New pharmacological technologies in the clinical management of narcotic dependencies
Basic Pharmacology

An opioid is a chemical that works by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract.
<table>
<thead>
<tr>
<th>Opioid classification</th>
<th>Natural opiates</th>
<th>Semi-synthetic opioids</th>
<th>Synthetic opioids</th>
<th>Mixed antagonists</th>
<th>Antagonists</th>
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<tbody>
<tr>
<td></td>
<td>Opium, Morphine, Codeine</td>
<td>Heroin, Oxycodon, Hydrocodon, Hydrocodone, Oxymorphone, Hydromorphone</td>
<td>Methadone, Mepiridine, Fentanyl</td>
<td>Buprenorphine, Pentazocine</td>
<td>Naltrexone, Naloxone</td>
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<td></td>
<td>Thebaine, Papaverine, Nescapine</td>
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</table>
Bentley compounds

✓ Bentley compounds are a class of semi-synthetic opioids that were first synthesized from thebaine by K. W. Bentley.

✓ The compounds include: oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine and etorphine.

Compounds Possessing Morphine-Antagonising or Powerful Analgesic Properties.
Bentley compounds

- Etorphine - Immobilon is often used to immobilize elephants and other large mammals.
- Etorphine is available legally only for veterinary use and is strictly governed by law.
- Diprenorphine – Revivon is an opioid receptor antagonist that can be administered in proportion to the amount of etorphine used (1.3 times) to reverse its effects.
- Veterinary-strength etorphine is fatal to humans. For this reason the package as supplied to vets always includes the human antidote as well as Etorphine.

Endogenous opioids

Four classes of endogenous opioids:
enkephalins, endorphins, endomorphins, dynorphins

Endogenous opioids have a range of functions, including:
- Pain relief
- Induction in euphoria
- Regulation
Basic Pharmacology

✓ Opioids bind to specific opioid receptors in the nervous system and other tissues.

✓ There are three principal classes of opioid receptors, \( \mu, \kappa, \delta \) (mu, kappa, and delta), although up to seventeen have been reported, and include the \( \varepsilon, \iota, \lambda, \) and \( \zeta \) (Epsilon, Iota, Lambda and Zeta) receptors.
Opioid Receptors

Subtypes with known clinical significance

- μ (mu)
- δ (delta)
- κ (kappa)
- NOP1 (ORL-1)

- They are involved in the functioning of distinct physiological processes
Opioid Receptors

**μ(mu)-opioid receptor**

β-endorphins are endogenous ligands which exert their effects primarily through the μ-opioid receptor.

μ(mu)-opioid receptor (μ₁, μ₂, μ₃) mediates:

- **μ₁**: analgesia and physical dependence
- **μ₂**: respiratory depression, euphoria, miosis, reduced GI motility and physical dependence
- **μ₃**: unknown

Endomorphins are two novel endogenous opioid peptides. Endomorphin-1 and endomorphin-2 are tetrapeptides with the highest known affinity and specificity for the μ opioid receptor.

Leu-enkephalins, Met-enkephalins and delorphins are endogenous ligands which exert their effects primarily through the delta-opioid receptor

\( \delta (\delta 1 \text{ and } \delta 2) \) receptor mediates:

- Analgesia
- Antidepressant effects
- Physical dependence
- Many delta agonists may also cause seizures at high doses

Opioid Receptors

K (kappa)-opioid receptor

Dynorphins are endogenous ligands which exert their effects primarily through the κ-opioid receptor.

Kappa receptor (K1, K2 and K3) mediates:

✓ analgesia
✓ sedation
✓ miosis
✓ inhibition of ADH (anti-diuretic hormone) release
✓ dysphoria

Salvinorin A12 is a potent and selective κ-opioid receptor agonists. The κ-opioid receptor also mediates the action of the hallucinogenic side effects of opioids such as pentazocine (Talwin NX).

