A Clinical Approach to Peripheral Neuropathy
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Introduction & Goals
- Practical and succinct approach to the identification and treatment of clinical Peripheral Neuropathy
- Topics associated with Peripheral Neuropathy will be presented
  - Anatomy
  - History
  - Diagnostic workup
  - Treatment
  - Case Study
- Goal of presentation: Present a better understanding regarding Peripheral Neuropathy
Introduction

- Neuropathy definition - A functional disturbance or pathological change in the peripheral nervous system

- Prevalence of peripheral neuropathy is estimated to be between 2% and 8%

- More than 100 types of peripheral neuropathy have been identified

Anatomy
Anatomy

- The peripheral nerves include:
  - Cranial Nerves
    - (not the 2nd CN)
  - Spinal Nerve Roots
  - Dorsal Root Ganglia
  - Peripheral Nerve Trunks and their Terminal Branches
  - Peripheral Autonomic Nervous System
Classification

- Neuropathic disorders encompass
  - Disease of the neuron cell body (neuronopathy) and their peripheral processes (peripheral neuropathy)

- Neuronopathies
  - Anterior horn cell disorders
    - Motor neuron disease
  - Dorsal root ganglion disorders
    - Sensory neuronopathy (ganglionopathy)

- Peripheral Neuropathies
  - Axonopathies
  - Myelinopathies
Classification

- Mononeuropathies: Damage to only one nerve
  - Focal neuropathies include compressive neuropathies such as
    - Carpal tunnel syndrome
    - Ulnar neuropathy at the elbow
    - Peroneal neuropathy at the fibular head

- Mononeuritis multiplex: Damage of two or more isolated nerves in separate areas of the body
  - A multifocal neuropathy suggests a mononeuritis multiplex
    - Vasculitis
    - Diabetes

- Polyneuropathy: Damage to multiple nerves affecting all limbs.

Symptoms

- Motor Symptoms
  - Positive symptoms-Inappropriate spontaneous nerve activity
    - Cramps
    - Twitching
    - Myokymia (involuntary muscular movement on skin)

  - Negative symptoms-Reduced nerve activity
    - Weakness
    - Fatigue
    - Wasting

  - Positive symptoms may present earlier in the disease process

  - Weakness may not be appreciated until 50% to 80% of nerve fibers are lost
Symptoms

- Sensory Symptoms
  - Positive symptoms - Inappropriate spontaneous nerve activity
    - Burning or lancing pain
    - Buzzing and tingling paresthesia
    - Discomfort to sensory stimuli normally not painful (allodynia)
    - Increased sensitivity to painful stimuli (hyperalgesia)

- Negative motor symptoms - Reduced nerve activity
  - Hypoesthesia (reduced sense of touch or sensation)
  - Gait abnormalities
  - Difficulty determining hot from cold
  - Worsening balance

History

- HPI
  - What is the disease onset, location, duration & progression
  - Onset
    - Symmetrical or asymmetrical
  - Location
    - Involvement of arms, legs, trunk or cranial nerve region
  - Duration
    - Is it acute, subacute or chronic
  - Progression
    - Steadily progressive
    - Fluctuating
    - Stepwise
History

- Medical, Surgical & Family History
  - Endocrinopathies
    - Diabetes mellitus
    - Hypothyroidism
  - Renal insufficiency
  - Hepatic dysfunction
  - Connective tissue disorders
  - Cancer
    - Nutritional deficiency
    - Chemotherapy side effects
    - Paraneoplastic syndrome
  - Surgeries
    - Bariatric
    - Multiple orthopedic surgeries
    - Multiple “entrapped nerve” surgeries

History

- Social History
  - Occupation
    - Toxic exposure to solvents, glues, fertilizers, oils & lubricants
  - Sexual History
    - HIV
    - Hepatitis C
  - Recreational drug use
    - Vasculitis secondary to cocaine use
  - Excessive alcohol intake
  - Dietary habits
    - Strict vegan diet
  - Smoking
    - Paraneoplastic disease
  - Childhood history
    - Clumsiness or poor athletic performance may suggest hereditary cause
History

