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**Review**

# Mechanisms and pharmacology of diabetic neuropathy – experimental and clinical studies

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**Abstract:**
Neuropathic pain is the most common chronic complication of diabetes mellitus. The mechanisms involved in the development of diabetic neuropathy include changes in the blood vessels that supply the peripheral nerves; metabolic disorders, such as the enhanced activation of the polyol pathway; *myo*-inositol depletion; and increased non-enzymatic glycation. Currently, much attention is focused on the changes in the interactions between the nervous system and the immune system that occur in parallel with glial cell activation; these interactions may also be responsible for the development of neuropathic pain accompanying diabetes. Animal models of diabetic peripheral neuropathy have been utilized to better understand the phenomenon of neuropathic pain in individuals with diabetes and to define therapeutic goals. The studies on the effects of antidepressants on diabetic neuropathic pain in streptozotocin (STZ)-induced type 1 diabetes have been conducted. In experimental models of diabetic neuropathy, the most effective antidepressants are tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors. Clinical studies of diabetic neuropathy indicate that the first line treatment should be tricyclic antidepressants, which are followed by anticonvulsants and then opioids. In this review, we will discuss the mechanisms of the development of diabetic neuropathy and the most common drugs used in experimental and clinical studies.

**Key words:**
neuropathic pain, diabetic neuropathy, therapy, antidepressants, anticonvulsants, opioids, neuroimmune interactions

## Introduction

The World Health Organization estimates that the global prevalence of diabetes is currently approaching 5%; thus, this disease can be called an epidemic of the 21st century. Diabetes is considered a major cause of mortality and morbidity [56], and statistically, diabetic neuropathy is the second most common cause of post-traumatic nerve damage [23]. Therefore, clinical reality suggests the need for the effective treatment of neuropathic pain accompanying diabetes. There are three main types of diabetes: insulin-dependent diabetes mellitus (type 1), non-insulin-dependent diabetes mellitus (type 2) and gestational diabetes. Diabetes mellitus is a group of metabolic diseases characterized by high blood glucose concentration, frequent urination, and increased thirst and hunger. Thus, diabetes is one of the leading causes of neuropathy worldwide. Diabetic neuropathy is not always painful, however, 12% of all diabetic patients are affected with symptomatic painful diabetic neuropathy [44], the most common chronic and earliest occurring complication. Diabetic neuropathy affects all peripheral nerves including pain

fibres, motor neurons and the autonomic nervous system [44]. The pathogenesis of diabetic neuropathy is complicated, and the mechanism of this disease remains poorly understood. It has been suggested that hyperglycemia is responsible for changes in the nerve tissue [56]. There are two main suppositions of this proposed mechanism: vascular and metabolic [10]. The current hypothesis suggests that neuroimmune interactions actively contribute to the onset and persistence of pain in diabetes [3]. In addition, the participation of glial cells in the processes accompanying the development of diabetic neuropathic pain has been recently investigated [41]. Therefore, to better understand the mechanisms underlying the development of painful diabetic neuropathy, animal models of diabetes type 1 and diabetes type 2 have been used to explore this disease entity [60].

The drugs currently used for the treatment of diabetic neuropathic pain include antidepressants, such as tricyclic antidepressants or duloxetin [4]; anticonvulsants, such as pregabalin [12]; and typical analgesics, such as tapentadol [45], and these may be used individually or in combination [25, 67]. However, knowledge concerning the pathogenesis of diabetic neuropathic pain is not sufficient to propose an efficient therapy for the long-lasting reduction of pain symptoms and increase the satisfaction of diabetic patients. The use of typical painkillers is not satisfactory in alleviating neuropathic pain, further supporting attempts to develop improved pain-relieving methods.

Therefore, in this review, we will discuss the putative mechanisms for the development of diabetic neuropathy and the involvement of glial cells in this process based on observations from *in vivo* models. We will also describe studies of the most frequently used drugs for the relief of diabetic neuropathic pain in the clinic and in animal diabetic neuropathic pain models.

## Mechanisms of diabetic neuropathy development

The pathological mechanisms implicated in diabetic neuropathy, include microvascular damage, metabolic disorders, and changes in the interactions between neuronal and immunological systems in parallel with glial cell activation [14, 35, 42].

