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"The Causes of Peripheral Neuropathy and Treatment Options"

- **MONDAY, November 9th, 7:00pm**

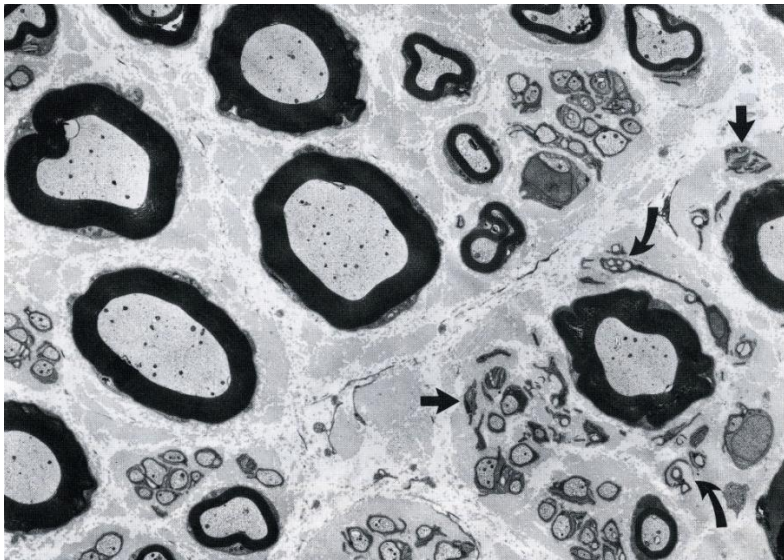
Peripheral Neuropathy

- Any disease of peripheral nerves is referred to as 'Peripheral Neuropathy'
- Peripheral neuropathies are quite common
 - ~2.4% of the general population
 - ~8% of individuals older than 55 years
- A vast majority of peripheral neuropathies are chronic and not life threatening

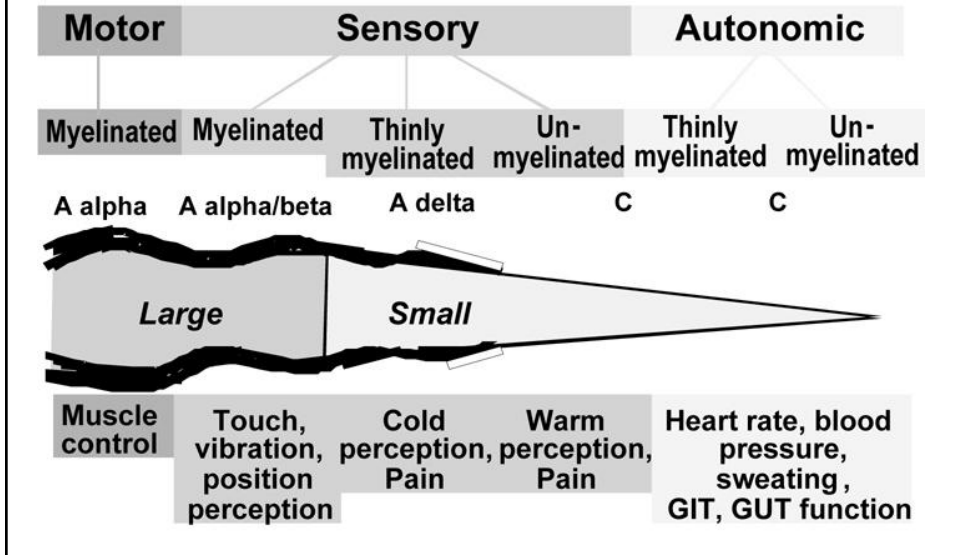
Peripheral Nerves

- Consist of motor, sensory, and autonomic fibers
- Motor nerve fibers
 - Muscle and voluntary movements
- Sensory nerve fibers
 - Transmit sensory information from external and internal organs to CNS and serve balance, protective, and homeostatic functions
- Autonomic nerve fibers
 - Involuntary functions such as heart rate, BP, sweating, bowel, or bladder

Normal peripheral nerves



Different nerve fiber types



Peripheral Neuropathies

- Symptoms

	Positive symptoms	Negative symptoms
Sensory Small fibers	Pain, paresthasias	Numbness/lack of sensation
Sensory Large fibers		Poor balance
Motor	Cramps, fasciculations	Weakness, atrophy
Autonomic	Diarrhea, hyperhidrosis	Orthostatic hypotension, impotence, anhydrosis

