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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

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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.

REFERENCES

1 **International Diabetes Federation**. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation, 2013

2 **Boulton AJ**, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; **28**: 956-962 [PMID: 15793206 DOI: 10.2337/diacare.28.4.956]

3 **Tesfaye S**, Boulton AJ, Dickenson AH. Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. *Diabetes Care* 2013; **36**: 2456-2465 [PMID: 23970715 DOI: 10.2337/dc12-1964]

4 **Boulton AJ**, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. *N Engl J Med* 2004; **351**: 48-55 [PMID: 15229307 DOI: 10.1056/NEJMcp032966]

5 **Tesfaye S**, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, Witte DR, Fuller JH. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005; **352**: 341-350 [PMID: 15673800 DOI: 10.1056/NEJMoa032782]

6 **Low PA**, Dotson RM. Symptomatic treatment of painful neuropathy. *JAMA* 1998; **280**: 1863-1864 [PMID: 9846782 DOI: 10.1001/jama.280.21.1863]

7 **Harris M**, Eastman R, Cowie C. Symptoms of sensory neuropathy in adults with NIDDM in the U.S. population. *Diabetes Care* 1993; **16**: 1446-1452 [PMID: 8299433 DOI: 10.2337/diacare.16.11.1446]

8 **Bansal V**, Kalita J, Misra UK. Diabetic neuropathy. *Postgrad Med J* 2006; **82**: 95-100 [PMID: 16461471]

9 **Quattrini C**, Tesfaye S. Understanding the impact of painful diabetic neuropathy. *Diabetes Metab Res Rev* 2003; **19** Suppl 1: S2-S8 [PMID: 12577252 DOI: 10.1002/dmrr.360]

10 **Gore M**, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. *J Pain Symptom Manage* 2005; **30**: 374-385 [PMID: 16256902 DOI: 10.1016/j.jpainsymman.2005.04.009]

11 **Freeman R**. New and developing drugs for the treatment of neuropathic pain in diabetes. *Curr Diab Rep* 2013; **13**: 500-508 [PMID: 23771401 DOI: 10.1007/s11892-013-0396-6]

12 **Sorensen L**, Molyneaux L, Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes. *Diabetes Care* 2006; **29**: 883-887 [PMID: 16567832 DOI: 10.2337/diacare.29.04.06.dc05-2180]

13 **Young RJ**, Zhou YQ, Rodriguez E, Prescott RJ, Ewing DJ, Clarke BF. Variable relationship between peripheral somatic and autonomic neuropathy in patients with different syndromes of diabetic polyneuropathy. *Diabetes* 1986; **35**: 192-197 [PMID: 3002887 DOI: 10.2337/diab.35.2.192]

14 **Dobretsov M**, Hastings SL, Romanovsky D, Stimers JR, Zhang JM. Mechanical hyperalgesia in rat models of systemic and local hyperglycemia. *Brain Res* 2003; **960**: 174-183 [PMID: 12505670 DOI: 10.1016/S0006-8993(02)03828-3]

15 **Oyibo SO**, Prasad YD, Jackson NJ, Jude EB, Boulton AJ. The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: a pilot study. *Diabet Med* 2002; **19**: 870-873 [PMID: 12358878 DOI: 10.1046/j.1464-5491.2002.00801.x]

16 **Romanovsky D**, Wang J, Al-Chaer ED, Stimers JR, Dobretsov M. Comparison of metabolic and neuropathy profiles of rats with streptozotocin-induced overt and moderate insulinopenia. *Neuroscience* 2010; **170**: 337-347 [PMID: 20600635 DOI: 10.1016/j.neuroscience.2010.06.059]

17 **Sheetz MJ**, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA* 2002; **288**: 2579-2588 [PMID: 12444865 DOI: 10.1001/jama.288.20.2579]

18 **Baynes JW**, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* 1999; **48**: 1-9 [PMID: 9892215 DOI: 10.2337/diabetes.48.1.1]

19 **Oates PJ**. Polyol pathway and diabetic peripheral neuropathy. *Int Rev Neurobiol* 2002; **50**: 325-392 [PMID: 12198816]

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

21 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820 [PMID: 11742414 DOI: 10.1038/414813a]

22 **Giacco F**, Brownlee M. Oxidative stress and diabetic complications. *Circ Res* 2010; **107**: 1058-1070 [PMID: 21030723 DOI: 10.1161/CIRCRESAHA.110.223545]

23 **Baynes JW**. Role of oxidative stress in development of complications in diabetes. *Diabetes* 1991; **40**: 405-412 [PMID: 2010041 DOI: 10.2337/diab.40.4.405]

24 **Obrosova IG**, Mabley JG, Zsengellér Z, Charniauskaya T, Abatan OI, Groves JT, Szabó C. Role for nitrosative stress in diabetic neuropathy: evidence from studies with a peroxynitrite

