VOLUME C

Pharmacological Treatment for Drug Use Disorders

Drug Treatment for Special Populations

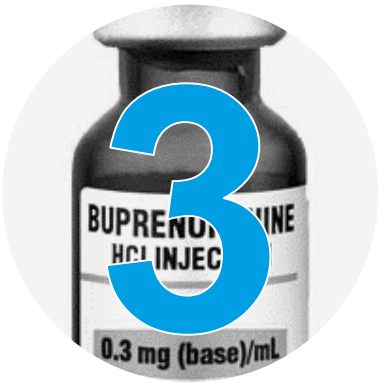
Treatnet

Module 2

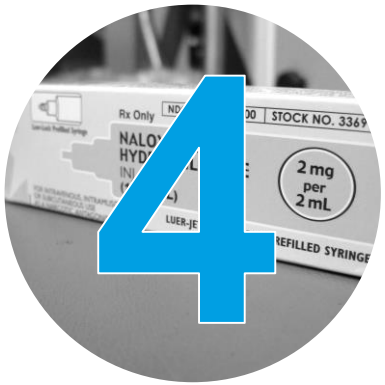
Basics of opioid dependence
Pharmacotherapy options

Opioids: Definition, effects and treatment implications

Opioid dependence treatment with Methadone



Opioid dependence treatment with Buprenorphine



Opioid antagonist treatment

Workshop 3

Opioid dependence treatment with Buprenorphine

Training objectives

At the end of this workshop you will be able to:

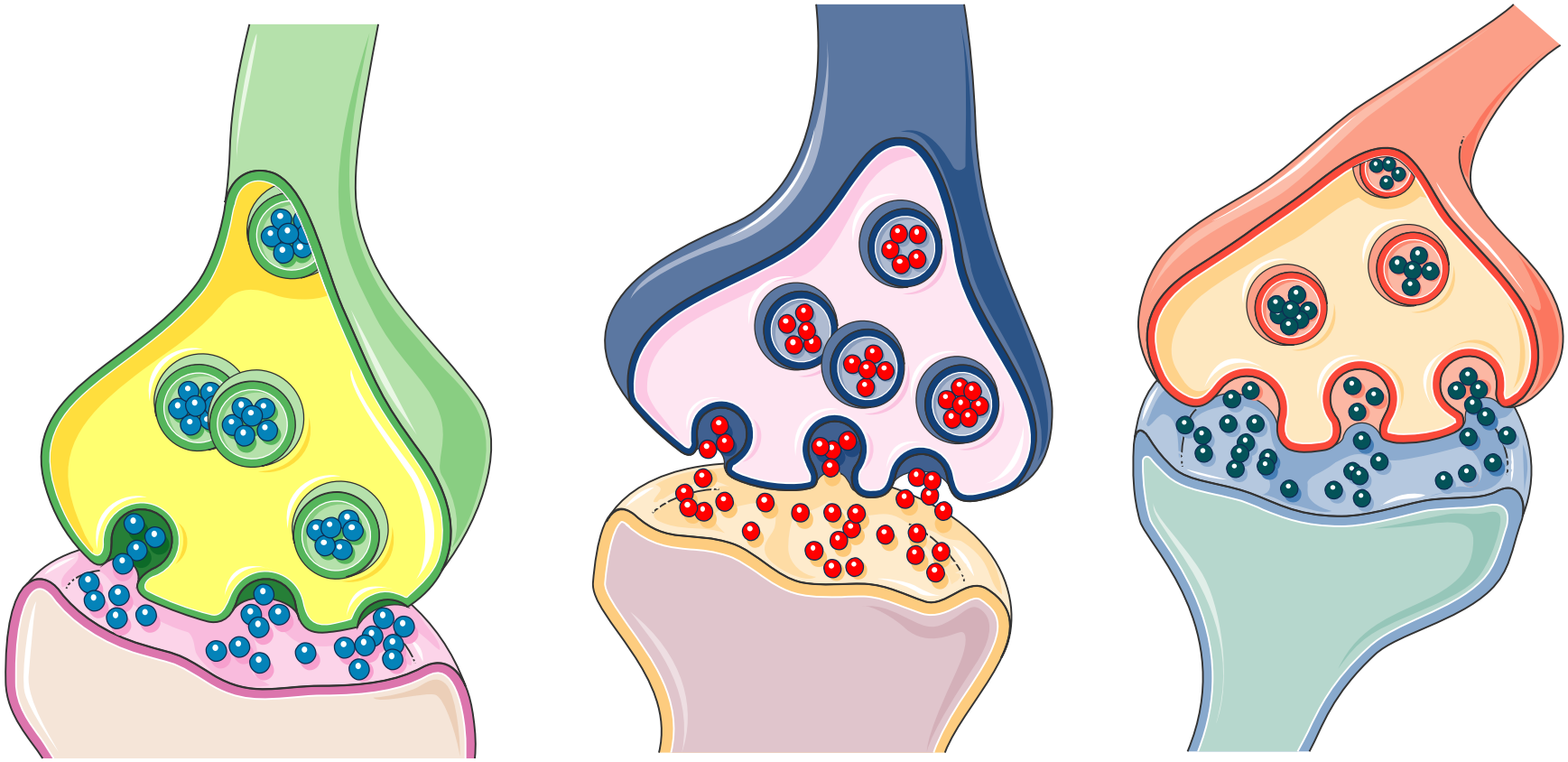
- Apply withdrawal protocols using Buprenorphine in line with the principles of maintenance treatment
- Discuss the evidence for Buprenorphine treatment
- Implement effective practices in the implementation of Buprenorphine treatment
- Appropriately address concurrent use of other drugs and alcohol during Buprenorphine treatment
- Identify contraindications and medication interactions with Buprenorphine

