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REVIEW

Diabetic neuropathic pain: Physiopathology and treatment

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Abstract

Diabetic neuropathy is a common complication of both type 1 and type 2 diabetes, which affects over 90% of the diabetic patients. Although pain is one of the main symptoms of diabetic neuropathy, its pathophysiological mechanisms are not yet fully known. It is widely accepted that the toxic effects of hyperglycemia play an important role in the development of this complication, but several other hypotheses have been postulated. The management of diabetic neuropathic pain consists basically in excluding other causes of painful peripheral neuropathy, improving glycemic control as a prophylactic therapy and using medications to alleviate pain. First line drugs for pain relief include anticonvulsants, such as pregabalin and gabapentin and antidepressants, especially those that act to inhibit the reuptake of serotonin and noradrenaline. In addition, there is experimental and clinical evidence that opioids can be helpful in pain control, mainly if associated with first line drugs. Other agents, including for topical application, such as capsaicin cream and lidocaine patches, have also been proposed to be useful as adjuvants in the control of diabetic neuropathic pain, but the clinical evidence is insufficient to support their use. In conclusion, a better understanding of the mechanisms underlying diabetic neuropathic pain will contribute to the search of new therapies, but also to the improvement of the guidelines to optimize pain control with the drugs currently available.

Key words: Diabetes; Neuropathic pain; Hyperglycemia; Anticonvulsants; Antidepressants

Core tip: Diabetic neuropathic pain is a common complication of diabetes and the most common form of neuropathic pain. In this review, we will discuss the various factors that may contribute to the pathogenesis of diabetic neuropathic pain, including metabolic, vascular, autoimmune and oxidative stress-related mechanisms. In addition, we will review the possibilities of pain treatment, taken into consideration the first line drugs clinically used, the antidepressants and anticonvulsants, but also other options such as opioids, tapentadol and drugs for topical use, such as lidocaine and capsaicin cream.

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INTRODUCTION

According to the International Diabetes Federation, 382 million people worldwide are currently affected by diabetes[1], one of the leading causes of neuropathy[2]. The distal symmetrical polyneuropathy (DSPN) is the commonest clinical form of diabetic neuropathy, affecting more than 90% of the patients[3]. Generally, DSPN affects the toes and distal foot, but slowly progresses proximally to involve the feet and legs in a stocking distribution. It is also characterized by a progressive loss of nerve fibers affecting both the autonomic and somatic divisions, thereby diabetic retinopathy and nephropathy can occur[3]. Foot ulceration and painful neuropathy are the main clinical consequences of DSPN, linked with higher morbidity and mortality[4]. Frequently, patients look for medical help only when pain appears[5], a symptom that affects 10% to 26% of this population[6,7].

Diabetic neuropathic pain (DNP) is characterized by tingling, burning, sharp, shooting, and lancinating or even as electric shock sensations[3,8]. It is usually considered moderate to severe and often worse at night, causing sleeping disturbs. The pain can be constant and accompanied of cutaneous allodynia, which can substantially affect the quality of life of patients, impacting the ability to perform daily activities and having a negative influence on mood. The pain may also be a reason of withdrawal of recreational and social activities and may be associated with depression[3,9,10].

The pathogenesis of DNP is not fully understood. Several theories have been proposed to explain the pain related to the diabetic neuropathy, such as changes in the blood vessels that supply the peripheral nerves; metabolic and autoimmune disorders accompanied by glial cell activation, changes in sodium and calcium channels expression and more recently, central pain mechanisms, such as increased thalamic vascularity and imbalance of the facilitatory/inhibitory descending pathways[3]. Additionally, several risk factors are associated with DNP including worsening glucose tolerance, older age, longer diabetes duration, drinking alcohol and cigarette smoking[10].

Currently, only three agents are approved in the United States for the treatment of DNP: duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, pregabalin, an anticonvulsant, and the dual-effect drug tapentadol, an opioid receptor agonist and norepinephrine reuptake inhibitor[11]. However, as pain relief is unsatisfactory for most patients, several pharmacological interventions have been used based on pre-clinical and/or clinical evidence, as well as an inference of mechanism of action.

