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MANAGING DIABETIC PERIPHERAL NEUROPATHY: A REVIEW

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Diabetic Peripheral Neuropathy (DPN) is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.[1] But, as per ADA guidelines, although DPN is a diagnosis of exclusion, complex investigations to exclude other conditions are rarely needed.[2] DPN is a heterogeneous group of disorders that affect different parts of the nervous system leading to diverse subclinical and clinical manifestation. This article will discuss the classification, pathophysiology and review the current management for treating peripheral diabetic neuropathy, and briefly mentions future treatment options.

EPIDEMIOLOGY

Diabetic neuropathy is common, especially in the western world, and is present in up to 50% of the older type 2 diabetic patients.[4] Chronic neuropathic pain is present in 13 – 26% of diabetic patients. DPN, which is the most relevant clinical manifestation, affects approximately 30% of the hospital-based population and approximately 25% of community-based patients.[3] The incidence of DPN is approximately 2% per year and most patients remain asymptomatic for 5 years after diagnosis.

The total annual cost of DPN and its complications in the US is $4.6 and $13.7 billion dollars respectively. Up to 27% of the direct medical cost of diabetes may be attributed to DPN.[5]

Even though numerous classifications have been described, Thomas et al., originally propose the classification that was adapted by the ADA (**Figure 1**).

The diabetic neuropathies are heterogeneous, affecting different parts of the nervous system, and present with diverse clinical manifestations that may be focal or diffuse. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy (primarily involving of the feet) and the autonomic neuropathies.[6,7]

Generalized symmetric polyneuropathy is more diffuse, commonly with an insidious onset, and usually progressive. Half of patients can be asymptomatic. Examples of generalized symmetric polyneuropathy include acute sensory (rare and follows sudden changes in glycemic control), chronic sensiromotor diabetic neuropathy (most common with frequent pain, burning and stabbing sensation), and autonomic neuropathy (diffuse subclinical dysfunction, usually confined to one or two organ systems).[8] Focal and multifocal neuropathies have a sudden onset and improve over time.

These isolated peripheral nerve lesions may be a feature in older diabetic patients -- examples include, truncal neuropathy, cranial neuropathies, and diabetic amyotrophy.[8]

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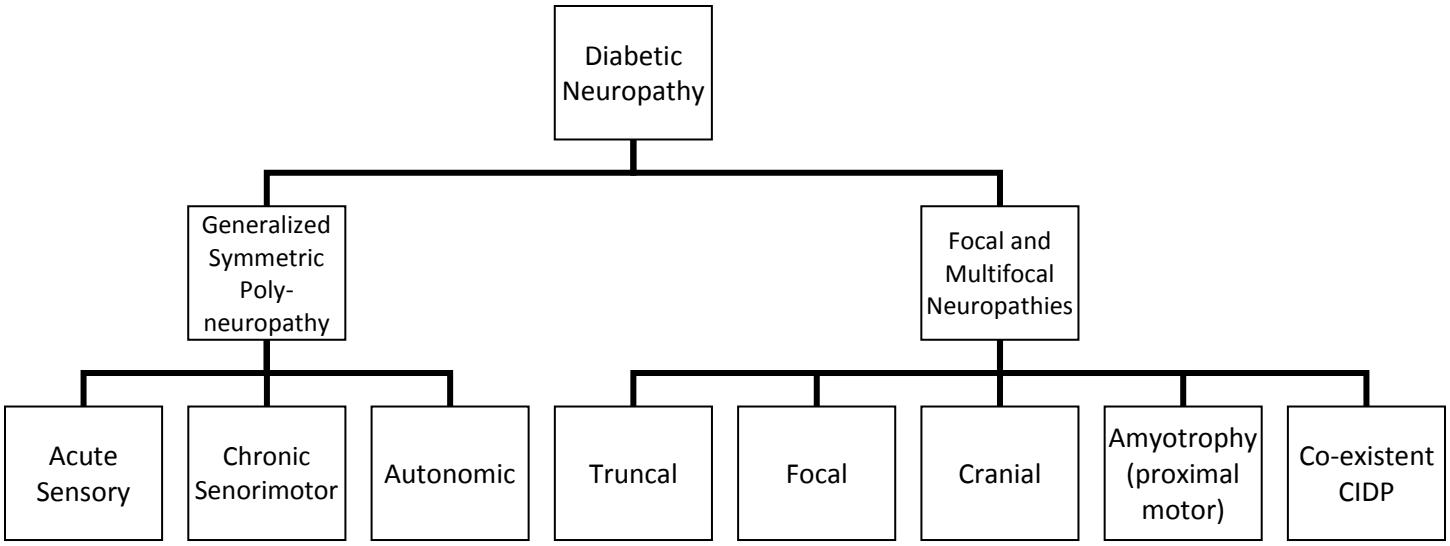

