I want a new drug!
New(er) drugs in pain management

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CDM forum- Update Pain Management
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Conflicts of Interest

• Clinical Coordinator VGH
• I work in the VIHA Pain Program
• National Faculty Member, Knowledge Transfer, CPS
• I have been paid honorariums for educational presentations by Pfizer, Merck, Glaxo
Outline/Learning Objectives

Pharmacology, evidence for efficacy, tolerability profile, potential place in therapy for.....

• Tapentadol IR & CR (Nucynta®)
• Oxycodone/Naloxone PR (Targin®)
• Buprenorphine transdermal (Bu-Trans®)
I want a new drug!
Huey Lewis & the News

http://www.youtube.com/watch?feature=player_detailpage&v=N6uEMOeDZsA
I want a new drug! What other song and artist had similarities with this song in 1984 that Huey Lewis ended up suing Columbia Pictures for plagiarism?

1. *What’s love got to do with it?* – Tina Turner
2. *Footloose* – Kenny Logins
4. *Dancing in the Dark* – Bruce Springsteen
Answer... *Ghostbusters* – Ray Parker Jr.
Tapentadol
(Nucynta®)
- IR 50, 75, & 100mg tablets
- ER 50, 100, 150, 200, 250mg tablets
Tapentadol (Nucynta®)

- Synergistic dual mechanism of action (MOR-NRI)
  - Weak mu opioid receptor (MOR) agonist
  - Norepinephrine re-uptake inhibitor (NRI)

- 50 x less affinity for receptor than morphine, yet provides ~1/3 analgesia that of morphine

Tapentadol-equi-analgesic dose

• Studies comparing TAP CR: Oxy CR
  – Ratio of 5:1

• Translates into oral TP: Morphine Oral
  – Ratio of 3.5:1

Tapentadol improvement over tramadol?

- Does not require metabolic activation (like tramadol & codeine)
- Produces no active metabolites
- Has no significant drug interactions
- Not influence by genetic polymorphisms of the cytochrome P450 system
- Minimal serotonergic effects – significant reduced risk of serotonin syndrome

Figure 6. (a) Tapentadol versus oxycodone for moderate to severe pain (dichotomous outcomes). (b) Tapentadol versus oxycodone for moderate to severe pain (continuous outcomes). SE = standard error; IV = inverse variance; CI = confidence interval; PGIC = Patient Global Impression of Change; Disc = discontinuations; AE = adverse events; SAE = Serious AE.

Tapentadol IR-Acute pain

• Efficacious mod-severe acute pain:
  – Third molar extraction
  – Bunionectomy
  – Degenerative dx

• 50-70mg -`not inferior’ to 10mg oxycodone

Tapentadol-extended release

• Comparable analgesia to Oxycodone CR in:
  – OA knee
  – Chronic low back pain
  – Diabetic neuropathy

• Less side effects leading to discontinuation

• Significantly improved GI tolerability

Safety/Tolerability

• Potential for all typical opioid-induced ADRs
  – Improved GI tolerability compared to others well documented but still is reported
  – CNS- somnolence / dizziness
  – Block NE uptake-? Increase BP-theoretical
  – Respiratory depression- not reported
  – Minimal abuse potential (CR designed to resist mechanical alteration)
  – Mild withdrawal syndrome

Tapentadol- dosing

• Immediate release- acute pain
  – 50-75mg = oxycodone 10mg
  – 50-75mg q4-6h as required
  – MAX: 600mg/day

• Extended release-chronic pain
  – Opioid-naïve- start with 50mg q12h
  – Rotation: If on opioids < 140mg MEDD
  – Maximum: 250mg q12h (500mg/day)

Tapentadol-dosing

- No dose adjustment mid-mod renal impairment or mild hepatic impairment
- Reduce dose & frequency in moderate hepatic impairment (C-P score 7-9;Class B)
- Not studied in severe renal or hepatic impairment
- Contraindicated with MO inhibitors (NE potential leading to hypertensive crises)

