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IN PALLIATIVE CARE

Interprofessional Webinar Series

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Drug Therapy for Neuropathic Pain in the Medically Ill

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Neuropathic Pain in Serious Medical Illness

- Definition and epidemiology
- Mechanisms
- Assessment
- Treatment

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Cancer-Related Neuropathic Pain: Definitional Challenges

- Changing Definitions
  - Older: Pain from a lesion or dysfunction of the nervous system
  - Newer: Pain caused by lesion or disease of the somatosensory nervous system

http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm

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Neuropathic Pain: Epidemiology

- 1 – 6% overall prevalence in the general population
- ***19% – 39% of patients with cancer pain***
- In general, associated with high illness burden and health care utilization

Attal N, et al, *Pain*, 2011;152:2836; Bennett et al, *Pain*, 2012;153:359; Smith BH, Torrance N, Curr Pain Headache Rep 2012;16:191.

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Neuropathic Pain: Mechanisms

- Multiple mechanisms, which may vary by
  - Medical diagnosis
  - Site of neurological lesion
  - Inferred pathophysiology
  - Other factors

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Neuropathic Pain: Variation

- Examples of medical diagnoses
  - Chemotherapy-induced polyneuropathy
  - Malignant plexopathy
  - Post-stroke central pain syndrome
  - Complex regional pain syndrome

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Neuropathic Pain: Variation

- Neurological localization
  - Polyneuropathy
  - Mononeuropathy(ies)
  - Radiculopathy
  - Myelopathy
  - Encephalopathy

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Neuropathic Pain: Variation

- Inferred pathophysiology
  - Distinguishes pain with “peripheral generators” and pain with “central generators”

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Inferred Pathophysiologies and Biological Processes

- **Peripheral processes**
  - Transduction dysfunction
  - Peripheral sensitization
  - Membrane excitability at primary afferents
- **Central processes**
  - Synaptic transmission dysfunction
  - Central sensitization
  - Reduced inhibition

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Inferred Pathophysiologies and Biological Processes

- **Peripheral: Membrane excitability**
  - Changes in concentration/types of sodium channels
  - Many other processes
- **Central: Sensitization**
  - Established role for NMDA receptor complex
  - Glial activation and pro-inflammatory cytokines increase and sustain activity in afferent neurons
  - Many other processes