- Medications
  - HIV related medications & chemotherapy are most common cause of toxic neuropathy
  - Quinolones
  - Vitamin B6 greater than 50-100mg daily may induce neuropathy

Physical exam

- Orthostatic vital signs could identify dysautonomia
- Skin & mucous membrane
  - Vasculitic rash (purpura, livedo reticularis)
  - Hyperpigmentation (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS])
  - Oral ulcers (Behcet disease, HIV)
  - Salivary gland swelling, dry eyes or mouth (Sarcoidosis, Sjogrens syndrome)
  - Extremity hair loss (hair follicle degeneration)
Physical exam

- Integumentary changes
  - Mee lines in nails (arsenic or thallium poisoning)
  - Alopecia (hypothyroidism, amyloidosis, thallium poisoning)
  - Curly hair (giant axonal neuropathy)
  - Distal calf hair loss (axonal polyneuropathy)
- Skeletal deformities
  - Hammer toes, pes cavus, kyphoscoliosis suggestive of inherited polyneuropathy
- Nerve enlargement
  - Demyelinating neuropathy
  - Neoplasia in neurofibromatosis
  - Leprosy

Physical exam

- Cranial nerve exam looking for
  - Anosmia (inability to perceive odor)
    - Refsum disease- autosomal recessive neurologic disease that results from the over-accumulation of phytanic acid in cells and tissues.
    - Vitamin B12 deficiency
  - Optic atrophy
    - Inherited neuropathies with central and peripheral demyelination
  - Anisocoria or impaired pupillary light reflexes
    - Parasympathetic dysautonomia
  - Impaired ocular motility
    - Botulism
    - Miller Fischer syndrome
  - Trigeminal sensory loss
    - Sjogren syndrome
  - Facial weakness
    - Guillian-Barre syndrome [GBS]
Physical exam

- Motor exam
  - Atrophy of intrinsic hand and foot muscles
    - Most neuropathies cause distal weakness causing intrinsic muscle atrophy, clawed feet and hammer toes
  - Weakness of flexion and extension of the small toes and great toe extension
  - Angle greater than 130 degrees between the shin and the unsupported foot suggests ankle dorsiflexion weakness
  - 2nd and 5th hand digit abductors are often effected first

Physical exam

- Sensory Examination
  - To test large fiber function
    - Vibration
    - Joint position
    - Light touch
  - To test small fiber function
    - Pinprick
    - Temperature
    - Light touch
  - To test large and small fiber function
    - Light touch
Physical exam- large fiber function

- Vibratory perception (Large Fiber)
  - 128-Hz tuning fork
  - Great toe, malleolus, tibial tuberosity, finger and wrist
  - The time interval until vibratory perception is lost is measured
    - Young adult should appreciate vibration at the great toe for a minimum of 15 seconds
    - Value may decline by 1 second per decade
    - Vibratory perception of less than 10 seconds for any age is abnormal

Physical exam- large fiber function

- Joint position testing
  - Less sensitive than vibratory for large fiber function
  - May only be impaired in severe cases
  - Joint position is tested in large toe and second finger at the distal interphalangeal joint
  - Hold digit at the lateral borders with movement excursion minimal.
  - Proximal joints are tested if distal impairment is present
Physical exam- large & small fiber function

- Light touch
  - Evaluates low thresholds mechanoreception
    - Detection of light touch or stroking represents a measure of low threshold sensory perception
    - Impairment to 10g microfilaments is associated with increased risk of unappreciated trauma

Physical exam- small fiber function

- Small fiber evaluation
  - Evaluate pain and temperature
    - Apply sharp stimuli without applying pressure
    - Difficulty distinguishing between sharp and dull stimulation
      - Loss of nociceptive fibers relative to low threshold mechanoreceptor fibers
Physical exam- large & small fiber function