decomposition catalyst. *FASEB J* 2005; **19**: 401-403 [PMID: 15611153]
25 **Drel VR**, Pacher P, Vareniuk I, Pavlov I, Ilnytska O, Lyzogubov VV, Tibrewala J, Groves JT, Obrosova IG. A peroxynitrite decomposition catalyst counteracts sensory neuropathy in streptozotocin-diabetic mice. *Eur J Pharmacol* 2007; **569**: 48-58 [PMID: 17644085 DOI: 10.1016/j.ejphar.2007.05.055]
26 **Vareniuk I**, Pavlov IA, Drel VR, Lyzogubov VV, Ilnytska O, Bell SR, Tibrewala J, Groves JT, Obrosova IG. Nitrosative stress and peripheral diabetic neuropathy in leptin-deficient (ob/ob) mice. *Exp Neurol* 2007; **205**: 425-436 [PMID: 17475250 DOI: 10.1016/j.expneurol.2007.03.019]
27 **Cunha JM**, Jolivalt CG, Ramos KM, Gregory JA, Calcutt NA, Mizisin AP. Elevated lipid peroxidation and DNA oxidation in nerve from diabetic rats: effects of aldose reductase inhibition, insulin, and neurotrophic factors. *Metabolism* 2008; **57**: 873-881 [PMID: 18555826 DOI: 10.1016/j.metabol.2008.01.021]
28 **Ozkul A**, Ayhan M, Yenisey C, Akyol A, Guney E, Ergin FA. The role of oxidative stress and endothelial injury in diabetic neuropathy and neuropathic pain. *Neuro Endocrinol Lett* 2010; **31**: 261-264 [PMID: 20424576]
29 **Ziegler D**, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, Samigullin R, Tritschler H, Munzel U, Maus J, Schütte K, Dyck PJ. Efficacy and safety of antioxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. *Diabetes Care* 2011; **34**: 2054-2060 [PMID: 21775755 DOI: 10.2337/dc11-0503]
30 **Mijnhout GS**, Alkhalaf A, Kleefstra N, Bilo HJ. Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes? *Neth J Med* 2010; **68**: 158-162 [PMID: 20421656]
31 **Ruessmann HJ**. Switching from pathogenetic treatment with alpha-lipoic acid to gabapentin and other analgesics in painful diabetic neuropathy: a real-world study in outpatients. *J Diabetes Complications* 2009; **23**: 174-177 [PMID: 18403218 DOI: 10.1016/j.jdiacomp.2008.02.002]
32 **Tang J**, Wingerchuk DM, Crum BA, Rubin DI, Demaerschalk BM. Alpha-lipoic acid may improve symptomatic diabetic polyneuropathy. *Neurologist* 2007; **13**: 164-167 [PMID: 17495764 DOI: 10.1097/01.nrl.0000263703.78318.2b]
33 **Arora S**, Pomposelli F, LoGerfo FW, Veves A. Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely after successful lower extremity revascularization. *J Vasc Surg* 2002; **35**: 501-505 [PMID: 11877698 DOI: 10.1067/mva.2002.121126]
34 **Doupis J**, Lyons TE, Wu S, Gnardellis C, Dinh T, Veves A. Microvascular reactivity and inflammatory cytokines in painful and painless peripheral diabetic neuropathy. *J Clin Endocrinol Metab* 2009; **94**: 2157-2163 [PMID: 19276232 DOI: 10.1210/jc.2008-2385]
35 **Cameron NE**, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* 2001; **44**: 1973-1988 [PMID: 11719828 DOI: 10.1007/s001250100001]
36 **Tuck RR**, Schmelzer JD, Low PA. Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy. *Brain* 1984; **107** (Pt 3): 935-950 [PMID: 6478183 DOI: 10.1093/brain/107.3.935]
37 **Jin HY**, Lee KA, Song SK, Liu WJ, Choi JH, Song CH, Baek HS, Park TS. Sulodexide prevents peripheral nerve damage in streptozotocin induced diabetic rats. *Eur J Pharmacol* 2012; **674**: 217-226 [PMID: 21641343 DOI: 10.1016/j.ejphar.2011.05.059]
38 **Malik RA**, Tesfaye S, Thompson SD, Veves A, Sharma AK, Boulton AJ, Ward JD. Endoneurial localisation of microvascular damage in human diabetic neuropathy. *Diabetologia* 1993; **36**: 454-459 [PMID: 8314451 DOI: 10.1007/BF00402283]
39 **Pavy-Le Traon A**, Fontaine S, Tap G, Guidolin B, Senard JM, Hanaire H. Cardiovascular autonomic neuropathy and other complications in type 1 diabetes. *Clin Auton Res* 2010; **20**: 153-160 [PMID: 20354891 DOI: 10.1007/s10286-010-0062-X]
40 **Czyzyk A**. [Epidemiology of vascular disease in diabetes mellitus]. *Pol Arch Med Wewn* 1986; **76**: 129-136 [PMID: 3575142]
41 **Fuchs D**, Birklein F, Reeh PW, Sauer SK. Sensitized peripheral nociception in experimental diabetes of the rat. *Pain* 2010; **151**: 496-505 [PMID: 20832942 DOI: 10.1016/j.pain.2010.08.010]
42 **Eaton SE**, Harris ND, Ibrahim S, Patel KA, Selmi F, Radatz M, Ward JD, Tesfaye S. Increased sural nerve epineurial blood flow in human subjects with painful diabetic neuropathy. *Diabetologia* 2003; **46**: 934-939 [PMID: 12819899 DOI: 10.1007/s00125-003-1127-3]
43 **Archer AG**, Roberts VC, Watkins PJ. Blood flow patterns in painful diabetic neuropathy. *Diabetologia* 1984; **27**: 563-567 [PMID: 6530051 DOI: 10.1007/BF00276968]
44 **Jelicic Kadic A**, Boric M, Vidak M, Ferhatovic L, Puljak L. Changes in epidermal thickness and cutaneous innervation during maturation in long-term diabetes. *J Tissue Viability* 2014; **23**: 7-12 [PMID: 24361118 DOI: 10.1016/j.jtv.2013.11.002]
45 **Shun CT**, Chang YC, Wu HP, Hsieh SC, Lin WM, Lin YH, Tai TY, Hsieh ST. Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. *Brain* 2004; **127**: 1593-1605 [PMID: 15128619 DOI: 10.1093/brain/awh180]
46 **Said G**, Baudoin D, Toyooka K. Sensory loss, pains, motor deficit and axonal regeneration in length-dependent diabetic polyneuropathy. *J Neurol* 2008; **255**: 1693-1702 [PMID: 18825430 DOI: 10.1007/s00415-008-0999-z]
47 **Quattrini C**, Harris ND, Malik RA, Tesfaye S. Impaired skin microvascular reactivity in painful diabetic neuropathy. *Diabetes Care* 2007; **30**: 655-659 [PMID: 17327336 DOI: 10.2337/dc06-2154]
48 **Inkster ME**, Cotter MA, Cameron NE. Treatment with the xanthine oxidase inhibitor, allopurinol, improves nerve and vascular function in diabetic rats. *Eur J Pharmacol* 2007; **561**: 63-71 [PMID: 17291486 DOI: 10.1016/j.ejphar.2006.12.029]
49 **Brown MJ**, Asbury AK. Diabetic neuropathy. *Ann Neurol* 1984; **15**: 2-12 [PMID: 6370098 DOI: 10.1002/ana.410150103]
50 **Said G**, Slama G, Selva J. Progressive centripetal degeneration of axons in small fibre diabetic polyneuropathy. *Brain* 1983; **106** (Pt 4): 791-807 [PMID: 6652463 DOI: 10.1093/brain/106.4.791]
51 **Stewart JD**, Low PA, Fealey RD. Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. *Muscle Nerve* 1992; **15**: 661-665 [PMID: 1324425 DOI: 10.1002/mus.880150605]
52 **Dickenson AH**, Matthews EA, Suzuki R. Neurobiology of neuropathic pain: mode of action of anticonvulsants. *Eur J Pain* 2002; **6** Suppl A: 51-60 [PMID: 11888242]
53 **Ochoa JL**, Torebjörk HE. Paraesthesiae from ectopic impulse generation in human sensory nerves. *Brain* 1980; **103**: 835-853 [PMID: 6254609 DOI: 10.1093/brain/103.4.835]
54 **Black JA**, Cummins TR, Plumpton C, Chen YH, Hormuzdiar W, Clare JJ, Waxman SG. Upregulation of a silent sodium channel after peripheral, but not central, nerve injury in DRG neurons. *J Neurophysiol* 1999; **82**: 2776-2785 [PMID: 10561444]
55 **He XH**, Zang Y, Chen X, Pang RP, Xu JT, Zhou X, Wei XH, Li YY, Xin WJ, Qin ZH, Liu XG. TNF-α contributes to up-regulation of Nav1.3 and Nav1.8 in DRG neurons following motor fiber injury. *Pain* 2010; **151**: 266-279 [PMID: 20638792 DOI: 10.1016/j.pain.2010.06.005]
56 **Roy ML**, Narahashi T. Differential properties of tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels in rat dorsal root ganglion neurons. *J Neurosci* 1992; **12**: 2104-2111 [PMID: 1318956]
57 **Felts PA**, Yokoyama S, Dib-Hajj S, Black JA, Waxman SG. Sodium channel alpha-subunit mRNAs I, II, III, NaG, Na6 and hNE (PN1): different expression patterns in developing rat nervous system. *Brain Res Mol Brain Res* 1997; **45**: 71-82 [PMID: 9105672 DOI: 10.1016/S0169-328X(96)00241-0]
58 **Ogata N**, Ohishi Y. Molecular diversity of structure and function of the voltage-gated Na+ channels. *Jpn J Pharmacol* 2002; **88**: 365-377 [PMID: 12046980 DOI: 10.1254/jjp.88.365]
59 **Galloway C**, Chattopadhyay M. Increases in inflammatory mediators in DRG implicate in the pathogenesis of painful neuropathy in Type 2 diabetes. *Cytokine* 2013; **63**: 1-5 [PMID:

23664770 DOI: 10.1016/j.cyto.2013.04.009]
60 **Hong S**, Morrow TJ, Paulson PE, Isom LL, Wiley JW. Early painful diabetic neuropathy is associated with differential changes in tetrodotoxin-sensitive and -resistant sodium channels in dorsal root ganglion neurons in the rat. *J Biol Chem* 2004; **279**: 29341-29350 [PMID: 15123645 DOI: 10.1074/jbc.M404167200]
61 **Cheng KI**, Wang HC, Chuang YT, Chou CW, Tu HP, Yu YC, Chang LL, Lai CS. Persistent mechanical allodynia positively correlates with an increase in activated microglia and increased P-p38 mitogen-activated protein kinase activation in streptozotocin-induced diabetic rats. *Eur J Pain* 2014; **18**: 162-173 [PMID: 23868758 DOI: 10.1002/j.1532-2149.2013.00356.x]
62 **Craner MJ**, Klein JP, Renganathan M, Black JA, Waxman SG. Changes of sodium channel expression in experimental painful diabetic neuropathy. *Ann Neurol* 2002; **52**: 786-792 [PMID: 12447933 DOI: 10.1002/ana.10364]
63 **Akopian AN**, Sivilotti L, Wood JN. A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature* 1996; **379**: 257-262 [PMID: 8538791 DOI: 10.1038/379257a0]
64 **Herzog RI**, Cummins TR, Waxman SG. Persistent TTX-resistant Na+ current affects resting potential and response to depolarization in simulated spinal sensory neurons. *J Neurophysiol* 2001; **86**: 1351-1364 [PMID: 11535682]
65 **Sun W**, Miao B, Wang XC, Duan JH, Wang WT, Kuang F, Xie RG, Xing JL, Xu H, Song XJ, Luo C, Hu SJ. Reduced conduction failure of the main axon of polymodal nociceptive C-fibres contributes to painful diabetic neuropathy in rats. *Brain* 2012; **135**: 359-375 [PMID: 22271663 DOI: 10.1093/brain/awr345]
66 **Singh JN**, Jain G, Sharma SS. In vitro hyperglycemia enhances sodium currents in dorsal root ganglion neurons: an effect attenuated by carbamazepine. *Neuroscience* 2013; **232**: 64-73 [PMID: 23262239 DOI: 10.1016/j.neuroscience.2012.12.011]
67 **Misawa S**, Sakurai K, Shibuya K, Isose S, Kanai K, Ogino J, Ishikawa K, Kuwabara S. Neuropathic pain is associated with increased nodal persistent Na(+) currents in human diabetic neuropathy. *J Peripher Nerv Syst* 2009; **14**: 279-284 [PMID: 20021569 DOI: 10.1111/j.1529-8027.2009.00239.x]
68 **Hoeijmakers JG**, Faber CG, Merkies IS, Waxman SG. Channelopathies, painful neuropathy, and diabetes: which way does the causal arrow point? *Trends Mol Med* 2014; **20**: 544-550 [PMID: 25008557 DOI: 10.1016/j.molmed.2014.06.003]
69 **Han C**, Hoeijmakers JG, Ahn HS, Zhao P, Shah P, Lauria G, Gerrits MM, te Morsche RH, Dib-Hajj SD, Drenth JP, Faber CG, Merkies IS, Waxman SG. Nav1.7-related small fiber neuropathy: impaired slow-inactivation and DRG neuron hyperexcitability. *Neurology* 2012; **78**: 1635-1643 [PMID: 22539570 DOI: 10.1212/WNL.0b013e3182574f12]
70 **Bierhaus A**, Fleming T, Stoyanov S, Leffler A, Babes A, Neacsu C, Sauer SK, Eberhardt M, Schnölzer M, Lasitschka F, Neuhuber WL, Kichko TI, Konrade I, Elvert R, Mier W, Pirags V, Lukic IK, Morcos M, Dehmer T, Rabbani N, Thornalley PJ, Edelstein D, Nau C, Forbes J, Humpert PM, Schwaninger M, Ziegler D, Stern DM, Cooper ME, Haberkorn U, Brownlee M, Reeh PW, Nawroth PP. Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. *Nat Med* 2012; **18**: 926-933 [PMID: 22581285 DOI: 10.1038/nm.2750]
71 **Wood H**. Diabetes: Methylglyoxal mediates hyperalgesia in patients with painful diabetic neuropathy. *Nat Rev Neurol* 2012; **8**: 354 [PMID: 22688780 DOI: 10.1038/nrneurol.2012.103]
72 **Han Y**, Randell E, Vasdev S, Gill V, Gadag V, Newhook LA, Grant M, Hagerty D. Plasma methylglyoxal and glyoxal are elevated and related to early membrane alteration in young, complication-free patients with Type 1 diabetes. *Mol Cell Biochem* 2007; **305**: 123-131 [PMID: 17594057 DOI: 10.1007/s11010-007-9535-1]
73 **Andersson DA**, Gentry C, Light E, Vastani N, Vallortigara J, Bierhaus A, Fleming T, Bevan S. Methylglyoxal evokes pain by stimulating TRPA1. *PLoS One* 2013; **8**: e77986 [PMID: 24167592 DOI: 10.1371/journal.pone.0077986]