Place in Therapy

**WHO Analgesic Stepladder**

- **Step 1** - Non-opioid ± adjunct
  - No Pain
  - Mild

- **Step 2** - Mild opioid ± non-opioid ± adjuncts (codeine, tramadol)
  - Moderate

- **Step 2.75** - Tapentadol = < 140mg MEDD
  - Severe

- **Step 3** - Strong opioid ± non-opioid ± adjuncts (morphine, HM, fentanyl)

WHO=World Health Organization

MEDD= Morphine Equivalent Daily Dose

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Neuropathic Pain Algorithm
adapted from CPS consensus statement 2007

Topical Lidocaine if focal or PHN

TCA or Gabapentin/Pregabalin

SNRI (Venlafaxine or Duloxetine)

First Line Therapies

Second Line Therapies

Tramadol or CR Opioids

Third Line Therapies

?Tapentadol CR
DPN only?

MISC – minimal evidence (Cannabinoids, methadone, other anticonvulsants

Tapentadol - in summary

• “Mild” opioid with analgesic efficacy comparable to lower doses of strong opioids (less than 140mg MEDD)
• Advantages over Tramadol & Codeine
• Used in ‘non-responders’ to other mild opioids in those that stronger opioids not desired
• Significantly improved GI tolerability compared to stronger opioids (Oxycodone)
• Some evidence for DPN
Oxycodone/Naloxone (Targin®)

- Developed to counteract opioid-induced constipation (OIC)
  - Minimal tolerance to this OIC
  - Significantly affects patient’s quality of life
  - Sometimes difficult to manage with laxatives
  - Often affects adherence and then subsequent pain control

Oxycodone /Naloxone CR

• Combination of:
  – Oxycodone- strong mu agonist → analgesia
  – Naloxone –mu receptor antagonist → rapid onset, high receptor affinity reverses opioid binding
  • IV – used as an antidote
  • Oral – effect predominantly in the gut can reverse OIC

Naloxone-First pass effect

1. Oral administration oxycodone/naloxone
2. NAL- high affinity for opioid receptors in gut reversing OIC
3. NAL-rapid/extensive metabolism → only 2% bioavailable
4. OXY- significant portion available to elicit centrally mediated mu receptor analgesia
Oxycodone /Naloxone CR 2:1 ratio

• Ratio 2:1 oxycodone/naloxone determined optimal:
  – 5mg/2.5mg CR tablet
  – 10mg/5mg CR tablet
  – 20mg/10mg CR tablet
  – 40mg/20mg CR tablet

• Some diarrhea at higher doses→ reversal of OIC vs GI withdrawal symptoms

Evidence/studies

• Oxy/naloxone CR vs Oxycodone CR
  – No loss of analgesia
  – Increase in spontaneous BM per week (median 3.0 vs 1.0) after 4 weeks treatment
  – Lower laxative intake
  – Significant reduction in the Bowel Function Index (ease, completeness, judgment)
    • 26.9 pts vs 9.4 pt (P<0.001)

## Safety/Tolerability

### Table 3- Incidence of Adverse Events: Double-blind safety population (Phase III study)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo N=158</th>
<th>Oxycodone PR N=151</th>
<th>Oxycodone /Naloxone PR n=154</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ADR</td>
<td>83 (52.5%)</td>
<td>80 (53%)</td>
<td>86 (55.8%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (5.1%)</td>
<td>18 (11.9)</td>
<td>13 (8.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (4.4%)</td>
<td>4 (2.6%)</td>
<td>8 (5.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (7.0%)</td>
<td>12 (7.9%)</td>
<td>10 (6.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (3.2%)</td>
<td>7 (4.6%)</td>
<td>8 (5.2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (2.5%)</td>
<td>8 (5.3%)</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (3.8%)</td>
<td>9 (6.0%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (7.0%)</td>
<td>6 (4.0%)</td>
<td>5 (3.2%)</td>
</tr>
</tbody>
</table>