FIGURE 1. Classification scheme proposed by Thomas et al. (Adapted from Mahmood[6])

PATHOGENESIS

The pathology of DPN is characterized by poorly controlled glycemia that leads to progressive nerve fiber loss. Nerve fiber loss subsequently gives rise to symptoms such as pain, parasthesiae and loss of sensation. A number of biochemical mechanisms have been proposed which may contribute to the development of diabetic neuropathy (**Table 1**).

TREATMENT

The main goal for the treatment and management of diabetic neuropathy is proper glycemic control. Current treatment algorithms recommend treatment with tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentin/pregabalin, lidocaine, or partial/full μ-opioid agonists, depending on clinical presentation and patient factors (**Figure 2**).

Tricyclic Antidepressants (TCAs)

TCAs have been evaluated extensively in the treatment of DPN (**Table 2**). The assumed mechanism of pain relief is via the inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems. These agents also antagonize NDMA receptors that mediate hyperalgesia and allodynia. Amitriptyline, imipramine and clomipramine induce a balance reuptake inhibition of both norepinephrine and serotonin, whereas, desipramine, is a relatively selective norepinephrine reuptake inhibi-

TABLE 1. Theoretical biochemical mechanisms in diabetic neuropathy.[6]

Nonenzymatic Glycation	Excess glucose, reacts with proteins, nucleotides and lipids to form advanced glycation end products which induce biochemical damage and impair nerve blood flow.
Oxidative Stress	Increased production of free radicals, whose mechanism is not fully understood. May lead to direct damage of the blood vessels, resulting in nerve ischemia and advanced glycation end-product reactions.
Polyol Pathway	Intracellular glucose levels are raised in nerves, leading to saturation of the normal pathway, and reduced nerve myoinositol, decreased membrane Na/K ATPase activity, impaired axonal transport and structural breakdown of nerves, causing abnormal action potentials.
Nerve Growth Factor Abnormalities	Decreased expression of nerve growth factor and its receptor, trk A, reduces retrograde axonal transport of nerve growth factor and diminishes Substance P and calcitonin gene – related peptide, which are potent vasodilators, leading to hypoxia and nerve conduction velocity, and ultimately degradation of axonal structure.
PKC-beta Pathways	Hyperglycemia activates this complex intracellular signaling cascade process, leading to vascular contractility and permeability, ultimately leading to degradation of axonal structure.

