



# Adjuvant Analgesics: Evidence-Based Use for Cancer Pain

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# Cancer Pain: Role of Opioid Therapy

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- There is broad agreement that ***opioid therapy is first-line for moderate or severe chronic pain due to an active, serious or life-threatening illness, particularly when the disease is advanced***



# Adjuvant Analgesics

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- Evolving definition
  - Drugs added to an opioid regimen to enhance analgesia or manage opioid-related side effects
  - Drugs with indications other than pain which may be analgesic in specific circumstances
  - ***Drugs with primary clinical uses other than pain which may be analgesic in specific circumstances***



# Adjuvant Analgesics

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- With few exceptions, the use of the adjuvant analgesics for cancer pain is extrapolated from observations in other populations



# Categories of Adjuvant Analgesics

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- Based on data from trials and clinical experience, the adjuvant analgesics can be categorized as
  - Multipurpose analgesics
  - Drugs used for neuropathic pain
  - Drugs used for bone pain
  - Drugs used for pain due to bowel obstruction



# Categories of Adjuvant Analgesics

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- Multipurpose analgesics
  - Clinical trials suggest benefit for varied types of pain syndromes and etiologies
  - Classes
    - Corticosteroids
    - Antidepressants
    - Alpha-2 adrenergic agonists
    - Cannabinoids
    - Botulinum toxin type A
    - Topical therapy: Lidocaine, capsaicin, and others



# Corticosteroids

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- Systematic review of RCTs in cancer pain
  - 15 studies, 1926 participants
  - **Weak** evidence of short-term efficacy
  - Incomplete documentation of adverse effects
- One randomized trial in cancer pain patients demonstrated efficacy for comorbid symptoms—  
anorexia and fatigue



# Corticosteroids

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- Based on clinical experience, used for varied types of pain
  - Bone pain
  - Peripheral neuropathic pain
  - Pain due to bowel obstruction
  - Pain due to expansion of organ capsules
  - Pain related to lymphedema
  - Headache
  - Other conditions
- Extensive clinical experience and potential benefit for comorbid symptoms like fatigue supports use in advanced illness



# Analgesic Antidepressants



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- Classes

- Tricyclic antidepressants

- 3° amine drugs: amitriptyline, imipramine, doxepin
- 2° amine drugs: desipramine, nortriptyline

- SNRIs

- Duloxetine, minalcipran, venlafaxine, desvenlafaxine

- SSRIs

- Paroxetine, citalopram, others

- Others

- Bupropion
- Mirtazapine

# Analgesic

# Antidepressants

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- Analgesic efficacy

- Strong evidence for SNRIs and TCAs, with a suggestion that SNRIs are more efficacious than TCAs
- Of the tricyclics: 3° amine drugs (amitriptyline) are probably more efficacious than 2° amine drugs (nortriptyline)
- SSRIs, mirtazapine, and bupropion: Limited evidence and uncertain efficacy

- Side effects

- 3° TCAs have more side effects than 2° TCAs, which have more side effects than SNRIs/SSRIs/bupropion

# Analgesic

# Antidepressants

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- Based on safety and likelihood of efficacy, best choices would be a **SNRI** or a **2<sup>o</sup> amine tricyclic drug**
  - Most evidence supports **duloxetine**
  - Also consider
    - The 2<sup>o</sup> amine tricyclic drugs **desipramine** or **nortriptyline**
    - Other SNRIs
- Other antidepressants rarely used

# Analgesic

# Antidepressants

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- Although antidepressants are multipurpose analgesics and may be considered for any chronic pain, they are typically used in the medically ill for ***opioid-refractory neuropathic pain***



# Neuropathic Cancer Pain

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- Other first-line adjuvant analgesics
  - ***Antidepressants***: SNRIs [NNT = 6.4] and tricyclic antidepressants [NNT = 3.6]
  - ***Gabapentinoids***: Gabapentin [NNT = 6.3] and pregabalin [NNT = 7.7]
  - ***Topical lidocaine*** [NNT = 10.6]



# Gabapentinoids

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- Gabapentinoid mechanism
  - Inhibit calcium currents by modulating the voltage-dependent calcium channels  $\alpha 2\delta$ -1 subunit
  - Also activate the descending noradrenergic pain inhibitory system coupled to spinal  $\alpha 2$  adrenoceptors
- Patients may respond to gabapentin, to pregabalin, or to both
- Pregabalin has more stable PK than gabapentin, with easier titration and faster onset of effect



# Other Adjuvant Analgesics for Neuropathic Cancer Pain

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- Other multipurpose analgesics
  - Cannabinoids
  - Other topical therapies
  - Botulinum toxin type A
  - Alpha-2 adrenergic agonists
- Other drugs for neuropathic pain
  - Other anticonvulsants
  - Sodium channel blockers
  - NMDA receptor antagonists
  - Gabaergic drugs



