

Buprenorphine Flavors & formulations... Past, Present and Future

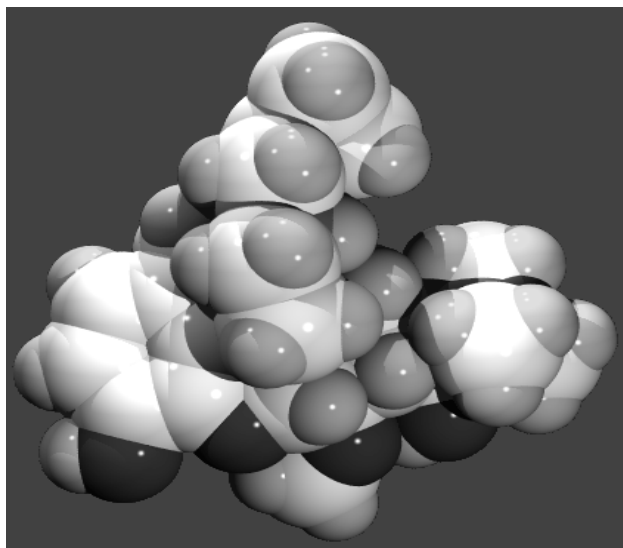
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Clinical Research Physician at large
Private Practice, Culver City, CA
Medical Director, Common Ground Westside

Disclosures

- Current speaker Orexo pharmaceuticals
- Current speaker and consultant, BDSI pharmaceuticals
- Current consultant, Braeburn Pharmaceuticals
- Former consultant and speaker Reckitt Benkiser

Buprenorphine



1969: RX6029 is born

- After 10 years of attempting to synthesize an opioid compound "with structures substantially more complex than morphine [that] could retain the desirable actions whilst shedding the undesirable side effects (addiction)"
- Trials on humans began in 1971

Campbell N. D., Lovell A. M. (2012). "The history of the development of buprenorphine as an addiction therapeutic". *Annals of the New York Academy of Sciences* 1248: 124–139. [doi:10.1111/j.1749-6632.2011.06352.x](https://doi.org/10.1111/j.1749-6632.2011.06352.x).