Oxycodone /Naloxone CR (Targin®)-dosing

• Opioid naïve start 5/2.5 twice daily
• Max daily dose: 40/20mg twice daily
• Rotation: Opioids < 120mg MEDD or 80mg Oxy daily dose
• Concerns with any hepatic impairment would diminish first past effect & thereby reduce oxycodone effect

WHO Analgesic Stepladder

**Step 1** - Non-opioid ± adjunct

**Step 2** - Mild opioid ± non-opioid ± adjuncts
   *(codeine, tramadol)*

**Step 2.75** – Targin®-Oxy max dose: 80mg/day = ~120 MEED

**Step 3** - Strong opioid ± non-opioid ± adjuncts
   *(morphine, HM, fentanyl)*

**WHO**=World Health Organization

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Oxycodone/Naloxone PR – In summary

- Comparable analgesia to Oxycodone CR
- Limits of dosing up to 80mg oxycodone/day = 120mg MEDD due to impact of naloxone on gut (diarrhea)
- Improved GI tolerability compared to oxycodone alone
- Decreased risk of abuse/diversion
Buprenorphine (BUP)

- Semi-synthetic opioid analgesic
  - Sublingual – Suboxone®
    - Buprenorphine/Naloxone
    - Approved for opioid withdrawal management
  - Low dose transdermal (Bu-Trans®)
    - 5, 10 & 20 mcg/hour 7 day patch
    - Approved for chronic pain
BUP-partial agonist in vitro
Pure agonist action in vivo

- Full Agonist: Full activity, High affinity
- Partial Agonist: Low intrinsic activity, High affinity
- Antagonist: No activity, High affinity

Source: Mike Stillings, Reckitt Benckiser, Inc.
Buprenorphine- Pharmacodynamics

• Low intrinsic activity – ceiling effect (12-16mg)
• Main antinociception spinal cord → less effect on brain (?? Less abuse potential)
• Slow association (take-up on receptor)
• Slow dissociation (off receptor)
  – Reduced severity of withdrawal
  – May require naloxone infusion to detox

Plosker GL. Buprenorphine 5, 10 and 20 ug/hr transdermal patch. Drugs 2011:71(18): 2491-2509.
Buprenorphine- Pharmacodynamics

• Mu receptor occupancy rate low (< 50%):
  – Allows co-administration other opioids
  – Reduced refractory period if rotating to another

• Antagonistic at the Kappa receptor→ translates into reduced dyspnea/dependence

• Main active metabolite (norbuprenorphine) potent delta receptor agonist:
  – Efficacy in bone pain (delta opioid receptors are present on pain fibre within bone)

Plosker GL. Buprenorphine 5, 10 and 20 ug/hr transdermal patch. Drugs 2011:71(18): 2491-2509.
Buprenorphine low dose transdermal Evidence

• Osteoarthritis hip or knee
  – Better than placebo
  – Equivalent to sublingual BUP
  – Noninferior to acetaminophen + Codeine (regularly scheduled)
  – Noninferior to CR tramadol (up to 200mg/day)

• Low back pain
  – Better than placebo dose > 5 mcg/hr

Plosker GL. Buprenorphine 5, 10 and 20 ug/hr transdermal patch. Drugs 2011:71(18): 2491-2509.
Buprenorphine Safety/Tolerability

• Mild to moderate intensity/mostly 1st month

• Most frequently reported ADRs (> 10%)
  – Headache (more frequent in younger popln)
  – Dizziness
  – Somnolence
  – Constipation
  – Dry mouth
  – Nausea/Vomiting
  – Application site reactions- pruritis/erythemia (25%)

Buprenorphine
Respiratory Depression

• Low risk of respiratory depression
• Ceiling effect demonstrated in trials in healthy volunteers
• Possibly related to kappa receptor antagonist
• Potentially problematic if used with other CNS depressants or in overdose situation
Buprenorphine- more advantages