PHYSIOPATHOLOGY OF NEUROPATHIC PAIN IN DIABETES

Although there is a great advance in understanding the pathophysiological mechanisms leading to the development of diabetic complications, there is not yet a plausible hypothesis to explain why some patients develop the painful form of disease while others do not. In general, researchers seek to elucidate neuropathy underlying mechanisms as a bigger event, and include pain and other sensorial manifestations as direct consequences of neuropathy. However, interestingly, pain intensity normally is not associated with neuropathy severity, and can occur even in the absence of nerve injuries[12,13]. In this review, it will be addressed the pathophysiological mechanisms currently believed to promote the DNP.

In this sense, the mechanisms that lead to DNP are not fully understood, although there is a consensus that toxic effects of hyperglycemia represent an important factor for the development of this complication[14,15]. Nonetheless, other factors besides hyperglycemia should not be discarded[16], and will be discussed as follows.

Polyol pathway hyperactivity

Metabolic disorders are the primary cause of diabetic neuropathy. Hyperglycemia, induced through decreased of insulin secretion or insulin resistance, is responsible for the enhanced of the polyol pathway activity. The rate-limiting first enzyme of this pathway aldose reductase catalyzes the formation of sorbitol from glucose, with the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to $NADP^+$. Sorbitol is further oxidized to fructose by sorbitol dehydrogenase, which is coupled with the reduction of nicotinamide adenine dinucleotide (NAD^+) to NADH. It is described that during hyperglycemic states, the affinity of aldose reductase for glucose is higher, generating intracellular osmotic stress due to accumulation of sorbitol, since sorbitol does not cross cell membranes. Interesting, the nerve damage following the diabetic state seems not to be due to this osmotic stress since it has been reported insignificant sorbitol concentrations in the nerves of diabetic patients[17-19]. However, the current accepted hypothesis states that polyol pathway hyperactivity is pathogenic primarily by increasing the turnover of cofactors such as NADPH and NAD^+, which leads to a decrease in the reduction and regeneration of glutathione, as well as to an increase of advanced glycation end products (AGEs) production and activation of diacylglycerol and protein kinase C (PKC) isoforms. Depletion of glutathione could be the primary cause of oxidative stress and be related to the accumulation of toxic species[19]. In fact, aldose reductase inhibitors are effective in preventing the development of diabetic neuropathy in animal models, but they have demonstrated disappointing results and dose-limiting toxicity in human trials[20].

Oxidative and nitrosative stress

As already mentioned, the polyol pathway activation could be the primary cause of oxidative stress associated

with diabetes. However, oxidative stress could be also initiated by autoxidation of glucose and their metabolites, increased intracellular formation of AGEs, increased expression of the receptor for AGEs and its activating ligands, altered mitochondrial function, activation of PKC isoforms and overactivity of the hexosamine pathway[21-23]. Moreover, there is mounting evidence that oxidative stress is caused by enhanced free radical formation due to glucose metabolism itself and/or deficits in antioxidant defense and it may play a major role among the putative pathogenic mechanisms of diabetic neuropathy. It seems that, in addition to oxidative stress, reactive nitrogen species, especially the peroxynitrite also play an important role in the development of diabetes and its complications[24-26]. Although it has been clearly demonstrated significant changes in oxidative status in animal models of diabetes[27], tissue concentrations of known carbonyl compounds are nearly negligible and plasma ET-1, nitric oxide, catalase and glutathione levels did not differ in neuropathic diabetic patients when compared to non-neuropathic diabetic ones[28]. In line with this observation, clinical results have been contradictory for antioxidants as alpha lipoic acid, ranging from little benefit[29,30] to interesting advantages[31,32].

Microvascular changes

DNP is frequently associated with microvascular impairment[33,34]. In clinical and preclinical studies, it was found that peripheral perfusion is reduced, not only in the nervous tissue[35,36], but also in the skin[37], being an important physiological evidence of microvasculature alteration. As a result, nerve ischemia occurs, caused by raise in wall thickness and hyalinization of the basal lamina of vessels that nurse peripheral nerves[38,39], together with luminal reduction[38]. These alterations are caused by plasma protein scape of capillary membrane to endoneurium, promoting swelling and augmented interstitial pressure in the nerves, accompanied by higher capillary pressure, deposition of fibrin and thrombus development[40]. Hyperglycemia *per se* can evoke nerve hypoxia, especially in sensory nerves, altering their electrical stability[41]. Apparently controversial data from clinical studies described that diabetic patients suffering from the DNP presented higher levels of intravascular oxygen and augmented blood flow in the lower limbs than painless patients. Nevertheless, authors still consider a hypoxic state inside the endoneurium[42]. Alternatively, a potential sympathetic dysfunction can be the cause of higher blood flow[43].