Changes in the blood vessels supplying the peripheral nerves underlie the mechanisms involved in microvascular damage and hypoxia. These changes are based on increases in wall thickness with the hyalinization of the vessel walls and the basal lamina of arterioles and capillaries, leading to nerve ischemia [42]. Through revised primary capillary membrane to the endoneurium penetrates the plasma protein, causing swelling and increased interstitial pressure in the nerves as well as capillary pressure, fibrin deposition and thrombus formation [10]. Pathological studies of the proximal and distal segments of the nerve have shown multifocal fibre loss along the length of the nerves, suggesting ischemia as a pathogenetic contributor [15].

Metabolic disorders are the primary cause of diabetic neuropathy. A hyperglycemic state accompanying diabetes type 1, which is induced through decreased insulin secretion, is responsible for the enhanced activation of the polyol pathway (Fig. 1). In the hyperglycemic state, the affinity of aldose reductase for glucose is increased, leading to the increased production of sorbitol. Sorbitol does not cross cell membranes and accumulates intracellularly in the nervous tissue, thus generating osmotic stress. Osmotic stress increases the intracellular fluid molarity as well as water influx, Schwann cell damage and nerve fibre degeneration [38]. Furthermore, upregulation of the NADPH oxidase complex results in oxidative stress through reduced glutathione production, decreased nitric oxide concentrations and increased reactive oxygen species concentrations (Fig. 1) [31]. Free radicals, oxidants, and some unidentified metabolic factors activate the nuclear enzyme poly(ADP-ribose) polymerase (PARP), which is a fundamental mechanism in the development of diabetic complications, including neuropathy [14]. Moreover, a nitric oxide deficit and increased oxygen free radical activity are responsible for microvascular damage and hypoxia [35].

*Myo*-inositol depletion also causes diabetic neuropathy. Excess sorbitol accumulates in nervous tissue, which leads to and causes osmotic stress and tissue damage. Simultaneously, decreases in the concentration of *myo*-inositol reduce ATP-ase $Na^+/K^+$ activity, which is important in impulse conduction. Under normal conditions, the *myo*-inositol content is approximately 30-fold higher in peripheral nerves than in plasma [8]. In the nerve, 20% of the *myo*-inositol is bound to phosphoinositides, which are associated with

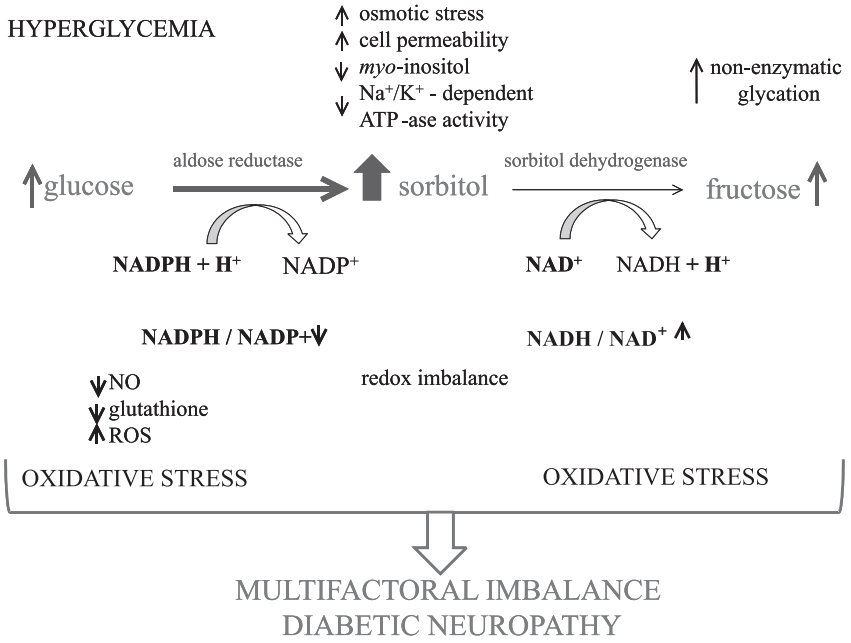


**Fig. 1.** Multifactorial etiology of diabetic neuropathy. Hyperglycemia leads to enhanced activation of the polyol pathway, oxidative stress and non-enzymatic glycation. These factors either interact or independently function toward the development of diabetic neuropathy, directly affecting nerve tissues or nutrient vascular tissues [31, 38, 52, 54]

