



Improving the Management of Diabetes: A Focus on Diabetic Neuropathy

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*“All we can do for diabetic neuropathy (DN) is
make the diagnosis and commiserate with the
patient”*

(The Lancet editorial 1994).

Prevalence of Diabetes Mellitus (DM)

- Worldwide: 194 million people
- USA: 18,2 million (18% of people > 65)
- About 40 % of U.S. adults ages 40-74 (41 million people) have abnormal blood glucose levels without having DM.
- Many will develop type-2 DM in the next 10 years. (In the DPP, about 10 % of participants in the placebo group developed DM each year)
- Total annual cost in 2002: \$132 billion (one out of every 10 health care dollars spent)

Diabetic Neuropathy (DN)

- DN is the most common and troublesome complication of DM, leading to great morbidity and mortality, and resulting in a huge economic burden for diabetes care ¹⁻⁴
- most common form of neuropathy in the developed countries of the world
- accounts for more hospitalizations than all the other diabetic complications combined, and is responsible for 50% to 75% of non-traumatic amputations.

Diabetic Neuropathy

- occurs equally in type-1 and type-2 DM, and in various forms of acquired diabetes ⁵
- The major morbidity is foot ulceration, the precursor of gangrene and limb loss ⁶
- Neuropathy increases the risk of amputation:
 - 1.7 - fold
 - 12 - fold with deformity (also a consequence of neuropathy)
 - 36 - fold with history of previous ulceration.
- 85,000 amputations in the US each year, 1 every 2 minutes, and neuropathy is considered to be the major contributor in 87% of cases.

Diabetic Neuropathy

- 5-year mortality rate after lower extremity amputation: 39 to 68 %
- After an amputation, the chance of another amputation of the same extremity or of the opposite extremity within 5 years is as high as 50 %

Pathogenesis of DPN

Heterogenous with causative factors:

- Microvascular insufficiency
- oxidative stress
- nitrosative stress
- defective neurotrophism
- autoimmune-mediated nerve destruction

Diabetic Neuropathy: Pathophysiology

- not a single disorder but a heterogeneous group of conditions that involves different parts of the somatic and autonomic nervous systems.
- Neuropathies may be *focal* or *diffuse*, *proximal* or *distal*, *small -fiber*, *large-fiber*, *autonomic*.
- The focal neuropathies include entrapment syndromes that occur in 30% of patients with DM.
- The focal mononeuritides are vascular assaults and heal spontaneously and need supportive therapy.
- The proximal neuropathies: chronic, inflammatory demyelinating conditions that occur 11 times more frequently in the diabetic population and respond well to intravenous immunoglobulin IgG or immunosuppressive treatments.
- Diabetes Control and Complications Trial (DCCT) - only 1/3 as many with tight control compared to regular control got neuropathy

Neuropathic pain - Discussion

- Noxious stimuli and pain impulses are transmitted from the injury site to the cortex, via *rapid* A- δ or A- β fibers and *slow* C-fibers
- A- δ fibers are larger, myelinated, fast (6-30m/s) conducting fibers that allow for precise localization of the pain and carry touch, vibration and proprioception. These produce the sensation of sharp pricking pain, known as 'first' or 'protopathic' pain

Neuropathic pain - Discussion

- C-fibers are *small*, unmyelinated, slow (0.5 – 2 m/s) conducting fibers carrying pain and temperature. Pain is poorly localized, and described as a dull ache or throbbing
- It is know as epicritic or 'second' pain

Symptoms of Neuropathy:

eg. Distal Symmetric (sensorimotor)

Polyneuropathy

- Early on most distal neuropathy patients are *asymptomatic*
- **Sensory**- '*stocking glove*': numbness, tingling
 - C-fiber pain: burning, dysesthesia, allodynia
 - Large-fiber: gnawing or aching +/- ulcers
 - Severe, spontaneous, lancinating
 - Later: intensity gain, worse at night +/- ulcers
 - progressive sensorimotor loss
 - Lastly: severe sensory loss, sensory ataxia, muscle atrophy of hands, +/- ulcers
 - feet, neuropathic arthropathy (Charcot joint)
- recent evidence based on intraepidermal nerve-fiber changes has identified a subset of painful neuropathies that are associated with impaired glucose tolerance and dysmetabolic syndrome, and precede the onset of diabetes.

