The Pharmacotherapy of Chronic Pain
Rwanda Zero Pain Pain Conference 2019

Mary Lynch MD
Pharmacology, Anesthesia, Perioperative Medicine & Pain Management, and Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada
Presenter Disclosures

Mary E Lynch

• Relationships with commercial interests:
  - Grant Research support: CIHR, InnovaCorp
  - Founding Member, President, Panag Pharm Inc.
  - Clinical trial: Cannimed
• Not-For-Profit Organizations:
  - Founding PI and Board Member, CCIC
  - Opioid committee Canadian Pain Society
Current Options for Management of Chronic Pain

- “Pain Management”
- Education
- Therapeutic exercise
- Psychological techniques
- Trials of modality based therapies
  - TENS
  - Acupuncture
- Complimentary Rx
  - Qigong
  - Osteopathy
- Pharmacotherapy
- NSAIDS
- Antidepressants
- Anticonvulsants
- Opioids
- Dual action (methadone, tramadol)
- Cannabinoids
- Topicals
Tricyclic and SNRI Antidepressants are Analgesic

- Over 40 RCTs in the literature
- Analgesic effect is independent of the antidepressant effect
- Analgesia occurs earlier and at lower doses than the antidepressant effect
- Effective in sharp, lancinating and chronic dysesthetic types of pain
# Analgesic Antidepressants

## Analgesic Antidepressants

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COMMON TRADE NAME</th>
<th>THERAPEUTIC RANGE FOR PAIN (MG/24H)</th>
<th>HALF-LIFE (H)</th>
<th>NEUROTRANSMITTER PROFILE</th>
<th>MOST COMMON SIDE EFFECTS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>5HT</td>
</tr>
<tr>
<td>tricyclics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| amitriptyline | Elavil           | 10-150*                             | 10-46        | +++|+++|>30|>10|>30|>30|>10|>2
| doxepin     | Sinequan          | 10-150*                             | 8-36         | +++|++|>30|>10|>10|>30|>10|<2
| trimipramine| Surmontil         | 10-150*                             | 7-30         | ++ |+ |>30|>10|>10|>10|>10|<2
| imipramine  | Tofranil          | 10-150*                             | 4-34         | +++|+++|>10|>30|>10|>30|>10|>10
| clomipramine| Anafranil         | 10-150*                             | 17-37        | +++|++++|>2|>10|>10|>30|>10|>10
| desipramine | Norpramin         | 10-150*                             | 12-76        | ++++|++|>2|>2|>2|>10|>2|>2
| nortriptyline| Aventyl           | 10-100*                             | 13-88        | +++|+++|>2|>2|>2|>10|>10|<2
| serotonin/norepinephrine reuptake inhibitors |        |                                     |              |    |    |          |                          |                |            |              |             |        |         |
| venlafaxine | Effexor           | 37.5-225                            | 3-7 (parent) | ++ |++++|>10|>10|<2|>10|>10|>30
| duloxetine  | Cymbalta           | 60-120                              | 10           | +++|++++|>10|<10|<2|>10|>10|>10

