In the name of God

Treatment Diabetic peripheral Neuropathy

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Neuropathic pain

- Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”

- ✓ It affects approximately 7%–10% of the general population

- ✓ DPN, a common complication of diabetes,is a major cause of morbidity, mortality, and poor quality of life (QoL) in patients with diabetes the pooled prevalence of DPN in patients with diabetes as 30%

Risk factors associated with neuropathic pain in DPN

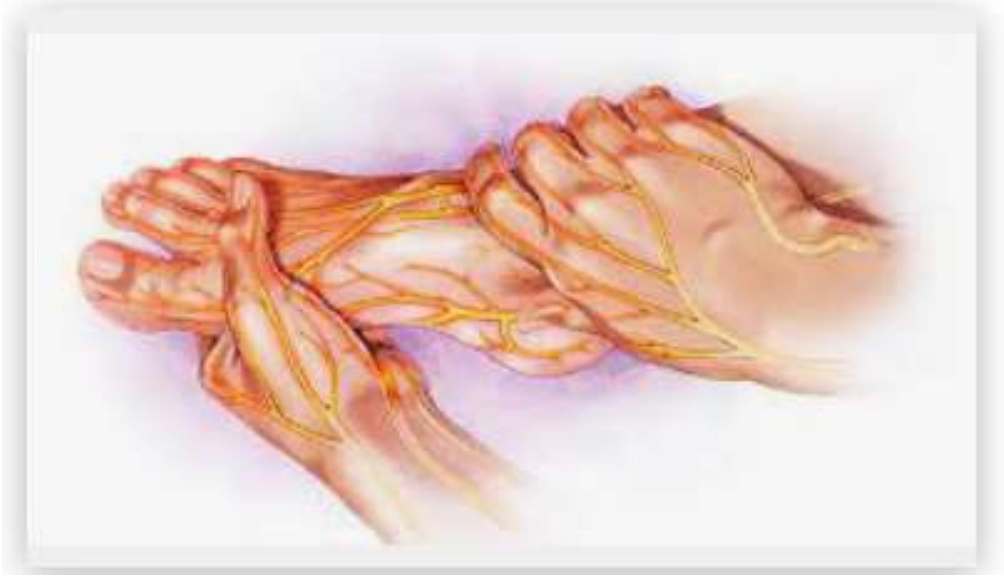
- Gender,
- Duration of diabetes
- Poor glycemic control
- DPN causes a length-dependent ‘stocking‘ or ‘stocking glove‘pattern of sensory loss
- DPN can affect large-diameter myelinated A-beta somatic fibers (‘large fibers‘), which are responsible for joint position, vibration and touch/protective sensation

CLASSIFICATION OF DIABETIC NEUROPATHIES

- ✓Distal symmetric sensorimotor polyneuropathy
- ✓Small fiber neuropathy
- ✓Acute severe distal sensory polyneuropathy
- ✓Autonomic neuropathy
- ✓Diabetic neuropathic cachexia
- ✓Hypoglycemic neuropathy
- ✓Treatment-induced neuropathy (insulin neuritis)
- ✓Polyradiculopathy
- ✓Diabetic radiculoplexopathy
- ✓Mononeuropathies
- ✓Cranial neuropathies (in particular, oculomotor)

Diabetic peripheral neuropathy

- IT is typically a slowly progressive sensory predominant neuropathy
- Patients initially experience sensory loss in the toes and feet that result from length dependent dysfunction of nerve fibers



Diabetic peripheral neuropathy

This distal ‘‘dying back’’ type of neuropathy is consistent with a metabolic disturbance in the peripheral nervous system

symptoms, such as decreased sensation and numbness, or ‘‘positive’’ symptoms such as prickling, burning, or aching sensations

Diabetic peripheral neuropathy

- Small myelinated and unmyelinated fibers convey sensations of light touch, pain, and temperature, while large fibers are responsible for vibratory sensation and joint position sense

- Significant weakness is not a common finding in early diabetic neuropathy

- There may be weakness of the toe flexor and extensor muscles, and subclinical motor involvement can be documented on electrodiagnostic testing.

