

What's New in Diabetic Neuropathy?

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WWW.IHS.GOV

- MEDICAL PROGRAMS
 - DIVISION OF DIABETES AND PREVENTION
 - DM₂ DIABETES AND NEUROPATHY
 - Quick Guide Cards
 - DM Treatment Algorithms
- DIABETES CARE 2011; 34 (supplement 1)
- NEUROLOGY prepublished online April 11, 2011
- JAMA 2009; 302(13): 1451-1458.

Type 2 Diabetes - Neuropathy

Usual Presentation: Begins in feet, progresses proximally; is often symmetrical but may present atypically
Symptoms: chronic or undulating pain, numbness, tingling, burning or occasionally shooting or stabbing pain

Prevention and Treatment of Neuropathic Pain Syndrome

- Maintain glycemic control
- Smoking cessation and/or alcohol cessation/reduction
- Consider alpha lipoic acid 600mg daily (OTC supplement)

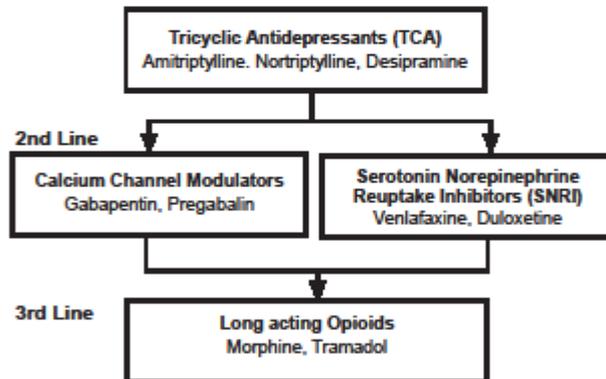
Goal of therapy: Reduce symptoms by ~50%

Non-Prescription therapy

Consider alpha lipoic acid 600mg daily (more effective than vitamin B)

Prescription therapy

1st Line - TCAs are efficacious and low cost; consider contraindications



Common reasons for treatment failure:

- Dosing too low
- Inadequate trial; requires 2-8 weeks of tx to observe symptom reduction
- Expecting elimination of symptoms; treatment reduces symptoms by ~50%
- Incorrect diagnosis; If doubt, refer to pain specialist or neurologist
- If patient does not respond or has adverse effects, change medication class
- If patient has some but inadequate relief, ↑ dose then consider adding or changing medications

Type 2 Diabetes - Neuropathy

1st Line Tricyclic Antidepressant (TCA)
Amitriptyline 25-150mg daily may help with sleep disorders
Nortriptyline 25-150mg daily less sedating, less anticholinergic
Desipramine 25-150mg daily less sedating, less anticholinergic
Side effects: sedation, dry mouth, blurred vision, weight gain, urinary retention
Other benefits: improvement of depression and insomnia
Caution: personal/family history of dysrhythmia or sudden cardiac death, glaucoma, suicide risk, seizure disorder; caution autonomic neuropathy (may cause orthostatic sx) - get standing BPs

2nd Line Calcium Channel Modulators
Gabapentin (Neurontin®) 100-1,200mg TID
Pregabalin (Lyrica®) 50-200mg TID
Side effects: sedation, dizziness, peripheral edema
Other benefits: improvement of insomnia, fewer drug interactions
Caution: cardiac disease, glaucoma, suicide risk, seizure disorder

Serotonin Norepinephrine Reuptake Inhibitors (SNRI)
Venlafaxine (Effexor®) 75-225 mg daily starting dose: 37.5mg
Duloxetine (Cymbalta®) 60 mg daily starting dose: 30mg

Side effects: sedation, dry mouth, blurred vision, weight gain, urinary retention
Other benefits: improvement of depression and insomnia
Caution: renal insufficiency; do not stop abruptly - taper dose

3rd Line Long Acting Opioids
Morphine (MS Contin®) start at low dose and titrate gradually
 Or other long-acting opioid
Tramadol (Ultram®)
Side effects: sedation, nausea, constipation (always prescribe stool softener);
Caution: abuse, suicide risk; short-acting opioids not recommended for long term

