Dr Alistair Dunn

General Practitioner

Whangarei

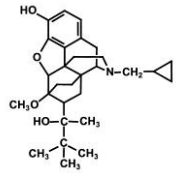
Buprenorphine as a New Opiate Substitute - Concurrent Workshop Repeated

Saturday, 17 August 2013	Start 8:30am	Duration: 55mins	Picasso
	Start 9:35am	Duration: 55mins	Picasso

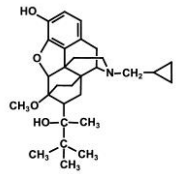
NORTHLAND DISTRICT HEALTH BOARD

Te Poari Hauora Ā Rohe O Te Tai Tokerau


BACK
TO THE FUTURE


HO
O
N–CH2
CH3O
HO–C–CH3
CH3
C
CH3
CH3

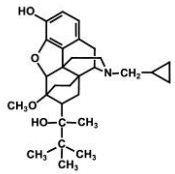
- 1982
- “Temgesic” = Buprenorphine
- Sublingual opiate analgesic 0.2 mg
- Popular drug of abuse
- 1991
- “Temgesic NX” = Bup & Nalxone
- Nalxone added to deter abuse
- 1999
- Eventually taken off the market



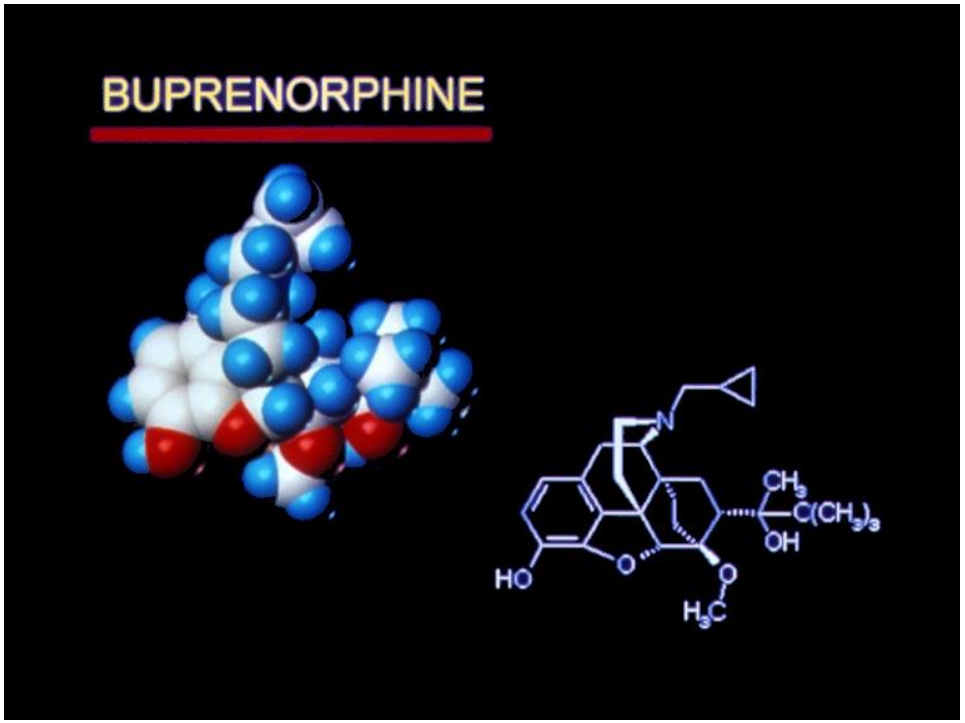
BACK TO THE FUTURE

Buprenorphine 2013

- “Norspan” transdermal patch low dose 5-20 mcg/hr not funded
- “Temgesic” injection 0.3 mg / ml ampule premed & vet
- “Subutex” sublingual tablet 2mg , 8mg – unavailable in NZ
- “Suboxone” sublingual tablet 2mg , 8mg - Bup & Naloxone