Diagnostic Criteria for Diabetic Neuropathy

	Possible DSPN	Probable DSPN	Confirmed Clinical DSPN	Subclinical DSPN
Signs or symptoms[a]	X		X	
Signs and symptoms (any two of the following: neuropathic symptoms, decreased distal sensation, or decreased/absent ankle reflexes)		X		
Abnormal nerve conduction study			X	X

DSPN = diabetic sensory polyneuropathy.

[a] Symptoms may include decreased sensation, positive neuropathic sensory symptoms (eg, "asleep numbness," "prickling" or "stabbing," "burning," or "aching" pain) predominantly in the toes, feet, or legs. Signs may include symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes.

Diabetic peripheral neuropathy

- The majority of patients note mild to moderate discomfort associated with the neuropath but up to 25% may report a painful diabetic neuropathy

- This is typically described as a deep aching pain with a burning or electric/shooting quality that is typically located in the feet

- The pain can be exacerbated by activity but is often worst at night

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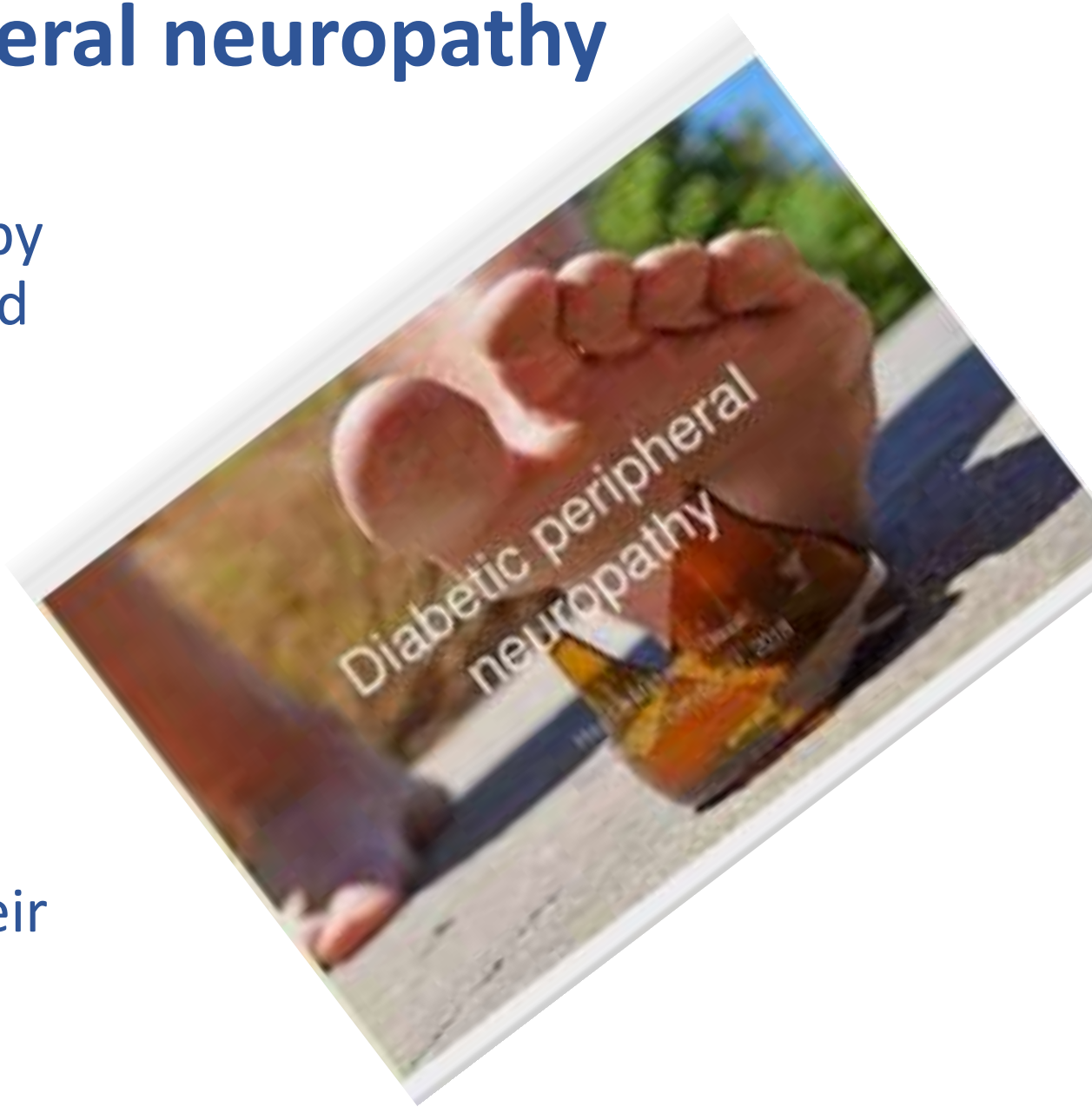
Diabetic peripheral neuropathy

- Small fiber neuropathy is characterized by superficial burning pain in the feet caused by preferential involvement of the small unmyelinated nerve fibers that mediate pain, temperature sensation, and autonomic function.