Buprenorphine for opioid dependence

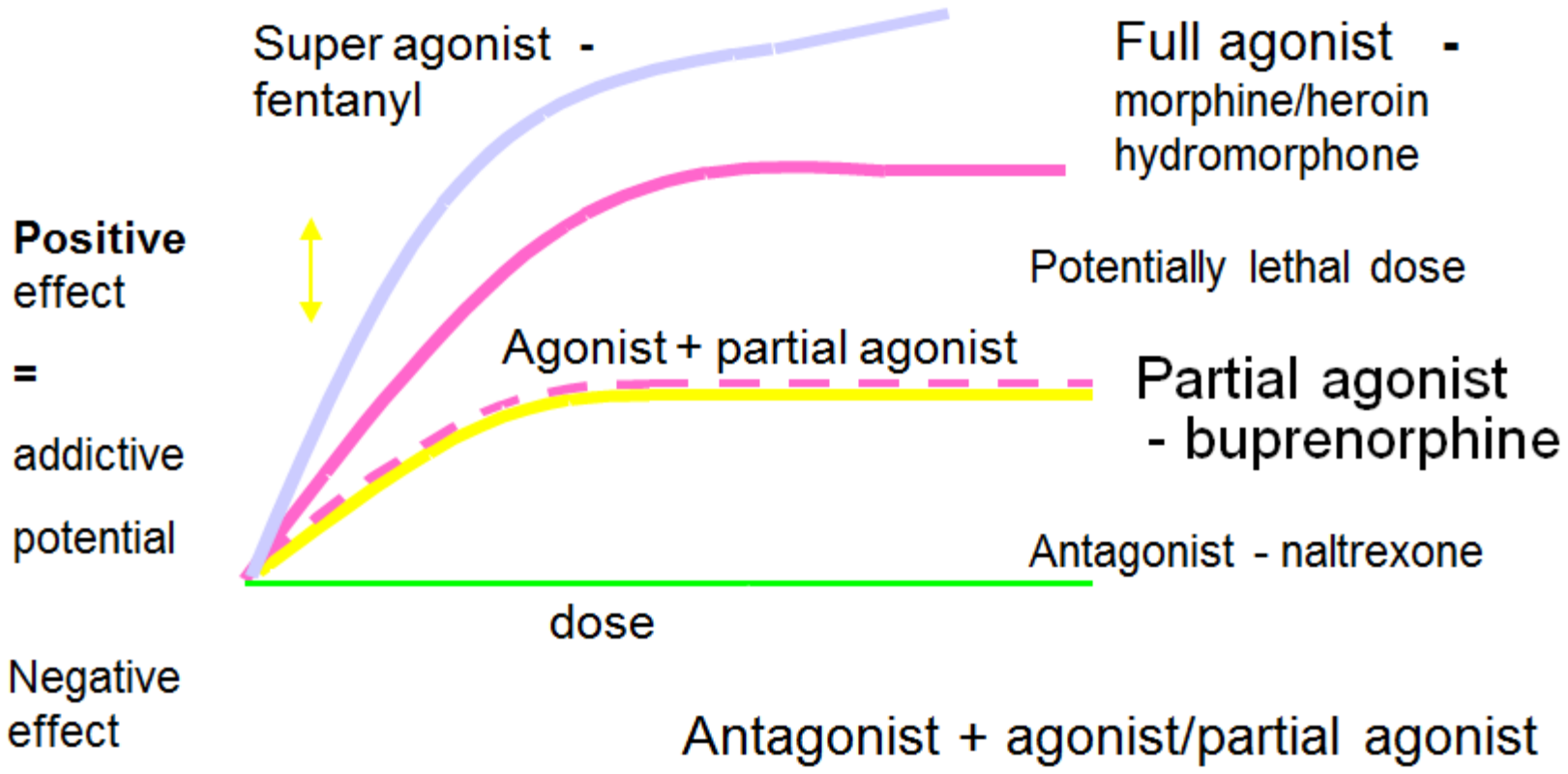
Buprenorphine overview

- Buprenorphine is a Thebaine derivative (classified in the law as a narcotic)
- High potency
- Produces sufficient agonist effects to be detected by the patient
- Available as a parenteral analgesic (typically 0.3 - 0.6 mg im or iv every 6 or more hours)
- Long duration of action when used for the treatment of opioid dependence contrasts with its relatively short analgesic effects

Buprenorphine pharmacology



μ- Efficacy and opiate dependence



Buprenorphine: unique properties, affinity and dissociation

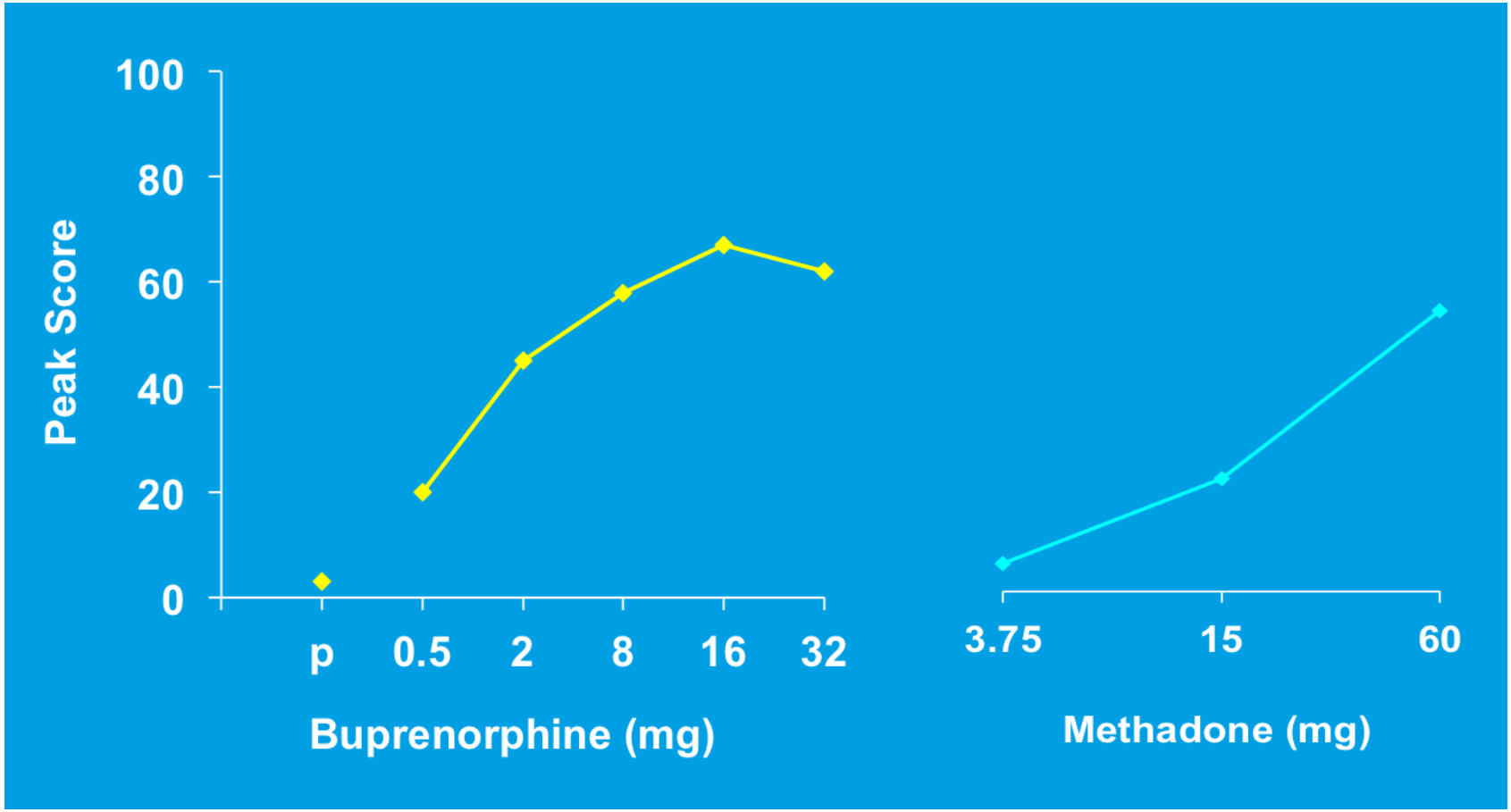
Buprenorphine has:

- High affinity for μ-opioid receptor
  - competes with other opioids and blocks their effects
- Slow dissociation from mu opioid receptor
  - prolonged therapeutic effect for opioid dependence treatment (contrasts to its relatively short analgesic effects)