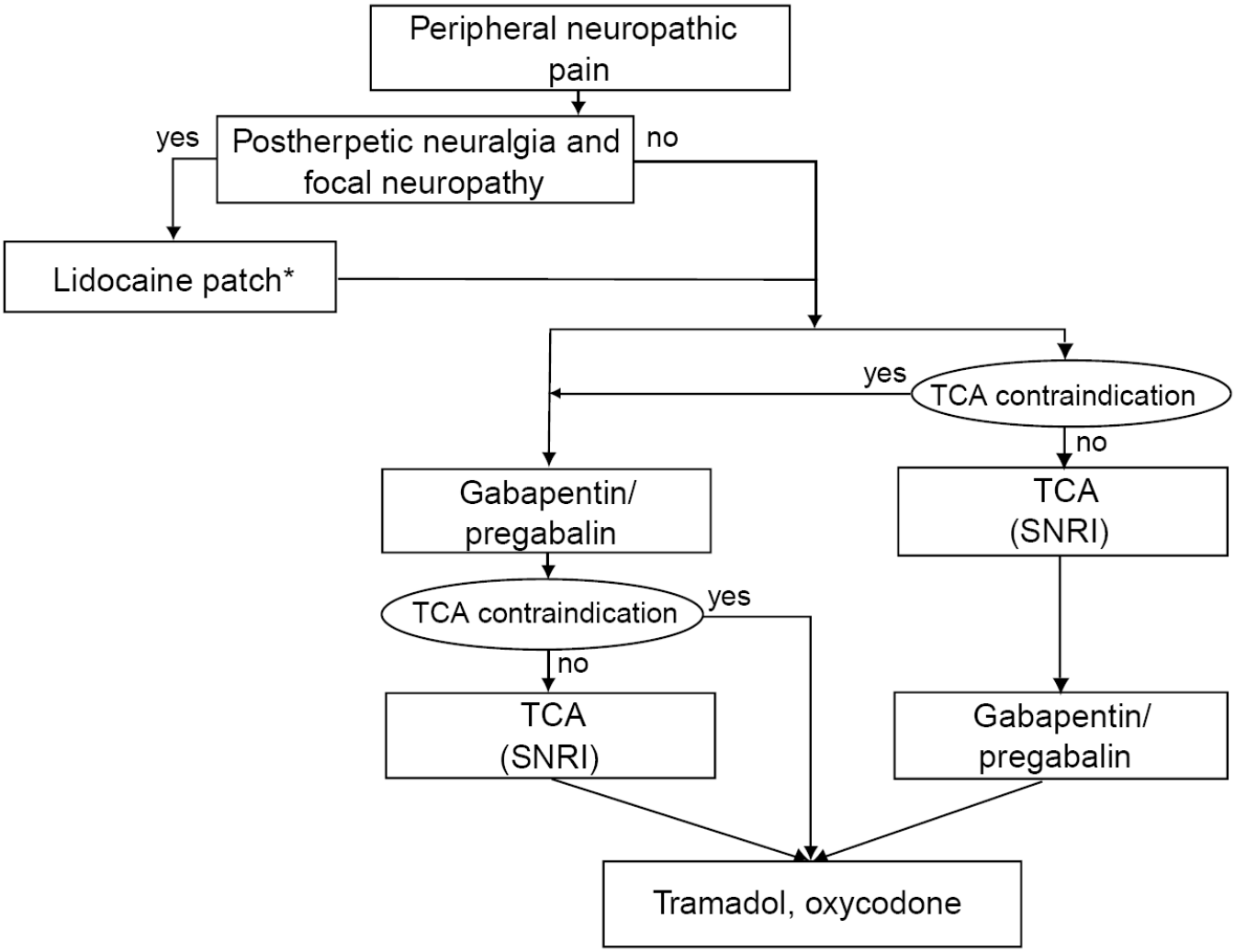

FIGURE 2. Proposed algorithm for the treatment of peripheral neuropathic pain.[11]
* Pain relieving effect of topical lidocaine had been shown in patients with allodynia.
TCA = tricyclic antidepressants; **SNRI** = serotonin norepinephrine reuptake inhibitor

tor.[12]

Amitriptyline is frequently the drug of first choice, but alternatively, nortriptyline or desipramine may be chosen for their less pronounced sedative and anticholinergic effects. The onset of efficacy for TCAs usually occurs within two weeks.[12]

Numerous placebo-controlled RCTs show TCAs to be efficacious in providing pain relief caused by some peripheral neuropathies. Studies generally demonstrate that when TCAs are compared vs. placebo, they are significantly superior in relieving pain (**Table 3**). Finnerup et al., combined separate randomized, placebo-controlled trials using a numbers needed to treat (NNT) analysis. HE showed that 1 patient would be expected to obtain ≥ 50% pain relief for every 3.1 (2.7 – 3.7) patients treated.[11] Sindrup et al.,[15] and Vrethem et al.,[16] compared imipramine vs. venlafaxine and amitriptyline vs. maprotiline, respectively, with both studies using a placebo-controlled group. They found no difference between treatment arms with respect to pain relief. TCA adverse effects include sedation, dry mouth and cardiac toxicity (**Table 2**). However, due to their low cost, once daily dosing, and efficacy studies, TCAs are often chosen as first line therapy in peripheral diabetic neuropathy or peripheral neuropathic pain.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Two SNRIs, duloxetine and venlafaxine have shown efficacy in diabetic peripheral neuropathic pain. Duloxetine; in doses of 60mg and 120mg/day significantly improved pain relief and reduced the average 24-hour pain intensity score (**Table 4**).[17,18,19] There was no significant difference between 60mg and 120mg daily doses of duloxetine. Ziegler et al., demonstrated that for every 1 patient to achieve ≥50% pain