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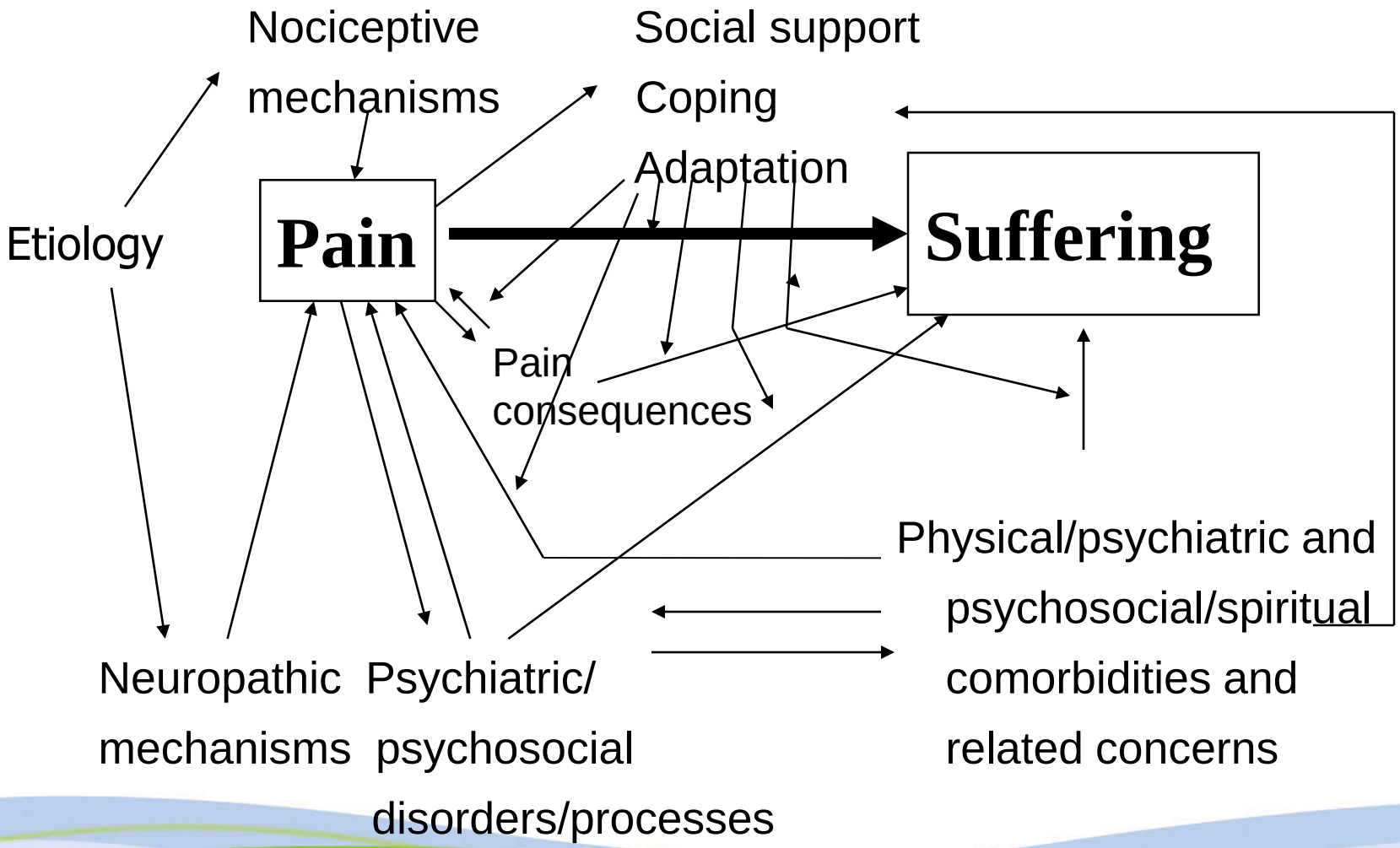
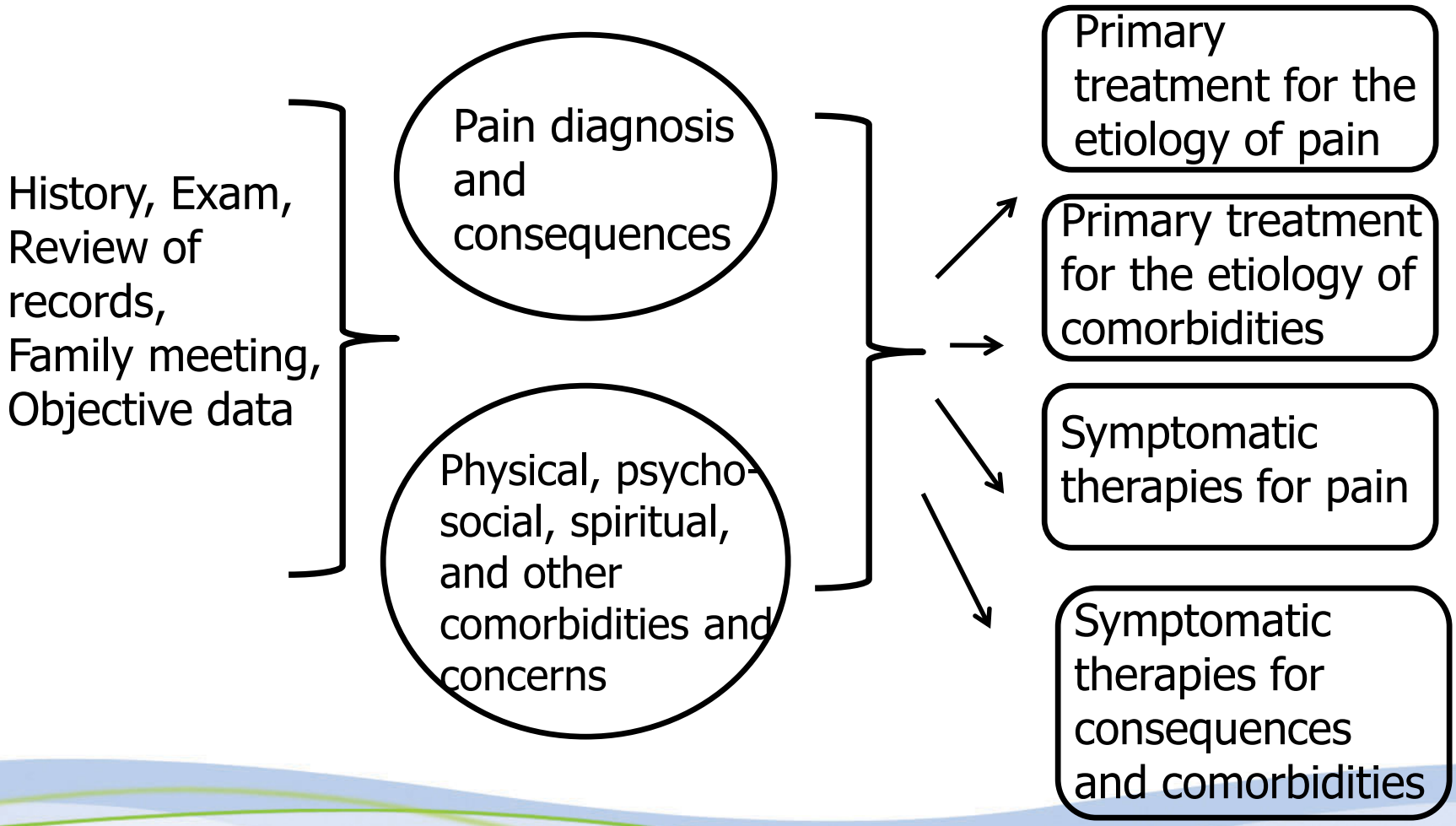
Neuropathic Pain: Challenges in Assessment

