Buprenorphine Treatment:
Comparing methadone and buprenorphine for OUD treatment

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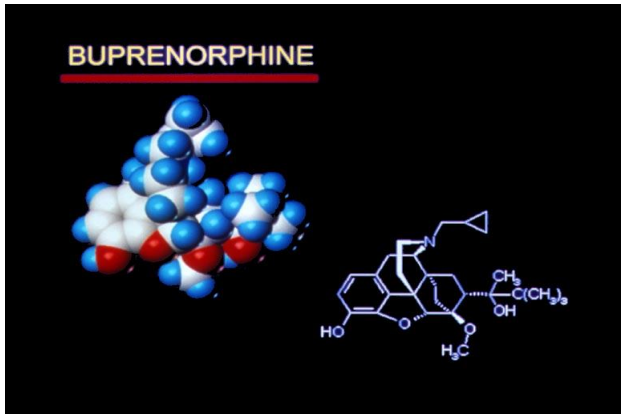

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Opioid Receptors

- Various receptor subtypes:
  - μ (mu), δ (delta), κ (kappa) and ORL-1
- Involved in different physiological processes
- μ-opioid receptor mediates:
  - Analgesic effects
  - Euphoria
  - Some side effects:
    - Respiratory depression
    - Sedation
    - Dependence
    - Constipation

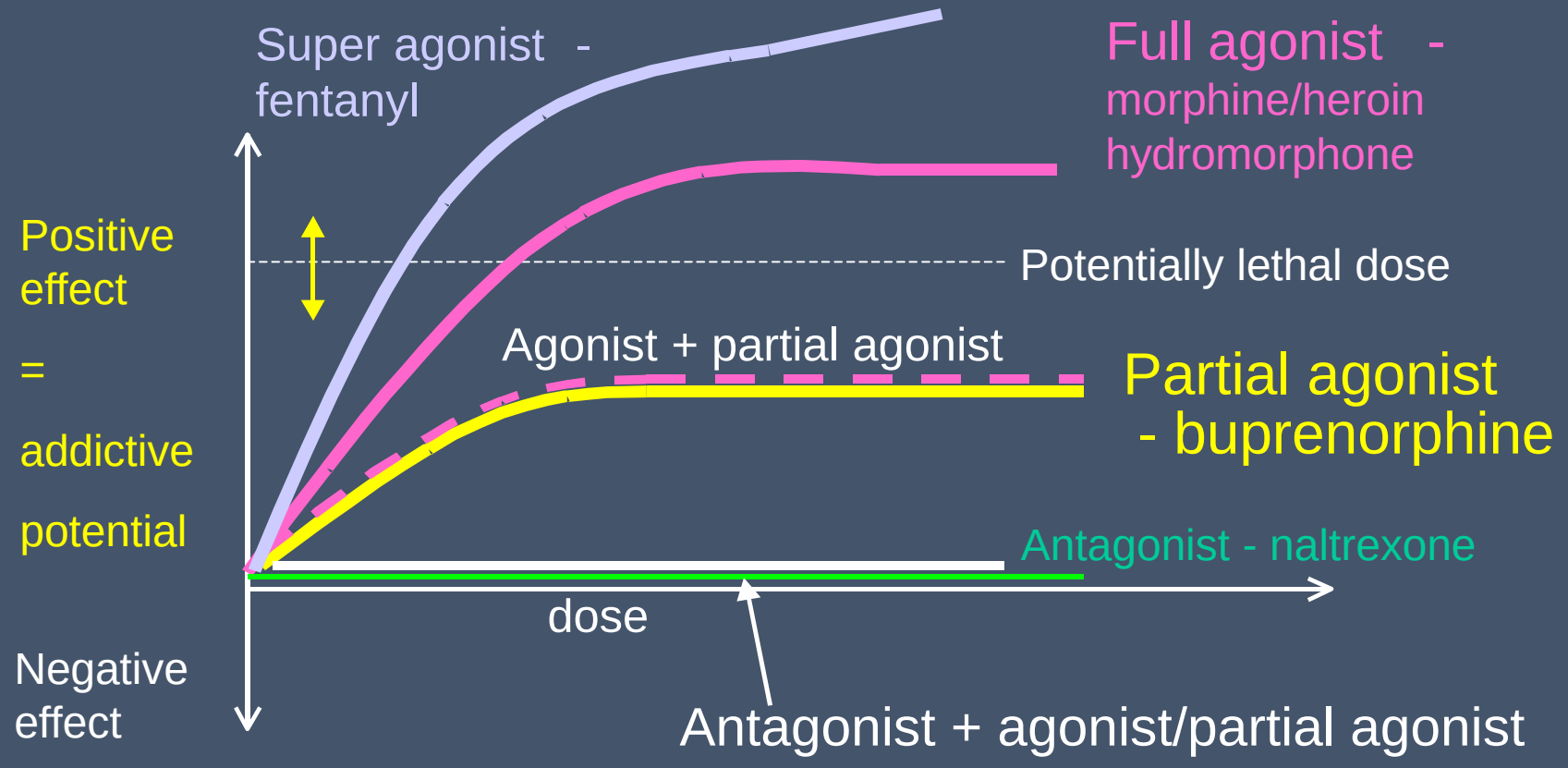
What determines opioid effects?

- 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 or antagonist?