- Testing large & small myelinated nerves
  - Light touch & pin testing
  - Establish an area of normal sensation for comparison
  - Compare proximal and distal locations
    - Face, arm and leg
    - Right and left side
- Initial screen may include
  - Test bilaterally at the
    - Forehead, cheek & chin
    - Lateral upper arm & palmar surface of digits 2 & 5
    - Lateral thigh and anteromedial and anterolateral gastrocnemius
    - Distal dorsum of great toe & lateral sole toward the plantar aspect
  - Temperature (small fiber function) can be assessed with tuning fork

Physical exam

- Reflex testing
  - Ankle hyporeflexia or areflexia
    - Common in large fiber neuropathy
    - Reserved in small fiber neuropathy
  - Reflexes may be preserved in mild to moderate large fiber neuropathy
  - Reflexes diminish with age
    - Absent ankle jerk at age 80 may be normal
Physical exam

- Gait examination
  - Can reveal subtle weakness not noted on manual muscle testing
    - Toe walking
    - Heel walking
    - Tandem walking
    - Squatting and hopping
  - Foot drop may result in steppage gait
  - Wide based gait or difficulty with tandem gait may highlight subtle sensory ataxia

Characterization of Neuropathy

- Tempo of onset and duration
  - Most neuropathies are chronic and progressive with insidious onset
  - Hyperacute lesions over 2 to 72 hours may suggest
    - Vasculitic lesions causing mononeuropathy multiplexes
  - Acute presentation and progression ≤ 1 month suggests
    - GBS
    - Vasculitis
    - Porphyria
    - Infectious etiology (diphtheria, Lymes disease)
    - Toxic drug exposure (arsenic, thallium, chemotherapeutic agents, dapsone)
  - Subacute onset of neuropathy ≤ 6 months can suggest
    - Toxic neuropathy
    - Nutritional deficiency
    - Malignancy
    - Paraneoplastic syndromes
    - Some metabolic abnormalities
Characterization of Neuropathy

- Tempo of onset and duration
  - Neuropathy with relapsing and remitting course suggest
    - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
    - Porphyria
    - Hereditary neuropathy with liability to pressure palsies (HNPP)
    - Toxic exposure
    - Vasculitis
  - In critical illness setting, development of weakness over days
    - Most likely related to critical illness myopathy
    - Can be caused by critical illness neuropathy

Characterization of Neuropathy

- Motor versus sensory
  - It is rare for neuropathies to be purely motor or sensory
  - Although most neuropathies are mixed they may predominately reflect dysfunction of one fiber type
  - During history taking sensory symptoms often overshadow motor symptoms
Characterization of Neuropathy

- Neuropathies with predominant motor involvement
  - GBS
  - CIDP
  - Multifocal motor neuropathy (MMN)
  - Porphyria
  - Diptheria
  - Lead intoxication
  - Botulism
  - Hereditary neuropathies
  - Toxic exposure to dapsone, amiodarone and vincristine

Characterization of Neuropathy

- Neuropathies with predominant sensory involvement
  - Diabetes mellitus
  - Vitamin B12 deficiency
  - HIV
  - Amyloidosis
  - Leprosy
  - Sarcoidosis
  - Sjogren syndrome
  - Uremia
  - Paraneoplastic syndromes
  - B6 intoxication
  - Hereditary neuropathies
Characterization of Neuropathy

• Autonomic Neuropathy
  - Autonomic dysfunction may be seen as a component of:
    - Generalized polyneuropathy
    - Small fiber neuropathy
    - Predominantly autonomic neuropathy.
  - Autonomic nerves outnumber somatic nerves however somatic neuropathy is greater than autonomic neuropathy
  - Common causes of predominant autonomic symptoms
    - Diabetes Mellitus
    - Amyloidosis
    - GBS

