

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

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Disclosure

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- He has also served as an occasional consultant to Reckitt/Benckiser, Titan Pharmaceuticals, and US World Meds

Key Properties of Buprenorphine: Ceiling Effect

- Pharmacologic ceiling effect for buprenorphine provides high safety profile
- Ceiling effect on respiratory depression

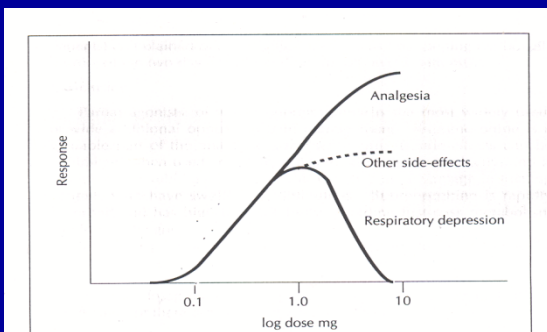
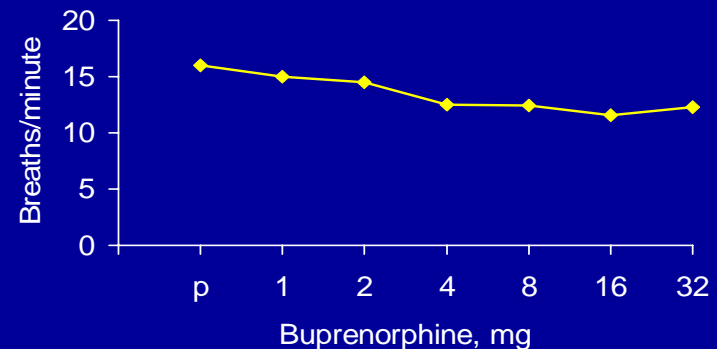
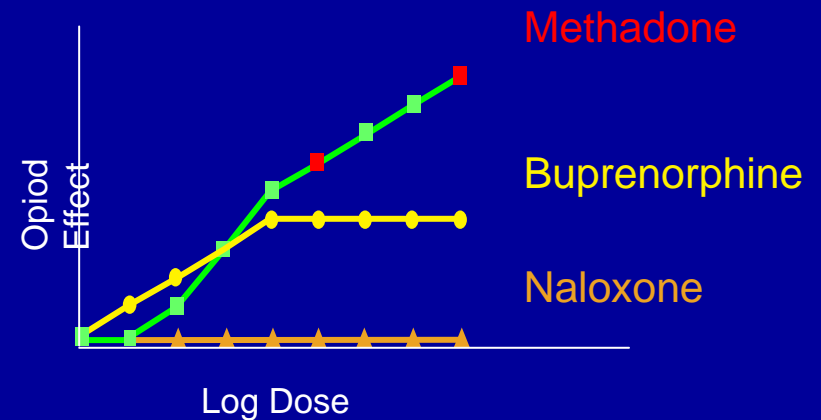
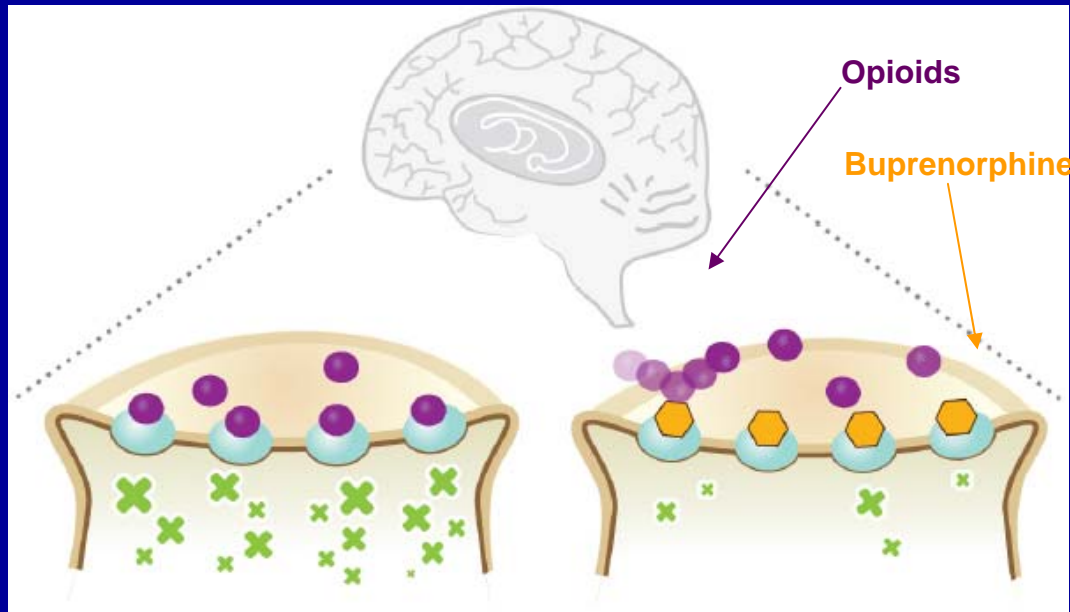


