Non opioid pharmacologic treatments for pain

Lynn Kohan MD
University of Virginia
Objectives

• Review non-opioid medications that can be used to treat neuropathic and non-neuropathic pain
• Understand how co-morbidities might alter prescribing
CASE

• Pt with multiple co-morbidities
  • CKD—GFR 45
  • DM with PDN
  • HTN
  • s/p recent MI
  • H/O ETOH abuse
Complaints

• PDN
• Axial LBP—mild moderate multilevel spondylosis
• Painful knee OA—moderate tricompartmental OA
What are next steps?

• Nociceptive pain
  • Knee OA
  • Facet arthropathy

• Neuropathic pain
  • PDN
HHS task force
Non-Neuropathic Pain, Non-Cancer Pain

• **NSAIDs and acetaminophen** 1\textsuperscript{st} line classes of medications following standard dosing schedules.

• Further classes of medication depend on the patient’s response and can include (depending on specific pain syndromes)
  • Muscle relaxants (e.g., tizanidine, baclofen)
  • **Topical agents** in addition to other multimodal approaches.
  • Additional consideration should be given to **SNRIs** indicated for chronic musculoskeletal pain.
HHS task force - Neuropathic pain

Consider anti-neuropathic medication

- TCAs
- Anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, oxcarbazepine)
- SNRIs (e.g., duloxetine, venlafaxine)
- Topical analgesics, such as lidocaine and capsaicin.
Health and Human Services Task Force Recommendations

NSAIDS

- Choice may matter.

<table>
<thead>
<tr>
<th>Group</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid derivates</td>
<td>Acetylsalicylic acid (Aspirin)</td>
</tr>
<tr>
<td></td>
<td>Sodium salicylate</td>
</tr>
<tr>
<td></td>
<td>Diflunisal</td>
</tr>
<tr>
<td></td>
<td>Salicylsalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td></td>
<td>Olsalazine</td>
</tr>
<tr>
<td>Para-aminophenol derivatives</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Indol and indene acetic acid</td>
<td>Indomethacyn</td>
</tr>
<tr>
<td></td>
<td>Sulindac</td>
</tr>
<tr>
<td></td>
<td>Etodolac</td>
</tr>
<tr>
<td>Hetercaryl acetic acid</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td></td>
<td>Neproxen</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
</tr>
<tr>
<td></td>
<td>Fenoprofen</td>
</tr>
<tr>
<td></td>
<td>Oxaprozin</td>
</tr>
<tr>
<td>Anthranilic acid (fenemates)</td>
<td>Mefenamic acid</td>
</tr>
<tr>
<td></td>
<td>Meclofenamic acid</td>
</tr>
<tr>
<td>Enolic acid derivatives (oxicams)</td>
<td>Piroxicam</td>
</tr>
<tr>
<td></td>
<td>Tenoxicam</td>
</tr>
<tr>
<td></td>
<td>Meloxicam</td>
</tr>
</tbody>
</table>

Kowalski 2015
Searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the reference lists of relevant articles for trials published between Jan 1, 1980, and Feb 24, 2015, with at least 100 patients per group.

Pt’s with knee and/or hip OA
• Conclusions:
  • NSAIDS are effective in treating OA pain.
  • Diclofenac 150mg/day was the most effective in terms of pain and physical function.

NSAID Risks

FIGURE: RELATIVE RISK OF UPPER GI COMPLICATIONS (A), MYOCARDIAL INFARCTION (B), AND ACUTE RENAL FAILURE (C) BETWEEN LOW-MEDIUM AND HIGH NSAID DOSES\textsuperscript{2,8,19}

(A) Upper Gi Complications

\begin{align*}
\text{Low-medium dose} & : 2.4 \\
\text{High dose} & : 4.9
\end{align*}

(B) Myocardial Infarction

\begin{align*}
\text{Low-medium dose} & : 1.23 \\
\text{High dose} & : 1.57
\end{align*}

(C) Acute Renal Failure

\begin{align*}
\text{Low-medium dose} & : 2.51 \\
\text{High dose} & : 3.38
\end{align*}

Gi = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

Topical NSAIDS

• Advantages
  • Strong Evidence in support of topical NSAIDS
    • Osteoarthritis Research Society International (OARSI) guidelines (2019)
      • High quality evidence, large # of pt’s showed modest benefits over 3 months
  • Minimal adverse effects
    • Mild skin reactions, low systemic absorption

Topical NSAIDs

  - Strongly recommended for patients with GI or CV risk factors

Good for our pt.
Non-NSAID Topicals

- Lidocaine patch 5%
- Capsaicin
- Compound formulations

- Better for well localized neuropathic pain.
- Beyond the scope of this lecture.
Anticonvulsants

