

## Recent Updates in Treatment of Diabetic Neuropathy

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### **Abstract**

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Diabetic neuropathy (DN) is the most common microvascular complication which progressively leads to neuronal degeneration. Consequently, DN is associated with sensory symptoms such as pain, numbness, tingling, pins and needles, prickling and pinching and eventually loss of sensation. Symptoms are considered moderate to severe and may worsen at night, causing sleeping disturbs. Neuropathic pain can be constant and accompanied by cutaneous allodynia, which can affect the performance of daily activities of diabetic patients. The mechanisms that cause diabetic neuropathic pain (DNP) are not fully understood, although toxic effects of hyperglycaemia considered an important factor for the development of this complication.

**Keywords:** Diabetic Neuropathy, Physiopathology, Oxidative and Nitrosative Stress.

### **Diabetic Neuropathy**

Diabetic neuropathy (DN) is the most common microvascular complication which progressively leads to neuronal degeneration. Consequently, DN is associated with sensory symptoms such as pain, numbness, tingling, pins and needles, prickling and pinching and eventually loss of sensation. Symptoms are considered moderate to severe and may worsen at night, causing sleeping disturbs (Schreiber et al., 2015).

Neuropathic pain can be constant and accompanied by cutaneous allodynia, which can affect the performance of daily activities of diabetic patients (Quattrini and Tesfaye, 2003).

### **Physiopathology of Neuropathic Pain in Diabetes**

The mechanisms that cause diabetic neuropathic

pain (DNP) are not fully understood, although toxic effects of hyperglycaemia considered an important factor for the development of this complication (Oyibo et al., 2002).

### **Polyol pathway hyperactivity**

Metabolic disorders are the main reason for DN. Hyperglycaemia, produced as a result of decreasing in insulin secretion or insulin resistance, is responsible for the boosted of the polyol pathway activity. The formation of sorbitol from glucose with the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to NADP<sup>+</sup> is catalyzed by aldose reductase enzyme. Furthermore, Sorbitol is oxidized to fructose by sorbitol dehydrogenase enzyme, which is coupled with the reduction of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) to NADH. In diabetic patients, aldose reductase has a greater affinity for glucose, that leads to the

accumulation of sorbitol which doesn't cross cell membranes causing intracellular osmotic stress (Oates, 2002; Sheetz and King, 2002). However, the present hypothesis states that polyol pathway hyperactivity is pathogenic due to increase in the turnover of cofactors such as NADPH and NAD<sup>+</sup>, which leads to a decrease in the reduction and regeneration of glutathione. In addition, an increase of advanced glycation end products (AGEs) production and activation of diacylglycerol and protein kinase C (PKC) isoforms are involved. Glutathione depletion could be the primary cause of oxidative stress and be related to the accumulation of toxic species (Oates, 2002). In fact, aldose reductase inhibitors could be effective in preventing the development of DN in animal models, but they have demonstrated disappointing results and dose-limiting toxicity in human trials (Chalk et al., 2007).

### Oxidative and Nitrosative Stress

As previously mentioned, the primary cause of oxidative stress associated with diabetes is due to polyol pathway activation. However, oxidative stress could be caused by a) Autoxidation of glucose and its metabolites. b) The intracellular formation of AGEs and augmentation of its activating ligands. c) Changes in mitochondrial function. d) Activation of PKC isoforms.

e) over activity of the hexosamine pathway (Brownlee, 2001).

Besides oxidative stress, reactive nitrogen species, particularly the peroxynitrite also play a vital role in the development of diabetes and its complications (Obrosova et al., 2005; Vareniuk et al., 2007).

Though it has been obviously demonstrated significant changes in oxidative status in diabetic animal models (Cunha et al., 2008), tissue concentrations of known carbonyl compounds are nearly insignificant. The plasma ET-1, nitric oxide, catalase and glutathione levels are almost the same in neuropathic diabetic patients compared to non-neuropathic diabetic ones (Ozkul et al., 2010).