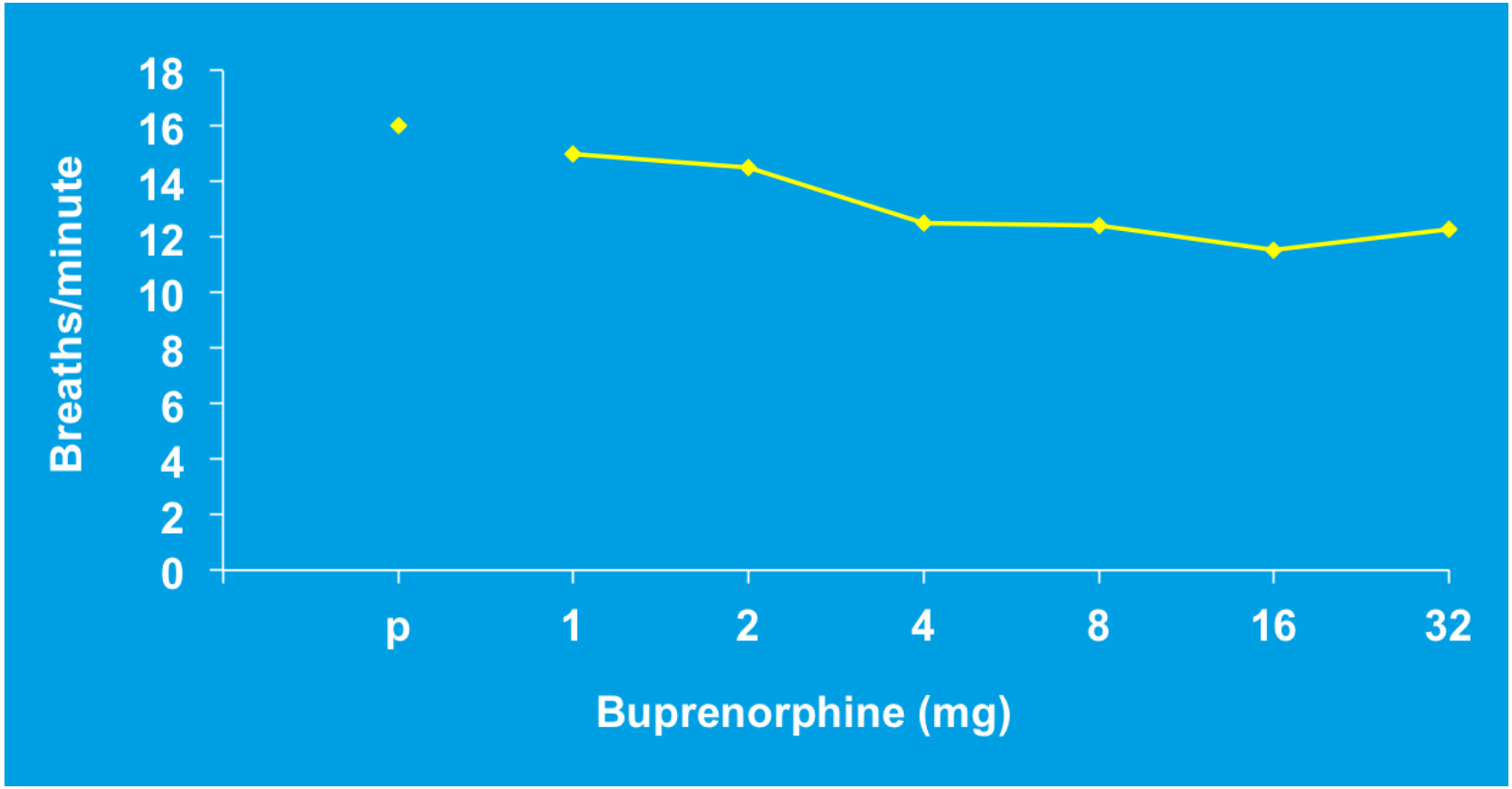
Buprenorphine: clinical pharmacology

- Partial agonist
  - High safety profile/ceiling effect
  - Low dependence
- Tight receptor binding at mu receptor
  - Long duration of action
  - Slow onset mild abstinence
- Antagonist at k receptor

