act as partial sodium channel blockers, although the exact mechanism is not fully elucidated. The most commonly used TCAs includes amitriptyline, clomipramine, desipramine, imipramine and nortriptyline, which all appear to have a comparable effect although amitriptyline is the drug that has been thoroughly investigated in PDN. TCAs have been evaluated versus placebo in 21 RCTs, of which only five were included in a Cochrane review from 2007 due to insufficient data reportage in the remaining studies. An analysis of these five smaller studies indicated NNT for improvement of symptoms of 1.3 (95% CI 1.2-1.5) in PDN [104]. Since this meta-analysis, no new evidence comparing TCAs with placebo has become available, although a rather small study compared amitriptyline to duloxetine and pregabalin without significant differences in neither efficiency or side effects [105]. Despite their relatively low NNT, the clinical use of TCAs is often associated with a significant burden of side effects, limiting clinical use of the doses tested in clinical trials. In a meta-analysis of efficacy and safety comparing amitriptyline, duloxetine, gabapentin, pregabalin, valproate and venlafaxine, the authors found that amitriptyline was the least safe agent for this indication [106]. Side effects commonly associated with TCA-usage include anticholinergic side effects like xerostomia, urinary retention, obstipation and difficulties with accommodation as well as cardiac- and psychological side effects like cardias arrhythmias, somnolence, fatigue, dizziness and insomnia [107]. TCAs are also associated with a clinically significant increase in body weight.

SNRIs are antipsychotic agents used to treat painful neuropathy. The group primarily consists of duloxetine and venlafaxine, where duloxetine has an additional weak effect on the reuptake of dopamine. Duloxetine was evaluated against placebo in seven RCTs, including 2,203 people with DPN displaying a standardized mean difference (SMD) between the active drug and placebo of 1.33 (95% CI 1.82-0.86) [108–115]. Six of these studies were also included in a Cochrane meta-analysis from 2014 with a corresponding NTT for at least 50% pain reduction of 5.0 (95% CI 4.0-7.0) for treatment with 60 mg duloxetine daily [116]. Venlafaxine was previously tested in only two RCTs (n=304), which were both included in a Cochrane meta-analysis from 2015 reporting an SMD between venlafaxine and placebo of 1.53 (95% CI 2.41-0.65). However, the authors also concluded that the level of evidence supporting the use of venlafaxine was very sparse and stated that only some third-tier evidence of benefit was available and that this arose from studies with methodological limitations and considerable risk of bias [117]. Based on the largest study alone, the NNT for a 50% reduction in pain intensity for 150 mg venlafaxine in PDN was 6 (no CI reported), but was associated with clinically meaningful electrocardiogram changes [118]. Other side effects commonly associated with SNRI-usage include nausea, somnolence, dizziness, constipation and dyspepsia, while rare, but serious, adverse events like Steven-Johnson syndrome and glaucoma also have been reported. In contrast to other first-line treatments, SNRIs do not cause weight gain [107].

Sodium channel blockers exercise their effect by blocking voltage-gated sodium channels to lower the excitability of peripheral nerves. The drug group mainly consists of carbamazepine and its successor oxcarbazepine, which was only evaluated in three RCTs (n= 634) with an SMD of 0.45 (95% CI 0.68-0.21) [115,119–121]. However, only a single trial was included in a Cochrane meta-analysis from 2017 [122]. From this trial, the authors found an NTT with oxcarbazepine 600-1800 mg daily of 6.0 (95% CI 3.0-41.0) for a 50% pain reduction. Still, the drug was later withdrawn from clinical trials due to significant side effects, including toxic drug eruption and the need for close monitoring of blood concentrations [121]. Due to its mechanisms of action oxcarbazepine has also been analysed as a potential drug for personalised treatment of specific phenotypes of PDN [123]. In that study, the authors found that subgrouping their study-population based on QST-measurements could reduce the NNT from 6.9 (95% CI 4.2-22.0) in the total sample to 3.9 (95% CI 2.3-12) in the sub-grouped population. Other anticonvulsants like topiramate and lamotrigine have also been tested in PDN, but generally produced disappointing results [124,125]. Side effects associated with the use of sodium channel blockers include dizziness, somnolence, vomiting and agitation [107].

Calcium channel modulators are another group of drugs used to treat PDN through inhibition of the a2δ unit of the calcium channel. The group consists of pregabalin, gabapentin and ziconotide, with the latter being limited by its need for intrathecal administration and lack trials conforming its effectiveness in PDN [126]. Pregabalin is one of the most extensively studied agents for the treatment of PDN [127–136]. In a large meta-analysis from 2014 that included 9 trials involving 2,056 participants, the authors found an NNT to achieve a 50% pain reduction of 7.7 (95% CI 5.0-20.0) with a corresponding SMD of 0.79 (95% CI 1.15-0.48) [137]. Since the publication of this meta-analysis, a few new RCTs have become available. Amongst these is a large Chinese study comparing pregabalin 300 mg daily to placebo has become available, including 623 people with PDN [138]. In the study, pregabalin failed to reach statistical significance concerning the primary outcome, which was change in mean pain score over a week, although a post-hoc analysis excluding a single site with questionable compliance changed this completely (p-value from 0.056 to 0.014). Pregabalin did however, reach statistical significance in several secondary endpoints, including measurements as more than 50% reduction in pain intensity [138]. Another newer study is an international multi-centre study focusing on PDN and pain on walking (n= 203) [139]. In this study, pregabalin 150-300 mg daily also failed to reach its primary outcomes, which were a mean pain score over the last 7 days and pain on walking, although the study did have several limitations, including potential carryover effect and low pregabalin dosage. Gabapentin has been studied in seven RCTs, which were all included in a Cochrane meta-analysis updated in 2017 [136,140–146]. In this analysis (n= 1,331), the authors report an NNT of 6.6 (95% CI: 5.0-9.7) with gabapentin 1200-3000 mg daily to achieve a 50% reduction in pain intensity indicating comparable intra-class drug effectiveness.

The corresponding SMD for gabapentin versus placebo have previously been reported to be 0.73 (95% CI: 1.54-0.09) [115]. Since this review, no new evidence regarding efficiency has become available through RCTs. Common side effects include somnolence, dizziness, headaches and elevated liver enzymes, as well as a significant increase in body weight [107].

N-methyl-D-aspartic receptor (NMDA) antagonists are traditionally used to treat post-operative pain, but has also been studied in people with PDN. A relatively small study found that the agent dextromethorphan (30 mg daily) had pain-relieving properties in PDN, and these findings were later confirmed in combination with quinidine (45 mg daily) in a larger multi-centre trial [147,148].

Opioids are well-examined pain-reducing medication, which mimic the actions of endogenous opioid peptides by interacting with the μ, δ, or κ opioid receptors. However, the use of opioids in the management of PDN remains controversial due to the lack of large trials with long duration and well-established NNT/NNH-ratios. Furthermore, long-term treatment with opioids is often associated with decreasing efficiency as well as opioid dependency and abuse, while adverse effects like nausea, dizziness, constipation, itching and orthostatic hypotension also remain common occurrences [149]. Some of the most used opioids with indication for neuropathic pain are oxycodone, tramadol and tapentalol. Oxycodone was evaluated for the use in neuropathic pain in a Cochrane meta-analysis in 2016, including 637 patients from five RCTs [150]. Here, the authors report little evidence supporting the long-term treatment with oxycodone in PDN, reporting an NNT for 30% pain reduction of 5.7, but with a corresponding NHH of 4.6. Tramadol is one of the oldest drugs used to treat PDN [151], which was also tested for long-term use in PDN [152], but since the indication for treatment of PDN, a limited amount of RCTs have been conducted regarding its efficacy. However, two RCTs have recently examined the drug in PDN, although one used it as a comparator to a potential new drug labelled GRT9906 [153,154]. The NTTs reported for more than 50% pain reduction were 4.3 (95% CI 2.4-20) and 3.9 (95% CI 2.4-11.5), respectively. Tapentalol is an opioid with a unique dual action that combines norepinephrine reuptake inhibition with weak affinity for the μ-opioid receptor resulting in reduction of the classic side effects associated with opioid use. Tapentalol was initially only available in solution from or as an immediate-release tablet, but later became available as an extended-release (ER) film coated tablet for oral administration, that has now been approved for treatment of neuropathic pain and PDN. Tapentalol ER has been studied in several RCTs. In an open-label 3-week phase III trial in 588 people with PDN poorly responsive to previous analgesics, treatment with 200-500 mg tapentalol daily resulted in a significant pain reduction compared to placebo [155]. The 395 responders were then randomly assigned to tapentalol or placebo for further 12 weeks using individualised dosages, resulting in at least 30% pain reduction in 54% in the treatment group [155]. Atypical opioids (tramadol and tapentalol) were evaluated together based on treatment of 1,177 persons with PDN in 5 different RCTs with a SMD of 0.69 (95% CI 0.80-0.56) [115].