In line with this observation, clinical results have been conflicting for antioxidants as alpha lipoic acid, ranging from little benefit (Mijnhout et al., 2010; Ziegler et al., 2011) to meaningful advantages (Tang et al., 2007).

### Microvascular changes

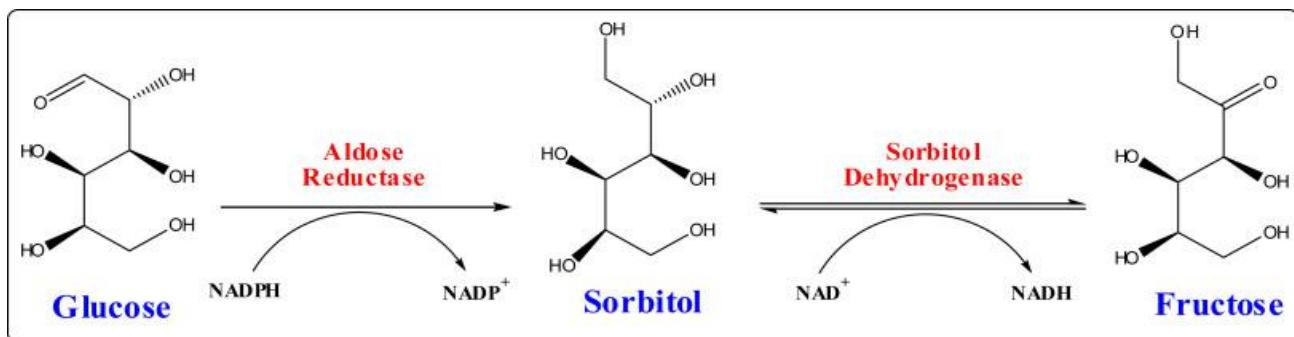
DN is frequently associated with microvascular

impairment (Arora et al., 2002; Doupis et al., 2009). In clinical and preclinical studies, a reduction in peripheral perfusion in the nervous tissue (Cameron et al., 2001), and also in the skin was observed (Jin et al., 2012). This can be considered as an important physiological evidence of microvasculature alteration.

Nerve ischemia occurs as a result of increases in wall thickness and hyalinization of the basal lamina of vessels that supply peripheral nerves (Malik et al., 1993; Pavly-Le Traon et al., 2010), together with luminal reduction (Malik et al., 1993). These changes are caused by plasma protein escape of the capillary membrane to endoneurium, inducing swelling and increase in interstitial pressure in the nerves, accompanied by higher capillary pressure, sedimentation of fibrin and thrombus development. Hyperglycaemia can trigger nerve hypoxia, especially in sensory nerves, changing their electrical stability (Fuchs et al., 2010). Apparently argumentative data from clinical studies described that diabetic patients suffering from the DNP had a significant difference of levels of intravascular oxygen and increases blood flow in the lower limbs than painless patients. Though, authors still consider a hypoxic state inside the endoneurium. Otherwise, a potential sympathetic dysfunction can be the cause of higher blood flow (Eaton et al., 2003).

Both diabetic patients and animals have shown a progressive nerve loss in proximal and distal segments (Jelicic Kadic et al., 2014; Shun et al., 2004), That cause a reduction of intraepidermal nerve fibre density (Sorensen et al., 2006). Consequently, axonal degeneration and regeneration occur frequently in asymptomatic patients. Besides axonal retraction and regeneration, myelin sheath alteration related to hyperglycaemia are detected. The observed demyelination can be related to Schwann cells altered capacity to support normal myelin sheath (Said et al., 2008).

The endothelial function in diabetic patients with neuropathy is also altered. The vasodilatation induced by acetylcholine (i.e., the endothelium-dependent response) in dermal vessels of diabetic patients is reduced in comparison with nondiabetic subjects. In addition, vasoconstriction mediated by the sympathetic system (i.e., endothelium-independent response)



**Figure 1. The polyol metabolic pathway. The pathway contains aldose reductase and sorbitol dehydrogenase enzymes. It plays a vital role in the development of diabetic complications.**

is also defective, which can also be involved in the pathophysiology of DN and then, in the DNP (Quattrini et al., 2007).