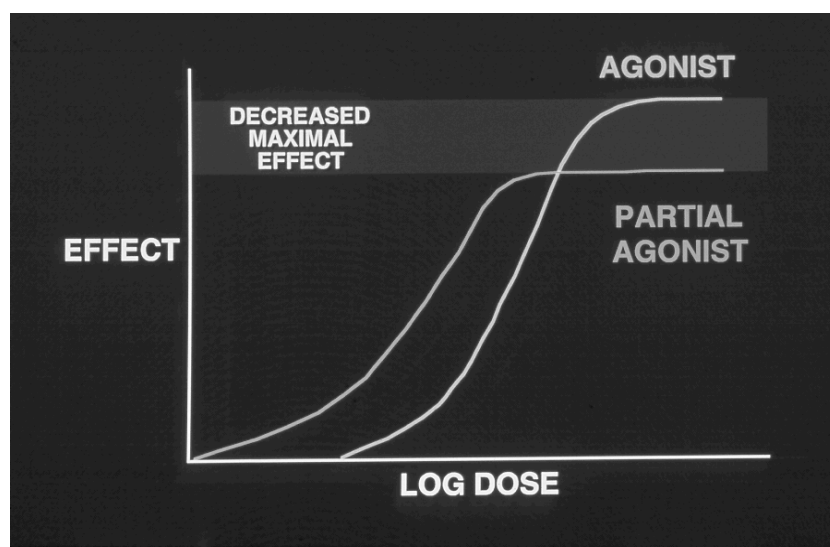
Buprenorphine: Clinical Pharmacology

Partial Agonist

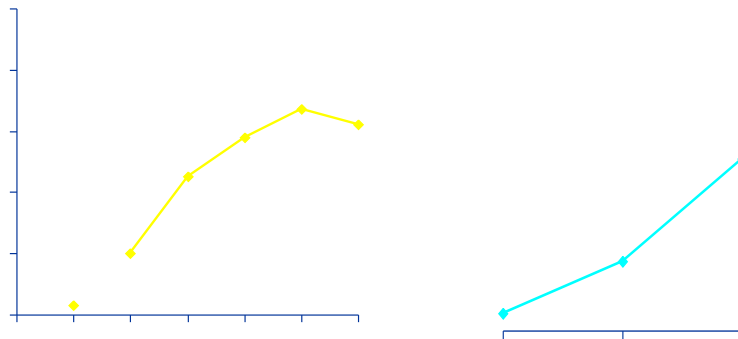
- high safety profile/ceiling effect
- low level of physical dependence
- partial substitution for highly addicted patients
- “Less bounce to the ounce”

Tight Receptor Binding

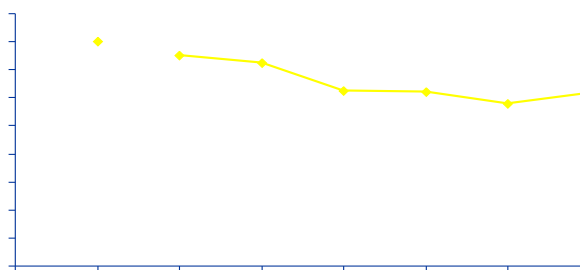
- long duration of action
 - Half life 20–70 hours, mean 37 hours
- slow onset mild abstinence
- precipitates withdrawal in highly dependent patients



Good Effect

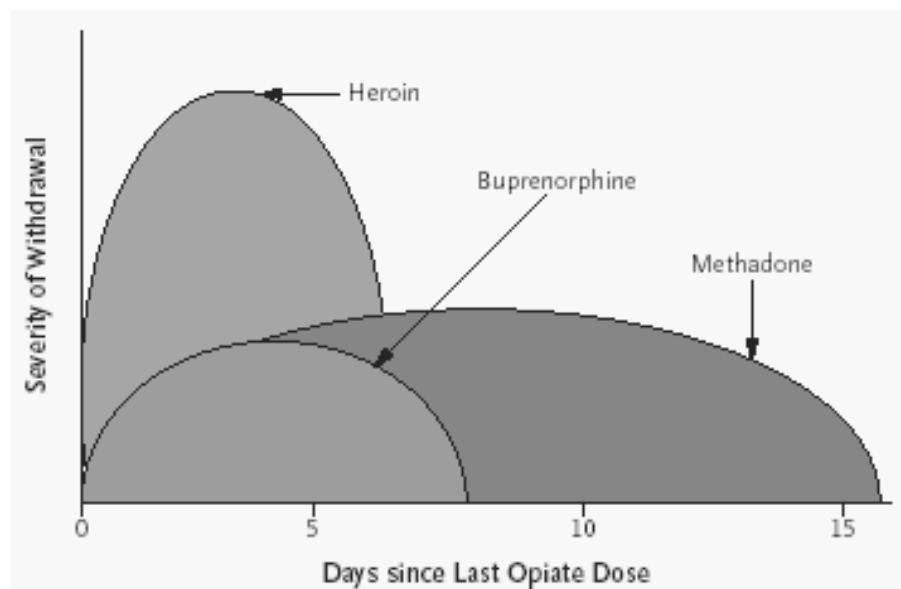


Respiration



Buprenorphine for Opiate Use Disorder:

- Suppresses withdrawal
- Substitutes for street opiates
- Blocks subsequently administered opiates
- Safety in long term use



Subutex® buprenorphine alone

- Approved: October 8, 2002
- Subutex Discontinued 2011 because marketing protection expired
- Dosing: Tablet, Sublingual 8mg and 2mg
- Generic mono product remains available
- COST: apx \$4.50 per pill
 - Generic pill