Combination therapy not well studied; Some evidence for the combination of gabapentin and nortriptyline. Caution with drug interactions (e.g. serotonin syndrome risk w/ tramadol and many antidepressant meds)

If above medications are not efficacious, contraindicated, or if intolerable adverse events occur, may consider:

- *Bupropion (Wellbutrin®)*
- *Topiramate (Topamax®)*
- *Citalopram (Celexa®)*
- *Paroxetine (Paxil®)*
- *Topical capsaicin (for localized pain)*
- *Topical lidocaine (for localized pain)*

Drug names in *italics* are not included in the IHS National Core Formulary
 References: AmJMed 2009;122:S22-S32, Diabetes Care 2009;32:S414-419, JAMA 2009;302:1451-1458, BMJ 2009;339:b3002

Case Presentation

- 60 year old R handed NA man with a ten year history of DM II. His A1c falls between 9 and 10. He adheres to medication regimes but has trouble sticking to diet and exercise recommendations. He has never mentioned nerve pain or numbness until you ask him at his annual visit.
- About 5 years ago he began to note stabbing pains in all toes. He noted some woody numbness of both feet and imbalance on uneven surfaces. Numbness has migrated to mid-shins. The pain has progressed and become bothersome. He feels like he is walking on broken glass. His feet burn at night, and the touch of the sheets feels painful. He thinks he has bad circulation.

Case Presentation

- PMH: HTN, hyperlipidemia
- PSH: bunionectomy
- P+SH: no drugs, EtOH
- FMH: DM
- Meds: lisinopril, metformin, Lantus
- ROS: He admits dizziness, erectile dysfunction, constipation, nocturnal diarrhea, weight gain

Case Presentation: Exam

- BP lying 120/80 sitting 110/80 standing 80/64.
- P 100 R 12 T 98.4 W 295 lb.
- Heart, lungs, neck, normal. Extremities hairless with dry, callused skin of feet, pulses intact.
- MS – normal.
- CN II-XII - normal aside from miotic pupils.
- Motor – 4+/5 dorsiflexion of great toe .
- Sense – decreased PP and cold sensation to knees. Absent vibration perception to mid-shin.
- CBM – tandem poor, casual normal, cannot walk on heels .
- DTRs – BRJ 1/1 BJ 1/1 TJ 1/1 KJ tr/tr AJ o/o.

Thinking

- Classic presentation for chronic, long standing diabetic neuropathy with sensorimotor involvement, one of the microvascular complications.
- People associate numbness, but not pain, with neuropathy, think “bad circulation.” This is chronic already.
- He likely has autonomic neuropathy.

ADA Definition, Recommendations

- Symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates.
- *Diabetes Care* 33: 2285-2293, 2010
- Screen at diagnosis and yearly for DPN using simple tests. EP studies are rarely necessary.
- Screen for autonomic neuropathy.
- Medications improve quality of life.
- *Diabetes Care* 34 (supplement 1): S8, 2011.

Diabetic Neuropathies

Focal/Multifocal

- Mononeuropathy
 - Median
 - Ulnar >>> Radial
- Multiple lesions “mononeuritis multiplex” RARE
- Amyotrophy, proximal motor neuropathy
 - Deep, burning thigh pain
 - Progressive, asymmetric proximal weakness
 - Marked quadriceps wasting & absent knee jerk(s)

Polyneuropathy

- Diabetic peripheral neuropathy, polyneuropathy, sensorimotor neuropathy
- Acute sensory neuropathy
 - Very poor control or DKA, rapid glycemic control, or weight loss
 - Small fiber, normal exam
 - Resolves in a year
- Autonomic neuropathy
 - Orthostatic hypotension
 - Gastroparesis, constipation, nocturnal diarrhea
 - Bladder hypomotility
 - Sexual dysfunction
 - Sudomotor and pupil abnormalities