The oxidative stress as described above may cause the microvascular changes, although treatment with antioxidant agents can retain regular perfusion, restoring the sensory transmission in type 1 diabetic model (Inkster et al., 2007).

### Microglial activation

Glial cells play an essential role in the pathogenesis of many diseases of the nervous system, including chronic pain states. Glia consist of both macroglia (including astrocytes, radial cells and oligodendrocytes) and microglia cells, which are mainly responsible for maintaining homeostasis, form myelin, and provide support and protection for neurons from both central and peripheral nervous system (Mika et al., 2013).

Microglial cells cover less than 20% of spinal glial cells but there is a vigorous proliferation at spinal level in response to dorsal root ganglia and spinal cord after nerve injury (Kettenmann and Verkhratsky, 2008). Activation of microglia arises immediately after peripheral nerve injury, lasting for less than 3 months, and is responsible for a production of several inflammatory mediators as cytokines, chemokines, and cytotoxic substances such as nitric oxide and free radicals, leading to a pro inflammatory milieu (Vydyananathan et al., 2005).

Diabetes has effect on all glial cells of the spinal cord since chronic microglial activation was detected in streptozotocin-induced diabetic rats lasting from 4 weeks (Tsuda et al., 2008; Wodarski et al., 2009) to 6 or 8 months (Cheng et al., 2014; Toth et al., 2010). This microglial activation has been related with sensorial changes and up-regulation of Nav1.3 sodium channels in the dorsal root ganglia (DRG) (Cheng et al., 2014), possible

through p38 mitogen activated protein kinase dependent mechanism (Crown, 2012; Suzuki et al., 2011).

On the other hand, 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 influence the functional support and role of astrocytic cells in the nervous tissue, such as the clearance of neurotransmitters within the synaptic cleft (Afsari et al., 2008).

### Central sensitization

Diabetic neuropathic pain (DPN) may be a consequence of both peripheral and central nervous system (CNS) changes (Chen and Pan, 2002; Maier et al., 2010). During DNP, primary afferents are sensitized, inducing dorsal horn hyperactivity and neuroplastic alterations in central sensory neurons (Chen and Pan, 2002). The common occurrence of allodynia in DNP patients is due to changes in CNS pain processing (Aslam et al., 2014).

The increased glutamate release from primary afferents in the spinal cord in DN can lead to the hyperactivity of spinal neurons (Li et al., 2010; Wang et al., 2007). Moreover, spinal N-Methyl-D-aspartate (NMDA) receptor expression is augmented (Bai et al., 2014), generating increased and more frequent excitatory postsynaptic currents in the lamina II (Wang et al., 2007). Moreover, it has been described that cAMP response element-binding protein signalling, which directly regulates NMDA receptors activity (Kim et al., 2012), is enhanced in DNP (Bai et al., 2014; Sanchez and Sharma, 2009).

Enhanced spinal NMDA expression and glutamate release might contribute to spinal cord

hyperactivity. On the other hand, metabotropic receptors for neurotransmitter  $\gamma$ -Aminobutyric Acid ( $\text{GABA}_B$ ) receptors are downregulated in the spinal cord in DN (Bai et al., 2014).

Activation of  $\text{GABA}_B$  receptors causes inhibition of NMDA receptor activity by direct inhibition of voltage-sensitive  $\text{Ca}^{2+}$  channels (Pérez-Garcí et al., 2006) and the opening of inwardly rectifying  $\text{K}^+$  channels (Sodickson and Bean, 1996).

Additionally, the activation of  $\text{GABA}_B$  receptor causes downregulation of NMDA receptors at the spinal level in diabetic rats (Bai et al., 2014).

Considering the significance of central sensitization in the hypersensitivity associated with DNP, targeted therapies that aim to control spinal neurons hyperexcitability are valuable in pain regulator in this condition, as will be discussed below.