As a result of nerve ischemia, both diabetic patients and animals have shown a progressive nerve loss in proximal and distal segments[44,45], resulting in reduction of intraepidermal nerve fiber density[12]. Consequently, axonal degeneration and regeneration also occurs, but more frequently in patients that do not experience pain. Besides axonal retraction and regeneration, another structural modification related to hyperglycemia is myelin sheath alteration. The observed demyelinization can be related to Schwann cells altered capacity to support normal myelin sheath[46].

It is also important to point out that endothelial function in patients with DNP is also altered. The vaso dilatation induced by acetylcholine (*i.e.,* the endothelium-dependent response) in dermal vessels of diabetic patients was reduced in comparison with healthy volunteers. In addition, vasoconstriction mediate by the sympathetic system (*i.e.,* endothelium-independent response) was also defective, what can also be implicated in the pathophysiology of diabetic neuropathy and then, in the DNP[47].

It is believed that one potential cause of the microvascular changes described above may be the oxidative stress, since the treatment with antioxidant agents can maintain regular perfusion, restoring sensory transmission in type 1 diabetes model[48].

Channels sprouting

Damaged nerve endings are believed to contribute to pain in DNP[49,50]. The most accepted hypothesis states that disturbed action potentials can be produced by damaged nerve endings, being interpreted by central nervous system (CNS) as pain or dysesthesias[51]. Changes in ion channel expression in peripheral fibers are direct consequences of nerve injury, leading to hyperexcitability[52], that is far linked with neuropathic pain[53].

In this regard, up-regulation of voltage-gated sodium channels (Nav) has been widely demonstrated in neuropathic pain models[54,55]. These channels are involved in generation and transmission of action potential, and can be classified into sensitive (TTX-S) or resistant (TTX-R) to tetrodotoxin[56]. There are several reports that the TTX-S channels Nav1.3, which primary function relays during the embrionary development[57], and Nav1.7, that is constitutively expressed in peripheral sensory neurons[58], are both up-regulated in the dorsal root ganglion (DRG) of diabetic animals[59-61]. Nav1.3 expression was also found increased in small and large diameter DRG neurons of diabetic rats presenting allodynia[62]. Considering TTX-R sodium channels, Nav1.8 and Nav1.9 are normally expressed in peripheral nociceptive neurons[63], playing an important role in the generation of electrical activity in DRG[64]. Intriguingly, DRGs of allodynic diabetic rats showed a reduction of Nav1.8 expression in the following days after diabetes induction[62], and this reduction lasted 6 mo post diabetes induction[61], indicating that other sodium channels may play an important role in DNP. The same reduction was detected for Nav1.6, another TTX-S channel, normally present at Ranvier nodes[60,62].

In addition, an increase of Nav1.6, Nav1.7 and Nav1.8 phosphorylation is another feature observed in the diabetic state, which leads to augmentation in their activity. Thus, both abnormal expression and function of TTX-R and TTX-S sodium channels is linked to abnormal activity of nociceptive fibers[60]. In this way, Sun *et al*[65] showed that TTX-S and TTX-R sodium

currents are increased in small neurons in the DRG of diabetic animals, being this related not only with sensory disturbances, but also with the rise of efficiency of conductance in polymodal C fibers, which in turn, facilitates nociceptive transmission.

In a recent *in vitro* study, it has been described that hyperglycemia evokes higher TTX-R Na^+ currents in a time and concentration-dependent manner, demonstrating a straight relationship between glucose levels and biophysical changes[66]. In DNP patients, it was reported an increase in nodal Na^+ currents when compared to painless diabetic patients, what can also contribute to hyperexcitability in peripheral nerves[67].

A new concept proposed by Hoeijmakers *et al*[68], links the beginning of pancreatic beta cells failure and DNP with genetic disruptions on Nav1.7 channels. Since both pancreatic beta cells and peripheral neurons express Nav1.7 channels, a susceptible genetic background could facilitate generation of *Nav1.7* mutations, leading to gain-of-function that evokes beta cell lesions, and thereafter, diabetes and hyperexcitability in neurons[69]. According to these authors, this theory could explain why some patients have neuropathy before diabetes onset[68].