First Generation drugs:
Phenytoin (Dilantin)
Valproic Acid (Depakote)
Carbamazpine (Tegretol)

Second Generation Drugs:
Gabapentin (Neurontin)
Pregabalin (Lyrica)
Lamotrigine (Lamictal)
Oxcarbazipine (Trileptal)
Topiramate (Topamax)
Felbamate (Felbatol)
Levetiracetam (Keppra)
Zonisamide (Zonegran)
Vigabatrin (Sabril)
Tiagabine (Gabitril)
How to choose which anticonvulsant

• Efficacy
• Co-morbidities
• Polypharmacy
• Our pt is on gabapentin 300mg tid.

• Are there concerns about dosing and/or efficacy?

• It is not properly renally dosed
Renal dosing

### Table 1

Recommended dose adjustments based on varying degrees of renal impairment

<table>
<thead>
<tr>
<th>CrCl cutoff</th>
<th>Gabapentin</th>
<th>Pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–59 mL/min</td>
<td>700 mg BID</td>
<td>150 mg BID</td>
</tr>
<tr>
<td>15–29 mL/min</td>
<td>700 mg once a day</td>
<td>75 mg BID</td>
</tr>
<tr>
<td>&lt;15 mL/min</td>
<td>300 mg once a day</td>
<td>75 mg once a day</td>
</tr>
</tbody>
</table>

Supplemental doses in hemodialysis:
- Gabapentin: 100–300 mg post dialysis
- Pregabalin: 75–150 mg post dialysis

**Abbreviation:** CrCl, creatinine clearance.

<table>
<thead>
<tr>
<th>Renal Function Creatinine Clearance (mL/min)</th>
<th>Total Daily Dose Range (mg/day)</th>
<th>Dose Regimen (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>900-3600</td>
<td>300 TID 400 TID 600 TID 800 TID 1200 TID</td>
</tr>
<tr>
<td>&gt;30-59</td>
<td>400-1400</td>
<td>200 BID 300 BID 400 BID 500 BID 700 BID</td>
</tr>
<tr>
<td>&gt;15-29</td>
<td>200-700</td>
<td>200 QD 300 QD 400 QD 500 QD 700 QD</td>
</tr>
<tr>
<td>15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100-300</td>
<td>100 QD 125 QD 150 QD 200 QD 300 QD</td>
</tr>
</tbody>
</table>

**Post-Hemodialysis Supplemental Dose (mg)<sup>b</sup>**

| Hemodialysis | 125<sup>b</sup> | 150<sup>b</sup> | 200<sup>b</sup> | 250<sup>b</sup> | 350<sup>b</sup> |

<sup>a</sup> For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

<sup>b</sup> Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.
• What is a high enough dose to determine efficacy?
  • 1800 mg/day (generally as 600mg tid) is minimum effective dose

• So should we try pregabalin instead?

Gabapentin and Pregabalin

• How are they similar and how are they different?
<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Indication</th>
<th>Side effects</th>
<th>Interaction</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Alpha 2 delta subunit of the Ca channel</td>
<td>Neuropathic pain, chronic pain</td>
<td>LE edema, weight gain, sedation, dizziness, N.V, ataxia, fetal malformation, bone demineralization, Stevens-Johnson Syndrome</td>
<td>Antacids (limit bioavailability) Minimal drug interactions</td>
<td>renal</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Alpha 2 delta subunit of the Ca channel</td>
<td>Neuropathic pain, fibromyalgia</td>
<td>LE edema, weight gain, sedation, dizziness, N.V, ataxia, fetal malformation, bone demineralization, Stevens-Johnson Syndrome</td>
<td>Antacids (limit bioavailability) Minimal drug interactions</td>
<td>renal</td>
</tr>
</tbody>
</table>
Bioavailability

**Gabapentin**
- Does not have linear bioavailability
- Therefore absolute bioavailability decreases from 60-33% when doses increase from 900mg to 3600mg

- **Pregabalin**
  - Linear pharmacokinetics are a range of doses
  - Greater bioavailability >90%
  - May explain lower reported side effects
Gabapentin to pregabalin conversion.