Pathogenic treatment is a pharmacological treatment thought to influence directly on some of the proposed mechanisms behind the development of DPN. This is in contrast to most of the therapeutic options mentioned earlier, which generally target multiple organs and even multiple receptors, thus increasing the number of adverse events related to the treatment. The most mentionable products include α-lipoic acid, C-peptide, benfotiamine and aldose-reductase inhibitors [101]. However, none of these products has been approved for treatment of PDN by the FDA. α-Lipoic acid is an antioxidant meant to protect against oxidative stress, and as increased free-radical production and defective antioxidant mechanisms are thought to be some of the mechanisms behind the development of DPN, α-lipoic acid is thought to halt development of neuropathy and might improve symptoms of PDN [156]. α-Lipoic acid has mostly been studied as a drug for intravenous administration (300-600 mg), where a recent meta-analysis has found significant pain-lowering effects with a good safety profile, although many included studies suffer from poor methodological quality [157]. α-Lipoic acid has also been studied as oral treatment (600-1800 mg) with positive results, although the clinical relevance remains uncertain due to the lack of definitive evidence from large RCTs [158]. Aldose reductase inhibition has also been suggested as a potential therapeutic target, as aldose reductase acts as an important enzyme in the polyol pathway involved in the metabolism of glucose when the high glucose levels caused by diabetes saturate the hexokinase [159,160]. Therefore, several aldose reductase inhibitors (ARIs) have been developed and examined in both DPN and PDN with mixed results mainly due to their significant adverse effects, but also limited efficacy [161, 162]. One ARI, epalrestat, has been studied in a prospective 3-year follow-up study, indicating potential preventive abilities in halting the development of DPN[163]. Benfotiamine is a lipid-soluble derivate of vitamin B1 that allows penetration of nerve membranes. Benfotiamine can reduce the presence of advanced glycation end products (AGE), which are thought to be a major player in the pathophysiology of especially microvascular complication, like neuropathy, in diabetes[164]. Benfotiamine has been examined in several short term clinical trials with some studied indicating a favourable effect on neuropathic symptom scores[165–167], although these findings could not be repeated in trials with longer duration[168]. C-peptide is an amino acid component of proinsulin traditionally used to evaluate endogenous insulin-production. However, studies in diabetic rats-models have suggested that C-peptide can reverse some structural and functional changes caused by mainly type 1 diabetes, by indirectly stimulating the Na^+/K^+-ATPase[169]. C-peptides has only been tested in few human studies, but displayed promising results in some smaller trials[170,171].

Other treatments for PDN include local or topical treatment with either capsaicin, clonidine, isobide dinitrate, lidocaine or botulinum toxin A. Capsaicin is an alkaloid derived from red chilli peppers and has been tested in PDN as either 0.075% capsaicin cream applied four times daily[172–174] or recently as a 8% capsaicin patch (Qurtenza)[175]. Capsaicin has also been examined in other doses and in combina-

tion with doxepin 3.3%, which led to a 20% reduction in skin irritation otherwise associated with topical capsaicin treatment although this was not specific to PDN[176]. Based on a review of 5 RCTs using capsaicin 0.075% the treatment was considered low efficiency[115]. Clonidine is a presynaptic α-2-adrenergic receptor agonist. Clonidine is mostly used in neuropathic pain as topically applied clonidine gel, which was accessed in a meta-analysis from 2015 including a total of 344 people with PDN[177]. Unfortunately, clonidine gel was no better than placebo for inducing more than 50% pain reduction, although a slight significance was found compared to placebo when analysing the data as more than 30% pain reduction although the clinical meaning remains uncertain. Based on this data, the NNT would be 8.3 (95% CI 4.3-50.0) although evidence is sparse. Isorbide dinitrate has been proposed as a pain-reducing agent in PDN due to the proposed mechanisms of nitric oxide in the pathogenesis of DPN. Isorbide dinitrate has only been assessed as a spray in one small RCT with limited evidence[178]. Lidocaine is an analgesic that alters signal conduction in neurons by prolonging inactivation of voltage-gated sodium channels[179]. The pain-reducing probabilities of lidocaine were studied in 204 persons with PDN as 5% lidocaine plasters and compared to pregabalin in one open-label, non-inferiority RCT[180]. In this study, lidocaine was non-inferior to pregabalin regarding response-rate and seemed to have a more favourable safety-profile with fewer side effects. However, further studies are needed to confirm the efficacy. Lidocaine has also been examined with positive results as intravenous infusions in intractable PDN[181,182], and as the oral analogue, mexiletine, with limited efficiency[183–186]. Botulinum toxin type A is a neurotoxic protein that exerts its effect by inactivating key proteins required for nerve activation. Its use in PDN was studied in two small RCTs indicating a beneficial effect although larger studies are needed to confirm the results[187,188].

Some people with PDN may not achieve adequate pain-relief using traditional pharmacological intervention due to either lacking efficiency or overwhelming side effects. Therefore, several nonpharmacological alternatives have been proposed, including transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation and frequency-modulated electromagnetic neural stimulation [101, 189]. A meta-analysis from 2013 including eight studies (n= 318), which mainly consists of RCTs with lower quality, found that six of the eight studied showed significant improvements in the treatment arms, indicating a beneficial effect, although high quality evidence is currently not available[190]. A few studies have also examined the effect of spinal cord stimulation in PDN[191,192], with one study indicating beneficial effects even after 24 months of follow-up[193]. While the evidence of this treatment remains sparse new studies are currently in the pipeline for the future[194]. Acupuncture has also been proposed as a good alternative treatment option for intractable neuropathic pain in diabetes displaying uniformly good results. However, a systematic review from 2013 evaluating the available RCTs concluded, that no clinically relevant conclusion could be drawn from available literature, due to a high risk of bias and lack of internationally acknowledged endpoints[195].

CONCLUSION

DPN and PDN are complex conditions associated with significant morbidity and equally high mortality. Despite the high number of new methods proposed to diagnose the conditions, researchers and clinicians are still challenged by the lack of well-validated methods for early detection as well as for grading and risk stratification of people with diabetes. Furthermore, the continuous usage of old bedside methods solely detecting abnormalities in the largest nerve fibres limits the possibility for early detection and intervention, which again limits the chance for successful clinical trials.

Treatment that restores nerve function has yet to be found and translated into large clinical trials, and even though several pathogenic treatments have been proposed, clinicians still struggle to treat PDN due to limited efficiency of current treatment options in combination with broad contraindications and significant side effects. While several studies concerning treatment effect of various drugs exist, only a few studies have been conducted in recent years, and even fewer provides a direct comparison of the proposed first line drugs.

PERSPECTIVES FOR THE FUTURE

Despite a large number of new and exciting methods for early detection of particularly small fibre neuropathy, the lack of a well-established gold standard to validate novel methods against, have led to the fact that both researchers and clinicians are yet to agree on and standardize the use of many of the newer methods. To perform meaningful multicentre trials, the research community must first have agreeable, standardized, highly sensitive methods for quantification of nerve fibre function, so that a potentially beneficial effect of disease modifying treatment can be detected even though the initial effect is small. Therefore, more studies comparing the different methods and their relation to the clinical manifestation of DPN are needed, so that future studies can be provided with reliable endpoints and quantitative measurements of pain. If future studies should be reliant on one endpoint alone, or a combination of measurements, remains unknown, but the fact that enhanced diagnostic tools will benefit future treatment is undeniable. One of the first steps towards the agreement on new gold standards would be a direct quantitative method comparison. However, such an analysis has proven difficult to preform, mainly due to the fact that the field of neuropathic research is characterized by varying study designs, different definitions and a broad spectrum of outcomes measures. Furthermore, sub-classification of PDN and personalized treatment regimens based on disease subtype accessed through deep phenotyping may pave the way for improved NNT/NNH-ratios for both new and existing drugs. Finally, enhanced classification and personalization should also lead to an increased usage of agents targeting the proposed pathophysiologic mechanisms of DPN, so that global side effects associated with the unspecific targeting of the symptomatic treatment could be reduced. Novel agents that target the pathophysiology of DPN have also been of increasing interest, and while only a few of them have been tested specifically in PDN, the most prominent ones could potentially be studied in people with diabetes in the future. For example, an angiotensin II type 2 receptor

(AGTR2)-antagonist named EMA401 is currently being developed. This drug was previously tested in a phase IIa study demonstrating efficacy and safety in postherpetic neuralgia[196], thus might have potential in PDN as well. Another example is the development of subtype-selective sodium channel blockers specific for $Na_V1.7$ channels. Here, several trials are ongoing, including studies on compounds named BIIB074[197] and TV-45070[198].