Signs of Neuropathy

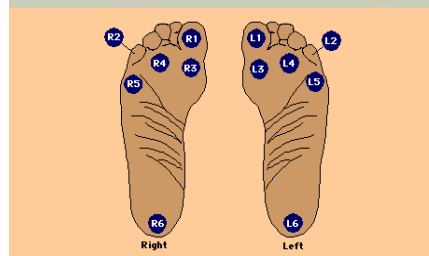
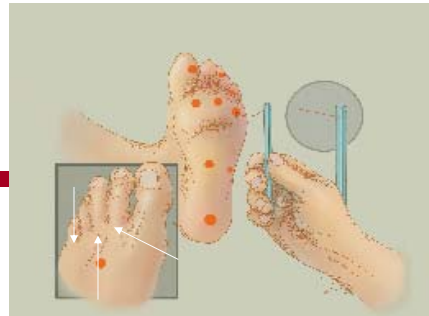
- Screening Guidelines: Quantitative Somatosensory Threshold Test with Semmes-Weinstein 5.07 (10g) monofilament
- Reproducible buckling stress
- Identified by manufacturer numbers: 1.65 to 6.65 (higher the stiffer)
- Three commonly used: 4.17, 5.07 and 6.10
- Forces to buckle: 1g , 10g and 75 g
- 1 gram: + neuropathy risk
- 10 gram: + ulceration risk (vibration sense predicts ulcer risk too)
- Daily patient use ↓ foot ulceration by 54 %

The Foot Exam

- **Foot exam:** Initial + Annual
- **Visual inspection** each visit
- **Podiatry referral** annually

Technique:

- Supine, quiet, closed eyes
- "Yes-No" method
- Apply \perp till buckle for 1 sec.
- 5 -10 tries
- 1st, 3rd, 5th MT heads + big toe
- Some tested all toes.
- Medial + lateral midfoot, heel
- Dorsal (see arrows)
- Insensitive if ≥ 1 failed



Testing sites for pressure sensation in evaluation of diabetic foot. The monofilament used to evaluate pressure sensation should be tested at each of the 12 sites shown, which represent the most common sites of ulcer formation. Failure to detect cutaneous pressure at any site indicates that the patient is at high risk for future ulceration.

Risk Assessment Guidelines

- **Risk Category 1:** \emptyset sensory loss, \emptyset deformity, palpable pulses, \emptyset ulcer history
→ *annual foot exam*
- **Risk Category 2:** + sensory loss, \emptyset deformity, palpable pulses, \emptyset ulcer history
→ *biannual foot exam*
- **Risk Category 3:** + sensory loss, + deformity, +/- palpable pulses, \emptyset ulcer history
→ *bimonthly foot exam*
Debridement: nails, calluses, depth shoes
- **Risk Category 4:** + sensory loss, + deformity, +/- palpable pulses, + ulcer history
→ *bimonthly foot exam*
Debridement: nails, calluses, depth shoes
Custom modification to shoe inserts

Types of Diabetic Neuropathy

- Focal (Mononeuritis)
- Entrapment
- Diffuse
- Proximal
- Distal
- Small-fiber (incl. Autonomic)
- Large-fiber

Mononeuritides

- Sudden in onset, vascular in nature, resolution in weeks
- CN III, VI, VII, and peripheral nerves -- median, ulnar, peroneal, and posterior tibial -- with the medial and lateral plantar nerves
- Pain localized to the nerve distribution but may spread
- Weakness confined to the muscles supplied
- The tendency of diabetic platelets to hyperaggregate and the increased thrombogenicity (elevated fibrinogen, PAI-1) need to be targeted for prevention of these occurrences

Mononeuritides

- **BEWARE:** These same nerves tend to be caught up in an entrapment process

– Key differences in the clinical presentation:

Entrapment - is a chronic insidious process

Mononeuritides – acute like many other vascular insults

Mononeuritis

Entrapment

Onset Sudden

Usually single nerves but may be multiple nerves

Common nerves: CN III, VI, VII, and VII
ulnar, median, and peroneal

Not progressive and resolves spontaneously

Treatment: symptomatic

Onset gradual

Single nerves exposed to trauma

Common nerves: median, ulnar, peroneal, medial, and lateral plantar

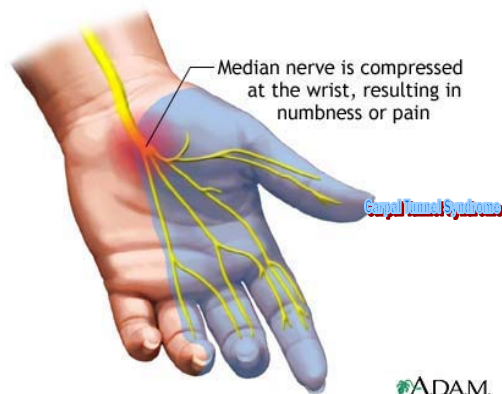
Progressive

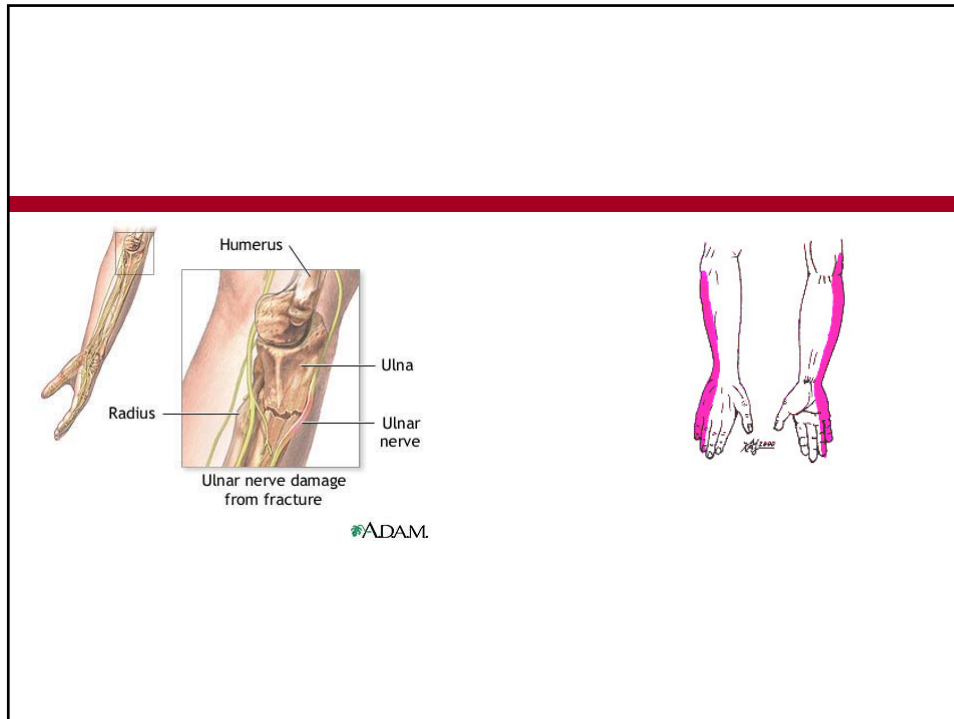
Treatment: rest, splints, diuretics, NSAID's, steroid injections, and surgery for paralysis

Compression (Entrapment) Neuropathy

- Carpal tunnel syndrome - numbness and tingling in thumb, index, middle fingers
- Ulnar neuropathy at the elbow - numbness and tingling in little, ring fingers
- Peroneal neuropathy at the knee - numbness on top of foot and foot drop

Carpal Tunnel Syndrome





Distal Symmetric Polyneuropathies

- Most common of the neuropathic syndromes in diabetes
- Pathogenesis: metabolic events, microvascular insufficiency, oxidative stress, loss of neurotrophism, and autoimmune-mediated nerve destruction.
- Metabolic events that contribute include hyperglycemia, polyol accumulation, accumulation of advanced glycation end products, deficiencies of antioxidants, and certain fatty acids.
- Sensory abnormalities in feet and legs (numbness, tingling, pain)
- Weakness in feet and distal legs (difficulty lifting feet)
- Sores on feet
- If severe, similar symptoms may occur in hands
- Treatment of hyperglycemia slows progression
- Promising results have been obtained with aldose reductase inhibitors, the antioxidant alpha-lipoic acid, and dihomo gamma-linolenic acid.