### **Adenosine monophosphate kinase (AMPK)**

AMPK (Adenosine monophosphate kinase) is a heterotrimeric Ser/Thr protein kinase is activated by changes in intracellular AMP: ATP ratio. Upon stimulation, AMPK inhibits energy consuming anabolic activities such as protein translation (Hardie, 2007). AMPK stimulation mediates these effects greatly via inhibition of mammalian target of rapamycin (mTOR) signalling (Hardie, 2007). AMPK activation has also been related to inhibition of mitogen activated protein kinase (MAPK) signaling (Kim et al., 2001; Melemedjian et al., 2011).

Several studies have suggested that AMP-activated protein kinase (AMPK) activators can reverse mechanical allodynia in neuropathic pain models and the ability of these compounds to negatively regulate protein synthesis in sensory afferents (Asiedu et al., 2016; Melemedjian et al., 2011; Wang et al., 2018).

AMPK activators such as metformin and A769662 decrease the excitability of DRG neurons (Melemedjian et al., 2011). Augmented excitability of these neurons after injury is widely assumed to cause higher activity result in burning pain that is a characterized feature of neuropathic pain (Baron et al., 2010). Although it still exhibited *in vivo*, the profound influence of AMPK activators on DRG excitability supposes that they might reverse mechanical hypersensitivity along with spontaneous pain related with persistent neuropathic pain in

humans. Metformin might prevent neuropathic pain through AMPK pathway (Melemedjian et al., 2011). Metformin has been demonstrated to decrease mechanical allodynia in lumbar radiculopathy pain activated by spinal nerve ligation in rats and nerve injury in mice (Taylor et al., 2013). Thus, this suggest the neuroprotective effect of metformin on sensation and its potential in ameliorating neuropathic pain in diabetes mellitus.

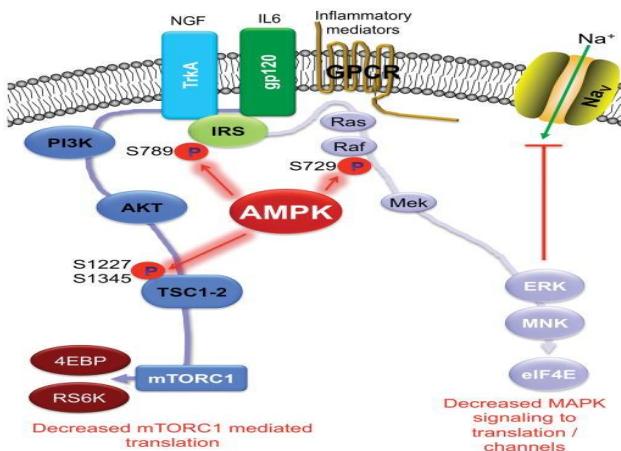
Systemic administration of AMPK activators (either metformin or A769662) to rodents after peripheral nerve injury reduces mechanical hypersensitivity, results start 2–3 days after treatment (Melemedjian et al., 2011, 2013). Obviously, within 7 days, these compounds produced a total resolution of mechanical hypersensitivity that lasted even after discontinuation of treatment, confirming the idea that AMPK activators have disease-modifying properties that develop over the course of treatment.

### **Mammalian Target of Rapamycin (mTOR)**

Mammalian target of rapamycin (mTOR) is considered as a serine and threonine protein kinase that triggers the various signals together to control the fundamental cellular functions such as induction of protein translation in addition to cell growth (McDaniel et al., 2002).

Mammalian target of rapamycin complex 1 (mTORC1) is regulated by upstream activation of tyrosine kinase receptors (Trks) and engagement of the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) signaling. When mTORC1 is enhanced, it catalyses phosphorylation of a family of proteins that bind to the 5'm7GTP Cap structure (5'Cap) of mRNAs (Gingras et al., 2004).