Opioid Receptors

Nociceptin opioid receptor (NOP1- OLR-1)

- Nociceptin is the endogenous ligand for the nociceptin receptor (NOP1)
- Nociceptin is an opioid-related peptide, but it does not act at the classic opioid receptors and its actions are not antagonized by the opioid antagonist naloxone.
- Nociceptin is a potent anti-analgesic.
- There is some evidence that nociceptin may be involved in the phenomenon of opioid-induced hyperalgesia
  Individuals taking opioids might develop an increasing sensitivity to noxious stimuli, even evolving a painful response to previously non-noxious stimuli (allodynia).

NOP1 receptor mediates:

- Anxiety
- Depression
- Development of tolerance to mu agonists
- Nociception
- Food intake
- memory processes
- cardiovascular and renal functions
- spontaneous locomotor activity
- gastrointestinal motility

Opioid Receptors

Epsilon – opioid receptor

Epsilon receptor is stimulated by the endogenous opioid peptide beta-endorphin, which induces the release of Met-enkephalin, which, in turn, acts on spinal delta 2-opioid receptors to produce antinociception.


Opioid Receptors

- Receptor affinity
  - How tightly the drug binds to the receptor

- Dissociation
  - How fast the drug leaves the receptor

- Intrinsic activity
  - How much the drug stimulates the receptor
Agonist and antagonist

• **Full agonists** – bind to the µ receptor producing an almost linear increase in physiological effect:
  - Opium, morphine, codeine, heroin, methadone

• **Partial agonists** – bind to the µ receptor but have a ‘ceiling’ effect on receptor activation:
  - Buprenorphine: The agonist effects of buprenorphine (32 mg) increase linearly with increasing doses until it reaches a plateau and no longer continue to develop respiratory depression with further doses, meaning “ceiling effect”.
  - A compound that has an affinity for & stimulates physiological activity at the same cell receptors as opioid agonists but that produces only a partial (i.e., submaximal) bodily response.

• **Antagonists** – bind to the µ receptor but do not produce a biological response and are able to block agonist effects: naloxone, naltrexone, nalmefene

*Nalmefene (Revex)* is an opioid receptor antagonist and used primarily in the management of alcohol dependence, and also has been investigated for the treatment of other addictions such as pathological gambling and shopping.
Selective antagonists

- All of the opioid antagonists used in medicine are non-selective, either blocking all three opioid receptors, or blocking the mu-opioid receptor but activating the kappa receptor.
- However for scientific research selective antagonists are needed which can block one of the opioid receptors but without affecting the other two.
- This has led to the development of antagonists which are highly selective to one of the three receptors;
- Cyprodime is a selective mu opioid receptor antagonist
- Naltrindole is a selective delta opioid receptor antagonist
- Norbinaltorphimine is a selective kappa opioid receptor antagonist


Understanding Opioid Effects

- Potentially lethal dose
- Positive effect = addictive potential
- Negative effect

Super agonist - fentanyl

Full agonist - morphine/heroin, hydromorphone

Potentially lethal dose

Agonist + partial agonist

Partial agonist - buprenorphine

Antagonist - naltrexone

Antagonist + agonist/partial agonist

Dose
Opioid use characteristics..

- Abused primarily for euphoric ("rush") and analgesic ("Nirvana") effects
- Effects might be influenced by:
  - Route of administration
  - Onset of action - Rate of transfer across blood-brain barrier/lipophilicity
  - Level of intrinsic activity
  - Duration of action/half-life
Opioid use characteristics.