# Cannabinoids

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- Strong preclinical support for analgesic efficacy of both CB1 and CB2 agonists
- RCTs of THC in central pain and nabilone in fibromyalgia
- Positive RCTs of nabiximols (mostly THC plus cannabidiol) in central pain and in cancer pain
  - However, there are also negative RCTs in cancer pain
  - Overall, results in cancer pain support designation as a multipurpose analgesic, but more data are needed



# Topical Adjuvant Analgesics



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- Level of evidence varies, but there are data from RCTs supporting benefit in neuropathic pain, joint pain, skin/wound pain
  - Lidocaine 5% patch and creams
  - NSAIDs, e.g., ASA and diclofenac
  - Low concentration (0.025% or 0.075%) capsaicin
  - Amitriptyline
  - Amitriptyline plus ketamine
  - Clonidine
  - Menthol
  - Opioids

# Topical Adjuvant Analgesics



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

# Botulinum

## Toxin Type A

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- Blocks the release of acetylcholine from nerve endings
- Approved for migraine in the US
- Evidence for efficacy in peripheral neuropathic pain and painful muscle spasm
- Duration of effect is months
- Low risk, relative high cost

# $\alpha$ -2 Adrenergic Agonists



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- Clonidine, tizanidine and dexmedetomidine are multipurpose analgesics based on RCT data in varied acute and chronic pain syndromes
- In RCT, intrathecal clonidine worked for cancer-related neuropathic pain
- Tizanidine usually better tolerated than clonidine
- Consider early use of tizanidine for painful muscle spasm

# Non-gabapentinoid Anticonvulsants



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- Other anticonvulsants are occasionally tried for neuropathic pain
- Evidence of efficacy is limited
- Older anticonvulsants have some evidence
  - Carbamazepine (trigeminal neuralgia)
  - Sodium divalproex (migraine)
  - Phenytoin

# Non-gabapentinoid Anticonvulsants



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- Some newer anticonvulsants have very limited evidence of analgesic efficacy
  - Oxcarbazepine
  - Lacosamide

# Non-gabapentinoid Anticonvulsants



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- Some newer anticonvulsants have minimal to no evidence of analgesic efficacy
  - Clonazepam
  - Levetiracetam
  - Topiramate
  - Zonisamide
  - Tiagabine
  - Lamotrigine

# Sodium Channel Blockers



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- There is limited evidence that intravenous lidocaine is analgesic in varied pain syndromes
  - Clinical experience supports anecdotal use for severe opioid-refractory neuropathic pain in advanced illness
- There is limited evidence that oral mexiletine, tocainide, flecainide are analgesic
  - Seldom used because of relatively high side effect liability



# NMDA-Receptor

## Antagonists

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

# NMDA-Receptor

## Antagonists

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- Largest placebo-controlled RCT of ketamine for cancer pain was negative
- RCTs of dextromethorphan positive in DPN and negative in PHN; limited data for memantine and amantadine
- Many RCTs of ketamine plus opioids in varied conditions show mixed but generally favorable results
- 4 RCTs of ketamine plus opioids in cancer pain: no conclusion possible
- Recent evidence suggests ketamine efficacy in treatment-refractory depression

# NMDA-Receptor

## Antagonists

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- Despite lack of high-quality evidence, ketamine is used in advanced illness for opioid-refractory pain
  - Brief, hours-days, infusion by IV or SQ
  - Oral use of injectable or compounded drug
- Co-administered benzodiazepine or neuroleptic reduces risk of side effects
- Other NMDA antagonists rarely tried for refractory pain



# Adjuvant Analgesics for Bone Pain

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- Osteoclast inhibitors
  - Bisphosphonates (e.g., pamidronate)
  - Calcitonin
  - Denosumab
- Other drugs
  - Radiopharmaceuticals (e.g., Sr<sup>89</sup>, Sm<sup>153</sup>)
  - Corticosteroids
  - Nonsteroidal anti-inflammatory drugs

# Adjuvant Analgesics for Bone Pain



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- Consider multipurpose adjuvant analgesics
- Consider adjuvant analgesics used for neuropathic pain



# Adjuvant Analgesics: Evidence-Based Use for Cancer Pain

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- **Conclusions**

- Numerous adjuvant analgesics offer options for pain management when opioid therapy yields an unsatisfactory outcome
- Evidence is best for a few drugs used predominantly to manage neuropathic pain or bone pain
- Studies are needed to improve the evidence base for the use of many other drugs now considered empirically for diverse types of pain