Subutex® buprenorphine alone

- Approved: October 8, 2002
- Originally only prep indicated for induction
- Dosing: Tablet, Sublingual 8mg and 2mg
- Discontinued 2011



Buprenorphine/Naloxone combo *SUBOXONE*

4 parts buprenorphine: 1 part naloxone

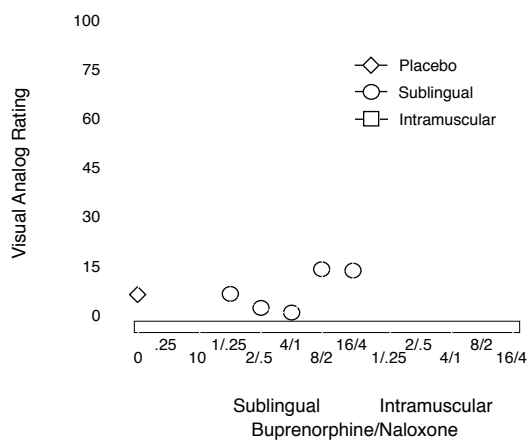
Sublingual: Opiate agonist effect from
buprenorphine

Intravenous: Opiate antagonist effect from
naloxone

**Addition of Naloxone Reduces
Abuse Potential**

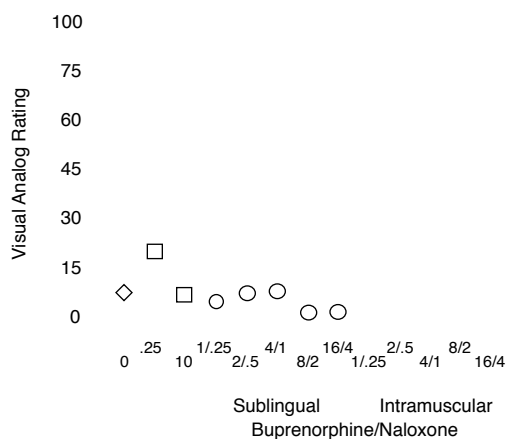
- Naloxone will block buprenorphine's effects by the IV but not the sublingual route
- Sublingual absorption of buprenorphine @ 70%; naloxone @ 10%
- If injected, BUP/NX will precipitate withdrawal in a moderately to severely dependent addict

“Does the Drug Have Any Good Effects?”



Stoller, Bigelow, Walsh & Strain (2001) Psychopharmacology, 154: 230-242.

“Does the Drug Have Any Bad Effects?”



Stoller, Bigelow, Walsh & Strain (2001) Psychopharmacology, 154: 230-242.

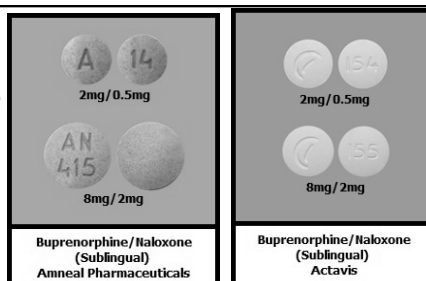
Suboxone Tablet

(buprenorphine/naloxone)



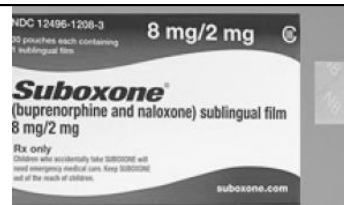
- Approved: October 8, 2002-
- Chemical Type: 4 New Combination
 - Review Classification: P Priority Review Drug, O Orphan Drug
- Dosing: 2MG/0.5mg, 8MG/2mg; Tablet, Sublingual
- -Discontinued: 2012

Buprenorphine/naloxone Tablet



- Generic appeared: 2012
- Numerous manufactures
- Dosing: 2MG/0.5mg, 8MG/2mg; Tablet, Sublingual
- COST: apx \$4.50 per 8mg pill