Dose substitution was carried out as follows:

<table>
<thead>
<tr>
<th>Daily Dose of Gabapentin Pre-Switch (mg/day)</th>
<th>Daily Dose of Pregabalin Post-Switch (mg/day) (Using Twice Daily Dosing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–900</td>
<td>150</td>
</tr>
<tr>
<td>901-1500</td>
<td>225</td>
</tr>
<tr>
<td>1501-2100</td>
<td>300</td>
</tr>
<tr>
<td>2101-2700</td>
<td>450</td>
</tr>
<tr>
<td>2700 or higher</td>
<td>600</td>
</tr>
</tbody>
</table>

Table 1
Recommended dose adjustments based on varying degrees of renal impairment

<table>
<thead>
<tr>
<th>CrCl cutoff</th>
<th>Maximum recommended dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–59 mL/min</td>
<td>Gabapentin1 700 mg BID</td>
</tr>
<tr>
<td></td>
<td>Pregabalin2 150 mg BID</td>
</tr>
<tr>
<td></td>
<td>100 mg TID</td>
</tr>
<tr>
<td>15–29 mL/min</td>
<td>700 mg once a day</td>
</tr>
<tr>
<td></td>
<td>75 mg BID</td>
</tr>
<tr>
<td></td>
<td>50 mg TID</td>
</tr>
<tr>
<td>&lt;15 mL/min</td>
<td>300 mg once a day</td>
</tr>
<tr>
<td></td>
<td>75 mg once a day</td>
</tr>
<tr>
<td>Supplemental doses in hemodialysis</td>
<td>100–300 mg post dialysis</td>
</tr>
<tr>
<td></td>
<td>75–150 mg post dialysis</td>
</tr>
</tbody>
</table>

Abbreviation: CrCl, creatinine clearance.
Gabapentin Efficacy
• Search of RCTs in Medline and Embase between 2014-2017

• Gabapentin at doses of **1800-3600mg** can provide **good pain relief** to some people with **PHN and PDN**

• Evidence for **other subtypes of neuropathic pain** is **very limited**

• Overall: Moderate quality of evidence

• **No difference** in serious effects compared to placebo.
• **Somnolence and dizziness** more common with gabapentin than placebo.
Pregabalin 2019 Cochrane Review

• Best evidence for **PHN and PDN**
  • Effective dose **300mg**
• May help pt’s with post-traumatic neuropathic pain (moderate quality)
• May help with central neuropathic pain (low quality)
• Studies show **NO EVIDENCE** of benefit for 600mg pregabalin in **HIV neuropathy** (2 studies) (moderate quality)
• **Limited evidence of benefit in neuropathic back pain or sciatica, neuropathic cancer pain, or polyneuropathy**

Pregabalin efficacy—Cochrane Review

• Somnolence and dizziness more common than placebo

• Serious side effects were no different than placebo
### Calcium channel α2-δ ligands

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Titration Schedule</th>
<th>Duration for Titration</th>
<th>Side Effects</th>
<th>Renal Insufficiency</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>100–300 mg at bedtime or 100–300 mg 3 times daily</td>
<td>Increase by 100–300 mg every 1–7 d as tolerated, until pain relief</td>
<td>3–8 wk for titration + 2 wk at maximum dose</td>
<td>Sedation, dizziness, peripheral edema</td>
<td>Renal insufficiency</td>
<td>Improvement of sleep disturbance, no clinically significant drug interactions</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>50 mg 3 times daily or 75 mg twice daily</td>
<td>Increase to 300 mg daily after 3–7 d, then by 150 mg every 3–7 d as tolerated, until pain relief</td>
<td>4 wk</td>
<td>Sedation, dizziness, peripheral edema</td>
<td>Renal insufficiency</td>
<td>Improvement of sleep disturbance, improvement of anxiety, no clinically significant drug interactions</td>
</tr>
</tbody>
</table>

Side effects

• Gabapentin and pregabalin
  • Sedation and dizziness common
  • Increasing evidence of misuse and abuse
    • Euphoric effects
    • Increase risk amongst current or past opioid or benzo users

• Our pt has an active history of ETOH abuse. Does this matter?

Goodman CW and Brett AS. NEJM 2017
Gabapentin/pregabalin abuse?

**The Gabapentin High**
Gabapentin users have reported a range of subjective experiences:
- Euphoria (golden bliss of the world)
- Enhanced sociability
- A state of relaxation, but also 'zombie-like' effects
- A sedative/opiate-like buzz with no discernible comedown
- Psychedelic/MDMA-like effects

**Gabapentin Abusers Experience Euphoria and Calm**
- Gabapentin frequently misused with other substances:

  **Opioids—56% (Or More)**

  **Muscle Relaxants Or Anxiety Medications—27%**

  **Other Illicit Substances—8.6%**

And The Best Rehab Centers For Treatment
WHO'S AT RISK OF LYRICA ADDICTION?