cell membrane phospholipids. The remaining pool of *myo*-inositol in the nerves is present in a free/unbound form. Phosphoinositides are metabolically active cell phospholipids associated with the cell membrane. The phosphatidylinositol cycle involves the transformation of phospholipids accompanied by cell activation, and this cycle is important for the conduction of nerve impulses [16]. Under normal conditions, the $Na^+/K^+$ ATP-ase activity in the nerve maintains a lower concentration of sodium in the peripheral nerves compared to the plasma [27]. In diabetes, *myo*-inositol deficiency is observed in the nerves, resulting from the inhibition of the sodium-dependent uptake of *myo*-inositol and severe changes to the polyol pathway. The reduced *myo*-inositol concentration causes the insufficiency of renal ATP-ase $Na^+/K^+$, the enzyme necessary to generate nerve depolarization (Fig. 1). As a result, the conduction of stimuli is reduced [10, 52]. Sundkvist et al. showed that high *myo*-inositol levels are associated with nerve regeneration, despite the low levels of this polyol observed in diabetic patients in the clinic. Therefore, the elevation of *myo*-inositol levels might be considered a compensatory mechanism to prevent nerve damage [51].

Increased non-enzymatic glycation/glycoxidation (glycation processes involving oxidation) of proteins also plays an important role in the development of diabetic neuropathy (Fig. 1) [54]. In a hyperglycemic state, the increased levels of glucose and fructose result in covalent binding of these sugars to proteins, nucleotides or lipid molecules without control by an enzyme. This process applies to the structural proteins of the nerve and the blood vessels supplying these nerves, and the products of these transformations, advanced glycation products (AGE), alter cellular functions. AGEs cause a number of disorders, including focal thrombus formation and vasoconstriction, and affect cellular DNA. Furthermore, protein glycation might decrease cytoskeletal assembly, induce protein aggregation, and provide ligands for cell surface receptors [54]. AGE microcirculation leads to changes in the vessels resulting from prior hyperglycemic conditions, as the level of AGEs is not decreased by normoglycemia. Furthermore, AGEs have been implicated in the formation of free radicals. The induction of the non-enzymatic glycation structural proteins of nerve fibres leads to excessive rigidity and impaired axonal transport [5] because tubulin glycation leads to the inhibition of GTP-dependent tubulin polymerization [62]. AGEs have been identified not only in myelinated and unmyelinated fibres but also in the perineurium, endothelial cells, and pericytes of endoneurial microvessels. Moreover, the receptors for advanced glycation (RAGE) and glycation products are expressed in peripheral neurons [54]. Interactions between macrophages and AGE-myelin might also influence or contribute to the segmental demyelination associated with diabetic neuropathy [57].

A growing body of evidence indicates that the activation of non-neuronal cells (microglia, astrocytes

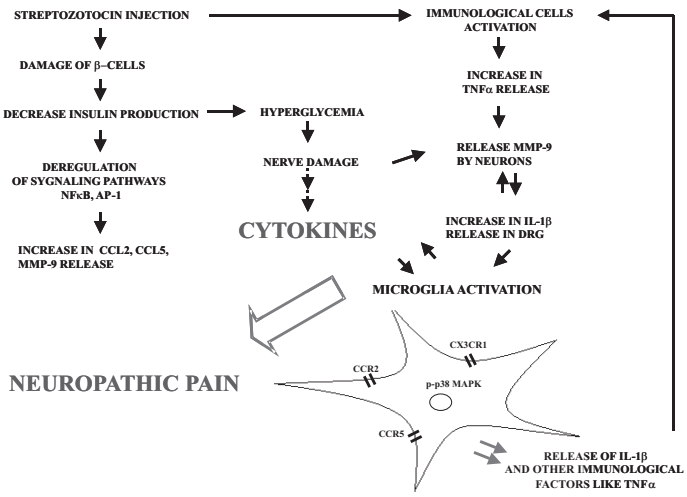


**Fig. 2.** A proposed diagram of the cytokine network in the pathogenesis of streptozotocin-induced peripheral neuropathic pain [3, 49, 68]