Diabetic Neuropathy

- Most common (90%) is DSMPN, DPN
- Symmetric, length-dependent injury to peripheral nerves
- Axonal
- 16% -60% of diabetics; half have pain
- Frequently untreated (40%)
- A microvascular complication, like kidney and retina
- Pivotal component of foot disease and morbidity

Classic Symptoms

- Pain worsens at night and improves with walking
- Aching, lancination, burning
- Location 96% feet, 69% balls of feet, 67% toes, 54% dorsal feet, 37% plantar feet, 39% hands, 37% calves, 32% heels
- Allodynia
- Hyperalgesia, hyperpathia
- Numbness
- Paresthesia, dysesthesia



Red Flags – Wrong Diagnosis

- Pronounced asymmetry
- Predominant motor deficits, one nerve or one root, cranial neuropathy
- Pain with walking relieved by rest
- Rapid progression despite ideal control
- Symptoms and deficits in arms only
- Family history non-diabetic neuropathy
- Cannot confirm diagnosis by exam (good reflexes and vibration perception, *e.g.*)
- Labs: TSH, B₁₂, SPIEP, RPR

Patient Education

- A condition that can develop in diabetics.
- High blood sugar can cause nerve damage in feet and legs. The damage slows down nerve signals to the muscles and skin. It can cause the nerves to send wrong signals at wrong times, which can cause pain. Sometimes the nerves can stop communicating completely, and that can lead to numbness and weakness.
- People with neuropathy have many symptoms. Some people already have nerve symptoms when DM is diagnosed. Symptoms tend to develop slowly over years.
- The nerves and organs that control automatic body processes may be hurt by diabetes. Some people develop dizziness on standing. Sweating may increase or decrease. Upset stomach, constipation, and nighttime diarrhea may occur. Bladder control and sexual function may be bothered. This is called autonomic neuropathy.

Diabetic Neuropathy Symptom Score

- *Are you experiencing unsteadiness in walking?*
- *Do you have burning or aching of feet or legs?*
- *Do you have prickling sensations of feet or legs?*
- *Do you have numbness of feet or legs?*

SCORE

0=No DPN 1-4=PN

Reliability 0.64; Sensitivity 79%; Specificity 78%

Michigan Neuropathy Screening Instrument – A. History

1. Are your legs and/or feet (LAOF) numb?
2. Do you ever have any burning pain in LAOF?
3. Are your feet too sensitive to touch?
4. Do you get muscle cramps in LAOF?
5. Do you ever have any prickling feelings in your LAOF?
6. Does it hurt when the bed covers touch your skin?
7. When you get into tub or shower, are you able to tell hot water from cold water?
8. Have you ever had open sore on foot?
9. Has your doctor ever told you that you have diabetic neuropathy?
10. Do you feel weak all over most of the time?
11. Are your symptoms worse at night?
12. Do your legs hurt when you walk?
13. Are you able to sense your feet when you walk?
14. Is the skin on your feet so dry that it cracks open?
15. Have you ever had an amputation?

MNSI - History

- For printable forms:
<http://www.med.umich.edu/mdrtc/profs/survey.html#mnsi>
- Self administered by patient
- Score “Yes” to 1-3, 5-6, 8-9, 11-12, 14-15 one point each
- Score “No” for 7 and 13 as 1 point each
- #4 is a measure of impaired circulation and #10 general asthenia, no points
- Max history score = 13

MNSI - Physical

TEN POINTS MAX	0 POINT FOR EACH SIDE	0.5 POINT FOR EACH SIDE	1 POINT FOR EACH SIDE
APPEARANCE	NORMAL		ABNORMAL
ULCERATION	ABSENT		PRESENT
ANKLE JERKS	PRESENT	PRESENT/ REINFORCE- MENT	ABSENT
VIBRATION PERCEPTION	PRESENT	DECREASED	ABSENT
MONOFILA- MENT	NORMAL	REDUCED	ABSENT

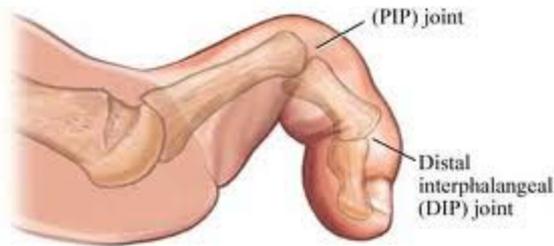
MNSI - Appearance

- Inspect for excessively dry skin, callus, fissures, ulceration, or deformities
- Deformities include flat feet, hammer toes, overlapping toes, claw toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot), and amputation.