### Tricyclics
- Amitriptyline (Elavil): 10-150 mg, half-life 10-46 h, NA: +++ 5HT: +++ SEDATION: >30 ORTHOSTATIC HYPOSTENSION: >10 WEIGHT GAIN: >30 DRY MOUTH: >30 CONSTIPATION: >10 GI DISTRESS: >2
- Doxepin (Sinequan): 10-150 mg, half-life 8-36 h, NA: +++ 5HT: ++ SEDATION: >30 ORTHOSTATIC HYPOSTENSION: >10 WEIGHT GAIN: >10 DRY MOUTH: >30 CONSTIPATION: >10 GI DISTRESS: <2
- Trimipramine (Surmontil): 10-150 mg, half-life 7-30 h, NA: ++ 5HT: + SEDATION: >30 ORTHOSTATIC HYPOSTENSION: >10 WEIGHT GAIN: >10 DRY MOUTH: >10 CONSTIPATION: >10 GI DISTRESS: <2
- Imipramine (Tofranil): 10-150 mg, half-life 4-34 h, NA: +++ 5HT: +++ SEDATION: >10 ORTHOSTATIC HYPOSTENSION: >30 WEIGHT GAIN: >10 DRY MOUTH: >30 CONSTIPATION: >10 GI DISTRESS: >10
- Clomipramine (Anafranil): 10-150 mg, half-life 17-37 h, NA: +++ 5HT: ++++ SEDATION: >2 ORTHOSTATIC HYPOSTENSION: >10 WEIGHT GAIN: >10 DRY MOUTH: >30 CONSTIPATION: >10 GI DISTRESS: >10
- Desipramine (Norpramin): 10-150 mg, half-life 12-76 h, NA: ++++ 5HT: ++ SEDATION: >2 ORTHOSTATIC HYPOSTENSION: >2 WEIGHT GAIN: >2 DRY MOUTH: >10 CONSTIPATION: >2 GI DISTRESS: >2
- Nortriptyline (Aventyl): 10-100 mg, half-life 13-88 h, NA: +++ 5HT: +++ SEDATION: >2 ORTHOSTATIC HYPOSTENSION: >2 WEIGHT GAIN: >2 DRY MOUTH: >10 CONSTIPATION: >10 GI DISTRESS: <2

### Serotonin/Norepinephrine Reuptake Inhibitors
- Venlafaxine (Effexor): 37.5-225 mg, half-life 3-7 (parent) 9-13 (metabolite), NA: ++ 5HT: +++ SEDATION: >10 ORTHOSTATIC HYPOSTENSION: >10 WEIGHT GAIN: <2 DRY MOUTH: >10 CONSTIPATION: >10 GI DISTRESS: >10
- Duloxetine (Cymbalta): 60-120 mg, half-life 10 h, NA: ++++ 5HT: ++++ SEDATION: >10 ORTHOSTATIC HYPOSTENSION: <10 WEIGHT GAIN: <2 DRY MOUTH: >10 CONSTIPATION: >10 GI DISTRESS: >10
Anticonvulsants

• Good evidence for analgesic action in neuropathic pain
• On the basis of ability to ↓ neuronal excitability “neuromodulators”
• Mechanisms of action vary among agents
  – Sodium or calcium channel blockade
<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Dose mg/day</th>
<th>Mech</th>
<th>Indication</th>
<th>SE</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>1200-3600</td>
<td>N-type voltage gated Ca++ blocker</td>
<td>PHN DN Mixed neuropathic</td>
<td>Dizziness Sedation Ataxia Confusion</td>
<td>Does not require metabolism in the liver</td>
</tr>
<tr>
<td></td>
<td>(1800-2400)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150-600</td>
<td>N-type voltage gated Ca++ blocker</td>
<td>PHN DN FM Spinal cord injury</td>
<td>Dizziness Somnolence Nausea</td>
<td>Analgesic effect within 3 days, no liver metabolism</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200-2000</td>
<td>Na+ channel blocker</td>
<td>TN</td>
<td>Sedation Dizziness Rash</td>
<td>Do CBC and liver function</td>
</tr>
<tr>
<td></td>
<td>(400-800)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>200-400</td>
<td>Na+ channel blocker</td>
<td>TN DN Post stroke pain Spinal cord injury</td>
<td>Mild rash to serious dermatologic reactions***</td>
<td>Do CBC and liver function</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>600-1200</td>
<td>Na+ channel blocker</td>
<td>TN</td>
<td>Sedation Headache Dizziness Rash</td>
<td>Do CBC and liver function</td>
</tr>
<tr>
<td><em>Ketoanalog of carbamazepine</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>50-200</td>
<td>Na+ Ca++ channel blocker Potentiate GABA Blocks glutamate</td>
<td>Migraine prophylaxis (3 large negative trials in DN)</td>
<td>Paresthesia Fatigue Nausea Dizziness Ataxia Metab acidosis</td>
<td>Modest effect, only 1 less migraine per month in 3 large RCTs Monitor serum bicarb</td>
</tr>
</tbody>
</table>
Anticonvulsants
Summary