- Dependence diagnosis is strictly defined by DSM-IV-TR (2000) and ICD 10 (1992) criteria.
- Continuous unsupervised (legal and illegal) use might lead to the necessity to increase needed dose in order to reach desired effect: “tolerance”.
- Tolerance elevates plateau.
- Doses beyond plateau lead to overdose.
- Inverse tolerance means that decreasing doses elevates effects.
- Reduction or cessation of used narcotic substances might lead to withdrawal symptoms and signs (syndrome):
  - Yawning
  - Mydriasis
  - sweating
  - Lacrimation
  - Anxiety
  - Piloerection
  - Diarrhea
  - rhinorrea
Buprenorphine Pharmacology

- Mu partial opioid agonist
- NOP-1 agonist
- Kappa antagonist
- Delta antagonists

- The antinociceptive effect of buprenorphine mediated primarily by the mu opioid receptor is attenuated by the ability of the drug to activate the NOP-1 receptor
- Partial agonism at the mu opioid receptor and antagonism at the kappa or delta opioid receptor (“anti-physical dependence”) have been considered as possible underlying mechanisms for the ceiling effect
Buprenorphine Pharmacology

- High Mu receptor affinity and receptor occupancy:
  - Up to 90% at 16mg of BP
  - Full blockade or attenuated effect of additional ingested opioids
- Lower intrinsic activity than full agonists:
  - Favourable safety profile (ceiling effect)
  - Lower street value (in comparison to opiates)
  - Lower abuse potential (in comparison to opiates)
Buprenorphine Pharmacology

- Partial Agonism
- “Ceiling Effect”
- Successful high dose transfers
- Ceiling/Plateau observed on side effects

Ceiling effect is defined as the phenomenon in which a drug reaches a maximum effect, so that increasing the drug dosage does not increase its effectiveness.

Buprenorphine exerts a full agonist effect against pain in man.

Buprenorphine induces “ceiling effect” in respiratory depression but not in analgesia.

There is a “ceiling effect” or plateau to subjective effects.

“Ceiling effect” is to side effects but not therapeutic effects.
Buprenorphine activates NOP-1

ORL-1 (Opioid Receptor-Like)

✓ Buprenorphine activates NOP-1 receptors
✓ Supraspinal activation of the NOP-1 receptor counteracts the antinociceptive and rewarding actions of opiates
✓ The antinociceptive effect of buprenorphine mediated primarily by the mu partial agonism is attenuated by the ability of the drug to activate the NOP-1 receptor
✓ NOP-1 activation may limit dependence potential
✓ Partial agonism at the mu opioid receptor and antagonism at the kappa or delta opioid receptor have been considered as possible underlying mechanisms for the ceiling effect.
Dysfunction of the endogenous kappa opioid system may contribute to opioid dependence through the appearance of dysphoria.

Kappa opiate agonists may produce dysphoria and psychotomimetic effects in humans.

Buprenorphine has proved to possess antidepressant, anxiolitic effects, anti-craving, anti-dysphoric and antipsychotic properties in psychiatric patients.

“The antipsychotic potency of the partial opiate agonist buprenorphine was evaluated in 10 neuroleptic-free schizophrenic patients suffering from frequent hallucinations, delusions, and severe formal thought disorders. Buprenorphine had a pronounced antipsychotic effect, which lasted about 4 hours, in patients with schizophreniform disorders (N = 4) and paranoid schizophrenia (N = 3)”


Buprenorphine treating profile

- Slow receptor dissociation leads to:
  - Longer duration of action
  - Milder withdrawal
- Lower physical dependence potential than full agonists
- Limited development of tolerance
- Ceiling effect on respiratory depression
  - Increased safety against overdose
  - Safer Induction schedules
- Relatively slow access to receptors
- Sublingually, but NOT orally, active
Buprenorphine
Rapid onset of action

- Readily absorbed sublingually
  - 5-10 min for Buprenorphine absorption
- Rapid onset of action: 30-60 min
- Peak plasma levels at 1-4 hs
- Peak subjective/physiological effect at 1-4 h
- Distribution: 96% protein bound
  - Alpha & beta globulin
Duration of effects

- Duration of action is dose related
  - low dose : 4 – 12 hrs
  - med dose : ~ 24 hrs
  - high dose : 2 – 3 days

