What alternatives are there to the use of opioid analgesics in the treatment of chronic pain in light of existing evidence and its limitations?

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Disclosures

Abbott
Sanofi
Bristol Myers Squibb
Allergan
Xenoport
Boehringer-Ingelheim
NUVO
Hind Health Care
Depomed
Alternatives to opioid analgesics

- Drugs most rigorous criteria for efficacy
- Dietary factors not well studied, but potentially important
  - Alpha lipoic acid, acetyl-L-carnitine
- Cognitive-Behavioral Therapy, mindfulness-based tx, educational and group programs
- Exercise regimens
- CAM approaches – many types

Lee and Raja, PAIN 2011; Bell et al, PAIN in press
Alternatives to opioid analgesics

- **Device-based Tx (stimulators, pumps)**
  - Extremely costly initially and for maintenance
  - Long term efficacy relative to drugs uncertain

- **Nerve blocks**
  - Little prospectively gathered data on long-term benefit
  - Epidural steroids widely used, even for spinal pain types where benefit has not been demonstrated
  - Costly!

- **High strength capsaicin application**
  - Effective from 2 weeks onward – substantial initial pain worsening is a risk
  - Administered in office - need to pretreat for procedure pain
Medication Considerations

*Selecting the proper medication*

- Safety and tolerability in older persons
  - Polypharmacy
- Onset of action
  - Relieve patient’s symptoms quickly
- Ease of use
  - Dosing schedule
  - Dosing consistency
Effective Drug Categories

- Antidepressants
- Anticonvulsants
- Topicals
- Opioids
Efficacy of Antidepressants

- **Tricyclics:** highly effective in most pain disorders; also block sodium channels
  - Studies have important limitations
- **SSRIs:** no efficacy or reduced efficacy
- **SNRIs:** duloxetine, milnacipran, venlafaxine effective
  - Duloxetine most intensively studied; consistent efficacy in trials
Tricyclic Antidepressants: Adverse Events

- Commonly reported AEs:
  - Blurred vision
  - Cognitive changes
  - Constipation
  - Dry mouth
  - Orthostatic hypotension
  - Sedation
  - Sexual dysfunction
  - Tachycardia
  - Urinary retention
  - WEIGHT GAIN

- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

Caution: all tricyclic antidepressants and venlafaxine have a high fatality rate from overdose compared to SSRIs.

AEs = adverse events.
Anticonvulsants: A Large and Diverse Family

<table>
<thead>
<tr>
<th>Na+ channel blocking</th>
<th>Other mechanisms</th>
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<tbody>
<tr>
<td>carbamazepine</td>
<td>gabapentin</td>
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<tr>
<td>lamotrigine</td>
<td>pregabalin</td>
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<tr>
<td>oxcarbazepine</td>
<td>valproate</td>
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<td>phenytoin</td>
<td>clonazepam</td>
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<td>topiramate</td>
<td>tiagabine</td>
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<tr>
<td>zonisamide</td>
<td>levetiracetam</td>
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<tr>
<td>lacosamide</td>
<td>barbiturates</td>
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<tr>
<td>(mexiletine, tocainamide, flecainide)</td>
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Gabapentin and Pregabalin

- Both FDA approved for pain
- Anticonvulsants: alpha-2-delta subunit on neuronal calcium channels
- Requires active transport system for absorption across intestinal wall - high doses poorly absorbed
- Well tolerated; serious adverse effects rare
  - dizziness and sedation common
  - adjust dose for renal impairment
- No significant drug interactions
- Generic gabapentin available
- Gabapentin prodrug and gastric retention versions
Gabapentin for acute pain

- Effective for acute post-operative pain (>11 published studies)
- Single dose (900 mg) reduces acute zoster pain and allodynia

Berry and Petersen, *Neurology* 2005
Gabapentin in PHN Results (UK): Reduction in Pain Score as Early as 1 Week

Additional benefits of using doses greater than 1800 mg/day were not demonstrated

Topical vs Transdermal Drug Delivery Systems

Topical (lidocaine patch 5%)
- Peripheral tissue activity
- Applied directly over painful site
- Insignificant serum levels
- Systemic side effects unlikely

Transdermal (fentanyl patch)
- Systemic activity
- Applied away from painful site
- Serum levels necessary
- Systemic side effects unlikely
Topicals

- Lidocaine patch - protective vehicle; low systemic uptake; approved for PHN
- NSAID topicals – several options
- Capsaicin OTC - neurotoxin selectively activates c-nociceptors to produce burning pain (may be severe with initial applications)
- Other drugs and compounded drug combinations available; data anecdotal; unclear if topical or transdermal action
- Benefit outside of neuropathic pain and OA uncertain
Does existing clinical trial data allow a fair comparison of opioids with non-opioids?

- Few studies directly compare the classes by using a crossover design or randomize across classes in a parallel design
  - Raja and Gilron studies important examples, but are small
  - Both indicate opioids more efficacious than a TCA or gabapentin
- Partially enriched enrollment in many opioid trials
- Subject populations may differ
  - Many potential subjects unwilling to try opioids
‘Rational’ Polypharmacy

- Combine approaches with evidence of efficacy in controlled clinical trials
  - Limited number of longer term prospective combination trials
- Avoid unfavorable drug interactions (kinetic/AE)
  - Multiple drugs all producing sedation
- Avoid duplication
- Eliminate ineffective tx before starting new tx
- Therapies for which there is only anecdotal evidence should always be 2nd or 3rd line
Three Caveats

How representative are the subjects in efficacy trials?

How consistent are the results of trials?

What proportion of the available data is accessible?
Response to sequential treatment trials and duotherapy in epilepsy

Likelihood of success no different if first drug ‘old’ vs ‘new’

Thank you to Ken Laxer
Fifteen Studies of Qutenza were reported to FDA.
Snapshot and Scorecard: The RReACT Database
373 analgesic trials posted on ClinicalTrials.gov

Thank you to Kaitlin Greene and Robert Dworkin

- PHN – 93 trials
  - 57 completed
  - 36 have results
  - 23 published in peer-reviewed literature (40%)

- 164 studies DPN
  - 106 completed
  - 72 have results
  - 29 published in peer-reviewed literature (39%)

- 116 studies Fibromyalgia
  - 66 completed
  - 44 have results
  - 29 published in peer-reviewed literature (44%)