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

Not applicable.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in preparing the manuscript. The authors received no specific grant from any funding agency. Aalborg University and Steno Diabetes Center North Jutland paid salary to investigators but were otherwise not involved in the preparation or content of the article. The conclusions in the article reflect the opinions of the authors and not their affiliated institutions.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Vinik AI, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. Endocrinol Metab Clin North Am 2013; 42(4): 747-87. http://dx.doi.org/10.1016/j.ecl.2013.06.001 PMID: 24286949

[2] Hicks CW, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Curr Diab Rep 2019; 19(10): 86. http://dx.doi.org/10.1007/s11892-019-1212-8 PMID: 31456118

[3] Divisova S, Vlckova E, Hnojcikova M, *et al.* Prediabetes/early diabetes-associated neuropathy predominantly involves sensory small fibres. J Peripher Nerv Syst 2012; 17(3): 341-50. http://dx.doi.org/10.1111/j.1529-8027.2012.00420.x PMID: 22971096

[4] Løseth S, Stålberg E, Jorde R, Mellgren SI. Early diabetic neuropathy: thermal thresholds and intraepidermal nerve fibre density in patients with normal nerve conduction studies. J Neurol 2008; 255(8): 1197-202. http://dx.doi.org/10.1007/s00415-008-0872-0 PMID: 18574618

[5] Smith AG, Ramachandran P, Tripp S, Singleton JR. Epidermal nerve innervation in impaired glucose tolerance and diabetes-associated neuropathy. Neurology 2001; 57(9): 1701-4. http://dx.doi.org/10.1212/WNL.57.9.1701 PMID: 11706115

[6] Breiner A, Lovblom LE, Perkins BA, Bril V. Does the prevailing hypothesis that small-fiber dysfunction precedes large-fiber dysfunction apply to type 1 diabetic patients? Diabetes Care 2014; 37(5): 1418-24. http://dx.doi.org/10.2337/dc13-2005 PMID: 24574353

[7] Thomas PK. Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. Diabetes 1997; 46(Suppl. 2): S54-7. http://dx.doi.org/10.2337/diab.46.2.S54 PMID: 9285500

[8] Umapathi T, Tan WL, Loke SC, Soon PC, Tavintharan S, Chan YH. Intraepidermal nerve fiber density as a marker of early diabetic neuropathy. Muscle Nerve 2007; 35(5): 591-8. http://dx.doi.org/10.1002/mus.20732 PMID: 17221881

[9] Tesfaye S, Vileikyte L, Rayman G, *et al.* Toronto Expert Panel on Diabetic Neuropathy. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev 2011; 27(7): 629-38. http://dx.doi.org/10.1002/dmrr.1225 PMID: 21695762

[10] Tesfaye S, Boulton AJM, Dyck PJ, *et al.* Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010; 33(10): 2285-93. http://dx.doi.org/10.2337/dc10-1303 PMID: 20876709

[11] Pop-Busui R, Boulton AJM, Feldman EL, *et al.* Diabetic neuropathy: A position statement by the American diabetes association. Diabetes Care 2017; 40(1): 136-54. http://dx.doi.org/10.2337/dc16-2042 PMID: 27999003

[12] Brock C, Hansen CS, Karmisholt J, *et al.* Liraglutide treatment reduced interleukin-6 in adults with type 1 diabetes but did not improve established autonomic or polyneuropathy. Br J Clin Pharmacol 2019; 85(11): 2512-23. http://dx.doi.org/10.1111/bcp.14063 PMID: 31338868

[13] Kennedy WR, Navarro X, Goetz FC, Sutherland DER, Najarian JS. Effects of pancreatic transplantation on diabetic neuropathy. N Engl J Med 1990; 322(15): 1031-7. http://dx.doi.org/10.1056/NEJM199004123221503 PMID: 2320063

[14] Wahren J, Foyt H, Daniels M, Arezzo JC. Long-acting C-peptide and neuropathy in type 1 diabetes: A 12-month clinical trial. Diabetes Care 2016; 39(4): 596-602. http://dx.doi.org/10.2337/dc15-2068 PMID: 26884473

[15] Apfel SC. Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold? Int Rev Neurobiol 2002; 50: 393-413. http://dx.doi.org/10.1016/S0074-7742(02)50083-0 PMID: 12198818

[16] Vinik AI, Bril V, Kempler P, *et al.* MBBQ Study Group. Treatment of symptomatic diabetic peripheral neuropathy with the protein kinase C β-inhibitor ruboxistaurin mesylate during a 1-year, randomized, placebo-controlled, double-blind clinical trial. Clin Ther 2005; 27(8): 1164-80. http://dx.doi.org/10.1016/j.clinthera.2005.08.001 PMID: 16199243

[17] Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994; 17(11): 1281-9. http://dx.doi.org/10.2337/diacare.17.11.1281 PMID: 7821168

[18] Young MJ, Boulton AJM, Macleod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population 1993; 36

[19] Dyck PJ, Sherman WR, Hallcher LM, *et al.* Human diabetic endoneurial sorbitol, fructose, and myo-inositol related to sural nerve morphometry. Ann Neurol 1980; 8(6): 590-6. http://dx.doi.org/10.1002/ana.410080608 PMID: 7212646

[20] Bril V, Tomioka S, Buchanan RA, Perkins BA. mTCNS Study Group. Reliability and validity of the modified Toronto Clinical Neuropathy Score in diabetic sensorimotor polyneuropathy. Diabet Med 2009; 26(3): 240-6. http://dx.doi.org/10.1111/j.1464-5491.2009.02667.x PMID: 19317818

[21] Valk GD, de Sonnaville JJJ, van Houtum WH, *et al.* The assessment of diabetic polyneuropathy in daily clinical practice: reproducibility and validity of Semmes Weinstein monofilaments examination and clinical neurological examination. Muscle Nerve 1997; 20(1): 116-8. http://dx.doi.org/10.1002/(SICI)1097-4598(199701)20:1<116::AID-MUS19>3.0.CO;2-2 PMID: 8995595

[22] Valk GD, Nauta JJP, Strijers RLM, Bertelsmann FW. Clinical examination versus neurophysiological examination in the diagnosis of diabetic polyneuropathy. Diabet Med 1992; 9(8): 716-21. http://dx.doi.org/10.1111/j.1464-5491.1992.tb01879.x PMID: 1395463

[23] Meijer JWG, van Sonderen E, Blaauwwiekel EE, *et al.* Diabetic neuropathy examination: a hierarchical scoring system to diagnose

distal polyneuropathy in diabetes. Diabetes Care 2000; 23(6): 750-3.
http://dx.doi.org/10.2337/diacare.23.6.750 PMID: 10840990

[24] Dyck PJ, Karnes J, O'Brien PC, Swanson CJ. Neuropathy Symptom Profile in health, motor neuron disease, diabetic neuropathy, and amyloidosis. Neurology 1986; 36(10): 1300-8.
http://dx.doi.org/10.1212/WNL.36.10.1300 PMID: 3762934

[25] Meijer JWG, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH, Links TP. Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. Diabet Med 2002; 19(11): 962-5.
http://dx.doi.org/10.1046/j.1464-5491.2002.00819.x PMID: 12421436

[26] Dyck PJ, Litchy WJ, Lehman KA, Hokanson JL, Low PA, O'Brien PC. Variables influencing neuropathic endpoints: The rochester diabetic neuropathy study of healthy subjects. Neurology 1995; 45(6): 1115-21.
http://dx.doi.org/10.1212/WNL.45.6.1115 PMID: 7783874

[27] Bril V. NIS-LL: the primary measurement scale for clinical trial endpoints in diabetic peripheral neuropathy. Eur Neurol 1999; 41(Suppl. 1): 8-13.
http://dx.doi.org/10.1159/000052074 PMID: 10023123

[28] Dyck PJ, Davies JL, Litchy WJ, O'Brien PC. Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. Neurology 1997; 49(1): 229-39.
http://dx.doi.org/10.1212/WNL.49.1.229 PMID: 9222195

[29] Bril V, Perkins BA. Validation of the Toronto clinical scoring system for diabetic polyneuropathy. Diabetes Care 2002; 25(11): 2048-52.
http://dx.doi.org/10.2337/diacare.25.11.2048 PMID: 12401755

