Future of Buprenorphine for Pain: the Studies and Experience from Europe.

Walter Ling MD
Integrated Substance Abuse Programs UCLA
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lwalter@ucla.edu
www.uclaisap.org
Disclosure

• Dr Walter Ling has received unrestricted education grants from Reckitt/Benckiser and research support from Reckitt/Benckiser and Hythiam Inc.

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Key Properties of Buprenorphine: Ceiling Effect

• Pharmacologic ceiling effect for buprenorphine provides high safety profile

• Ceiling effect on respiratory depression

![Graph showing opioid effect vs. log dose for different drugs including Methadone, Buprenorphine, and Naloxone.](image)

Figure 1. The effect of increasing the dose of buprenorphine on the incidence of side-effects.
Key Properties of Buprenorphine:
High Affinity for $\mu$ Receptor

- Slow Disassociation Due to Tight Receptor Binding

- Blocks effects of subsequently administered opioid agonists
- Long duration of action
BUPRENORPHINE - HISTORY

1966  Discovery
1977  First Registration (UK) - Analgesia
1978  Launched in UK - Injection only
1978 - 1984 Major European Launch Programme
1982  Sublingual Product Introduced
Late 80’s  Buprenorphine Scheduled
1994  CRADA signed - Treatment Indication
1994  BBG established
1995  Buprenorphine (monopproduct) Registered in France
1996  Buprenorphine (monopproduct) Launched in France
1997  Global Partnership with Schering-Plough
## BUPRENORPHINE PRODUCTS

**Indicated for ANALGESIA**

**Trade Names in different countries**

<table>
<thead>
<tr>
<th>Product</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMGESIC</td>
<td>England</td>
</tr>
<tr>
<td>BUPREX</td>
<td>Spain, Portugal</td>
</tr>
<tr>
<td>BUPRENEX</td>
<td>USA</td>
</tr>
<tr>
<td>LEPETAN</td>
<td>Japan</td>
</tr>
</tbody>
</table>

**Injection**

<table>
<thead>
<tr>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3mg/ml</td>
</tr>
</tbody>
</table>

**Sublingual Tablets**

<table>
<thead>
<tr>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2mg, 0.4mg</td>
</tr>
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</table>

**Suppositories**

<table>
<thead>
<tr>
<th>Strength</th>
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</thead>
<tbody>
<tr>
<td>0.2mg, 0.4mg</td>
</tr>
</tbody>
</table>

**TEMGESIC – NX Sublingual Tablets** (New Zealand)

<table>
<thead>
<tr>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2mg Buprenorphine +0.2mg Naloxone</td>
</tr>
</tbody>
</table>
ANALGESIA

NEW SCIENTIFIC UNDERSTANDING

• Buprenorphine Unique
  eg Can be differentiated from Morphine, Fentanyl

• Cardioprotective Properties
  “Opioid receptors and Myocardial Protection:
  Do some Opioid Agonists Possess Cardioprotective Effects?”

• Opioids Effective in Managing Neuropathic Pains?

• Buprenorphine Plus

• Potential Buprenorphine “admixtures” / regimes
ANALGESIA - FUTURE

NEW PRODUCT DEVELOPMENT

• Transdermal Patch  (24 - 72hr)
• Buccal (transmucosal) Patch  12 - 24hr)
• Aerosol Delivery: nasal inhalation
Buprenorphine: Potent Analgesic

- 20-50 times potency of morphine
- Available worldwide for pain treatment
- Injectable formulation available in U.S.
- Usual analgesic dose: .2-.4 mg sl
- Higher dose for opiate dependence
Buprenorphine and Pain

- Animal data don’t predict human data
- Good potent analgesic
- Mild CVS effect, mild G-I effect
- Ceiling effect on respiratory depression
- Analgesia not compromised by ceiling effect.
- Effective for long term use, mos. to yrs.
Buprenorphine: Analgesic Profile

Rapid onset of action
Long duration of peak effect (60-120 min)
Long half life (3.5 hrs)
Analgesic action up to 8 hrs.
No apparent analgesic ceiling effect at doses below 300 mg Ms equivalent; no inverted U
Ceiling effect on respiratory depression
Low physical dependence profile

Figure 1. The effect of increasing the dose of buprenorphine on the incidence of side-effects.
Safety Profile of Buprenorphine

- Adverse effects associated with Buprenorphine (16 mg/day) are similar to those observed with other opioids

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>SL Buprenorphine (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>36.4</td>
<td>22.4</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>25.2</td>
<td>37.4</td>
</tr>
<tr>
<td>Pain</td>
<td>22.4</td>
<td>18.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14.0</td>
<td>15.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>15.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.1</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Meaningful Pain Reduction

• Using a VAS or Numeric scale of 0-10
  – (4-6= mod pain; 7-10= severe pain)