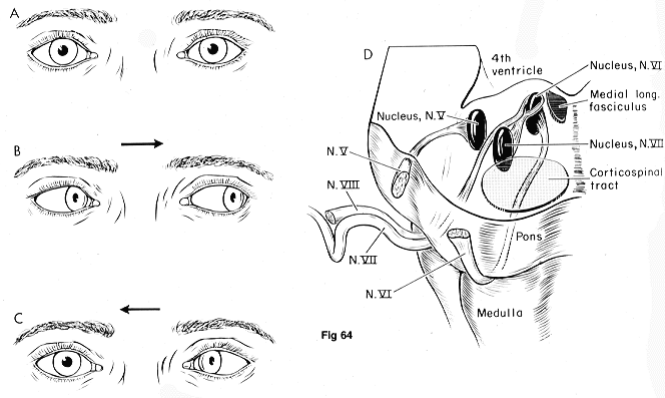
Diffuse Proximal Neuropathies (Diabetic Amyotrophy)

- M>F, middle-age to elderly, usually unilateral, with recent weight loss
- Syn. Diabetic Femoral Neuropathy
- Starts with severe, persistent, deep pain in thigh, hips and buttocks, followed by weakness and finally atrophy of proximal pelvis muscle groups (Gower's maneuver)
- Knee Jerk is lost: sensation is normal
- Misdiagnosed as '*L4 lesion*' (BUT iliopsoas and quadriceps weakness, and no loss of medial thigh sensation)
- Exclude chronic inflammatory disorders: demyelinating polyneuropathies, vasculitides, monoclonal gammopathies, and immune-mediated demyelination with apoptosis of neurons (all of which are more common in diabetics), however,
- these conditions (90%) should be excluded before Dx of 'Diabetic' Amyotrophy' (10%) is made. Amyotrophy-poor prognosis.
- treatment is supportive
- process resolves spontaneously over 12 -24 months

Cranial Neuropathy

- Cranial Nerves I - XII
- Diabetes most commonly affects the nerves that control eye movement
- $\text{Li}_3(\text{SO}_4)_6$ - especially CN III
- III- painful ophthalmoplegia with double vision and ptosis
- Usually gets better over 2 to 3 months

Cranial Neuropathy: Cranial Nerve VI palsy



Cranial Neuropathy Cranial Nerve IV

Cranial Neuropathy: Cranial Nerve III palsy

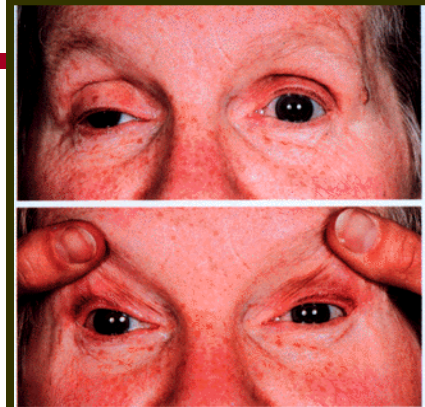


Fig. 12.19 Third nerve palsy in diabetes: there is a partial right ptosis with abduction and depression of the globe. The pupils were equal in size.

This 72 year old lady had a history of diabetes for 20 years. In 1973 she developed poor vision in the left eye. In 1982 she experienced pain above the right eye, followed by ptosis and diplopia. Examination showed a partial right third nerve paresis with pupil sparing. The paresis recovered.

Diabetic Autonomic Neuropathy (DAN)

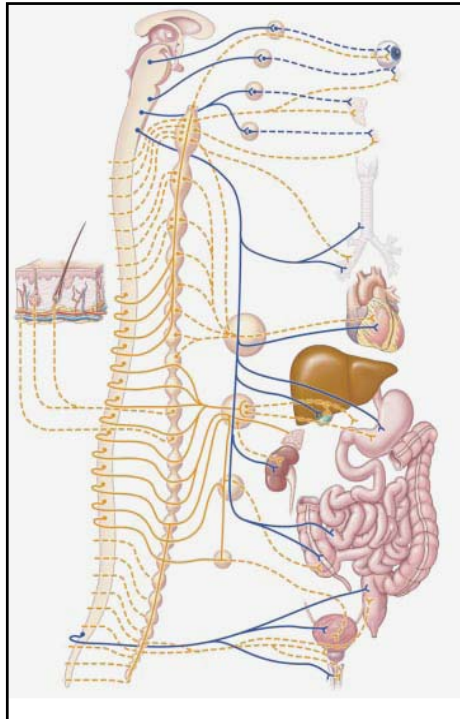
- The Ultimate 'stealth' complication
- One of the most common complications of DM
- Systems affected: CVS, GI , UG and Metabolic such as glucose counter regulation
- Once AN sets in, life can become quite dismal and the mortality rate approximates 25% to 50% within 5-10 years ^{11,12} (3× higher than patient without it)
- The 5-year mortality rate in patients with diabetic AN is three times higher than in diabetic patients without autonomic involvement ¹³