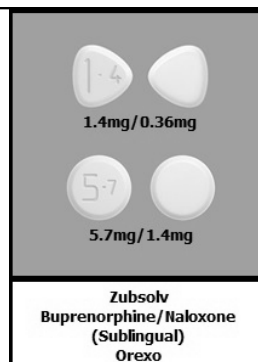
Suboxone Film® (buprenorphine/naloxone) Reckitt Benckiser



Doses

- Approved: August 30, 2010
 - Chemical Type: 4 New Combination
 - Review Classification: S Standard review drug
- Child resistant packaging
- Unique identifier on each film package
- Equivalent to Suboxone®pill
- 2mg/0.5mg
- 4mg/1mg
- 8mg/2mg
- 12mg/3mg
- COST: ~\$7.33 per film depending on dose
- Discount/copay cards available

Zubsolv® BUP HCl/NLX HCl

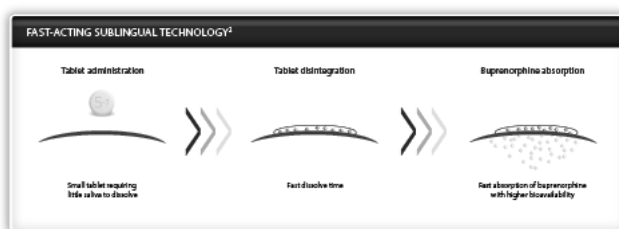


Approved: July 3, 2013

- Dosing:
 - 5.7mg BUP /1.4 MG nlx = 8mg Suboxone pill®
 - 1.4 MG BUP / .36 MG nlx = 2mg Suboxone pill®
- Menthol "minty" flavor
- Technology lowers oral pH to facilitate Bioavailability
- COST: ~\$7.33 per film depending on dose
 - Discount/copay cards available

ZUBSOLV Formulation

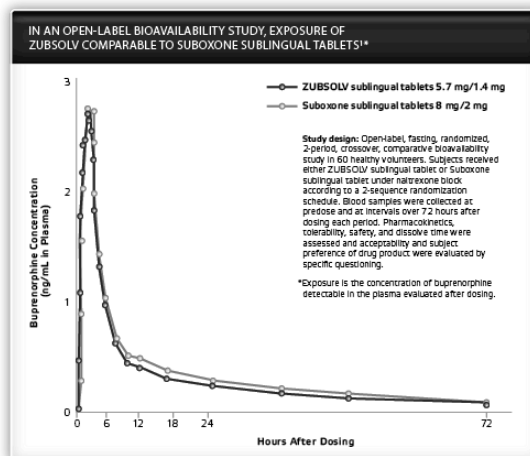
- The increased bioavailability of ZUBSOLV tablets compared to Suboxone tablets is probably due to a combination of features of the ZUBSOLV formulation
 - ZUBSOLV tablets are designed to disintegrate rapidly and release the buprenorphine particles quickly



Fischer A et al. *Drug Dev Ind Pharm*, 2013;Early Online:1–6
Data on file. Orexo US, Inc.

Buprenorphine Bioavailability –Study 003

- One 5.7mg ZUBSOLV tablet provides equivalent buprenorphine plasma exposure to one 8mg Suboxone tablet with ~30% less buprenorphine

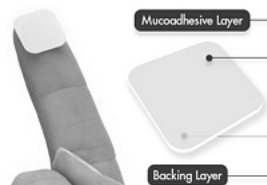


Fischer A et al. *Drug Dev Ind Pharm*, 2013;Early Online:1–6
Data on file. Orexo US, Inc.