Another interesting finding related to sodium channels modulation is the increased levels of methylglyoxal in type 2 diabetes DNP patients, when compared with those painless[70,71], and in complication-free type 1 diabetic patients[72]. This glycolytic metabolite can activate nerve endings through transient receptor potential cation channel subfamily A member 1 activation in the DRG[73], and also change the Nav1.7 and Nav1.8 function through posttranslational changes[70]. In line with this clinical observation, in preclinical models methylglyoxal was found to reduce nerve conduction velocity, to elevate calcitonin gene-related peptide release from sensory nerves and to induce thermal and mechanical sensibility[70]. In addition, in diabetic states methylglyoxal is also involved in the formation of AGEs[74].

Calcium channels can also be misregulated in a diabetic condition, leading to an enhanced calcium influx in sensory neurons[75], what can deflagrate both substance P and glutamate release[76]. It was verified in two different animal models of insulin dependent diabetes that high voltage activated Ca^{2+} current amplitudes were increased in small diameter neurons[75,77] and the activity of T-type channels (Cav3.2) is also augmented in small diameter fibers[78], what could be normalized by molecular knockdown of this calcium channel[79]. However, there was no translation of these results to patients in clinical trials[80]. A possible future target for pharmacological intervention over calcium channels has been proposed by Orestes and colleagues (2013), which observed that glycosilation of Cav3.2 augments the current density, accelerates kinetics, and also increases the number of channels on neuron membrane, which can be directly involved in DNP. Interestingly, the deglycosylation treatment with neuraminidase inhibits native calcium currents in nociceptors and completely and selectively reverses hyperalgesia in a pre-clinical model of type 2 diabetes[80].

Resting membrane potential can also be altered by K^+ voltage dependent channels (Kv), also participating in the electrical properties of neurons[81]. Regarding the currents generated by activation of these Kv channels in primary afferents there are two main types: rapidly inactivating A-type currents (I_A), and slowly inactivating currents (I_K)[82,83]. It was verified that the total density of Kv currents as well as the mRNA of I_A subunits of K_V 1.4, 3.4, 4.2 and 4.3 were reduced in large and medium size DRG neurons of diabetic rats[84]. So, this down regulation can increase neuronal excitability and peptide release[83], which might also participate in hyperexcitability of peripheral nerves of diabetic subjects.

Microglial activation

It is becoming increasingly recognized that glial cells play an important role in the pathogenesis of many diseases of the nervous system, including chronic pain states[85]. Glia comprises both macroglia (including astrocytes, radial cells and oligodendrocytes) and microglia cells, which are mainly responsible for maintain homeostasis, form myelin, and provide support and protection for neurons from both central and peripheral nervous system[85]. Normally, microglial cells comprise less than 20% of spinal glial cells but in response to dorsal root ganglia and spinal cord after nerve injury there is a robust proliferation at spinal level[86]. Activation of microglia occurs right after peripheral nerve injury, lasting for less than 3 mo, and is responsible for a production of several inflammatory mediators as cytokines, chemokines, and cytotoxic substances such as nitric oxide and free radicals, prompting to a pro inflammatory milieu[83]. Diabetes has impact on all glial cells of the spinal cord since persistent microglial activation was observed in streptozotocin-induced diabetic rats lasting from 4 wk[87,88] to 6 or 8 mo[61,89]. This microglial activation has been associated with sensorial changes and up-regulation of Nav1.3 sodium channels in the DRG[61], possible through p38 mitogen activated protein kinase dependent mechanism[90,91]. Conversely, diabetes is associated with a reduction in glial fibrillary acidic protein (*i.e.,* glial fibrillary acidic protein) immunoreactive astrocytes in the spinal cord, which may affect the functional support and role of astrocytic cells in the nervous tissue, such as the clearance of neurotransmitters within the synaptic cleft[92]. Considering the potential of microglial activation in driving spinal sensitization, in the near future, drugs that target these cells may become an important therapeutic alternative in chronic pain control.

Central sensitization

As already demonstrated in different neuropathic pain states, DNP may be a consequence of both peripheral and CNS changes[93,94]. It was well described that during DNP, primary afferents are sensitized, inducing dorsal horn hyperactivity and neuroplastic changes in

central sensory neurons[93]. The common occurrence of allodynia in DNP patients supports the idea that CNS pain processing is altered[95].