Peripheral Neuropathies: Patterns

- Length-dependent (glove stocking, distal symmetric)
- Focal
- Multifocal

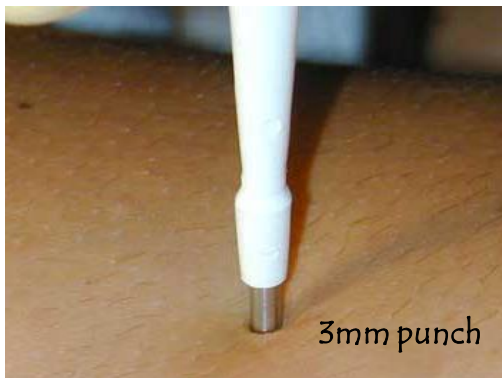
Evaluation of Peripheral Neuropathies: History and Physical Exam

- Pertinent features:
 - Medical history
 - DM, HIV, other autoimmune diseases
 - Medications
 - Include vitamins (e.g. B6 in megavitamins), chemotherapy, and OTC medications
 - Family history
 - History of high arches, hammer toes
- Examination
 - Sensory, motor, tendon reflexes, BP changes

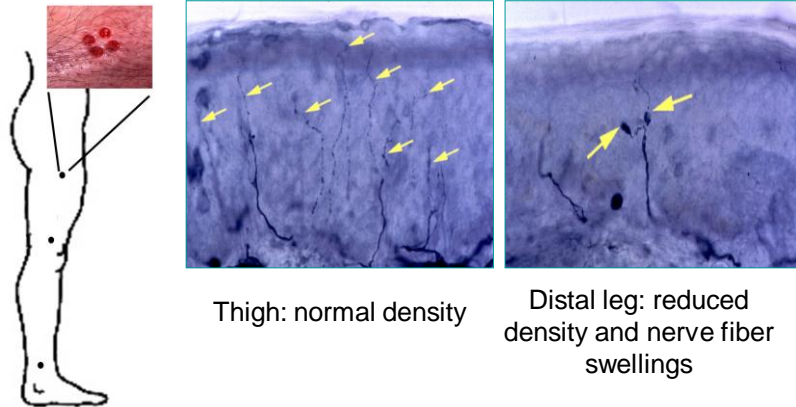
Ancillary testing for confirmation of diagnosis

- **NCS/EMG**
- **Skin biopsy**
 - most sensitive, but invasive
- **Blood work up**
- **Nerve biopsy**
- QSART and QST
 - less sensitive, specialized equipment
- Imaging
 - MRI, MR neurography, CT myelogram

Skin biopsy technique



Ancillary testing - Skin biopsy



Thigh: normal density

Distal leg: reduced density and nerve fiber swellings

Nerve biopsy

- Routine nerve biopsy in patients with idiopathic neuropathy is of very low yield and not indicated
- Indications
 - vasculitis
 - amyloid neuropathy
 - CIDP (some cases)
 - multifocal leprosy

Causes of Neuropathies

Diabetes (metabolic)

- Diabetes is the commonest cause of neuropathy in USA
- Every patient with peripheral neuropathy should have at least one 75 gm two hour oral glucose tolerance test
- Diabetes could not only be the cause of neuropathy but it also can be a 'co-morbidity' for non-diabetic neuropathies

Diabetes

- Symmetric sensory or sensory-motor neuropathy
- Focal or multifocal
- Autonomic
- Lumbosacral plexopathy (amyotrophy)

Other metabolic neuropathies

- Advanced renal failure (uremia)
- Hypothyroidism
- Porphyria
- Screening for these conditions is by blood and/or urine testing

Nutritional neuropathies

- Deficiencies
 - Vit B12, Vit B1, Vit B6, Vit E, serum copper?
- Toxicity
 - Vit B6
- Deficiency and toxicity
 - Alcohol (history)
- Celiac disease
- Bariatric surgery
- Gastrointestinal disease
- Screening by blood testing and duodenal biopsy for celiac disease and GI work up

Infections

- HIV, HZV, CMV
- Hepatitis C associated neuropathies
- Lyme disease
- Leprosy (Asia, Africa, it can rarely be seen in Texas)
- Diphtheria
- Diagnosis is established by blood, CSF, or bacterial tests, and skin or nerve biopsy

Immune neuropathies

- Guillain-Barre syndrome
(AIDP, AMAN/AMSAN, MFS)
- CIDP (different variants)
- Multifocal motor neuropathy with conduction block
- Sarcoid
- Diagnosis by history, exam, electrodiagnostic testing, CSF, and nerve biopsy

Connective tissue disorders

- Sjogren's
- SLE
- Mixed connective tissue disease
- Scleroderma
- Rheumatoid Arthritis
- Vasculitis
 - PAN, Wegner's, Churg-Strauss
- Diagnosis by blood tests and salivary gland biopsy and nerve biopsy for vasculitis