Charcot



Joint Abnormalities



Skin Abnormalities



MNSI - Vibration

- Test bilaterally using 128 hz tuning fork over dorsum great toe bony prominence of DIP
- Examiner can feel for 5 sec longer than normal subject on great toe. Most can feel for 12 sec.
- Own finger < 10 sec, present
- Reduced if own finger > 10 sec
- Absent if no vibration perception



Tuning Fork for Your Entire Sensory Exam



MNSI - Ankle Reflexes

- Sitting position, foot dependent, pt relaxed
 - Foot relaxed and slightly dorsiflexed
 - Achilles percussed directly
- Reflex present
- Reflex present with Jendrassic maneuver
- Reflex absent with Jendrassic reinforcement

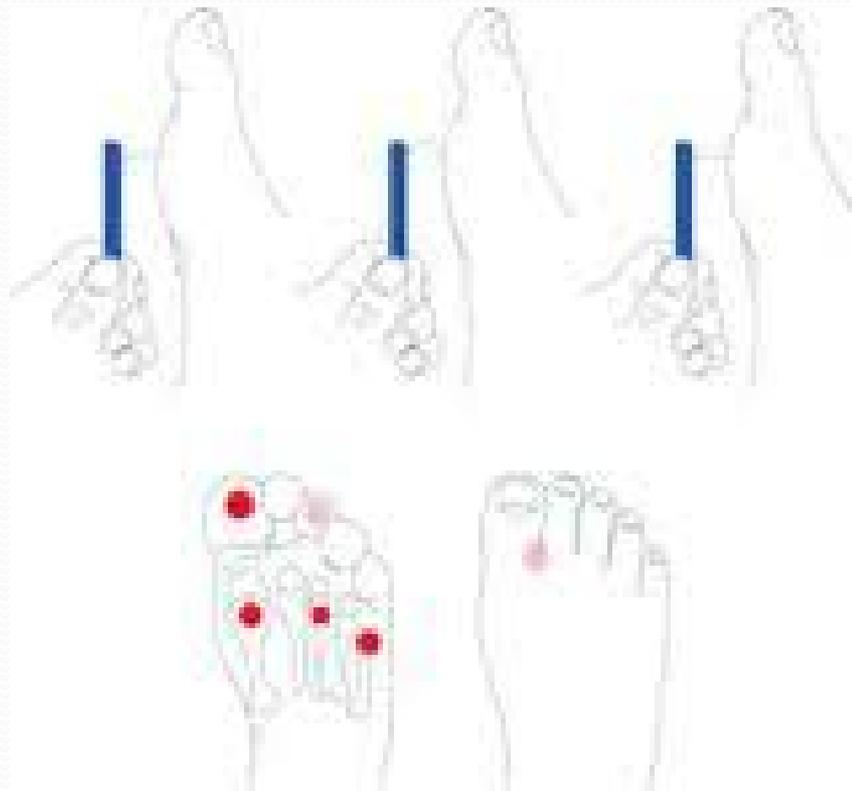


MNSI - Monofilament

- Foot supported; eyes closed
- Pre-stress 10 gm monofilament with 4-6 perpendicular applications to dorsum of finger
- Apply perpendicular to point of bending for 1 sec, release
- Apply to dorsum of great toe between nail fold and DIP for 1 sec, even pressure, 10 times: 8/10 normal; 1-7 reduced; 0 absent
- IHS/ADA: Apply to plantar great toe and 1,3,5 metatarsal heads
- Even one site insensate is high risk foot
- 2011 ADA recommends testing vibration, pinprick, or ankle jerks

- (Diabetes Care 2011: 34 (supplement 1): S37.)

