PERIPHERAL NEUROPATHY: A CLOSER LOOK FOR CLINICIANS

TNP 30TH ANNUAL CONFERENCE

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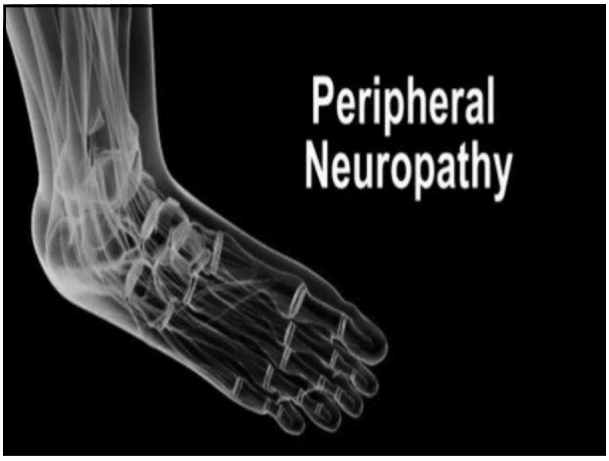
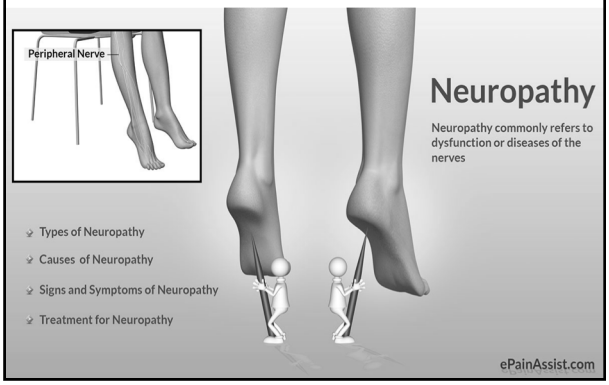


OBJECTIVES

By the end of this session, attendants will be able to

1. Define and state prevalence of peripheral neuropathy
2. Classify peripheral Neuropathy
3. State causes of Peripheral
4. Identify symptoms of Peripheral
5. Discuss available treatments of peripheral neuropathy

PERIPHERAL NEUROPATHY



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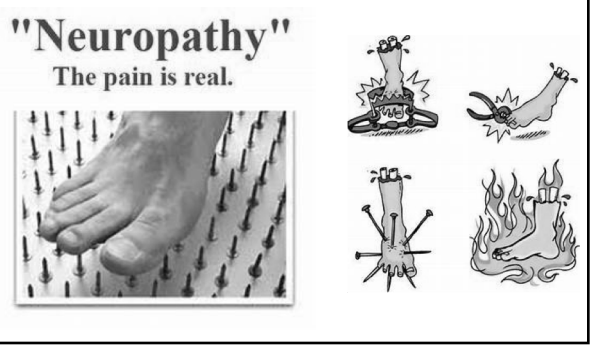

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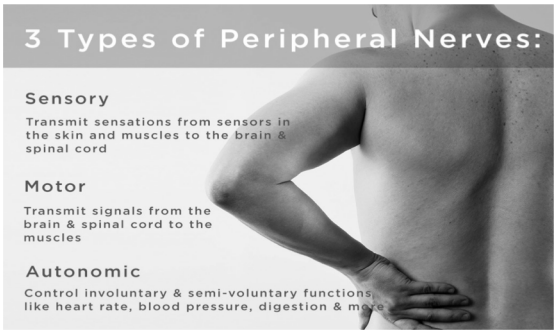
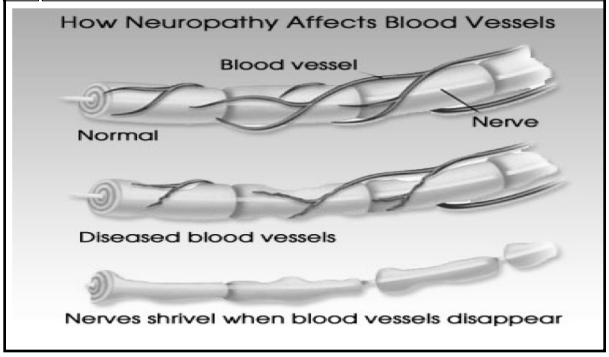


PERIPHERAL NEUROPATHY

- A condition that develops as a result of damage to peripheral nervous system (PNS)
- PNS is the vast communications network that transmits information between the brain, spinal cord, and other body areas
- Peripheral nerves send sensory information to and from the brain and spinal cord (e.g. feet are cold; to muscles to generate movement)
- Damage to PNS interferes and distorts with these vital connections.