Diabetic Autonomic Neuropathy (DAN)

- Causative association: poor glycemic control, long duration of diabetes, increasing age, higher BMI
- The DCCT showed intensive control reduced prevalence of AN by 53%
- Increased urinary albumin excretion is related to AN ^{14,15}
- AN is also an independent risk factor for stroke ¹⁶
- Diagnosis of exclusion (see table)

DAN The Autonomic System

- is primarily efferent, transmitting impulses from the central nervous system to peripheral organs.
- Has an afferent component with two divisions—parasympathetic and sympathetic
 - work in balanced opposition to control the heart rate, the force of cardiac contraction, the dilatation and constriction of blood vessels, the contraction and relaxation of smooth muscle in the digestive and urogenital systems, the secretions of glands, and pupillary size.



- Pupillary**
 - Decreased diameter of dark-adapted pupil
 - Argyll-Robertson type pupil
- Metabolic**
 - Hypoglycemia unawareness
 - Hypoglycemia unresponsiveness
- Cardiovascular**
 - Tachycardia, exercise intolerance
 - Cardiac denervation
 - Orthostatic hypotension
 - Heat intolerance
- Neurovascular**
 - Areas of symmetrical anhidrosis
 - Gustatory sweating
 - Hyperhidrosis
 - Alterations in skin blood flow
- Gastrointestinal**
 - Constipation
 - Gastroparesis diabeticorum
 - Diarrhea and fecal incontinence
 - Esophageal dysfunction
- Genitourinary**
 - Erectile dysfunction
 - Retrograde ejaculation
 - Cystopathy
 - Neurogenic bladder
 - Defective vaginal lubrication

Differential diagnosis of DAN

- Idiopathic orthostatic hypotension
- Shy-Drager syndrome
- Panhypopituitarism
- Pheochromocytoma
- Chagas disease
- Amyloidosis
- Hypovolemia caused by poor glycemic control or diuretics
- Effects of insulin
- Complications from vasodilators (nitrates, calcium channel blockers, hydralazine)

Differential Diagnosis of DAN

- Complications from sympathetic blockers (methyldopa, clonidine, prazosin, guanethidine, phenothiazine, tricyclic antidepressants)
- Orthostatic hypotension caused by alcoholic neuropathy
- Congestive heart failure
- Other causes of diarrhea, constipation, and gastrointestinal dysfunction
- Other causes of genitourinary and erectile dysfunction
- Other causes of pedal edema
- Hypoglycemia unresponsiveness and unawareness occurring with intensive glycemic control
- The Argyll-Robertson pupil of syphilis

Cardiac DAN

- AN associated with high risk of CAD in patients with or without DM ¹⁷
 - The incidence of cardiac autonomic neuropathy rises parallel with the known duration of diabetes
 - Signs: Lack of HR variability during deep breathing (early sign)
Resting Tachycardia (early sign)
Limited Exercise tolerance
Prolonged QTc
Abnormal circadian BP rhythm
Blunted CAD symptoms
- 1. Lack of HR variability during deep breathing:**
- 1.6% < 5 years of DM had this sign
 - 6.2% 5-9 years of DM
 - 12% > 9 years of DM
- DCCT Trial

Cardiac DAN

2. Resting tachycardia:

- > 100 beats/ minute is abnormal
- a heart rate that does not respond to mild exercise indicates nearly complete cardiac denervation ¹⁸

3. Limited exercise tolerance:

- impaired sympathetic and parasympathetic responses that normally augment cardiac output and redirect peripheral blood flow to skeletal muscles
- also reduced by a reduced ejection fraction, systolic dysfunction, and decreased diastolic filling

Cardiac DAN

4. A prolonged corrected QT (QTc) interval:

- sensitive, non-invasive, and simple predictor of cardiac dysautonomia
- indicates an imbalance between right and left sympathetic innervation ¹⁹
- may be at greater risk for arrhythmias.