- The relaxing nature of Pregabalin can cause a psychological attachment to those in high stress professions.

- Studies show that the potential for Lyrica abuse is similar to that of Valium.
Gabapentin and pregabalin: controlled substances

• Large increase in gabapentin prescribing
  • 2012-2016 increased by 64%
  • In 2017, 68 million prescriptions
  • 10\textsuperscript{th} most commonly prescribed medicine
  • Classified as Schedule V controlled substance in Kentucky, Michigan, Tennessee, and \textbf{Virginia}

• Pregabalin
  • Classified as controlled (Schedule V) since its release on the market in 2005

Peckman AM Subst Abuse 2018
Providers Share Experience with Patients’ Gabapentinoid Abuse

How frequently have you seen abuse of pregabalin/gabapentin in your pain patient population (eg, early refill requests, euphoria)?

- Pregabalin:
  - Not at all: 60%
  - Rarely: 34%
  - About half of the time: 3%
  - Most of the time: 3%

- Gabapentin:
  - Not at all: 56%
  - Rarely: 29%
  - About half of the time: 9%
  - Most of the time: 6%

Polls conducted on practicalpainmanagement.com (as of 5/15/2019)
Is it really dangerous?

• Gabapentinoid overdoses can range from benign symptoms to death

• Evoy et al.
  • 6 cases of pregabalin overdose
  • 31 cases of gabapentin overdose

Regulations

Scheduled Drug

- Kentucky
- Tennessee
- Virginia
- Michigan
- NY trying to make schedule VI

PMP

- Minnesota
- Ohio
- Virginia
- Wyoming
- West Virginia
- Massachusetts
- N Dakota
- Nebraska
- NJ
So what can you do?

- Monitor for
  - Changes in pt’s mood
  - Frequent requests for early refills
  - Requests for rapid increases in doses
  - Multiple prescribers
  - Asking to pay out of pocket instead of through insurance

- Can monitor for gabapentin in urine
Our pt?

- I would still try to do a switch to pregabalin and monitor him closely.
Other Anti-convulsants?

- **Topiramate**
  - Best when concomitant HA disorder
  - Good for weight loss
  - Good for ETOH dependence
  - Always ask about glaucoma and kidney stone history
  - Dose: Start at 25 or 50mg qhs. Increase by 25 or 50 mg each week until you are at 50mg to 100mg bid.
  - Can increased up to 200mg bid.
  - Max dose 400mg
  - Decrease dose in CKD
    - CR Cl 10-70—decrease dose 50%
    - CR Cl <10—decrease dose 75%
  - Caution advised in liver disease
Other Anti-convulsants?

• **Oxcarbazepine**
  • Best for TN
  • Monitor Na levels
  • Dose: Start at 75 or 150mg qhs. Increase q week until you are at 300mg bid.
  • Max dose 2400mg
  • Decrease dose in CKD
    • CR Cl 10-50—decrease dose by 25%
    • CR Cl <10 decrease dose by 50%
  • Mild-mod liver disease—no adjustment
  • Severe liver disease—caution
Other Anti-convulsants?

- **Zonisamide**
  - Most similar to topiramate
  - Advantage of once a day dosing
  - Monitor Na
  - Weight loss
  - Dose: Start at 25-50mg qday. Increase by 25-50mg q week until you are at 300mg q day. Max dose 600mg.
  - CKD—caution, titrate slowly
  - Liver disease--caution, titrate slowly
ACMs

• Start low and go slow
• Understand pharmacokinetics and MOA differences
• Can combine more than one, but choose one with different MOA
• Titrate to appropriate dose before considered failed
• Push dose to efficacy or side effects
• Often max effectiveness of neuropathic pain is found at 50-100% of the anti-epileptic dose.
Antidepressants

• TCAs and SNRI’s most efficacious in pain as opposed to SSRIs

• TCA   NNT 2-3
• SNRI   NNT 4-5
• Anticonvulsants NNT 4-7
How to choose?

• Ask about sleep
• If on SSRI, ask how well it works for them
• Ask about other serotonin meds
  • (remember cyclobenzaprine, triptans, methadone, ultram)
  • (be cognizant of P450 effects—trazadone, Wellbutrin)
• Recognize who is at risk for side effects
TCAs

Secondary TCAs

• Desipramine
• **Nortriptyline**
• Protriptyline

Tertiary TCAs

• Imipramine
• Clomipramine
• Trimipramine
• **Amitriptyline**
• Butriptyline
• Doxepin
• Dosulepin
Mechanism of action of tricyclic antidepressants
TCAs

- Smalls studies show efficacy in **PDN, PHN, and central pain**
- Numerous studies show efficacy in **HA**
- Analgesic effect is seen whether pt is depressed or not
- Analgesia does not correlate with resolution of depression

- Analgesia takes days to weeks at doses of 25-150mg/day
  - Faster and at lower doses than typical for depression

Burch R. Curr Treatment Opin Neurol 2019
Welsch WJ et al Cochrane Database Syst Rev 2018
### Table I: Considering Comorbidities with TCAs and SNRIs.