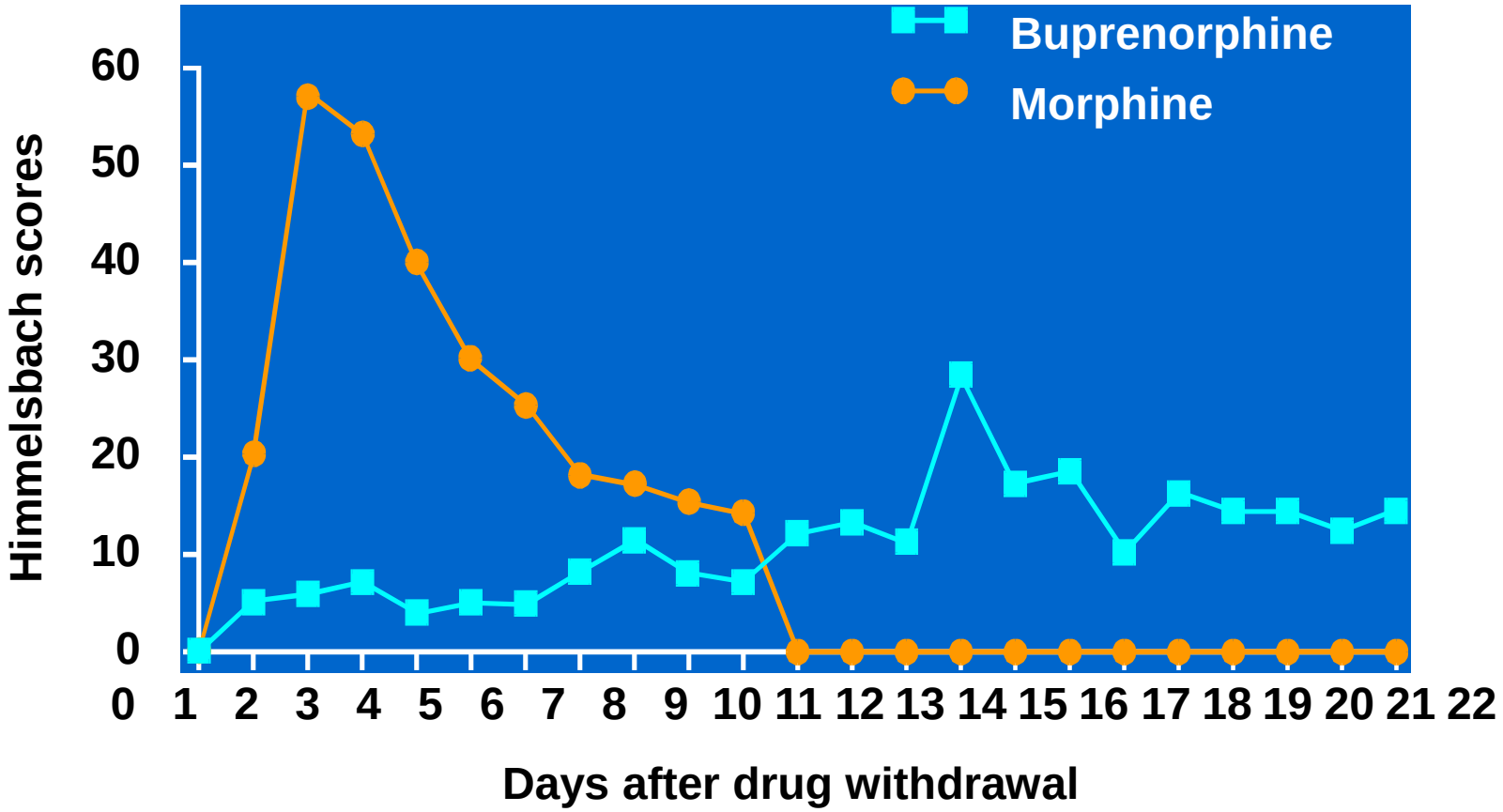
Subjects rating of drugs' good effect

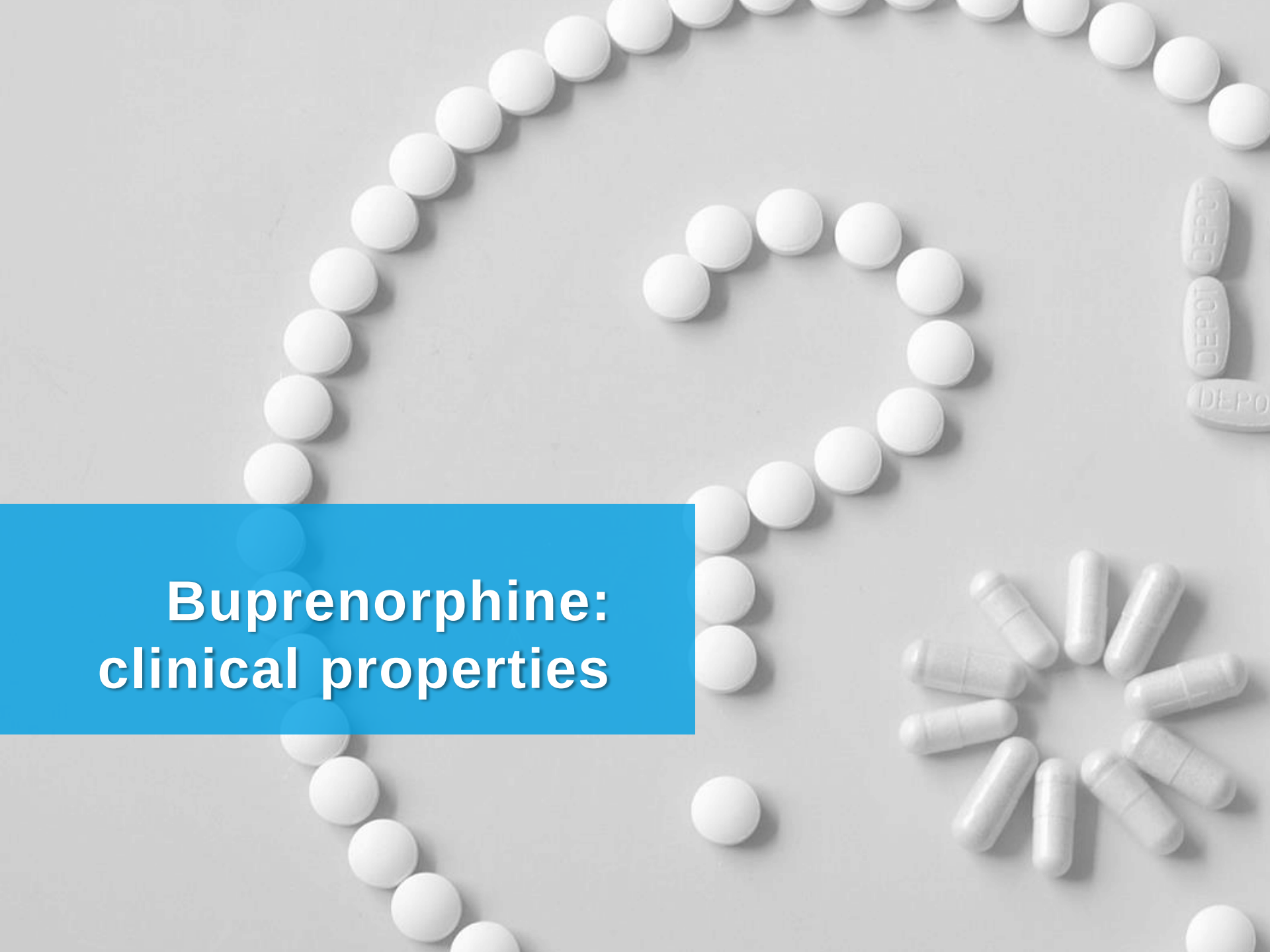


Buprenorphine's effect on respiration



Intensity of abstinence symptoms



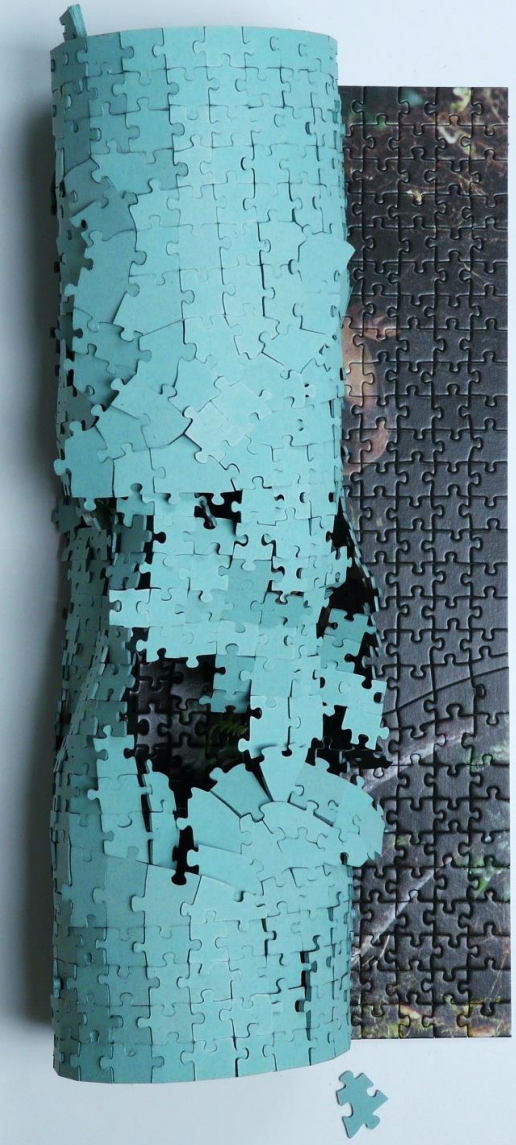


Buprenorphine: clinical properties

Buprenorphine: Clinical implications of pharmacological properties

Properties of Buprenorphine	Clinical implications
• Opiate-like effects	• Reduces cravings • Increases treatment retention
• Prevents or alleviates heroin withdrawal symptoms	• Can be used for maintenance or withdrawal treatment
• Long duration of action	• Allows for once-a-day to three-times-a-week dosing
• Ceiling on dose response effect.	• Safer in overdose, as high doses in isolation rarely result in fatal respiratory depression
• Sublingual preparation	• Safer in accidental overdose (e.g. in children) as poorly absorbed orally
• Diminishes the effects of additional opioid use (e.g. heroin)	• Diminishes psychological reinforcement of continued heroin use • May complicate attempts at analgesia with opioid agonists (e.g. morphine)
• Modified withdrawal precipitated by opioid antagonists	• Treatment with naltrexone can be commenced within 5–7 days of Buprenorphine
• Side effect profile similar to other opioids • Generally well tolerated, with most side effects transient	• May complicate management of opioid overdose requiring high naloxone doses.

Metabolism and excretion



- High percentage of Buprenorphine bound to plasma protein
- Metabolised in liver by cytochrome P450 3A4 enzyme system into Buprenorphine and other metabolites

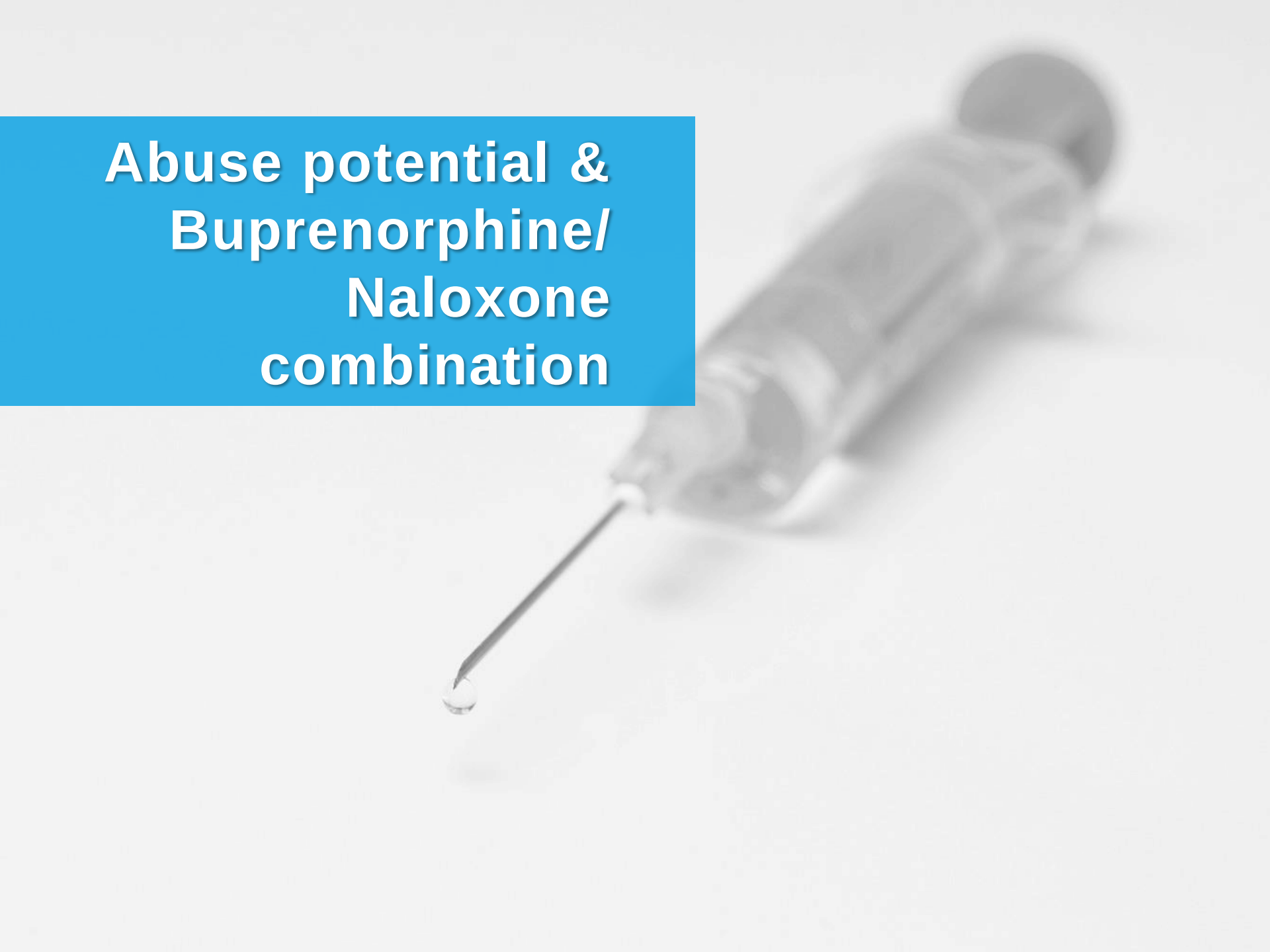
Buprenorphine: Safety overview

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

Buprenorphine:
Interaction with other medicines

Drug	Effect	Drug	Effect
Boceprevir	↑ sedation, respiratory depression	**Cimetidine**	↑ Buprenorphine level
Ritonavir	Buprenorphine level possibly ↑	**Domperidone**	↓ effects of domperidone
Tipranavir	tipranavir level ↓	**MAOIs**	possible CNS excitation /↓
Alcohol	↑ hypotensive, sedative effects	**Metoclopramide**	↓effects of metoclopramide
General Anaesthetics	↑ effects of general anaesthetics	**Moclobemide**	possible CNS excitation/↓
Tricyclic antidepressants	sedative effects possibly ↑	**Nalmefene**	Avoid
Antihistamines	sedative effects possibly ↑	**Selegiline**	Avoid
Antipsychotics	↑ hypotension, sedation	**Sodium Oxybate**	↑ effects of sodium oxybate
Anxiolytics and Hypnotics	↑ sedative effect		