TABLE 2. Prescribing recommendations for pharmacologic management of diabetic peripheral neuropathy.

CLASS	MEDICATIONS	STARTING DOSE	TITRATION	MAX DOSE/DAY	MAJOR SIDE EFFECTS	PRECAUTIONS	OTHER BENEFITS
TCAs	Amitriptyline (Elavil)®	10 - 25 mg	↑ by 25mg daily, as tolerated , until pain relief	100 mg	Sedation, dry mouth, blurred vision, weight gain, urinary retention	• Cardiac disease, glaucoma, suicide risk, orthostatic hypotension, concomitant use of tramadol • CI in unstable angina, recent MI, heart failure, history of ventricular arrhythmias, QTc prolongation.	Improvement of depression, insomnia, and low cost
	Clomipramine (Anafranil)®	10 - 25 mg		100 mg			
	desipramine (Norpramin)®	10 - 25 mg		100 mg			
	imipramine (Tofranil)®	10 - 25 mg		100 mg			
	nortriptyline (Pamelor)®	10 - 25 mg		100 mg			
SNRIs	duloxetine (Cymbalta)®	30 mg	↑ to 60mg daily after 1 week.	120 mg	Nausea, somnolence, dizziness, constipation, dry mouth and reduced appetite, ↑ BP at higher doses.	Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol	Improvement in depression
	venlafaxine (Effexor)®	75 mg	↑ by 75mg each week, as tolerated until pain relief.	225 mg			
Calcium channel α_2-δ ligands	Pregabalin (Lyrica)®	50 mg	↑ to 300mg QD after 3-7 d, then by 150mg/day every 3-7 d, until pain relief.	300 -600 mg	Sedation, dizziness, and peripheral edema.	Renal insufficiency	Improvement of sleep disturbance, no clinically important DIs.
	Gabapentin (Neurontin)®	300 mg	↑ by 100-300mg 3x daily every 1-7 days, as tolerated until pain relief	1800 – 3600 mg	Sedation, dizziness, and peripheral edema	Renal insufficiency	Improvement of sleep disturbance, no clinically important DIs.
Opioid agonist	Oxycodone, (Oxycontin)®, morphine (MS Contin)®, methadone	10-15 mg morphine every 4 h or prn (or equianalgesic doses for others)	After 1-2 wk, convert total daily dose to LA opioid analgesic and continue short acting med prn	No maximum dosage.	Nausea/vomiting, constipation, drowsiness, dizziness, respiratory depression.	History of substance abuse, suicide risk, driving impairment during treatment initiation.	Rapid onset of analgesic benefit.
	Tramadol (Ultram)®	50mg once or twice daily	↑ by 50-100mg daily in divided doses every 3-7 days, as tolerated until pain relief	400mg daily. (>75 yr: 300mg daily)	Nausea/vomiting, constipation, drowsiness, dizziness, seizures	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SNRI or TCA.	Rapid onset of analgesic benefit
Others	Topical lidocaine 5% patch (Lidoderm)®	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for 12-18 h	Local erythema, rash.	None	No systemic side effects.
	Capsaicin[10] 0.075% cream (Capsicum)®	Maximum of 4 topical applications/day	None needed	Maximum of 4 topical applications/day	Drug-induced body odor, edema, skin irritation	None	

↑ = increased; **d** = day; **h** = hour; **DIs** = drug interactions; **CI** = contraindicated; **prn** = as needed

TABLE 3. Clinical trials of TCAs for the treatment of diabetic peripheral neuropathy.