PERIPHERAL NEUROPATHY

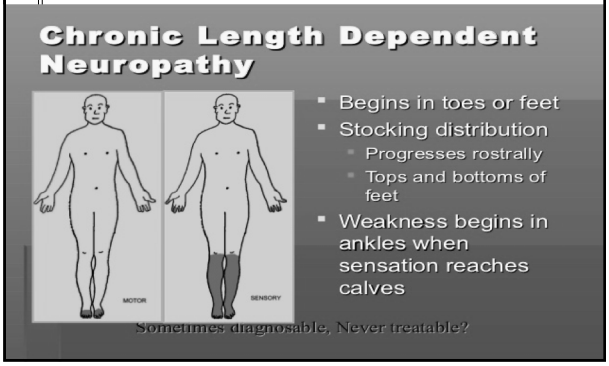


PERIPHERAL NEUROPATHY

Characteristics

- Damage may be to axons or myelin sheath or both
- Can present in a variety of forms and follow different patterns
- Most common pattern of clinical involvement is length-dependent, sensory predominant, and clinically mild/mod symmetrical, begins in the longest nerves at their terminal i.e. distal foot
  - Involves positive (prickling, tingling, burning) or negative (lack of feeling) sensory symptoms

PERIPHERAL NEUROPATHY



PERIPHERAL NEUROPATHY

Characteristics

- Can present acutely or chronically
- Sensory and/or motor symptoms in diffuse, length-independent pattern, involves both proximal and distal limbs suggest a pattern of polyradiculoneuropathy
- In acute forms such as GBS, symptoms are sudden, have rapid progression and slow resolution
- Chronic form patterns begin subtly and progress slowly
- There maybe periods of relief and relapses

PERIPHERAL NEUROPATHY

Axonal Neuropathy	Demyelinating Neuropathy
Usually Gradual and insidious Onset	Usually Acute or subacute
Large and long long axons are affected early, hence initially lower extremeties are affected	Diffuse process. Starts in lower limbs.But not always distal
Stocking-glove sensory motor loss results in symmetrical distal clinical signs in legs and arms	Generalized Weakness and mild sensory loss.
Distal involvement	Proximal and distal involvement
Ankle jerk lost early and proximal tendon reflexes preserved	All reflexes are lost early
Muscle wasting Common	Relatively absent
CSF Proteins normal	CSF Proteins elevated(since nerve roots are involved
Slow Recovery	Rapid Recovery
Residual deformity Common	Residual deformity less common
Normal Conduction normal or slightly lowered	Nerve Conduction is slowed

PERIPHERAL NEUROPATHY

Classifications

- More than 100 types of peripheral neuropathies
- In general, classified according to nerve damage
- Mononeuropathy or polyneuropathy
- Symptoms vary depending on:

1. Motor Nerve damage
2. Sensory Nerve damage
3. Autonomic Nerve damage

PERIPHERAL NEUROPATHY

- **Motor Nerve Damage**
  - Commonly associated with muscle weakness
  - May include painful cramps, fasciculations
  - Muscle atrophy
  - Decreased reflexes

PERIPHERAL NEUROPATHY

- **Sensory Nerve Damage:** Variety of symptoms b/c of broad range of functions
  - Damage to larger sensory fibers (enclosed in myeli)
    - impairs touch (felt most in hands and feet) - decrease in sensation
    - loss of reflexes
    - loss of position sense
  - Damage to smaller fibers (w/o myelin sheath)
    - impairs pain & temperature sensations (injury from a cut, infected wound, angina

PERIPHERAL NEUROPATHY

- **Autonomic Nerve Damage**
  - Parasympathetic & sympathetic nerve of PNS control nearly every organ of the body
  - Symptoms are diverse
    - Inability to sweat normally: heat intolerance
    - Loss of bowel & bladder control
    - Inability to regulate blood pressure
    - Malfunction GI muscle may cause symptoms: diarrhea, constipation, or incontinence