In this process the phosphorylation of eukaryotic initiation factor (eIF) binding protein (BP) 4E-BP is initiated when 4E-BP is phosphorylated by mTORC1, 4E-BP dissociates from eIF4E, the 5' cap binding protein, allowing for more efficient association of eIF4E with eIF4A (a deadbox family helicase) and eIF4G (a scaffolding protein) (Gingras et al., 2004). These three proteins create an efficient unit called the eIF4F complex. This eIF4F complex is linked to



**Figure 2. AMPK signaling pathways. regulation and downstream effects.**

efficient translation of target messenger ribonucleic acid (mRNAs) and is a significant regulatory endpoint for mTORC1 signaling (Sonnenberg, 2008). Increased mTORC1 activity is clearly linked to plasticity in nociceptors. First, rapamycin, a highly selective inhibitor of mTORC1, reduces plasticity enhanced by endogenous mediators that act via receptors expressed by nociceptive neurons (Melemedjian et al., 2010; Price et al., 2007). Also, rapamycin declines the sensitivity of a subset of nociceptors thought to play a vital role in mechanical hypersensitivity following injury (Géranton et al., 2009; Jiménez-Díaz et al., 2008) and reverses neuropathic mechanical hypersensitivity in rats (Melemedjian et al., 2013) and mice (Obara et al., 2011).

Control changes in synaptic strength between nociceptors and CNS neurons could be achieved by mTORC1 that transmits nociceptive information to the brain via alterations in postsynaptic expression of plasticity-related genes.

However, another explanation is that presynaptic effects in the dorsal roots, which contain the central projections of DRG neurons, predominate, as there is also evidence that mTORC1 activity in these axons contributes to neuropathic pain (Géranton et al., 2009). While continuing research is still explaining the molecular details of how mTORC1 controls nociceptor and dorsal horn neuron plasticity, it is clear that mTORC1 is a critical molecular signaling hub underlying pathological pain. Mitogen activated protein kinase (MAPK) is another signaling pathway linking extracellular signals to translation in neurons, including nociceptors.

The MAPK isoforms extracellular signal-regulated kinases (ERK) and p38, which play important roles in nociceptor excitability and synaptic plasticity in the CNS, phosphorylate eIF4E at Ser 209 via MAP kinase interacting kinase (Pyronnet et al., 1999).

Two MNK isoforms are noticed in mammalian genomes and both are expressed in the nervous system. MNK-enhanced phosphorylation of eIF4E is thought to regulate the translation of a subset of mRNAs (Furic et al., 2010). mRNAs whose translation is decreased in the absence of eIF4E phosphorylation encode cytokines, chemokines, and other plasticity-associated proteins (Herdy et al., 2012). Among these mRNAs is the matrix metalloprotease isoform 9 (MMP9) (Gkogkas et al., 2014), which is located in the DRG. It is organized by injury and/or by chronic opioid exposure, and is complicated in pathological pain (Ji et al., 2009; Kawasaki et al., 2008; Liu et al., 2012). ERK or p38 signaling to eIF4E through MNK1/2 is also involved in the progress of pain plasticity by endogenous factors that signal via this pathway through their similar cell surface receptors.

## Symptomatic treatment

The choice of first-line and second-line agents differs between guidelines due to fundamental methodological differences in the criteria employed to define efficacy. However, most guidelines recommend usually using tricyclic agents (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs) or  $\gamma$ -aminobutyric acid (GABA) analogues (gabapentin or pregabalin) as first-line agents followed by opioids and topical treatments (Spallone, 2012). Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed for short-term analgesia, primarily when it seemed not to be DN.

## Antidepressants

Antidepressants along with pregabalin/gabapentin (voltage-dependent calcium channels  $\alpha$ 2 $\delta$  subunit ligands) are considered as first-line drugs of choice for neuropathic pain (Attal et al., 2010; Dworkin et al., 2007; Finnerup et al., 2010, 2015). Specific antidepressants with analgesic effects include tricyclic antidepressants (TCA), which are serotonin noradrenaline reuptake inhibitors (SNRI), also known as new antidepressants.