- Patients may report deep aching pain, shooting pain in their toes, tingling, and numbness and commonly report that their feet are persistently cold.



Diabetic peripheral neuropathy

- Clinical findings include reduced distal pain and cold perception, sympathetic vasomotor changes (pallor alternating with ruber, cyanosis, and mottling), and, rarely, true allodynia. Strength and reflexes are often normal

- Small fiber neuropathies are often seen in patients with impaired glucose tolerance

Diabetic peripheral neuropathy

- Patients with insensate feet are especially prone to developing foot ulcerations; education regarding proper foot care is especially important in this population

- In addition, patients with diabetes mellitus are at a higher risk of falls because of a combination of risk factors including sensory loss and impaired proprioception and spinal reflexes

AUTONOMIC NEUROPATHY

- It is important to recognize the presence of diabetic autonomic neuropathy in patients because of its impact not only on morbidity but also on mortality

- Specifically, the presence of cardiac autonomic neuropathy is associated with an increased mortality risk

AUTONOMIC NEUROPATHY

- The symptoms of diabetic autonomic neuropathy :
  - ✓Resting tachycardia
  - ✓Exercise intolerance
  - ✓Orthostatic hypotension
  - ✓Abnormal sweat patterns
  - ✓Gastric motor abnormalities
  - ✓Pupillary abnormalities
  - ✓Erectile dysfunction

DIABETIC LUMBOSACRAL AND CERVICAL RADICULOPLEXUS NEUROPATHY/DIABETIC AMYOTROPHY

Diabetic lumbosacral and cervical radiculoplexus neuropathy

- It typically affects older patients (older than 50 years) and usually men
- Most patients with diabetic lumbosacral radiculoplexus neuropathy (DLRPN) have type 2 diabetes mellitus, but they may present prior to diagnosis of diabetes mellitus
- DLRPN is frequently associated with weight loss, but its occurrence is often not related to glucose control or duration of diabetes mellitus

Diabetic lumbosacral and cervical radiculoplexus neuropathy

- DLRPN classically starts with severe unilateral pain in the back, hip, or thigh that spreads to involve the entire limb and can involve the other leg within weeks to months

Diabetic lumbosacral and cervical radiculoplexus neuropathy

- Typically, DLRPN remains asymmetric Shortly after the onset of pain, proximal weakness can be detected
- Weakness and atrophy may initially be focal, but they can become widespread and bilateral
- Physical examination reveals weakness of hip flexors, adductors, and extensors. Profound atrophy of the thigh can be seen. There may also be involvement of the ankle dorsiflexors and plantar flexors

Diabetic lumbosacral and cervical radiculoplexus neuropathy

- ❑ Usually knee and ankle reflexes are absent
- ✓ Symptoms can worsen in a stepwise or progressive manner for up to 18 months
- ✓ Eventually symptoms will stabilize, and the majority of patients will experience gradual improvement, although permanent weakness may result
- ✓ Footdrop is common, resulting from failure to reinnervate distal segments
- ✓ In approximately one-third of cases, weakness occurs in arm muscles and is attributed to a cervicobrachial radiculoplexopathy

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DIAGNOSIS

1- Electrodiagnostic studies

- Nerve conduction studies frequently cannot differentiate DLRPN from diabetic sensorimotor polyneuropathy, but asymmetries in compound muscle action potential amplitudes may occur

- Findings on EMG and nerve conduction studies indicate a multifocal process involving the lumbosacral roots, plexus, and peripheral nerves There may also be autonomic involvement

- In addition, a plexus MRI may show nerve root enhancement

DIAGNOSIS

2-CSF analysis

- An elevated protein level with a normal cell count, which indicates involvement at the root level
- Evidence suggests an ischemic injury from microvasculitis as the underlying pathology

