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Diabetic Neuropathic Pain: An Update and Novel Pharmacological Strategies for Relief of Pain

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Diabetic neuropathy is one of the most painful complications of diabetes mellitus, involving progressive neuronal damage and dysfunction and up to 30% of patients with diabetes mellitus developed diabetic neuropathy. Pain caused by diabetic neuropathy is debilitating and often is refractory to classical analgesic, including morphine. The mechanisms underlying cause of diabetic neuropathic pain are complex and both peripheral and central components of the sensory systems are reported to be involved in progression and maintenance of neuropathy. This study summarises data on pathogenesis and on existing and new analgesics such as NSAIDS, opioids, anti-epileptic, membrane stabilising and anti-depressant drugs, that are the mainstay of treatment for alleviating diabetic neuropathic pain. In addition, novel pharmacological approaches and strategies for analgesics such as use of drug combination and their implications will be discussed.

Key words: Diabetic neuropathy, analgesics, antidepressant, anti-epileptic, opioids

INTRODUCTION

Diabetes Mellitus (DM) is reported to affect more than 100 million people worldwide in 2006 and is projected to affect more than 350 million by 2030 (Wild *et al.*, 2004). Painful Diabetic Neuropathy (PDN) may constitute a considerable clinical problem and a burdensome condition worldwide (Hoffman *et al.*, 2009). Various neuropathic symptoms, including hyperalgesia, allodynia, hypoesthesia and spontaneous pain, often develop in early stages, but may occur at any stage (Ramos *et al.*, 2007). These symptoms of painful diabetic neuropathy are highly unpleasant for the individuals and affect their quality of life (Hoffman *et al.*, 2009; Connor’O, 2009). Various classes of drug are currently under investigation to treat neuropathic pain but still there is no gold standard therapeutic approach or treatment to manage this difficult to treat pain (James *et al.*, 2008; Ziegler, 2010). Therefore, there is an urgent need to search for some novel strategies based approaches or new drugs for alleviating PDN, especially those with novel mechanisms of action where a combination of beneficial- rather than side-effect may be achieved. Pain caused by diabetic neuropathy is debilitating and often is refractory to classical analgesics, including morphine (Raghavendra *et al.*, 2004). The

mechanisms involved in genesis of diabetes -induced neuropathy are complex and poorly understood (Tesfaye, 2009; Ziegler, 2010). Accumulating evidence indicates that one of the major causes of diabetic peripheral neuropathy is oxidative stress (Ozkul *et al.*, 2010), formation of advanced glycation end product (Sugimoto *et al.*, 2008), increased flux through the polyol pathway that leads to accumulation of sorbitol and fructose (Chen *et al.*, 2010a), myo-inositol depletion and reduction in Na⁺-K⁺-ATPase activity (Pop-Busui *et al.*, 2010), deficits in neurotrophism leading to reduced expression and depletion of neurotrophic factors such as nerve growth factor (Stuart *et al.*, 2000), neurotrophin-3 and insulin-like growth factor (Shimoshige *et al.*, 2010), as well as alterations in axonal transport (Kuwabara and Misawa, 2008), PARP over-activation (Negi *et al.*, 2010) (Fig. 1). In addition to abnormalities of peripheral afferent nerves, altered sensory processing in the spinal cord may contribute to the development of diabetic neuropathic pain (Losest *et al.*, 2008; Morgado *et al.*, 2009). Other factors, such as upregulation of spinal excitatory glutamate receptors and increased release of glutamate and substance P, are also implicated in the development of spinal hypersensitivity in diabetes (Anjaneyulu *et al.*, 2008). Therefore, a thorough understanding of molecular

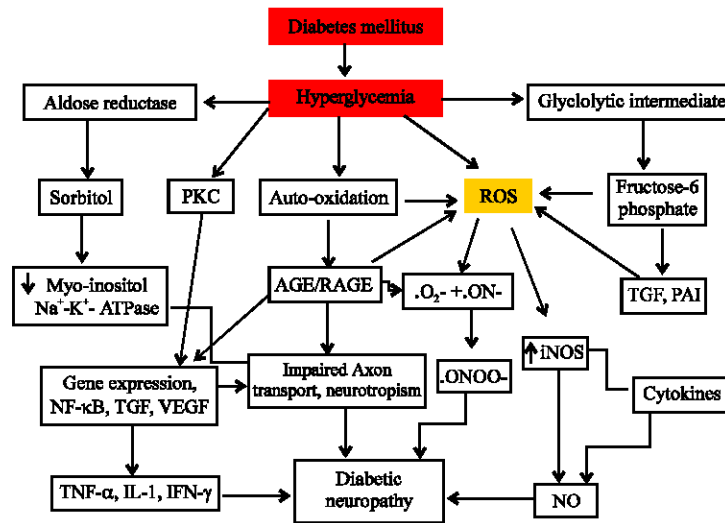


Fig. 1: Hyperglycemia induced generation of mitochondrial ROS, sorbitol and formation of AGEs initiates a vicious circle by activating stress-sensitive pathways such as NF-κB, p38 MAPK and Jak/STAT, polyol (sorbitol) and hexosamine pathways, PKC and RAGE. Hyperglycemia-induced glycation of protein, lipid, nucleic acid, increased sorbitol and pro-inflammatory cytokines exerts a positive feedback on ROS and RNS synthesis and potentiates PKC-mediated vascular dysfunction by altering gene expression as well as vascular function and structure. MAPK: Mitogen Activated Protein Kinase; PKC: Protein Kinase-C; NO: Nitric Oxide; AGE/RAGE: Advanced Glycation End product (receptor); ROS: Reactive Oxygen Species; TGF: Transforming Growth Factor; PAI: Plasminogen Activation Inhibitor; Nf-κB: Nuclear factor kappa-B

mechanism based therapeutic options and of the likely benefits and potential adverse effects of each option should be considered.