and immune cells) plays an important role in the development of neuropathic pain [34], and these cells are activated under hyperglycemic conditions in the spinal cord [11, 55]. Studies have shown that glia strongly influence the synaptic communication between neurons, leading to pathological pain [58]. Several studies have shown that in the spinal cord, activated microglia play a crucial role in neuropathic pain through the release of proinflammatory cytokines, which are common mediators of allodynia and hyperalgesia (Fig. 2) [34, 58]. Recent reports suggest the involvement of proinflammatory factors derived from activated microglia in diabetes-induced allodynia [55, 68] and the involvement of the p38 MAPK pathway in dorsal horn microglia in diabetes-induced hyperalgesia [11]. There are many reports implicating the release of pro-inflammatory cytokines from glia and immune cells as a pathomechanism for neuropathic pain of different origins. In rats, painful neuropathy accompanies type 1 diabetes and is associated with the release of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNFα [3], while a decrease in insulin production causes the increased release of metalloproteinase MMP-9 and monocyte chemotactic protein-1 (MCP-1) [49]. Active glial cells, particularly microglia, which are resident macrophages of the central nervous system, are responsible for signalling between components of the nervous and immune systems. Pabreja et al. [41] showed that microglia might be responsible for the initiation of neuropathic pain states. Similar results in rat models of diabetic neuropathy have demonstrated that the pre-emptive administration of minocycline attenuates the development of pain that is associated with decreased levels of IL-1β and TNFα. These results support the hypothesis that spinal microglia become activated under hyperglycemic conditions, leading to the elevation of proinflammatory cytokines and oxidative stress. Moreover, Bishnoi et al. observed significantly increased levels of proinflammatory cytokines (IL-1β, IL-6, and TNFα) in the spinal cord in a rat model of diabetes induced through streptozotocin (STZ) administration [3]. Thus, the initiation of the pain process during diabetic neuropathy is mediated through proinflammatory cytokines, such as TNFα, IL-1β, IL-2, and IL-6, that are released from activated microglia.

The determination of the role of numerous immune factors released during diabetic neuropathy from nerve and immune cells will broaden our understanding of the underlying pathomechanisms. For this reason, it is important to understand how glial cell activation products, particularly those released from microglia, influence the development of neuropathic pain in diabetic neuropathy and whether the inhibition of glia activation affects the release of pro- and anti-inflammatory cytokines, thus reducing pain.

## Diabetic neuropathy – experimental studies

### Animal models of diabetic neuropathy

Diabetic peripheral neuropathy is one of the most common consequences of diabetes and might be associated with diabetes type 1 and type 2. The mecha-

**Tab. 1.** Experimental rodent models of diabetic neuropathic pain [60]

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|---|
| **TYPE 1** |
| • **Spontaneous-induced diabetes** |
| Type 1 diabetic insulinopenic BB/Worchester Rats |
| NOD Mice |
| LETL Rats |
| Akita Mice spontaneous type 1 diabetes |
| • **Chemo-induced pancreatic toxicity** |
| Streptozotocin-induced diabetes |
| Alloxan-induced diabetes |
| **TYPE 2** |
| • **Spontaneous-induced diabetes** |
| Type 2 diabetic hyperinsulinemic BBZDR / Worchester Rats |
| Tsumura Suzuki Obese Diabetes (TSOD) mice |
| Otsuka Long-Evans Tokushima Fatty (OLETF) |
| • **Dietary-induced diabetes** |
| High-fat diet-fed mice |
| • **Genetic-induced diabetes** |
| Zucker diabetic fatty rat |
| Obese leptin-deficient (ob/ob) mice |
| Leptin receptor-deficient (db/db) mice |
| Nonobese diabetic mice – Goto-Kakizaki strain |
| • **Stress-induced diabetes** |
| • **Streptozotocin/high fat diet model of type 2 diabetes** |

nism of this neurological impairment remains unknown, and the proposed therapies are inefficient. Animal models of diabetic peripheral neuropathy provide a better opportunity to study this phenomenon and determine therapeutic goals. In 2012, Wattiez et al. [60] demonstrated that it is possible to study diabetes using experimental diabetic models of neuropathic pain from both type 1 and 2 (Tab. 1). A PubMed search using the keywords "diabetic neuropathy" yields 20,350 results published between 1945 and 2013, whereas a search with "diabetic neuropathy in animal model" yields 1,865 results published between 1964 and 2013. The development of good models to study this phenomenon facilitates the characterization of the pathology of these diseases and the identification of molecular targets, parallel with pharmacological strategies for improving clinical care.