- Full agonists – bind to the receptor producing an almost linear increase in physiological effect:
  - Methadone, morphine, heroin
- Partial agonists – bind to the receptor but have less than maximal effect on receptor activation:
  - Buprenorphine
- Antagonists – bind to the receptor but do not produce a biological response; are able to block agonist effects:
  - Naloxone, naltrexone, nalmefene

Understanding Opioid Effects



Opioid Agonist Treatment (OST)

- Works by:
  - eliminating withdrawal symptoms
  - reducing or eliminating cravings
  - blocking the euphoric effects from additional heroin use
- Longer in treatment the greater the gains
- Substantially reduces but does not always eliminate heroin use
- Protects from BBV and reduces HIV risk
- Reduces risk of overdose death
- Reduces criminal behavior

OST: Advantages of Treatment

- Suppresses opioid withdrawal
- Legal and affordable – reduced participation in crime
- Few long-term side-effects
- Pure – no ‘cutting agents’ present
- Oral or sublingual administration
- Once daily dose
- Counselling and support assists long-term lifestyle changes
- Slow reduction and withdrawal from treatment can be negotiated with minimal discomfort

Methadone Pharmacokinetics

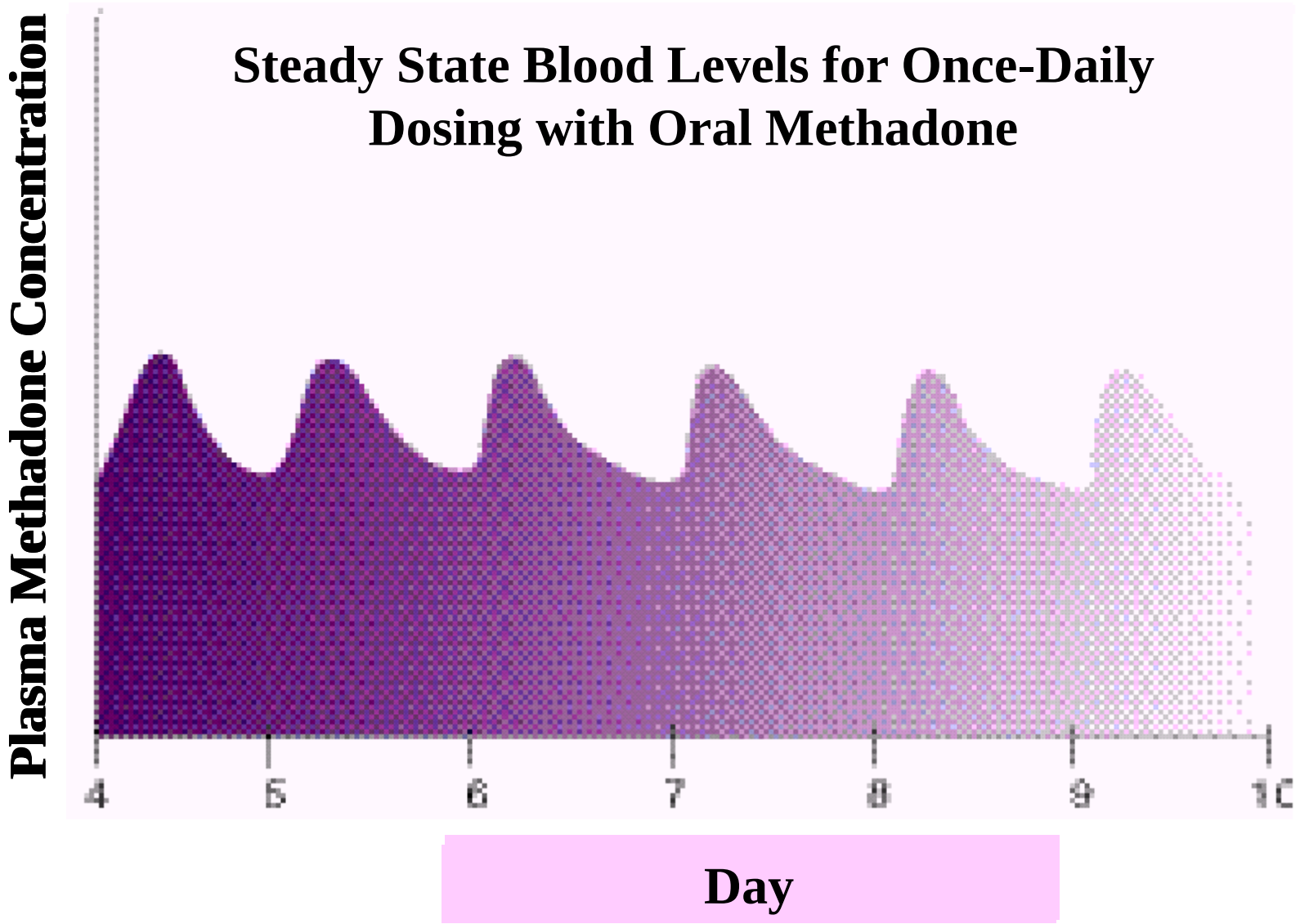
- good oral bioavailability
- Peak plasma concentration after 2-4 hrs
- 96% plasma protein bound
- Mean half-life around 24 hrs
- steady state after 3-10 days