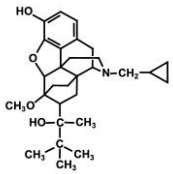
Buprenorphine & Naloxone = Suboxone®



Alistair Dunn

Northland DHB

Community Mental Health & Addiction Service



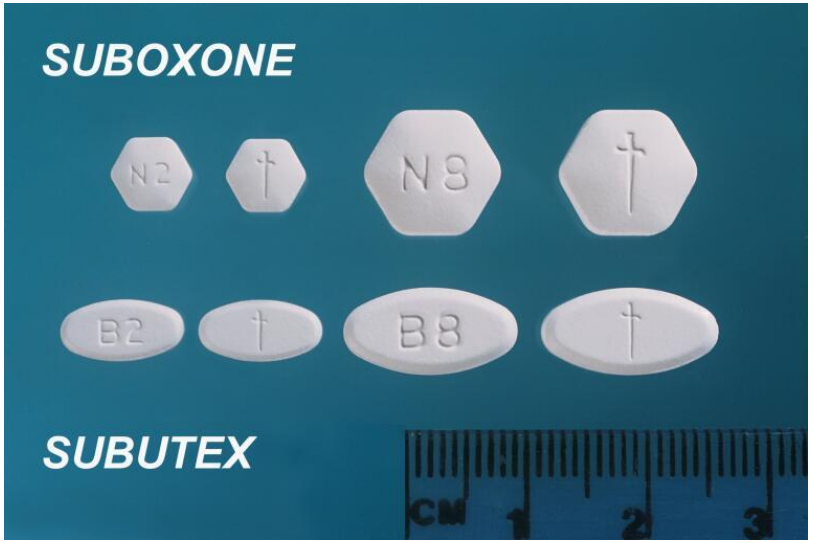
Registration

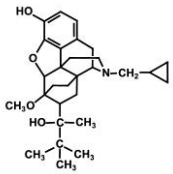
Subutex - Buprenorphine

- 8mg, 2mg & 0.4mg sublingual tablets
- UNAVAILABLE IN NEW ZEALAND

Suboxone – Buprenorphine/Naloxone

8/2mg & 2/0.5mg sublingual tablet



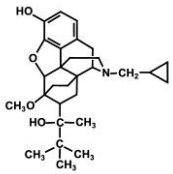


Special Authority

- PHARMAC Funding 1st July 2012 for treatment opioid dependence

CRITERIA

- Patient is opioid dependent and
- engaged with approved Opiate Substitution Treatment (“OST”) service
- Applicant works in approved OST service
- For opiate detox (1mth) or OST maintenance (1 year)



Buprenorphine Pharmacology

- Semi synthetic opioid
- Partial Agonist for the *mu* (μ) opioid receptor and antagonist for the *kappa* (κ) receptor
- High affinity for the *mu* opiate receptor
  - **Binds more tightly to the receptor than most other opiate agonists or antagonists**
- Slow association and dissociation rate from the receptor[3]
  - Long duration of action, low physical dependence liability, milder withdrawal
- Highly lipophilic[1]

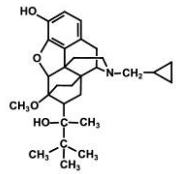
Opiate Receptors

3 main types

***Mu* (μ)**
Analgesia
Euphoria
Respiratory depression

***Kappa* (κ)**
Analgesia
Dysphoria
Diuresis

***Delta* (δ)**
Analgesia
Neurotransmitter release[2]



1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).
2. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e: http://www.accessmedicine.com/content.aspx?aID=940653.
3. Martindale: The Complete Drug Reference, 2009, Pharmaceutical Press (http://www.medicinescomplete.com/mc/martindale/current/)

Agonist or Antagonist?

- Full Agonist

  - binds to the receptor producing an almost linear increase in physiological effect

  e.g. Heroin, Methadone, Morphine

- Partial Agonist

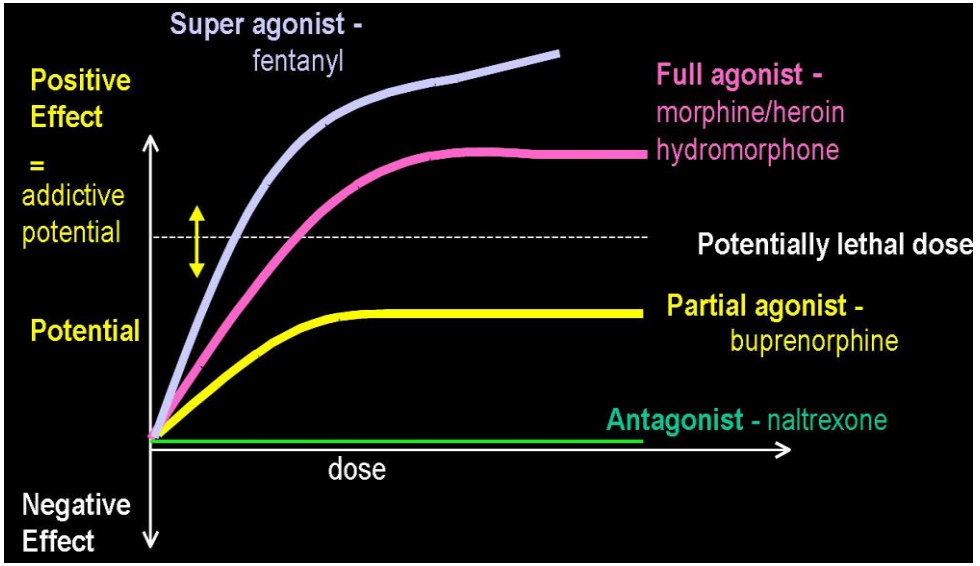
  - binds to the receptor but has a 'ceiling' effect on receptor activation

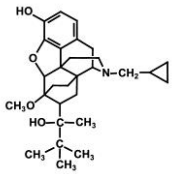
  e.g. Buprenorphine

- Antagonist

  - binds to the receptor but does not produce a biological response and is able to block agonist effects

  e.g. Naltrexone[1]

