Adjuvant Analgesics

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Disclosures

- PsychU: consultant
- Otsuka pharmaceutical: consultant (Abilify Maintena, Rexulti)
- Litigation consultant: “Expert witness” for US DOJ & civilian cases
- Buckeye Community Health Plan: pharmacy & therapeutics committee
Objectives

- Review use of TCAs
- Review use of SSRIs
  - Treatment algorithm
- Review use of SNRIs
- Benzodiazepines – lack of evidence
  - The “opioids” of psychiatry
- Atypical antipsychotics

TCAs

- Most studied anti-depressants for pain, amitriptyline has the most evidence
- Dosing difference between pain (10-25mg/day) and anti-depressant/anxiolytic doses (150-300mg/day).
- Some patients may have pain relief at low doses, but others will require full anti-depressant doses for pain relief.
  - Inform patients they may experience pain relief before improvement in their mood.
- Start low (25 mg day) and titrate up slowly (25mg every 3 days).
TCAs

- Amitriptyline (5-HT > NE reuptake)
  - Very sedating, strongly anti-cholinergic
- Imipramine (5-HT > NE reuptake)
  - Moderately sedating, highest incidence of orthostatic hypotension
- Nortriptyline (NE > 5-HT reuptake)
  - Metabolite of amitriptyline, least likely to cause orthostatic hypotension
- Desipramine (NE > 5-HT reuptake)
  - Metabolite of imipramine, least anti-cholinergic side effects

SSRIs

- Disappointing for pain relief
  - Escitalopram may be the exception.
- Citalopram, fluoxetine and paroxetine have shown some statistically significant benefit but clinical improvement is very mild and NNT is high (~7).
- However, excellent medications for depression and anxiety.
Escitalopram & pain

- A 2010 randomized, non-blinded 12-week study, N=80, compared duloxetine 60mg daily vs escitalopram 20mg/day in patients with CLBP.¹
  - Both treatments were found to significantly improve pain at 12 weeks measured by VAS (-2.3 for escitalopram vs -2.45 for duloxetine) independent of mood effect.


SSRIs & bleeding

- ↑ risk of bleeding (GI bleeding, hemorrhagic stroke) alone and in combination with antiplatelet drugs²
  - SSRI + aspirin ↑ risk by 42%
  - SSRI + aspirin + clopidogrel ↑ risk by 57%
  - Effects begin as early as 7 days after initiation²
    - Intra-platelet concentrations of serotonin decrease by >80%³⁻⁵

Venlafaxine (Effexor)

- 5-HT, NE & DA reuptake inhibition
  - NE >150 mg/day, DA >225 mg/day
- Mild increases in blood pressure and heart rate
- Very short half-life, therefore can have severe discontinuation syndrome (dizziness, anxiety, dysphoria, insomnia, paresthesias)
  - Taper over 2-4 weeks
- Increased risk of serotonin syndrome with tramadol?
- Desvenlafaxine (Pristiq)
  - Active metabolite
  - Easier to titrate (50 – 200mg)
  - Depression response rates of only 43-60%, lower than 60-70% of most other antidepressants

Duloxetine (Cymbalta)

- "Balanced" 5-HT and NE reuptake inhibition
- Most FDA approvals for pain
- Must be dosed properly
  - 30mg PO QAM x 1 week, then 60mg PO QAM thereafter
  - Titrate up by 30mg increments to 120mg max
- May take 1-3 weeks for any improvement in pain and may need up-titration, therefore consider treatment for 8-12 weeks for a full therapeutic trial.
Milnicipran (Savella)

- Approved for fibromyalgia in the US, for depression in Europe
- 3x more NE than 5-HT reuptake inhibition
- Must be titrated slowly up to initial goal of 50 mg BID.
  - Begin 12.5mg PO QHS, then titrate up.
- 50% of patients who don’t get pain relief at 50mg BID will have pain relief at 100mg BID dose.

Levomilnicipran (Fetzima)

- SNRI
- Dose: 40-120mg daily
  - Begin 20mg/day x 2-3 days, then increase to 40mg
- Blah
- Side effects:
  - ~10% of patients become newly hypertensive and ~10% develop orthostatic hypotension
    - ↑ SBP 7-9 mmHg
  - Nausea (15-20%), Constipation (10%), Sweating (10%)
<table>
<thead>
<tr>
<th>Brand name</th>
<th>Velafaxine</th>
<th>Duloxetine</th>
<th>Milnicipran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effexor (USA); Efexor (Europe)</td>
<td>Cymbalta (USA); Cymbalta, Yentreve (Europe)</td>
<td>Savella (USA), Ixel (Europe)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-HT:NE reuptake ratio</th>
<th>1:30</th>
<th>1:1</th>
<th>1:3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression dose</td>
<td>150-375 mg/day for IR 75-225 mg/day for ER</td>
<td>60-120 mg/day</td>
<td>100-200 mg/day</td>
</tr>
<tr>
<td>Pain dose</td>
<td>&gt;225 mg/day</td>
<td>60-120 mg/day</td>
<td>100-200 mg/day</td>
</tr>
<tr>
<td>Side effects</td>
<td>37% nausea, 23% somnolence, 22% dry mouth, 19% dizziness, 18% insomnia</td>
<td>24% nausea, 33% dry mouth, 10% somnolence, 10% fatigue, 10% constipation</td>
<td>37% nausea, 18% headache, 16% constipation, 12% insomnia, 10% dizziness</td>
</tr>
<tr>
<td>Other</td>
<td>Memory issues at higher doses; withdrawal symptoms unless tapered</td>
<td>Worsens glycemic control; very rare hepatic failure</td>
<td>15-20% of non-hypertensive patients will develop hypertension</td>
</tr>
</tbody>
</table>