5. Abnormal circadian pattern of blood pressure:

- BP rises at night, falls in early morning. Correlates with postural hypotension due to cardiovascular autonomic neuropathy ²⁰

Cardiac DAN

6. Blunted symptoms of CAD:

- asymptomatic owing to 'subclinical' neuropathy^{21,22}
- Painless ischemia significantly more frequent in patients with AN than in those without it (38% vs 5%).
- Result of damaged afferent nerves.
- Framingham study: 39% had asymptomatic MI by electrocardiography^{23, 24}
- One study²⁵: Mortality rate after *asymptomatic* MI = 47%
Mortality rate after *symptomatic* MI = 35%

Cardiac DAN

- Altered MI diurnal variation:
 - In Non-DM: risk of acute MI highest morning.
 - In DM : risk of acute MI highest in evening (and lowest in morning).
 - Morning blunting is the result of AN altered sympathovagal balance and reduced nocturnal vagal activity^{26,27}
- Conclusion: chest pain in a diabetic is considered myocardial until proven otherwise!!
- *duration* of diabetes is a stronger predictor than diabetic control in the overall prognosis of diabetes
- Some suggest HRV and Orthostatic pressure checks 5 years after diagnosis

Subclinical Neuropathy

- **Diagnosis:**
 - (1) abnormal electrodiagnostic tests with decreased nerve-conduction velocity or decreased amplitudes
 - (2) abnormal quantitative sensory tests for vibration, tactile, and thermal warming and cooling thresholds
 - (3) quantitative autonomic function tests revealing diminished HRV with deep breathing, Valsalva maneuver, and postural testing^{9,10}
 - The results of quantitative autonomic function tests also include diminished sudomotor function, increased pupillary latency, and abnormalities in gastrointestinal function as well as disturbed skin neurovascular responses

Gastrointestinal DAN

- **Constipation:** most common
- **Diarrhea:** Hypermotility (sympathetic inhibition), bacterial overgrowth, pancreatic insufficiency, bile salt irritation
 - Treatment: Imodium, Antibiotics, Pancrease, Cholestyramine
- **Gastroparesis:** bloating, early satiety, nausea, and vomiting
 - Treatment: frequent small meals, Reglan, Erythromycin

Genitourinary DAN

- **Impaired parasympathetic innervation:** bladder hypotonia, incomplete bladder emptying, dribbling, and overflow incontinence . Dx: post-void residual > 150cc. (Crede maneuver)
 - **Treatment:** Bethanechol but side effects: salivation, lacrimation, diarrhea, and bronchoconstriction. α -Blockers help by relaxing the urinary sphincter, postural hypotension (fall risk)
 - Intermittent catheterization or indwelling catheter

Genitourinary DAN

- **Erectile dysfunction (ED):** 50 M, 30% W. Onset < 10 years; initially loss of morning erections.
 - Is a marker for vascular disease and sudden death from MI!!
 - Autonomic ED accompanied virtually always by ankle jerk absence and loss of VS over large toes
 - Early Sx: \downarrow rigidity and tumescence
 - Loss of erection, retrograde ejaculation *often without* \downarrow libido, orgasmic function or potency!

Genitourinary DAN

- Determine psychogenic from organic ED

Treatment:

- Avoid alcohol, smoking, offending medications
- optimize glucose control
- Viagra (beware nitrates)
- Corpus cavernosum prostacyclin injections
- Penile implants
- Pumps

Genitourinary DAN

TABLE 5

**Drugs known to cause
erectile dysfunction that are
used by diabetic patients**

Antihypertensive agents

Beta-blockers
Thiazide diuretics
Spironolactone
Methyldopa
Reserpine

**Agents acting on the central nervous
system**

Phenothiazines
Haloperidol
Tricyclic antidepressants

Drugs acting on the endocrine system

Estrogens
Antiandrogens
Gonadotropin antagonists
Spironolactone
Cimetidine
Metoclopramide
Fibric acid derivatives
Alcohol
Marijuana

Retrograde Ejaculation

- Damage to efferent sympathetic nerves coordinating simultaneous closure of internal vesicle sphincter and relaxation of the external vesicle sphincter during ejaculation
- Absence of sperm in semen and presence of semen in urine
- Only problem if patient wanting to father children

Female Sexual Function

- Decreased arousal
 - Decreased lubrication
 - Painful intercourse
- Rx: lubricants, vaginal estrogen, ?topical sildenafil

Sudomotor Neuropathy

- Sudomotor neuropathy may cause hyperhidrosis and heat intolerance in the upper torso or anhidrosis in the lower extremities
- Temperature elevation is rare
- Extremity skin may feel pruritic and may display thinning, hair loss, dryness, flaking, cracks, increased callus formation, and nail dystrophies
- These skin changes increase the risk of ulceration.