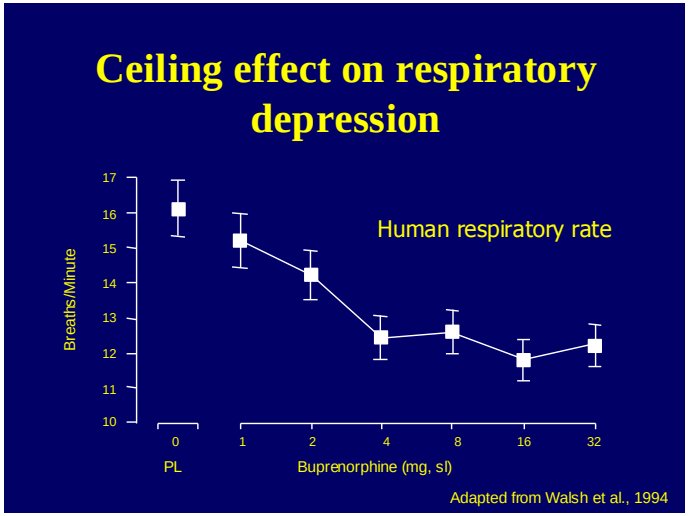


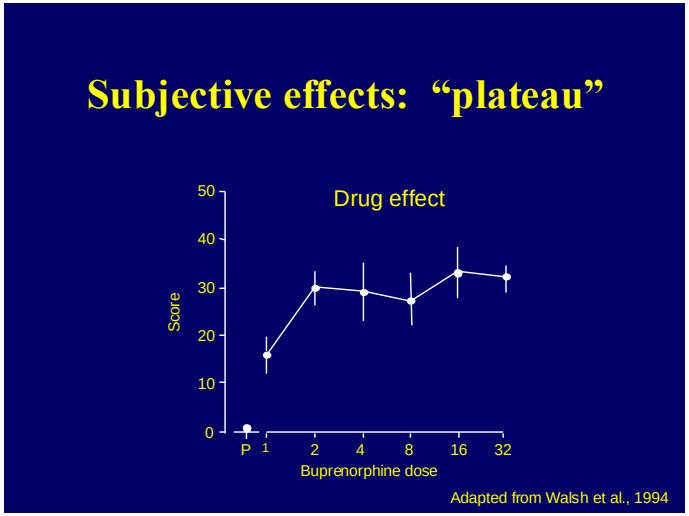


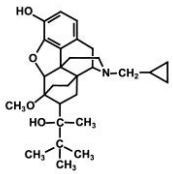
1. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11e: http://www.accessmedicine.com/content.aspx?aID=940653.

Ceiling Effect

- Walsh *et al* (1994) demonstrated that buprenorphine has a ceiling effect for subjective 'drug liking' effects and respiratory depression, consistent with its partial agonist classification[1]



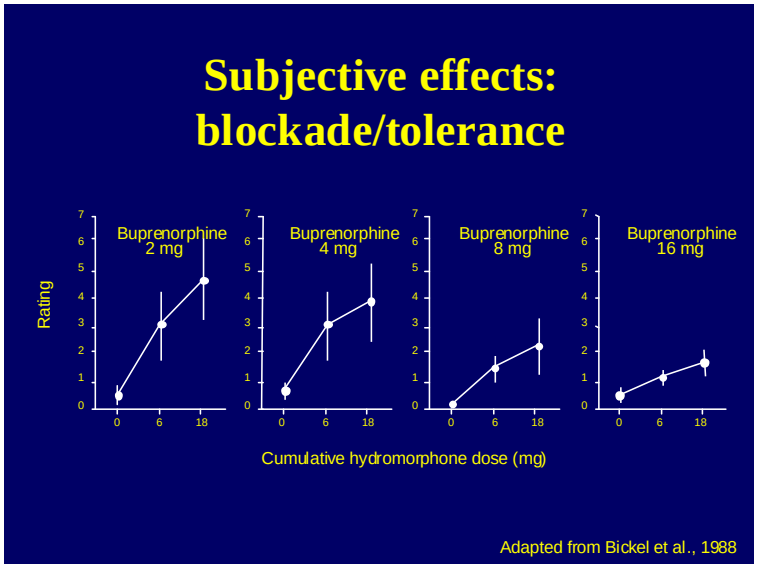


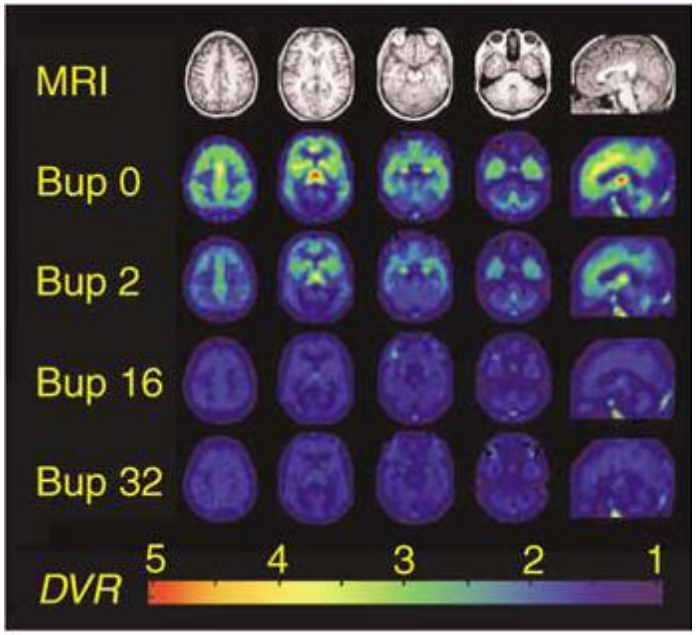


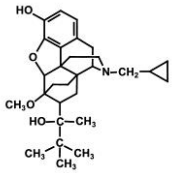
1. Walsh SL *et al*, Clin Pharmacol Ther. (1994) 55:569-580