Characterization of Neuropathy

• Autonomic neuropathy
  - If autonomic neuropathy is acute or subacute consider
    - Autoimmune autonomic ganglionopathy
    - Paraneoplastic syndrome
    - GBS
    - Botulism
    - Toxic neuropathies
    - Acute porphyria
  - If chronic autonomic neuropathies consider
    - Diabetes Mellitus
    - Amyloidosis (familial and primary)
    - Inherited disease (Hereditary sensory and autonomic neuropathy [HSAN])
    - Fabry disease
    - Sjogren syndrome
    - Toxic and infectious neuropathy including HIV
## Characterization of Neuropathy

- **Demyelinating neuropathy**
  - Demyelinating features include
    - Weakness without atrophy
    - Early involvement of proximal reflexes and myokymia
    - Distal reflex loss (ankle jerks) with proximal reflexes is common in length dependent neuropathy
  
- **Etiology of demyelinating neuropathy include**
  - Genetic (Charcot-Marie-Tooth [CMT] type 1) HNPP
  - Refsum disease Metachromatic leukodystrophy
  - GBS MMN
  - Paraproteinemia-related neuropathy Diptheria
  - Infectious neuropathy
    - HIV, Lymes, leprosy, hepatitis C, diptheria and toxin related neuropathies (n-hexane, amiodarone)
  - CIDP
    - CIDP may be associated with systemic disease including
      - Infections, inflammatory bowel disease, metabolic conditions, and connective tissue disorders

## Characterization of Neuropathy

- **Axonopathies have a classic symmetric length dependent pattern of symptom evolution**
  - Sensory symptoms
    - Symptoms start in the feet which are supplied by the longest axons
    - After dyesthesias and numbness ascend to the calves the fingertips become effected
    - The legs, forearms and eventually anterior chest can become involved
  
- **Motor symptomatology first affects**
  - Intrinsic foot muscles causing toe flexor weakness and clawed toe
  - Anterior tibial compartment muscle weakness then causes ankle dorsiflexion weakness
    - Plantar flexion is relatively preserved.
  - The intrinsic hand muscles become involved only after calf muscles are involved
  - Motor weakness is usually greater in extensor groups than corresponding flexor groups
  
- **Many chronic axonopathies remain idiopathic**
Diagnostic testing in Peripheral Neuropathy

- AAN Guidelines for distal symmetric polyneuropathy
  - Fasting blood glucose
  - 2-hour glucose tolerance test is more sensitive than Hemoglobin A1c
  - Electrolytes
  - Complete blood count & differential
  - Vitamin B12
    - When value is below 400 pg/mL
      - Test methylmalonic acid and homocysteine
  - Erythrocyte Sedimentation Rate
  - Thyroid Stimulating Hormone
  - Serum immunfixation electrophoresis (IFE)
    - Serum IFE is more sensitive than Serum Protein electrophoresis (SPEP) in detecting monoclonal gammopathy
    - Quantitative Igs (IgG, IgA, IgM) may suggest lymphoproliferative disorders

- Test with the highest yield of abnormality are
  - Blood glucose
  - B12 with methylmalonic acid and Homocysteine
  - Serum immunfixation electrophoresis (IFE)

Diagnostic testing in Peripheral Neuropathy

If initial tests are not revealing test focusing on individual diseases should be considered

- Vasculitis and connective tissue disorders
  - C-reactive protein
  - Antinuclear antibody
  - Double stranded DNA
  - SS-A and SS-B
  - Rheumatoid factor
  - Proteinase 3
  - Myeloperoxidase complement
  - Angiotensin Converting enzyme (ACE)
  - Hepatitis B & C panels
  - Cryoglobulins

- Infectious Conditions
  - Lymes titer
  - Rapid Plasma Reagin
  - HIV
Diagnostic Testing in Peripheral Neuropathy