PATHOGENESIS OF PDN

Advanced glycation end-products pathway: Long standing hyperglycaemia has been reported to be involved in the formation of Advanced Glycation End-products (AGEs) (Lukic *et al.*, 2008; Yamagishi, 2009). AGEs are heterogeneous modified intracellular and extracellular bio-molecules formed via a non-enzymatic reaction between reducing sugars and amine residues on proteins, lipids, or nucleic acids (Barbosa *et al.*, 2008). Extracellular protein AGEs include plasma and matrix proteins that disrupt cellular adhesion and activate the receptor for AGEs (RAGE) (Yan *et al.*, 2010). Activation of RAGE or AGE-RAGE interaction induces oxidative stress (Yamagishi, 2009), Protein Kinase C (PKC) and the transcription of nuclear factor kappa B (NF- κ B) (Bierhaus *et al.*, 2001; Toth *et al.*, 2008). NF- κ B is a pleiotrophic gene regulator that regulates genes involved in promoting inflammatory reactions and neuronal dysfunction (Bierhaus *et al.*, 2001; Haslbeck *et al.*, 2005). Hyperglycaemia is reported to increase the levels of AGE and RAGE in diabetic patients (Lukic *et al.*, 2008). The RAGE expression in the peripheral nervous system rises cumulatively in diabetes patients and relates to progressive pathological changes (Toth *et al.*, 2008; Yan *et al.*, 2010). Diabetic mice lacking RAGE showed significant improvement in PDN and diminished expression of NF- κ B and PKC as compared to wild type diabetic model (Haslbeck *et al.*, 2005; Cameron and Cotter, 2008). Collectively, the biochemical damage induced by AGEs results in increase ROS, impaired nerve blood flow and diminished neurotrophic support contributes to neuronal injury (Loeth *et al.*, 2008; Yan *et al.*, 2010).

The polyol pathway: Increased flux, through the polyol-pathway leading to multiple biochemical abnormalities in the diabetic nerve, is thought to play a significant role in the pathogenesis of diabetic neuropathy (Sango *et al.*, 2006; Takafumi *et al.*, 2008). In polyol pathway, glucose is converted into sorbitol by Aldose Reductase (AR) and sorbitol dehydrogenase oxidises, sorbitol to fructose (Maria, 2005). Nicotinamide Adenosine Dihydrogen Phosphate (NADPH) is consumed by aldose reductase-mediated reduction of glucose to sorbitol (Srinivasan *et al.*, 2007) and NADPH is required for regeneration of antioxidant enzyme glutathione (GSH) thus deficient amount of glutathione contributes to oxidative stress (Kaneto *et al.*, 2001).

Moreover, conversion of glucose to sorbitol induced osmotic stress and to restore osmotic equilibrium to cell, other osmolytes, particularly taurine and myo-inositol, are effluxes from cells. Depletion of taurine and myo-inositol in nerve cells are implicated in PDN (Sima *et al.*, 1997; Trevor *et al.*, 2009) and supplementation of taurine and myo-inositol prevented neuropathic deficits (Pop-Busui *et al.*, 2001; Trevor *et al.*, 2009). On the other hand, excess formation of fructose in polyol pathway promotes advanced glycation end product as well as depletes NADPH, further augmenting Reactive Oxygen Species (ROS) mediated damage of cellular protein, lipid and neuron (Srinivasan *et al.*, 2007; Sugimoto *et al.*, 2008).

Aldose-Reductase Inhibitors (ARI), block the increased activity of aldose reductase, the rate-limiting enzyme that converts glucose to sorbitol (Ramirez and Borja, 2008), reduces sorbitol level implicated in PDN (Takafumi *et al.*, 2008). Transgenic mice over-expressing aldose reductase in Schwann cells shown severe nerve conduction velocity deficit and oxidative stress under hyperglycaemic stress (Song *et al.*, 2003). On the contrary, aldose reductase deficiency or inhibitors improves nerve conduction velocity deficits, Wallerian degeneration and nerve regeneration in diabetic animals (Chen *et al.*, 2010b). The first trials of ARIs in diabetic neuropathy were carried out 20 years ago and offer attractive therapeutic option to treat PDN (Ramirez and Borja, 2008). Later on, various compounds have been evaluated such as alrestatin, sorbinil, ponalrestat, tolrestat, epalrestat, zopolrestat and zenarestat for the treatment of PDN (Bril *et al.*, 2009; Shimoshige *et al.*, 2009). Long-term treatment with ranirestat (AS-3201), a potent aldose reductase inhibitor, has been reported to suppress diabetic neuropathy and cataract formation in rats (Takafumi *et al.*, 2008). However, clinical trials with ARIs discomfited and shown lack of efficacy and potential toxicity. Therefore, subsequent clinical evaluation of ARI such as sorbinil tolrestat, ponalrestat and zopolrestat were halted due to lack of efficacy in PDN (Brown *et al.*, 2004; SRTRG, 1993). Epalrestat is the only ARI drug approved and marketed in Japan and India for PDN (Manish *et al.*, 2009).