Blockade Effect

- Buprenorphine demonstrates dose related blockade effect of other opioids, due to high occupancy rate of receptors[1]
  - A 16 mg dose results in a 85-92% reduction in μ receptor availability
  - A 32 mg dose results in a 94-98% reduction in μ receptor availability[2]



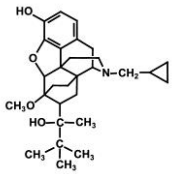




1. Bickel WK *et al*, J Pharmacol Exp Ther (1988) 247:47-53
2. Greenwald MK et al, Neuropsychopharmacolgy (2003) 28, 2000-2009

Dosing Suboxone/Subutex

- Subutex/Suboxone is a sublingual tablet, and should be placed under the tongue
- Tablet should be given to the patient in a clean dry cup, touching of the tablets should be avoided.
- Takes between 2-10 minutes to dissolve the whole tablet
  - individual variation occurs
  - National Guidelines recommend where diversion is a concern, the tablet should be broken into 4 or 5 pieces, not crushed to a powder
- Supervision is required, unless patients qualify for take home doses.[1]

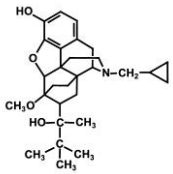


1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Onset of Effect

When administered sublingually:

- Onset of action is between 30-60 minutes
- Peak plasma concentrations occurs within 1-2 hours
- Peak subjective/physiological effects occur in 1-4 hours[1] (dose related)

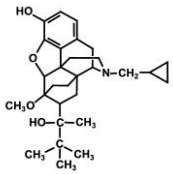


1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Duration of Action

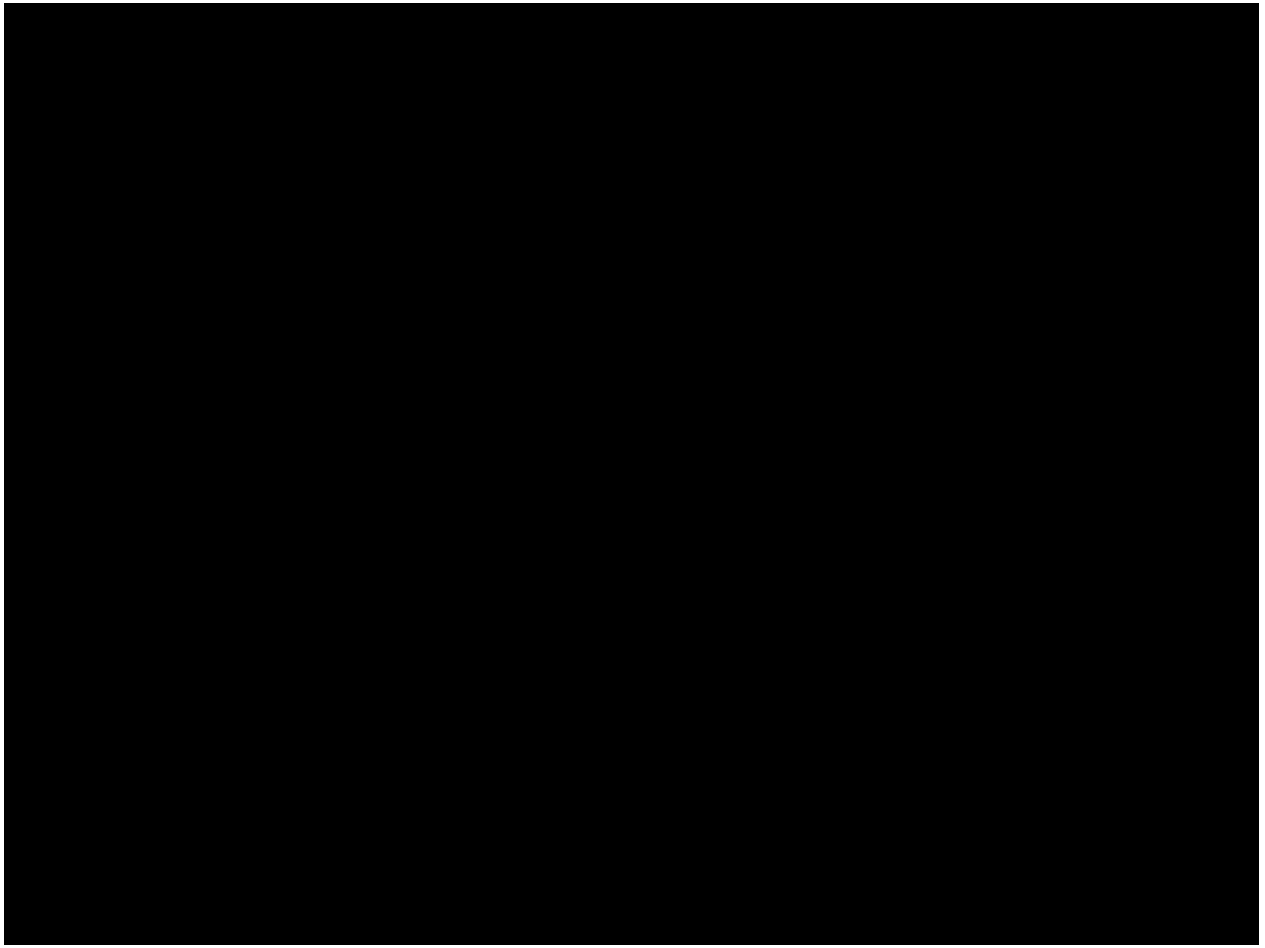
- Duration of action is dose related
- Mean elimination half-life 34.6 hrs
  - metabolised in the liver by CYP3A4 pathway
- Steady state equilibrium is achieved after 3 – 7 days[1]
- 3 times a week dosing
  - There is high inter-individual variability