<table>
<thead>
<tr>
<th>Medication class</th>
<th>May be beneficial for</th>
<th>May be harmful for</th>
<th>Renal/Hepatic dose adjustments or contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs(^{14})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Elderly</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Neuropathic pain</td>
<td>Dementia/cognitive impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low back pain</td>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibromyalgia</td>
<td>Glaucoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbid mental health diagnoses</td>
<td>BPH seizures</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNRIs(^{5,7,8,10,12,13,15-20})</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low back pain</td>
<td>Hypertension</td>
<td>Duloxetine avoid CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>Neuropathic pain</td>
<td>QTc prolongation (venlafaxine)</td>
<td>Avoid duloxetine with chronic liver disease, cirrhosis, heavy alcohol use</td>
</tr>
<tr>
<td></td>
<td>Fibromyalgia</td>
<td>Bleeding when combined with other meds</td>
<td>Reduce venlafaxine 25 to 50% with mild to moderate renal impairment</td>
</tr>
<tr>
<td></td>
<td>Comorbid mental health diagnoses</td>
<td>Duloxetine with heavy alcohol use</td>
<td>Reduce venlafaxine dose 50% with severe renal impairment</td>
</tr>
</tbody>
</table>

---

TCAs = tricyclic antidepressants. SNRIs = serotonin norepinephrine reuptake inhibitors.

---

Kominek C. Considering comorbidities when selecting medications for chronic pain management. PPM 18(13).
### Table 1
Prescribing recommendations for first-line medications and for opioid agonists

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Starting Dosage</th>
<th>Titration</th>
<th>Maximum Dosage</th>
<th>Duration of Adequate Trial</th>
<th>Major Side Effects</th>
<th>Precautions</th>
<th>Other Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressant medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary amine TCAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline(^a)</td>
<td>25 mg at bedtime</td>
<td>Increase by 25 mg daily every 3–7 d, as tolerated, until pain relief</td>
<td>150 mg daily; if blood level of active drug and its metabolite is &lt;100 ng/mL (mg/mL), continue titration with caution</td>
<td>6–8 wk with ≥2 wk at maximum tolerated dosage</td>
<td>Sedation, dry mouth, blurred vision, weight gain, urinary retention</td>
<td>Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol</td>
<td>Improvement of depression, improvement of insomnia, low cost</td>
</tr>
<tr>
<td>Desipramine(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSNRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30 mg once daily</td>
<td>Increase to 60 mg once daily after 1 wk</td>
<td>60 mg twice daily</td>
<td>4 wk</td>
<td>Nausea</td>
<td>Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol</td>
<td>Improvement of depression</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg once or twice daily</td>
<td>Increase by 75 mg each week, as tolerated until pain relief</td>
<td>225 mg daily</td>
<td>4–6 wk</td>
<td>Nausea</td>
<td>Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation</td>
<td>Improvement of depression</td>
</tr>
</tbody>
</table>

TCAs

- Doses
  - Nighttime


<table>
<thead>
<tr>
<th>Medications</th>
<th>Antidepressant dose</th>
<th>Pain dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>100–300 mg daily</td>
<td>25–150 mg daily</td>
</tr>
<tr>
<td>Nortripyline</td>
<td>75–150 mg daily</td>
<td>25–150 mg daily</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60–120 mg daily</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75–225 mg daily</td>
<td>37.5–225 mg daily</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50–100 mg daily</td>
<td>200–400 mg daily</td>
</tr>
</tbody>
</table>
SNRIs

• 4 available in the US

• **Venlafaxine** (FDA approved for depression)
• Desvenlafaxine (FDA approved for depression)
• **Duloxetine** (FDA approved for FM, MSK, neuropathic pain)
• Milnacipran (FDA approved for FM)
Antidepressants

• TCA (anticholinergic and sedative)
  • Side effects
    • Postural hypotension
    • Dry mouth
    • Sedation
    • Concern in elderly
  • Other risks
    • Serotonin syndrome
    • Cardiac conduction abnormalities
    • Lethal overdose