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PATHOGENESIS OF DIABETIC NEUROPATHY

- Several trials have established a clear link between impaired glycemic control, neuropathy, and retinopathy
- Increase in glucose above normal is associated with an increased risk of end organ injury, including neuropathy
- Hyperlipidemia in addition to hyperglycemia may be important in the pathogenesis of diabetic neuropathy

MANAGEMENT OF DIABETIC NEUROPATHY

(1) treatment of risk factors

(2) Diet and exercise lifestyle intervention

(3) Considering administration of α-lipoic acid

Anticonvulsants

1-Pregabalin

- Calcium channel subunit α2-δ binder
- It has been approved by the US Food and Drug Administration (FDA) for painful DSPN The dosage ranges from 150 to 300 mg daily
- More than 30–50% pain improvement
- Untoward effects include water retention, visual disturbances, drowsiness, ataxia, euphoria, and vertigo
- The FDA approved dosage for treatment of DPN is 50 mg TID (150 mg/day) at initiation and can be titrated up to 100 mg TID (300 mg/day) to achieve adequate effect

Anticonvulsants

2-Gabapentin

- ❑ Calcium channel subunit α2-δ binder
- ❖ It has the same therapeutic target as pregabalin
- ✓ Relieve pain among DSPN subjects and combination with venlafaxine seems to provide additional benefit
- ➢ Use of gabapentin for the treatment of DSPN as a second-line therapy after pregabalin
- ➢ Dosing for chronic pain starts at 300 mg/day and is titrated up until suitable pain relief is achieved with effective doses ranging from 1800 mg to 3600 mg per day

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Anticonvulsants

- In patients with chronic kidney disease, the doses of gabapentin and pregabalin need to be adjusted:

➢ The renal clearance (CrCl ≤ 30 mL/min) requires dose adjustment, with a recommended dose of gabapentin of 300 mg daily and pregabalin of 75 mg daily

❖ Gabapentin has been associated with sleepiness, dizziness, suicidal behaviour, withdrawal-precipitated seizure frequency, multi-organ hypersensitivity, systemic symptoms, and drug reaction with eosinophili

❖ The recommended dose is 900–3600 mg/d

❖ Other anticonvulsants have been used as well (carbamazepine, lamotrigine, lacosamide, etc.), with variable results

Antidepressants

- Antidepressants including serotonin and norepinephrine reuptake inhibitors (SNRIs) like duloxetine and venlafaxine treat chronic neuropathic pain by increasing the activity of noradrenergic and serotonergic neurons in the descending pathways of the dorsal horn
- These descending neurons inhibit the activity of dorsal horn neurons, suppressing excessive input, which is perceived as pain, from reaching the brain
- Tricyclic antidepressants (TCAs), likewise, block monoamine reuptake, including serotonin and norepinephrine, and are also used to treat chronic pain, especially neuropathic pain

Antidepressants

1-Duloxetine

- Recommended as a first-line treatment for neuropathic pain by the AAN and the ADA
- TEAEs(Treatment-Emergent AEs) that were significantly more common with 120 mg/day duloxetine treatment than placebo include constipation dry mouth, hyperhidrosis, decreased appetite, anorexia, weakness, nausea, and severe somnolence

Duloxetine

- The recommended dosage of duloxetine for DPN is 60 mg/day, and lower initial doses may be used in cases with tolerability concerns or renal impairment, which is a common complication of diabetes

Duloxetine

- The duloxetine label includes a black box warning for the potential emergence or worsening of suicidal thinking or behavior in children and young adults, while frequently reported AEs include nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis

Antidepressants

2-Venlafaxine

- Is mechanistically similar to duloxetine
- The reported AEs in this trial were nausea, somnolence, and electrocardiogram abnormalities, and there was no significant difference in the rate of serious AEs between subjects receiving placebo (10%) or 150–225 mg/day venlafaxine ER (12%)