[30] Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. Muscle Nerve 1988; 11(1): 21-32.
http://dx.doi.org/10.1002/mus.880110106 PMID: 3277049

[31] Bastyr EJ III, Price KL, Bril V. MBBQ Study Group. Development and validity testing of the neuropathy total symptom score-6: questionnaire for the study of sensory symptoms of diabetic peripheral neuropathy. Clin Ther 2005; 27(8): 1278-94.
http://dx.doi.org/10.1016/j.clinthera.2005.08.002 PMID: 16199253

[32] Cornblath DR, Chaudhry V, Carter K, *et al.* Total neuropathy score: validation and reliability study. Neurology 1999; 53(8): 1660-4.
http://dx.doi.org/10.1212/WNL.53.8.1660 PMID: 10563609

[33] Ziegler D, Hanefeld M, Ruhnau KJ, *et al.* Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant α-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). Diabetologia 1995; 38(12): 1425-33.
http://dx.doi.org/10.1007/BF00400603 PMID: 8786016

[34] Rolke R, Magerl W, Campbell KA, *et al.* Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006; 10(1): 77-88.
http://dx.doi.org/10.1016/j.ejpain.2005.02.003 PMID: 16291301

[35] Vollert J, Attal N, Baron R, *et al.* Quantitative sensory testing using DFNS protocol in Europe: an evaluation of heterogeneity across multiple centers in patients with peripheral neuropathic pain and healthy subjects. Pain 2016; 157(3): 750-8.
http://dx.doi.org/10.1097/j.pain.0000000000000433 PMID: 26630440

[36] Shy ME, Frohman EM, So YT, *et al.* Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Quantitative sensory testing: Report of the therapeutics and technology assessment subcommittee of the American academy of neurology. Neurology 2003; 60(6): 898-904.
http://dx.doi.org/10.1212/01.WNL.0000058546.16985.11 PMID: 12654951

[37] Malik RA. Why are there no good treatments for diabetic neuropathy? Lancet Diabetes Endocrinol 2014; 2(8): 607-9.
http://dx.doi.org/10.1016/S2213-8587(14)70067-1 PMID: 24746878

[38] Vollert J, Maier C, Attal N, *et al.* Stratifying patients with peripheral neuropathic pain based on sensory profiles: algorithm and sample size recommendations. Pain 2017; 158(8): 1446-55.
http://dx.doi.org/10.1097/j.pain.0000000000000935 PMID: 28595241

[39] Dyck PJ, Overland CJ, Low PA, *et al.* Cl vs. NPhys Trial Investigators. Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: Cl vs. NPhys trial. Muscle Nerve 2010; 42(2): 157-64.
http://dx.doi.org/10.1002/mus.21661 PMID: 20658599

[40] Malik RA. Which test for diagnosing early human diabetic neuropathy? Diabetes 2014; 63(7): 2206-8.
http://dx.doi.org/10.2337/db14-0492 PMID: 24962918

[41] Dyck PJ, Norell JE, Tritschler H, *et al.* Challenges in design of multicenter trials: end points assessed longitudinally for change and monotonicity. Diabetes Care 2007; 30(10): 2619-25.
http://dx.doi.org/10.2337/dc06-2479 PMID: 17513707

[42] Kong X, Lesser EA, Potts FA, Gozani SN. Utilization of nerve conduction studies for the diagnosis of polyneuropathy in patients with diabetes: a retrospective analysis of a large patient series. J Diabetes Sci Technol 2008; 2(2): 268-74.
http://dx.doi.org/10.1177/193229680800200217 PMID: 19885354

[43] Holland NR, Stocks A, Hauer P, Cornblath DR, Griffin JW, McArthur JC. Intraepidermal nerve fiber density in patients with painful sensory neuropathy. Neurology 1997; 48(3): 708-11.
http://dx.doi.org/10.1212/WNL.48.3.708 PMID: 9065552

[44] Kennedy WR, Wendelschafer-Crabb G, Johnson T. Quantitation of epidermal nerves in diabetic neuropathy. Neurology 1996; 47(4): 1042-8.
http://dx.doi.org/10.1212/WNL.47.4.1042 PMID: 8857742

[45] Lauria G, Cornblath DR, Johansson O, *et al.* European Federation of Neurological Societies. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol 2005; 12(10): 747-58.
http://dx.doi.org/10.1111/j.1468-1331.2005.01260.x PMID: 16190912

[46] Lauria G, Hsieh ST, Johansson O, *et al.* European Federation of Neurological Societies; Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol 2010; 17(7): 903-912, e44-e49.
http://dx.doi.org/10.1111/j.1468-1331.2010.03023.x PMID: 20642627

[47] Bakkers M, Merkies ISJ, Lauria G, *et al.* Intraepidermal nerve fiber density and its application in sarcoidosis. Neurology 2009; 73(14): 1142-8.
http://dx.doi.org/10.1212/WNL.0b013e3181bacf05 PMID: 19805731

[48] Gøransson LG, Mellgren SI, Lindal S, Omdal R. The effect of age and gender on epidermal nerve fiber density. Neurology 2004; 62(5): 774-7.
http://dx.doi.org/10.1212/01.WNL.0000113732.41127.8F PMID: 15007129

[49] Lauria G, Bakkers M, Schmitz C, *et al.* Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. J Peripher Nerv Syst 2010; 15(3): 202-7.
http://dx.doi.org/10.1111/j.1529-8027.2010.00271.x PMID: 21040142

[50] Smith AG, Howard JR, Kroll R, *et al.* The reliability of skin biopsy with measurement of intraepidermal nerve fiber density. J Neurol Sci 2005; 228(1): 65-9.
http://dx.doi.org/10.1016/j.jns.2004.09.032 PMID: 15607212

[51] McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fiber density: normative reference range and diagnostic efficiency. Arch Neurol 1998; 55(12): 1513-20.
http://dx.doi.org/10.1001/archneur.55.12.1513 PMID: 9865794

[52] Koskinen M, Hietaharju A, Kyläniemi M, *et al.* A quantitative method for the assessment of intraepidermal nerve fibers in small-fiber neuropathy. J Neurol 2005; 252(7): 789-94.
http://dx.doi.org/10.1007/s00415-005-0743-x PMID: 15789134

[53] Wöpking S, Scherens A, Haussleiter IS, *et al.* Significant difference between three observers in the assessment of intraepidermal nerve fiber density in skin biopsy. BMC Neurol 2009; 9: 13.
http://dx.doi.org/10.1186/1471-2377-9-13 PMID: 19335896

[54] Provitera V, Gibbons CH, Wendelschafer-Crabb G, *et al.* A multicenter, multinational age- and gender-adjusted normative dataset

for immunofluorescent intraepidermal nerve fiber density at the distal leg. Eur J Neurol 2016; 23(2): 333-8. http://dx.doi.org/10.1111/ene.12842 PMID: 26493160

[55] Nolano M, Biasiotta A, Lombardi R, *et al.* Epidermal innervation morphometry by immunofluorescence and bright-field microscopy. J Peripher Nerv Syst 2015; 20(4): 387-91. http://dx.doi.org/10.1111/jns.12146 PMID: 26309146

[56] Lauria G, Dacci P, Lombardi R, *et al.* Side and time variability of intraepidermal nerve fiber density. Neurology 2015; 84(23): 2368-71. http://dx.doi.org/10.1212/WNL.0000000000001666 PMID: 25972491

[57] Karlsson P, Porretta-Serapiglia C, Lombardi R, Jensen TS, Lauria G. Dermal innervation in healthy subjects and small fiber neuropathy patients: a stereological reappraisal. J Peripher Nerv Syst 2013; 18(1): 48-53. http://dx.doi.org/10.1111/jns5.12007 PMID: 23521644

[58] Karlsson P, Møller AT, Jensen TS, Nyengaard JR. Epidermal nerve fiber length density estimation using global spatial sampling in healthy subjects and neuropathy patients. J Neuropathol Exp Neurol 2013; 72(3): 186-93. http://dx.doi.org/10.1097/NEN.0b013e318284e849 PMID: 23399897

[59] Rosenberg ME, Tervo TM, Immonen IJ, Müller LJ, Grönhagen-Riska C, Vesaluoma MH. Corneal structure and sensitivity in type 1 diabetes mellitus. Invest Ophthalmol Vis Sci 2000; 41(10): 2915-21. http://dx.doi.org/10.1016/S0304-5412(12)70418-3 PMID: 10967045