- Diagnosis complicated by
  - Heterogeneous phenomenologies
  - Mixed syndromes common
  - Comorbidities common in the medically ill
    - Wounds and ulcers
    - Cognitive impairment

Neuropathic Pain: Challenges in Assessment



Pain Management: Developing the Plan of Care



Symptomatic Treatment of Pain Related to Serious Illness

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Pharmacotherapy

- Nonopioids
- "Adjuvant" analgesics
- Opioids

Psychological

- Psycho-educational
- CBT
- Others

Interventional

- Injection therapy
- Neural blockade
- Implant therapies

Rehabilitative therapies

- Physical/Occupational therapy
- Modalities/orthotics

Integrative therapies

- Acupuncture
- Chiropractic
- Music therapy
- Others

Neuromodulation

- - TENS and transcranial
- - Invasive types

Lifestyle changes

- - Weight loss

Pharmacotherapy of Neuropathic Pain

- Pharmacotherapy is the mainstay approach
- First-line treatment is an opioid
- Consider other analgesics if opioid does not optimize outcomes
  - Many options, most extrapolated from noncancer pain
  - Relatively few RCTs and very few comparative trials
- Other approaches is selected cases

Dworkin RH, et al, Arch *Neurol.* 2003;60:1524-1534.
Finnerup NB, et al, *Pain*. 2005;118(3):289-305.