**Table 1: Pharmacological Treatment of Diabetic Peripheral Neuropathy**

Medication	Recommended dose	Comment
<b>Antidepressants</b>		
Amitriptyline	25–100 mg, at bedtime	Not recommended over duloxetine or venlafaxine. AEs include dry mouth, urinary retention, sedation, vertigo, constipation. Monitor BP, heart rate, ECG before and during initiation; weight; mental status. Avoid use in patients older than 60 years of age.
Desipramine	10–25 mg titrated to 100–150 mg at bedtime	Safer alternative to amitriptyline (less-severe anticholinergic effects, less sedation). Preferred TCA for elderly patients. AEs include dry mouth, sedation, dizziness, confusion, orthostatic constipation, urinary retention, blurred vision, weight gain, arrhythmias. Monitor BP, heart rate, ECG before and during initiation; weight; mental status.
Duloxetine (Cymbalta)	60 mg/day	First drug approved for treatment of DPN (2004). AEs include nausea, somnolence, hyperhidrosis, anorexia, vomiting, constipation, fatigue, dry mouth. Monitor BP, mental status, liver enzymes. Avoid use in hepatic impairment; avoid use with CrCl < 30 mL/min.
Venlafaxine	75–225 mg/day	AEs include nausea, somnolence, ECG changes. Monitor BP, cholesterol, heart rate. May be added to gabapentin for better response.
<b>Anticonvulsants</b>		
Carbamazepine	600 mg/day (200 mg TID) to 800 mg day (200 mg QID) 60,91	AEs include agitation, dry mouth, sedation, ataxia, nausea, vomiting, blurred vision, confusion, fatigue, nystagmus, aplastic anemia (rare). Monitor CBC with platelet count, reticulocytes, serum iron, lipid panel, liver function tests, urinalysis, BUN, serum carbamazepine levels, thyroid function tests, serum sodium, ophthalmic exams (papillary reflexes); observe patient for excessive sedation.
Gabapentin	900–3,600 mg/day in three divided doses	AEs include dizziness, somnolence, diarrhea, fatigue, GI upset, peripheral edema. Monitor serum levels of concomitant antiepileptic therapy. Reduce dosage if GFR < 60 mL/min.
Pregabalin (Lyrica)	150 mg/day (50 mg TID) to 300 mg/day (100 mg TID)	Second agent approved for treatment of DPN (2004). AEs include somnolence, dizziness, peripheral edema, weight gain. Monitor degree of sedation, symptoms of myopathy or ocular disturbance, weight gain/edema, creatine phosphokinase, skin integrity (in diabetic patients). Treatment may lead to physical or psychological dependence.
Valproate sodium	500–1,200 mg/day in two or three divided doses	AEs include elevated liver enzymes, nausea. Monitor liver enzymes, CBC with platelet count.
<b>Opioids</b>		
Morphine sulfate	15–30 mg every 12 to	Typical opioid effects should be expected (e.g., constipation, somnolence, dizziness, nausea, vomiting, itchiness). Chronic

(MS Contin)	24 hours	use may lead to tolerance, frequent dose escalation, and hyperalgesia. Data are insufficient to recommend this drug over oxycodone, dextromethorphan, or tramadol.
Oxycodone CR (OxyContin)	Maximum dosage: 120 mg/day in two divided doses of CR formulation	Typical opioid effects should be expected (e.g., constipation, somnolence, dizziness, nausea, vomiting, itchiness). Chronic use may lead to tolerance, frequent dose escalation, and hyperalgesia. Data are insufficient to recommend this drug over dextromethorphan, morphine sulfate, or tramadol.
<b>Opioid-Like Analgesics</b>		
Dextromethorphan	400 mg/day in four divided doses	Dissociative anesthetic with powerful psychedelic effects at high doses. Primary AE is sedation (at recommended doses). Data are insufficient to recommend this drug over oxycodone, morphine sulfate, or tramadol.
Tapentadol (Nucynta ER)	50–250 mg BID	Third agent approved for DPN treatment (2012). AEs include nausea, dizziness, somnolence, constipation, vomiting, headache. Potential for addiction, abuse, misuse; life-threatening respiratory depression; neonatal opioid withdrawal syndrome; interaction with alcohol.
Tramadol	210 mg/day in two or four divided doses	AES include nausea, sedation, constipation, headache, dry mouth, urinary retention, confusion, tremor, seizures. Monitor respiratory rate, BP, heart rate, signs of tolerance or abuse. Data are insufficient to recommend this drug over oxycodone, morphine sulfate, or dextromethorphan
<b>Topical Medications</b>		
Capsaicin (cream) (Trixaicin HP)	0.075% TID or QID.	May be used as adjunct to oral medications. AEs include localized stinging, burning, and itching; coughing; sneezing; rash. Monitor skin breakdown.
Lidocaine patch (Lidoderm)	Maximum of three 5% medicated patches applied once for up to 12 hours within a 24-hour period.	May be used as adjunct to oral medications. Key AEs include application-site reactions (e.g., blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation).
AE = adverse event; AWP = average wholesale price; BID = twice daily; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CR = controlled release; CrCl = creatinine clearance; DPN = diabetic peripheral neuropathy; ECG = electrocardiogram; ER = extended release; GI = gastrointestinal; GFR = glomerular filtration rate; QID = four times daily; TCA = tricyclic antidepressant; TID = three times daily		