- Metabolism And Excretion
  - Cytochrome P450 mediated
    - CYP3A4 main
    - also CYP2D6, CYP1A2, CYP2C9 and CYP2C19
      - genetic variability

    $\Rightarrow$ risk of drug interactions

Methadone Pharmacodynamics

- full opioid agonist
  - Main action on mu receptors
    - inhibit adenyl cyclase = ⬇ cAMP
    - ⬆ potasium channel opening
    - ⬇ calcium channel opening
  - also inhibit serotonin reuptake
  - also non competitive antagonist NMDA receptor


Steady State Blood Levels for Once-Daily Dosing with Oral Methadone
Plasma Methadone Concentration
4
5
6
7
8
9
10
Day

Limitations Of Methadone Maintenance Treatment

- Daily supervised dosing
- Risk of overdose
- Tolerance and dependence
- Variable duration of action
- Diversion

History of Buprenorphine

- Developed 1970’s
- Registered as analgesic 1980's
- Clinical research with heroin users
  - Phase II mid 1980’s
  - Phase III randomised trials late 1980’s early 1990’s
- Sublingual tablet (Subutex®) developed mid 1990’s
- Registered for opiate dependence treatment
  - France 1995
  - Australia 2000
- Suboxone tablet 2003
- Suboxone Film 2012
- Approved for opioid addiction treatment in 40 countries
- Depot buprenorphine 2019

Buprenorphine Pharmacokinetics

- **Bioavailability**
  - high first pass metabolism
    - Poor oral bioavailability
    - Fair sublingual bioavailability
    - Good parenteral bioavailability
- **Metabolism And Excretion**
  - High percentage plasma protein bound
  - Metabolized in liver by cytochrome P450 CYP3A4 enzyme system only

Buprenorphine Pharmacodynamics

- Partial mu receptor agonist
    - Ceiling effect with increasing doses
    - Mild physical dependence
    - Modest withdrawal signs and symptoms
- high affinity for mu receptor
    - competes with other opioids and blocks their effects
- onset of action 30-60 min
- peak action 1-2 hours
- long duration of action that is dose dependent
    - slow receptor disassociation
    - lipophillic
    - enterohepatic cycling

Safety Overview

- Safe medication (acute and chronic dosing)
- Primary side effects: like other mu agonist opioids (e.g., nausea, constipation), but may be less severe
- No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance
- No evidence of organ damage with chronic dosing

Duration of effects

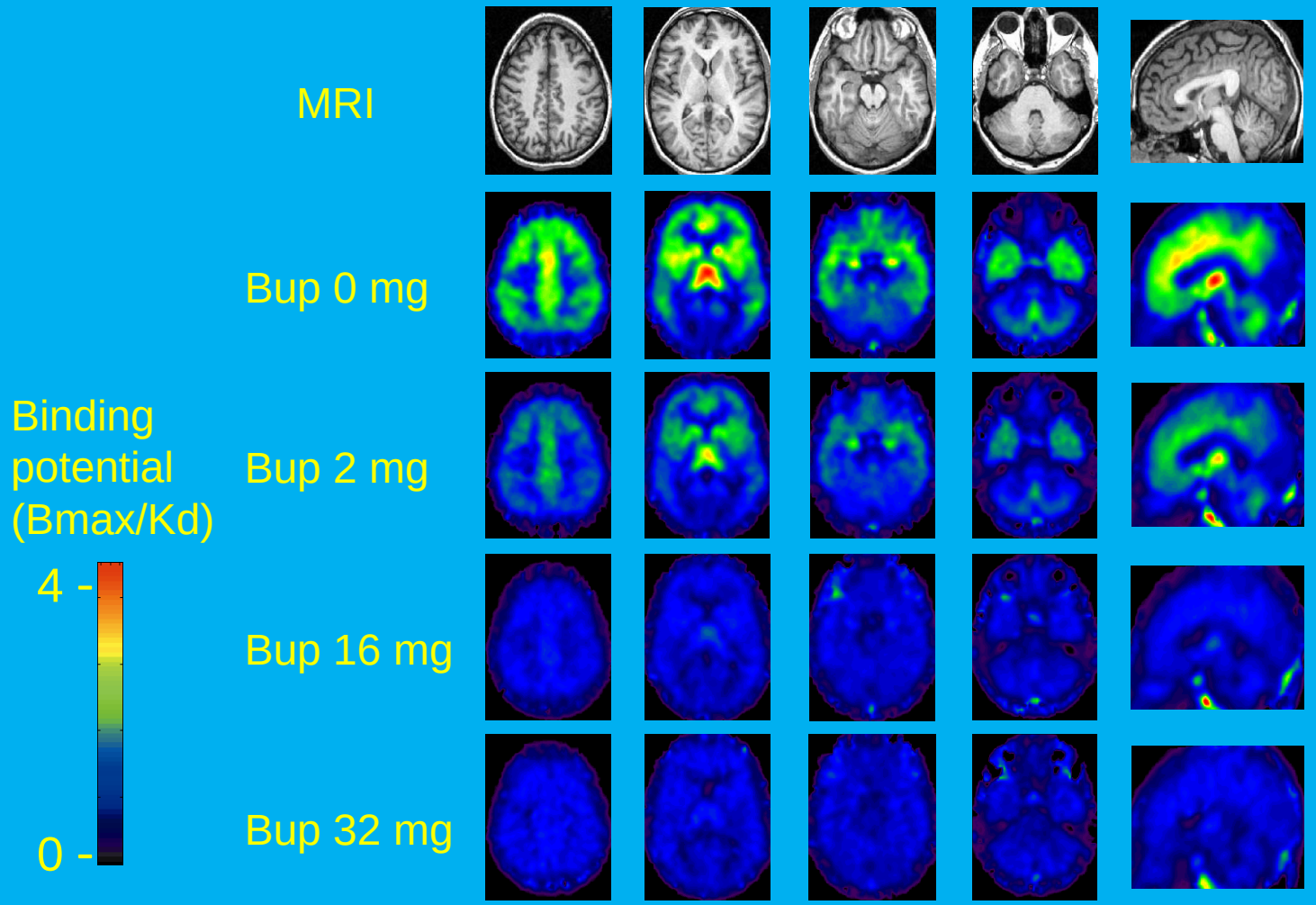
- Onset of action 30 – 60 minutes
- Peak effects: 1 – 4 hours
- Duration of action is dose related
    - low dose : 4 – 12 hrs
    - med dose : ~ 24 hrs
    - high dose : 2 – 3 days
- Steady state equilibrium achieved after 3 days