Among the factors that can lead to the hyperactivity of spinal neurons in diabetic neuropathy is the increased glutamate release from primary afferents in the spinal cord[96,97]. Moreover, spinal N-Methyl-D-aspartate (NMDA) receptor expression is augmented in this condition[98], generating increased and more frequent excitatory post synaptic currents in the lamina Ⅱ[97]. Additionally, it has been described that cAMP response element-binding protein signaling, which directly regulates NMDA receptors activity[99] is enhanced in DNP[98,100]. Thus, it is plausible that augmented NMDA expression and glutamate release might contribute to spinal cord hyperactivity. On the other hand, $GABA_B$ receptors seem to be downregulated in the spinal cord in diabetic neuropathy[98]. Activation of $GABA_B$ receptors results in inhibition of NMDA receptor activity through a direct inhibition of voltage-sensitive Ca^{2+} channels[101] and opening of inwardly rectifying K^+ channels[102]. Furthermore, $GABA_B$ receptor activation also causes downregulation of NMDA receptors at the spinal level in diabetic rats[98]. Considering the importance of central sensitization in the hypersensitivity associated with DNP, strategies that aim to control spinal neurons hyperexcitability are very useful in pain control in this condition, as will be discussed bellow.

Brain plasticity

Functional changes in pain processing areas in the CNS, besides the spinal cord, have been ultimately linked with DNP[103], in a tight relation to increased peripheral input[93,104]. Among these areas, marked changes in the thalamus, cortex and rostroventromedial medulla (RVM) have been reported in DNP patients and or experimental models.

The ventral posterolateral nucleus (VPL) of the thalamus is the main receiving area of nociceptive stimuli that is processed in the spinal cord[105]. Projection neurons reach the thalamus trough the spinothalamic tract (STT), which represents a major ascending nociceptive pathway. It has been demonstrated that in diabetic rats, these neurons present increased spontaneous activity, enlargement of the receptive field and augmented responses to mechanical noxious and innocuous stimuli. The hyperexcitability of STT neurons probably accounts to hypersensitivity to external stimuli and spontaneous pain[93], increased in primary afferents activity[93,104] and to plastic changes in spinal neurons[93].

In addition, in studies that assessed brain imaging in diabetic rats it was reported increased activity not only at VPL, but also in different thalamic nuclei that control sensory-motor aspects[106]. In diabetic patients, a recent study showed increased activation of diverse brain areas, including medial thalamus after application of noxious thermal stimuli in feet[107]. Moreover, it has been described that DNP patients has a marked reduction in the levels of N-acetyl-aspartate (NAA) levels in the thalamus compared to painless diabetic individuals[108]. It is important to point out that patients with brain disorders in which neuronal loss or dysfunction are involved have consistently decreases in brain NAA concentrations[109]. Other clinical finding related to thalamus alterations in diabetic patients is that subjects with painful type 1 diabetic neuropathy presented increased thalamus blood flow, when compared with those without pain, which was considered to reflect higher neuronal activity[110]. Taking account the thalamus relevance in the nociceptive pathway, it is plausible to suggest that the alterations reported in this area might contribute to the development and/or maintance of DNP[108,110].

Likewise, in a model of type 1 diabetes, increased glutamate transmission was reported in the anterior cingulate cortex a brain area involved in the processing of the affective-motivational dimension of pain[111]. The consequence of higher stimulation of this area by glutamate is suggested to be a sustained negative perception of affective component of pain[111].

Changes in the endogenous pain control system have also been described in pre-clinical and clinical studies of DNP. The RVM is a structure that receives direct influences of periaqueductal gray matter, which is, in turn, affected by other structures, such as amygdala and hypothalamus[112]. Three different populations of cells have been describe within the RVM: activation of ON cells act in a pronociceptive way, while activation of OFF cells has the opposite effect[113] and neural cells which activation is still contradictory and remains to be better clarified[114,115]. In diabetic animals, there is evidence of a reduction on the OFF cells and increase on the ON cells population. In addition, basal activity is augmented in ON cells, and reduced in OFF cells, in a resultant misbalance between pain facilitatory and inhibitory descending modulation in diabetic animals[103]. After noxious mechanical stimulation in the periphery, there was no difference between diabetic and control ON cells activity. Thus, the mechanical hyperalgesia detected in diabetic rats could be associated with OFF cells impairment and consequently reduction on descending inhibitory tone[103].