Treatment of Diabetic Neuropathy - I

- Best Rx is prevention !!!
- Diabetics should do three things to help prevent the complications of diabetes:
 - 1) Achieve ideal body weight
 - 2) Maintain regular exercise
 - 3) Maintain good control of glucose level

Treatment of Diabetic Neuropathy - II

- Protect tissues from injury (check feet every day, good shoes, beware of excess heat or cold)
- Medications can provide symptomatic relief from pain

Treatment of Diabetic Neuropathy - III

- Medications for Neuropathic Pain:
 - Topical capsaicin
 - Antidepressants (amitriptyline, nortriptyline, imipramine)
 - Anticonvulsants (gabapentin, carbamazepine, clonazepam, phenytoin)
 - Narcotics (avoid unless nothing else works)

Topical Capsaicin

- active principle of hot chili pepper
- selectively stimulate unmyelinated C fibre afferent neurons
- release of substance P
- Prolonged application of capsaicin reversibly depletes stores of substance P
- reduces or abolishes the transmission of painful stimuli from the peripheral nerve fibres to the higher centres

Tricyclic Antidepressants TCA's

- Side Effects (cholinergic): dry mouth, sedation (fall risk), urinary retention, blurred vision (fall risk), cardiac arrhythmias incl. heart block, postural hypotension
- Dosing: *'Start low, go slow'*
- Tertiary amines (nortriptyline), less cholinergic

Cymbalta (Duloxetine)

- Only SNRI FDA approved for DPN
- Other use: Depression
- Only moderate reduction in average pain reduction
- Side Effects: nausea, dry mouth, constipation, dizziness, fatigue, somnolence and sexual dysfunction.
- Monitor LFT's
- May be preferable over TCA's in elderly and cardiac patients

Anticonvulsants

- Drug Effectiveness Review Project (DERP) final report December 2004:
 - no clear evidence of superior effectiveness of one antiepileptic drug over another
 - TCAs and anticonvulsants were generally equivalent with NNT for at least 50% pain ↓
- Traditionally Carbamazepine the drug of choice
- Side

Carbamazepine (Tegretol)

- Side Effects: ataxia, dizziness, confusion, blurred vision
 - Severe: aplastic anemia, hepatotoxicity, Stevens-Johnson, TEN, SIADH,
- Avoid rapid discontinuation

Gabapentin (Neurontin)

- In a head-to-head trial comparing gabapentin to amitriptyline, both drugs were found to be equally effective and equally tolerated in the treatment of DPN
- Due to good safety data and freedom from drug interactions, gabapentin may be preferred to TCAs in the elderly

Pregabalin (Lyrica)

- Newest anticonvulsant, pregabalin is structurally and mechanistically similar to gabapentin.
- In randomized placebo-controlled trials, pregabalin at doses of 300 and 600mg/day (divided TID) was effective for the treatment of painful diabetic neuropathy
- SIDE effects: somnolence, dizziness, and peripheral edema.
- Until head-to-head comparisons have been made, there appear to be no advantages to using pregabalin over gabapentin.

Lamotrigine (Lamictal)

- Mechanism: Blocks sodium channels and inhibits release of glutamate
- One double-blind, placebo-controlled, randomized trial (n=59) demonstrated a modest, but significant, reduction in pain intensity scores compared to placebo at doses ranging from 200 to 400mg/day
- Lamotrigine failed to demonstrate superiority over placebo on two secondary outcome pain scales
- Side Effects: Stevens-Johnson, TEN
- Not recommended first-line for the treatment of neuropathic pain

Efficacy of Drug Treatments for Diabetic Neuropathy

Drug	Controlled trials	NNT	NNH
Antidepressants	16	3.4	2.7 (2.1-3.9)
TCA	8	3.5	3.2 (2.3-5.2)
SSRI	3	Not efficacious	
Anticonvulsants	3	2.7	2.7 (2.2-3.4)
Phenytoin	1	NA	3.2 (2.1-6.3)
Carbamazepine	1	NA	NA
Gabapentin	2	NA	2.6 (2.1-3.3)
Valproate	1	NA	Rare
Top Capsaicin	4	4 (2.9-6.7)	NA
Lidocaine patch	0	NA	NA

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