Abuse potential & Buprenorphine/ Naloxone combination



Buprenorphine: Abuse potential

- Buprenorphine is abusable (epidemiological, human laboratory studies show)
- Diversion and illicit use of analgesic form (by injection)
- Relatively low abuse potential compared to other opioids
- Consider Buprenorphine+Naloxone (Suboxone) if potential for diversion

Overdose with Buprenorphine

- Low risk of clinically significant problems
- No reports of respiratory depression in clinical trials comparing Buprenorphine to Methadone
- Buprenorphine's ceiling effect make it less likely to produce clinically significant respiratory depression
- However, reports of fatal overdose when Buprenorphine was combined with other CNS depressants (reviewed later in this section)

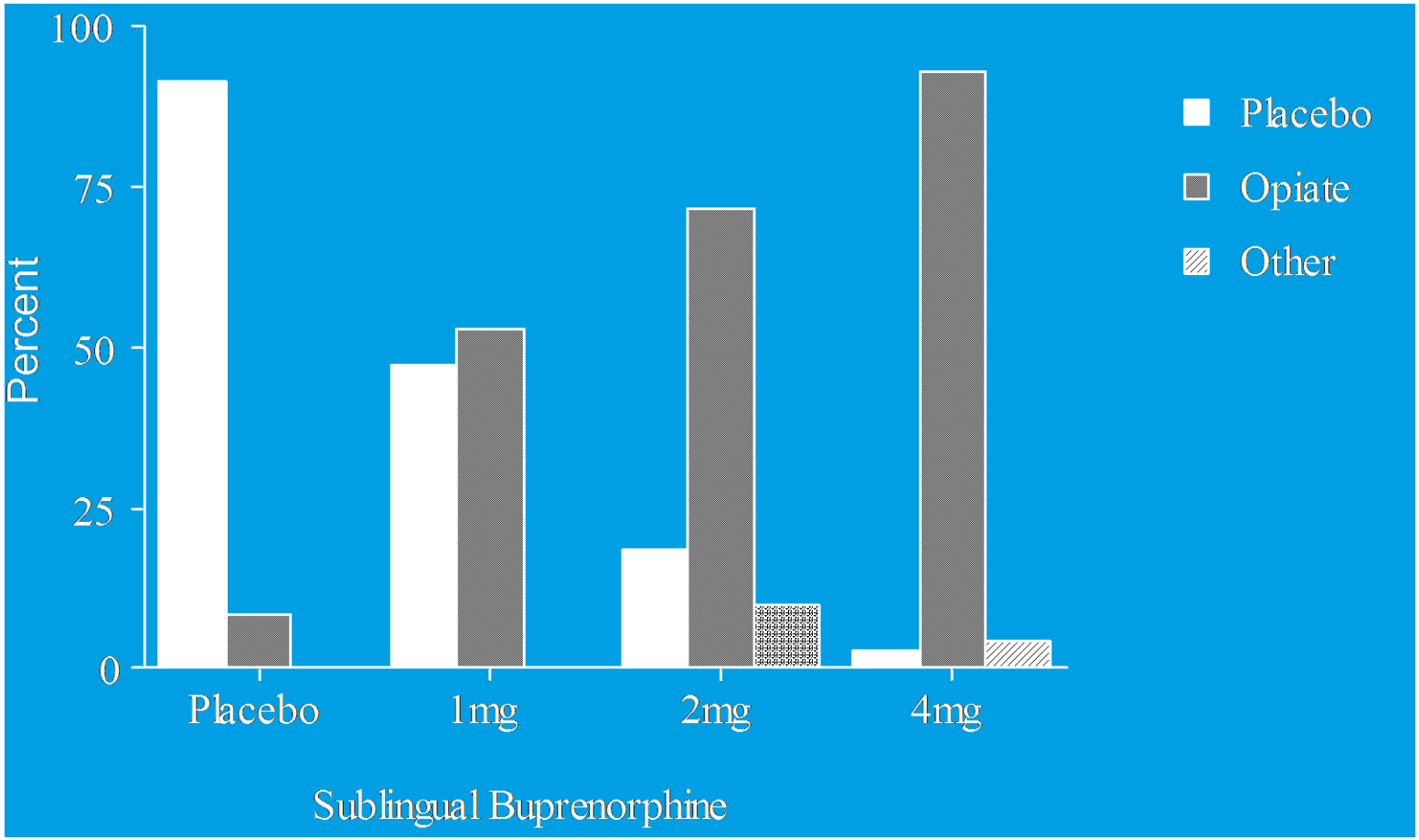
Interaction with benzodiazepines and other sedating drugs

- Reports of death when Buprenorphine injected with benzodiazepines (BZD)
- Potential for similar effect with other sedatives
- Mechanism leading to death is not known
- Not clear if any patients have died from use of sublingual Buprenorphine combined with oral BZD
- Most deaths appear to have been related to injection of the combination of dissolved Buprenorphine tablets with benzodiazepine

Interaction with BZD and other sedating drugs

The combination product (Buprenorphine with Naloxone, Suboxone®) designed to ↓ risk of injecting Buprenorphine, so the risk of misuse of Buprenorphine with benzodiazepines should be decreased with the availability of Buprenorphine/Naloxone

Buprenorphine's abuse potential



Buprenorphine: Diversion and misuse

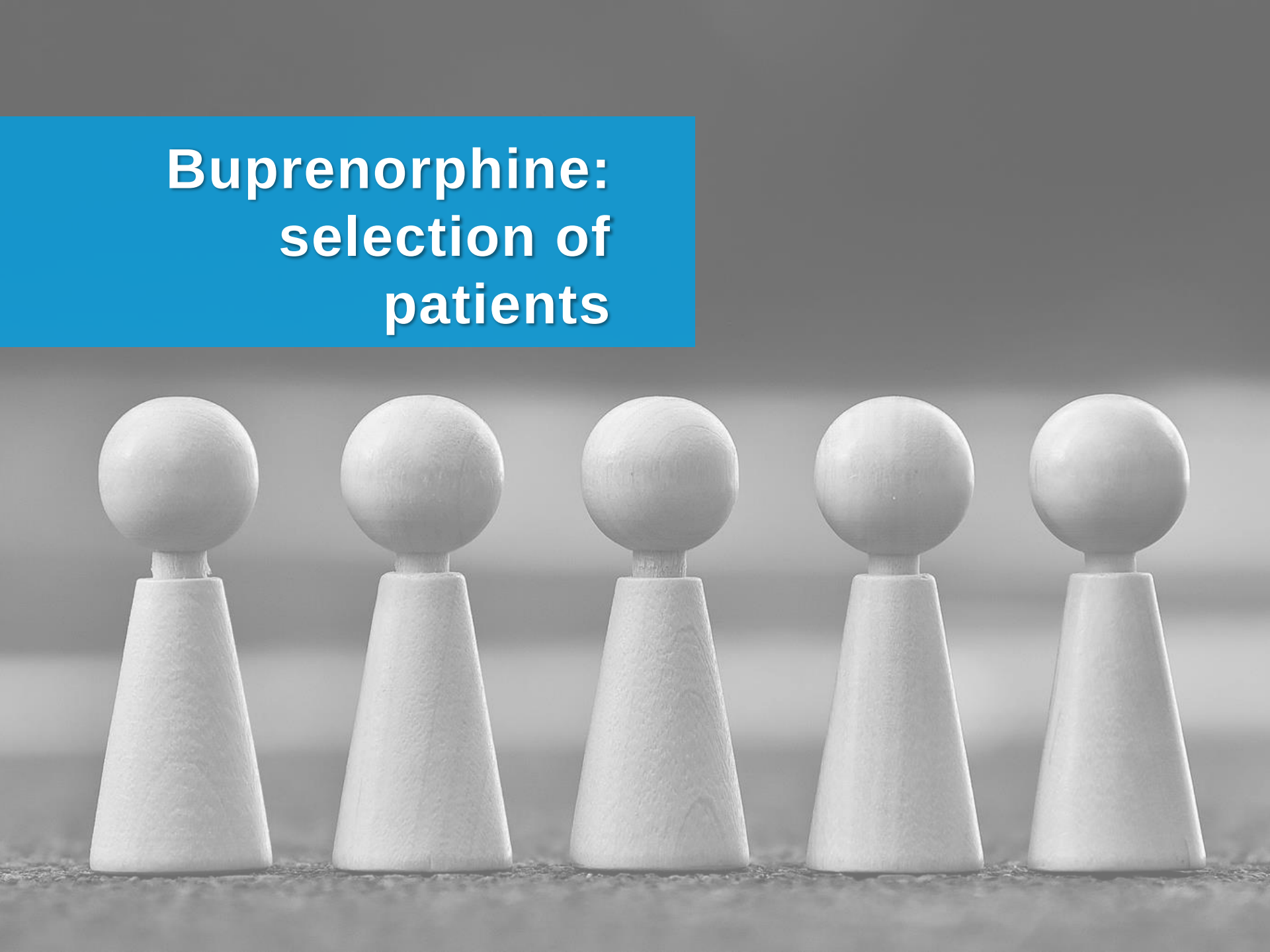
Four possible groups that might attempt to divert and abuse Buprenorphine / naloxone parenterally:

- Persons physically dependent on illicit opioids
- Persons on prescribed opioids (e.g., Methadone)
- Persons maintained on Buprenorphine/Naloxone
- Persons abusing, but not physically dependent on opioids

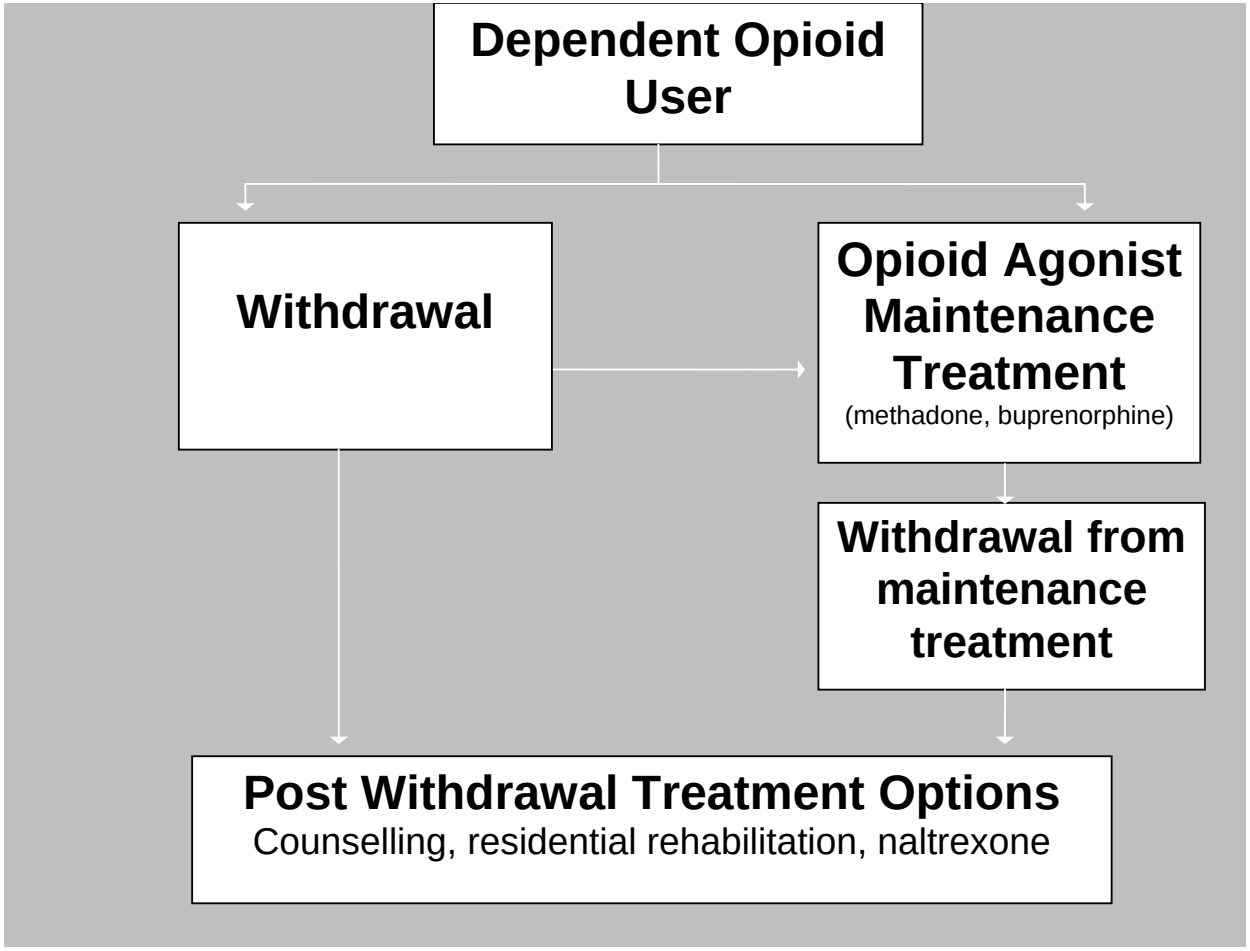
Combination of Buprenorphine and Naloxone

- Combination tablet containing Buprenorphine with Naloxone in 4:1 ratio, if taken under tongue – predominant Buprenorphine effect
- If dissolved and injected Buprenorphine, it would have predominant Naloxone effect (precipitated withdrawal)
- Reduces risk of abuse

Buprenorphine: selection of patients



Treatment pathways for dependent opioid users



Assessment questions

- Is the patient dependent on opioids?
- Is the patient aware of other available treatment options?
- Does the patient understand the risks, benefits, and limitations of Buprenorphine treatment?
- Is the patient expected to be reasonably compliant?
- Is the patient expected to follow safety procedures?

Assessment questions

- Is the patient psychiatrically stable?
- Is the patient taking other medications that may interact with Buprenorphine?
- Are the psychosocial circumstances of the patient stable and supportive?
- Is the patient interested in out-patient clinic or hospital based Buprenorphine treatment?
- Are there resources available in the office to provide appropriate treatment?

Patients who may be unsuitable for Buprenorphine

- Significant untreated psychiatric comorbidity
- Active or chronic suicidal or homicidal ideation or attempts
- Multiple previous treatments for drug abuse with frequent relapses
- Poor response to previous treatment attempts with Buprenorphine
- Significant medical complications
- Dependence on high doses of benzodiazepines/ other CNS depressants (including alcohol)

Choice of medication for maintenance: Methadone or Buprenorphine

If both suitable, Methadone to be prescribed as 1st choice, but consider the following:

- Patients preference
- Level of opioid use
- Risk of diversion
- Risk of overdose
- Prescribers experience with medication
- Patients treatment history
- History of prescribed & illicit drug use

Choice of agonist for maintenance: Methadone or Buprenorphine

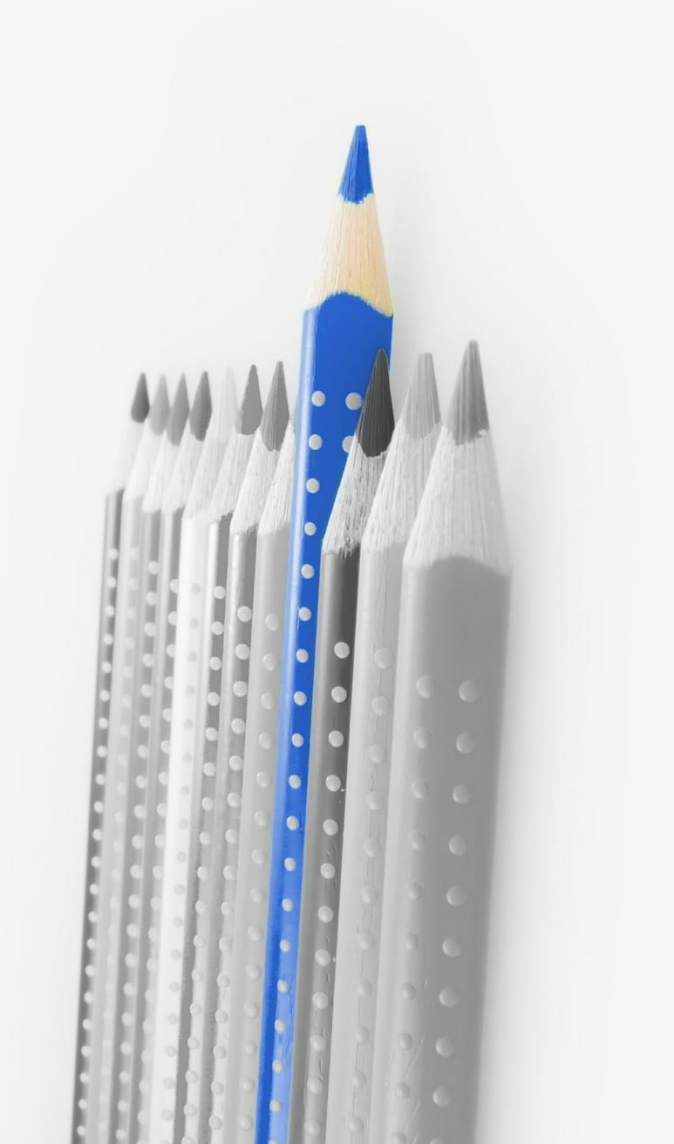
Factor for consideration	Methadone	Buprenorphine
High level of opioid use	✓	
Risk of diversion		✓ (Suboxone)
Risk of overdose		✓ (if used alone)
Treatment history	Better retention	
Prescribed & illicit drug use		↓ interaction with hepatic enzyme inducers/inhibitors
Sedation	More	Less
Quick dose titration		✓
Patients with risk of ↑ QTc		✓
c/c pain conditions requiring opioid analgesia	✓	