Hexosamine pathway: The hexosamine pathway is activated when excess metabolite of glycolysis accumulated and was implicated in diabetes-induced oxidative stress and complications (James *et al.*, 2008). Fructose-6 phosphate is a metabolic intermediate of glycolysis. However, during glucose metabolism some fructose-6 phosphate is shunted from the glycolytic pathway to the hexosamine pathway and is converted to glucosamine-6 phosphate by glutamine fructose-6

phosphate amidotransferase (GFAT) (Srinivasan *et al.*, 2007). The end-product of this pathway, UDP-N acetylglucosamine (UDP-GlcNAc), is a substrate for the glycation of important intracellular factors including transcription factor, thereby affecting the expression of many genes including Plasminogen Activator-Inhibitor (PA-I) and Transforming Growth Factors (TGF) and leads to diabetic microvascular complications (Du *et al.*, 2000; Kaneto *et al.*, 2001). Inhibition of GFAT block the transcription of TGF and PA-I and are shown beneficial effect in PDN (Maria, 2005; Srinivasan *et al.*, 2007). In addition, the hexosamine biosynthesis inhibitor azaserine prevents endothelial inflammation and dysfunction under hyperglycemic condition through antioxidant effects (Angana *et al.*, 2009).

Protein kinase C pathway: The Protein Kinase C (PKC) pathway is an additional mechanism implicated in hyperglycemia induced neuropathy (Evcimen and King, 2007). Increased glucose levels stimulate diacylglycerol (DAG), which in turn activates PKC and PKC- β isoform which is known to contribute in PDN (Gerald and King, 2010). Selective inhibitors of PKC- β such as ruboxistaurin ameliorated several neuropathic deficits in experimental diabetic neuropathy (Carolina *et al.*, 2007a; Danis and Sheetz, 2009). In a Phase II-clinical trial, ruboxistaurin at a dose of doses of 32-64 mg day⁻¹ attenuated neuropathic symptoms and deficits, including overall neurologic examination and patient global assessment (Carolina *et al.*, 2007b). We await the results of ruboxistaurin trials, a selective PKC- β inhibitor and the possibility of the future trials with other isoform selective PKC drugs for the treatment of PDN.

OXIDATIVE STRESS AND PDN

Increased oxidative stress is a unifying mechanism in the causation of PDN (Vincent *et al.*, 2010). Antioxidant treatment have proven benefits in PDN (Pazdro and Burgess, 2010; Skalska *et al.*, 2010). Hyperglycaemia induced activation of polyol, hexosamine pathway and formation of advanced glycation end products are known to increase the production of Reactive Oxygen Species (ROS) that contribute to nerve injury (Johansen *et al.*, 2005; Friederich *et al.*, 2009). In normal neuron, ROS production is tightly regulated. The free radical superoxide is generated by mitochondrial electron transfer chain when nicotinamide adenine dinucleotide (NADH) is oxidised to NAD⁺. Superoxide produced in diabetic and hyperglycemic conditions rapidly combines with NO and the formed peroxynitrite causes protein nitration or nitrosylation, lipid peroxidation, DNA damage and cell

death and has direct toxic effects on the nerve tissue leading to neuropathic pain (Obrosova *et al.*, 2007a; Drel *et al.*, 2010). Mitochondria in neuron is sensitive to oxidative damage-which results impaired energy regulatory function that leads to loss of neuronal function and the development of PDN (Friederich *et al.*, 2009). Moreover, excess generation of mitochondrial ROS due to hyperglycemia initiates a vicious circle by activating stress-sensitive pathways such as NF- κ B, p38 MAPK, Jak/STAT, PKC and pro-inflammatory cytokines that contribute to diabetic complications (Fabio *et al.*, 2001; Ziegler, 2008). In addition, hyperglycaemia increases the formation of potent oxidant peroxynitrite, which is formed by the combination of superoxide anion radical with nitric oxide and the formed peroxynitrite has been documented to play a key role in experimental and clinical diabetic neuropathy (Obrosova *et al.*, 2007b; Drel *et al.*, 2010). Peroxynitrite causes nitration and nitrosylation of biomolecules including proteins, lipids, DNA and has a direct toxic effect on neurones leading to diabetic complication (Obrosova *et al.*, 2007b; Drel *et al.*, 2010).