Some studies have also addressed the levels of the main neurotransmitters of the endogenous pain control system in different areas of the CNS in diabetic rats, but they have shown discrepant results. While some researchers found reduced release of norepinephrine in the spinal cord in diabetic rats[116], others have described opposite findings[117]. There is also evidence of diminished norepinephrine levels in supra spinal areas, such as brainstem and thalamus, but higher concentration in the cortex of diabetic animals[118]. Additionally, impaired spinal opioid-induced release of serotonin (5HT) has been demonstrated in diabetic rats, and this finding may be related to opioid hyporesponsiveness in experimental DNP[119]. Increased norepinephrine and 5HT levels in the spinal cord, as well as, augmented expression of norepinephrine and 5HT in RVM neurons

was also demonstrated in diabetic rats[117]. Considering the facilitatory role of serotoninergic and noradrenergic descending modulation during chronic pain, these changes may probably account for enhanced pain during diabetic neuropathy[117]. There is also clinical evidence for misbalance between excitatory and inhibitory neurotransmitters in the CNS of diabetic patients with positive symptoms of neuropathy. In this regard, it has been found reduced levels of GABA and higher levels of glutamate in the posterior insula of diabetic patients, as well as a higher glutamate/GABA ratio within the thalamus[120]. These changes may contribute to pain development in DNP, but further studies are necessary to determine their clinical significance.

TREATMENT OF DNP

DNP continues to represent a therapeutic challenge as its pathophysiology is not yet fully understood and pain relief is still unsatisfactory. The pharmacological treatments, with exception to those targeted to the glycemic control, are symptomatic, not focused on the pathophysiological mechanisms, limited by side effects[3,121] and by the development of tolerance[121].

A wide variety of drugs, used alone or in combination, has been shown to significantly reduce neuropathic pain compared with placebo in randomized controlled trials, but pain relief remains inadequate for most patients[122]. Generally, in clinical trials, treatment is considered successful if patients would obtain 50% of reduction in the pain level[123-125] associated with some additional beneficial effects on sleep, fatigue, depression and quality of life[125]. Thus, the management of this condition basically consists of excluding other causes of painful peripheral neuropathy, improving glycemic control as a prophylactic therapy and using medications to alleviate pain[126].

Despite of multimodal and multidisciplinary approaches to the treatment, the primary pathway is pharmacologically based[127]. Three different agents have regulatory approval in the United States for the treatment of DNP: pregabalin, duloxetine and tapentadol[11,128]. However, as pain relief is still suboptimal and challenging for clinicians[95], drugs from various pharmacological classes have been used and some of them are included in this review.

Anticonvulsants

Pregabalin was the first anticonvulsant to receive approval from the Food and Drug Administration (FDA) for the treatment of postherpetic neuralgia, DNP[129,130] and neuropathic pain after spinal cord injury[131]. Pregabalin is a GABA analogue that selectively binds to pre-synaptic voltage-gated calcium channels containing the α2δ subunit in the brain and spinal cord, causing inhibition of the release of excitatory neurotransmitters[128,132]. Moreover, $\alpha 2\delta 1$ subunits are responsible for increasing the functional expression of these channels, as a consequence of increased trafficking. Thus, the analgesic action of pregabalin is also proposed to be the result of impaired trafficking of $\alpha 2\delta 1$ subunit with a consequent diminished expression of functional calcium channels[133].

Several clinical trials evaluating pregabalin in DNP showed efficacy in the management of this condition[3,134,135] with a number needed to treat (NNT) of 6.3[125]. In addition to its analgesic effects, pregabalin presents anxiolytic activity[132,135] and it has a beneficial effect on sleep and quality of life[132], contributing, therefore, to improve the general condition of the patients. The side effects include dizziness, somnolence, peripheral edema, headache and weight gain[3].

Some guidelines have also recommended gabapentin to treat DNP[136]. Besides pregabalin, gabapentin is the only other anticonvulsant drug that demonstrated efficacy in the treatment of this condition[128] with an NNT of 5.8[137]. Gabapentin and pregabalin have a similar mechanism of action and the first is licensed for neuropathic pain in the United Kingdom, but not in the United States[128]. Some clinical trials have suggested that gabapentin and pregabalin present better analgesic efficacy than tricyclic antidepressants or opioids[138] and other important aspects of these drugs include their tolerability and lack of serious toxicity[139].