Bunavail®

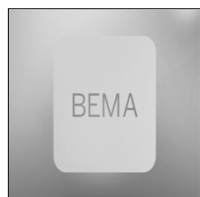
BUP HCI/NLX HCI

Biodelivery SCI INTL



- Approved June 6, 2014
- BioErodible MucoAdhesive (**BEMA**®)
 - 2.1MG BUP / .3 MG nlx = 4mg Suboxone pill®
 - 4.2MG BUP/.7MG nlx = 8mg Suboxone pill®
 - 6.3 MG BUP/1 MG nlx = 12 mg Suboxone pill®
- Efficient delivery system & potential for fewer side effects due to less swallowed buprenorphine
- COST: ~\$7.33 per film depending on dose
 - Discount/copay cards available

BEMA: BioErodible MucoAdhesive



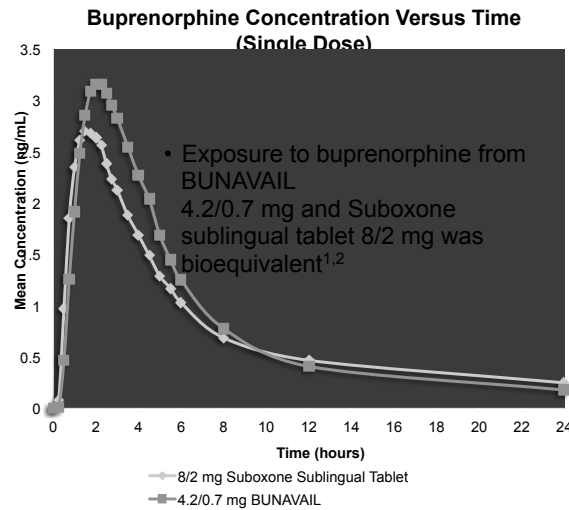
[BEMA technology
video]



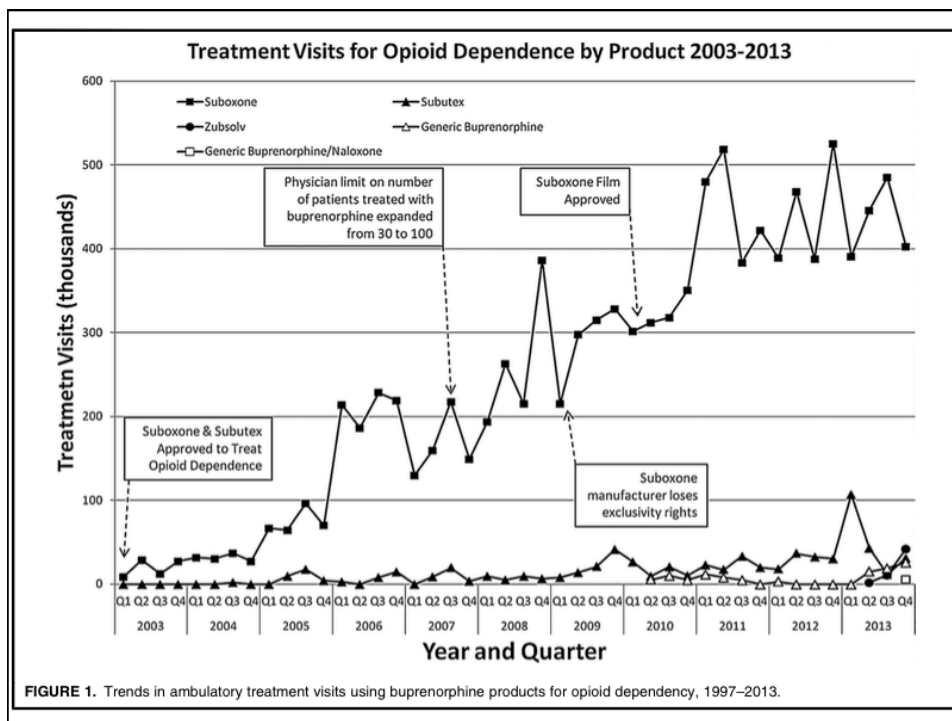
The printed
mucoadhesive
layer with active
drug goes on the
inside of the
cheek