PERIPHERAL NEUROPATHY

Etiology of neuropathy suggested by involvement of predominant fiber types

Motor	Sensory	Autonomic
Guillain-Barré syndrome	Diabetes	Amyloidosis
CIDP	Uremia	Diabetes
Multifocal motor neuropathy	Alcohol	Guillain-Barré syndrome
Charcot-Marie-Tooth disease	HIV	Porphyria
Myeloma	Paraneoplastic	Hereditary sensory neuropathy
Diabetes	Sjögren syndrome	
Diphtheria	Connective tissue diseases	
	Toxins/medications	
	Vitamin B12 deficiency	

PERIPHERAL NEUROPATHY

Berkshire East NHS Community Health Services

Peripheral Neuropathy

- **Dysfunction of sensory, motor and autonomic nerves:**
- **Loss of protective pain sensation – increased susceptibility to foot ulceration**
- **Motor – high medial longitudinal arch, clawed toes, prominent metatarsals**
- **Autonomic – dry, fissured skin, sweat loss, distended dorsal veins**

Working with you for Better Health

PERIPHERAL NEUROPATHY

- **Causes**
- ***Inherited***
- Charcot-Marie-Tooth
- ***Acquired***
- Physical Injury: Trauma or repetitive stress
- Disease or disorders (metabolic or endocrine, small vessel, autoimmune, kidney, neuromas, infections, toxins: medications, environmental/industrial, ETOH
- ***Idiopathic***

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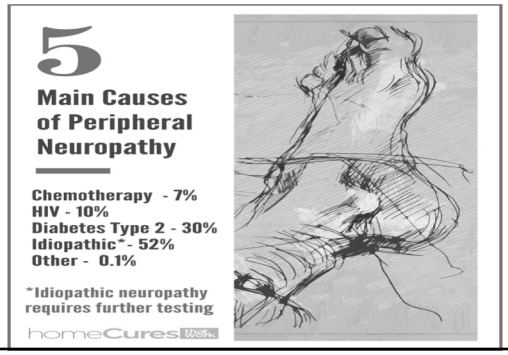

PERIPHERAL NEUROPATHY

Category	Examples
Traumatic	Incision, compression, stretching
Metabolic	Diabetes, renal failure, hypothyroidism, amyloid
Malignancy	Especially small cell carcinoma of the lung
Drugs	Isoniazid, phenytoin, nitrofurantoin
Toxins	Lead, alcohol
Infections	Leprosy (the commonest cause worldwide), Lyme disease, HIV
Inflammatory	Guillain-Barré, sarcoid
Vascular	Prolonged ischaemia, polyarteritis nodosa, rheumatoid disease
Genetic	Charcot-Marie-Tooth disease, porphyria
Vitamin deficiencies	B1, B6, B12, nicotinic acid

PERIPHERAL NEUROPATHY

Table 1: Causes of Peripheral Neuropathy

- Diabetes mellitus
- Shingles (post-herpetic neuralgia)
- B12 deficiency
- Alcoholism
- Autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus)
- Lyme disease
- Syphilis
- HIV
- Exposure to toxins, such as lead and chemotherapies
- Hereditary disorders, such as Charcot-Marie-Tooth

PERIPHERAL NEUROPATHY

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Diphtheria	Connective tissue diseases	
	Toxins/medications	
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PERIPHERAL NEUROPATHY

Disorders associated with small-fiber neuropathy pattern

Diabetes mellitus
Impaired glucose tolerance
Alcohol abuse
Antineoplastic agents
Renal failure
Sjögren syndrome
Systemic lupus erythematosus
Sarcoidosis
Monoclonal gammopathy
Hepatitis C virus
Human immunodeficiency virus
Celiac disease
Amyloidosis (hereditary and acquired)
Cancer (paraneoplastic)
Hereditary sensory and autonomic neuropathy
Fabry disease
Tangier disease