Buprenorphine Pharmacology
Therapeutic Reality vs Lab. Findings

- Partial Agonism and Ceiling Effect
  - Referred to as ‘Partial efficacy’

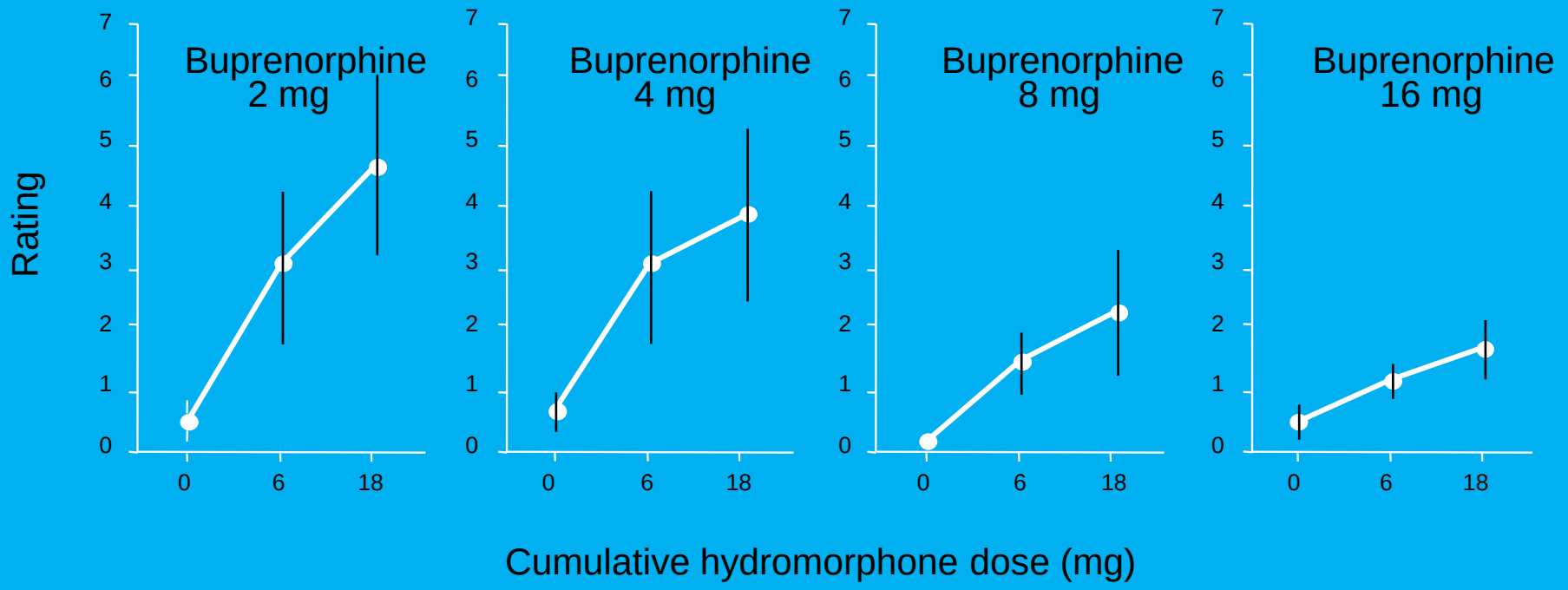
  YET
  - Analgesic models Bup > or ~ Morphine
  - Increasing doses increases analgesia
    - Doses up to 11mg (Budd)
  - High and low dependents equally ‘held’
  - Successful high dose transfers
    - 600-900mg Methadone (Gilhooly)
  - Ceiling/Plateau observed on side effects
    - Respiratory depression, BP and HR (Walsh, Preston)
      - Bell Shaped Dose Response Curve