74 **Thornalley PJ**. Glycation in diabetic neuropathy: characteristics, consequences, causes, and therapeutic options. *Int Rev Neurobiol* 2002; **50**: 37-57 [PMID: 12198817 DOI: 10.1016/S0074-7742(02)50072-6]
75 **Hall KE**, Liu J, Sima AA, Wiley JW. Impaired inhibitory G-protein function contributes to increased calcium currents in rats with diabetic neuropathy. *J Neurophysiol* 2001; **86**: 760-770 [PMID: 11495948]
76 **White DM**, Zimmermann M. The bradykinin-induced release of substance P from nerve fibre endings in the rat saphenous nerve neuroma is not related to electrophysiological excitation. *Neurosci Lett* 1988; **92**: 108-113 [PMID: 2460804 DOI: 10.1016/0304-3940(88)90751-3]
77 **Hall KE**, Sima AA, Wiley JW. Opiate-mediated inhibition of calcium signaling is decreased in dorsal root ganglion neurons from the diabetic BB/W rat. *J Clin Invest* 1996; **97**: 1165-1172 [PMID: 8636427 DOI: 10.1172/JCI118530]
78 **Jagodic MM**, Pathirathna S, Nelson MT, Mancuso S, Joksovic PM, Rosenberg ER, Bayliss DA, Jevtovic-Todorovic V, Todorovic SM. Cell-specific alterations of T-type calcium current in painful diabetic neuropathy enhance excitability of sensory neurons. *J Neurosci* 2007; **27**: 3305-3316 [PMID: 17376991 DOI: 10.1523/JNEUROSCI.4866-06.2007]
79 **Messinger RB**, Naik AK, Jagodic MM, Nelson MT, Lee WY, Choe WJ, Orestes P, Latham JR, Todorovic SM, Jevtovic-Todorovic V. In vivo silencing of the Ca(V)3.2 T-type calcium channels in sensory neurons alleviates hyperalgesia in rats with streptozocin-induced diabetic neuropathy. *Pain* 2009; **145**: 184-195 [PMID: 19577366 DOI: 10.1016/j.pain.2009.06.012]
80 **Mendis S**, Kumarasunderam R. The effect of daily consumption of coconut fat and soya-bean fat on plasma lipids and lipoproteins of young normolipidaemic men. *Br J Nutr* 1990; **63**: 547-552 [PMID: 2383532 DOI: 10.2337/db13-0813]
81 **Kim J**, Wei DS, Hoffman DA. Kv4 potassium channel subunits control action potential repolarization and frequency-dependent broadening in rat hippocampal CA1 pyramidal neurones. *J Physiol* 2005; **569**: 41-57 [PMID: 16141270 DOI: 10.1113/jphysiol.2005.095042]
82 **Everill B**, Rizzo MA, Kocsis JD. Morphologically identified cutaneous afferent DRG neurons express three different potassium currents in varying proportions. *J Neurophysiol* 1998; **79**: 1814-1824 [PMID: 9535950]
83 **Vydyanathan A**, Wu ZZ, Chen SR, Pan HL. A-type voltage-gated K+ currents influence firing properties of isolectin B4-positive but not isolectin B4-negative primary sensory neurons. *J Neurophysiol* 2005; **93**: 3401-3409 [PMID: 15647393 DOI: 10.1152/jn.01267.2004]
84 **Cao XH**, Byun HS, Chen SR, Cai YQ, Pan HL. Reduction in voltage-gated K+ channel activity in primary sensory neurons in painful diabetic neuropathy: role of brain-derived neurotrophic factor. *J Neurochem* 2010; **114**: 1460-1475 [PMID: 20557422 DOI: 10.1111/j.1471-4159.2010.06863.x]
85 **Mika J**, Zychowska M, Popiolek-Barczyk K, Rojewska E, Przewlocka B. Importance of glial activation in neuropathic pain. *Eur J Pharmacol* 2013; **716**: 106-119 [PMID: 23500198 DOI: 10.1016/j.ejphar.2013.01.072]
86 **Kettenmann H**, Verkhratsky A. Neuroglia: the 150 years after. *Trends Neurosci* 2008; **31**: 653-659 [PMID: 18945498 DOI: 10.1016/j.tins.2008.09.003]
87 **Tsuda M**, Ueno H, Kataoka A, Tozaki-Saitoh H, Inoue K. Activation of dorsal horn microglia contributes to diabetes-induced tactile allodynia via extracellular signal-regulated protein kinase signaling. *Glia* 2008; **56**: 378-386 [PMID: 18186080 DOI: 10.1002/glia.20623]
88 **Wodarski R**, Clark AK, Grist J, Marchand F, Malcangio M. Gabapentin reverses microglial activation in the spinal cord of streptozotocin-induced diabetic rats. *Eur J Pain* 2009; **13**: 807-811 [PMID: 18977160 DOI: 10.1016/j.ejpain.2008.09.010]
89 **Toth CC**, Jedrzejewski NM, Ellis CL, Frey WH. Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain. *Mol Pain* 2010; **6**: 16 [PMID: 20236533 DOI: 10.1186/1744-8069-6-16]