PERIPHERAL NEUROPATHY

Disorders causing sensory neuropathy and ataxia

- Acute onset
  - Idiopathic sensory neuropathy
  - GBS variant
- Subacute onset
  - Paraneoplastic neuropathy
  - Platinum-based chemotherapy
  - Sjögren syndrome
  - Pyridoxine toxicity
- Chronic
  - Chronic idiopathic ataxic neuropathy
  - Tropical ataxic neuropathy (human T-lymphotropic virus type 1)
  - Hereditary sensory neuropathies
  - Mitochondrial neuromyopathy

PERIPHERAL NEUROPATHY

Neuropathies causing a pattern of multiple mononeuropathies

- Axon loss
  - Vasculitis
  - Amyloidosis
  - Lymphoma
  - Diabetes
  - Sarcoidosis
  - Leprosy
- Demyelination
  - CIDP
  - GBS
  - Multifocal motor neuropathy
  - Hereditary liability to pressure palsies

PERIPHERAL NEUROPATHY

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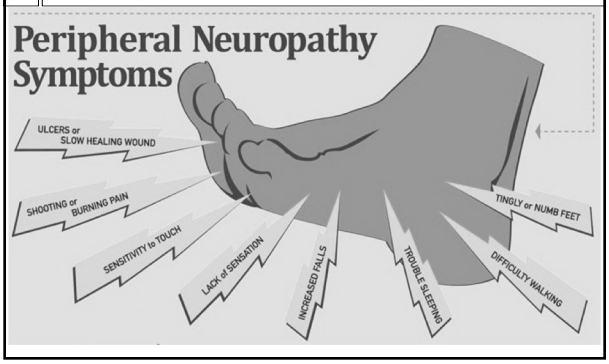

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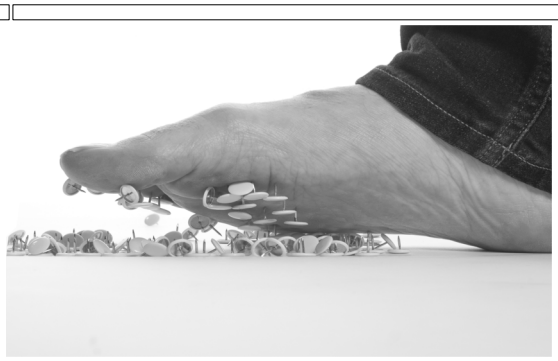


PERIPHERAL NEUROPATHY

3 distinct clinical challenges for clinicians

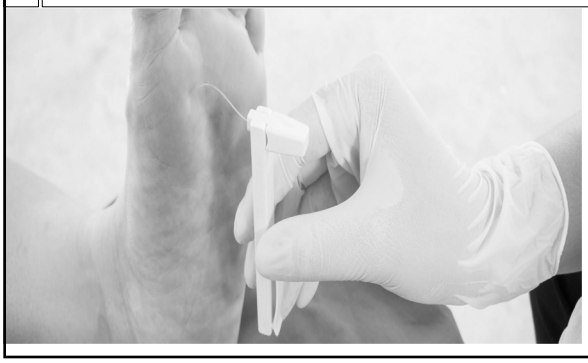
- How to efficiently and effectively screen for peripheral neuropathy in asymptomatic patients
- How to clinically stratify patients presenting with symptoms to determine who benefits from specialty consultation and what testing is needed for patients who do not
- How to treat symptoms of painful neuropathy.

PERIPHERAL NEUROPATHY (PN)

Screening asymptomatic patients

- Annual screening is recommended for diabetic pts
- Clinical history cannot be solely used for screening & single mode screening tools is not recommended
- Screening tools:
  - Light touch perception 10-g Semmes-Weinstein Monofilament
  - Vibration testing with a 128-Hz tuning fork
  - Superficial pain (pinprick) perception
  - Testing of ankle deep tendon reflexes

PERIPHERAL NEUROPATHY (PN)



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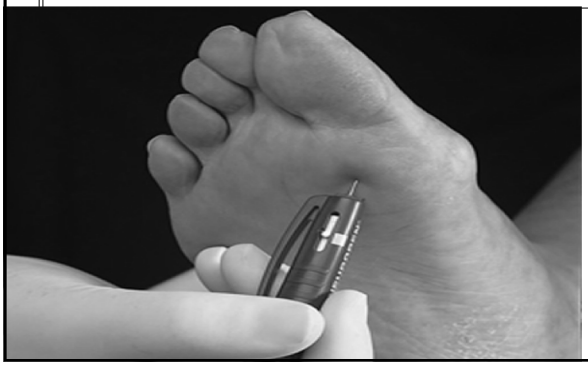