Poly (ADP-ribose) polymerase pathway (PARP): Oxido-nitrosative stress has been implicated in DNA single-strand breakage, followed by over activation of PARP, which contribute to PDN (Obrosova *et al.*, 2007a; Negi *et al.*, 2010). PARP is a nuclear enzyme that acts as a DNA-nick sensor and facilitates DNA repair. The PARP acts by cleaving Nicotinamide Adenine Dinucleotide (NAD⁺) to nicotinamide and ADP ribose residues attached to nuclear proteins (Maureen and Bonner-Weir, 1999). This result in NAD⁺ depletion and the metabolic pathway that depends upon NAD⁺ such as glycolysis and mitochondrial respiration are impaired. Further, depletion of NAD⁺ leads to changes in gene transcription and expression, increased free radical and oxidant concentration and diversion of glycolytic intermediates to other pathogenic pathways such as PKC, AGE formation and nitro-sative stress (Maureen and Bonner-Weir, 1999). The PARP inhibition or gene deficiency shown to counteract intraepidermal nerve fiber loss and neuropathic pain in advanced diabetic neuropathy (Olga *et al.*, 2006; Obrosova, 2009). Moreover, concurrent targeting of nitrosative stress-PARP pathway has been reported to corrects functional, behavioral and biochemical deficits in experimental diabetic neuropathy (Negi *et al.*, 2010).

Involvement of cytokines and chemokines: Hyperglycaemia is known to increase inflammatory mediators including C-reactive protein, interleukin-2 (IL-2), IL-6 and TNF- α in both type-1 and type-2 DM (Goldberg, 2009; Lawrence and Catherine, 2010). Higher levels of

pro-inflammatory cytokines correlate with the incidence of neuropathy (Yu *et al.*, 2009). Spinal proinflammatory cytokines such as TNF- α , IFN γ and ILs are powerful pain-enhancing signals that contribute to neuropathic pain (Juan and Carmen, 2008; Doupis *et al.*, 2009). In addition, hyperglycaemia induced ROS and AGEs activate intracellular inflammatory signalling to up-regulate NF- κ B (Iwasaki *et al.*, 2007; Toth *et al.*, 2008). NF- κ B is a pleiotropic gene regulator that regulates the expression of various diffusible factors including cytokines (Cameron and Cotter, 2008). Pro-inflammatory cytokines are also known to increase the expression of inducible Nitric Oxide Synthetase (iNOS) and like cytokines (Malin *et al.*, 1996; Koch *et al.*, 2007). The iNOS both induces and is induced by NF- κ B, leading to a vicious cycle of inflammation (Iwasaki *et al.*, 2007; Drel *et al.*, 2010). The NO generated by iNOS directly modulates the blood supply to nerves and participates in macro and microvascular changes following injury (Obrosova *et al.*, 2007a, b; Vareniuk *et al.*, 2008). The NO has direct role in axon and myelin breakdown following an injury (Pamela and Benjamin, 1998) and also contributes to the development of hyperalgesia and allodynia (Grover *et al.*, 2000; Chen *et al.*, 2010b). Genetic knockout nitric oxide synthase mice failed to display nerve-injury induced mechanical hypersensitivity (Guan *et al.*, 2007). Thus cytokines and NO are seems to play a key role in initiation and maintenance of neuropathic pain and inhibition or blockage of cytokines is an attractive therapeutic approach in PDN (Yu *et al.*, 2009). Long-term treatment of diabetic rats with cyclosporine, an inhibitor of interleukin-2, attenuated STZ-induced neuropathic pain (Taliyan *et al.*, 2010a).

Pharmacological treatment of PDN based on their mechanism of action: Various classes of drugs are being examined and used for the treatment of neuropathic pain and strict glycaemic control is remains the best preventive measure for neuropathy (Ziegler *et al.*, 2009). The Diabetes Control and Complications Trial (DCCT) has reported that strict glycaemic control in patients with DM not only decreased the incidence of neuropathy but also slowed its progression by 50-55% (DCCT, 1993; Pop-Busui *et al.*, 2010). However, more than 30-40% patients are unable to achieve complete pain relief, even after glycaemic control (Kaye *et al.*, 2003; Ziegler, 2008). Chronic hyperglycemia is associated with the loss of myelinated and unmyelinated fibers, Wallerian degeneration and blunted nerve-fiber reproduction (Pamela and Benjamin, 1998). Further, hyperglycaemia is known to attenuate motor nerve conduction velocity and Nerve Blood Flow (NBF) (Saini *et al.*, 2004). The patho-

physiologic mechanisms that underlie these changes are not clearly understood, however, various mechanisms has been proposed (Fig. 1), such as oxidative stress, the formation of sorbitol and advanced glycosylation end products, activation of PKC, increased proinflammatory cytokines and iNOS, that consequently leads a cascade of various signalling mechanism that contribute to PDN (Tesfaye, 2009; Ziegler, 2010). Therefore, a thorough understanding of molecular mechanism based therapeutic approach and of the likely benefits and potential adverse effects of each option should be considered. Newer agents have been designed to favorably influence the underlying process, rather than for symptomatic pain relief (Brian and Kathie, 2007). Approaches to prevention or treatment of diabetic neuropathy include the intensive treatment of hyperglycaemia, aldose reductase inhibition, anti-oxidant, AGE-inhibitor, cytokines inhibitors/antagonist and various symptomatic treatments (Chong and Brandner, 2006; Ziegler, 2010) (Table 1).