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Pharmacotherapy in Neuropathic Pain

- Opioid analgesics
- “Adjuvant” (nontraditional) analgesics
- Nonopioid analgesics

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Opioids in Neuropathic Pain

- ***NOT*** correct: "Neuropathic pain is 'resistant' to opioids"
- Limited data suggest
  - Neuropathic pain may be less opioid responsive than nociceptive pain
  - Poorly responsive syndromes are more likely to be neuropathic
- ***But*** opioids are clearly efficacious

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Opioids in Neuropathic Pain

- Positive trials of oxycodone in DPN and PHN
- Positive trial of methadone in mixed types of neuropathic pain
- Positive trial of morphine in PHN
- Positive trial of levorphanol in peripheral and central neuropathic pain

Gimbel JS et al: *Neurology.* 2003;60:927-934.
Watson CP, Babul N: *Neurology. 1998;*50:1837-1841.
Morley JS et al: *Palliat Med.* 2003;7:576-587.
Raja SN et al: *Neurology.* 2002;59:1015-1021.
Rowbotham MC, et al: *NEJM.* 2003;348:1223-1232.

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Opioids in Neuropathic Pain

- Positive systematic review of tramadol (5 trials)
- Positive trial of morphine + gabapentin, and morphine alone, relative to gabapentin in patients with DPN or PHN

Duhmke RM, et al. Cochrane Database Syst Rev. 2004:CD003726.
Gilron I, et al: *NEJM*. 2005;352:1324-1334.

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Pharmacotherapy of Neuropathic Pain

- "Adjuvant analgesics"
  - Traditional definition
    - ***Drugs with indications other than pain which may be analgesic in specific circumstances***
  - Numerous drugs in diverse classes, some now specifically indicated for pain
  - Use in neuropathic pain in the medically ill extrapolated from observations in other populations

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Categories of Adjuvant Analgesics

- Multipurpose analgesics
  - Corticosteroids
  - Antidepressants
  - Alpha-2 adrenergic agonists
  - Cannabinoids
  - Topical therapies
- Other drugs used for neuropathic pain
- Other drugs used for musculoskeletal pain
- Other drugs used for bone pain
- Other drugs used for bowel obstruction

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Approach to the Use of Adjuvant Analgesics for Neuropathic Pain

- First-line
  - Corticosteroid in the setting of advanced illness
  - Gabapentinoid ***or*** analgesic antidepressant
  - Topical drugs
- Second-line
  - Other multipurpose analgesics
  - Other adjuvant analgesics for neuropathic pain

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Corticosteroids

- Limited evidence but wide use as multipurpose analgesics
  - Neuropathic pain
  - Bone pain
  - Capsular pain
  - Lymphedema
  - Headache
  - Other conditions

Leppert W, Buss T, Curr Pain Headache Rep 2012:16:307

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Analgesic Antidepressants

- Classes
  - Tricyclic antidepressants
    - 3^{o} amines: amitriptyline, imipramine, doxepin
    - 2^{o} amines: desipramine, nortriptyline
  - SNRIs: duloxetine, minalcipran, venlafaxine, desvenlafaxine
  - SSRIs: paroxetine, citalopram, others
  - Others: bupropion

Dharmaskaktu P, *J Clin Pharmacol* 2012;52:6; Sindrup et al, *Basic Clin Pharmacol Toxicol*. 2005;96:399-409; Dworkin RH, et al, Arch *Neurol.* 2003;60:1524-1534. Finnerup NB, et al, *Pain*. 2005;118(3):289-305

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Analgesic Antidepressants

- Based on safety and likelihood of efficacy, most reasonable choices would be 2º amine drugs or SNRIs
  - Desipramine or nortriptyline
  - Duloxetine
  - Also consider bupropion

Gabapentinoid Anticonvulsants

- Gabapentin and pregabalin
  - Act via voltage-gated calcium channel, modulating alpha-2-delta protein
  - Positive RCT's in many disorders
    - Gabapentin: RCT in neuropathic cancer pain
  - Less efficacious than TCAs, but first-line drug because of safety
    - Not hepatically metabolized
    - No drug-drug interactions
    - Side effects usually tolerable