- Anti-hyperalgesic effect
- Low risk/mild withdrawal due to slow receptor dissociation & gradual decline in levels when patch removed
- Low term advantages
  - Lacks effect on HPA and HPG axis
  - Lacks immunosuppression effects shown with other opioids

Buprenorphine-QTc Prolongation

- Studies in healthy volunteers showed QTc internal prolongation by 9.2 msec with the 40mcg/hour transdermal

- Caution: Long QT syndrome; co-admin with Class 1A/III antiarrhythmics; unstable cardiac dx
Buprenorphine dose initiation/titration

- Supplemental IR analgesia during titration
- Opioid-naïve – start with 5 mcg/hr patch
- Rotation: (patients on < 80mg MEDD)
  - MEDD < 30 mg
    - 5 mcg/hr
  - MEDD 30-80 mg
    - 10 mcg/hr
    - 20 mcg/hr
BUP transdermal- PK-Absorption

• Absorption-affected by application site
  - Recommended-outer arm, upper chest, upper back and side of chest (26% less than others)
  - Non-approved sites (abdomen, thigh, OA site)-less absorption
  - Low body fat – less absorption

Plosker GL. Buprenorphine 5, 10 and 20 ug/hr transdermal patch. Drugs 2011:71(18): 2491-2509.
Site Rotation important

- Repeated use of same site can doubles drug exposure/site reactions
- Manufacturer provides an “Application Site Tracker”
- Two methods of disposal
  - FF= fold sticky sides together and flush down toilet
  - PDU = patch disposal unit provided by manufacturer

<table>
<thead>
<tr>
<th>Week</th>
<th>Date applied</th>
<th>Date Removed</th>
<th>Disposal FF /PDU</th>
<th>Upper outer arm</th>
<th>Upper back</th>
<th>Upper chest</th>
<th>Upper side of chest</th>
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</thead>
<tbody>
<tr>
<td>One</td>
<td>Nov 1</td>
<td>Nov 8</td>
<td>FF</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>Nov 8</td>
<td>Nov 15</td>
<td>PDU</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>Nov 15</td>
<td>Nov 22</td>
<td>FF</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Four</td>
<td>Nov 22</td>
<td>Nov 29</td>
<td>PDU</td>
<td></td>
<td></td>
<td>L</td>
<td></td>
</tr>
</tbody>
</table>
BUP-Pharmacokinetics

- Peaks in 3 days – Do not titrate dose up before peak is achieved and effects assessed.
- Wear continuously for 7 days
What cytochrome P450 isoenzyme metabolizes the largest percentage of drugs?

1. CYP 2C9
2. CYP 2D6
3. CYP 3A4
4. CYP 1A2
What cytochrome P450 isoenzyme metabolizes the largest percent of drugs?

- CYP 2C9
- CYP 2D6
- **CYP 3A4** 50% - Abx, statins, CCB, BZD
- CYP 1A2
**BUP- Elimination**

- Metabolized by cytochrome P450-3A4 to norbuprenorphine – active metabolite
  - ~40 fold lower effects
  - Only clinically relevant interactions with protease inhibitors atazanavir and efavirenz

- NO dosage adjustment required in renal impairment
Place in Therapy

**WHO Analgesic Stepladder**

**Step 1** - Non-opioid ± adjunct

**Step 2** - Mild opioid ± non-opioid ± adjuncts
*(codeine, tramadol)*

**Step 2-3 alternatives**
- TAP < 140 MEDD
- TARGIN® < 120 MEDD
- BUP LDTD< 80mg MEDD

**Step 3** - Strong opioid ± non-opioid ± adjuncts
*(morphine, HM, fentanyl)*

WHO=World Health Organization

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Buprenorphine Low dose transdermal

In summary

- Comparable to lower dose opioids < 80mg MEDD
- Convenient once weekly dosing
- Suitable for patients with swallowing difficulties
- Generally safe in elderly/renal impairment
- Low risk ceiling effect for respiratory depression
- Antihyperalgesic effect can be beneficial