Anti-depressants and anti-epileptics: The first line therapy of drugs used to treat PDN are antidepressants (tricyclic antidepressants) (TCAs), anti-epileptics and Selective Serotonin Reuptake Inhibitors (SSRI) drug (Wong, 2008; Sibia *et al.*, 2009). The TCA was studied for neuropathic pain in late 1950 and are known to act by inhibiting serotonin and noradrenaline reuptake. The first medication studied in a randomized, controlled trial for the treatment of PDN was amitriptyline in late 1977, that led to a plethora of synthetic drugs and various TCA agents tested for the treatment of PDN (Saarto and Wiffen, 2007; Bansal *et al.*, 2009). Several double blind, placebo controlled, crossover clinical trials have demonstrated the efficacy of the TCAs such as amitriptyline, imipramine, clomipramine and desipramine (Max *et al.*, 1991; Sindrup *et al.*, 2003). Among them, amitriptyline/nortriptyline and desipramine are found effective and are considered first choice TCAs for treating painful diabetic neuropathy (Gilron *et al.*, 2009). Although, amitriptyline and desipramine relieve pain in many patients with painful diabetic neuropathy, side effects often preclude effective treatment (Max *et al.*, 1991). Moreover, second generation antidepressant, SSRIs include fluoxetine, paroxetine, sertraline and citalopram, have not yet been FDA approved to treat painful neuropathy because they have been found to be no more efficacious than placebo in several controlled trials. On the contrary, venlafaxine, a third generation TCA has been demonstrated to produce significant pain relief as compared with placebo in a double blind, placebo controlled study (Rowbotham *et al.*, 2004;

Table 1: Mechanism based pharmacological treatment for PDN

TCA agents	MOA	Dose (mg)	Side effects
First line treatment for diabetic painful neuropathy			
Amitriptyline	Inhibit reuptake of NA, 5-HT	75-150	Sedation, blurred vision, weight gain, urinary retention, CVS toxicity
Desipramine	Do	100-200	
Duloxetine*	Dual inhibitor of reuptake of NA and 5-HT	60-120	Nausea, vomiting, hepatic dysfunction
Venlafaxine	Do	75-250	Do
Anticonvulsant			
Carbamazepine	Inhibit Na ⁺ channel	200-400	Dizziness, ataxia, aplastic anaemia
Lamotrigine	Inhibit Na ⁺ channel and increase GABA	150-300	Rashes
Pregabalin*	α2 binding-decrease Ca ⁺⁺	300-600	Dizziness, ataxia, sedation, euphoria, ankle, edema and weight gain
Gabapentin	Do	1800-3600	Do
Second line drug treatment for diabetic painful neuropathy			
Morphine	Agonist μ-receptor	10-15	Sedation, constipation, dizziness, addiction
Oxycodone CR	Do	20-100	Sedation, constipation, dizziness
Tramadol	Weak-μ-agonist+inhibit NA and 5-HT reuptake	150-400	Nausea/vomiting, drowsiness, dizziness
Third line treatment for diabetic painful neuropathy			
Capsaicin cream	Deplete Sub-P	0.075% qid/bid	Burning, local erythema, rash
Lidocaine cream or gel	Inhibit Na ⁺ channel	5% qid/bid	Local erythema, rash
ALA	Anti-oxidant	600-800	Nausea

MOA: Mode of action; NA: Nor-adrenaline, 5-HT: 5-hydroxytryptaline (serotonin), *Approved for PDN

Kadiroglu *et al.*, 2008). Duloxetine (Cymbalta) is the first antidepressant drug, which equally inhibit reuptake of serotonin and nor-adrenaline manufactured by Ely-lily, approved by the FDA in 2004 for the treatment of diabetic neuropathic pain and fibromyalgia (Acuna, 2008; Sultan *et al.*, 2008). Moreover, duloxetine is equally effective in the treatment of diabetic peripheral neuropathic pain as two anticonvulsants, gabapentin and pregabalin, which are pharmacologically unrelated to duloxetine (Goldstein *et al.*, 2005; Sibilial *et al.*, 2009). However, TCA treatment is known to be associated with various side effects such as dry mouth, sweating, dizziness and sedation (Hall *et al.*, 2010). In addition, recently, a retrospective study, including 58,956 person years follow-up on TCA therapy, indicates severe cardiac toxicity and TCAs are contraindicated in heart disease, epilepsy and glaucoma patients (Table 1).

Anti-epileptics: Antiepileptic drugs originally developed for preventing seizure are now in broad use for the treatment of PDN (Sindrup *et al.*, 2005). Carbamazepine was first anti-epileptic agents tested in late 1969 for neuropathic pain (Rull *et al.*, 1969; Chakrabarti and Samantaray, 1976). Carbamazepine and phenytoin are known to block the voltage gated sodium channels and both reduced PDN as compared to placebo (Jia *et al.*, 2006), however, due to various side effect, their use for the treatment of PDN is not recommended (Yamada *et al.*, 2002). Lamotrigine is another anticonvulsant reported to produce favourable results in the treatment of PDN (Vinik *et al.*, 2007). Lamotrigine has multiple actions, blockade of voltage gated sodium channels, decreased

presynaptic calcium currents to inhibit the release of glutamate and increased GABA levels in the brain (Pop-Busui, 2007). Gabapentin and pregabalin, both produces analgesia via binding to the α2-δ site of L-type voltage gated calcium channels and decreasing calcium influx (Sibilial *et al.*, 2009). Various multicentre double blind, randomized, placebo controlled trial, have demonstrated that extended gabapentin or pregabalin at a dose from 900 to 3600 mg day⁻¹, significantly reduced pain of PDN compared with placebo (Sandercock *et al.*, 2009; Chou *et al.*, 2009). Pfizer has marketed an anti-epileptic agents, gabapentin, under the brand name of neurotonin an adjunct for seizure in late 1983 and the benefits of this drug for other conditions, like neuropathy, soon became known (Kenneth *et al.*, 1999). Another drug also developed by Pfizer, pregabalin (Lyrica), is an analogue of Gamma-Amino Butyric Acid (GABA) was approved by Food and Drug Administration (FDA) in 2005, for use in neuropathic pain associated with diabetic peripheral neuropathy (Beghi, 2004; Stump, 2009) (Table 1).