• Good when you suspect a neuropathic component, also approved for fibromyalgia
• Best evidence for gabapentin and pregabalin in PHN and DN
• Carbamazepine (maybe oxcarbazepine) is still best for treatment of trigeminal neuralgia
• Secondary role for Lamotrigine TN, DN
Opioids

- Critical in the management of acute and cancer pain
- Prevention of chronic pain
- Appropriate in 18% of people with chronic pain conditions
Opioids

Mechanism of Action

• Linked to G proteins (inhibit adenylyl cyclase activity)
• Close voltage gated Ca channels on presynaptic nerve terminals
  – ↓calcium influx
  – ↓neurotransmitter release
• Open K channels
  – Hyperpolarization
  – Decrease neuronal excitability
  – Inhibit postsynaptic neurons
• Overall effect is inhibitory
GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

IMPROVING PRACTICE THROUGH RECOMMENDATIONS

CDC's Guideline for Prescribing Opioids for Chronic Pain is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

1. Nonpharmacological therapy and nonopioid pharmacological therapies are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacological therapies and nonopioid pharmacological therapies, as appropriate.

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain reduction, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is a clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

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"One Size Fits All" Doesn't Fit When It Comes to Long-Term Opioid Use for People with Chronic Pain

M. E. Lynch & J. Katz

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The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

Malmatler
Jason Buxton
Associate Professor, Department of Anesthesiology
Associate Professor, Department of Health Research Methods, Evidence, and Impact
McMaster University, N0C 2109
1200 Main St. West, Hamilton, Ontario, Canada, L8S 4L3
buxtonj@mcmaster.ca
Opioids
For Chronic Non-cancer Pain
the Evidence:

- 96 RCTs involving 26,169 participants
- Evidence from high quality studies showed opioid use was associated with statistically significant but small improvements in pain and physical functioning
Specific opioid agonists

- **Phenanthrenes**
  - Morphine, hydromorphone, oxycodone, codeine
- **Phenylpiperidines**
  - Fentanyl, sufentanyl, meperidine
- **Phenylheptylamines**
  - Methadone
Initiating a trial of opioid

• Which agent?
• Dosing:
  – Start low, go slow
  – Time contingent
  – Regular or long acting
• Side effects:
  • Sedation
  • Constipation
  • Nausea, sweating, itching, swelling
  • Endocrine? HPG and HPA suppression, thyroid?
Adverse effects in context

• Addiction: In appropriately screened patients low risk
  – If no past history of substance use disorder low risk
  – Important to screen for risk and provide appropriate structure
    • Regular follow-up and documentation
    • If needed contracts, urine screening, daily dispensing
## Liaison Committee on Pain and Addictions Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Addiction                 | A primary, chronic, neurobiologic disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following:  
  • Impaired control over drug use  
  • Compulsive use  
  • Continued use despite harm  
  • Craving                                                                                                                                  |
| Physical dependence       | A state of adaptation manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist |
| Tolerance                 | A state of adaptation in which exposure to the drug results in changes that result in a diminution of one or more of the drug’s effects over time |
Dual Action Opioids

- **Tramadol**
  - Weak opioid
  - Monoaminergic effects

- **Methadone**
  - Strong opioid
  - NMDA antagonist
  - Monoaminergic
• **RCTs of Combinations**

  - Pregabalin+duloxetine in fibro, 2016
  - Morphine+nortriptyline, 2015
  - NTI+gabapentin in NP, 2009
  - Morphine+gabapentin in NP, 2005
## Topicals

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Pennsaid (diclofenac) Voltaren emugel</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Zostrix</td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline 2-4% &amp; Ketamine (1-2%)</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Topical A OTC Topical CBD/THC</td>
</tr>
</tbody>
</table>
Summary

• Pharmacotherapy should be used along with active strategies

• Medications for chronic pain
  – Acetaminophen and NSAIDS
  – Tricyclic and SNRI antidepressants
  – Anticonvulsants
    • gabapentin, pregabalin, carbamazepine
  – Opioids and Cannabinoids