Tricyclic Antidepressants: Adverse Effects

• Commonly reported AEs (generally anticholinergic):
  - blurred vision
  - cognitive changes
  - constipation
  - dry mouth
  - orthostatic hypotension
  - sedation
  - sexual dysfunction
  - tachycardia
  - urinary retention

• Fewest AEs:
  - Desipramine
  - Nortriptyline
  - Imipramine
  - Doxepin
  - Amitriptyline

• Most AEs:
  - Desipramine
  - Nortriptyline
  - Imipramine
  - Doxepin
  - Amitriptyline
SNRI’s

• MOA

• Presynaptic inhibition of reuptake of SE and NE in pain inhibitory pathways

• Peripheral mechanisms involving β2-adrenergic receptors and the opioid system

• Mood elevating effects of the meds may also contribute to improved pain scores

SNRIs

• Shown to be effective in numerous neuropathic pain disorders
• Analgesic effect independent from effect on mood (< 12% of effect of duloxetine at 60 or 120mg was attributed to improved mood or anxiety)
• Considered 1st line along with TCAs and gabapentenoids

Duloxetine Overall Efficacy

• Strongest evidence for **PDN and Fibromyalgia**

• Strong evidence also for **Knee OA**

• Adverse effects common but not serious
  • Sedation, nausea, constipation, HA, dry mouth, dizziness

• **NNH for 60mg for all neuropathic conditions was 18.**

Duloxetine overall efficacy

• Neuropathic pain:
  • 120 mg not more efficacious than 60mg and was associated with more side effects

• OA pain
  • Pt’s may need higher doses (even up to 120 mg) to be efficacious

Getting back to our pt.

• Likely would avoid TCAs given recent MI

• What about duloxetine?
  • Renal adjustment not necessary bc his GFR is >30
  • Not recommended in liver failure
Venlafaxine

• Phenylethylamine antidepressant
  • Blocks serotonin and norepinephrine
  • May also exert analgesia via both opioid and adrenergic effects
  • Blocks serotonin>NE>dopamine (increasing doses)

• Less commonly prescribed for pain than duloxetine and less compelling evidence

• Effective dose for pain:
  • 150-225 mg per day
Venlafaxine

• Caution
  • Htn, seizures

• Adverse effects:
  • Itching, chills, sweating, vertigo, HA, GI complaints, orthostatic dizziness, lethargy, hot flashes, difficulty urinating.
  • Higher doses can increase htn
<table>
<thead>
<tr>
<th>Medication</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venlafaxine</strong></td>
<td><strong>Cochrane Review—6 RCTs</strong></td>
</tr>
<tr>
<td></td>
<td>4 studies were cross over trials</td>
</tr>
<tr>
<td></td>
<td>Studied doses of 50-225 mg daily</td>
</tr>
<tr>
<td></td>
<td>Most pt’s had PDN</td>
</tr>
<tr>
<td></td>
<td>All were small sample size and of short duration</td>
</tr>
<tr>
<td><strong>Conclusion:</strong></td>
<td>Demonstrated benefit but no need to change current neuropathic guidelines in favor of venlafaxine</td>
</tr>
<tr>
<td><strong>Desvenlaxine</strong></td>
<td><strong>Allen et al 2017</strong></td>
</tr>
<tr>
<td></td>
<td>Multi-centered, randomized, placebo-controlled study</td>
</tr>
<tr>
<td></td>
<td>Not found to be effective in treating FM</td>
</tr>
<tr>
<td></td>
<td>Trial stopped early bc no efficacy</td>
</tr>
<tr>
<td><strong>Conclusions:</strong></td>
<td>should not be used prior to trial of duloxetine or TCA</td>
</tr>
<tr>
<td><strong>Nausea and dizziness common side effects</strong></td>
<td>Allen et al 2014</td>
</tr>
<tr>
<td></td>
<td>Randomized, placebo-controlled study</td>
</tr>
<tr>
<td></td>
<td>Doses of 50, 100, 200, 400 mg vs placebo for PDN</td>
</tr>
<tr>
<td></td>
<td>Doses of 200 and 400mg daily effective at relieving pain after 13 weeks</td>
</tr>
</tbody>
</table>

Antidepressants

• Caution CYP450 interactions
  • 1A2, 2D6, 3A4
So final plan:

- Sometimes difficult to prescribe medications in patients with co-morbidities.
- Tx choices can often be limited
- Can try topicals
- Would switch from 300mg gabapentin tid to pregabalin 150mg bid
  - Less risk for side effects given pt’s comorbidities
  - OK dosing in light of his liver and renal dysfunction
• Remember to give therapy a chance to work
• At least 1 month trial at dose often necessary
Take home points