Backonja et al, *JAMA*. 1998;280:1831-1836. Rowbotham M, JAMA. 1998;280:1837-1842.
Caraceni et al, *J Clin Oncol,* 2004;22:2909-2914

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Gabapentinoid Anticonvulsants

- Gabapentin vs. pregabalin
  - Pregabalin has more stable PK than gabapentin, with easier titration and faster onset of effect
  - Pregabalin has positive effects on sleep and anxiety
  - May respond to one or the other, both or neither
  - Common side effects: somnolence, mental clouding, edema, weight gain

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Gabapentinoid Anticonvulsants

- Gabapentin
  - Starting dose 100 – 300 mg qd
  - Effective dose 300 – 1200 TID or higher
- Pregabalin
  - Starting dose 25 – 75 mg qd
  - Effective dose 150 – 300 mg BID

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Topical Adjuvant Analgesics

- RCTs support benefit in neuropathic, joint pain, skin/wound pain
  - Lidocaine 5% patch and creams
  - NSAIDs, e.g., ASA and diclofenac
  - Low concentration (0.025% or 0.075%) capsaicin
  - TCAs, e.g., doxepin, amitriptyline
  - Opioids (?)
  - Others

Galer et al, *Pain*, 80:533-538, 1999; Brühlmann et al, *Clin Exp Rheumatol* 21:193, 2003; Ellison et al, JCO, 15:2974-2980, 1997; Mcleane, *Br J Clin Pharm*, 49:574-579, 2000; Webster LR et al, *J Pain* 11:972-82, 2010; LeBon B et al, *J Pain Symptom Manage* 37:913-7, 2009

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Topical Adjuvant Analgesics

- Capsaicin 8%
  - Approved for PHN
  - Apply for 60 min
  - When efficacious, benefit can persist for months
  - 1 year of safety data with repeated use

Simpson DM, et al. *JPSM* 2010;39:1053-64.
Webster LR, et al. *J Pain*. 2010;11:972-82

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Approach to the Use of Adjuvant Analgesics for Neuropathic Pain

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α-2 Adrenergic Agonists

- RCTs support efficacy of clonidine, tizanidine, and dexmedatomidine
- In RCT, intrathecal clonidine worked for cancer-related neuropathic pain
- **Tizanidine** usually better tolerated than clonidine

Giovannani MP, et al, Med Res Rev 29:339, 2009

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Cannabinoids

- Strong preclinical support for analgesic efficacy of both CB1 and CB2 agonists
- RCTs of THC in central pain and nabilone in fibromyalgia
- Recent positive RCTs of new formulation (nabiximols=THC plus cannabidiol) in central pain and in cancer pain

Svendsen et al, *BMJ*, 329:253, 2004; Skrabek et al, *J Pain* 9:164, 2008; Berman et al, *Pain*, 112:299-306, 2004; Portenoy RK et al, *J Pain* 13:438, 2012

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Non-gabapentinoid Anticonvulsants

- Other anticonvulsants have little of evidence of efficacy and are selected by trial and error
- Older anticonvulsants have some evidence
  - Carbamazepine (trigeminal neuralgia)
  - Sodium divalproex (migraine)
  - Phenytoin

Wiffen P, et al, Cochrane Database Syst Rev., 2005;20:CD001133

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Non-gabapentinoid Anticonvulsants

- Some newer anticonvulsants have very limited evidence
  - Topiramate (Topamax®)
  - Oxcarbazepine (Trileptal®)
  - Lamotrigine (Lamictal®)
  - Lacosamide (Vimpat®)

Wiffen P, et al, Cochrane Database Syst Rev., 2005;20:CD001133

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Non-gabapentinoid Anticonvulsants

- Some newer anticonvulsants have minimal to no evidence
  - Clonazepam
  - Levetiracetam
  - Zonisamide
  - Tiagabine