- Elimination half-life ~24 to 36 hours

- Steady state equilibrium achieved after 3 – 7 days
<table>
<thead>
<tr>
<th>BP Pharmacological property</th>
<th>BP Clinical implication</th>
</tr>
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<tbody>
<tr>
<td>Substitutes for heroin</td>
<td>Prevents withdrawal</td>
</tr>
<tr>
<td></td>
<td>Can be used for maintenance / withdrawal</td>
</tr>
<tr>
<td>Opiate-like effects</td>
<td>Reduces cravings</td>
</tr>
<tr>
<td></td>
<td>Increases treatment retention</td>
</tr>
<tr>
<td>‘Blocks’ effects of other opiates</td>
<td>Reduces heroin use</td>
</tr>
<tr>
<td>Long duration of action</td>
<td>Daily or alternate day dosing possible</td>
</tr>
<tr>
<td>Side effects</td>
<td>Similar to other opiates, but less sedating and safer in overdose</td>
</tr>
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</table>
Precipitated withdrawal

Buprenorphine has a higher affinity (stronger binding ability) it expels existing opioids and blocks others from attaching. As a partial agonist, the buprenorphine has a limited opioid effect.

Opioids replaced and blocked by buprenorphine
Precipitated withdrawal

✓ People switching from other opiates should wait until mild to moderate withdrawal symptoms are encountered.

✓ Failure to do so can lead to the rapid onset of intense withdrawal symptoms, known as precipitated withdrawal.

✓ For short acting opioids such as codeine, hydrocodone, oxycodone, hydromorphone, pethidine, heroin, and morphine, 12–24 hours from the last dose is generally sufficient.

✓ For longer acting opioids such as methadone, 2–3 days from the last dose is needed to prevent precipitated withdrawal.
How to avoid precipitated withdrawal from Buprenorphine

- Administer 1st buprenorphine dose when objective signs of withdrawal are present (piloerection)
- Induction with BP or and BP-Nx can be achieved with no precipitated withdrawal
- Concomitant medications: clonidine, antihistamines, antidepressants with sedative effects
COWS
Clinical opiate withdrawal scale

COWS (Clinical Opiate Withdrawal Scale) is a measure that evaluates the severity of opiate withdrawal symptoms. Treatment with a dose of codeine for withdrawal or maintenance, along with the appearance of physical withdrawal symptoms, only occurs when Codeine Withdrawal Score (COWS) is elevated. Providing early codeine treatment may cause severe withdrawal symptoms - PRICIPITATE WITHDRAWAL!
<table>
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<tr>
<th>Symptoms</th>
<th>Scores</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Resting pulse rate</td>
<td>0-4</td>
<td>0=80 or less; 1=81-100; 2=101-120; 4=120 or greater</td>
</tr>
<tr>
<td>Sweating</td>
<td>0-4</td>
<td>0=none; 4=sweat streaming from face</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0-5</td>
<td>0=sits still; 5=unable to sit still (even for a few seconds)</td>
</tr>
<tr>
<td>Pupil size</td>
<td>0-5</td>
<td>0=normal; 5=dilated (only iris rim visible)</td>
</tr>
<tr>
<td>Bone or joint aches</td>
<td>0-4</td>
<td>0=none; 4=severe discomfort</td>
</tr>
<tr>
<td>Runny nose or tearing</td>
<td>0-4</td>
<td>0=none; 4=constant</td>
</tr>
<tr>
<td>GI upset</td>
<td>0-5</td>
<td>0=none; 5=multiple episodes of vomiting or diarrhea</td>
</tr>
<tr>
<td>Tremor</td>
<td>0-4</td>
<td>0=none; 4=gross tremor</td>
</tr>
<tr>
<td>Yawning</td>
<td>0-4</td>
<td>0=none; 4=yawning several times/minute</td>
</tr>
<tr>
<td>Anxiety &amp; Irritability</td>
<td>0-4</td>
<td>0=none; 4=severe, precluding participation</td>
</tr>
<tr>
<td>Gooseflesh skin</td>
<td>0-5</td>
<td>0=smooth; 5=prominent piloerection</td>
</tr>
</tbody>
</table>

COWS=Clinical Opiate Withdrawal Scale; GI=gastrointestinal.