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### Practical Treatment Guidelines

- The most common reason for treatment failure is inadequate dose or inadequate time of treatment.
  - Can take up to 12 weeks to notice effects
  - Of patients with no improvement at 4, 6, and 8 weeks, 50%, 33% and 30% eventually did have response at 12 weeks.¹

- There is no benefit to combining an SSRI and SNRI

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Where to start?\textsuperscript{1,2,3}

- 1\textsuperscript{st} line treatment is SSRI or SNRI
  - Pain + depression = duloxetine
  - SSRI = escitalopram, sertraline

- If that doesn’t work switch to another SSRI or SNRI

- Still no response? Consider referral for augmentation/combination strategies
  - Use of atypical antipsychotics, combinations of two antidepressants, lithium augmentation

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BZDs & Anxiety

- Posttraumatic Stress Disorder (PTSD)
  - American Psychiatric Association (APA) practice guidelines\(^1\) – not even mentioned
  - Canadian Psychiatric Association (CPA)\(^2\) – not recommended
  - National Institute for Health and Clinical Excellence (NICE)\(^3\) – not even mentioned
  - UpToDate\(^4\) – “no evidence to support continued use”

\(^1\) [http://psychiatryonline.org/content.aspx?bookid=28\&sectionid=1682793#156514]
\(^2\) [http://publications.cpa-apc.org/browse/documents/2333]
\(^3\) [http://pathways.nice.org.uk/pathways/post-traumatic-stress-disorder]
\(^4\) Stein MB. Pharmacotherapy for posttraumatic stress disorder. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013.

BZDs & Anxiety

- Panic Disorder
  - APA\(^2\) – “selective serotonin reuptake inhibitors, SNRIs, and TCAs are all preferable to benzodiazepines”
  - CPA\(^2\) – SSRI & SNRI are first line medications
  - NICE\(^3\) – SSRI or imipramine/clomipramine
  - UpToDate\(^4\) – “we recommend SSRIs as the first-line medication treatment for panic disorder”

\(^1\) [http://psychiatryonline.org/content.aspx?bookid=18&sectionid=6882793#195412]
\(^2\) [http://publications.cpa-apc.org/media.php?mid=4443]
\(^3\) [http://pathways.nice.org.uk/pathways/panic-disorder]
\(^4\) Roy-Byrne PP. Pharmacotherapy for panic disorder. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013.
BZDs & Anxiety

- Generalized Anxiety Disorder (GAD)
  - APA – no practice guideline
  - Systematic review/meta-analysis\(^1\): fluoxetine, sertraline, duloxetine, escitalopram
  - CPA\(^2\) – begin with SSRI/SNRI, switch to another SSRI/SNRI if not effective
  - NICE\(^3\) – begin with sertraline, then another SSRI/SNRI, then pregabalin
    - “Do not offer a benzodiazepine for the treatment of GAD.”
  - UpToDate\(^4\) – SSRI & SNRIs


BZDs & Insomnia

- APA, CPA & NICE – no guidelines
- UpToDate\(^1\)
  - Treat the underlying condition
  - Sleep hygiene
  - CBT
  - Then medications
- Literature
  - BZDs decrease sleep latency by 4 minutes and increase sleep duration by ~62 minutes\(^2\)
  - Trazadone, zolpidem, eszopiclone, zaleplon, doxepin (3-50mg QHS), quetiapine

BZDs as muscle relaxants

- UpToDate³ – “benzodiazepines should not be used for long-term treatment of chronic low back pain “
- 2 Cochrane reviews:
  - No benefit versus placebo in inflammatory arthritis²
  - In acute LBP, mildly better than placebo. In chronic LBP no evidence of benefit³


BZD & Abuse

- Patient who abuse opioids often take a BZD 1-2 hours after to augment the “high”²
- Patient with a history of BZD abuse report diazepam gives the greatest high, followed by alprazolam & lorazepam.²
- ~30% of patients with CNCP are on concurrently prescribed BZDs & opioids³
  - 40-60% of patients with chronic pain abuse BZDs⁴

BZDs – other considerations

- Chronic BZD use is associated with persistent memory deficits that people do not develop tolerance to.\(^1\,^2,^3\)

- A prospective population based study from France followed patients with 15 year follow-up. It found that new onset benzodiazepine use after the age of 65 was associated with a 50% increase in risk of dementia.\(^4\)


Antipsychotics – all “off label”

- Olanzapine (zyprexa)
  - Effective for fibromyalgia, acute cluster HA, chronic migraine, chronic daily HA
  - Has shown opioid sparing effect in cancer patients

- Aripiprazole (abilify)
  - Case reports show benefit in chronic neck and back pain
  - Very mild side effect profile suggests more research is indicated.

- Quetiapine (seroquel)
  - Has been shown to improve sleep, but no effect on pain in fibromyalgia
AAPM poster presentation 2016

- SR of atypical antipsychotics for pain management
- Olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone are the only AAs with published studies in pain syndromes
- Olanzapine and quetiapine have the most combined studies (10 and 4, respectively)
- Olanzapine has shown preliminary and consistent efficacy in fibromyalgia and headache/migraine
- All other AAs (quetiapine included) fail to demonstrate efficacy in various pain syndromes and/or lack robust study designs.

Jiminez X. A review of atypical antipsychotics in pain management: olanzapine demonstrates potential. AAPM Poster presentation 2016

"Trust me, Wen, no one is ever actually allergic to Oxycontin."