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**Diabetic Peripheral Neuropathic Pain: Evaluating Treatment Options**

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**Disclosures**

- Speaker's Bureau: Allergan, Ipsen

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## Learning Objectives

- Discuss practical approaches to the evaluation and management of diabetic peripheral neuropathy pain
- Review the medical evidence behind recommended pharmacological treatments for pain in DPN
- Compare older and newer guidelines for pharmacological management of painful DPN

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**"Absence of Evidence is Not Evidence of Absence"**

Or is it….

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## DPN Pain

- Neuropathic pain: pain caused by a lesion or disease of the somatosensory nervous system
- Often presents with pain in area of sensory loss, spontaneous pain, and evoked pain (hyperalgesia, allodynia)
- DPN is a common long-term complication of DM—can affect function and QOL
- Most common type: distal symmetric sensorimotor
- Pain is estimated to affect 30%-50% of diabetics (out of estimated 29.1M in the US by the CDC)

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## DPN Pain Management

- First widely accepted step: optimize glycemic control (despite clear lack of evidence and even some contradictory results)
- Second: stepwise pharmacological approaches and algorithms generally used; comparative effectiveness is unclear partially due to scarcity of head-to-head trials

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## Evaluation/Diagnosis

- Diagnosis of DPN is clinical
- Based on hx of neuropathic pain and confirmatory examination findings establishing deficits associated with neuropathy
  - Decreased or altered sensation
    - Monofilament, vibration, Romberg
  - Depressed MSRs, atrophy

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## Evaluation/Diagnosis (cont'd)

- Intermittent or continuous symptoms of pain described as burning, stabbing, tingling, numb, hot, cold, or itching in a distal-to-proximal 'stocking →glove' distribution
- Pain often symmetrical/worsens at night

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## Evaluation/Diagnosis (cont'd)

- Glycemic control not the only factor
- Components of MetS may be potential risk factors since these CV risk factors cluster with hyperglycemia
- Obese individuals (even those w/o DM or pre-diabetes) have a higher prevalence of neuropathy than lean individuals; they also have higher pain scores and lower QOL[1]
- No such effect for other MetS components[1]

[1]Callaghan, et al. JAMA Neurol 2016

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## Adjuvants/Co-Analgesics

- Any medication with analgesic properties but with a primary indication other than analgesia
  - Includes various medication classes
- May be used alone or in combination with opioids or other analgesics; DPN pain mostly managed with adjuvants

Portenoy RK and McCaffery M. In: Pain Clinical Manual, 2nd ed. 1999
Portenoy RK. In: Oxford textbook of palliative Medicine, 2nd ed. 1998

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## Adjuvant Analgesics

- Antidepressants
- Anticonvulsants
- Bisphosphonates
- Corticosteroids
- Local anesthetics
- Muscle relaxants
- Neuroleptics
- **NMDA antagonists**
- **Topical agents**
- Others

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## Choosing Considerations

- Polypharmacy issues
  - Additive adverse effects
  - Dual benefits
  - Medical comorbidities
- A call for patience…
  - Often require multiple dose titrations
  - May take days to weeks to achieve adequate response

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## Clinical Guidelines

- IASP—algorithm for neuropathic pain treatment[1]
- AANEM, AAN, and AAPM&R—guidelines for management of painful diabetic neuropathy[2]
- WIP systematic review and meta-analysis[3]
- ACP umbrella systematic review[4]
- AAN systematic review[5]

[1] Finnerup NB, et al. Pain 2005
[2] Bril, et al. Muscle & Nerve 2011
[3] Snedecor, et al. Pain Practice 2013
[4] Griebeler, et al. Ann Int Med 2014
[5] Waldfogel, et al. Neurology 2017

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## IASP Algorithm

- Not specific to DPN
- Used NNT and NNH paradigm
- Lowest NNT ———————> Highest NNT
- TCAs < CMZ <DXMP < opioids < gabapentin/< SNRIs

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## IASP Algorithm (cont'd)

| Agent | NNT | NNH |
|---|---|---|
| TCA | 2.1 | 14.7 |
| Carbamazepine | 2.3 | 21.7 |
| Dextromethorphan | 2.5 | 8.8 |
| Opioids | 2.6 | 17.1 |
| Tramadol | 3.5 | 9.0 |
| Gabapentin/Pregabalin | 4.6 | 17.8 |
| SNRI | 5.5 | nd |
| Capsaicin | 11 | 11.5 |

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## 2011 Clinical Guidelines Recommendations