PERIPHERAL NEUROPATHY

- **<u>Evaluation of Chronic, Length-Dependent Peripheral Neuropathy</u>**

1. Detailed history (including family history)
2. Physical examination
3. Ancillary testing
4. Serologic evaluation

<u>Note</u>: Etiology of 74% to 82% yield with above

PERIPHERAL NEUROPATHY

Serology Evaluation

- CBC
- Renal function
- LFT
- ESR
- Hemoglobin A_{1C}
- TSH
- Serum protein electrophoresis
- Vit B_{12}
- Infections (HIV, Lyme disease)

PERIPHERAL NEUROPATHY

- **<u>Neuropathies that require specialty consultation</u>**

1. Acute, subacute in onset
2. Rapidly progressive
3. Severe, functionally limiting
4. Length independent (polyradiculoneuropathy)
5. Multifocal
6. Motor predominant
7. Associated with severe dysautonomia

PERIPHERAL NEUROPATHY

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- Alcoholism
- Autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus)
- Lyme disease
- Syphilis
- HIV
- Exposure to toxins, such as lead and chemotherapies
- Hereditary disorders, such as Charcot-Marie-Tooth

Disorders causing a predominant neuropathy pattern in the upper extremity

Lead intoxication

Porphyria

Vasculitis

Chronic inflammatory demyelinating neuropathy

Multifocal motor neuropathy

Hereditary liability to pressure palsies

TABLE 4. Diagnostic tests used to evaluate diabetic peripheral neuropathy

Test	Purpose
Autonomic tests	In patients with symptoms of autonomic neuropathy, to evaluate their blood pressure in different positions and their ability to sweat
Electromyography	To measure the electrical discharge in muscles
Monofilament testing	To determine sensitivity to touch
Nerve conduction studies	To measure how quickly nerves in the upper and lower extremities conduct electrical signals
Quantitative sensory testing	To assess how nerves respond to vibration and changes in temperature

Roles of electrodiagnostic studies in evaluating peripheral neuropathy

- Confirmation and localization
  - Confirm peripheral nerve disease
  - Localize nerve disease
- Assessment of fiber-type involvement
  - Motor
  - Large sensory
  - Small fiber: sensory and autonomic
- Determining the distribution of nerve involvement
  - Distal symmetric
  - Polyradiculoneuropathy
  - Multiple mononeuropathies (mononeuropathy multiplex)
  - Upper extremity predominant
- Identifying the underlying pathophysiologic process
  - Axon loss
  - Demyelination
  - Mixed
  - Channelopathy
- Determining the severity of fiber involvement
  - Mild
  - Moderate
  - Severe
- Monitoring recovery or treatment effect

PERIPHERAL NEUROPATHY

Differential dx

Common

- Diabetes (30% of cases)
  - 2/3 of DM
- Idiopathic (30% of cases)
- Post herpetic neuralgia
- Mechanical
  - Disc compression
  - OA [(+) in 19.9% of OK elderly]
  - Inflammation
  - Carpal tunnel (5.8% of ♀, 0.6% of ♂)
- GI/Malnutrition
  - Alcoholic (1/3 of Spanish alcoholics)
  - B12 (5% of OK elderly)
  - B6

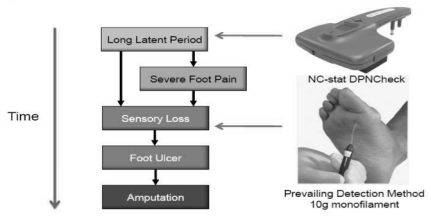
Other interesting ones

- Infectious
  - Hep B/C (1.3% of OK elderly)
  - Lyme disease, HIV, CMV, Leprosy, Chagas
- Drugs/Toxins/Chemotx
  - Isoniazid, Hydralazine, Lithium, Flagyl, Amit riptyline, statins, retroviral, Dapsone
  - Taxol, Vincristine
  - EtOH, arsenic, cyanide, Pb, Hg, thallium
- Immune-mediated (6.3% of OK elderly)
  - Guillain-Barré
  - MGUS/AMM, Sjogrens, Lupus, Vasculitic
- Inflammatory
  - Parsonage-Turner
- Cancer-related
  - Paraproteinemic (discovered in 10% of (-) workup cases)
  - Paraneoplastic syndrome
- Hereditary (0.6% of OK elderly)
  - Charcot Marie Tooth, Fabry's, familial amyloid neuropathy, porphyria