Backing layer
designed to facilitate
unidirectional flow of
medicine

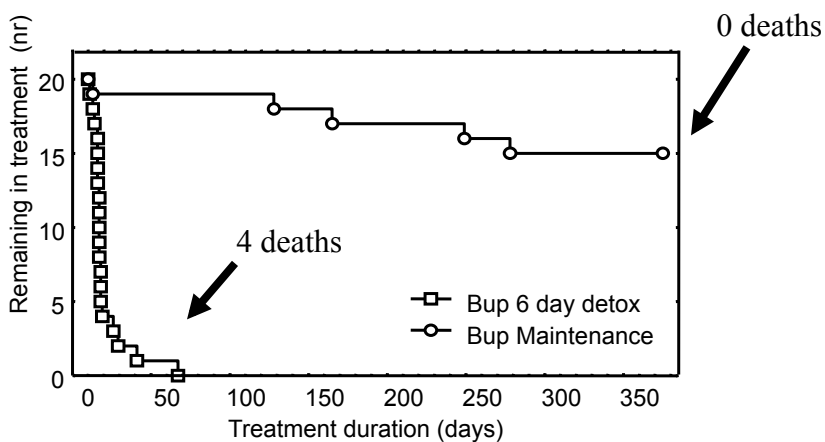
BUNAVAIL 4.2/0.7 mg and Suboxone Sublingual Tablet 8/2 mg Are Bioequivalent for Buprenorphine



1. Data on file. BDSI. 2. Bunavail [package insert]. Raleigh, NC: BioDelivery Sciences International, Inc; 2014.



Buprenorphine: Retention and Mortality



All Patients received group CBT
Relapse Prevention, Weekly
Individual Counseling, 3x Weekly
Urine Screens. n=20 per group

Kakko J, Lancet 2003

Buprenorphine Diversion

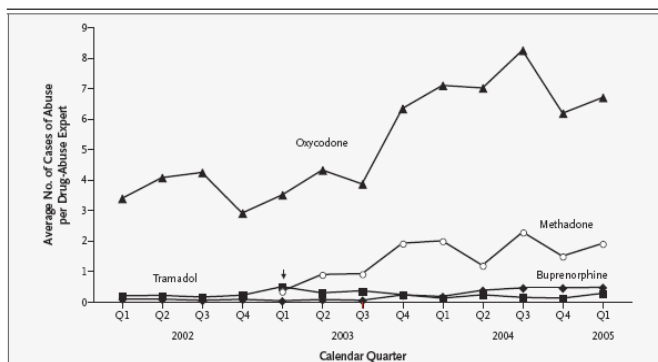


Figure 1. Average Number of Cases of Abuse of Buprenorphine Products, Methadone, Tramadol, and Oxycodone per Drug-Abuse Expert.
The arrow indicates the launch date of buprenorphine for use in office-based treatment of opioid dependence.
Q denotes quarter.

OXYCODONE

METHADONE

BUPRENORPHINE

Cicero, NEJM 2005

Buprenorphine: Potent Analgesic

- 20-50 times potency of morphine
- Available worldwide for pain treatment
- Injectable and patch formulations available in U.S.
- Usual analgesic dose: 0.2-0.4 mg sl
- Higher doses and sublingual for opiate dependence