90 **Suzuki N**, Hasegawa-Moriyama M, Takahashi Y, Kamikubo Y, Sakurai T, Inada E. Lidocaine attenuates the development of diabetic-induced tactile allodynia by inhibiting microglial activation. *Anesth Analg* 2011; **113**: 941-946 [PMID: 21788310 DOI: 10.1213/ANE.0b013e31822827a2]

91 **Crown ED**. The role of mitogen activated protein kinase signaling in microglia and neurons in the initiation and maintenance of chronic pain. *Exp Neurol* 2012; **234**: 330-339 [PMID: 22062045 DOI: 10.1016/j.expneurol.2011.10.019]

92 **Afsari ZH**, Renno WM, Abd-El-Basset E. Alteration of glial fibrillary acidic proteins immunoreactivity in astrocytes of the spinal cord diabetic rats. *Anat Rec* (Hoboken) 2008; **291**: 390-399 [PMID: 18360886 DOI: 10.1002/ar.20678]

93 **Chen SR**, Pan HL. Hypersensitivity of spinothalamic tract neurons associated with diabetic neuropathic pain in rats. *J Neurophysiol* 2002; **87**: 2726-2733 [PMID: 12037174]

94 **Maier C**, Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F, Gierthmühlen J, Flor H, Geber C, Huge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihöfner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uçeyler N, Valet M, Wasner G, Treede RD. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010; **150**: 439-450 [PMID: 20627413 DOI: 10.1016/j.pain.2010.05.002]

95 **Aslam A**, Singh J, Rajbhandari S. Pathogenesis of painful diabetic neuropathy. *Pain Res Treat* 2014; **2014**: 412041 [PMID: 24891949 DOI: 10.1155/2014/412041]

96 **Li JQ**, Chen SR, Chen H, Cai YQ, Pan HL. Regulation of increased glutamatergic input to spinal dorsal horn neurons by mGluR5 in diabetic neuropathic pain. *J Neurochem* 2010; **112**: 162-172 [PMID: 19840219 DOI: 10.1111/j.1471-4159.2009.06437.x]

97 **Wang XL**, Zhang HM, Chen SR, Pan HL. Altered synaptic input and GABAB receptor function in spinal superficial dorsal horn neurons in rats with diabetic neuropathy. *J Physiol* 2007; **579**: 849-861 [PMID: 17218355 DOI: 10.1113/jphysiol.2006.126102]

98 **Bai HP**, Liu P, Wu YM, Guo WY, Guo YX, Wang XL. Activation of spinal GABAB receptors normalizes N-methyl-D-aspartate receptor in diabetic neuropathy. *J Neurol Sci* 2014; **341**: 68-72 [PMID: 24787504 DOI: 10.1016/j.jns.2014.04.002]

99 **Kim JH**, Roberts DS, Hu Y, Lau GC, Brooks-Kayal AR, Farb DH, Russek SJ. Brain-derived neurotrophic factor uses CREB and Egr3 to regulate NMDA receptor levels in cortical neurons. *J Neurochem* 2012; **120**: 210-219 [PMID: 22035109 DOI: 10.1111/j.1471-4159.2011.07555.x]

100 **Sanchez AP**, Sharma K. Transcription factors in the pathogenesis of diabetic nephropathy. *Expert Rev Mol Med* 2009; **11**: e13 [PMID: 19397838 DOI: 10.1017/S1462399409001057]

101 **Pérez-Garci E**, Gassmann M, Bettler B, Larkum ME. The GABAB1b isoform mediates long-lasting inhibition of dendritic Ca2+ spikes in layer 5 somatosensory pyramidal neurons. *Neuron* 2006; **50**: 603-616 [PMID: 16701210 DOI: 10.1016/j.neuron.2006.04.019]

102 **Sodickson DL**, Bean BP. GABAB receptor-activated inwardly rectifying potassium current in dissociated hippocampal CA3 neurons. *J Neurosci* 1996; **16**: 6374-6385 [PMID: 8815916]

103 **Silva M**, Amorim D, Almeida A, Tavares I, Pinto-Ribeiro F, Morgado C. Pronociceptive changes in the activity of rostroventromedial medulla (RVM) pain modulatory cells in the streptozotocin-diabetic rat. *Brain Res Bull* 2013; **96**: 39-44 [PMID: 23644033 DOI: 10.1016/j.brainresbull.2013.04.008]

104 **Chen X**, Levine JD. Hyper-responsivity in a subset of C-fiber nociceptors in a model of painful diabetic neuropathy in the rat. *Neuroscience* 2001; **102**: 185-192 [PMID: 11226682 DOI: 10.1016/S0306-4522(00)00454-1]

105 **Naderi A**, Asgari AR, Zahed R, Ghanbari A, Samandari R, Jorjani M. Estradiol attenuates spinal cord injury-related central pain by decreasing glutamate levels in thalamic VPL nucleus in male rats. *Metab Brain Dis* 2014; **29**: 763-770 [PMID: 24879046 DOI: 10.1007/s11011-014-9570-z]

106 **Paulson PE**, Wiley JW, Morrow TJ. Concurrent activation of the somatosensory forebrain and deactivation of periaqueductal gray associated with diabetes-induced neuropathic pain. *Exp Neurol* 2007; **208**: 305-313 [PMID: 17936273 DOI: 10.1016/j.expneurol.2007.09.001]

107 **Tseng MT**, Chiang MC, Chao CC, Tseng WY, Hsieh ST. fMRI evidence of degeneration-induced neuropathic pain in diabetes: enhanced limbic and striatal activations. *Hum Brain Mapp* 2013; **34**: 2733-2746 [PMID: 22522975 DOI: 10.1002/hbm.22105]