Score: 5-12 mild; 13-24=moderate; 25-36=severe.

How to avoid precipitated withdrawal from Buprenorphine

- Wiser use of concomitant associated medications can help during induction phase
- Clonidine (Normopressan and Clonnirit)
- Prothiazone
- Antidepressants with sedative effects:
  - Mirtazapine
  - Trazodone
  - Bonserin
  - Amitryptiline, doxepin
- BZ (with extreme caution)
- Small doses of second generation anti-psychotics (off-label)
Buprenorphine precipitated withdrawal

- Generally starts 30–90 min after first dose
- Generally reaches peak ($C_{\text{max}}$) within 90 – 180 minutes after first dose
- Minor symptoms may continue after second or third dose
- Symptoms and signs might persist with continued narcotic use
Buprenorphine hydrochloride can be administered by intramuscular injection, intravenous infusion, transdermal patch, sublingual film, sublingual tablets or an ethanolic liquid oral solution.

It is not administered orally due to very high first-pass metabolism.

Buprenorphine is metabolised by the liver, via CYP3A4 isozymes of the cytochrome P450 enzyme system, into norbuprenorphine (by $N$-dealkylation).
Buprenorphine Metabolism

- The glucuronidation of buprenorphine is primarily carried out by UGT1A1 and UGT2B7, and that of norbuprenorphine by UGT1A1 and UGT1A3.
- These glucuronides are then eliminated mainly through excretion into the bile.
- The elimination half-life of buprenorphine is 20–73 hours (mean 37).
- Due to the mainly hepatic elimination, there is no risk of accumulation in patients with renal impairment.
Common adverse drug reactions associated with the use of buprenorphine are similar to those of other opioids and include: nausea and vomiting, drowsiness, dizziness, headache, memory loss, cognitive and neural inhibition, perspiration, itchiness, dry mouth, miosis, orthostatic hypotension, male ejaculatory difficulty, decreased libido, and urinary retention.
Buprenorphine adverse effects

- Constipation and CNS effects are seen less frequently than with morphine.

- Hepatic necrosis and hepatitis with jaundice have been reported with the use of buprenorphine, especially after intravenous injection of crushed tablets.
Buprenorphine adverse effects

- The most severe and serious adverse reaction associated with opioid use in general is respiratory depression, the mechanism behind fatal overdose.
- Buprenorphine behaves differently than other opioids in this respect, as it shows a ceiling effect for respiratory depression.
- Moreover, former doubts on the antagonisation of the respiratory effects by naloxone have been disproved: Buprenorphine effects can be antagonised with a continuous infusion of naloxone.
Buprenorphine adverse effects

• Concurrent use of buprenorphine and CNS depressants such as alcohol or benzodiazepines (flumazenil) is contraindicated as it may lead to fatal respiratory depression.

• Benzodiazepines, in prescribed doses, are not contraindicated in individuals who are tolerant to either opioids or benzodiazepines.
People on medium- to long-term maintenance with Suboxone or Subutex do not have a risk of overdose from buprenorphine alone, no matter what dosage is taken or route of administration it is taken by, due to the "ceiling effect" on respiratory depression.

Overdoses occurring in maintenance patients are cases of multiple-drug intoxication, usually buprenorphine taken with excessive amounts of ethanol and/or benzodiazepine drugs.