• Non-opioid Medications are available
  • Proven efficacy for various neuropathic and non-neuropathic pain disorders
  • Check for co-morbidities
  • Check to make sure that dose is considered efficacious before considered failed trial
  • Check to make sure trial duration was adequate before considering failed trial
  • Try 1 new systemic medication at a time
Future

• Migraine
  • Calcitonin gene related peptide antagonists
  • Serotonin agonists

• Neuropathic pain
  • Angiotensin II type 2 receptor antagonists
  • Selective sodium-channel blockers (Nav 1.7)
  • Vanilloid receptor antagonists for neuropathic pain
Future

• Biomarkers
  • Use of biomarkers to predict likelihood that a treatment will be effective by targeting the pain mechanisms in each pt

• Molecular profiling in rare pain conditions cause by gene variants that code for specific sodium channels

• Brain imaging to assess pain and emotion
References

• Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states—maybe it is all in their head. *Best Pract Res Clin Rheumatol*. 2011;25(2):141-154. PMID: 22094191


References


References


• Toth et al. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Medicine 2010; 11: 456–465

References


• Burch R. Curr Treatment Opin Neurol 2019

• Welsch WJ et al Cochrane Database Syst Rev 2018

• Chou R et al. Cochrane Database Syst Rev 2016
References

- Kominek C. Considering comorbidities when selecting medications for chronic pain management. PPM 18(13).
References


• Di Stefano G, Truini A, Cruccu G. Current and innovative pharmacological options to treat typical and atypical trigeminal neuralgia. Drugs 2018;78:1433-42.

References


References

References


References


Other resources for home
Table 2. Nonopioid Analgesic Agents for Acute and Chronic Pain. *

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Indication</th>
<th>Side Effects and Risks</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>650 mg orally every 4 to 6 hr; maximum dose, 4000 mg/day; also available as injection</td>
<td>Mild-to-moderate pain</td>
<td>Overdose can cause liver damage</td>
<td>No evidence of an effect on neuropathic pain</td>
</tr>
<tr>
<td>Aspirin</td>
<td>350–650 mg orally every 4 hr; maximum dose, 1600 mg/day; individual doses for rheumatic diseases</td>
<td>Mild pain (temporary use), inflammatory rheumatic diseases</td>
<td>Nausea, dyspepsia, abdominal pain, bleeding tendency, tinnitus, headache, dizziness, insomnia, hypersensitivity reactions, risk of gastrointestinal bleeding</td>
<td>Contraindicated in patients with known hypersensitivity; should not be used in children under 16 yr of age (risk of Reyes's syndrome); no evidence of an effect on neuropathic pain</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Dose depends on the specific drug</td>
<td>Mid-to-moderate pain; pain associated with inflammation</td>
<td>Nausea, dyspepsia, diarrhea, constipation, headache, dizziness, somnolence, hypersensitivity reactions, risk of gastrointestinal bleeding, myocardial infarction, stroke</td>
<td>Contraindicated in patients with known hypersensitivity; recommended dose is the lowest effective dose for the shortest period; no evidence of an effect on neuropathic pain</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>25–150 mg orally once daily or in two divided doses; maximum single dose, 75 mg; daily doses above 75 mg should be used with caution in patients &gt; 65 yr of age</td>
<td>Neuropathic pain (first-line therapy), fibromyalgia, prevention of tension headache or migraine</td>
<td>Somnolence, tremor, dizziness, dry mouth, constipation, nausea, vomiting, increased risk of suicidal thoughts</td>
<td>Patients with poor metabolism of CYP2D6 require lower doses; abrupt discontinuation should be avoided; caution recommended in patients with recent myocardial infarction or cardiac rhythm disorders; caution required if used with other serotonergic agents</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60–120 mg orally once daily or in two divided doses</td>
<td>Neuropathic pain (first-line therapy), fibromyalgia, prevention of tension headache or migraine</td>
<td>Nausea, headache, dry mouth, somnolence, increased blood pressure, increased risk of suicidal thoughts</td>
<td>Abrupt discontinuation should be avoided; caution required if used with other serotonergic agents</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900–3600 mg orally in three divided doses</td>
<td>First-line therapy for neuropathic pain</td>
<td>Dizziness, somnolence, peripheral edema, fever, infection, nausea, lack of coordination, blurred vision, increased risk of suicidal thoughts</td>
<td>Dose adjustment required in patients with compromised renal function; misuse, abuse, and dependence have been reported</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300–600 mg/day orally in two divided doses</td>
<td>Neuropathic pain (first-line therapy), fibromyalgia, prevention of tension headache or migraine</td>
<td>Dizziness, somnolence, peripheral edema, fever, infection, nausea, weight gain, disorientation, blurred vision, increased risk of suicidal thoughts</td>
<td>Dose adjustment required in patients with compromised renal function; misuse, abuse, and dependence have been reported</td>
</tr>
<tr>
<td>Lidocaine, 1.8% or 5% patch</td>
<td>1-3 patches applied to intact skin for up to 12 hr</td>
<td>Peripheral neuropathic pain</td>
<td>Application site pain, pruritus, erythema, and skin irritation</td>
<td>Approved by FDA and EMA for postherpetic neuralgia only</td>
</tr>
<tr>
<td>Capsaicin, 8% patch</td>
<td>1-4 patches applied to intact skin for 30 or 60 min every 3 mo</td>
<td>Peripheral neuropathic pain</td>
<td>Application site pain and erythema, transient increase in blood pressure, risk of reduced sensation</td>
<td>Applied by a health care professional wearing nitrile gloves</td>
</tr>
</tbody>
</table>