PERIPHERAL NEUROPATHY

Diabetic Neuropathy is Progressive

Late Diagnoses → Missed Treatment Opportunities



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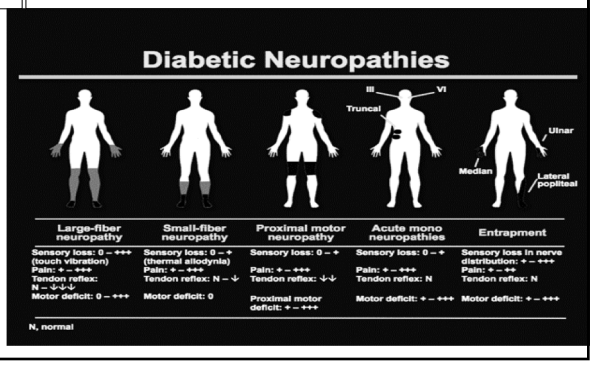
CONFIDENTIAL NEUROMetrix

PERIPHERAL NEUROPATHY



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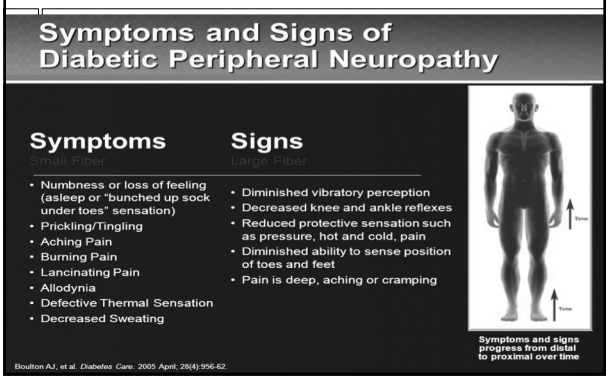

PERIPHERAL NEUROPATHY

- **Symptomatic Management** (Primary goal):

1. Evaluation of neuropathy
2. Identify etiology & treat causes (DM, B12 deficiency, or toxic exposure)
3. Treatment is to prevent progression of symptoms
4. Commonly, symptoms linger/persist.

PERIPHERAL NEUROPATHY

- **Symptomatic Management**

1. Most limiting symptom is neuropathic pain (burning, pins and needles, electrical, or shooting pain)
2. Most RCT have focused on diabetic or post-herpatic neuralgia pain, so treatment algorithms have been focused on the two

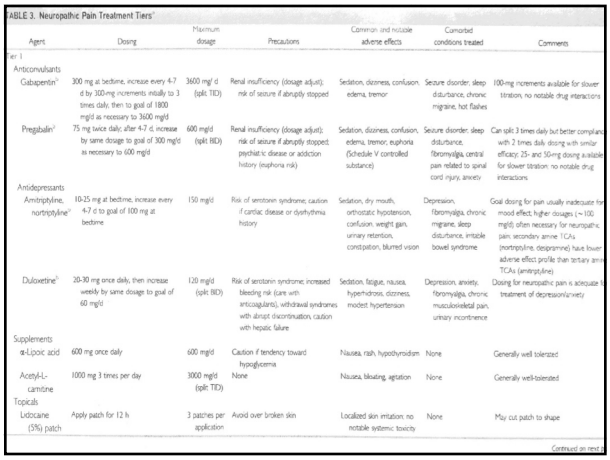

TABLE 3. Neuropathic Pain Treatment Tiers[1]