Prolonged pain causes anxiety accompanied by an advanced depressive state and enhanced pain sensations. Therefore, antidepressant medications may be effective against chronic pain by their actions to improve the depressive state. Antidepressants decrease neuropathic pain, however, even when the patient is not in a depressive state (Fishbain et al., 1998). In addition, the pharmacological effects of antidepressants on

depression usually take approximately two to four weeks to be observed from the time the drug is first taken, however the analgesic effects on chronic pain noticeable in as little as few days to one week (Onghena and Van Houdenhove, 1992). Thus, the analgesic effects of antidepressants on chronic pain expected involve a mechanism different from that producing their antidepressive effects.

The pharmacologic effects of antidepressants inhibit the reuptake of noradrenaline and serotonin (5-HT) neurotransmitter by binding to their transporters consequently levels of NA and 5-HT in the synaptic cleft (Bertón and Nestler, 2006; Dharmshaktu et al., 2012; Micó et al., 2006; Sindrup et al., 2005).

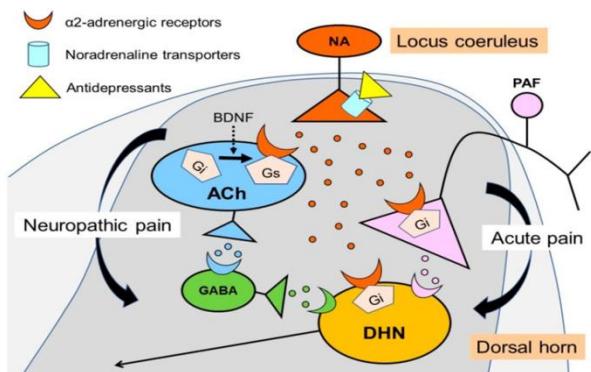
An antidepressant that impedes reuptake of both noradrenaline and 5-HT has superior analgesic effects than a drug that selectively inhibits reuptake of only one of these neurotransmitters. Noradrenaline plays a greater role than 5-HT in the analgesic action through its action on  $\alpha_2$ -adrenergic receptors.

The  $\alpha_2$ -adrenergic receptors in the dorsal horn of the spinal cord are coupled to the inhibitory G protein, which inhibits the presynaptic voltage-gated  $\text{Ca}^{2+}$  channels in the dorsal horn of the spinal cord that stops the release of excitatory neurotransmitters from primary afferent fibers. Moreover, G protein-coupled inwardly rectifying  $\text{K}^+$  channels are opened on the post-synaptic spinal cord dorsal horn cells, the cell membranes are hyperpolarized, and excitability is reduced (Pan et al., 2008).

### **Calcium Channel $\alpha_2$ - $\delta$ Ligands (Gabapentin & Pregabalin)**

Both Gabapentin and pregabalin bind to voltage-gated calcium channels at the  $\alpha_2$ - $\delta$  subunit and inhibit neurotransmitter release. They have shown efficacy vs placebo in several NP conditions (Dworkin et al., 2007; Finnerup et al., 2005). Although gabapentin and pregabalin have few drug interactions, both can cause dose-dependent vertigo and drowsiness, which can be diminished by beginning with lower dosages and increasing carefully. Both medications also need dosage restriction in patients with renal inefficiency, and dosage modifications can be prepared in relation to creatinine clearance.