* The drugs listed are those commonly used, but the list does not include all analgesics used for all pain conditions. CYP2D6 denotes cytochrome P-450 2D6, EMA European Medicines Agency, FDA Food and Drug Administration, and NSAID nonsteroidal antiinflammatory drug.
† Doses are given for adults.
‡ For a comprehensive list of side effects, risks, contraindications, and warnings, refer to the product information for each drug.
§ Other tricyclic antidepressants (imipramine, desipramine, and nortriptyline) have not been evaluated as extensively for the treatment of pain but may be associated with more acceptable side-effect profiles.
¶ The starting dose is lower.
<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (Neurontin, Horzont, Gralise®)</td>
<td>Postherpetic neuralgia</td>
<td>Blocks the α2δ subunit of calcium channel; blocks calcium influx; reduces excitatory amino acids (i.e., glutamate)</td>
<td>1200-3600 mg t.i.d.</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>Peripheral diabetic neuropathy, postherpetic neuralgia, fibromyalgia</td>
<td>Blocks the α2δ subunit of calcium channel; blocks calcium influx; prevents presynaptic release of neurotransmitters; reduces excitatory amino acids (i.e., glutamate)</td>
<td>75-300 mg/day</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Trigeminal neuralgia</td>
<td>Blocks sodium and calcium currents</td>
<td>400-1200 mg t.i.d.</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Neuropathic pain</td>
<td>Blocks sodium currents; reduces excitatory amino acids (i.e., glutamate)</td>
<td>300-600 mg t.i.d. (nightly for not generic)</td>
</tr>
<tr>
<td>Oxicarbamazepine (Trileptal)</td>
<td>Trigeminal neuralgia</td>
<td>Blocks sodium and calcium currents</td>
<td>300-1200 mg bid</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>Migraine prophylaxis</td>
<td>Blocks sodium currents; increases GABA; reduces excitatory amino acids (i.e., glutamate)</td>
<td>50-400 mg bid or nightly at bedtime</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>Trigeminal neuralgia</td>
<td>Blocks sodium currents; reduces excitatory amino acids (i.e., glutamate)</td>
<td>50-300 mg bid</td>
</tr>
<tr>
<td>Valproate (Depakote)</td>
<td>Migraine prophylaxis</td>
<td>Blocks sodium currents; increases GABA</td>
<td>500-1500 mg bid</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>Neuropathic pain; lancinating neuropathic pain</td>
<td>Increases GABA</td>
<td>0.5 to 2 or 3 mg nightly at bedtime</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>Peripheral diabetic neuropathy, fibromyalgia</td>
<td>Serotonin and norepinephrine reuptake inhibitor</td>
<td>20-60 mg/day</td>
</tr>
<tr>
<td>Milnacipran (Savella)</td>
<td>Fibromyalgia</td>
<td>Serotonin and norepinephrine reuptake inhibitor</td>
<td>100-200 mg/day</td>
</tr>
<tr>
<td>Venlafaxine (Generic)</td>
<td>Neuropathic pain</td>
<td>Serotonin and norepinephrine reuptake inhibitor</td>
<td>150-300 mg/day</td>
</tr>
</tbody>
</table>

* Oxcarbazepine is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

bid, twice a day; GABA, gamma-aminobutyric acid; t.i.d, three times a day
NNT

• Celecoxib 2.1
• TCA 2.1
• Ibuprofen 2.5
• Pregabalin 3.7
• Gabapentin 5.1
• Duloxetine 5.1
• Topical capsaicin (0.75/8%) 7/12