Agent	Dosing	Maximum dosage	Precautions	Common and notable adverse effects	Comorbid conditions treated	Comments
Tier 1						
Anticonvulsants						
Gabapentin[2]	300 mg at bedtime, increase every 4-7 d by 300-mg increments initially to 3 times daily, then to goal of 1800 mg/d as necessary to 3600 mg/d	3600 mg/ d (split TID)	Renal insufficiency (dosage adjust); risk of seizure if abruptly stopped	Sedation, dizziness, confusion, edema, tremor	Seizure disorder; sleep disturbance, chronic migraine, hot flashes	100-mg increments available for slower titration; no notable drug interactions
Pregabalin[2]	75 mg twice daily; after 4-7 d, increase by same dosage to goal of 300 mg/d as necessary to 600 mg/d	600 mg/d (split BID)	Renal insufficiency (dosage adjust); risk of seizure if abruptly stopped; psychiatric disease or addiction history (euphoria risk)	Sedation, dizziness, confusion, edema, tremor; euphoria (Schedule V controlled substance)	Seizure disorder; sleep disturbance, fibromyalgia, central pain related to spinal cord injury, anxiety	Can split 3 times daily but better compliance with 2 times daily dosing with similar efficacy; 25- and 50-mg dosing available for slower titration; no notable drug interactions
Antidepressants						
Amitriptyline, nortriptyline[3]	10-25 mg at bedtime, increase every 4-7 d to goal of 100 mg at bedtime	150 mg/d	Risk of serotonin syndrome; caution if cardiac disease or dysrhythmia history	Sedation, dry mouth, orthostatic hypotension, confusion, weight gain, urinary retention, constipation, blurred vision	Depression, fibromyalgia, chronic migraine, sleep disturbance, irritable bowel syndrome	Goal dosing for pain usually inadequate for mood effect; higher dosages (> 100 mg/d) often necessary for neuropathic pain; secondary amine TCAs (nortriptyline, desipramine) have lower adverse effect profile than tertiary amine TCAs (amitriptyline)
Duloxetine[3]	30-30 mg once daily, then increase weekly by same dosage to goal of 60 mg/d	120 mg/d (split BID)	Risk of serotonin syndrome; increased bleeding risk (care with anticoagulants), withdrawal syndromes with abrupt discontinuation; caution with hepatic failure	Sedation, fatigue, nausea, hyperhidrosis, dizziness, modest hypertension	Depression, anxiety, fibromyalgia, chronic musculoskeletal pain, urinary incontinence	Dosing for neuropathic pain is adequate for treatment of depression/anxiety
Supplements						
α-Lipoic acid	600 mg once daily	600 mg/d	Caution if tendency toward hypoglycemia	Nausea, rash, hypotyhroidism	None	Generally well tolerated
Acetyl-L-carnitine	1000 mg 3 times per day	3000 mg/d (split TID)	None	Nausea, bloating, agitation	None	Generally well-tolerated
Topicals						
Lidocaine (5%) patch	Apply patch for 12 h	3 patches per application	Avoid over broken skin	Localized skin irritation; no notable systemic toxicity	None	May cut patch to shape

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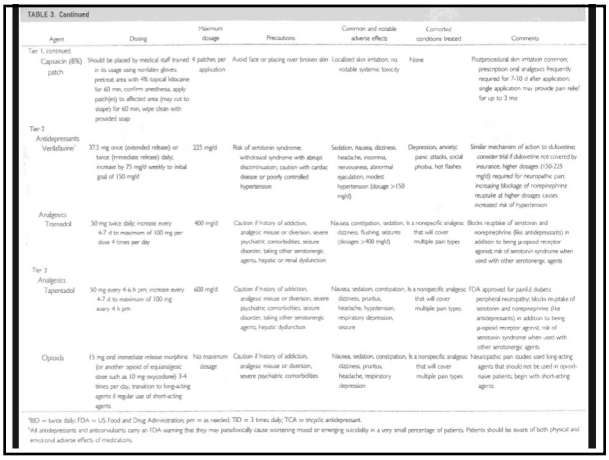