Paraproteinemias and related hematological disorders

- Monoclonal gammopathy of unknown significance (MGUS)
- Multiple myeloma
- Amyloid (acquired)
- Lymphoma/Leukemia
- Waldenstrom's macroglobulinemia
- Diagnosis is established by blood, urine, X-rays/CT scans, and bone marrow biopsy; nerve biopsy for diagnosis of amyloid

Toxic neuropathies

- Metals (arsenic, lead, mercury, thallium)
- Insecticides (organochlorines, organophosphates, carbamates)
- Industrial agents; solvents (toluene, n-hexane, xylene), acrylamide
- **Chemotherapeutic agents** (vinca alkaloids, cisplatin, taxol, docetaxel, suramin, Bortezomib)
- Other drugs: amiodarone, perhexilene, furadantin, thalidomide, isoniazid, dapson, antiretrovirals
- Diagnosis by history, blood, and/or urine, hair or nail testing and rarely nerve biopsy

Neuropathy associated with cancer

- Commonest cause is chemotherapy
- Paraneoplastic neuropathy
- Tumor infiltration of the nerves (very rare)
- Diagnosis by blood testing for immune markers, scans including PET/CT scans, CSF studies, rarely nerve biopsy

Hereditary neuropathies

- Transmitted in autosomal dominant, recessive, and X-linked modes
- Motor-Sensory neuropathies, CMT, are the commonest
- Hereditary sensory and autonomic neuropathies
- Amyloid
- Fabry's disease
- Diagnosis by history, examination of the family, and gene testing if available

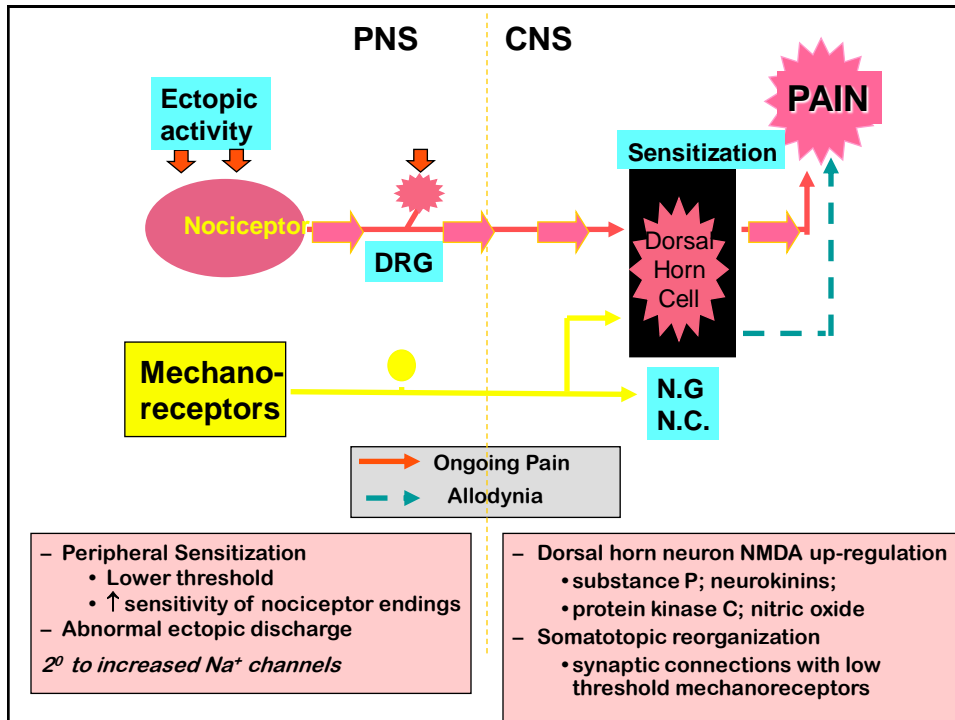
Entrapment neuropathies

- Common sites
 - Median nerve at the wrist
 - Ulnar nerve at the elbow
 - Peroneal nerve at the fibular head
 - Tibial nerve in tarsal nerve
- Common causes
 - Diabetes, hypothyroid, amyloid, hereditary neuropathies, connective tissue disorders
- Diagnosis by history, exam, and electrodiagnostic testing

Principles of treatment

- Specific treatments for underlying disorders, if available
- Therapies to enhance nerve repair (experimental stages)
- Symptomatic treatments
 - Pain management
 - Management of autonomic symptoms
 - Management of gait and stability issues
 - Foot care
 - Adaptive devices

MANAGEMENT OF NEUROPATHIC PAIN



Neuropathic pain: common features

- Fluctuations are extremely common
- Any kind of emotional or physical stress aggravate neuropathic symptoms
- Paradoxical appearance of pain at time of rest
- Secondary depression and anxiety are very common and should be treated