- Additional testing if a specific disease is suspected
  - Chest x-ray or CT to evaluate for Sarcoidosis
  - PET scan or CT of chest, abdomen and pelvis if malignancy is suspected
  - Skeletal survey and bone marrow biopsy if lymphoproliferative disease is suspected
  - Salivary gland biopsy for Sjogren syndrome
  - Endoscopy and duodenal biopsy for Celiac disease
  - Colonoscopy for Inflammatory Bowel Disease
  - Cerebral Spinal Fluid if infectious or neoplastic cause of neuropathy is suspected
    - HIV, Cytomegalovirus, Lyme disease, West Nile disease cause pleocytosis
    - Dysimmune neuropathy associated with elevated protein with normal cell counts
  - MRI can document
    - Nerve root enhancement in CIDP
    - Nerve root clumping in arachnoiditis
    - Nerve enlargement in tumors

Electrodiagnostic Testing in Peripheral Neuropathy

- Electrodiagnostic testing refers to nerve conduction studies (NCS) and needle electromyography (EMG)
- These test are standard for large fiber neuropathy BUT ARE OFTEN NORMAL IN SMALL FIBER NEUROPATHY
- Electrodiagnostic testing may help exclude mimics of polyneuropathy
  - Myopathy
  - Neuropathy
  - Plexopathy
  - Polyradiculopathy
- Electrodiagnostic testing augments ability to
  - Assess motor vs. sensory involvement
  - Severity of neuropathy
  - Distribution of neuropathic dysfunction
  - Relative extent of axonopathy versus myelopathy
  - May be repeated in time to assess progression of disease
Electrodiagnostic Testing in Peripheral Neuropathy

- **NCS**
  - Electrical stimulation and recording over a nerve or muscle using surface electrodes
  - The size and shape of the waveform are assessed.
    - Sensory nerves reveal Sensory Nerve Action Potentials (SNAP)
    - Muscle nerves reveal Compound Muscle Action Potentials (CMAP)
  - Parameters include
    - Latency
    - Amplitude
    - Conduction velocity (CV)
    - Duration
  - F wave studies reflect conduction over the entire length of the nerve
  - Tibial H reflex is the electrophysiologic equivalent of the S1 reflex and assess both sensory and nerve conduction

- **Needle EMG** assess electrical activity of the voluntary muscles
  - Helps localize the distribution or dysfunction based on the distribution and amplitude of fibrillations and sharp waves along with Motor Unit Potential (MUP) morphology
  - At rest, the presence of fibrillation and positive sharp waves indicate spontaneous discharge of individual muscle fibers
  - These findings suggest denervation of muscle fibers
  - Motor unit potential (MUP) may suggest
    - A neurologic lesion with reinnervation (increase duration, amplitude and polyphasia)
    - A myopathic lesion (brief duration, low amplitude, and polyphasia)
  - With activation of the muscle, the recruitment pattern may be divided into 2 components
    - Interference pattern
    - Firing rate
  - In neuropathy, there may be an increased firing frequency in association with decreased interference pattern
  - In myopathy, there may be an early recruitment of MUPs with a low amplitude envelope of the interference pattern
Diagnostic Testing in Peripheral Neuropathy

- Skin biopsy
  - Skin biopsy is becoming the standard for assessment of unmyelinated cutaneous nerves
  - Intraepidermal small nerve fibers convey pain and temperature sensation from the skin and maintain autonomic function
  - Skin sampling is done by either skin punch or less commonly skin blister technique

Diagnostic Testing in Peripheral Neuropathy

- Nerve biopsy
  - Nerve biopsy has become less important because of progress in electrodiagnostic, laboratory and genetic testing

- Neurophysiologic testing
  - Magnetic stimulation may assess conduction in proximal segments such as the femoral nerve or cauda equina
    - In general has limited use in peripheral neuropathy
  - Somatosensory-evoked potentials (SSEPs) may localize sensory symptoms to the nerve/plexus/root and evaluate proximal nerve segments that are inadequately assessed by NCS
Diagnostic Testing in Peripheral neuropathy