[60] Malik RA, Kallinikos P, Abbott CA, *et al.* Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. Diabetologia 2003; 46(5): 683-8. http://dx.doi.org/10.1007/s00125-003-1086-8 PMID: 12739016

[61] Hertz P, Bril V, Orszag A, *et al.* Reproducibility of in vivo corneal confocal microscopy as a novel screening test for early diabetic sensorimotor polyneuropathy. Diabet Med 2011; 28(10): 1253-60. http://dx.doi.org/10.1111/j.1464-5491.2011.03299.x PMID: 21434993

[62] Pacaud D, Romanchuk KG, Tavakoli M, *et al.* The reliability and reproducibility of corneal confocal microscopy in children. Invest Ophthalmol Vis Sci 2015; 56(9): 5636-40. http://dx.doi.org/10.1167/iovs.15-16995 PMID: 26313299

[63] Petropoulos IN, Manzoor T, Morgan P, *et al.* Repeatability of in vivo corneal confocal microscopy to quantify corneal nerve morphology. Cornea 2013; 32(5): e83-9. http://dx.doi.org/10.1097/ICO.0b013e3182749419 PMID: 23172119

[64] Mehra S, Tavakoli M, Kallinikos PA, *et al.* Corneal confocal microscopy detects early nerve regeneration after pancreas transplantation in patients with type 1 diabetes. Diabetes Care 2007; 30(10): 2608-12. http://dx.doi.org/10.2337/dc07-0870 PMID: 17623821

[65] Azmi S, Jeziorska M, Ferdousi M, Petropoulos IN, Ponirakis G, Marshall A, *et al.* Early nerve fibre regeneration in individuals with type 1 diabetes after simultaneous pancreas and kidney transplantation

[66] Perkins BA, Lovblom LE, Bril V, *et al.* Corneal confocal microscopy for identification of diabetic sensorimotor polyneuropathy: a pooled multinational consortium study. Diabetologia 2018; 61(8): 1856-61. http://dx.doi.org/10.1007/s00125-018-4653-8 PMID: 29869146

[67] Guthoff RF, Zhivov A, Stachs O. In vivo confocal microscopy, an inner vision of the cornea - a major review. Clin Exp Ophthalmol 2009; 37(1): 100-17. http://dx.doi.org/10.1111/j.1442-9071.2009.02016.x PMID: 19338608

[68] Chen X, Graham J, Dabbah MA, *et al.* Small nerve fiber quantification in the diagnosis of diabetic sensorimotor polyneuropathy: comparing corneal confocal microscopy with intraepidermal nerve fiber density. Diabetes Care 2015; 38(6): 1138-44. http://dx.doi.org/10.2337/dc14-2422 PMID: 25795415

[69] Alam U, Jeziorska M, Petropoulos IN, *et al.* Diagnostic utility of corneal confocal microscopy and intra-epidermal nerve fibre density in diabetic neuropathy. PLoS One 2017; 12(7)e0180175 http://dx.doi.org/10.1371/journal.pone.0180175 PMID: 28719619

[70] Kalteniece A, Ferdousi M, Azmi S, *et al.* Corneal confocal microscopy detects small nerve fibre damage in patients with painful diabetic neuropathy. Sci Rep 2020; 10(1): 3371. http://dx.doi.org/10.1038/s41598-020-60422-7 PMID: 32099076

[71] Andersen ST, Grosen K, Tankisi H, *et al.* Corneal confocal microscopy as a tool for detecting diabetic polyneuropathy in a cohort with screen-detected type 2 diabetes: ADDITION-Denmark. J Diabetes Complications 2018; 32(12): 1153-9. http://dx.doi.org/10.1016/j.jdiacomp.2018.09.016 PMID: 30309785

[72] Tavakoli M, Hossain P, Malik RA. Clinical applications of corneal confocal microscopy. Clin Ophthalmol 2008; 2(2): 435-45. http://dx.doi.org/10.2147/opth.s1490 PMID: 19668734

[73] Tavakoli M, Ferdousi M, Petropoulos IN, *et al.* Normative values for corneal nerve morphology assessed using corneal confocal microscopy: a multinational normative data set. Diabetes Care 2015; 38(5): 838-43. http://dx.doi.org/10.2337/dc14-2311 PMID: 25633665

[74] Benarroch EE, Low PA. The acetylcholine-induced flare response in evaluation of small fiber dysfunction. Ann Neurol 1991; 29(6): 590-5. http://dx.doi.org/10.1002/ana.410290604 PMID: 1892361

[75] Stevens MJ, Edmonds ME, Douglas SL, Watkins PJ. Influence of neuropathy on the microvascular response to local heating in the human diabetic foot. Clin Sci (Lond) 1991; 80(3): 249-56. http://dx.doi.org/10.1042/cs0800249 PMID: 1850685

[76] Yajnik CS, Kantikar VV, Pande AJ, Deslypere JP. Quick and simple evaluation of sudomotor function for screening of diabetic neuropathy. ISRN Endocrinol 2012; 2012103714 http://dx.doi.org/10.5402/2012/103714 PMID: 22830040

[77] Mayaudon H, Miloche PO, Bauduceau B. A new simple method for assessing sudomotor function: relevance in type 2 diabetes. Diabetes Metab 2010; 36(6 Pt 1): 450-4. http://dx.doi.org/10.1016/j.diabet.2010.05.004 PMID: 20739207

[78] Papanas N, Papatheodorou K, Christakidis D, *et al.* Evaluation of a new indicator test for sudomotor function (Neuropad) in the diagnosis of peripheral neuropathy in type 2 diabetic patients. Exp Clin Endocrinol Diabetes 2005; 113(4): 195-8. http://dx.doi.org/10.1055/s-2005-837735 PMID: 15891953

[79] Papanas N, Papatheodorou K, Papazoglou D, Kotsiou S, Maltezos E. A prospective study on the use of the indicator test Neuropad® for the early diagnosis of peripheral neuropathy in type 2 diabetes. Exp Clin Endocrinol Diabetes 2011; 119(2): 122-5. http://dx.doi.org/10.1055/s-0030-1261934 PMID: 20690070

[80] Sharma S, Vas PR, Rayman G. Assessment of diabetic neuropathy using a point-of-care nerve conduction device shows significant associations with the LDIFLARE method and clinical neuropathy scoring. J Diabetes Sci Technol 2015; 9(1): 123-31. http://dx.doi.org/10.1177/1932296814551044 PMID: 25231114

[81] Bostock H, Cikurel K, Burke D. Threshold tracking techniques in the study of human peripheral nerve. Muscle Nerve 1998; 21(2): 137-58. http://dx.doi.org/10.1002/(SICI)1097-4598(199802)21:2<137::AID-MUS1>3.0.CO;2-C PMID: 9466589

[82] Hennings K, Frahm KS, Petrini L, Andersen OK, Arendt-Nielsen L, Mørch CD. Membrane properties in small cutaneous nerve fibers in humans. Muscle Nerve 2017; 55(2): 195-201. http://dx.doi.org/10.1002/mus.25234 PMID: 27366884

[83] Potenzieri C, Undem BJ. Basic mechanisms of itch. Clin Exp Allergy 2012; 42(1): 8-19. http://dx.doi.org/10.1111/j.1365-2222.2011.03791.x PMID: 21645138

[84] Schmelz M. Itch Processing in the Skin. Front Med (Lausanne) 2019; 6: 167-7. http://dx.doi.org/10.3389/fmed.2019.00167 PMID: 31380380

[85] Group TDC. N Engl J Med 1993; 329: 977-86. http://dx.doi.org/10.1056/NEJM199309303291401 PMID: 8366922

[86] Martin CL, Albers JW, Pop-Busui R. DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014; 37(1): 31-8. http://dx.doi.org/10.2337/dc13-2114 PMID: 24356595

[87] Ohkubo Y, Kishikawa H, Araki E, *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; 28(2): 103-17. http://dx.doi.org/10.1016/0168-8227(95)01064-K PMID: 7587918

[88] Turner R. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131): 837-53. http://dx.doi.org/10.1016/S0140-6736(98)07019-6 PMID: 9742976

[89] Ismail-Beigi F, Craven T, Banerji MA, *et al.* ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010; 376(9739): 419-30. http://dx.doi.org/10.1016/S0140-6736(10)60576-4 PMID: 20594588

[90] Charles M, Ejskjaer N, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek A. Prevalence of neuropathy and peripheral arterial disease and the impact of treatment in people with screen-detected type 2 diabetes: the ADDITION-Denmark study. Diabetes Care 2011; 34(10): 2244-9. http://dx.doi.org/10.2337/dc11-0903 PMID: 21816977