Antidepressants

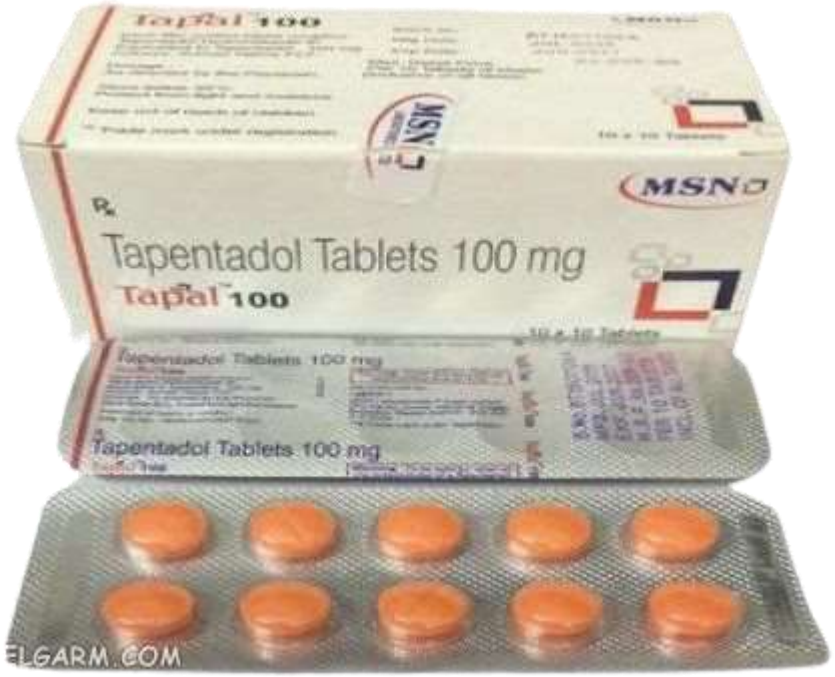
3-Amitriptyline

- Is the most commonly used TCA for treating DPN
- The high risk of AEs requires careful monitoring and this drug is best suited as a last resort
- Common AEs encountered with TCAs include gastrointestinal issues, orthostatic hypotension, dry mouth, urinary retention, and QTc prolongation, and this safety profile reflects concurrent actions at histaminergic, adrenergic, and cholinergic receptors

Opioids

- **1-Tapentadol**

❑Centrally acting opioid analgesic that exerts its analgesic effects by inhibiting the μ-opioid receptor and noradrenaline uptake



1-Tapentadol

- The FDA approved prolonged-release tapentadol for painful DSPN, based on data from two clinical trials in which patients titrated with an optimal dose of tapentadol were arbitrarily requested to continue with that dose or to change it with placebo
- Importantly, a recent systematic review and meta-analysis by the Special Interest Group on Neuropathic Pain within the International Pain Study Association found that evidence supporting the effectiveness of tapentadol in reducing neuropathic pain is inconclusive. Finally, addiction is a serious concern with long-term opioid use

Topical Treatment

1-Capsaicin

- A natural alkaloid
- This is thought to desensitize afferent Aδ and C fibers
- Two forms of capsaicin are available for the treatment of painful DSPN: a low-dose cream (0.075%)] and a high-dose (8%) patch
- A series of studies have provided evidence of pain relief among subjects who received capsaicin cream
- A dosage of 0.075% four times daily is recommended for the treatment of painful DSPN
- A notable disadvantage is local adverse effects mainly stinging, burning, and erythema

Topical Treatment

1-Capsaicin

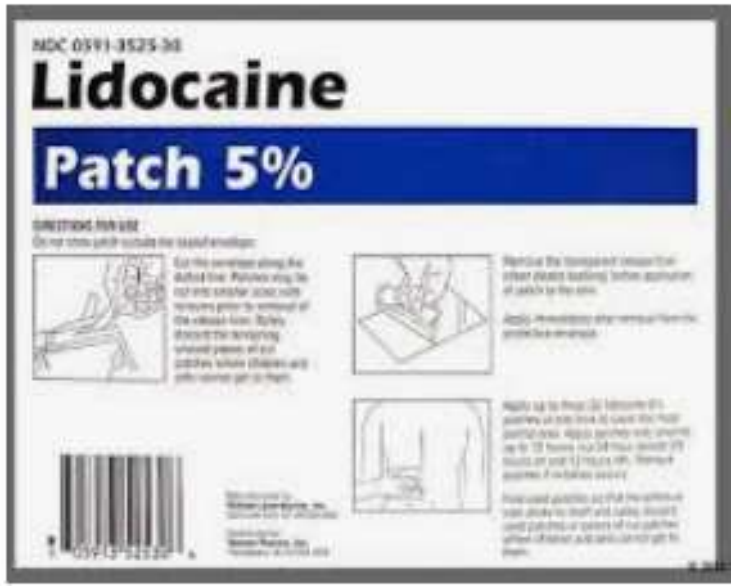
- Nonetheless, some evidence points to superiority in comparison with oral pregabalin, duloxetine, and gabapentin for pain relief among DSPN patients