Figure 1. The effect of increasing the dose of buprenorphine on the incidence of side-effects.

Key Properties of Buprenorphine: High Affinity for μ 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 (monoprodut) Registered in France
1996	Buprenorphine (monoprodut) Launched in France
1997	Global Partnership with Schering-Plough

BUPRENORPHINE PRODUCTS

Indicated for ANALGESIA

Trade Names in different countries

TEMGESIC
(England)

BUPREX
(Spain, Portugal)

BUPRENEX
(USA)

LEPETAN
(Japan)

Injection

0.3mg/ml

Sublingual Tablets

0.2mg, 0.4mg

Suppositories

0.2mg, 0.4mg

TEMGESIC – NX Sublingual Tablets (New Zealand)

0.2mg Buprenorphine +0.2mg Naloxone

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)

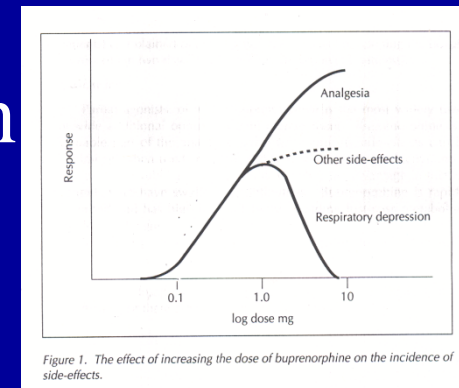
Long half life (3.5 hrs)

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



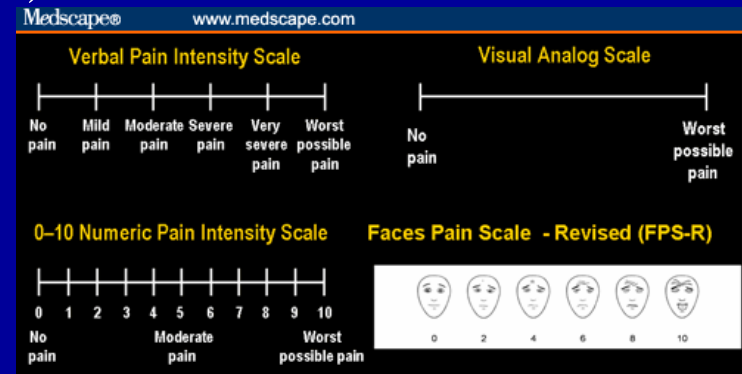
Safety Profile of Buprenorphine

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

Adverse Event	SL	
	Buprenorphine	Placebo
	(%)	(%)
Headache	36.4	22.4
Withdrawal	25.2	37.4
Pain	22.4	18.7
Insomnia	14.0	15.9
Nausea	15.0	11.2
Constipation	12.1	2.8

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 appears— combined effects reduced to buprenorphine effects alone.
 - Babette Kogel et al European J Pain 9 (2005) 599-611
 - In animal model

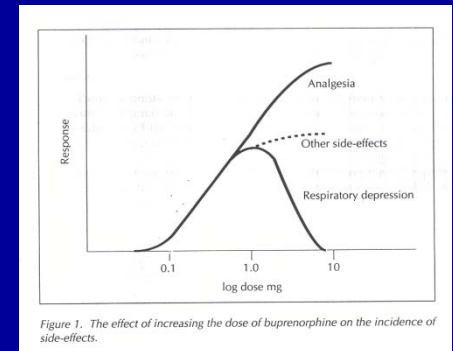
Analgesic Effects of Buprenorphine: Interactions with agonists and antagonists

- 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.

– Babette Kogel et al European J Pain 9 (2005) 599-611

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
 - Ballantyne JC & LaForge KS Pain: 129 (2007) 235-255

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...