## Pharmacology of experimental diabetic neuropathy

### Antidepressants

We have identified a number of studies on the role of antidepressants in STZ-induced diabetes type 1, but information concerning the potential influence of antidepressants in other animal models of diabetic neuropathic pain, as shown in Table 1, is still lacking. The best studied antidepressants in animal models of diabetic neuropathy are tricyclic antidepressants, which are first line therapies for the clinical treatment of diabetic neuropathic pain. Many studies have demonstrated the antiallodynic and antihyperalgesic effects of amitriptyline, the most common antidepressant tested in the STZ-induced diabetic neuropathic pain model. Using an STZ pain model, Yamamoto et al. showed that a single oral administration of amitriptyline was ineffective in diminishing allodynia in the early phase of diabetes; however, amitriptyline treatment was effective when the disease was fully developed [66]. Thus, many studies have shown contradictory results concerning the administration of amitriptyline and the extent of diabetes. For example, the acute intraperitoneal administration of amitriptyline in diabetic rats also exhibited major effects on thermal allodynia and mechanical hyperalgesia [2]. However, the results of other studies have suggested that amitriptyline does not attenuate mechanical allodynia, even after chronic administration [28]. Treatment with clomipramine and desipramine induces weak analgesia in STZ-induced diabetic hyperalgesia [9]. Other classical TCAs (imipramine, doxepin, and nortriptyline) or TeCAs (amoxapine and maprotiline) have not been tested in an animal model of diabetic neuropathy.

Currently, a large number of studies have been focused on the role of SSRIs and SNRIs in STZ-induced diabetic neuropathy. Some results have shown that fluoxetine (SSRI) attenuates thermal hyperalgesia in mice [1]. Tembhurne and Sakarkar demonstrated that chronic treatment (9 weeks) with fluoxetine reduces pain perception in rats [53]. In contrast, Sounvoravong et al. demonstrated that fluoxetine alone shows no effect in the von Frey and tail-pinch tests, but the co-administration of this compound with morphine significantly enhanced its antinociceptive and antiallodynic effects in mice [50]. The SSRIs fluvoxamine and paroxetine exhibit antiallodynic effects in the rats

[22]. These authors also showed that the intrathecal administration of milnacipran (SNRI) produced antiallodynic effects in a dose-dependent manner [22]. In our studies, using a single injection of milnacipran in mice 7 days after STZ administration, a slight decrease in neuropathic pain syndromes, such as allodynia and hyperalgesia, was observed. Other researchers have demonstrated that chronic intraperitoneal injection with milnacipran and duloxetine reduced mechanical hyperalgesia in diabetic rats [59]. This result has been associated with increasing levels of adenosine, suggesting the involvement of the adenosinergic pathway in the antinociceptive effect of duloxetine [26]. Other studies have also shown that the systemic and spinal, but not peripheral, administration of duloxetine alleviates tactile allodynia in rats [36]. Another SNRI, venlafaxine, exhibited significant effects on thermal allodynia and mechanical hyperalgesia in rat diabetic neuropathic pain models [2]. Venlafaxine also increased the analgesic activity of morphine with acute co-administration, but in chronic treatment, this compound attenuated opioid efficacy in STZ-induced hyperalgesia [6].

There are other antidepressants that have not been tested in animal models of diabetic neuropathy, including the SSRI escitalopram; the SNRI desvenlafaxine; MAOIs, such as harmaline, iproclozide, iproniazid, isocarboxazid, toloxatone, tranylcypromine, nialamide, and moclobemide; and atypical antidepressants, such as bupropion, trazodone, mirtazapine and nefazodone.