[91] Gaede P, Vedel P, Larsen N, Jensen GVH, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348(5): 383-93. http://dx.doi.org/10.1056/NEJMoa021778 PMID: 12556541

[92] Duckworth W, Abraira C, Moritz T, *et al.* VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360(2): 129-39. http://dx.doi.org/10.1056/NEJMoa0808431 PMID: 19092145

[93] Malik RA, Williamson S, Abbott C, *et al.* Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. Lancet 1998; 352(9145): 1978-81. http://dx.doi.org/10.1016/S0140-6736(98)02478-7 PMID: 9872248

[94] Didangelos T, Tziomalos K, Margaritidis C, *et al.* Efficacy of Administration of an Angiotensin Converting Enzyme Inhibitor for Two Years on Autonomic and Peripheral Neuropathy in Patients with Diabetes Mellitus. J Diabetes Res 2017; 20176719239 http://dx.doi.org/10.1155/2017/6719239 PMID: 28373993

[95] Ruggenenti P, Lauria G, Iliev IP, *et al.* DEMAND Study Investigators. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: the delapril and manidipine for nephroprotection in diabetes (DEMAND) randomized clinical trial. Hypertension 2011; 58(5): 776-83. http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.174474 PMID: 21931073

[96] Davis TME, Yeap BB, Davis WA, Bruce DG. Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. Diabetologia 2008; 51(4): 562-6. http://dx.doi.org/10.1007/s00125-007-0919-2 PMID: 18193189

[97] Nielsen SF, Nordestgaard BG. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study. Lancet Diabetes Endocrinol 2014; 2(11): 894-900. http://dx.doi.org/10.1016/S2213-8587(14)70173-1 PMID: 25217178

[98] Gaist D, Jeppesen U, Andersen M, García Rodríguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case-control study. Neurology 2002; 58(9): 1333-7. http://dx.doi.org/10.1212/WNL.58.9.1333 PMID: 12011277

[99] Cohen KL, Harris S. Efficacy and safety of nonsteroidal anti-inflammatory drugs in the therapy of diabetic neuropathy. Arch Intern Med 1987; 147(8): 1442-4. http://dx.doi.org/10.1001/archinte.1987.00370080078016 PMID: 3115210

[100] Spallone V. Management of painful diabetic neuropathy: guideline guidance or jungle? Curr Diab Rep 2012; 12(4): 403-13. http://dx.doi.org/10.1007/s11892-012-0287-2 PMID: 22623150

[101] Javed S, Petropoulos IN, Alam U, Malik RA. Treatment of painful diabetic neuropathy. Ther Adv Chronic Dis 2015; 6(1): 15-28. http://dx.doi.org/10.1177/2040622314552071 PMID: 25553239

[102] Selvarajah D, Petrie J, White D, *et al.* OPTION-DM group. Multicentre, double-blind, crossover trial to identify the Optimal Pathway for TreatIng neurOpathic paiN in Diabetes Mellitus (OPTION-DM): study protocol for a randomised controlled trial. Trials 2018; 19(1): 578. http://dx.doi.org/10.1186/s13063-018-2959-y PMID: 30348206

[103] Tesfaye S, Wilhelm S, Lledo A, *et al.* Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain 2013; 154(12): 2616-25. http://dx.doi.org/10.1016/j.pain.2013.05.043 PMID: 23732189

[104] Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev 2007; CD005454(4)CD005454 http://dx.doi.org/10.1002/14651858.CD005454.pub2 PMID: 17943857

[105] Boyle J, Eriksson MEV, Gribble L, *et al.* Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 2012; 35(12): 2451-8. http://dx.doi.org/10.2337/dc12-0656 PMID: 22991449

[106] Rudroju N, Bansal D, Talakokkula ST, *et al.* Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: a network meta-analysis. Pain Physician 2013; 16(6): E705-14. PMID: 24284851

[107] Griebeler ML, Morey-Vargas OL, Brito JP, *et al.* Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med 2014; 161(9): 639-49. http://dx.doi.org/10.7326/M14-0511 PMID: 25364885

[108] Wernicke JF, Pritchett YL, D'Souza DN, *et al.* A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006; 67(8): 1411-20. http://dx.doi.org/10.1212/01.wnl.0000240225.04000.1a PMID: 17060567

[109] Raskin J, Pritchett YL, Wang F, *et al.* A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med 2005; 6(5): 346-56. http://dx.doi.org/10.1111/j.1526-4637.2005.00061.x PMID: 16266355

[110] Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005; 116(1-2): 109-18. http://dx.doi.org/10.1016/j.pain.2005.03.029 PMID: 15927394

[111] Gao Y, Ning G, Jia WP, *et al.* Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China. Chin Med J (Engl) 2010; 123(22): 3184-92. http://dx.doi.org/10.3760/cma.j.issn.0366-6999.2010.22.003 PMID: 21163113

[112] Yasuda H, Hotta N, Nakao K, Kasuga M, Kashiwagi A, Kawamori R. Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan. J Diabetes Investig 2011; 2(2): 132-9. http://dx.doi.org/10.1111/j.2040-1124.2010.00073.x PMID: 24843472

[113] Gao Y, Guo X, Han P, *et al.* Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo. Int J Clin Pract 2015; 69(9): 957-66. http://dx.doi.org/10.1111/ijcp.12641 PMID: 25939897

[114] Rowbotham MC, Arslanian A, Nothaft W, *et al.* Efficacy and safety of the α4β2 neuronal nicotinic receptor agonist ABT-894 in patients with diabetic peripheral neuropathic pain. Pain 2012; 153(4): 862-8. http://dx.doi.org/10.1016/j.pain.2012.01.009 PMID: 22386472

[115] Waldfogel JM, Nesbit SA, Dy SM, *et al.* Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. Neurology 2017; 88(20): 1958-67. http://dx.doi.org/10.1212/WNL.0000000000003882 PMID: 28341643

[116] Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014; 2014(1)CD007115 http://dx.doi.org/10.1002/14651858.CD007115.pub3 PMID: 24385423

[117] Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev 2015; 2017(8)CD011091 http://dx.doi.org/10.1002/14651858.CD011091.pub2 PMID: 26298465

[118] Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004; 110(3): 697-706. http://dx.doi.org/10.1016/j.pain.2004.05.010 PMID: 15288411

[119] Grosskopf J, Mazzola J, Wan Y, Hopwood M. A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. Acta Neurol Scand 2006; 114(3): 177-80. http://dx.doi.org/10.1111/j.1600-0404.2005.00559.x PMID: 16911345

[120] Beydoun A, Shaibani A, Hopwood M, Wan Y. Oxcarbazepine in painful diabetic neuropathy: results of a dose-ranging study. Acta Neurol Scand 2006; 113(6): 395-404. http://dx.doi.org/10.1111/j.1600-0404.2006.00631.x PMID: 16674606

[121] Dogra S, Beydoun S, Mazzola J, Hopwood M, Wan Y. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. Eur J Pain 2005; 9(5): 543-54. http://dx.doi.org/10.1016/j.ejpain.2004.11.006 PMID: 16139183

[122] Zhou M, Chen N, He L, Yang M, Zhu C, Wu F. Oxcarbazepine for neuropathic pain. Cochrane Database Syst Rev 2017; 12CD007963 http://dx.doi.org/10.1002/14651858.CD007963.pub3 PMID: 29199767

[123] Demant DT, Lund K, Vollert J, *et al.* The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. Pain 2014; 155(11): 2263-73. http://dx.doi.org/10.1016/j.pain.2014.08.014 PMID: 25139589

[124] Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate Diabetic Neuropathic Pain Study Group. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand 2004; 110(4): 221-31. http://dx.doi.org/10.1111/j.1600-0404.2004.00338.x PMID: 15355485

[125] Vinik AI, Tuchman M, Safirstein B, *et al.* Lamotrigine for treatment of pain associated with diabetic neuropathy: results of two randomized, double-blind, placebo-controlled studies. Pain 2007; 128(1-2): 169-79. http://dx.doi.org/10.1016/j.pain.2006.09.040 PMID: 17161535

[126] E. Brookes M. Eldabe S, Batterham A. Ziconotide Monotherapy: A Systematic Review of Randomised Controlled Trials. Curr Neuropharmacol 2016; 15: 217-31. http://dx.doi.org/10.2174/1570159x14666160210142056

[127] Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004; 110(3): 628-38. http://dx.doi.org/10.1016/j.pain.2004.05.001 PMID: 15288403

[128] Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004; 63(11): 2104-10. http://dx.doi.org/10.1212/01.WNL.0000145767.36287.A1 PMID: 15596757