STUDY (YEAR)	METHODS	STUDY GROUPS	RESULTS
Max, et al.[13] (1987) N = 29	6 wk, DB, PC, CO	Amitriptyline 25mg – 150mg vs. active placebo (benztropine 1mg + diazepam 5mg)	• Amitriptyline superior to PL in relieving pain at week 3 – 6.
Sindrup, et al.[14] (1990) N = 19	6 wk, DB, CO, PC	Clomipramine 50mg – 75mg vs. desipramine 50mg – 200mg vs. PL	• Clomipramine and desipramine significantly reduced symptoms vs. PL. • No difference between clomipramine and desipramine.
Sindrup, et al.[15] (2003) N = 40	12 wk, R, DB, PC, CO	Venlafaxine 225mg vs. Imipramine 150mg vs. PL	• Venlafaxine and imipramine significantly reduced the sum of individual pain scores compared with PL • No difference between venlafaxine and imipramine • NNT: 5.2 for venlafaxine, 2.7 for imipramine.
Vrethem, et al.[16] (1997) N = 37	4 wk, DB, R, PC, CO	Amitriptyline 75mg vs. Maprotiline 75mg vs. placebo	• Using GAPR, amitriptyline and maprotiline significantly reduced pain to a greater extent than PL • No difference between amitriptyline and maprotiline

wk = week; **DB** = double-blind; **PC** = placebo-controlled; **CO** = cross-over**; R** = randomized; **PL** = placebo

reduction, 5.2 (3.8 – 8.3, 95% CI for 60mg), and 4.9 (3.6 – 7.6, 95% CI for 120mg) patients needed to be treated respectively.[12] The most frequent adverse events in these trials included nausea, somnolence, dizziness, constipation, dry mouth and reduced appetite. Rowbotham et al., evaluated venlafaxine and observed significant pain reduction at higher doses when compared to placebo.[20] In addition, Sindrup et al.,[15] compared venlafaxine to imipramine and showed no significant difference between active drugs in relieving pain. The equivalent efficacy at higher doses vs. TCAs provides an option in the treatment of diabetic peripheral neuropathy.

Calcium Channel Modulators (α_2 - δ ligands)

Gabapentin and pregabalin are the two calcium channel modulators that are used in diabetic peripheral neuropathy. These agents bind voltage-gated calcium channels (at $\alpha 2 - \delta$ subunit) and interact with L-amino acid transporters, thus changing pain transmission and modulation. However, the exact mechanism of action of these drugs on neuropathic pain is not fully understood. Pregabalin has a six fold higher binding affinity for $\alpha 2 - \delta$ subunit than gabapentin, thus making it more specific. Pregabalin's shorter titration period may allow for a faster onset of action vs. gabapentin at providing pain relief.[12,21,22] Gabapentin and pregabalin significantly improve pain compared to placebo (**Table 5**). Treatment of 4.7 (4.0 – 5.6, 95% CI) patients results in1 patient achieving ≥ 50% reduction in neuropathic pain.[11] Gilron et al.,[23] and Morello et al.,[25] compared gabapentin against morphine and amitriptyline, respectively, and found no significant difference between the drugs when used alone. However, combination of morphine and gabapentin together at lower doses significantly improved pain relief when compared to either drug alone. Both gabapentin and pregabalin share the same adverse event

TABLE 4. Clinical trials of SNRIs for the treatment of diabetic peripheral neuropathy.

STUDY (YEAR)	METHODS	STUDY GROUPS	RESULTS
Wernicke, et al.[17] (2006) N = 334	12 wk, R, DB, PC	Duloxetine 60mg and 120mg vs. PL	• Both doses improved 24 hr mean PSS more than PL, beginning at wk 1 • No significant differences between the 2 doses
Goldstein, et al.[18] (2005) N = 457	12 wk, R, MC, DB, PG	Duloxetine 60mg and 120mg vs. PL	• Both doses improved 24 hr mean PSS more than PL at wk 1
Raskin, et al.[19] (2005) N = 348	12 wk, R, MC, DB, PG	Duloxetine 60mg and 120mg vs. PL	• Both doses improved 24 hr mean PSS more than PL • 120mg group had more frequent adverse events vs. other groups
Rowbotham, et al.[20] (2004) N = 244	6 wk, R, MC, DB, PC	Venlafaxine ER 75mg and 150-225 mg vs. PL	• Higher doses of venlafaxine significantly reduced VAS-PI and VAS-PR compared with PL

wk = week; **R** = randomized; **DB** = double-blind; **PC** = placebo-controlled; **MC** = multi-center**; PG =** parallel group; **PL** = placebo**; PSS** = pain severity score; **VAS-PI** = visual analog scale pain intensity; **VAS-PR** = visual analog scale pain relief