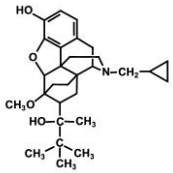
Dose	Duration of Action[2]
4 – 8mg	4- 12hrs
>8 – 16mg	~ 24hrs
>16 – 32mg	48 – 72hrs



1. Suboxone Product Information, TGA approved 27th July 2005.
2. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

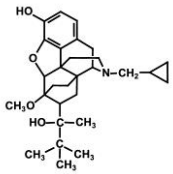
Duration of Action Video





Side Effects

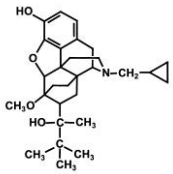
- Similar to other opioids
  - constipation
  - disturbed sleep
  - drowsiness
  - sweating
  - headaches
  - nausea
  - precipitated withdrawal
- Experience of side effects can be variable
  - side effects may be experienced with one opioid medication but not another[1]



1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Precipitated Withdrawal

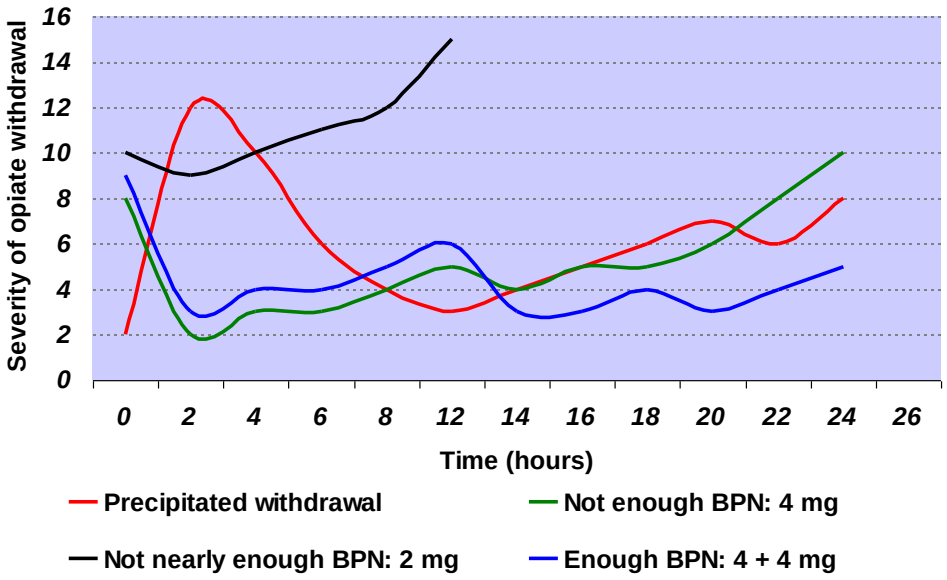
- Buprenorphine competes with and displaces full opioid agonists from receptors because of its high receptor affinity
- The lower intrinsic activity of buprenorphine compared to that of full agonists results in a precipitated withdrawal
- Commences 1-4hrs after 1st dose
- Symptoms are mild to moderate and may continue up to 12hrs after dose
- Minor symptoms can persist after 2nd or 3rd dose
- Symptoms may persist with continued opioid use[1]



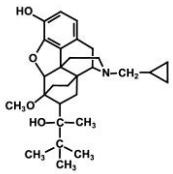
1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Precipitated Withdrawal

- Induction onto Buprenorphine should be done when objective signs of withdrawal are present
- To avoid precipitated withdrawal the National Guidelines recommend inducting Buprenorphine:
  - 4- 6hrs after last Heroin use
  - >24hrs after last low dose (<40mg) of Methadone
  - >36hrs after last medium dose (>40mg) of Methadone
- Induction onto Buprenorphine can be achieved with no precipitated withdrawal when these guidelines are followed[1]

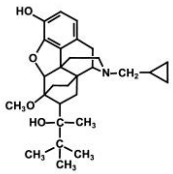


Adapted from Lintzeris et al 2003



1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Precipitated Withdrawal Video



Interactions

- Sedatives e.g. Alcohol, Benzodiazepines

  - Creates additive effect on opioid activity e.g. increased respiratory depression and increases overdose potential

- Opioid agonists e.g.. Heroin, Methadone

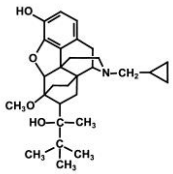
  - High affinity of Buprenorphine potentially displaces opioid agonists from binding to the receptors, potentially leading to precipitated withdrawal

- Opioid antagonists e.g. Naltrexone, Naloxone

  - A high dose of naloxone is required to reverse the effects of Buprenorphine

- Inducers/Inhibitors of cytochrome P450 3A4 hepatic enzymes e.g. HIV & HCV medications

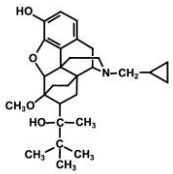
  - Limited clinical impact on Buprenorphine dosing[1]