108 **Sorensen L**, Siddall PJ, Trenell MI, Yue DK. Differences in metabolites in pain-processing brain regions in patients with diabetes and painful neuropathy. *Diabetes Care* 2008; **31**: 980-981 [PMID: 18299445 DOI: 10.2337/dc07-2088]

109 **Auer DP**, Wilke M, Grabner A, Heidenreich JO, Bronisch T, Wetter TC. Reduced NAA in the thalamus and altered membrane and glial metabolism in schizophrenic patients detected by 1H-MRS and tissue segmentation. *Schizophr Res* 2001; **52**: 87-99 [PMID: 11595395 DOI: 10.1016/S0920-9964(01)00155-4]

110 **Selvarajah D**, Wilkinson ID, Gandhi R, Griffiths PD, Tesfaye S. Microvascular perfusion abnormalities of the Thalamus in painful but not painless diabetic polyneuropathy: a clue to the pathogenesis of pain in type 1 diabetes. *Diabetes Care* 2011; **34**: 718-720 [PMID: 21282344 DOI: 10.2337/dc10-1550]

111 **Li W**, Wang P, Li H. Upregulation of glutamatergic transmission in anterior cingulate cortex in the diabetic rats with neuropathic pain. *Neurosci Lett* 2014; **568**: 29-34 [PMID: 24686190 DOI: 10.1016/j.neulet.2014.03.038]

112 **Millan MJ**. Descending control of pain. *Prog Neurobiol* 2002; **66**: 355-474 [PMID: 12034378 DOI: 10.1016/S0301-0082(02)00009-6]

113 **Morgan MM**, Fields HL. Pronounced changes in the activity of nociceptive modulatory neurons in the rostral ventromedial medulla in response to prolonged thermal noxious stimuli. *J Neurophysiol* 1994; **72**: 1161-1170 [PMID: 7807201]

114 **Carlson JD**, Maire JJ, Martenson ME, Heinricher MM. Sensitization of pain-modulating neurons in the rostral ventromedial medulla after peripheral nerve injury. *J Neurosci* 2007; **27**: 13222-13231 [PMID: 18045916 DOI: 10.1523/JNEUROSCI.3715-07.2007]

115 **Sugino S**, Namiki A, Yamakage M. Genetic differences in response properties of rostral ventromedial medulla neurons to the μ-opioid receptor agonist DAMGO in mouse inbred strains. *Neurosci Lett* 2012; **517**: 107-112 [PMID: 22546603 DOI: 10.1016/j.neulet.2012.04.038]

116 **Bitar MS**, Bajic KT, Farook T, Thomas MI, Pilcher CW. Spinal cord noradrenergic dynamics in diabetic and hypercortisolaemic states. *Brain Res* 1999; **830**: 1-9 [PMID: 10350553 DOI: 10.1016/S0006-8993(99)01284-6]

117 **Morgado C**, Silva L, Pereira-Terra P, Tavares I. Changes in serotoninergic and noradrenergic descending pain pathways during painful diabetic neuropathy: the preventive action of IGF1. *Neurobiol Dis* 2011; **43**: 275-284 [PMID: 21515376 DOI: 10.1016/j.nbd.2011.04.001]

118 **Ezzeldin E**, Souror WA, El-Nahhas T, Soudi AN, Shahat AA. Biochemical and neurotransmitters changes associated with tramadol in streptozotocin-induced diabetes in rats. *Biomed Res Int* 2014; **2014**: 238780 [PMID: 24971322 DOI: 10.1155/2014/238780]

119 **Suh HW**, Song DK, Wie MB, Jung JS, Hong HE, Choi SR, Kim YH. The reduction of antinociceptive effect of morphine administered intraventricularly is correlated with the decrease of serotonin release from the spinal cord in streptozotocin-induced diabetic rats. *Gen Pharmacol* 1996; **27**: 445-450 [PMID: 8723523 DOI: 10.1016/0306-3623(95)02059-4]

120 **Petrou M**, Pop-Busui R, Foerster BR, Edden RA, Callaghan BC, Harte SE, Harris RE, Clauw DJ, Feldman EL. Altered excitation-inhibition balance in the brain of patients with diabetic neuropathy. *Acad Radiol* 2012; **19**: 607-612 [PMID: 22463961 DOI: 10.1016/j.acra.2012.02.004]

121 **Boyle J**, Eriksson ME, Gribble L, Gouni R, Johnsen S, Coppini DV, Kerr D. 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**: 2451-2458 [PMID: 22991449 DOI: 10.2337/dc12-0656]

122 **Singleton JR**, Smith AG. The diabetic neuropathies: practical and rational therapy. *Semin Neurol* 2012; **32**: 196-203 [PMID: 23117944 DOI: 10.1055/s-0032-1329195]

123 **Huizinga MM**, Peltier A. Painful Diabetic Neuropathy: A Management-Centered Review. *Clinical Diabetes* 2007; **25**: 6-15 [DOI: 10.2337/diaclin.25.1.6]

124 **Tanenberg RJ**. Diabetic Peripheral Neuropathy: Painful or Painless. *Hospital Physician* 2009; **45**: 1-8

125 **Moore RA**, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2014; **4**: CD007938 [PMID: 24771480 DOI: 10.1002/14651858.CD007938]

126 **Snedecor SJ**, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. *Pain Pract* 2014; **14**: 167-184 [PMID: 23534696 DOI: 10.1111/papr.12054]

127 **Hurley RW**, Lesley MR, Adams MC, Brummett CM, Wu CL. Pregabalin as a treatment for painful diabetic peripheral neuropathy: a meta-analysis. *Reg Anesth Pain Med* 2008; **33**: 389-394 [PMID: 18774507 DOI: 10.1016/j.rapm.2008.02.012]

128 **Peltier A**, Goutman SA, Callaghan BC. Painful diabetic neuropathy. *BMJ* 2014; **348**: g1799 [PMID: 24803311 DOI: 10.1136/bmj.g1799]

129 **Verma V**, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: evidences and possible mechanisms. *Curr Neuropharmacol* 2014; **12**: 44-56 [PMID: 24533015 DOI: 10.2174/1570159X1201140117162802]

130 **Blommel ML**, Blommel AL. Pregabalin: an antiepileptic agent useful for neuropathic pain. *Am J Health Syst Pharm* 2007; **64**: 1475-1482 [PMID: 17617497 DOI: 10.2146/ajhp060371]