TABLE 5. Clinical trials of calcium channel modulators for the treatment of diabetic peripheral neuropathy.

STUDY (YEAR)	METHODS	STUDY GROUPS	RESULTS
Gilron, et al.[23] (2005) N = 57	4 wk, R, DB, APC, CO	Morphine 120mg alone vs. Morphine 60mg and Gabapentin 2400mg vs. Gabapentin 3200mg vs. Lorazepam 1.6mg	• Total scores on the SF-MPQ were 14.4 with PL, 10.7 with • gabapentin, 10.7 with morphine, and 7.5 with the gabapentin–morphine combination (p<0.05 for the combination vs. each other group).
Backonja, et al.[24] (1998) N = 165	8 wk, R, DB, PC, MC	Gabapentin 900mg to 3600mg vs. PL	• Gabapentin significantly reduced mean daily pain score compared with PL
Morello, et al.[25] (1999) N = 28	6 wk, R, DB, DD, CO	Gabapentin 900mg – 1800mg vs. Amitriptyline 25mg – 75mg	• No significant differences in MSDA scores between the two treatments • No significant period or carry-over effects seen.
Rosenstock, et al.[26] (2004) N = 146	8 wk, R, DB, PC, PG	Pregabalin 300mg/day vs. PL.	• Significantly greater improvement with pregabalin for mean pain scores, mean sleep interference scores, total SF-MPQ scores, SF-36 scores and POMS scores compared with PL
Lesser, et al.[27] (2004) N = 338	5 wk, R, DB, MC, PC	Pregabalin 300mg/day vs. Pregabalin 600mg/day vs. PL	• Both doses showed early and sustained improvement in mean pain score, weekly pain score, sleep interference score, PGIC, CGIC, SF-MPQ and SF-36 vs. PL.

wk = week; **R** = randomized; **DB** = double-blind; **APC** = active placebo-controlled; **PC** = placebo-controlled; **MC** = multi-center**; PG =** parallel group; **DD =** double dummy; **CO =** cross-over; **PL** = placebo**; SF-MPQ** = Short Form McGill Pain Questionnaire; **MSDA** = mean score diary analysis; **SF-36 =** Short Form Health Survey; **POMS** = Profile of Mood States; **PGIC** = Patient Global Impression of Change; **CGIC** = Clinical Global Impression of Change.

profile, including sedation, dizziness, peripheral edema. These drugs should be used with caution in patients with renal insufficiency.

Opioids

Opioids are potent μ-receptor agonists and mediate analgesia by changes in the perception of pain at the spinal cord.[28] Strong opioids like morphine, oxycodone and several others exhibit analgesic effects similar to TCAs and gabapentin in the setting of DPN.[23,25] However, opioids are not recommended as first line therapy due to concern over long term safety. In addition, opioids produce more side effects compared to gabapentin.[23] Opioids carry the potential for abuse, and are therefore not recommended as 1st line therapy.

Tramadol, a weak opioid, is a partial μ agonist and also inhibits reuptake of 5-HT and NE.[29] Sindrup et al.[32] and Harati et al.[33] showed tramadol significantly lowers overall pain when compared to placebo (**Table 6**). For one patient to achieve ≥ 50% neuropathic pain reduction, 2.5 (2.0 – 3.2, 95% CI) and 3.9 (2.7 – 6.7, 95% CI) patients need to be treated with strong opioids and tramadol, respectively.

The most common side effects with opioids are constipation, nausea, and sedation (**Table 2**).

TABLE 6. Clinical trials of opioids for the treatment of diabetic peripheral neuropathy.