Effects of Buprenorphine on μ-opioid receptor availability



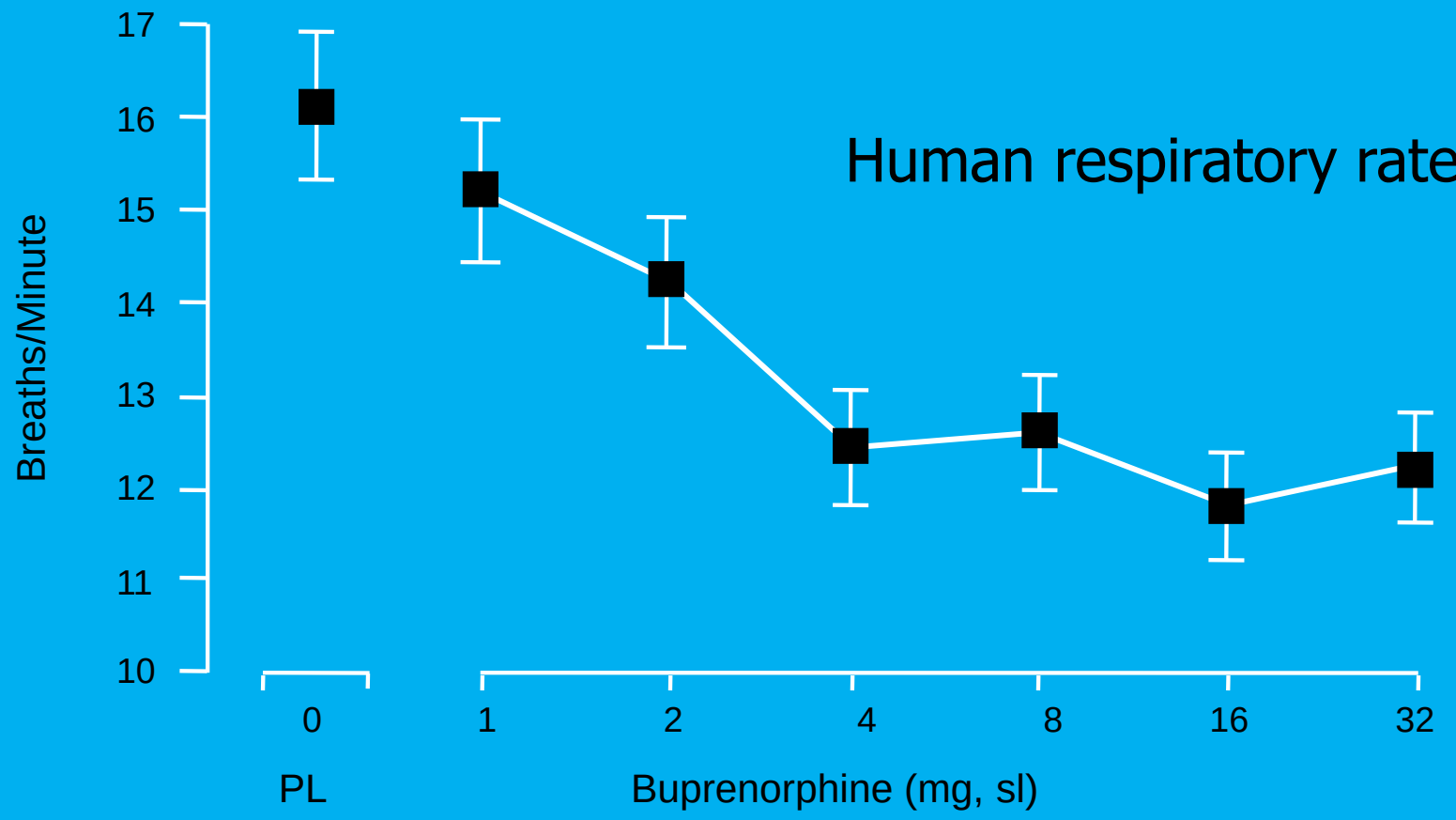
D Nutt. Personal communication

Subjective effects: blockade/tolerance



Adapted from Bickel et al., 1988

Ceiling effect on respiratory depression



Adapted from Walsh et al., 1994

Pharmacology - effects and benefits

- Slow receptor dissociation:
  - Longer duration of action
  - Milder withdrawal
- Lower physical dependence liability than full agonists
- Limited development of tolerance
- Ceiling effect on respiratory depression
  - Increased safety against overdose
- Relatively slow access to receptors

Sublingually, but NOT orally, active

Naloxone Pharmacology

- Competitive Mu opioid antagonist
- Not orally available (‘inactive’)
- Poor Sublingual availability
- Rapid access to Mu receptors (IV)
  - Precipitates withdrawal in opioid dependents
  - Blocks access of other opioids to receptor
- Relatively quick receptor dissociation
  - Short duration of action(T1/2 life 45mins)
- Mu receptor affinity:-
  - Bup>>Nx>Methadone>Heroin

Buprenorphine-Nx Pharmacology

- Sublingual Administration:-
  - Nx does NOT compromise absorption
  - Same Buprenorphine plasma levels from Bup and Bup-Nx
  - Buprenorphines' 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(Strain 2004)

Clinical Pharmacology: Sublingual Bup-Nx

- Comparison Bup-Nx (4-16mg) with Bup (16mg)
- No effect of Nx on bioavailability, or effects of Bup at 16mg dose level
- Many Nx plasma levels not detected
- Nx bioavailability not measurable
- Subjective and physiological effects similar

(Harris et al 2004)

Clinical Pharmacology: Intravenous Bup-Nx

- Nx gains rapid access to receptors
  - Precipitates withdrawal in opioid dependents
- Nx effects last up to 2 hrs
- Buprenorphine effects evident >1 hr later