- Quantitative Sensory testing
  - Administration of vibration, warm, cold, and heat to great toe or index finger to determine the threshold to the sensation

- Autonomic testing
  - Sympathetic and parasympathetic function are assessed using the following indices
    - Cardiovagal
    - Adrenergic
    - Sudomotor
  - Sympathetic sudomotor testing include
    - Sympathetic skin response (SSR)
    - Quantitative sudomotor axon reflex testing (QSART)
    - Thermoregulatory sweat testing (TST)

Diagnostic Testing in Peripheral Neuropathy

- Cardiovascular testing
  - In normal physiology the heart rate increases with inspiration and decreases with expiration
    - Heart rate variability assessment during deep breathing (HRDB)
      - Assess variability in successive R-R intervals at six breaths/minute
      - Variation is largely related to parasympathetic/vagal nerve pathways and is reduced in autonomic dysfunction
  - Valsalva maneuver assess cardiovascular and sympathetic vasomotor function

- Tilt table testing
  - Orthostatic hypotension associated with neuropathy occurs when small myelinated and unmyelinated baroreflex fibers in splanchnic vasculature are damaged
Diagnostic Testing in Peripheral Neuropathy

- DESPITE AN EXTENSIVE SEARCH FOR ETIOLOGY OF NEUROPATHY THE CAUSE REMAINS IDIOPATHIC IN A SUBSTANTIAL NUMBER OF PATIENTS, MOST COMMONLY IN ELDERLY PATIENTS WITH MILD DISEASE

Treatment of Neuropathic Pain

- Neuropathic pain may arise from a lesion or disease affecting the somatosensory system
- Examples of neuropathic pain include
  - Diabetic polyneuropathies
  - Postherpetic neuralgia
  - Trigeminal neuralgia
  - Central poststroke
  - Spinal cord injury
Treatment of Neuropathic Pain

- Patients with neuropathic pain generally exhibit
  - Spontaneous (stimulus-independent)
    - Continuous (foot pain in diabetic neuropathy)
    - Intermittent (pain paroxysms in trigeminal neuralgia)
  - Pain described as
    - Cold
    - Burning
    - Sharp
    - Squeezing
    - Shooting
    - Stabbing
    - Electric "shock-like"
  - Evoked (stimulus dependent)
    - Hyperalgesia or allodynia
    - Defined with reference to the evoking stimulus
    - May be provoked by
      - Brush
      - Pressure
      - Cold
      - Heat

Mechanisms of Neuropathic Pain

- Peripheral mechanisms
  - In animal models, abnormal neuronal activity has been noted in primary afferents and in the dorsal root ganglion
    - Mainly related to dysregulation of the synthesis or functioning of sodium channels
    - Potassium channels may be involved
  - Nerve injury induces up regulation of several receptor proteins including Transient Receptor Potential Vanilloid 1 (TRPV1)
    - TRPV1 is located on subtypes or peripheral nociceptive endings and is physiologically activated by noxious heat among other stimuli
    - After a nerve lesion TRPV1 is up regulated in uninjured nerve fibers which may induce heat hyperalgesia
Mechanisms of Neuropathic Pain

- Central mechanisms
  - Peripheral nerve lesions can induce central changes
  - Investigated in animals at the spinal cord and supraspinal levels
  - Modifications that can activate central noiceptive neurons
    - Modification of the modulatory controls of the transmission of noiceptive neurons
    - Anatomic reorganization (neuroplasticity) of the central noiceptive neurons
    - Microglial activation
    - Central sensitization (hyperexcitibility) of noiceptive neurons
      - Central sensitization probably depends on intracellular changes induced by the activation of NMDA receptors or other receptors by excitatory amino acids released by primary afferents.
      - It is unlikely that neuropathic pain is related to only one mechanism.
      - Each of the painful symptoms may correspond to distinct mechanisms and therefore respond to different treatments