[129] Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005; 6(4): 253-60. http://dx.doi.org/10.1016/j.jpain.2004.12.007 PMID: 15820913

[130] Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005; 115(3): 254-63. http://dx.doi.org/10.1016/j.pain.2005.02.032 PMID: 15911152

[131] Tölle T, Freynhagen R, Versavel M, Trostmann U, Young JP Jr. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. Eur J Pain 2008; 12(2): 203-13. http://dx.doi.org/10.1016/j.ejpain.2007.05.003 PMID: 17631400

[132] Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. BMC Neurol 2008; 8: 33. http://dx.doi.org/10.1186/1471-2377-8-33 PMID: 18796160

[133] Satoh J, Yagihashi S, Baba M, *et al.* Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Diabet Med 2011; 28(1): 109-16. http://dx.doi.org/10.1111/j.1464-5491.2010.03152.x PMID: 21166852

[134] Jiang W, Ladd S, Martsberger C, *et al.* Effects of pregabalin on heart rate variability in patients with painful diabetic neuropathy. J Clin Psychopharmacol 2011; 31(2): 207-13. http://dx.doi.org/10.1097/JCP.0b013e31820f4f57 PMID: 21346609

[135] Raskin P, Huffman C, Toth C, *et al.* Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clin J Pain 2014; 30(5): 379-90. http://dx.doi.org/10.1097/AJP.0b013e31829ea1a1 PMID: 23887339

[136] Rauck R, Makumi CW, Schwartz S, *et al.* A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. Pain Pract 2013; 13(6): 485-96. http://dx.doi.org/10.1111/papr.12014 PMID: 23186035

[137] Zhang SS, Wu Z, Zhang LC, *et al.* Efficacy and safety of pregabalin for treating painful diabetic peripheral neuropathy: a meta-analysis. Acta Anaesthesiol Scand 2015; 59(2): 147-59. http://dx.doi.org/10.1111/aas.12420 PMID: 25328117

[138] Mu Y, Liu X, Li Q, *et al.* Efficacy and safety of pregabalin for painful diabetic peripheral neuropathy in a population of Chinese patients: A randomized placebo-controlled trial. J Diabetes 2018; 10(3): 256-65. http://dx.doi.org/10.1111/1753-0407.12585 PMID: 28727270

[139] Huffman C, Stacey BR, Tuchman M, *et al.* Efficacy and safety of pregabalin in the treatment of patients with painful diabetic peripheral neuropathy and pain on walking. Clin J Pain 2015; 31(11): 946-58. http://dx.doi.org/10.1097/AJP.0000000000000198 PMID: 25565583

[140] Backonja M, Beydoun A, Edwards KR, *et al.* Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998; 280(21): 1831-6. http://dx.doi.org/10.1001/jama.280.21.1831 PMID: 9846777

[141] Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry 1999; 66(2): 251-2. http://dx.doi.org/10.1136/jnnp.66.2.251 PMID: 10071116

[142] Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clin Neuromuscul Dis 2001; 3(2): 53-62. http://dx.doi.org/10.1097/00131402-200112000-00002 PMID: 19078655

[143] Pérez HET, Sánchez GF. Gabapentin therapy for diabetic neuropathic pain. Am J Med 2000; 108(8): 689. http://dx.doi.org/10.1016/S0002-9343(00)00398-3 PMID: 10896633

[144] Sandercock D, Cramer M, Wu J, Chiang YK, Biton V, Heritier M. Gabapentin extended release for the treatment of painful diabetic peripheral neuropathy: efficacy and tolerability in a double-blind, randomized, controlled clinical trial. Diabetes Care 2009; 32(2): e20-0. http://dx.doi.org/10.2337/dc08-1450 PMID: 19171730

[145] Wiffen PJ, Derry S, Bell RF, *et al.* Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2017; 6CD007938 http://dx.doi.org/10.1002/14651858.CD007938.pub4 PMID: 28597471

[146] Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of ga-

bapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999; 159(16): 1931-7.
http://dx.doi.org/10.1001/archinte.159.16.1931 PMID: 10493324

[147] Sang CN, Booher S, Gilron I, Parada S, Max MB. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. Anesthesiology 2002; 96(5): 1053-61.
http://dx.doi.org/10.1097/00000542-200205000-00005 PMID: 11981142

[148] Shaibani AI, Pope LE, Thisted R, Hepner A. Efficacy and safety of dextromethorphan/quinidine at two dosage levels for diabetic neuropathic pain: a double-blind, placebo-controlled, multicenter study. Pain Med 2012; 13(2): 243-54.
http://dx.doi.org/10.1111/j.1526-4637.2011.01316.x PMID: 22314263

[149] Benyamin R, Trescot AM, Datta S, *et al.* Opioid complications and side effects. Pain Physician 2008; 11(2)(Suppl.): S105-20.
http://dx.doi.org/10.1007/978-3-540-35423-9_14 PMID: 18443635

[150] Gaskell H, Derry S, Stannard C, Moore RA. Oxycodone for neuropathic pain in adults. Cochrane Database Syst Rev 2016; 7CD010692
http://dx.doi.org/10.1002/14651858.CD010692.pub3 PMID: 27465317

[151] Harati Y, Gooch C, Swenson M, *et al.* Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998; 50(6): 1842-6.
http://dx.doi.org/10.1212/WNL.50.6.1842 PMID: 9633738

[152] Harati Y, Gooch C, Swenson M, *et al.* Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. J Diabetes Complications 2000; 14(2): 65-70.
http://dx.doi.org/10.1016/S1056-8727(00)00060-X PMID: 10959067

[153] Sindrup SH, Konder R, Lehmann R, *et al.* Randomized controlled trial of the combined monoaminergic and opioid investigational compound GRT9906 in painful polyneuropathy. Eur J Pain 2012; 16(6): 849-59.
http://dx.doi.org/10.1002/j.1532-2149.2011.00069.x PMID: 22337471

[154] Sindrup SH, Andersen G, Madsen C, Smith T, Brøsen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. Pain 1999; 83(1): 85-90.
http://dx.doi.org/10.1016/S0304-3959(99)00079-2 PMID: 10506675

[155] Schwartz S, Etropolski M, Shapiro DY, *et al.* Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011; 27(1): 151-62.
http://dx.doi.org/10.1185/03007995.2010.537589 PMID: 21162697

[156] Vincent AM, Callaghan BC, Smith AL, Feldman EL. Diabetic neuropathy: cellular mechanisms as therapeutic targets. Nat Rev Neurol 2011; 7(10): 573-83.
http://dx.doi.org/10.1038/nrneurol.2011.137 PMID: 21912405

[157] Han T, Bai J, Liu W, Hu Y. A systematic review and meta-analysis of α-lipoic acid in the treatment of diabetic peripheral neuropathy. Eur J Endocrinol 2012; 167(4): 465-71.
http://dx.doi.org/10.1530/EJE-12-0555 PMID: 22837391

[158] Ziegler D, Ametov A, Barinov A, *et al.* Oral treatment with α-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care 2006; 29(11): 2365-70.
http://dx.doi.org/10.2337/dc06-1216 PMID: 17065669

[159] Brownlee M. The pathobiology of diabetic complications: A unifying mechanism Diabetes. American Diabetes Association 2005; Vol. 54: pp. 1615-25.