- Level A evidence:
  - Pregabalin
- Level B evidence:
  - Gabapentin
  - Sodium valproate
  - Venlafaxine, duloxetine
  - Amitriptyline
  - Dextromethorphan
  - Morphine & oxycodone
  - Tramadol
  - Capsaicin 0.075%
  - Isosorbide dinitrate spray
  - Electrical stimulation

*AANEM, AAN and AAPM&R

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## 2011 Clinical Guidelines Recommendations

- **Not** recommended:
  - Oxcarbazepine
  - Lamotrigine
  - Lacosamide
  - Clonidine
  - Mexiletine
  - Pentoxifylline

  - Physical agents
  - Magnetic fields
  - Low-intensity laser
  - Reiki therapy

*AANEM, AAN and AAPM&R

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## Rehabilitation Interventions

- Increase stability and prevent falls
- Adaptive equipment to improve function, and QOL when disease symptoms progress
- May include splinting

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## Exercise

- Strengthening exercises moderately improve muscle strength in people with PN
- May reduce pain and help control hyperglycemia
- Should include: aerobic, flexibility, balance, and strength training

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## Clinical Guidelines

2014 ACP guidelines recommendations

- Network meta-analysis combining direct and indirect comparisons supports short-term effectiveness of:
  - Carbamazepine
  - Venlafaxine
  - Duloxetine
  - Amitriptyline
- As a group, SNRIs had a greater effect on pain than anticonvulsants and opioids

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## Clinical Guidelines (cont'd)

2014 ACP guidelines recommendations

- Patients receiving TCAs, SNRIs, and most anticonvulsants frequently reported somnolence and dizziness
- Xerostomia—most common anticholinergic effect of TCAs
- Nausea, constipation, and dyspepsia were prevalent among those using SNRIs
- Limited data about effects beyond 3 months
- Evidence is scant, mostly indirect, and often derived from brief trials with unclear or high risk for bias

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## Clinical Guidelines (cont'd)

New in the latest guidelines (AAN 2017):

- NOT effective
  - –Gabapentin (same as 2014; different than 2011)
  - –Opioids (different than 2011)
  - –Dextromethorphan (different than 2011)
  - –Capsaicin (different than 2011)
- Effective
  - –Oxcarbazepine (different from 2011)
  - –Tapentadol (new)
  - –Botulinum toxin (new)

**All with low SOE

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## Clinical Guidelines (cont'd)

- Confirmed again as effective:
  - –Moderate SOE
    - Duloxetine
    - Venlafaxine
  - –Low SOE
    - Pregabalin
    - TCAs
    - Tramadol

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## FDA Approval

- Duloxetine and pregabalin were approved for treatment of DPN pain in 2004
- Tapentadol ER in 2012—when opioid analgesia is required ATC over an extended period of time and alternative Tx options are inadequate

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## Antidepressants

- Analgesic activity relates to their ability to block the reuptake of serotonin and NE
  - Involved in modulation of spinal pain pathways
- Analgesia is not typically dependent on antidepressant activity
  - Onset of action may differ
- Multipurpose analgesics
  - Analgesic in a variety of chronic pain syndromes

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## Antidepressants (cont'd)

- TCAs
  - Tertiary amines (amitriptyline, imipramine)
  - Secondary amines (nortriptyline, desipramine)
- SSRIs
  - Fluoxetine, paroxetine, citalopram
- SNRIs
  - Duloxetine, venlafaxine

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## TCAs

- Considered first line therapy for painful DPN[1]
  - Amitriptyline most thoroughly studied
    - Consider secondary amines for those unable to tolerate
- Extensively studied in numerous pain states
- Analgesic effect occurs early
  - Occurs in the absence of depression[2,3]

*Start low and go slow.....*

1 Lynch *J Psychiatry Neurosci* 2001 2 Onghena and Houdenhove. *Pain* 1999
3 Max, et al. *NEJM* 1992) Leijon and Boivie. *Pain* 1989

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## Venlafaxine

- Inhibit reuptake of norepinephrine and serotonin
  - Also dopamine
  - Less anticholinergic effects (dry mouth, constipation)
  - Similar to TCA
- Effective dose: 75-225 mg/day (BID/TID dosing)
- Side effects
  - Nausea, somnolence, dizziness, constipation, dyspepsia, sexual dysfunction
- Precautions/drug interactions
  - Caution in hypertension
  - MAOIs, TCAs, SSRIs, tramadol

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## Duloxetine

- Balanced and selective serotonin and norepinephrine reuptake inhibitor (SNRI)
- 60 mg QD; rarely may need 120 mg
- $T^{1/2}$: 12 hrs; but no advantage of BID dose
- Start 30 mg x 1 wk; then increase to 60 mg (easy dosing schedule)
- Nausea is most significant S/E
- Drug interactions
  - TCAs, SSRIs, tramadol