NSAIDs: Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used for the treatment of PDN (Kellogg *et al.*, 2008). An increase level of cyclooxygenase-2 (COX-2) protein in the lumbar spinal cord and sciatic nerve has been demonstrated in diabetic patients that implicated in diabetes induced endoneurial nerve blood flow deficits (Pop-Busui *et al.*, 2002; Matsunaga *et al.*, 2007). Cox-2 selective inhibition and/or COX-2 gene inactivation provide protection against various neuropathy symptoms and deficits associated with PDN (Kellogg *et al.*, 2007). In addition, pro-inflammatory cytokines and inflammatory mediators

are known to increase the expression of inducible nitric oxide and COX-2 enzyme (Taliyan *et al.*, 2010b). Concurrent targeting of both COX-2 and iNOS may provide better result for the treatment of PDN. A few studies have been demonstrated ameliorative potential of combination of iNOS with selective COX-2 inhibitors in neuropathic pain in rats (Dudhgaonkar *et al.*, 2008). However, the effectiveness of COX-2 inhibitors or COX-2 with iNOS inhibitor is not yet proven in clinical studies. Great caution must be taken, when NSAIDS are used for the treatment of PDN due to their detrimental effects to Gastro-Intestinal Tract (GIT), renal and cardiac functions.

Opioids: Opioids such as morphine, fentanyl, oxycodone are strong analgesics with proven efficacy to manage chronic pain (Pergolizzi *et al.*, 2008; Riley *et al.*, 2008). However, their use in treatment of PDN is still a matter of debate, some studies indicating usefulness of opioids in PDN (Canta *et al.*, 2009; Attal *et al.*, 2010), whereas some other studies indicating inadequate efficacy of opioids in PDN (Karci *et al.*, 2004; Christoph *et al.*, 2010). Long term treatment with opioids are associated with side effect including constipation, urinary retention, impaired cognitive function, impaired immune function and many other issues such as analgesic tolerance and addiction (Raghavendra *et al.*, 2004; Taliyan *et al.*, 2010b). However, long acting opioids such as fentanyl, methadone and oxycodone were effective in PDN (Vallerand, 2003; Hays *et al.*, 2005; Riley *et al.*, 2008). Recently, various randomized, placebo controlled study demonstrated that slow release oxycodone 80 mg day⁻¹ significantly relieved PDN (Gimbel *et al.*, 2003; Hanna *et al.*, 2008) and improved health related quality of life (Watson *et al.*, 2003). Moreover, numerous clinical studies reported that pregablin and morphine/oxycodone prescribed together is more efficacious than one or either drug alone for alleviating PDN (Gilron *et al.*, 2005; Zin *et al.*, 2010).

Tramadol: Tramadol is a fruitful result of extensive studies in search of a desirable molecule which act by multiple mechanisms and is associated with fewer adverse effects (Harati *et al.*, 2000; Ebell, 2007). Tramadol is a centrally acting weak μ -opioid receptor agonist that also inhibits the reuptake of norepinephrine and 5-HT very much like TCA, leading to enhancement of endogenous pain inhibitory pathway (Tzschentke *et al.*, 2006; Reeves and Burke, 2008). In a randomized placebo, 6 week controlled study, tramadol significantly reduced pain and enhanced quality of life as compared with placebo and was well tolerated in the management of painful diabetic neuropathy (Christoph *et al.*, 2007; Freeman *et al.*, 2007). In addition, the risk of abuse with tramadol is less than

that with strong opioids analgesics such as morphine, oxycodone, methadone and fentanyl (Kazuhisa *et al.*, 2009; Wade and Spruill, 2009). The US Food and Drug administration approved tramadol for the management of moderate to severe pain in Nov-2008 (Wade and Spruill, 2009).

Alpha-lipoic acid: Alpha-Lipoic Acid (ALA), an anti-oxidant, has been reported to relieve pain associated with neuropathy in diabetic patients (Singh and Jialal, 2008). Alpha-lipoic acid used as a non-prescription dietary supplement for the treatment of PDN (Huang and Gitelman, 2008; Shay *et al.*, 2009). A randomized controlled trial that compared once-daily oral doses of 600 to 1800 mg of ALA to placebo, demonstrated that ALA significantly reduced symptoms of neuropathy in patients (Ziegler *et al.*, 2006; Liu *et al.*, 2007). In a meta-analysis comprising 1,258 patients, infusions of ALA (600 mg i.v per day) over a 3 week period, improved neuropathic symptoms and deficits (Alexander *et al.*, 2003; Liu *et al.*, 2007). More recently, a clinical trial (Sydney trial-2) has demonstrated, that oral lipoic acid (600 mg kg⁻¹ for 5 weeks) markedly attenuated PDN as compared with placebo (Ziegler *et al.*, 2006). These study provide evidence that treatment with alpha-lipoic acid improves nerve conduction velocity deficits, endoneurial blood flow and nerve Na⁺ K⁺ ATPase activity in experimental diabetes and in humans (Alexander *et al.*, 2003; Tankova *et al.*, 2005) and may improve positive neuropathic sensory symptoms by improving the imbalance between increased oxidative stress and depleted antioxidant defense even in patients with poor glycemic control (Huang and Gitelman, 2008; Skalska *et al.*, 2010). In addition, lipoic acid has fewer side effects than traditional treatments for neuropathy, such as gabapentin (Neurontin) and pregabalin (Lyrica) (Foster, 2007; Vallianou *et al.*, 2009) and are approved for PDN treatment in Germany (Ziegler *et al.*, 1999).