IHS - Monofilament



Treatment

- Glycemic control and correction of metabolic derangements should be first.
- Pain is difficult to treat and treatment is frustrating. Help establish realistic goals.
- Negative sensory symptoms are not symptomatically treatable. Weakness is not treatable.

Education

- Look at your feet daily and check for cuts, blisters, redness, nail problems.
- Wash in lukewarm (not hot) water, and check temperature with your elbow first.
- Dry your feet by blotting, especially between toes.
- Moisturize daily with Vaseline[®] or Crisco[®], not between toes.
- Wear shoes that fit well, have support, and room for toes.
- Shake your shoes and look inside before wearing them.
- Keep your feet warm and dry, especially in winter.

Education 2

- Wear clean, dry, soft socks and change daily.
- Never walk barefoot, even at home.
- Cut nails carefully and straight across.
- Never trim corns or calluses.
- Smoking cigarettes will make you worse by cutting oxygen to nerves.
- Drinking alcohol is poisonous to nerves.
- Crossing legs should be avoided.
- Moderate walking in well-fitting shoes is good.

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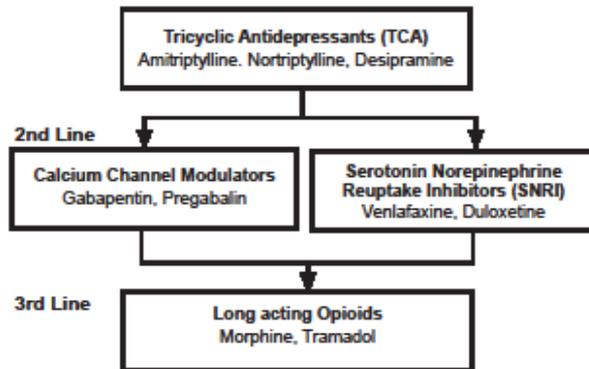
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IHS Guidelines 2010

- First Line
 - Desipramine
 - Amitriptyline
- Second Line
 - Calcium Channel Modulators
 - SNRIs
- Third Line
 - Long Acting Morphine
 - Tramadol

AAN Guidelines 2011

by Strength of Evidence

- **STRONG**
 - Pregabalin
- **MODERATE**
 - Anticonvulsants – gabapentin, valproate
 - Amitriptyline, venlafaxine, duloxetine
 - Capsaicin, isosorbide spray
 - Dextromethorphan, morphine, tramadol, oxycodone
- **INSUFFICIENT**
 - Desipramine, imipramine, fluoxetine
 - Nortriptyline and fluphenazine
 - Topiramate

AAN Recommendations

Recommended, in mg/day

- Pregabalin, 300-600 (\$150 300 bid)
- Gabapentin, 900-3600 (\$100)
- Sodium valproate, 500-1200
- Venlafaxine, 75-225 (\$115)
- Duloxetine, 60-120 (\$265)
- Amitriptyline, 25-100 (\$4)
- Dextromethorphan, 400 (!!)
- Morphine, 10-120
- Tramadol, 100-400 (\$100)
- Oxycodone, 10-120 (\$220)
- Capsaicin 0.075% QID (\$20)
- Isosorbide dinitrate spray
- Electrical stim 3-4 weeks

Not recommended

- Oxcarbazepine
- Lamotrigine
- Lacosamide
- Clonidine
- Pentoxifylline
- Mexiletine
- Magnetic field treatment
- Low-intensity laser
- Reiki therapy
- *****
- Lidoderm recommended with minimal evidence (\$775)

Beware

New FDA-approved-for-DPN medications “are likely to be no better and are considerably more expensive than older ones.”