All patients on buprenorphine maintenance are tolerant to opioids, and maintenance doses are always higher than the dose at which the "ceiling effect" on respiratory depression is reached.
Buprenorphine contraindications

- Like full agonist opiates, buprenorphine can cause drowsiness, vomiting and respiratory depression.
- Taking buprenorphine in conjunction with central nervous system (CNS) depressants in people who are not tolerant to either agent can cause fatal respiratory depression.
- Sedatives, hypnotics, and tranquilizers can be dangerous if ingested with buprenorphine by a person who is tolerant to neither opioids nor benzodiazepines.
- Co-intoxication with ethanol carries the greatest risk for lethal overdose.
## Comparison of methadone & buprenorphine profiles (I)

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<th>Methadone</th>
<th>Buprenorphine</th>
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<tr>
<td><strong>Classification</strong></td>
<td>Full µ agonist</td>
<td>Partial µ agonist</td>
</tr>
<tr>
<td><strong>Substitutes for heroin</strong></td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Blocks effects of heroin</strong></td>
<td>++ At high doses (e.g.&gt;60 mg)</td>
<td>++++ At low doses (e.g.&gt; 4 mg)</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Opiate-like</td>
<td>Less sedating Precipitated w/d</td>
</tr>
<tr>
<td><strong>Withdrawal on cessation</strong></td>
<td>+++ Described as severe &amp; prolonged</td>
<td>++ Less severe</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>-----------------------------------------</td>
</tr>
<tr>
<td><strong>Onset of effects</strong></td>
<td>30 – 60 min</td>
<td>30 – 60 min</td>
</tr>
<tr>
<td><strong>Peak effects</strong></td>
<td>3 – 6 hours</td>
<td>1 – 4 hours</td>
</tr>
<tr>
<td><strong>Duration of clinical effects</strong></td>
<td>16 to 30 hours</td>
<td>Up to 2 – 3 days at high doses</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic MES +++ Affected by liver function</td>
<td>Hepatic MES &amp; conjugation Less clinical impact of liver function</td>
</tr>
<tr>
<td><strong>Mode of administration</strong></td>
<td>Oral</td>
<td>Sublingual</td>
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<tr>
<td><strong>Drug interactions</strong></td>
<td>Sedatives Opioid antagonists</td>
<td>Sedatives Opioid agonists &amp;</td>
</tr>
</tbody>
</table>
Opioids to take into consideration……..

- Oxycodone: Percocet, Percodan, Oxycontin 10, 20, 40, 80 mg, OxyCod Syrup
- Oxicodone/Nx: Targin 10mg/5mg 20mg /10mg
- Propoxyphene: Proxol, Rogaan, Algolysin
- Morphine: MCR, MIR, Morphex
- Hydromorphone: Palladone SR, parenteral
- Fentanyl: Duragesic 25, 50, 75, 100 mcg/Hs
- Codeine: Cod-Acamol, Codical
- Buphrenorphine: Nopan (0.2 mg), BuTrans (5, 20, 20 mg), Subutex (2 and 8 mg)
- Buphrenorphine/Nx: Suboxone: 2mg/0.5 mg, 8mg/2mg
- Methadone: Adolan
- Tranmadol: Tramadex: 100mg, 200mg, 300mg
- **Opium: Opium pelvis 10%**
Naloxone pharmacology

- Naloxone has an extremely high affinity for μ-opioid receptors in the central nervous system and also has an antagonist action, though with a lower affinity, at κ- and δ-opioid receptors.
- Naloxone principally acts as a competitive antagonist at the Mu receptor:
  - Binds to the receptor
  - Prevents binding of other opioids to the receptor
  - Precipitates withdrawal when injected in opioid-dependent individuals
  - Short acting (1/2 life 45 minutes)
Naloxone pharmacology

Mu opioid inverse agonists: an inverse agonist is an agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that agonist.

- Not orally available (‘inactive’)
- Very poorly absorbed sublingually
- Rapid access to Mu receptors (IV)
- Relatively quick receptor dissociation
Naloxone is a μ-opioid receptor competitive antagonist and its rapid blockade of those receptors often produces rapid onset of withdrawal symptoms.