Antidepressants

Antidepressants represent the first line drugs in DNP management. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is rated level A for efficacy and is approved in the United States for the treatment of this condition. Additionally, some clinical trials have pointed out the effectiveness of duloxetine in other chronic pain conditions, such as fibromyalgia and chronic musculoskeletal pain[140,141].

Results from a meta-analysis that included randomized, double blind, placebo controlled studies in patients with DNP showed the superiority of duloxetine over placebo in reduction of pain severity and in Patient Global Impression of Improvement/Change, as well as efficacy similar to gabapentin and pregabalin[142]. Moreover, in a 2-wk open-label randomized trial in diabetic patients poorly responsive to gabapentin, duloxetine was able to reduce the pain score to levels similar to those achieved with pregabalin[143,144]. Furthermore, analgesic efficacy of duloxetine in the treatment of DNP is maintained over a 6-mo period[145], reinforcing its importance as a treatment option for this condition. The NNT for duloxetine varies from 1.3 to 5.1 in DNP patients[146,147], which experience more frequently nausea, somnolence and dizziness as side effects[146].

Venlafaxine is also a selective serotonin and noradrenaline reuptake inhibitor, that predominantly inhibits serotonin reuptake at low doses and noradrenaline at higher doses[148]. Venlafaxine was also shown to be effective in reducing pain intensity in diabetic neuropathic patients[149], with an NNT between 2.2 and 5.1 and a number needed to harm (NNH) of 9.6, to minor adverse effects, and of 16.2, for major adverse effects[150].

Tricyclic antidepressants can also be an alternative to

treat DNP[151]. Amitriptyline was shown to be as effective as gabapentin in a direct meta-analysis study[152] and as duloxetine in a randomized, double-blind, crossover trial[153]. Likewise, nortriptyline was reported as being as effective as gabapentin in attenuating neuropathic pain in a double-blind crossover trial enrolling diabetic patients[154].

Tricyclic antidepressants are estimated to have an NNT of 1.3[151,155], and an NNH from 4.2 to 10.7[151] in DNP. The most common side effects related to the use of these drugs are dry mouth, postural hypotension, arrhythmias, cognitive impairment, constipation and urinary retention, which are more frequently observed after amitriptyline than nortriptyline treatment[155].

Opioids

Opioids are recommended to be used as second or third line treatment for DNP[3,151]. One multicenter, randomized, placebo-controlled study reported the tramadol effectiveness to significantly improve scores on physical and social functioning ratings in patients with DNP, but beneath some side effects such as nausea, constipation, headache and somnolence[156]. Morphine was also shown to be effective in reducing mean daily pain scores related to diabetic neuropathy and postherpetic neuralgia[128,157]. Moreover, results of clinical trials indicated that diabetic neuropathic patients experienced a significant reduction in pain intensity and an improvement on quality of life during oxycodone treatment, compared to placebo-exposed group[158,159]. Besides, oxycodone improved gabapentin but not the pregabalin effectiveness in promoting DNP relief[160,161].

The clinical evidence for the effectiveness of opioids in the control of DNP is corroborated by some pre-clinical data, which have reported the effectiveness of morphine[162,163] and buprenorphine[164] in reducing thermal or mechanical hypersensitivity in DNP animal models.

There is also evidence that the anti-hyperalgesic effect of opioids is improved by the association with some drugs, such as the antidepressants amitriptyline, moclobemide and reboxetine[165]. In line with this idea, new molecules that integrate additional mechanisms to the opioid receptor agonism have been shown efficacy in reducing nociceptive behavior in animal models of DNP, such as the cebranopadol, a nociceptin/orphanin FQ peptide and opioid receptor agonist[166], and the mu-opioid receptor agonist and norepinephrine reuptake inhibitor, tapentadol[162,167]. The latter was approved by FDA for DNP treatment since 2012[11]. Tapentadol has been shown to be effective in the management of different types of chronic pain, including osteoarthritis knee pain, low back pain and DNP, with a tolerable safety profile[168,169]. Specifically concerning DNP, a randomized-withdrawal, placebo-controlled trial reported reduction of at least 30% in pain intensity in about 50% of the patients that received tapentadol[170]. Similar data were obtained in a recent clinical trial in diabetic neuropathic patients with moderate to severe pain, which experienced nausea (21.1%) and vomiting (12.7%) as side effects[171].