Injecting Suboxone

- Precipitates moderate–severe withdrawal syndrome in individuals dependent on full opioid agonists

- Effects of Naloxone are maximized when taken intravenously

- Effects of IV Suboxone are indistinguishable from IV Naloxone alone in individuals dependent on full opioid-agonists

Fudala et al., 1998

Buprenorphine-Nx Combination

4 part Buprenorphine: 1 part Naloxone

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†

	Buprenorphine	BupNX
Heroin-dependent	Agonist effect	Antagonist effect
Non-dependent	Mild agonist effect	Attenuated agonist effect
Methadone-maintained	Antagonist effect	Antagonist effect
Buprenorphine or BupNX maintained	Agonist effect	Agonist effect(attenuated)

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

Safety of Bup-Nx

- 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
- Safety not demonstrated in pregnancy

Mendelson et al., 1996

Buprenorphine-Nx Combination

- Summary:-
  - Efficacy and safety equivalent to that of Buprenorphine alone
  - Discourages IV misuse
  - Reduces street value
  - Reduces diversion potential

Side-effects

- Similar to other opioids
- Common in first few days-weeks and then generally subside
- Experience of side-effects variable
  - May experience side-effect to one opioid only
  - may experience similar side-effect with other opioids
- Not all symptoms are necessarily side-effects
  - consider other causes
  - ‘Expectancy’ factors may be important

Common Side-effects

- Headache
- Constipation
- Nausea
- Drowsiness, sedation
- Tiredness, lethargy
- Sleep disturbances
- Sweating
- Reduced libido

Drug Interactions

- Sedatives
  - Additive sedative effects to other sedatives
  - Can result in respiratory depression, heavy sedation, coma and death
- Opioid antagonists
- Opioid agonists
- Precaution with concomitant CYP3A4 inhibitors
  - e.g. protease inhibitors, ketoconazole, nifedipine, and some antiviral medications such as Atazanavir
  - may lead to increased plasma concentrations of buprenorphine

Pharmacological Reality!

- All opioids have abuse potential

- Some abuse of Buprenorphine is to be expected (unauthorised use):-
  - Based on the available research, one would predict this to be far less with Bup-NX than Buprenorphine

- Even with this leakage, Buprenorphine is an extremely safe medication and the French data show us that there is safety in the numbers…(Auriacombe)
  - Ratio of deaths/patients is 10x less with Buprenorphine than with Methadone