Buprenorphine: Potent Analgesic

- 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

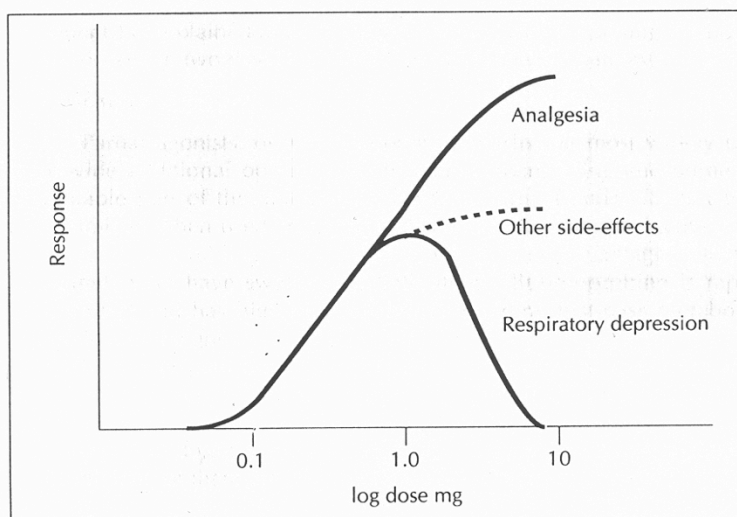


Figure 1. The effect of increasing the dose of buprenorphine on the incidence of side-effects.

Buprenorphine: Analgesic Use

- Surgical pain
 - Intra-operative, peri-operative, post-operative
- Labor pain
- Back pain
- Phantom pain
- Post-herpetic neuralgia
- Cancer pain

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 base is growing

Buprenorphine for Pain

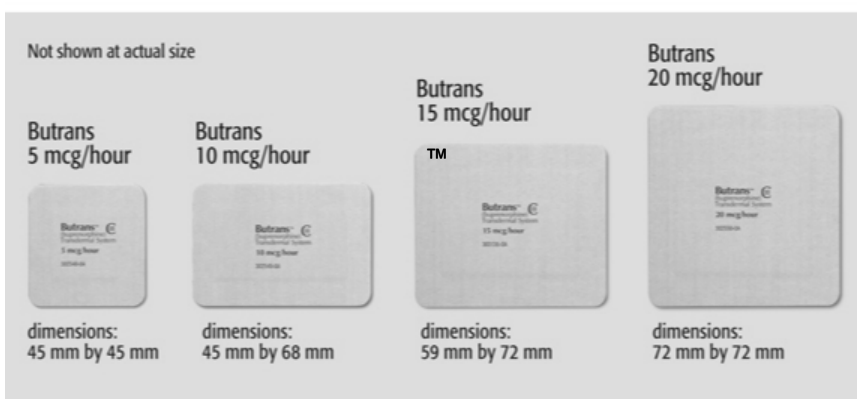
- **Buprenex®** 0.3mg IM/IV: (1975 US) solution for injection often used for acute pain, COST: apx \$13/injection
- **Temgesic®** (2008 UK) 324µg IM/IV:solution for injection often used for acute pain
- **Temgesic®** (2008 UK) 200mcg, 400mcg sublingual tablets for moderate to severe pain

Buprenorphine for Pain

- **Norspan ® (2005 UK)** transdermal patch used for chronic pain 5mcg/hr, 10mcg/hr, 20mcg/hr
- **Butrans ®(2010 US)** transdermal patch used for chronic pain 5mcg/hr, 7.5mcg/hr10mcg/hr, 15mcg/hr 20mcg/hr
 - Each patch lasts 1 week
 - COST \$40-120/patch depending on dose

Butrans®

BUTRANS—AVAILABLE DOSAGE STRENGTHS

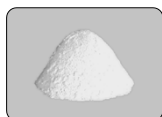


What's new coming down the pipeline?

- Probuphine™
- Bellbuca™
- 1 week injections
- 4 week injections
- Others?

PROBUPHINE™ Solid Matrix Formulation Facilitates Long-Term Delivery

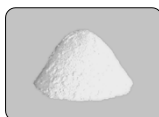
EVA polymer



Inert component
of several
approved products

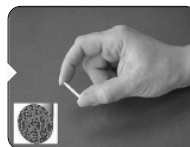


Buprenorphine



Approved for treatment
of opioid addiction, and
acute and chronic pain

**Blended
&
Extruded**



26 mm long,
2.5 mm diameter

Probuphine provides sustained release of
buprenorphine for up to 6 months

Probuphine is not radio-opaque

Discussion and Questions

Thank you for your participation and time!

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