Neuropathic Pain Treatments

![Image of Neuropathic Pain Treatments table]

TABLE 8-1 Summary of Evidence-Based Recommendations For Treatment of Peripheral Neuropathic Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main Mechanism of Action</th>
<th>Common Major Side Effects</th>
<th>Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranquilizers</td>
<td>Modulation of peripheral noiceptive transmission</td>
<td>Sedation, dizziness, somnolence</td>
<td>Benzodiazepines (e.g., clonazepam)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Modulation of central noiceptive transmission</td>
<td>Sedation, nausea, constipation</td>
<td>Tricyclic antidepressants (e.g., amitriptyline)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Modulation of central noiceptive transmission</td>
<td>Sedation, dizziness, ataxia</td>
<td>Carbamazepine, gabapentin</td>
</tr>
<tr>
<td>NMDA receptor antagonists</td>
<td>Modulation of central noiceptive transmission</td>
<td>Sedation, dizziness, ataxia</td>
<td>Ketamine, memantine</td>
</tr>
</tbody>
</table>

- Recommendations grading: A = good scientific evidence from placebo-controlled trials, B = some scientific evidence from Case-Control studies
- Table modified from Attal, N. et al.: Neuropathic Pain: Mechanisms, Therapeutic Approach and Interpretation of Clinical Trials. CONTINUUM: Lifelong Learning in Neurology. 18(1, Peripheral Neuropathy): 161-175, February 2012.
Neuropathic Pain Treatments

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Other Benefits</th>
<th>Efficiency</th>
<th>Level of Evidence</th>
<th>Starting Dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>Nortriptyline, Desipramine, Amitriptyline</td>
<td>Decrease depression</td>
<td>3-4</td>
<td>2</td>
<td>10 mg at bedtime; titrate up by 10 mg for 1-7 days.</td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>Duloxetine, Venlafaxine</td>
<td>Decrease depression</td>
<td>3-4</td>
<td>2</td>
<td>Start at 50 mg daily, titrate up by 50 mg/day until efficacy, not to exceed 300 mg daily.</td>
<td></td>
</tr>
<tr>
<td>Calcium channel alpha 2 delta ligands</td>
<td>Gabapentin, Pregabalin</td>
<td>Decrease pain and improve sleep</td>
<td>3-4</td>
<td>2</td>
<td>300 mg twice daily, can be titrated up to 3,600 mg/day.</td>
<td></td>
</tr>
<tr>
<td>Topical lidocaine, 5% lidocaine patches</td>
<td>Capsaicin patches</td>
<td>Analgesic effect</td>
<td>3-4</td>
<td>2</td>
<td>1-2 patches applied every 12 hours.</td>
<td></td>
</tr>
<tr>
<td>Opioid agonist</td>
<td>Tramadol, Methadone, Levorphanol</td>
<td>Analgesic effect</td>
<td>3-4</td>
<td>2</td>
<td>50 mg orally or rectally every 6 hours.</td>
<td></td>
</tr>
</tbody>
</table>

Case Study

- 60-year-old man with a history of type 2 diabetes mellitus referred to the neurology clinic for pain in his feet.
  - The patient was diagnosed with type 2 diabetes mellitus approximately 12 years ago.
  - Since that time he had adhered to his prescribed medication regimens but not to his diabetic diet.
  - Hemoglobin A1c level between 8% and 9%.
- About 5 years ago he started noticing
  - Pains in all of his toes
  - Numbness in his feet with some gait imbalance when walking on uneven surfaces
  - Since that time, the numbness had slowly migrated up to the middle of his shins
  - Pain has progressed and become quite bothersome
  - He reports it feels like walking on broken glass
  - He describes burning in his feet when lying down at night
  - The stabbing pains continued in his toes and has occurred in his shins
- Pain is considered to be 8 out of 10
- Past Medical History significant for hypertension, type 2 diabetes mellitus, and hypercholesterolemia
- Medications included lisinopril, metformin, and long-acting insulin
- He has No Known Drug Allergies
- He does not smoke, drink alcohol, or use illicit substances
- He worked as a computer programmer
- Strong family history of diabetes mellitus but no history of peripheral neuropathy or other neurologic diseases
- A complete 14-topic review of systems was obtained and was positive for erectile dysfunction and a 15 lb weight gain