- JAMA 2009; 302 (13): 1451-1458

Stepwise Management (IHS, JAMA)

- Assess pain quantitatively
- Identify relevant co-morbidities
- Explain diagnosis and treatment plan and establish realistic expectations (50% improvement)
- *Treat the diabetes*
- Titrate first line to tolerance, effect
- No relief, stop first line, start second line
- Partial relief, add second to first
- Third line last resort and consider adding from other classes
- Give adequate trial at adequate dose (8 wks)
- Try bupropion, topiramate, citalopram, paroxetine if all else fails

Remember

- This is chronic disease, and the *chronic effects* of drug therapies are unknown. Trials are short.
- No single medication has a robust effect on pain
 - Placebo up to 50% effective
 - Effectiveness poor in pain (11%) & QOL
 - Side effects high
 - Cost is high
- Pharmacologic treatment targets pain, not numbness
- Estimated numbers needed to treat (NNT) but not numbers needed to harm (NNH) available

Effect on Co-morbidities

	DULOX-ETINE	PREGABALIN	TRICYCLICS	OPIOIDS
DEPRESSION	GOOD	NEUTRAL	GOOD	NEUTRAL
OBESITY	NEUTRAL	BAD	NEUTRAL	NEUTRAL
ANXIETY	GOOD	GOOD	NA	NA
INSOMNIA	GOOD	GOOD	GOOD	NA
CAD	NEUTRAL	NEUTRAL	BAD	NEUTRAL
AUTONOMIC	NA	NA	BAD	BAD
FASTING GLUC	BAD SLIGHT	NEUTRAL	BAD SLIGHT	NA
LIVER FAILURE	BAD	NEUTRAL	VARIABLE	VARIABLE
RENAL FAILURE	BAD	ADAPTABLE	VARIABLE	VARIABLE
DRUG-DRUG	BAD	NEUTRAL	BAD	NEUTRAL

IHS Flowchart

- TCA if no contraindications
Consider capsaicin*
- Pregabalin or gabapentin
Venlafaxine or duloxetine
- Opioids

Amitriptyline

- Check standing BP before you start. Screen for autonomic neuropathy. EKG before start.
- NNT 2.1
- Contraindications: CAD, MAOI
- Start at 10-12.5 mg q hs and increase gently to 150 mg q hs over 6-8 weeks
- SE: orthostatic hypotension, constip, urinary retention, arrhythmia, wt gain, OD potential
- Sudden cardiac death
- Weight gain

Pregabalin (Lyrica©)

- Cost is same no matter size in mg. Capsule. NNT 4.2
- Consider titrating by adding doses instead of increasing mg per dose.
- Effective dose 100 – 200 mg TID. Start 100 mg qhs and add morning dose second week, midday dose third week. (or 25 –
- 50 tid start, 100 tid second, 150 tid third, 200 tid)
- Serious AE: rhabdomyolysis, ARF, glaucoma

Pregabalin (Lyrica©)

- Relative Contraindications: Renal insufficiency
CHF, HTN, Thiazolidinedione
- Adverse events: Edema, dizziness, somnolence, ataxia, tremor, blurred vision, weight gain
- Serious AE: rhabdomyolysis, ARF, glaucoma, increase PR, thrombocytopenia (all rare), seizure on sudden withdrawal
- Clinically significant weight gain (RR 6.2 to placebo) which increases with duration of use

Gabapentin

- In head to head trial with amitriptyline, it lost
- Effective at 900-3600 mg NNT 3.9
- Start 100-300 mg q hs for a week, then bid, then tid, then 600 tid, then 900 tid.
- Contraindications: severe kidney disease
- Few d-d interactions and no hepatic metabolism
- Side effects somnolence, dizziness, ataxia, nausea, dry mouth, constipation, leukopenia, weight gain

Topiramate (Topamax®)

- AAN: insufficient evidence to support
- Topiramate may cause marked weight loss. One study shows additive effectiveness with opiates.
- If you use opiates, consider addition.
- Start at 25 mg hs and titrate to 100 mg over 3 week.
- SE: paresthesias (banana), cognitive dysfunction, rare kidney stone, heat exhaustion so push fluids

Sodium Valproate (Depakote®)