Wiffen P, et al, Cochrane Database Syst Rev., 2005;20:CD001133

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Sodium Channel Blockers

- Oral mexiletine, tocainide, flecainide are analgesic in neuropathic pain
- Because of relatively high side effect liability from oral drugs, generally considered third-line
- Efficacy of IV lidocaine supported by RCTs
  - IV lidocaine is an option for severe neuropathic pain
  - Efficacy demonstrated at 5 mg/kg over 30 min

Tremont-Lukats IW, et al, Anesth Analg 2005;101:1738;
Oskarsson P et al, *Diabetes Care*, 1997;20:1594-1597.
Challapalli et al, Cochrane Database Sys Rev. 2005;CD003345

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NMDA-Receptor Antagonists

- NMDA receptor involved in neuropathic pain and opioid tolerance
- Commercially-available drugs
  - Ketamine
  - Memantine
  - Dextromethorphan
  - Amantadine

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NMDA-Receptor Antagonists

- 4 RCTs of ketamine plus opioids in cancer pain: no conclusion possible
- **Recent large, placebo-controlled RCT of ketamine for cancer pain was negative**
- 37 RCTs of ketamine plus opioids by single bolus or infusion show mixed but generally favorable results

Hardy J, et al, J Clin Oncol, 2012, epub; Subramaniam K, *Anesth Analg.* 2004;99:482-495.
Bell R, Cochrane Database Syst Rev. 2003;(1):CD003351; Nelson et al, *Neurology.* 1997;48:1212

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NMDA-Receptor Antagonists

- RCT of dextromethorphan positive in DPN and negative in PHN
- Very limited positive data for memantine and amantadine; several negative RCTs of memantine

Subramaniam K, *Anesth Analg.* 2004;99:482-495.
Bell R, Cochrane Database Syst Rev. 2003;(1):CD003351.
Nelson et al, *Neurology.* 1997;48:1212

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NMDA-Receptor Antagonists

- Based on clinical experience, ketamine still used in refractory pain
  - Brief, hours-days, infusion by IV or SQ
  - Oral use of injectable or compounded drug
  - Co-administered benzodiazepine or neuroleptic to reduce risk of side effects
- Ketamine also is used for palliative sedation
- Other NMDA antagonists rarely tried for refractory pain

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GABAergic Adjuvant Analgesics

- Baclofen
  - RCT in trigeminal neuralgia
  - Intrathecal baclofen may relieve neuropathic pain apart from spasticity
  - Used empirically for neuropathic pain as third-line agent
- Benzodiazepines
  - Clonazepam used for neuropathic pain despite lack of data

Fromm et al, *Ann Neurol*, 1984;15:240-244

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NSAIDs in Neuropathic Pain

- Generally viewed to be inefficacious but…
  - Commonly used (e.g., 20% of patients with SCI pain)
  - Strong evidence of prostaglandin-mediated mechanisms in some preclinical models
  - Limited positive clinical trials data
  - Conclusion: NSAIDs can be considered for a therapeutic trial

Widerstrom-Noga and Turk, *Spinal Cord.* 2003;41:600.
Cohen et al, *Arch Intern Med*. 1987;147:1442

Symptomatic Treatment of Pain Related to Serious Illness

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Neuropathic Pain in Serious Medical Illness

- Summary of treatment strategy
  - Treat etiology, if possible and appropriate
  - Titrate opioid
  - Consider
    - Corticosteroid depending on clinical setting
    - Then gabapentin or pregabalin, unless comorbid depression is present
    - If comorbid depression is present, consider desipramine, nortriptyline, or duloxetine
    - Always consider co-administered topical drug

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Neuropathic Pain in Serious Medical Illness

- Summary of treatment strategy
  - If initial drug is not effective, but there is some benefit, consider adding the second
  - Consider sequential trials, beginning with antidepressants and gabapentinoids, then others
  - If pain persists, consider referral to a pain specialist for interventions, if possible and appropriate

Dworkin RH, et al, *Pain*, 2007;132:237-251.
Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. *Pain*. 2005;118(3):289-305.

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Drug Therapy for Neuropathic Pain in the Medically Ill

Q/A