1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Suboxone

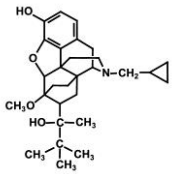
- Combination sublingual tablet comprising of buprenorphine and naloxone in a 4:1 ratio
- Available as 2mg/0.5mg and 8mg/2mg sublingual tablets in packs of 28 tablets[1]



1. Suboxone Product Information, TGA approved 27th July 2005.

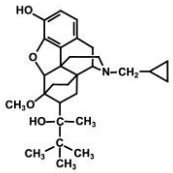
Naloxone Pharmacology

- Acts as a competitive antagonist at the *mu* receptor
  - Binds to the *mu* receptor
  - Prevents binding of other opioid agonists to the receptor
  - Reverses overdose of most opioids
  - Precipitates withdrawal when injected in opioid dependent individuals
  - Short half life (t = 1.1hrs)
  - Rapidly reaches and binds to the *mu* receptor ***when injected***[1]



1. Gilman et al, (1990) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 8th Ed, New York: Pergamon Press

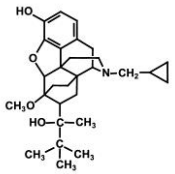
Naloxone Pharmacology Video



Suboxone Pharmacology

- ***Sublingual*** administration of the combination
  - Does not compromise buprenorphine absorption
  - Results in the same buprenorphine plasma levels as an equivalent Subutex dose
  - Onset of effect and time of peak effect is unaltered
  - Duration of action is unaltered
  - Naloxone bioavailability less than 10%, plasma levels too low for clinical effect

- ***Intravenous*** administration of the combination
  - Naloxone gains rapid access to the receptors leading to precipitated withdrawal
  - Naloxone effect lasts for around 2hrs
  - Buprenorphine effects evident > 1hr after administration
  - Duration of action is unaltered
  - Naloxone will block the effects of buprenorphine when administered IV, but not when administrated sublingually[1]

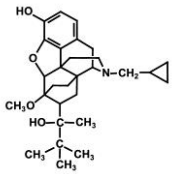


1. Stoller *et al*, Psychopharmacology (2001) 154:230-242

Suboxone Summary

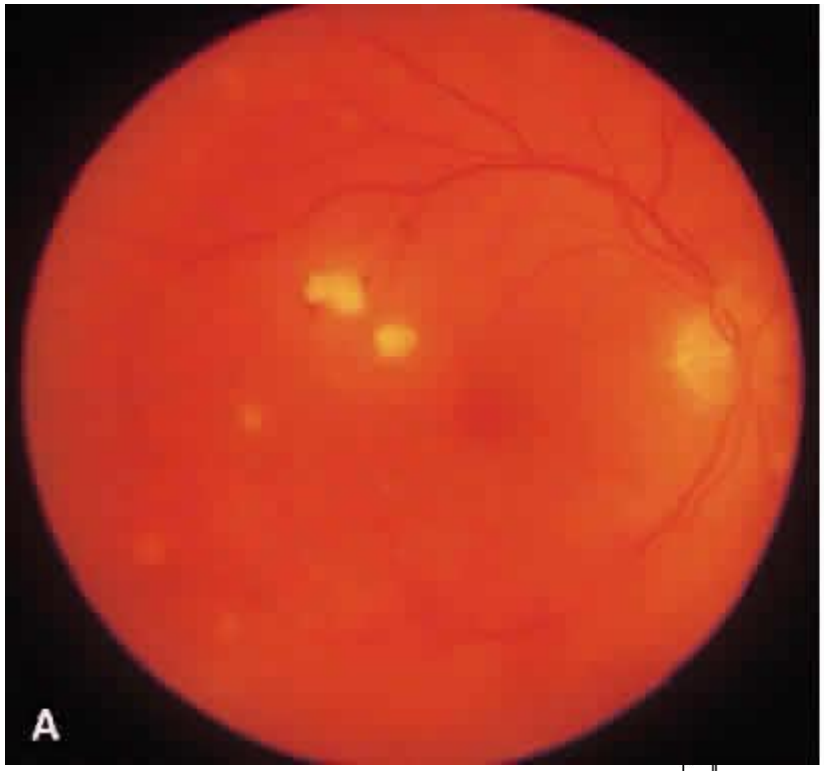
- Efficacy and safety is equivalent to Subutex

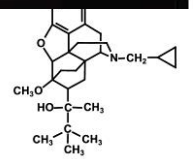
- Naloxone component added to
  - Discourage IV misuse
  - Diminish street value
  - Diminish diversion
  - Allow for take away dosing & increase treatment flexibility