Topical analgesics: As depicted in Table 1, Numerous topical analgesics such as capsaicin (Zostrix), mexilitine, lidocaine 5% patch (Lidoderm) or gel, doxepin (Zonalon) (Lorna *et al.*, 2004; Wong, 2008) and colindine gel (Campbell *et al.*, 2009) are gaining in popularity among pain specialists and can offer pain relief in PDN without potential systemic toxicity (Wong, 2008; Wolffa *et al.*, 2010).

Capsaicin: It has been recognized for almost 150 years that the topical application of the capsaicin produced pain relief (Lorna *et al.*, 2004). It is now recognized that capsaicin causes reversible depletion of the

neurotransmitter Substance-P (SP) from the sensory nerve endings, which are involved in hypersensitivity of neuron to painful stimuli (hyperalgesia) (De Felipe *et al.*, 1998). Topical application of capsaicin has been shown to reduce the pain of a variety of conditions, including post herpetic neuralgia (Watson *et al.*, 1993), painful diabetic neuropathy (Capsaicin Study Group, 1992; Tandan *et al.*, 1992) and osteoarthritis (Rains and Bryson, 1995; McCleane, 2000a). A meta-analysis of four randomized, double-blind, placebo-controlled trials of capsaicin (0.75%) in diabetic neuropathy found capsaicin more effective than placebo (McCleane and McLaughlin, 1998; Walker and McCleane, 2002). In addition, another double-blind study demonstrated that capsaicin was as effective as amitriptyline (Biesbroek *et al.*, 1995). The major limitation of capsaicin is that of burning discomfort and poor patient compliance because of the need for frequent applications and redness at application site (Rains and Bryson, 1995). Recently, it was reported that the burning discomfort associated with application of capsaicin is reduced by addition of glyceryl trinitrate (GTN) to capsaicin and improved compliance (McCleane, 2000b). The GTN is known to have an anti-inflammatory effect and this may augment the analgesia when combined with capsaicin (McCleane and McLaughlin, 1998; McCleane, 2000b). In a double blind, placebo controlled trial of 40 volunteers; the burning discomfort associated with application of capsaicin cream (0.025%) was compared to placebo, GTN cream (1.33%) and to the combination of capsaicin cream (0.025%) plus GTN cream 1.33%. This study demonstrated that after single application the addition of GTN to capsaicin significantly reduced the burning discomfort associated with application of capsaicin alone (McCleane and McLaughlin, 1998; Walker and McCleane, 2002).

Miscellaneous pharmacological agents: A large number of pharmacological agents including levodopa (Ertas *et al.*, 1998), baclofen (Anghinah *et al.*, 1994), nerve growth factor (Stuart *et al.*, 2000), gamma-linolenic acid (Hounsom *et al.*, 1998), acetyl-L Camintine (Evans, 2008), methylcobalamin (Sun *et al.*, 2005), mexilitine (Oskarsson *et al.*, 1997). NMDA-antagonist, i.e., dextromethorphan, cannabinoids, ketamine and memantine have been tested and shown promising results for the treatment of PDN (Sang *et al.*, 2002; Chen *et al.*, 2009). However, clinical data for these agents are still insufficient.

Novel pharmacological approaches to treat PDN: Inadequate pain relief in diabetic patients associated with painful neuropathy remains a major cause of suffering.

According to DCCT, strict glycemic control remains the best available treatment option for PDN, although other treatments are in development (DCCT, 1993; Pop-Busui *et al.*, 2010). Because of various mechanism involved in initiation and maintenance of neuropathic pain, a combined strategy is necessary to manage difficult to treat PDN (Eyigor *et al.*, 2009; Obrosova, 2009). Recently, combination of analgesics which act by different modes of action such as an opioid and a non opioid was fostered and constitute a valid approach to the treatment of chronic pain, where a reduction of individual doses and consequently of side effects, could be very important (Ziegler, 2008; Varrassi *et al.*, 2010). It has been demonstrated that combining of opioids with NMDA receptor antagonist (L-Dextromethorphan, or ketamine), alpha-2 receptor ligands such as gabapentin/pregablin (Hanna *et al.*, 2008; Gilron *et al.*, 2005) and antidepressant such as amitriptyline/nortriptyline provide adequate pain relief in PDN (Gilron *et al.*, 2009). However, some issues associated with use of combination of different drug, remain to be explored, such as the safety of poly-pharmacy and its effect on compliance, while clinical trials suggest that any improvement in efficacy may be outweighed by the increased incidence of side effects (Hanna *et al.*, 2008; Varrassi *et al.*, 2010).