Non pharmacological interventions

- Good sleep hygiene
- Gentle physical therapy
- Weight and lipid control
- Healthy diet
- Psychological counseling

Drugs for Neuropathic Pain

- | | |
|---------------------|--------------------------------|
| • TCAs** | • Oxcarbazepine* |
| • Phenytoin* | • Valproic acid* |
| • Carbamazepine** | • Tiagabine |
| • Duloxetine** | • Felbamate |
| • Lamotrigine* | • Benzodiazepines |
| • Gabapentin** | • Capsaicin |
| • Pregabalin** | • Alpha-lipoic Acid |
| • Topiramate* | • Mexiletine |
| • Tramadol** | • Dextromethorphan/Quinidine** |
| • Opioids** | |
| • Lidocaine Patch** | |
| • Venlaflexine | |
| • Bupropion | |

** and *clinical data support efficacy

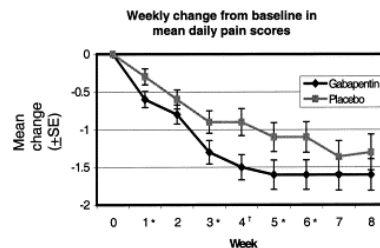
Neuropathic Pain: antidepressant

- Amitriptyline (tricyclic antidepressant)
 - Clearly effective in multiple trials
 - Reduces burning, aching, sharp, throbbing, and stinging pain
 - Dose-dependent effect; independent of effect on mood
 - Start 10 to 20 mg qhs; titrate up as needed
 - may require 150 mg/day for 6 weeks in some patients
 - Contraindications: heart block, recent MI, heart failure, urinary tract obstruction, orthostatic hypotension, narrow angle glaucoma
 - Increased AEs in patients with autonomic dysfunction
 - Gradual withdrawal to avoid rebound insomnia

McQuay HJ, et al. *Pain*. 1996;68:217-27.

Neuropathic Pain: antiepileptic

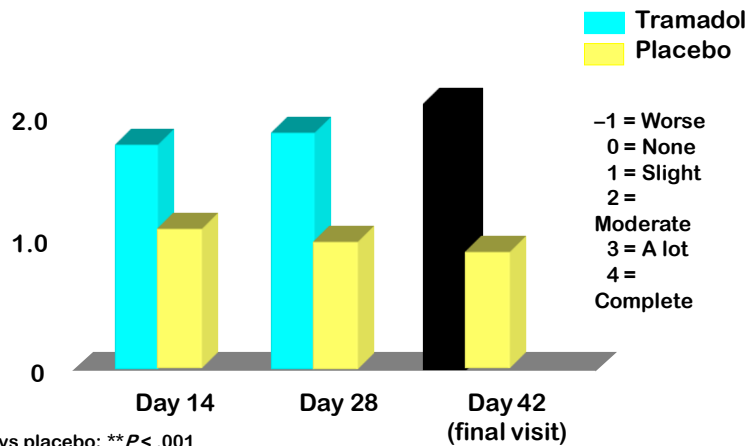
- Gabapentin
 - Effective in 3 double-blind controlled trials
 - Max dose unknown (up to 4800 mg/day) but average effective dose is 1800 mg/day
 - Start dose as low as 100 mg qhs and titrate slowly
 - Common adverse events: nausea, vomiting, GI distress, weight gain, edema, confusion



Neuropathic Pain: opioids

- Tramadol HCL/Ultracet®
 - Dual mechanism of action: mu-opioid and TCA
 - Effective for up to 6 months in double-blind controlled trials and an open trial
 - Max dose 2 tabs qid (older 2 tabs tid) but average effective dose across studies is 200 mg/d
 - Tramadol: start at 1 tab qhs, increase slowly
 - Ultracet®: may start as bid or higher
 - Side effects: GI and confusion (less with Ultracet)
 - Effect enhanced by acetaminophen (Ultracet)

Effect of Tramadol in Painful Diabetic Neuropathy Pain Relief Scores



Interventional therapy for neuropathic pain

- Nerve blocks
- Intrathecal pumps
- Spinal cord stimulator
- Sympathectomy/rhizotomy

Does Neuropathic Pain Disappear?

- Daousi et al. The natural history of chronic painful peripheral neuropathy in a community diabetes population. *Diabet Med* 2006, 23:1021–1024.
- 350 subjects with DM to find 56 with painful DPN (16%).
- At 5 year follow-up, 12 died, 14 lost, and 30 reinterviewed.
- 7 (23%) painfree, and the rest undertreated.