Case Study

- **Physical Examination**
  - Well-developed and well-nourished obese man in no acute distress
  - BP 110/70 mm Hg, P 75 beats/min, and RR 12 breaths/min
  - No bruits of the neck. Heart, Chest GI normal. Dorsalis pedis pulses good.
  - AAOx 3. Cranial nerve testing was normal
  - Motor strength was 5/5 throughout with the exception of
    - 4/5 toe dorsiflexion and toe plantar flexion
    - Tone was normal in the arms and legs
    - Extensor digitorum brevis atrophy was present in the feet.
- **Sensory Testing**
  - Pinprick and temperature perception was decreased below the knees bilaterally
  - Absent vibratory perception and mildly reduced proprioception in the toes
  - Reflexes were 1/4 in the arms, 1/4 at the knees, and absent at the ankles. Plantar responses were flexor bilaterally.
  - Coordination was normal on finger-nose-finger and heel-knee-shin testing bilaterally.
  - His gait was slightly wide-based but steady. He had difficulty with tandem walking

Case Study

- What does patient likely have?
- What test would you complete?
- Would you consider medication and if so which one?
Case Study

- The neurologist discussed with the patient that he had evidence of peripheral neuropathy more specifically sensorimotor peripheral neuropathy often seen in patients with diabetes mellitus.
- Labs: vitamin B₁₂, methylmalonic acid, thyroid-stimulating hormone, and serum protein electrophoresis
- The patient was also referred for nerve conduction studies and EMG to better characterize and grade the severity of his peripheral neuropathy.
- The patient was encouraged to strive for better glycemic control to prevent further complications related to diabetes mellitus.
- The patient was instructed to start pregabalin at 50 mg 3 times a day and then titrate this upward over the course of 2 weeks to a goal dose of 100 mg 3 times a day.
- Discussed common side effects, including dizziness and somnolence
- Visit concluded with a discussion of the importance of good foot hygiene to prevent complications such as diabetic foot ulcers.

Case Study

- 3 month follow-up
  - Patient felt he was doing well
    - He had been adhering to his diabetic diet and medication regimen
    - He had started to exercise and lost 10 lbs
    - His most recent hemoglobin A₁c was 6.8%.
  - Pregabalin had reduced pain level to 2 out of 10
    - He continued with 5/10 pain at bedtime causing sleep issues
    - He was not experiencing any side effects from the pregabalin
  - NCS/EMG consistent with sensorimotor axonal polyneuropathy
  - His laboratory workup was unremarkable.
  - Discussion regarding alternative treatment to help his pain
    - The patient was advised to stop pregabalin
    - He was prescribed amitriptyline 10 mg at bedtime, to be increased to 30 mg at bedtime over the next few weeks
Case Study

- 6 month followup (3 months later from 2nd appointment)
- Patient was still adhering to his diabetic diet and medication regimen
- He was continuing to exercise with most recent hemoglobin A1c of 6.4%.
- Amitriptyline had helped his pain symptoms dramatically
  - His new level of pain was 1 out of 10
  - He was no longer having difficulty with sleep
  - He was not having any medication side effects.
- The patient was content with the current level of pain control and did not want to take any more medicine.
- The patient elected to follow up as needed and was encouraged to call with any problems.

Thank You

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Bibliography

- Information from this talk comes from the following sources
  - Peripheral Neuropathy: Victor F. Politi, MD, Medical Director, St. Anthony’s School of Allied Health Professions, Physician Assistant Program
  - http://pharmacology-notes-free.blogspot.com