131 **Guy S**, Mehta S, Leff L, Teasell R, Loh E. Anticonvulsant medication use for the management of pain following spinal cord injury: systematic review and effectiveness analysis. *Spinal Cord* 2014; **52**: 89-96 [PMID: 24296804 DOI: 10.1038/sc.2013.146]

132 **Zilliox L**, Russell JW. Treatment of diabetic sensory polyneuropathy. *Curr Treat Options Neurol* 2011; **13**: 143-159 [PMID: 21274758 DOI: 10.1007/s11940-011-0113-1]

133 **Stahl SM**, Porreca F, Taylor CP, Cheung R, Thorpe AJ, Clair A. The diverse therapeutic actions of pregabalin: is a single mechanism responsible for several pharmacological activities? *Trends Pharmacol Sci* 2013; **34**: 332-339 [PMID: 23642658 DOI: 10.1016/j.tips.2013.04.001]

134 **Zychowska M**, Rojewska E, Przewlocka B, Mika J. Mechanisms and pharmacology of diabetic neuropathy - experimental and clinical studies. *Pharmacol Rep* 2013; **65**: 1601-1610 [PMID: 24553008]

135 **Patel N**, Mishra V, Patel P, Dikshit RK. A study of the use of carbamazepine, pregabalin and alpha lipoic acid in patients of diabetic neuropathy. *J Diabetes Metab Disord* 2014; **13**: 62 [PMID: 24926454 DOI: 10.1186/2251-6581-13-62]

136 **Ziegler D**, Schneider E, Boess FG, Berggren L, Birklein F. Impact of comorbidities on pharmacotherapy of painful diabetic neuropathy in clinical practice. *J Diabetes Complications* 2014; **28**: 698-704 [PMID: 24862108 DOI: 10.1016/j.jdiacomp.2014.04.004]

137 **Moore A**, Wiffen P, Kalso E. Antiepileptic drugs for neuropathic pain and fibromyalgia. *JAMA* 2014; **312**: 182-183 [PMID: 25005656 DOI: 10.1001/jama.2014.6336]

138 **Gilron I**, Flatters SJL. Gabapentin and pregabalin for the treatment or neuropathic pain: A review of laboratory and clinical evidence. *Pain Res Manage* 2006; **11** Suppl A: S16A-29A

139 **Freeman R**, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 2008; **31**: 1448-1454 [PMID: 18356405 DOI: 10.2337/dc07-2105]

140 **Attal N**, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T; European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; **17**: 1113-1e88 [PMID: 20402746 DOI: 10.1111/j.1468-1331.2010.02999.x]

141 **Pergolizzi JV**, Raffa RB, Taylor R, Rodriguez G, Nalamachu S, Langley P. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract* 2013; **13**: 239-252 [PMID: 22716295 DOI: 10.1111/j.1533-2500.2012.00578.x]

142 **Quilici S**, Chancellor J, Löthgren M, Simon D, Said G, Le TK, Garcia-Cebrian A, Monz B. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol* 2009; **9**: 6 [PMID: 19208243 DOI: 10.1186/1471-2377-9-6]

143 **Tanenberg RJ**, Irving GA, Risser RC, Ahl J, Robinson MJ, Skljarevski V, Malcolm SK. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. *Mayo Clin Proc* 2011; **86**: 615-626 [PMID: 21719618 DOI: 10.4065/mcp.2010.0681]

144 **Tesfaye S**, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, Cruccu G, Skljarevski V, Freynhagen R. 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**: 2616-2625 [PMID: 23732189 DOI: 10.1016/j.pain.2013.05.043]

145 **Skljarevski V**, Desaiah D, Zhang Q, Chappell AS, Detke MJ, Gross JL, Ziegler D. Evaluating the maintenance of effect of duloxetine in patients with diabetic peripheral neuropathic pain. *Diabetes Metab Res Rev* 2009; **25**: 623-631 [PMID: 19637208 DOI: 10.1002/dmrr.1000]

146 **Kalso E**, Aldington DJ, Moore RA. Drugs for neuropathic pain. *BMJ* 2013; **347**: f7339 [PMID: 24355386 DOI: 10.1136/bmj.f7339]

147 **Mercier A**, Auger-Aubin I, Lebeau JP, Schuers M, Boulet P, Hermil JL, Van Royen P, Peremans L. Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: an analysis of guidelines and systematic reviews. *BMC Fam Pract* 2013; **14**: 55 [PMID: 23641784 DOI: 10.1186/1471-2296-14-55]

148 **Cegielska-Perun K**, Bujalska-Zadrożny M, Tatarkiewicz J, Gąsińska E, Makulska-Nowak HE. Venlafaxine and neuropathic pain. *Pharmacology* 2013; **91**: 69-76 [PMID: 23183148 DOI: 10.1159/000345035]

149 **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**: 697-706 [PMID: 15288411 DOI: 10.1016/j.pain.2004.05.010]

150 **Deli G**, Bosnyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. *Neuroendocrinology* 2013; **98**: 267-280 [PMID: 24458095 DOI: 10.1159/000358728]

151 **Page N**, Deluca J, Crowell K. Clinical inquiry: what medications are best for diabetic neuropathic pain? *J Fam Pract* 2012; **61**: 691-693 [PMID: 23256101]

152 **Chou R**, Carson S, Chan BK. Gabapentin versus tricyclic antidepressants for diabetic neuropathy and post-herpetic neuralgia: discrepancies between direct and indirect meta-analyses of randomized controlled trials. *J Gen Intern Med* 2009; **24**: 178-188 [PMID: 19089502 DOI: 10.1007/s11606-008-0877-5]

153 **Kaur H**, Hota D, Bhansali A, Dutta P, Bansal D, Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. *Diabetes Care* 2011; **34**: 818-822 [PMID: 21355098 DOI: 10.2337/dc10-1793]

154 **Gilron I**, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 2009; **374**: 1252-1261 [PMID: 19796802 DOI:

10.1016/S0140-6736(09)61081-3]
155 **Saarto T**, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. *J Neurol Neurosurg Psychiatry* 2010; **81**: 1372-1373 [PMID: 20543189 DOI: 10.1136/jnnp.2008.144964]
156 **Harati Y**, Gooch C, Swenson M, Edelman S, Greene D, Raskin P, Donofrio P, Cornblath D, Sachdeo R, Siu CO, Kamin M. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998; **50**: 1842-1846 [PMID: 9633738]
157 **Gilron I**, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005; **352**: 1324-1334 [PMID: 15800228 DOI: 10.1056/NEJMoa042580]
158 **Watson CP**, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 2003; **105**: 71-78 [PMID: 14499422 DOI: 10.1016/S0304-3959(03)00160-x]
159 **Gimbel JS**, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003; **60**: 927-934 [PMID: 12654955]
160 **Hanna M**, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *Eur J Pain* 2008; **12**: 804-813 [PMID: 18262450 DOI: 10.1016/j.ejpain.2007.12.010]
161 **Zin CS**, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. *J Pain* 2010; **11**: 462-471 [PMID: 19962354 DOI: 10.1016/j.jpain.2009.09.003]
162 **Christoph T**, De Vry J, Tzschentke TM. Tapentadol, but not morphine, selectively inhibits disease-related thermal hyperalgesia in a mouse model of diabetic neuropathic pain. *Neurosci Lett* 2010; **470**: 91-94 [PMID: 20026182 DOI: 10.1016/j.neulet.2009.12.020]
163 **Nones CF**, Reis RC, Jesus CH, Veronez DA, Cunha JM, Chichorro JG. Orofacial sensory changes after streptozotocin-induced diabetes in rats. *Brain Res* 2013; **1501**: 56-67 [PMID: 23313875 DOI: 10.1016/j.brainres.2013.01.002]
164 **Canta A**, Chiorazzi A, Meregalli C, Carozzi V, Oggioni N, Lauria G, Lombardi R, Bianchi R, Porretta-Serapiglia C, Cavaletti G. Continuous buprenorphine delivery effect in streptozotocine-induced painful diabetic neuropathy in rats. *J Pain* 2009; **10**: 961-968 [PMID: 19595641 DOI: 10.1016/j.jpain.2009.04.003]
165 **Cegielska-Perun K**, Bujalska-Zadrożny M, Gąsińska E, Makulska-Nowak HE. Enhancement of antinociceptive effect of morphine by antidepressants in diabetic neuropathic pain model. *Pharmacol Rep* 2014; **66**: 228-234 [PMID: 24911074 DOI: 10.1016/j.pharep.2013.09.003]
166 **Linz K**, Christoph T, Tzschentke TM, Koch T, Schiene K, Gautrois M, Schröder W, Kögel BY, Beier H, Englberger W, Schunk S, De Vry J, Jahnel U, Frosch S. Cebranopadol: a novel potent analgesic nociceptin/orphanin FQ peptide and opioid receptor agonist. *J Pharmacol Exp Ther* 2014; **349**: 535-548 [PMID: 24713140 DOI: 10.1124/jpet.114.213694]
167 **Christoph T**, Schröder W, Tallarida RJ, De Vry J, Tzschentke TM. Spinal-supraspinal and intrinsic μ-opioid receptor agonist-norepinephrine reuptake inhibitor (MOR-NRI) synergy of tapentadol in diabetic heat hyperalgesia in mice. *J Pharmacol Exp Ther* 2013; **347**: 794-801 [PMID: 24051022 DOI: 10.1124/jpet.113.207704]
168 **Afilalo M**, Morlion B. Efficacy of tapentadol ER for managing moderate to severe chronic pain. *Pain Physician* 2013; **16**: 27-40 [PMID: 23340531]
169 **Taylor R**, Pergolizzi JV, Raffa RB. Tapentadol extended release for chronic pain patients. *Adv Ther* 2013; **30**: 14-27 [PMID: 23328938 DOI: 10.1007/s12325-013-0002-y]
170 **Schwartz S**, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, Rauschkolb C. 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**: 151-162 [PMID: 21162697 DOI: 10.1185/03007995.2010.537589]
171 **Vinik AI**, Shapiro DY, Rauschkolb C, Lange B, Karcher K, Pennett D, Etropolski MS. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care* 2014; **37**: 2302-2309 [PMID: 24848284 DOI: 10.2337/dc13-2291]
172 **Wolff RF**, Bala MM, Westwood M, Kessels AG, Kleijnen J. 5% lidocaine medicated plaster in painful diabetic peripheral neuropathy (DPN): a systematic review. *Swiss Med Wkly* 2010; **140**: 297-306 [PMID: 20458651]
173 **Kulkantrakorn K**, Lorsuwansiri C, Meesawatsom P. 0.025% capsaicin gel for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, placebo-controlled trial. *Pain Pract* 2013; **13**: 497-503 [PMID: 23228119 DOI: 10.1111/papr.12013]
174 **Vinik AI**, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. *Endocrinol Metab Clin North Am* 2013; **42**: 747-787 [PMID: 24286949 DOI: 10.1016/j.ecl.2013.06.001]
175 **Groninger H**, Schisler RE. Topical capsaicin for neuropathic pain #255. *J Palliat Med* 2012; **15**: 946-947 [PMID: 22849599 DOI: 10.1089/jpm.2012.9571]
176 **Casale R**, Mattia C. Building a diagnostic algorithm on localized neuropathic pain (LNP) and targeted topical treatment: focus on 5% lidocaine-medicated plaster. *Ther Clin Risk Manag* 2014; **10**: 259-268 [PMID: 24790451 DOI: 10.2147/TCRM.S58844]
177 **Sánchez-Vázquez R**, Briseño-Rodríguez G, Cardona-Muñoz EG, Gálvez-Gastélum FJ, Totsuka-Sutto SE, Garcia-Benavides L. Isosorbide dinitrate spray as therapeutic strategy for treatment of chronic venous ulcers. *Angiology* 2008; **59**: 64-71 [PMID: 18319224 DOI: 10.1177/0003319707303700]
178 **Yuen KC**, 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**: 1699-1703 [PMID: 12351464 DOI: 10.2337/diacare.25.10.1699]
179 **Rayman G**, Baker NR, Krishnan ST. Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. *Diabetes Care* 2003; **26**: 2697-2698 [PMID: 12941745 DOI: 10.2337/diacare.26.9.2697-a]

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