- A single application of this patch may provide up to 12 weeks of pain relief This should be performed under specialist supervision, with appropriate local anesthesia and monitoring for blood pressure increase, especially during the first hour following application

Topical Treatment

2-The 5% lidocaine plaster

- Is licensed for postherpetic neuralgia in approximately 50 countries around the world and for localized neuropathic pain in 11 Latin American countries
- The lidocaine molecule is a voltage-gated sodium channel inhibitor which blocks abnormally functioning neuronal sodium channels (in the dermal A-δ and C fibers)



2-The 5% lidocaine plaster

- Studies have provided evidence of pain relief in DSPN patients comparable to pregabalin ,amitriptyline, capsaicin, and gabapentin

- A maximum of three lidocaine patches 5% can be applied to intact skin once for 12 h within a 24-h period

- Adverse events include mild and transient application-site reactions—mainly erythema, edema, and a burning sensation

Topical Treatment

3-Topical clonidine

- Presynaptic α-2 adrenergic receptor agonist with antinociceptive activity, was associated with pain relief in DSPN in a small number of studies of low-to-moderate quality

- Clonidine gel 0.1% may be administered in single doses of 0.65 g of gel (0.65 mg of clonidine), three times daily so that the total daily dose should not exceed 3.9 mg for both feet.

- The administration is associated with only mild skin-site reactions

Pathogenesis-Oriented Treatment

- α-Lipoic acid is a natural thiol with potent antioxidant properties, and is used as a dietary supplement. In studies evaluating this indication, it has been administered orally at doses between 600 and 1800 mg and intravenously at 600 mg per day for 3 weeks, excluding weekends

- Both formulas have been recently characterized by the FDA as safe and effective treatment options for painful DSPN

- α-lipoic acid improved positive neuropathic symptoms (24.1% in favor of α-lipoic acid versus placebo), but failed to alter the neuropathy impairment score significantly

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Treatment algorithm (1st line treatment)

- **Gabapentin, pregabalin, TCAs, venlafaxine, and duloxetine as first line medications**
- Which agent to choose is largely determined by co-morbidities of the patient and side effect profiles of the medications
- Topical lidocaine for those with localized neuropathic pain and in those with concern for central nervous system side effects
- All three sources recommend titrating a first line medication to a maximum tolerated dose before switching to a second first line medication or combination therapy

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Treatment algorithm (2nd line treatment)

- 2 nd line All three algorithms also support opioid analgesics and tramadol as second line medications

- Concern exists over their long term use given their addiction potential, side effect profile, and waning effectiveness over time

- TCAs are the most affordable of the first line agents

- Gabapentin and venlafaxine are cheaper than pregabalin and duloxetine, respectively

Therapeutic options for painful diabetic neuropathy

Pharmacotherapies	Neuromodulation
Anti-convulsants Pregabalin Gabapentin	Intrathecal pain therapy
	Transcutaneous electrostimulation *
	Tonic SCS *
Topical Capsaicin	Burst SCS *
Opioids Tapentadol	10 kHz SCS *
Anti-depressants Duloxetine Amitriptyline * Venlafaxine *	

* Not FDA approved at the time of preparation of manuscript.