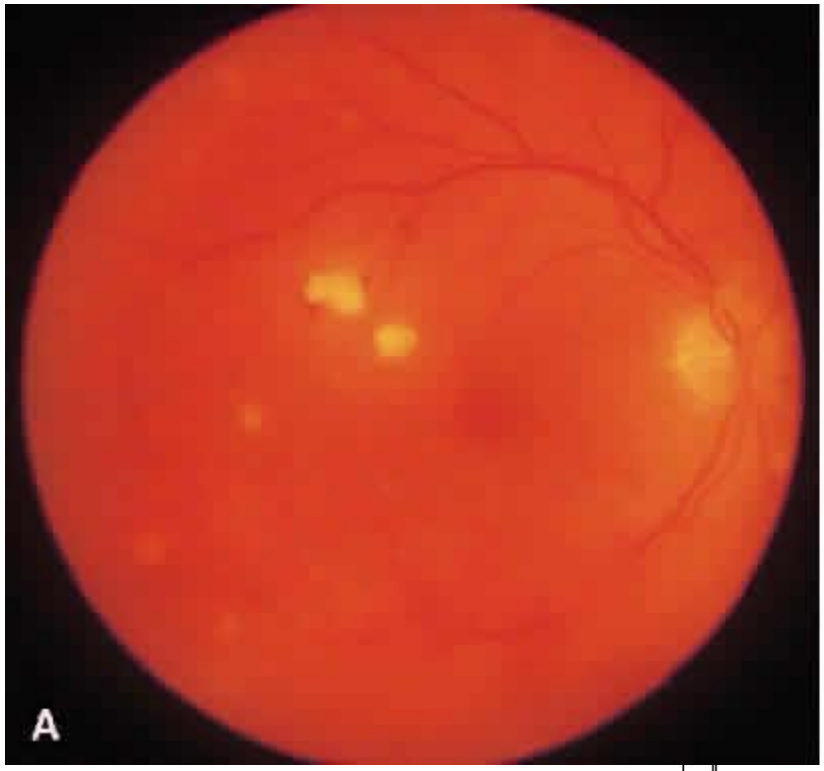
What’s this ?


Image Courtesy of Carlyn Wade
Copyright © 2002 Doctorfungus Corporation


A

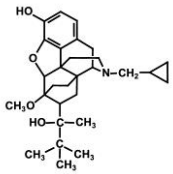

O
N–CH2
CH3O
HO–C–CH3
CH3
C
CH3
CH3

FUNGAL ENDOPTHALMITIS



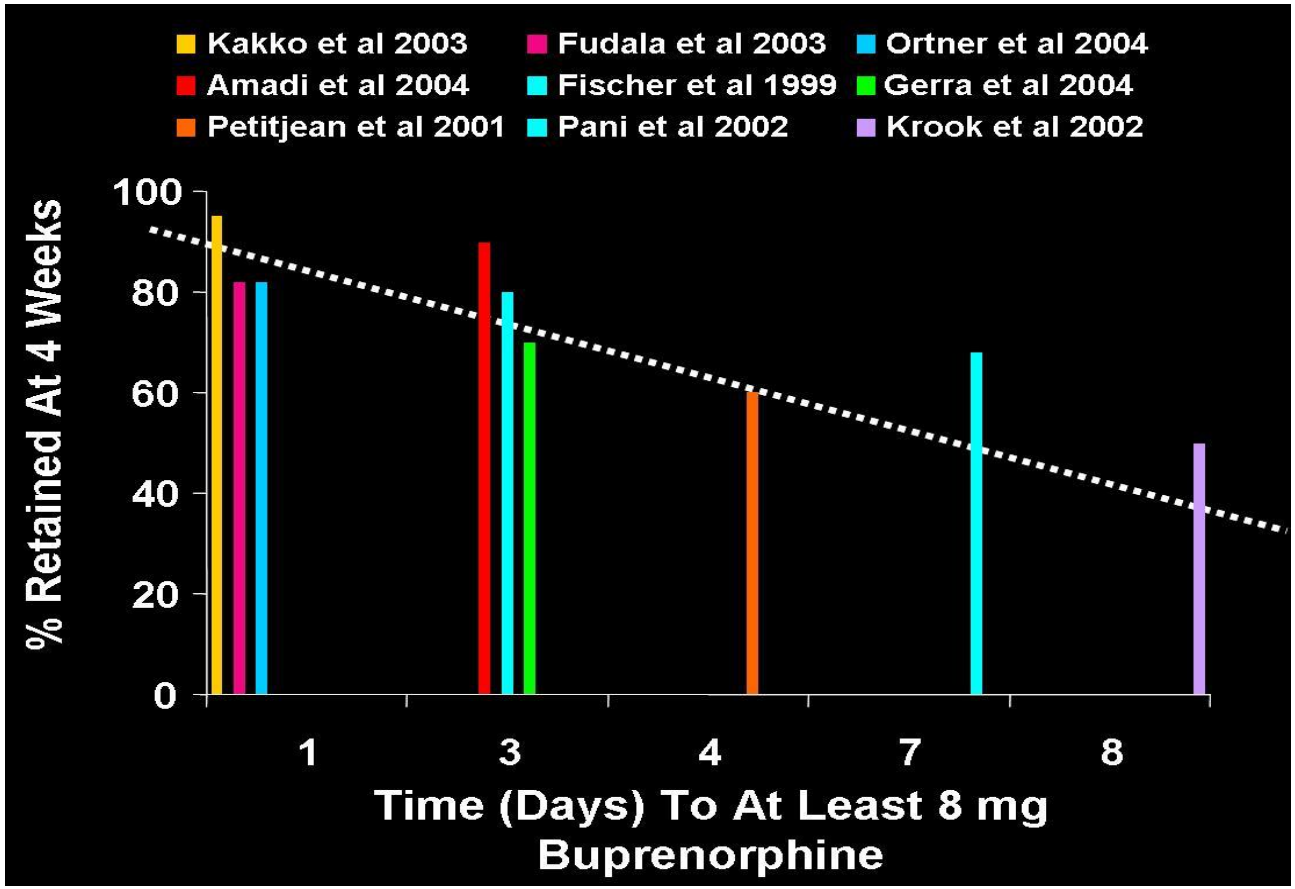
Induction

- National Clinical Guidelines for Buprenorphine recommend:
  - 8 mg should be achieved on the first day, usually given as a split dose, 4 hours apart to minimise the potential of precipitated withdrawal
  - Aim to achieve 12-16 mg by day 3
  - Prescriptions may be written as a fixed, increasing dose regime over the first week (e.g. 8 mg day 1, 12 mg day 2, 16 mg day 3)
  - Typically optimal doses at the end of the first week would be in the range of 12-24 mg[1]