### Anticonvulsants

Anticonvulsants have also been studied for treatment of diabetic neuropathy. Anticonvulsants can be divided into three groups. The first group includes CaV channel α2δ subunit ligands, such as pregabalin and gabapentin. The antiallodynic and analgesic effects of these drugs involve ligand binding to the α2δ-1 subunit of the CaV2.X. Martinez et al. showed that pregabalin relieves mechanical allodynia and thermal hyperalgesia in a rat STZ-induced diabetic pain model. Furthermore, the effect of pregabalin was limited by the suppression of CaVα2δ-1 expression in the spinal dorsal horn under conditions of neuropathic pain [30]. Gabapentin not only attenuated mechanical allodynia but also reduced microglia activation in a rat STZ-induced diabetic neuropathy model [64]. A second type of blockers includes the N-type CaV channels (CaV2.2) leconotide and ziconotide, which have shown dose-dependent analgesic activity after intravenous administration in a diabetic neuropathic pain model [24].

The dose-dependent reduction of mechanical allodynia through treatment with the sodium channel blockers lidocaine and mexiletine was demonstrated in a rat STZ model of diabetic neuropathy [33, 66]. Moreover, Mert and Gunes [33] showed that antinociceptive effects from A803467, a highly selective blocker of Nav1.8 channels, are observed in diabetic rats with painful neuropathy. Studies on primary sensory neurons have demonstrated that a number of antidepressants, including the tricyclic antidepressants amitriptyline, nortriptyline, imipramine, desipramine, and maprotiline, evoke effects through sodium channel blocking, thereby contributing to the antihyperalgesic efficacy of these compounds [13].

### Opioids

Although there is a large consensus on effectiveness of opioid drugs in nociceptive pain, the efficacy of these compounds in neuropathic pain has, until recently, been a matter of debate. Nielsen et al. [37] showed hyporesponsiveness to morphine in STZ-diabetic rats with long-term diabetes, however, in STZ-diabetic mice tapentadol was more effective than morphine in attenuating heat hyperalgesia, but both opioids reduce heat-induced nociception in dose-dependent manner [7]. In STZ-induced diabetic models, the decreased antiallodynic effect of morphine has been associated with a decrease in the release of specific endogenous opioids and impaired G-protein coupling to μ-opioid receptors [61]. The influence of the modulation of glial activity on the analgesic effects of morphine in neuropathic pain has been recently studied [34]. Our recent data suggested that the activation of microglial cells enhanced proinflammatory cytokine expression in the spinal cord, and changes in neuroimmune interactions are involved in the development of morphine tolerance in diabetic neuropathy [68].

## Diabetic neuropathy – clinical studies

### Types of diabetic neuropathy

There are no neurophysiological or morphological differences between patients with type 1 and type 2 diabe-

tes nor between diabetic patients with and without painful neuropathy [29]. Some people with diabetes have nerve damage without signs, others over time, may have symptoms such as tingling, numbness, loss of feeling or pain. Nerve problems can occur in every organ system, and therefore, diabetic neuropathy can be classified as peripheral, autonomic, proximal, or focal. The most common type of diabetic neuropathy is peripheral neuropathy, which causes pain or loss of feeling in the toes, feet, legs, hands, and arms. The autonomic neuropathy causes changes in digestion, bowel and bladder function, sexual response, and perspiration. It can also affect the nerves that serve the heart and control blood pressure, as well as nerves in the lungs and eyes. The proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs. The focal neuropathy results in the sudden weakness of one nerve or a group of nerves, causing muscle weakness or pain [65].

### Pharmacology of diabetic neuropathy

Diabetic neuropathic pain treatment is difficult because no specific relief medication is available. The American Diabetes Association recommends the use of tricyclic antidepressants, followed by anticonvulsants and opioids, such as tapentadol or oxycodone. In addition, maintenance of blood sugar levels within a narrow target range might delay the progression of peripheral neuropathy.

### Antidepressants

Tricyclic antidepressants (TCAs) have been shown to be effective for symptomatic pain relief in diabetic neuropathy and are used in 40% of cases [4, 21, 32, 47]. TCAs inhibit norepinephrine and/or serotonin reuptake within the central nervous system. Thus, TCAs, such as amitriptyline, nortriptyline, desipramine and imipramine, might provide relief for mild to moderate symptoms of pain, but these compounds might also cause a number of side effects, including dry mouth, sweating, sedation and dizziness. Max et al. [32] showed that amitriptyline is effective in alleviating the pain resulting from diabetic neuropathy, and the efficacy of this compound has also been confirmed in other studies [4]. Other TCAs, such as imipramine and desipramine, have demonstrated effectiveness in reducing the pain associated with diabetes [47]. Desipramine relieves diabetic neuropathy pain with an efficacy similar to that of amitriptyline [32]. Combined treatment with nortriptyline and fluphenazine has produced a significant reduction of pain in patients with diabetic polyneuropathy [18]. There are no available data concerning the clinical use of doxepin or tetracyclic antidepressants (TeCAs), such as amoxapine and maprotiline, which also relieve diabetic neuropathic pain.