Pregabalin	Up to 100 mg TID	50 mg TID	Escalate to 100 mg TID within 1 week of initiation based on tolerability	Inhibition of voltage gated calcium channels	Somnolence, blurred vision, difficulty with concentration/thinking, dry mouth, edema, weight gain Serious side-effects: Allergic reactions, suicidal thoughts, dizziness, fall and troubled breathing
Gabapentin *	1800 mg/day–3600 mg/day	300 mg QD	Increase to 300 mg BID and TID; then escalate dose at TID	Inhibition of voltage gated calcium channels	Dizziness, fall, somnolence, peripheral edema, and gait disturbance
Duloxetine	60 mg QD	≤60 mg/day	N/A	Serotonin/norepinephrine reuptake inhibitor	Nausea, somnolence, decreased appetite, constipation, fatigue, and dry mouth Serious side-effects: Suicidal thoughts, bleeding, and blurred vision
Topical Capsaicin	1–4 applications of 8% patch for 30 min every 3 months	1–4 applications of 8% patch for 30 min	Can be repeated not more than every 3 months	TRPV1 agonist	Application site erythema, pain, and pruritus Serious side-effects: Allergic reaction, dizziness, trouble breathing
Tapentadol	100 mg/day–250 mg/day (500 mg/day MRD)	50 mg BID	Individually titrated by 50 mg no more than twice daily every three days	μ-opioid receptor agonist and norepinephrine reuptake inhibitor	Nausea, constipation, dizziness, headache, and somnolence Serious side-effects: fall, seizures and difficult breathing
Amitriptyline #	10 mg/day–150 mg/day in the night. Maximum dose 150 mg	10–25 mg/day in the night	Increase by 10–25 mg/day every 3–7 days as tolerated	Serotonin/norepinephrine reuptake inhibitor	GI issues, orthostatic hypotension, dry mouth, urinary retention, constipation and QTc prolongation Serious side-effects: Arrhythmias, suicidal thoughts and muscle cramps
Venlafaxine #	150 mg/day–225 mg/day	75 mg/day in 2–3 divided doses	Increments of 75 mg/day every 4 days or more as tolerated	Serotonin/norepinephrine reuptake inhibitor	Nausea, somnolence, insomnia and dyspepsia Serious side-effects: dizziness, fall, hallucinations and increased heart rate

Non-Pharmacological Treatments: Neuromodulation

- The International Neuromodulation Society defines neuromodulation as medical technologies that reversibly enhance or suppress nervous system activity with the goal of treating disease and includes both implantable and non-implantable devices that deliver electrical, chemical, or other

- Types of neuromodulation tested in subjects include transcutaneous electrical nerve stimulation (TENS), intrathecal pain therapy, and spinal cord stimulation (SCS)

Non-Pharmacological Treatments: Neuromodulation

- Although such methods have been used with well documented success in conditions such as musculoskeletal pain or failed back surgery syndrome, few well-controlled studies have examined their use in DPN

- However, there is increased interest in new, non-opioid methods for treating neuropathic pain, and the use of neuromodulation is expected to expand in the coming years

1-Transcutaneous Electrical Nerve Stimulation TENS

- Is a non-invasive, inexpensive, and easy-to-use form of neuromodulation to treat both acute and chronic pain with few contraindications or AEs, and no known drug interactions

- Patients treated with TENS have electrical stimulation applied to the skin via adhesive electrodes using a variety of waveforms that are broadly classified as high frequency ,low frequency

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1-Transcutaneous Electrical Nerve Stimulation TENS

❖The mechanism is currently unknown, but may be:

❖improved microcirculation

✓Higher levels of beta endorphin and met-enkephalin

✓Increased expression of proteins including calcitonin gene regulating protein and nerve growth factor

✓Reduced inflammation

2-Intrathecal Pain Therapy

- Intrathecal pain therapy is a targeted drug delivery strategy to bypass first pass metabolism and the blood-brain barrier by delivering analgesic medication directly into the intrathecal cerebrospinal fluid via a pump and catheter to treat refractory chronic pain when conventional medical treatments are ineffective

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2-Intrathecal Pain Therapy

- Intrathecal therapy using either ziconotide or morphine is recommended and FDA-approved for chronic neuropathic pain such as that associated with DPN

- Ziconotide is recommended more strongly by the Polyanalgesic Consensus Conference (PACC) because it is supported by evidence from well-designed trials, unlike the use of morphine, and it is not associated with some of the serious AEs observed with opioids, especially respiratory depression

3-Conventional SCS

- Conventional SCS is administered with a variety of waveforms via electrode leads implanted in the epidural space