Naloxone also has an antagonist action, though with a lower affinity, at κ- and δ-opioid receptors.
Naloxone pharmacology

Side effects include: change in mood, increased sweating, nausea, nervousness, restlessness, trembling, vomiting, allergic reactions such as rash or swelling, dizziness, fainting, fast or irregular pulse, flushing, headache, heart rhythm changes, seizures and sudden chest pain.

It is a common misconception that the Naloxone in Suboxone initiates precipitated withdrawal. This is false. Naloxone can only initiate precipitated withdrawal if injected into a person tolerant to opioids other than buprenorphine. Taken sublingually Naloxone has virtually no effect.
Naloxone pharmacology

- Counteracting opiate overdose and addiction
- Preventing opioid abuse
- Depersonalization disorder
- CIPA - Congenital insensitivity to pain with anhidrosis
  It is an extremely rare disorder (1 in 125 million) that renders one unable to feel pain
- Valproate overdose

Use of naloxone in valproic acid overdose: case report and review: Roberge RJ and Francis EH
Suboxone

- A Buprenorphine - Naloxone combination
- Developed in response to previous reports of opioid misuse
- Designed specifically to decrease injectable abuse potential of Buprenorphine by out-of-treatment opioid users
- Tablets and films
BP-Nx Pharmacology

- Sublingual Administration:
  - Nx does NOT compromise Buprenorphine absorption
  - Same Buprenorphine plasma levels from Subutex and Suboxone
  - Buprenorphine time of onset and time of peak effect unaltered by Nx
  - Duration of action unaltered by Nx
  - Nx plasma levels undetectable at 8/2mg dose level
BP/Nx Adherence

- Buprenorphine is clinically effective when taken sublingually
- Negligible effect of naloxone via sublingual route
- Suboxone is reported as identical to buprenorphine alone in opioid-dependents
BP-Nx preparation

4 part buprenorphine: 1 part naloxone

BP 8mg / Nx 2mg
BP 2m / Nx 05mg

The right balance between agonist and antagonist effects

✓ Sublingual: Opiate agonist effect from buprenorphine
✓ Intravenous: Opiate antagonist effect from naloxone
### Buprenorphine vs. BupNX by injection †

<table>
<thead>
<tr>
<th>Condition</th>
<th>Buprenorphine</th>
<th>BupNX</th>
</tr>
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<tbody>
<tr>
<td>Heroin-dependent</td>
<td>Agonist effect</td>
<td>Antagonist effect</td>
</tr>
<tr>
<td>Non-dependent</td>
<td>Mild agonist effect</td>
<td>Attenuated agonist effect</td>
</tr>
<tr>
<td>Methadone-maintained</td>
<td>Antagonist effect</td>
<td>Antagonist effect</td>
</tr>
<tr>
<td>Buprenorphine or BupNX</td>
<td>Agonist effect</td>
<td>Agonist Effect (attenuated)</td>
</tr>
<tr>
<td>maintained</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†assuming some time interval has elapsed since last use of drug
Injecting Suboxone

• Effects of naloxone maximised by this route

• Naloxone gains rapid access to receptors
  ❖ Precipitates moderate-severe withdrawal in individuals dependent on full opioid agonists
  ❖ Nx effects last up to 2 hrs
  ❖ Buprenorphine effects evident >1 hr later

• Effects of IV Suboxone are indistinguishable from IV naloxone in individuals dependent on full opioid agonists
“The present study, conducted as part of the development of a buprenorphine/naloxone combination product, was designed to evaluate the individual and combined effects of intravenously administered buprenorphine and naloxone. This in-patient trial used a randomized, double-blind, crossover design. Ten opioid-dependent male subjects were stabilized and maintained on morphine, 15 mg given intramuscularly four times daily. Then, at 48- to 72-h intervals, subjects received one of the following by intravenous injection: (1) placebo, (2) morphine 15 mg, (3) buprenorphine 2 mg, (4) buprenorphine 2 mg/naloxone 0.5 mg, and (5) naloxone 0.5 mg. Both naloxone and buprenorphine/naloxone produced significant (P < 0.005) opioid withdrawal effects compared to placebo as assessed with the CINA scale, an instrument which utilizes subject- and observer-reported, as well as physiological parameters. The combination of buprenorphine with naloxone in a 4:1 ratio produced opioid antagonist-like effects which should limit its potential for intravenous abuse by opioid addicts”