Some antidepressants from the selective serotonin reuptake inhibitor (SSRI) family have also been used to treat diabetic neuropathy. Although Max et al. [32] showed that fluoxetine is not effective in patients with diabetic neuropathy, but the significant analgesic effects of other SSRIs, such as citalopram and paroxetine, have been recently demonstrated in two minor trials (20 and 15 patients) [48]. Otto et al. [40] showed that escitalopram was effective in 41 patients with painful diabetic neuropathy. The use of fluvoxamine to relieve the pain associated with diabetic neuropathy has been demonstrated in a single case concerning a 48-year-old man with a 14-year history of type 2 diabetes [39].

The serotonin and norepinephrine reuptake inhibitors (SNRIs) are also used in the clinic, despite their adverse effects. The antidepressant duloxetine is effective in relieving the pain associated with diabetic neuropathy, and there was no significant difference in analgesic efficacy between amitriptyline and duloxetine [4]. Rowbotham et al. [43] showed that venlafaxine moderately reduced pain in patients with painful diabetic neuropathy. Furthermore, patients with diabetic neuropathy who have not responded to gabapentin experienced pain relief upon the addition of venlafaxine, as the combination was moderately effective [46]. There is no information concerning the potential analgesic effects of other SNRIs, such as desvenlafaxine or milnacipran, in diabetic neuropathy in the clinic, although experimental studies have revealed positive effects (discussed in the next chapter).

Monoamine oxidase inhibitors (MAOIs), including harmaline, iproclozide, iproniazid, isocarboxazid, toloxatone, tranylcypromine, nialamide and moclobemide, have not been tested in clinical trials for any type of neuropathic pain, including diabetic neuropathy.

Some research studies have focused on the role of atypical antidepressants in reducing painful diabetic neuropathy syndromes. Wilson [63] examined 31 adult diabetic patients with painful distal polyneuropathy and showed that low doses of trazodone (50–100 mg/day) are effective treatment option. Nefazo-

done was effective in ameliorating the pain, paresthesias, and numbness associated with diabetic neuropathy [19]. Other atypical antidepressants, such as mirtazapine and bupropion, have not been examined in clinical trials for the treatment of diabetic neuropathy; however, there is some experimental evidence supporting the use of these compounds.

### Anticonvulsants

Drugs such as gabapentin and pregabalin, which are typically used to treat seizure disorders, have also been prescribed for diabetic neuropathic pain and are used in 25% of cases [21]. Studies [12, 25, 67] have shown that monotherapy with gabapentin or pregabalin produces clinically and subjectively meaningful pain relief in patients with painful diabetic neuropathy. Moreover, the co-administration of gabapentin with morphine and oxycodone results in improved analgesic effects at lower doses than treatment with either drug alone [17, 20]. Zin et al. [67] showed that pregabalin did not enhance the effectiveness of oxycodone in diabetic neuropathy.

### Opioids

Opioid analgesics, such as tapentadol [45], oxycodone [20] or morphine [17] might also be used to relieve diabetic neuropathic pain, however, are used alone only in 7% of cases [21].

## Summary

Diabetic neuropathic pain treatment is difficult because no specific relief medications are available, and the pathomechanism of diabetic neuropathic pain development is multidirectional and complicated. Many animal models of diabetes have been developed to better understand this disease, and more studies are needed to examine the potential role of antidepressants in diabetes treatment, as only the STZ-model has been well studied. As shown in this review, the mechanisms of the pathogenesis implicated in diabetic neuropathy include microvascular damage, metabolic disorders, and changes in the interaction between the neuronal and immunological systems associated with glial cell activation. The current medications used to reduce neuropathic pain syndromes during diabetes are not sufficient. Therefore, an increased understanding of neuroimmune interactions might provide new possibilities for the development of innovative therapies, particularly polytherapies, which can be successfully used in the clinic.

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