• For Moderate pain ( mean=6)
  – Meaningful reduction=2.4 (40%)
  – Very much better=3.5 (45%)

• For Severe pain (mean=8)
  – Meaningful reduction=4.0 (50%)
  – Very much better=5.2 (56%)

M. Soledad Cepeda et al.  Proc 10th world Cong on Pain
vol 24; pp 601-609 IASP press 2003
Buprenorphine: Analgesic Use

• Surgical pain
  – Intra-operative, peri-operative, post-operative
• Labor pain
• Back pain
• Phantom pain
• Post-herpetic neuralgia
• Cancer pain
Buprenorphine as Analgesic I

• Partial agonist: high safety profile; respiratory depression; flexible dosing; safe in elderly, debilitating illness; overdose

• Tight receptor binding: slow off set; long duration of action, less end of dose withdrawal

• Relatively few drug/drug interactions; patients needing multiple medications; HIV/AIDS pts.

• Primary clearance via GI tract; safe in pts with renal and liver diseases
Buprenorphine as Analgesic II

- Relatively less immunosuppressant; Mu effect countered by kappa effects; suitable for HIV/AIDS and neuropathathies.
- No apparent ceiling effects on analgesia; ceiling effects on respiration
- Kappa effect may be “anti-hyperalgesia”
- Some Na-channel insensitive neuropathic pain are unresponsive to morphine but responsive to buprenorphine
Buprenorphine in Acute Pain

• 30 x potency of Ms by intramuscular injection
• 8-12 x by epidural route (effect: 12-24 hrs)
• Long duration of action (8-12 hrs)
• Better analgesia cf. meperidine; comparable to morphine, hydromorphone, fentanyl
• Low incidence of respiratory depression (up to 7 mg iv given post-op)
• Nausea, vomiting, dizziness common
Buprenorphine for Chronic Pain

- Cancer and non-cancer pain
- 0.15-0.8 mg/dose q 6-8 hrs
- 0.3 mg=10 mg morphine
- Given SL, epidural, subcut, subarachnoid
- Comparable to Ms; less resp dep
- Given up to 12 wks.
- Experience not extensive
Buprenorphine for Chronic Pain

• Good for trans-dermal application
  – Lipophilic, High level analgesia Low adverse effects

• Transdermal patch (35-52.5-70 micro gm/hr)
  – Consistent delivery, desirable time course
  – Flexible dosing and compliance
  – Effective up to 7 days, used up to 18 mos

• Used in neuropathic pain (.3 mg=methadone 10 mg; usual dose 0.6 mg (20 mg methadone)
Analgesic Effects of Buprenorphine: Interactions with agonists and antagonists

• Buprenorphine plus morphine, oxycodone, hydromorphone and fentanyl in analgesic doses show additive or synergistic effects.
• Given in declining phase of buprenorphine, morphine and fentanyl show full effects.
• Only at very high supra-analgesic doses do antagonism appear—combined effects reduced to buprenorphine effects alone.
  – In animal model
Analgesic Effects of Buprenorphine: Interactions with agonists and antagonists

• In clinical analgesic range, switch between buprenorphine and full µ agonists can be done without loss of analgesic efficacy and without a refractory period between cessation of buprenorphine and start of new µ agonists.
Buprenorphine in Chronic Pain

- **SL bup vs SRMs** (Bach V. et al The Pain Clinic 1991; 4: 87-93)
  - 453 pts with chronic pain: 189 Ca related, 147 ischemic leg pain, 117 lbp, phantom, rhumatic & other pain
  - 0.6mg/d bup vs 60 mg Ms, median Tx 40 dys
  - Similar analgesia; fewer adv events for bup

- **Transdermal bup** 361 pts, 8 wks
  - VAS 7.7 improved to 3.4 at wk 8

- **Post-marketing, 13,179 pts transdermal bup**
  - Both Ca and Non-Ca pain; WHO steps 2-3 analgesics; 35-70 ug/h; Reduction in pain and in supp med. (Griessinger N. et al Curr Med Res Opin 2005; 21: 1147-1156)

- **Bup sucessfully co-administered with other opioids:** Ms; tramadol; acetaminophen
Buprenorphine for Neuropathic Pain

• Thought limited by its ceiling effect but not borne out clinically
• Tight binding & prolonged receptor occupancy thought limit ability to combine with other agonists also not borne out clinically
• Previously recommended to D/C or substitute with full agonist one week before surgery; also not borne out clinically.
• May well prove to be best treatment for chronic pain in opioid dependent patients
Summary

• Potent opioid analgesic with unique receptor binding and pharmacological profile
• Effective in many types of acute and chronic pain
• May be especially suited for neuropathic pain
• High potency and chemical profile lend itself to development of special delivery formulations
• The sublingual product available in the United States has not been studied for the treatment of pain
Thank you, thank you, and thank you…