[160] Oates PJ. Polyol pathway and diabetic peripheral neuropathy. Int Rev Neurobiol 2002; 50: 325-92.
http://dx.doi.org/10.1016/S0074-7742(02)50082-9 PMID: 12198816

[161] Boulton AJM, Kempler P, Ametov A, Ziegler D. Whither pathogenetic treatments for diabetic polyneuropathy? Diabetes Metab Res Rev 2013; 29(5): 327-33.
http://dx.doi.org/10.1002/dmrr.2397 PMID: 23381942

[162] Chalk C, Benstead TJ, Moore F. Aldose reductase inhibitors for the treatment of diabetic polyneuropathy. Cochrane Database Syst Rev 2007; (4): CD004572
http://dx.doi.org/10.1002/14651858.CD004572.pub2 PMID: 17943821

[163] Hotta N, Akanuma Y, Kawamori R, *et al.* Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. Diabetes Care 2006; 29(7): 1538-44.
http://dx.doi.org/10.2337/dc05-2370 PMID: 16801576

[164] Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol 2014; 18(1): 1-14.
http://dx.doi.org/10.4196/kjpp.2014.18.1.1 PMID: 24634591

[165] Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic polyneuropathy--a three-week randomized, controlled pilot study (BEDIP study). Int J Clin Pharmacol Ther 2005; 43(2): 71-7.
http://dx.doi.org/10.5414/CPP43071 PMID: 15726875

[166] Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. Exp Clin Endocrinol Diabetes 2008; 116(10): 600-5.
http://dx.doi.org/10.1055/s-2008-1065351 PMID: 18473286

[167] Stracke H, Lindemann A, Federlin K. A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. Exp Clin Endocrinol Diabetes 1996; 104(4): 311-6.
http://dx.doi.org/10.1055/s-0029-1211460 PMID: 8886748

[168] Fraser DA, Diep LM, Hovden IA, *et al.* The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. Diabetes Care 2012; 35(5): 1095-7.
http://dx.doi.org/10.2337/dc11-1895 PMID: 22446172

[169] Kamiya H, Zhang W, Sima AAF. C-peptide prevents nociceptive sensory neuropathy in type 1 diabetes. Ann Neurol 2004; 56(6): 827-35.
http://dx.doi.org/10.1002/ana.20295 PMID: 15497155

[170] Ekberg K, Brismar T, Johansson BL, Jonsson B, Lindström P, Wahren J. Amelioration of sensory nerve dysfunction by C-Peptide in patients with type 1 diabetes. Diabetes 2003; 52(2): 536-41.
http://dx.doi.org/10.2337/diabetes.52.2.536 PMID: 12540632

[171] Ekberg K, Brismar T, Johansson BL, *et al.* C-Peptide replacement therapy and sensory nerve function in type 1 diabetic neuropathy. Diabetes Care 2007; 30(1): 71-6.
http://dx.doi.org/10.2337/dc06-1274 PMID: 17192336

[172] Musharraf MU, Ahmad Z, Yaqub Z. Comparison of topical capsaicin and topical turpentine Oil for treatment of painful diabetic neuropathy. J Ayub Med Coll Abbottabad 2017; 29(3): 384-7.
PMID: 29076666

[173] The Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. Arch Intern Med 1991; 151(11): 2225-9.
http://dx.doi.org/10.1001/archinte.1991.00400110079017 PMID: 1953227

[174] Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. Diabetes Care 1992; 15(1): 8-14.
http://dx.doi.org/10.2337/diacare.15.1.8 PMID: 1737545

[175] Simpson DM, Robinson-Papp J, Van J, *et al.* Capsaicin 8% Patch in Painful Diabetic Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Study. J Pain 2017; 18(1): 42-53.
http://dx.doi.org/10.1016/j.jpain.2016.09.008 PMID: 27746370

[176] McCleane G. Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. Br J Clin Pharmacol 2000; 49(6): 574-9.
http://dx.doi.org/10.1046/j.1365-2125.2000.00200.x PMID: 10848721

[177] Wrzosek A, Woron J, Dobrogowski J, Jakowicka-Wordliczek J, Wordliczek J. Topical clonidine for neuropathic pain. Cochrane Database Syst Rev 2015; 8CD010967
http://dx.doi.org/10.1002/14651858.CD010967.pub2 PMID: 26329307

[178] Yuen KCJ, Baker NR, Rayman G. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind

placebo-controlled cross-over study. Diabetes Care 2002; 25(10): 1699-703.
http://dx.doi.org/10.2337/diacare.25.10.1699 PMID: 12351464

[179] Catterall WA. Molecular mechanisms of gating and drug block of sodium channels. Novartis Found Symp 2002; 241: 206-18.
http://dx.doi.org/10.1002/0470846682.ch14 PMID: 11771647

[180] Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. Curr Med Res Opin 2009; 25(7): 1663-76.
http://dx.doi.org/10.1185/03007990903047880 PMID: 19485723

[181] Kastrup J, Petersen P, Dejgård A, Angelo HR, Hilsted J. Intravenous lidocaine infusion--a new treatment of chronic painful diabetic neuropathy? Pain 1987; 28(1): 69-75.
http://dx.doi.org/10.1016/0304-3959(87)91061-X PMID: 3822496

[182] Viola V, Newnham HH, Simpson RW. Treatment of intractable painful diabetic neuropathy with intravenous lignocaine. J Diabetes Complications 2006; 20(1): 34-9.
http://dx.doi.org/10.1016/j.jdiacomp.2005.05.007 PMID: 16389165

[183] Wright JM, Oki JC, Graves L III. Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. Ann Pharmacother 1997; 31(1): 29-34.
http://dx.doi.org/10.1177/106002809703100103 PMID: 8997461

[184] Oskarsson P, Ljunggren JG, Lins PE. The Mexiletine Study Group. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. Diabetes Care 1997; 20(10): 1594-7.
http://dx.doi.org/10.2337/diacare.20.10.1594 PMID: 9314641

[185] Stracke H, Meyer UE, Schumacher HE, Federlin K. Mexiletine in the treatment of diabetic neuropathy. Diabetes Care 1992; 15(11): 1550-5.
http://dx.doi.org/10.2337/diacare.15.11.1550 PMID: 1468285

[186] Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet 1988; 1(8575-6): 9-11.
http://dx.doi.org/10.1016/S0140-6736(88)90999-3 PMID: 2891940

[187] Ghasemi M, Ansari M, Basiri K, Shaigannejad V. The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci 2014; 19(2): 106-11.
PMID: 24778662

[188] Chen WT, Yuan RY, Chiang SC, *et al.* OnabotulinumtoxinA improves tactile and mechanical pain perception in painful diabetic polyneuropathy. Clin J Pain 2013; 29(4): 305-10.
http://dx.doi.org/10.1097/AJP.0b013e318255c132 PMID: 23462284

[189] Bril V, England J, Franklin GM, *et al.* American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011; 76(20): 1758-65.
http://dx.doi.org/10.1212/WNL.0b013e3182166ebe PMID: 21482920

[190] Thakral G, Kim PJ, LaFontaine J, Menzies R, Najafi B, Lavery LA. Electrical stimulation as an adjunctive treatment of painful and sensory diabetic neuropathy J Diabetes Sci Technol 2013; 7: 1202-9.

[191] Slangen R, Schaper NC, Faber CG, *et al.* Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care 2014; 37(11): 3016-24.
http://dx.doi.org/10.2337/dc14-0684 PMID: 25216508

[192] de Vos CC, Meier K, Zaalberg PB, *et al.* Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain 2014; 155(11): 2426-31.
http://dx.doi.org/10.1016/j.pain.2014.08.031 PMID: 25180016

[193] van Beek M, Slangen R, Schaper NC, *et al.* Sustained treatment effect of spinal cord stimulation in painful diabetic peripheral Neuropathy: 24-Month Follow-up of a prospective Two-Center randomized controlled trial. Diabetes Care 2015; 38(9): e132-4.
http://dx.doi.org/10.2337/dc15-0740 PMID: 26116722

[194] Mekhail NA, Argoff CE, Taylor RS, *et al.* High-frequency spinal cord stimulation at 10 kHz for the treatment of painful diabetic neuropathy: design of a multicenter, randomized controlled trial (SENZA-PDN). Trials 2020; 21(1): 87.
http://dx.doi.org/10.1186/s13063-019-4007-y PMID: 31941531

[195] Chen W, Yang GY, Liu B, Manheimer E, Liu JP. Manual acupuncture for treatment of diabetic peripheral neuropathy: a systematic review of randomized controlled trials. PLoS One 2013; 8(9)e73764
http://dx.doi.org/10.1371/journal.pone.0073764 PMID: 24069229

[196] Rice ASC, Dworkin RH, McCarthy TD, *et al.* EMA401-003 study group. EMA401, an orally administered highly selective angiotensin II type 2 receptor antagonist, as a novel treatment for postherpetic neuralgia: a randomised, double-blind, placebo-controlled phase 2 clinical trial. Lancet 2014; 383(9929): 1637-47.
http://dx.doi.org/10.1016/S0140-6736(13)62337-5 PMID: 24507377

[197] Zakrzewska JM, Palmer J, Morisset V, *et al.* study investigators. Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial. Lancet Neurol 2017; 16(4): 291-300.
http://dx.doi.org/10.1016/S1474-4422(17)30005-4 PMID: 28216232

[198] Price N, Namdari R, Neville J, *et al.* Safety and Efficacy of a Topical Sodium Channel Inhibitor (TV-45070) in Patients With Postherpetic Neuralgia (PHN): A Randomized, Controlled, Proof-of-Concept, Crossover Study, With a Subgroup Analysis of the Nav1.7 R1150W Genotype. Clin J Pain 2017; 33(4): 310-8.
http://dx.doi.org/10.1097/AJP.0000000000000408 PMID: 28266963