Phases of Buprenorphine maintenance

Maintenance treatment with Buprenorphine for opioid addiction has 3 phases:

- **Induction:** Medically monitored start up of Buprenorphine therapy
- **Stabilization:** Has begun when a patient has discontinued/ greatly reduced use of drug of abuse, no longer has cravings, and is experiencing few/no side effects
- **Maintenance:** This phase is reached when patient is doing well on a steady dose. Duration of maintenance phase is individualized for each patient and may be indefinite. The alternative to this phase, once stabilization achieved, is medically supervised withdrawal

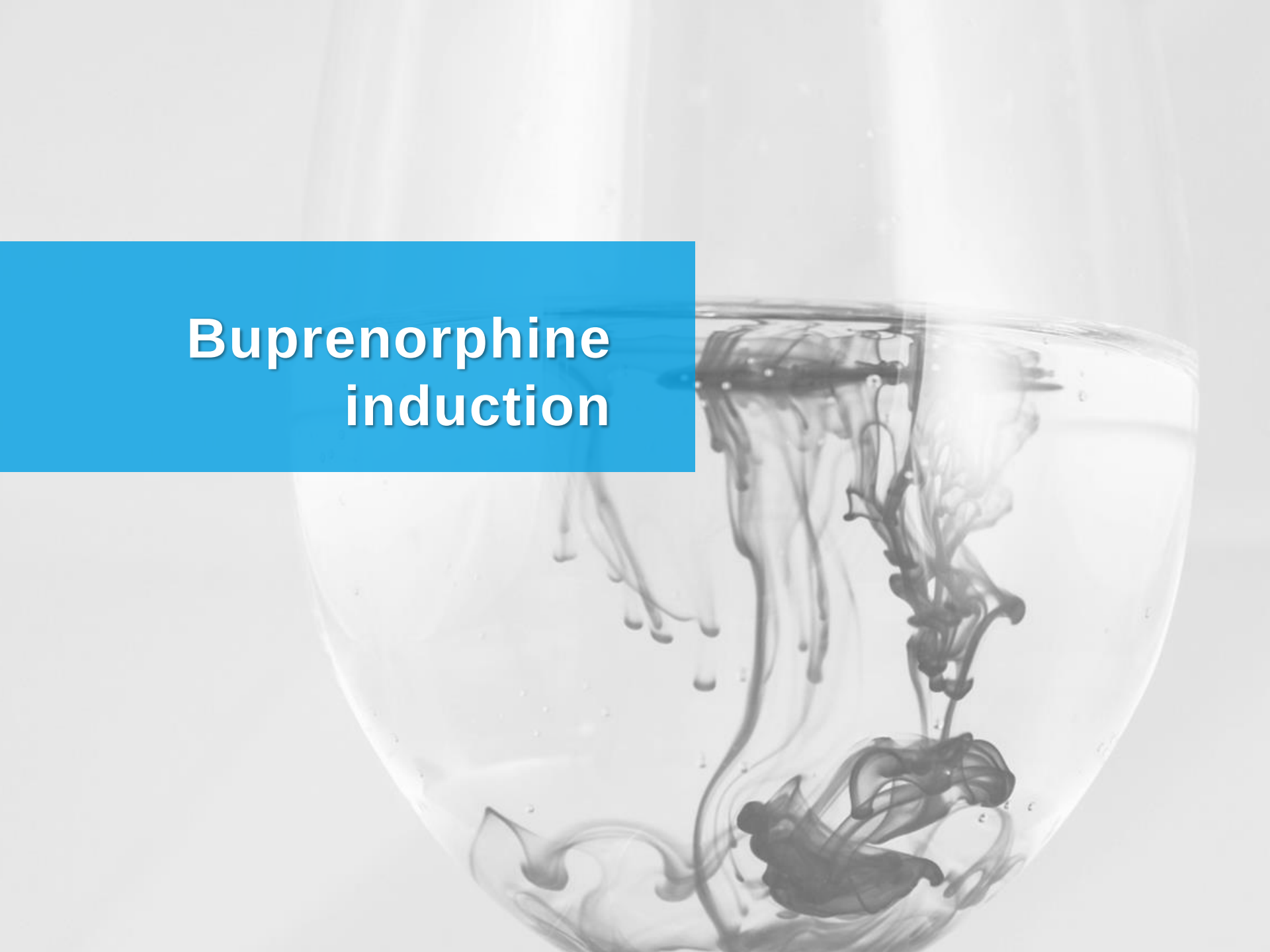
Where are we so far?



- What is the mechanism of Buprenorphine action?
- How safe is Buprenorphine?
- What are the risks of using Buprenorphine?
- How to select patients for Buprenorphine treatment?


Break

Buprenorphine induction



Buprenorphine induction

- The induction phase is the medically monitored start up of Buprenorphine therapy
- Buprenorphine is administered when an opioid-addicted individual has abstained from using opioids for 12–24 hours and is in the early stages of opioid withdrawal
- If the patient is not in the early stages of withdrawal, then the Buprenorphine dose could precipitate acute withdrawal
- Induction is typically initiated as observed therapy in the outpatient clinic

Buprenorphine induction goal

To find the dose of Buprenorphine at which the patient:

- Discontinues or markedly reduces use of other opioids
- Experiences no cravings
- Has no opioid withdrawal symptoms
- Has minimal/no side effects

Buprenorphine induction: identified issues

The **two identified problems** during Buprenorphine induction are:

1. Risk of precipitated withdrawal
2. Risk of premature dropping out of treatment

- Higher doses early in induction might ↑ retention in treatment, but may precipitate withdrawal in others
- Clinical judgement is required that takes into account all relevant factors in a particular case

Precipitated withdrawal

- The likelihood for Buprenorphine-precipitated withdrawal is low
- Buprenorphine-precipitated withdrawal seen in controlled studies has been mild in intensity and of short duration

Precipitated withdrawal

Factors that ↑ risk of Buprenorphine related precipitated withdrawal are:

- Higher levels of physical dependence
- A short time interval between last use of an opioid and first dose of Buprenorphine
- Higher first doses of Buprenorphine

Buprenorphine induction

Day 1

Give first dose for those patients:

- Who are in objective opioid withdrawal
- Whose last use of a short-acting opioid e.g., heroin, oxycodone, hydrocodone was more than 12–24 hours
- 4-8 mg of Buprenorphine
- 4/1–8/2 mg of Buprenorphine + Naloxone
- Monitor in clinic for up to 2 hours after first dose
- Relief of withdrawal symptoms should begin within 30-45 min after the first dose
- If unsure if patient is in the sufficient withdrawal, the first dose could be 2 mg followed by another 2 mg, given 0,5 – 1 hour later if the first dose is well tolerated

Buprenorphine induction

Day 1

If patient is not in opioid withdrawal at time of arrival at outpatient clinic, then assess time of last use and consider:

- Having them return another day
- Waiting in the clinic until evidence of withdrawal is seen
- Leaving clinic and returning later in the day (with strict instructions to not take opioids while away from the clinic)

Induction: Day 1
Precipitated withdrawal management

If withdrawal is precipitated by first dose consider:

- Use symptomatic treatment and repeat buprenorphine 2 mg after 2 hours
- The maximum first day dose can be higher than 8 mg for people with high level of physical dependence, up to 12 mg

- Can re-dose if needed (every 2-4 hours, if opioid withdrawal subsides and then reappears)
- Maximum first-day dose of 8mg Buprenorphine or 8/2 mg Buprenorphine / naloxone