TABLE 3. Continued

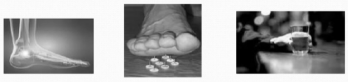
Agent	Dosing	Maximum dosage	Precautions	Common and notable adverse effects	Comorbid conditions treated	Comments
Tier 1, continued						
Capsaicin (8%) patch	Should be placed by medical staff trained in its usage using nonlatex gloves; pretreat area with 4% topical lidocaine for 60 min, confirm anesthesia, apply patch(es) to affected area (may cut to shape) for 60 min, wipe clean with provided soap	4 patches per application	Avoid face or placing over broken skin	Localized skin irritation; no notable systemic toxicity	None	Postprocedural skin irritation common; prescription oral analgesics frequently required for 7-10 d after application; single application may provide pain relief for up to 3 mo
Tier 2						
Antidepressants						
Venlafaxine[3]	37.5 mg once (extended release) or twice (immediate release) daily; increase by 75 mg/d weekly to initial goal of 150 mg/d	225 mg/d	Risk of serotonin syndrome; withdrawal syndrome with abrupt discontinuation; caution with cardiac disease or poorly controlled hypertension	Sedation, nausea, dizziness, headache, insomnia, nervousness, abnormal ejaculation; modest hypertension (dosage >150 mg/d)	Depression, anxiety, panic attacks, social phobia, hot flashes	Similar mechanism of action to duloxetine; consider trial if duloxetine not covered by insurance; higher dosages (150-225 mg/d) required for neuropathic pain; increasing blockage of norepinephrine reuptake at higher dosages causes increased risk of hypertension
Analgesics						
Tramadol	50 mg twice daily; increase every 4-7 d to maximum of 100 mg per dose; 4 times per day	400 mg/d	Caution if history of addiction, analgesic misuse or diversion, severe psychiatric comorbidities, seizure disorder, taking other serotonergic agents, hepatic or renal dysfunction	Nausea, constipation, sedation, dizziness, flushing, seizures (dosages >400 mg/d)	Is a nonspecific analgesic that will cover multiple pain types	Blocks reuptake of serotonin and norepinephrine (like antidepressants) in addition to being μ-opioid receptor agonist; risk of serotonin syndrome when used with other serotonergic agents
Tier 3						
Analgesics						
Tapentadol	50 mg every 4-6 h prn; increase every 4-7 d to maximum of 100 mg every 4 h prn	600 mg/d	Caution if history of addiction, analgesic misuse or diversion, severe psychiatric comorbidities, seizure disorder, taking other serotonergic agents, hepatic dysfunction	Nausea, sedation, constipation, dizziness, pruritus, headache, hypotension, respiratory depression, seizure	Is a nonspecific analgesic that will cover multiple pain types	FDA approved for painful diabetic peripheral neuropathy; blocks reuptake of serotonin and norepinephrine (like antidepressants); in addition to being μ-opioid receptor agonist; risk of serotonin syndrome when used with other serotonergic agents
Opioids	15 mg oral immediate release morphine (or another opioid of equianalgesic dose such as 10 mg oxycodone) 3-4 times per day; transition to long-acting agents if regular use of short-acting agents	No maximum dosage	Caution if history of addiction, analgesic misuse or diversion, severe psychiatric comorbidities	Nausea, sedation, constipation, dizziness, pruritus, headache, hypotension, respiratory depression	Is a nonspecific analgesic that will cover multiple pain types	Neuropathic pain studies used long-acting agents that should not be used in opioid-naive patients; begin with short-acting agents

[1]BID = twice daily; FDA = US Food and Drug Administration; prn = as needed; TID = 3 times daily; TCA = tricyclic antidepressant.
[2]All antidepressants and anticonvulsants carry an FDA warning that they may paradoxically cause worsening mood or emerging suicidality in a very small percentage of patients. Patients should be aware of both physical and emotional adverse effects of medications.

PERIPHERAL NEUROPATHY

Facts

- *Diabetes* and *alcoholism* are the most common causes of peripheral neuropathy in the United States
- The most common presentation of peripheral neuropathy is distal symmetric sensorimotor dysfunction



PERIPHERAL NEUROPATHY

Conclusion

- Peripheral Neuropathy is often seen by clinicians
- Screening can efficiently identify or rule out peripheral neuropathy with a combination of vibration and light touch testing.
- Most peripheral neuropathy (PN) are length-dependent, sensory predominant, and clinically mild/mod w/o notable functional limitations.
- Most PN can effectively be w/u & managed w/o specialty consultation.
- Neuropathic pain can effectively be treated with an algorithmic approach

PERIPHERAL NEUROPATHY

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PERIPHERAL NEUROPATHY

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