Buprenorphine maintenance treatment

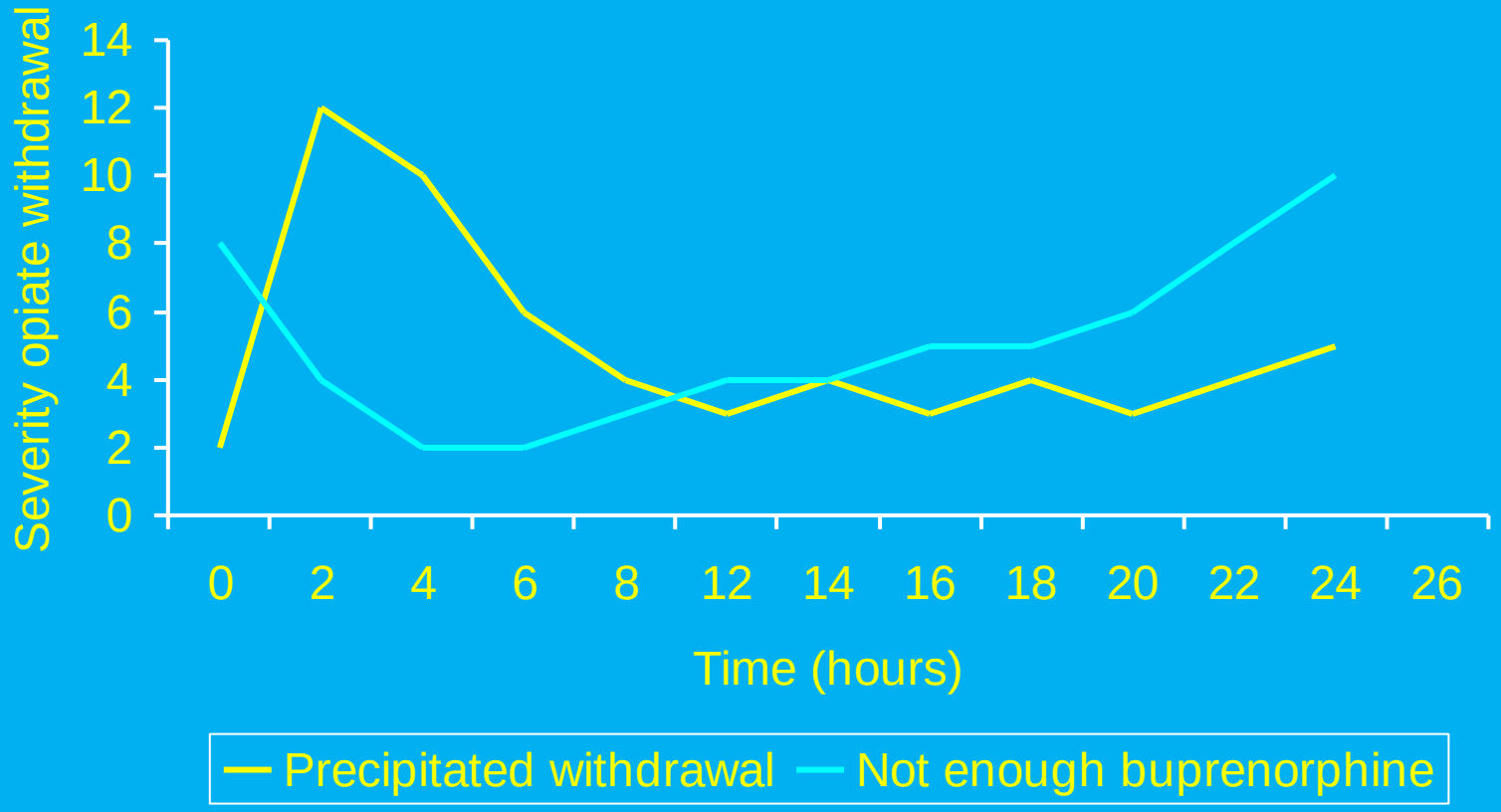
Buprenorphine Pharmacology

- High receptor affinity
  - Can result in precipitated withdrawal effects
- Precipitated withdrawal dependant upon:-
  - Time of dosing
  - Dose level of other agonist
  - Level of physical dependence

When does a Buprenorphine-precipitated withdrawal occur?

- Generally commences ~30–90 min after 1st dose
- Generally peaks within 90–180 min after 1st dose
- Minor symptoms may continue after 2nd or 3rd dose
- Symptoms may also persist with continued heroin/opioid use

Precipitated withdrawal or not enough Buprenorphine?



Adapted from Lintzeris et al., 2003

Buprenorphine Dose Induction

- Early studies - cautious induction schedules
  - Matched Methadone induction
  - Safety concerns with a new drug
  - Drop outs higher in first 2 weeks
  - Negative impact on retention rates
- Typical induction schedules were
  - 2,4,(6),8mg on consecutive days
  - 7 days to achieve 8mg dose(Italy)
  - 14 days to achieve 16mg dose(Switzerland)

Buprenorphine Dose Induction

- Reasons for drop-outs in first 2 weeks:-
  - Induction too slow
  - First dose too soon after last opioid use
    - Precipitated withdrawal
  - Clear headed feeling
    - Become anxious (uncomfortable with this ‘feel’)
    - Fear of precipitated withdrawal
    - Preference for ‘drugged’ feeling
  - Ease of withdrawal
    - Preference for detoxification

Buprenorphine Dose Induction

- Recommendations:-
  - Prepare patient for a ‘different feel’
  - First dose when withdrawal signs evident
  - Higher starting doses
  - More rapid dose escalation
  - Split doses possible
- Induction should be rapid and doses adjusted to clinical need as quickly as possible to reduce withdrawal and craving and prevent early drop-out
- A target dose of 16mg (or more) can be reached within 2-3 days by most patients

Key principles

- first dose of buprenorphine delayed until incipient withdrawal
  - measured by a validated scale e.g. Clinical Opiate Withdrawal Scale (COWS)
  - initiating from short-acting usually not associated with severe precipitated withdrawal.
  - Transfer from slow-release opioid preparations to shorter-acting preparations for several days prior to transfer

Doses should be adjusted

- following review of the patient assessing
  - side effects
  - features of withdrawal (suggesting not enough buprenorphine) or intoxication (suggesting too much buprenorphine or other drug use)
  - ongoing cravings
  - Other substance use

Alternate day dosing principles

- Doses greater than 16mg associated with increased duration of action
  - little or no increase in degree of opioid effect.
- stabilise on daily dosing before trying alternate-day dosing for two weeks