Others agents

The drugs discussed below are currently associated to the pharmacological treatments already described according to the patients' symptoms and needs in order to achieve a better relief of pain in DNP conditions. However, further studies are necessary, specially controlled clinical trials, to determine the more efficacious, safe and successful combinations to be applied in the management of DNP[128].

Capsaicin topical cream: Topical agents may be associated with fewer and less clinically significant adverse events than systemic agents[172]. In addition, the possibilities of drug interactions are markedly reduced with the use of local treatments, which represent good options for patients with multiple medical problems[128]. The capsaicin cream has been shown to be effective in the treatment of neuropathic conditions[150] and is approved for topical relief of neuropathic pain[128]. Capsaicin is the pungent component of hot chilli peppers[11] and an agonist of the transient receptor potential vanilloid 1. This receptor is a ligand-gated, nonselective cation channel, predominantly expressed on unmyelinated C nerve fibers[173], which, after repeated exposure to topical capsaicin, are depleted of their content of substance P and other neurotransmitters[173,174]. The C fibers depletion and desensitization reduce painful stimuli transmission from peripheral nerves to the central nervous system[173]. Some clinical trials have demonstrated the effectiveness of low-concentration (from 0.025% to 0.075%) capsaicin cream in DNP[11,174,175]. Higher concentrations are not indicated because of desensitization of nociceptive sensory nerve endings, which may increase the risk of skin injuries in DNP patients[173,174]. Some adverse effects include itching, stinging, erythema, transient burning sensation and initial pain at the application site, that diminishes with repeated use[132,175], leading many patients to withdraw from the treatment[128,173].

Lidocaine patch: Lidocaine patches act as peripheral analgesics with minimal systemic absorption and are used in combination with other analgesic drugs[132,172]. Lidocaine blocks sodium channels and counteracts the hyperexcitability of peripheral nociceptors that contributes to neuropathic pain[132,176]. The blockade reduces ectopic discharges and raises the peripheral sensory neuron discharge threshold[176]. The few DNP clinical trials that compared topical lidocaine with other relevant interventions suggested that the effects in pain reduction are comparable to other drugs, such as capsaicin, gabapentin, amitriptyline[172] and pregabalin[172,174]. Adverse events include local irritation[172], contact dermatitis and itching[132].

Alpha lipoic acid: The benefit provided by alpha

lipoic acid (ALA) in the treatment of DNP possibly is due to its direct effects on the neuropathy, by reducing the oxidative stress, which has been defined as an important factor in the physiopatology of the diabetic neuropathy[122]. Its antioxidant and anti-inflammatory actions may contribute to an all-round improvement of diabetic neuropathy symptoms[135]. In some clinical trials that evaluated ALA effect in diabetic patients, pain was not a primary end point. However, they have shown a moderate benefit in terms of pain reduction[132]. In a randomized double-blinded trial, ALA-treated patients reported a greater reduction in neuropathic pain when compared to placebo-treated subjects[122]. Compared to several drugs currently in use for DNP treatment, ALA has fewer side effects[30], being nausea and vomiting the most common[132].

Isosorbide dinitrate spray: Isosorbide dinitrate is a nitric oxide-dependent vasodilator with effects on both arteries and veins[177]. The improvement of pain and burning sensation could be associated with the increased generation of nitric oxide, improving microvascular blood flow[178]. In a clinical trial with diabetic patients, the isosorbide dinitrate spray reduced overall neuropathic pain and burning sensation in about 50% of the patients, which also reported improvement in their quality of life, with improvements in sleep, mobility and mood[178,179].

Final considerations about DNP treatment: Besides the fact of many diabetic complications can be reduced with improved blood glucose control and other lifestyle interventions[132,150], such as quit smoking and reducing alcohol consumption[150], the efficacy of these measures, as well as the pharmacological treatments on DNP are not predictable. The medications rated as level A based on their efficacy are able to reduce pain and improve some aspects of patients' quality of life, but are not able to fully eliminate pain or prevent/revert the neuropathy. Even their combination does not result in satisfactory pain control, being the best improvement in pain, restricted to 50% of relief for the majority of the patients. Considering the available pharmacological options, DNP treatment has to be based mainly on patients' symptoms, pain level and tolerance of side effects.

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