✔ Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts.
Fudala PJ, Yu E, Macfadden W, Boardman C, Chiang CN.
Suboxone may limit misuse

- Buprenorphine works when placed under tongue
- Naloxone works when injected
  - Very low sublingual/oral bioavailability
- Suboxone suppresses withdrawal and craving when taken sublingually
- Suboxone precipitates withdrawal when injected by opioid-dependent patients
Suboxone safety

- Well tolerated
- No apparent adverse clinical effects attributable to naloxone, even during induction
- No safety concerns following administration of 24/6 mg for up to a year
- Naloxone does not appear to interfere with the sublingual absorption of buprenorphine
Suboxone films

• In addition to the sublingual tablet, Suboxone is now marketed in the form of a sublingual film, available in both the 2 mg/0.5 mg and 8 mg/2 mg dosages.

• The film has some advantages over the traditional tablet in that it dissolves faster and, unlike the tablet, adheres to the oral mucosa under the tongue, preventing it from being swallowed or falling out.

• Patients favor its taste over the tablet.

• Each film strip is individually wrapped in a compact unit-dose pouch that is child-resistant and easy to carry and that it is clinically interchangeable with the Suboxone tablet and can also be dosed once daily.

• The film discourages misuse and abuse, as the paper-thin film is more difficult to crush and snort.

• Also, a 10-digit code is printed on each pouch which helps facilitate medication counts and therefore serves to deter diversion into the illegal drug market.
**OBJECTIVE:**
Sublingual buprenorphine appears useful in the treatment of opiate dependence. A combination sublingual dose of buprenorphine and naloxone could have less potential for parenteral use by opiate-dependent individuals. To estimate the abuse potential of a combination formulation, we assessed the parenteral effects of a buprenorphine and naloxone combination in untreated heroin addicts.

**METHODS:**
Eight healthy, opiate-dependent daily users of heroin were given, under double-blind conditions on four separate occasions, either (1) 2 mg buprenorphine, (2) 2 mg naloxone, (3) 2 mg buprenorphine and 2 mg naloxone combined, or (4) placebo as a single intravenous infusion during a 30-second interval. Opiate agonist and antagonist physiologic and subjective effects were measured. Data were analyzed by analysis of variance.

**RESULTS:**
Buprenorphine increased opiate intoxication and relieved withdrawal. The buprenorphine and naloxone combination precipitated opiate withdrawal and was unpleasant and dysphoric in all subjects. Fifty percent of the subjects were unable to distinguish between naloxone alone and the combined medications during the first hour of testing.

**CONCLUSIONS:**
The buprenorphine and naloxone combination has a low abuse potential in opiate-dependent daily heroin users.

Buprenorphine-Nx Combination

- Efficacy and safety equivalent to that of Buprenorphine alone
- Discourages IV use
- Reduces street value
- Reduces diversion potential
- Allows for self medication (‘take-home’)

Suboxone and Subutex

- Pharmacology is equivalent
- Pharmacokinetics and efficacy are equivalent
  - Dose-dependently blocks effects of other agonists
  - High affinity, slow dissociation, long acting
  - Partial mu-opioid agonist; ceiling effect at higher doses
- Clinical equivalence
  - Direct induction with Suboxone
  - Side effect profile comparable to that of Subutex
    - Nature of side effects and incidence levels
  - Less than daily dosing schedules
    - Alternate days
    - Three times a week
  - Detoxification protocols as for Subutex