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# Anticonvulsants

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## Gabapentin

- Considered by many 1st-line for neuropathic pain of many types
  - FDA approved for postherpetic neuralgia ('04)
- Level 1 evidence
  - Postherpetic neuralgia[1]
  - Diabetic neuropathy[2] (not anymore……)

1 Rowbotham, et al. *JAMA* 1998
2 Backonja, et al. *JAMA* 1998

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## Gabapentin vs Amitriptyline

- Randomized, double-blind, crossover study (n=25) patients with DPN
  - Gabapentin 900-1800 mg/day vs amitriptyline 25-75 mg/day
- Results:
  - Reduction in pain: greater with amitriptyline but no significant difference ($p = 0.26$)
  - Similar incidence of side effects
    - More weight gain with amitriptyline

Morello CM, et al. *Arch Int Med* 1999

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## Gabapentin

- Initial dose 300 mg/day—300 mg TID
- Increase by 300 mg/day every 2-7 days
- Usual effective dose 1800-3600 mg/day
  - Given 3 times daily (TID)
  - Sometimes higher doses required

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## Pregabalin

- GABA analogue:
  - Modulates stimulus-dependent Ca++ influx at nerve terminals
  - Increases extracellular [GABA] in the CNS
- Dosed BID-TID (up to 300 mg/day)
- Increased bioavailability (and faster titration) vs gabapentin
- Schedule V

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## Oxcarbazepine

- A keto-analog of carbamazepine
  - Shares the same mechanism of action
- Comparable analgesic efficacy to carbamazepine[1,2]
  - OCBZ 900-1200 mg/day ~ CBZ 400-1200 mg/day
- Better safety and tolerability profile compared with carbamazepine[2]
  - Dizziness, nausea, HA, drowsiness, ataxia, diplopia, fatigue, nervousness, LFTs, hyponatremia
  - No reported association with aplastic anemia

1 Lindstrom P. *Eur Neurol* 1987
2 Beydoun A, et al. (abstract) AAN, 54th annual meeting 2002.
3 Zhou et al. Cochrane Database Systematic Reviews 2013

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## Oxcarbazepine (cont'd)

- Sodium levels should be checked at baseline and frequently
  - Reported hyponatremic coma
  - Elderly, medically ill may be at greater risk
- Initial dose 150-300 mg/day
  - Increase by 150 mg every 3 days
- Usual effective dose 900-1800 mg/day
  - Dosed BID

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## Opioids

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## Tramadol

- MOA: binding of the parent drug and its metabolite to mu-opioid receptors, and weak inhibition of both NE and serotonin reuptake
- Low SOE but considered effective in DPN

Harati et al. Neurology 1998
Harati et al. J Diabetes Complications 2000

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## Tapentadol ER

- Synthetic μ-opioid agonist and norepinephrine reuptake inhibitor
- Starting dose: 50 mg BID
- Titrated to adequate analgesia with dose increases of 50 mg BID q 3 days to an effective dosing range of 100 to 250 mg BID
- Generally GI S/Es less severe than those of opioids

Schwartz et al. Curr Med Res Opin 2011; 27(1):151-62.
Vinik et al. Diabetes Care 2014; 37(8):2302-9.

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## Emerging Treatments for Neuropathic Pain

- Botulinum toxins
  - Extensive publications on multiple neurogenic inflammatory states; likely lots of publication and other biases
  - 2 RCTs of DPN pain (low n); both type A
  - "Relatively" expensive
  - Painful application

Yuan, et al. Neurology 2009
Ghasemi, et al. J Res Med Sci 2014

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## Emerging Treatments for Neuropathic Pain (cont'd)

- Proposed pathogenetic treatments
  - α-lipoic acid (decreases reactive oxygen formation)
  - Benfotiamine (prevents vascular damage in diabetes)
  - Aldose-reductase inhibitors (reduces flux through the polyol pathway)
  - Cannabinoids

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## Final Recommendations

- Depend greatly on patient's specific comorbidities/situation and cost
- TCAs/pregabalin/duloxetine/venlafaxine
  - Could also consider gabapentin/oxcarbazepine
  - Tapentadol/tramadol—later in select cases
  - Consider BTX for intractable cases

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## Conclusions

- Choose medications carefully
  - Consider comorbidities
- Have realistic expectations
  - Slow onset, need to titrate, toxicities, long-term use
  - Counsel patients regarding expectations and potential side effects
- Be persistent
  - Titrate doses to efficacy or toxicity

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## Conclusions (cont'd)

- Consider multiple agents
  - May allow lower doses of each
  - Toxicity and compliance issues
  - Concomitantly vs successively….

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## *Thanks!*

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