- Although sodium valproate may be effective in treating PDN, it is potentially teratogenic and should be avoided in diabetic women of childbearing age. Due to potential adverse effects such as weight gain and potential worsening of glycemic control, this drug is unlikely to be the first treatment choice for PDN.
- **You will probably regret using valproate in diabetics. If you do, add folate 1 mg q day and check CBC, AST**

Venlafaxine (Effexor ©)

- 75-225 mg daily (tid or XR daily) NNT 5.5
- Week 1: 37.5, increase over 4 weeks
- Contraindications: 14 days of MAO, tramadol, CAD
- SE: HA, nausea, sedation, constipation, diarrhea, HTN, seizures. Rare: SIADH
- Monitor BP, cholesterol, HR
- Add gabapentin, taper slowly once established

Duloxetine (Cymbalta®)

- 60 -120 mg daily, start at 30-60; NNT 4
- Contraindications: any liver dysfunction, EtOH, CrCl<30, MAOI, uncontrolled glaucoma, delayed gastric emptying, tramadol
- SE: nausea, somnolence, dizziness, dry mouth, constipation, sweating, weakness, HA, diarrhea
- Monitor: BP, liver enzymes

Opioids

- Dextromethorphan 400 mg dose and 58% dropped out. Robitussin caps 15 mg qid reasonable. Do not combine w SSRI or opiates.
- Tramadol
- Morphine
- Oxycodone
- Consider combining with gabapentin

Opioids

- The use of opioids for chronic nonmalignant pain has gained credence over the last decade due to the studies reviewed in this article.
- Both tramadol and dextromethorphan were associated with substantial adverse events (e.g., sedation in 18% on tramadol and 58% on dextromethorphan, nausea in 23% on tramadol, and constipation in 21% on tramadol).
- The use of opioids can be associated with the development of novel pain syndromes such as rebound headache and hyperpathia.
- Chronic use of opioids leads to tolerance and frequent escalation of dose.
- **Side effects: hyperpathia, hypogonadism, weight gain, constipation, death from drug-drug interactions. Explain in patient medication agreement along with guidelines for safe use.**

Capsaicin, Isosorbide, Lidoderm©

- Although **capsaicin** has been effective in reducing pain in PDN clinical trials, many patients are intolerant of the side effects, mainly burning pain on contact with warm/hot water or in hot weather.
- **It may take 8 weeks to work, as it works by depleting Substance P, and few are that patient.**
- Intolerance will develop rapidly, so have patient buy smallest size. Wash hands after application.
- **Isosorbide dinitrate** spray (Isocard©) 30 mg per actuation. 1 spray to each foot at bedtime. Contraindicated with NTG spray and with sildenafil and similar.
- SE: headache, dizziness
- **Lidoderm©** patches have scant evidence. Up to 3 patches can be applied to feet and ankles, 12 hours on, 12 hours off. Must be disposed of in sealed container.

Others

- Alpha-lipoic acid 600 mg daily may treat neuropathy and pain (*AAN says insufficient)
- Percutaneous nerve stimulation (AAN effective) 30 mins 3 times a week (TENS 30 min daily)
- Oil of evening primrose (omega 6/gamma linolenic acid) 360 – 480 mg daily; SE: bleeding, seizure (***)
- Borage seed or oil omega 6 also (***)
- Carnitine/CoE Q10 (***)
- Topical peppermint oil may be cooling and soothing (***)

*** = anecdotal

Autonomic Neuropathy

- Orthostatic hypotension: Jobst stockings, elevate HOB, small meals, salt, fludrocortisone, midodrine
- Gastroparesis: metoclopramide, erythromycin, ondansetron, promethazine, botulinum toxin to pylorus, gastric pacing
- Nocturnal diarrhea: trial of metronidazole or cephalosporin, loperamide 2-4 mg qid, diphenoxylate & atropine 2 tabs qid, codeine 30 mg qid, clonidine 0.1 mg at hs, trial of prokinetic agents
- Constipation: fiber in diet, exercise, usual agents
- Bladder hypomobility: Valsalva, Crede, bethanechol in extreme cases

Thank you

- Questions?
- Email jill.kimm@kdmc.net for slides.