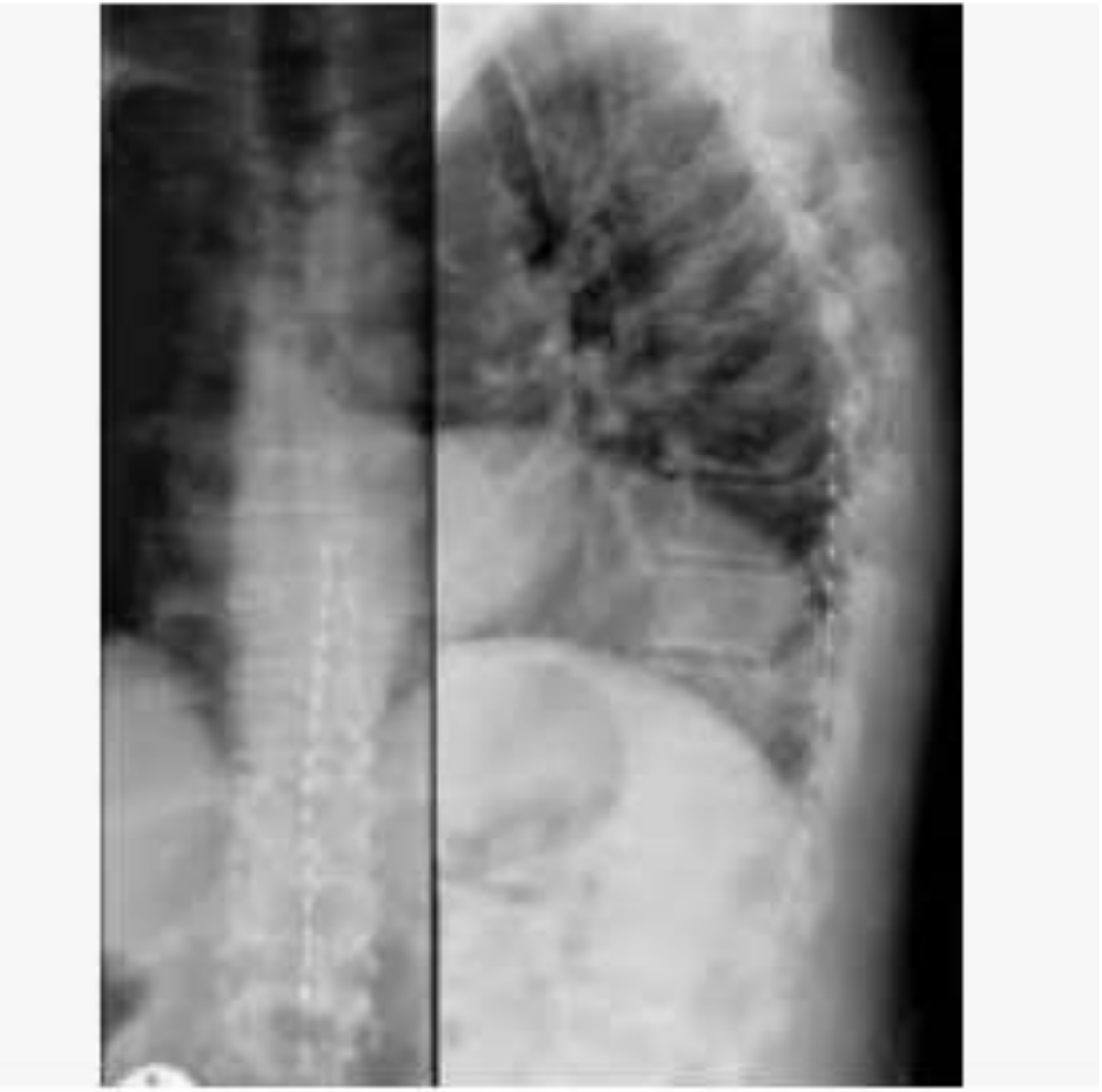
- Typically, a frequency of 40 Hz with a pulse width of 400 µs is delivered at intensities high enough to produce paresthesia, which is necessary to produce analgesic effects and must overlap the painful area

3-Conventional SCS

- Stimulation through the epidural electrodes activates large diameter spinal Aβ fibers in the dorsal column of the spine, which is thought to produce both pain relief and paresthesia, and the intensity of stimulation is correlated with the inhibition of wide-dynamic range neurons in the dorsal horn

3-Conventional SCS

- In addition, functional MRI imaging of patients undergoing tonic SCS at conventional frequencies has shown the activation of supraspinal areas that modulate pain transmission in the dorsal horn via descending serotonergic and noradrenergic projections



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