If successful can then be tried on three-times-a-week regimen

Alternate day dosing practice

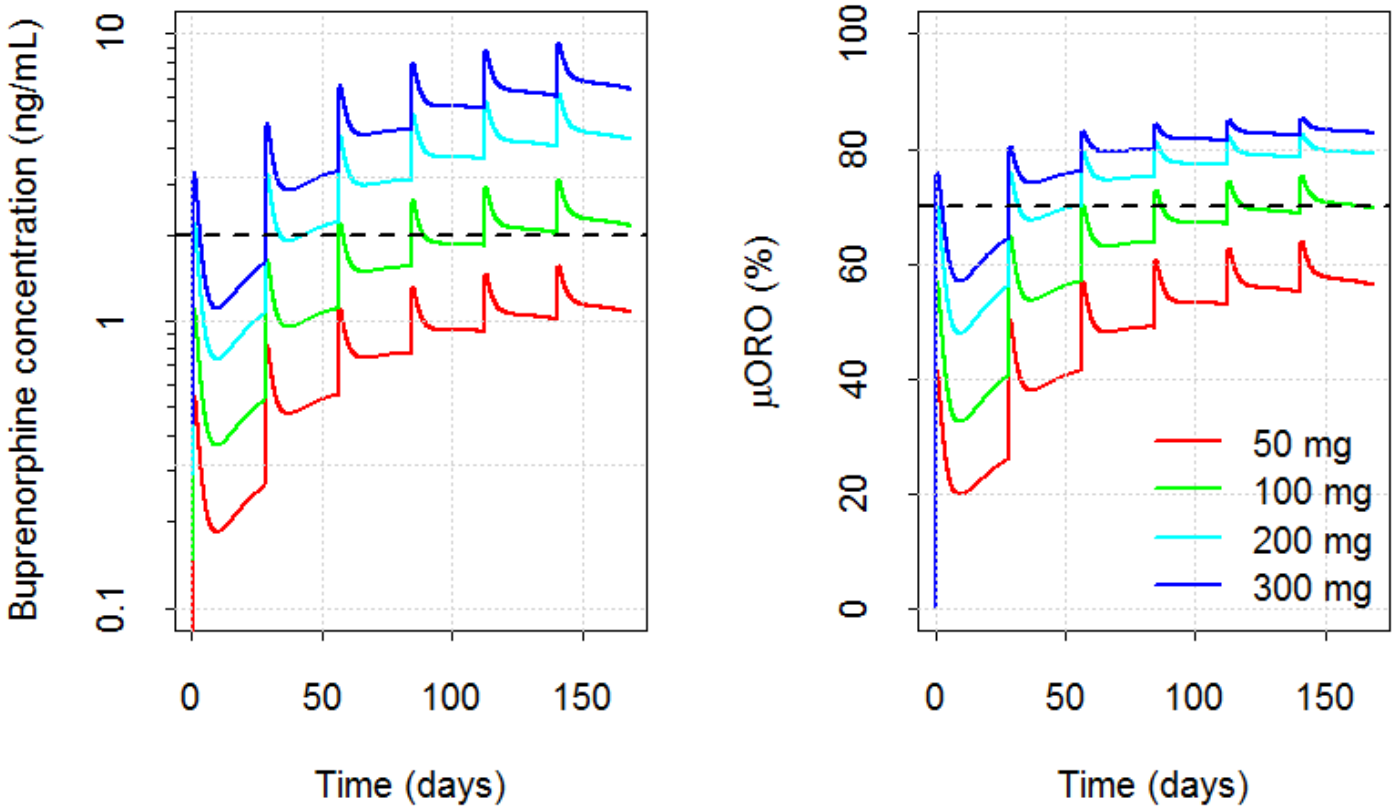
- Dose for 48-hour period initially double normal daily dose (to maximum of 32 mg).
- review after first or second 48-hour dose and adjust if needed
- three-times-a-week dosing
  - attempt after two week trial on alt day dosing
  - If 24-hour buprenorphine dose less than 12mg
    - 3-day dose is three times the 24-hour dose
  - If 24-hour dose is 12mg or greater, the 3-day dose should be 32mg

New innovations

- 2 different sustained release products
  - Indivior Sublocade: monthly
  - Camurus Buvidal: weekly or monthly

How they selected dosing for sublocade for opioid receptor occupancy (μORO) blocade

Mean predicted PK and μORO levels



300 mg dose

- Reaches target of 70% μORO after the first SC injection (C_{max})
- Mean predicted μORO levels were consistently > 70% for subsequent injections

100 mg dose

- Reaches target of 70% μORO at steady-state
- 2 initial doses of 300 mg required to reach effective levels more rapidly

Methadone: Advantages of Treatment

Advantages

- Suppresses opioid withdrawal
- Pure – no ‘cutting agents’ present
- Oral administration
- Once daily doses enable lifestyle changes
- Slow reduction and withdrawal can be negotiated with minimal discomfort
- Counselling and support assists long-term lifestyle changes
- Legal and affordable – reduced participation in crime
- Free in public methadone programs
- Few long-term side-effects

Disadvantages

- Initial discomfort to be expected during stabilisation phase
- Opioid dependence is maintained
- Slow withdrawal (preferably) negotiated and undertaken over a period of months
- Protracted withdrawal symptoms
- Can overdose, particularly with polydrug use
- Daily travel and time commitment

Buprenorphine vs. Methadone

Buprenorphine Advantages

- Relative ease of use
  i.e. ready transission from heroin withdrawal state or methadone
- Wider safety margin
- ‘Smoother’ opiate effect & less sedating than methadone
- Milder withdrawal
- Convenient (can dose every 2/7)
- Better receptor blocker
- Easier to taper than methadone

Buprenorphine Disadvantages

- Tablet easier to divert than film
- Increased time required for supervised dosage (to get dissolution).
- Bup-Nx not used in pregnancy

Flexible-dose methadone and buprenorphine comparison

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Retention in treatment	11	1391	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.73, 0.95]
1.1.1 Double-blind flexible dose studies	5	788	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.72, 0.95]
1.1.2 Open label flexible dose studies	6	603	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.02]
1.2 Morphine-positive urines	8	1027	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.23, 0.02]
1.3 Self-reported heroin use	4	501	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.28, 0.07]
1.4 Cocaine-positive urines	6	919	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.05, 0.25]
1.5 Benzodiazepine-positive urines	6	859	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.12, 0.22]
1.6 Criminal activity	2	328	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.31, 0.12]

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2014 , Issue 2 . Art. No.: CD002207

Choosing substitution maintenance medications

- Research has not identified whether certain types of clients respond better to buprenorphine / methadone

- The choice between methadone or buprenorphine depends upon:
  - Logistics of participating in treatment
  - Response to treatment
  - Individual variation in absorption, metabolism, clearance of medication
  - Side effects
  - Ease of withdrawal from medication
  - Client (and clinician) expectancy
  - Ability to transfer from methadone