Antidepressants increase noradrenaline via blocking of noradrenaline transporters at the terminal of the descending noradrenergic fiber from the locus coeruleus. Noradrenaline inhibits acute pain through  $\alpha_2$ -adrenergic receptors by pre-synaptic (inhibit neurotransmitters release) and post-synaptic (hyperpolarize cell membranes) mechanisms. In neuropathic pain states, however,  $\alpha_2$ -adrenergic receptors in the cholinergic interneurons change from inhibitory to excitatory through G-protein



**Figure 3. Schematic illustration of analgesic effects of antidepressants and noradrenaline in the dorsal horn of the spinal cord.**

switch (from Gi to Gs) by the effect of brain-derived neurotrophic factor (BDNF) increasing after nerve injury. Released acetylcholine bind to muscarinic receptors, by which produce analgesia thorough GABA release. PAF; primary afferent fibers, NA; noradrenaline, DHN; dorsal horn neurons, ACh; acetylcholine, Red circle; noradrenaline, Blue circle; acetylcholine, Green circle; GABA, Pink circle; excitatory neurotransmitters.

### **Alpha-lipoic acid**

Alpha-lipoic acid augmented the reduced glutathione (GSH) *in vivo* and *in vitro* (Brownlee et al., 1988; Nagamatsu et al., 1995). GSH is a vital endogenous antioxidant. That play an important role in redox-dependent mechanisms of several cellular processes (Low et al., 1997; Mitsui et al., 1999; Nagamatsu et al., 1995).

Alpha-lipoic acid is a free radical scavenger of peripheral nerve both *in vitro* and *in vivo* (Kozlov et al., 1999; Podda et al., 1994). Alpha-lipoic acid has further actions such as enhancing nerve growth factor and stimulating fiber regeneration (Dimpfel et al., 1990; Murase et al., 1993).

### **Vitamin B**

Deficiency of vitamin B12 (also known as cobalamin) resulting in a lack of methylcobalamin, has been related with significant neurological pathology, especially peripheral neuropathy (Andrès et al., 2004; Head, 2006). It is also accompanied with the onset of diabetic neuropathy. In patients with DPN, vitamin B12 deficiency may be triggered by the use of antidiabetic agents such as metformin (Liu et al., 2006; Ting et al., 2006).

Vitamin B12 and its coenzymes have been used to reduce pain. In some countries, vitamin B12 is categorized as an analgesic drug. It has been proposed that vitamin B12 may increase the availability and efficacy of noradrenaline and 5-hydroxytryptamine in the descending inhibitory nociceptive system (Jurna, 1998).

In animal models, morphological and histological evidence has also revealed that long-term administration of methylcobalamin enhances the synthesis and regeneration of myelin (Okada et al., 2010).

### **Donepezil**

Donepezil, a piperidine-based, reversible acetylcholinesterase inhibitor, is the most commonly pharmacological agent for the treatment of Alzheimer's disease (AD).

The first category of drugs approved by the US FDA for AD was cholinesterase inhibitors. Though donepezil's primary mechanism of action is

supposed to be enzyme inhibition, so stimulating central cholinergic neurotransmission, it may have further actions, such as combating glutamate-induced excitotoxicity (Takada et al., 2003) and prompting amyloid processing and deposition (Racchi et al., 2004; Svensson and Nordberg, 1998), which more directly influence the pathophysiology of AD.

Donepezil, as an acetylcholinesterase (AChE) inhibitor, exerts an additional beneficial effect via the nicotinic acetylcholine receptor (nAChR)-mediated cascade (Takada et al., 2003). ACh receptors provide neuroprotection against glutamate-induced excitotoxicity by stimulating the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) pathway (Asomugha et al., 2010). The stimulation of nAChRs could attenuate the downregulation of the surface level of glutamate receptors containing the subunits NR1/2A and NMDA receptor activity (Shen et al., 2010).

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