Opioids are strong analgesics and WHO has recommended the use of opioids for treatment of chronic pain (Boulton, 2005). However, addiction and development of analgesic tolerance to morphine in nerve injury or diabetes induced pain is the major hurdle in clinical practice (Raghavendra *et al.*, 2004; Carolina *et al.*, 2007b). Activation of N-methyl-D-aspartate (Wen *et al.*, 2008; Lin *et al.*, 2010), opioid receptor internalization/desensitization has been reported to play a key role in development of analgesic tolerance to morphine (Nishikawa *et al.*, 2004). Hyperglycaemia induced activation of MAPK (Cui *et al.*, 2006), PKC (Gerald and King, 2010), NO (Salvemini and Neumann, 2010) and increased productions of pro-inflammatory cytokines (Doupis *et al.*, 2009) are well reported mechanisms that contribute to morphine analgesic tolerance (Berger and Whistler, 2010).

Once tolerance to the analgesic effect of the opioids are observed and in order to avoid unnecessary further development of tolerance, simultaneous administration of other receptor mediated analgesics and opioids rotation of a more potent ligand such as methadone, fentanyl or oxycodone is advocated (Berger and Whistler, 2010). Although, tolerance development may result in use of staggering doses of opioids, there is no reason to evade the use of such strong analgesic agents. Development of

analgesic tolerance could be handled by various approaches such as the concept of multimodal analgesia, consisting of the simultaneous use of analgesics with a different mode of action, NMDA receptor blocker/antagonist and low dose μ -opioid receptor antagonist, can counteract tolerance development (Elizabeth *et al.*, 2010; Berger and Whistler, 2010). In addition, splenectomy in diabetic animals have been reported to restore analgesic effect of morphine (Taliyan *et al.*, 2010c).

Non-pharmacological therapies: Several non-pharmacological approaches such as physiotherapy, acupuncture and Transcutaneous Electrical Nerve Stimulation (TENS) have been reported to be effective for pain relief (Kalra *et al.*, 2007). Acupuncture as a management strategy for painful diabetic neuropathy is also supported by research (Ahn *et al.*, 2007; Zhang *et al.*, 2010). A pilot randomised clinical study has shown beneficial effect of acupuncture (traditional Chinese medicine versus Japanese acupuncture) in management of painful diabetic neuropathy (Ahn *et al.*, 2007). The TENS is another non-pharmacological approach, shown beneficial effect in the management for DNP (Rader and Barry, 2006). The TENS provides a mild electrical stimulation through the application of surface electrodes over the painful area (Goodnick *et al.*, 2000). The mild electrical current, generates heat that serves to relieve stiffness, improve mobility, was thought to relieve pain via release of endothelium dependent relaxing factor and endogenous opioids (Wei-Hua *et al.*, 2004; Kalra *et al.*, 2007). Similarly, interferential therapy (IFT) uses the strong physiological effects of low frequency electrical stimulation of nerves and has proven benefits in the managements of PDN.

CONCLUSIONS

Advancement in medical science offers great hope for the treatment of patients with diabetes and its complication and glycemic control is remains the best treatment for diabetes and/or diabetes induced complications including neuropathy (Pop-Busui *et al.*, 2010). In addition, anticonvulsants such as gabapentin, pregabalin and lamotrigine, antidepressants such as venlafaxine, duloxetine and amitryptaline, ion channel blockers, N-Methyl-D-Aspartic acid (NMDA) receptor antagonists, opioids and tramadol are used to manage diabetic complication but they merely provide symptomatic relief and do not modify the course of the disease (James *et al.*, 2008; Ziegler *et al.*, 2009; Varrassi *et al.*, 2010). Therefore, identification of underlying mechanisms is of greatest need to better

understand the failures with existing treatments and develop new approaches for diagnosis, prevention and managements of PDN. Combinations of opioids with non-opioid drugs have been demonstrated to offer benefits over single agent for treatment of PDN (Gilron *et al.*, 2005). However, safety and tolerability of combination in clinical practice is yet to be proven. Anticonvulsants such as gabapentin and antidepressants such as duloxetine are the most successful pharmacological agents and are common treatment options for PDN, but evidence of the long-term efficacy of mono-therapy with these drugs in human is still lacking. Thus, developing a drug, which can act by multiple mechanism and/or modify the underlying pathogenesis of painful diabetic neuropathy, would meet a critical unmet need. Tramadol is perhaps the best example that has opioid analgesic (μ -agonist) and serotonergic properties, theoretically, make it an attractive medication for diabetic neuropathy (Reeves and Burke, 2008). Similarly, another agent AVP-923 (Neurodex), is a combination of dextromethorphan and an inhibitor of its metabolizing enzyme CYP2D6 quinidine, underwent a Phase III trial for PDN and demonstrated significantly better pain relief than placebo (Olney and Rosen, 2010). Although, many experimental and clinical studies with novel pharmacological agents have been performed to determine the most optimal strategy for preventing and treating diabetic neuropathy, but the pharmacologic treatment for PDN remains a challenge for the clinician. Safety and tolerability remains a major aspect in any treatment decision. More studies on different drug mechanism, drug combinations, are needed and ideally, non-pharmacological methods for attenuating PDN should also be included.

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