STUDY	METHODS	STUDY GROUPS	RESULTS
Watson, et al.[30] (2003) N = 45	4 wk, R, DB, CO	Oxycodone CR 10mg – 40mg Q 12 H vs. APC of benztropine 0.25mg – 1mg Q 12 H	CR oxycodone significantly lowered mean daily pain, steady pain, brief pain, skin pain, and total pain compared to PL.
Gimbel, et al.[31] (2003) N = 159	6 wk, R, DB, PC, PG, MC	Oxycodone CR 10mg – 60mg Q 12 H vs. PL	CR oxycodone provided more analgesia vs. PL in the overall daily pain intensity.
Sindrup, et al.[32] (1999) N = 45	4 wk, R, DB,PC, CO	Tramadol 200mg/day to 400mg/day vs. PL	Tramadol lowered pain (p=0.001), paraesthesia (p=0.001), touch-evoked pain (p<0.001), allodynia (p=0.012) vs. PL.
Harati, et al.[33] (1998) N = 131	42 days, R, DB, PC, PG, MC	Avg. tramadol 210 mg/day vs. PL	Tramadol more effective (P < 0.001) than PL in MPIC.

wk = week; **R** = randomized; **DB** = double-blind; **APC** = active placebo-controlled; **PC** = placebo-controlled; **MC** = multi-center**; PG =** parallel group; **CO =** cross-over; **PL** = placebo**; MPIC** = mean pain intensity score

TABLE 7. Clinical trials of topical agents for the treatment of diabetic peripheral neuropathy.

STUDY	METHODS	STUDY GROUPS	RESULTS
Meier, et al.[35] (2003) N = 40	7 day, R, MC, PC, TW, CO	Lidocaine 5% patch vs. PL	Lidocaine 5% patch effective in reducing ongoing pain (P = 0.017), allodynia (P = 0.023) during the 1st 8 hours and over a period of 7 days (P = 0.018) in diverse focal PNPS.
The Capsaicin Study Group[36] N = 252	8 wk, R, MC, DB	Capsaicin 0.075% cream 4 times a day vs. PL (vehicle cream)	Capsaicin significantly improved pain as measured by PGES, decreased pain intensity and offered greater pain relief compared with PL

wk = week; **R** = randomized; **MC** = multi-center**; PC** = placebo-controlled; **TW** = two-way; **CO =** cross-over; **DB** = double-blind; **PL** = placebo**; MPIC** = mean pain intensity score; **PNPS** = peripheral neuropathic pain syndrome; **PGES** = Physician's Global Evaluation Scale

Topical Agents: Lidocaine & Capsaicin

Lidocaine produces analgesia via reversible nerve conduction blockade.[34] Conversely, capsaicin reduces substance P and flare response.[12] Both of these can be used as an add-on therapy for localized, pain. Lidocaine 5% patch effectively reduces ongoing pain and allodynia during the first 8 hours over a period of seven days.[25] Capsaicin significantly decreases overall pain relief. Finnerup et al., demonstrated that 1 patient would be expected to obtain ≥ 50% pain relief for every 6.7 (95% CI, 4.6 – 12) patients treated with capsaicin. Similarly, 4.4 (95% CI, 2.5 – 17) patients need to be treated with lidocaine for 1 patient to see ≥ 50% pain relief. Skin irritaton, erythema, and rash are common side effects with both drugs.

SUMMARY

DPN is a heterogeneous disease diagnosed by exclusion of other causes. There are numerous theories of DPN's pathophysiology, all of which result in nerve fiber loss. First line therapy for DPN is usually a TCA (amitriptyline) due to their once daily dosing and low cost. SNRIs (duloxetine, venlafaxine) are higher cost alternatives with similar efficacy when compared to TCAs. Strong evidence supports gabapentin as equally efficacious to TCAs. Although no head to head trial exists, pregabalin works the same as gabapentin with higher affinity.

Due to lack of long term safety data and potential concerns regarding abuse, strong opioids (morphine) are second line therapy. Weak opioids (tramadol) may be a better alternative than strong opioids. For patients whose DPN is not completely controlled with monotherapy, add-on treatment with either lidocaine patch or capsaicin may be effective.

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