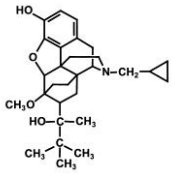


1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Induction vs. Retention

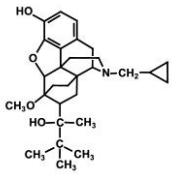


As presented by R Schottenfeld at Safer Options Conference, Prague, April 2006.



Maintenance

- National Clinical Guidelines recommend:
  - Regular review of client when trying to achieve stabilisation
  - Maintenance dose can be achieved within first week or two
  - Optimal maintenance doses are in the range of 12-24 mg/day
  - Maximum daily dose 32 mg[1]



1. Lintzeris N *et al*, National Clinical Guidelines & Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (2006).

Less than Daily Dosing

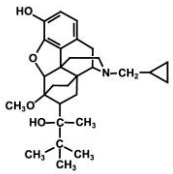
- Due to the pharmacology of buprenorphine, alternate day or thrice weekly dosing is possible

- Clients should be stabilised on daily dosing before considering a switch to alternate day dosing

- Dosing every other day at twice the individually titrated dose can be achieved
  - e.g. A patient maintained on 16 mg/day can be maintained on 32 mg every second day

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
32 mg	-	32 mg	-	16 mg	32 mg	-

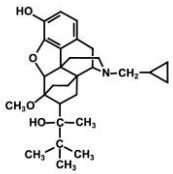
- Education and monitoring is important when switching to alternate day dosing[1]



1. Suboxone Product Information, TGA approved 27th July 2005.

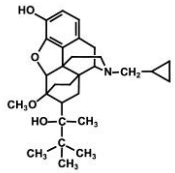
Suboxone Vs Methadone

- Fewer and milder side effects (sweats , sedation)
- More clear headed / improved cognitive function
- MUCH SAFER IN OPIATE OVERDOSE (ceiling to resp depression)
- Quicker induction and stabilisation
- Alternate day dosing vs “ takeaways “
- Superior option for detox / managing withdrawals
- **NO QT prolongation**
- Breast feeding : switch to Subutex



Clinical Implications

- Increasing numbers of OST patients will be taking Suboxone (20% in Australia)
- Greater recruitment and retention into OST
- More patients attempting to come off OST / detox
- GPs will be asked to prescribe Suboxone OST



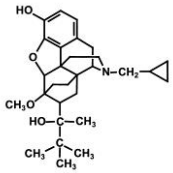
Hospital Presentations # 1: “The Dog ate it “

As for methadone , stolen / lost doses are *not* replaced .

Check with A&D service to verify dose & pharmacy . A&D service may allow an ‘advance’ of the half the next day’s dose to tide them over

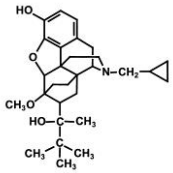
As with methadone , the very long half life means this is not usually a serious situation medically

After hours contact DAO , methadone co-ordinator , A&D service



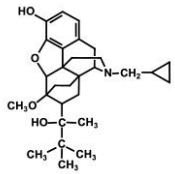
Hospital Presentation # 2 : acute pain

- Buprenorphine will block effect of morphine at usual doses
- CONTINUE Suboxone unchanged
- Try non-opiate & regional anaesthesia when possible
- If opiate needed use higher morphine doses or ‘super opiate’ eg Fentanyl



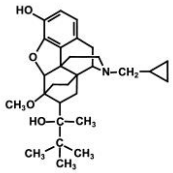
Hospital Presentation # 3 : Elective admission

- Liase with A&D service throughout admission , ‘challenging’ patients
- Early involvement of pain service
- Try non opiate / regional anaesthesia
- CONTINUE Suboxone unchanged
- Use ‘super opiate’ Fentanyl
- Or ? Ketamine (NMDA)
- If stop Suboxone ; opiate requirement will drop after 24 hrs , liase with service to restart Suboxone later



Hospital Presentations #4 : overdose

- Buprenorphine will not show up in urine drug screen as an opiate
- Generally safer in overdose than methadone or other opiates
- Still a risk in polydrug overdoses involving CNS depressants
- High doses Naloxone will be needed and for a long time



Questions ?

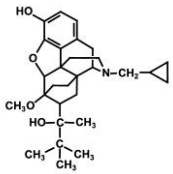
- 2010 Mercedes SLS AMG gull wing

Questions ?

- 1955 Mercedes 300 SL gull wing

Questions ?


AUTOWERELD.COM
AUTOWERELD.COM


HO
O
N–CH2
CH3O
HO–C–CH3
CH3
C
CH3
CH3