Buprenorphine induction: For long-acting opioids – Day 1

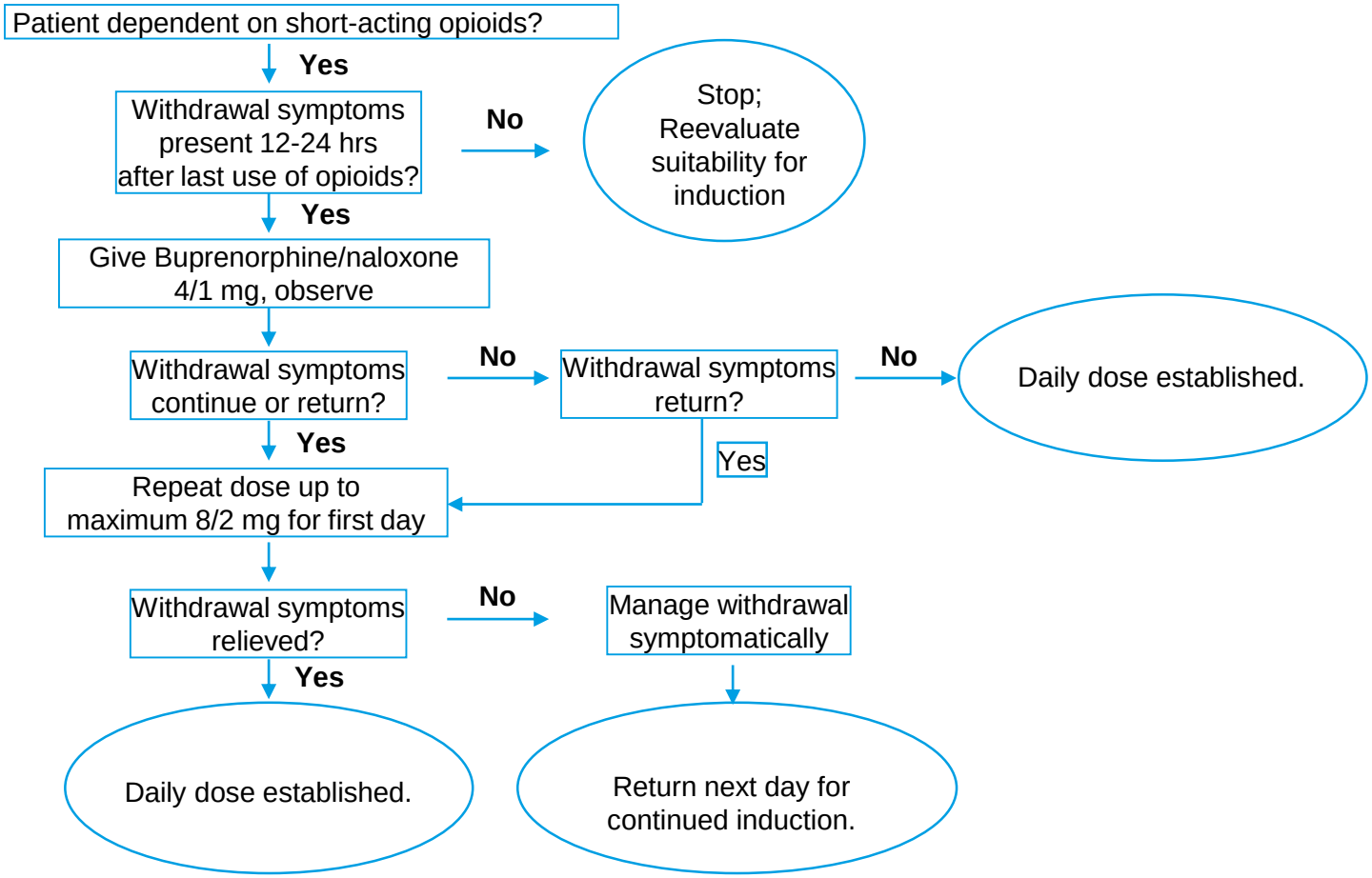
If dependent on long-acting opioids e.g., Methadone:

- Taper over at least 1 week, to Methadone ≤30 mg/day
- First dose of Buprenorphine to be given ≥ 24 hours after the last dose of Methadone

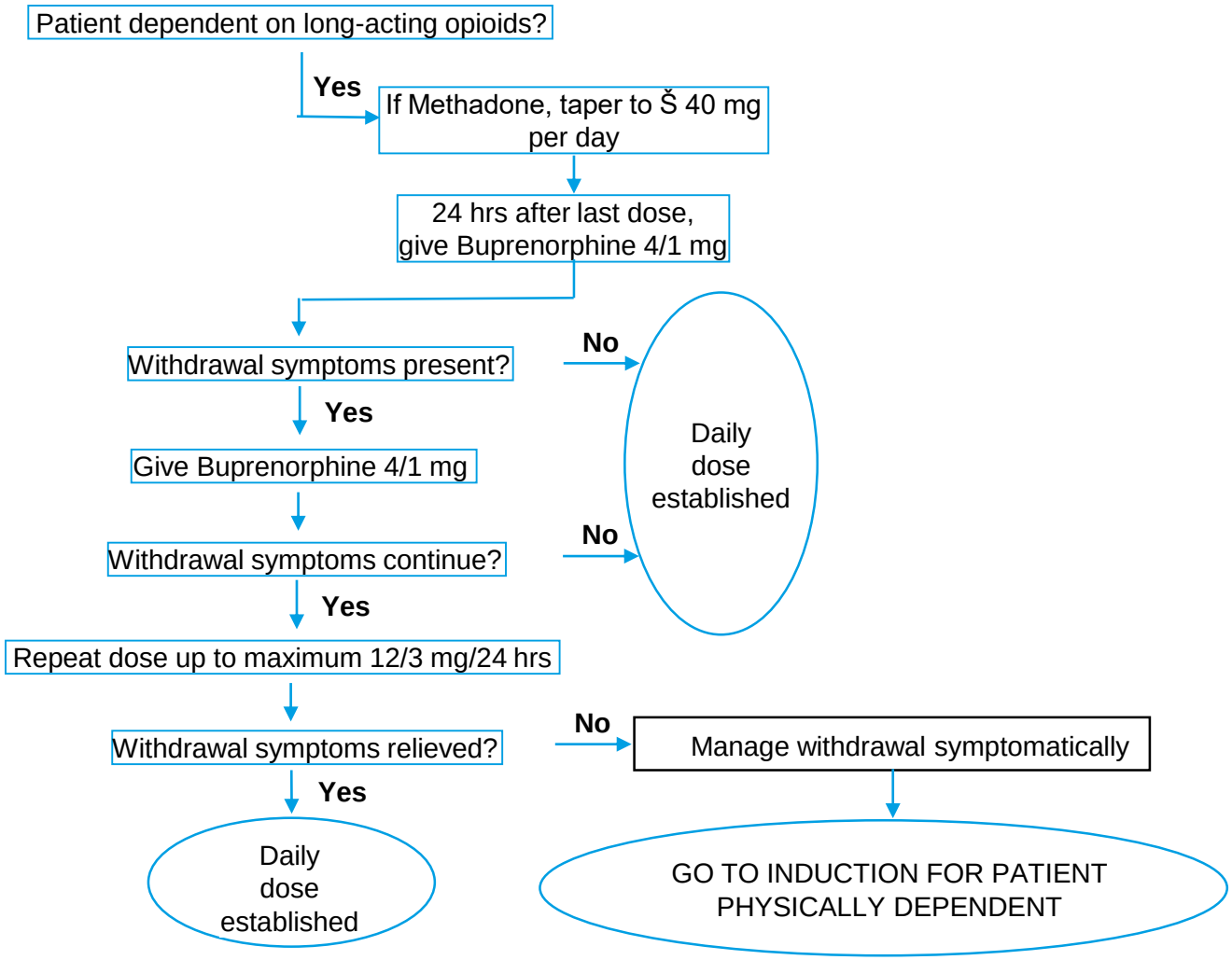
The first dose of Buprenorphine is 2 mg

- If Buprenorphine has precipitated withdrawal, a 2nd dose of 2 mg to be administered and repeated, if necessary, to a maximum of 8mg on Day 1

Induction: patient physically dependent on short-acting opioids – Day 1



Induction: patient physically dependent on long-acting opioids – Day 1



Buprenorphine induction:

Day 2

After day 1, procedure for Buprenorphine induction in patients dependent on heroin or Methadone are essentially same:

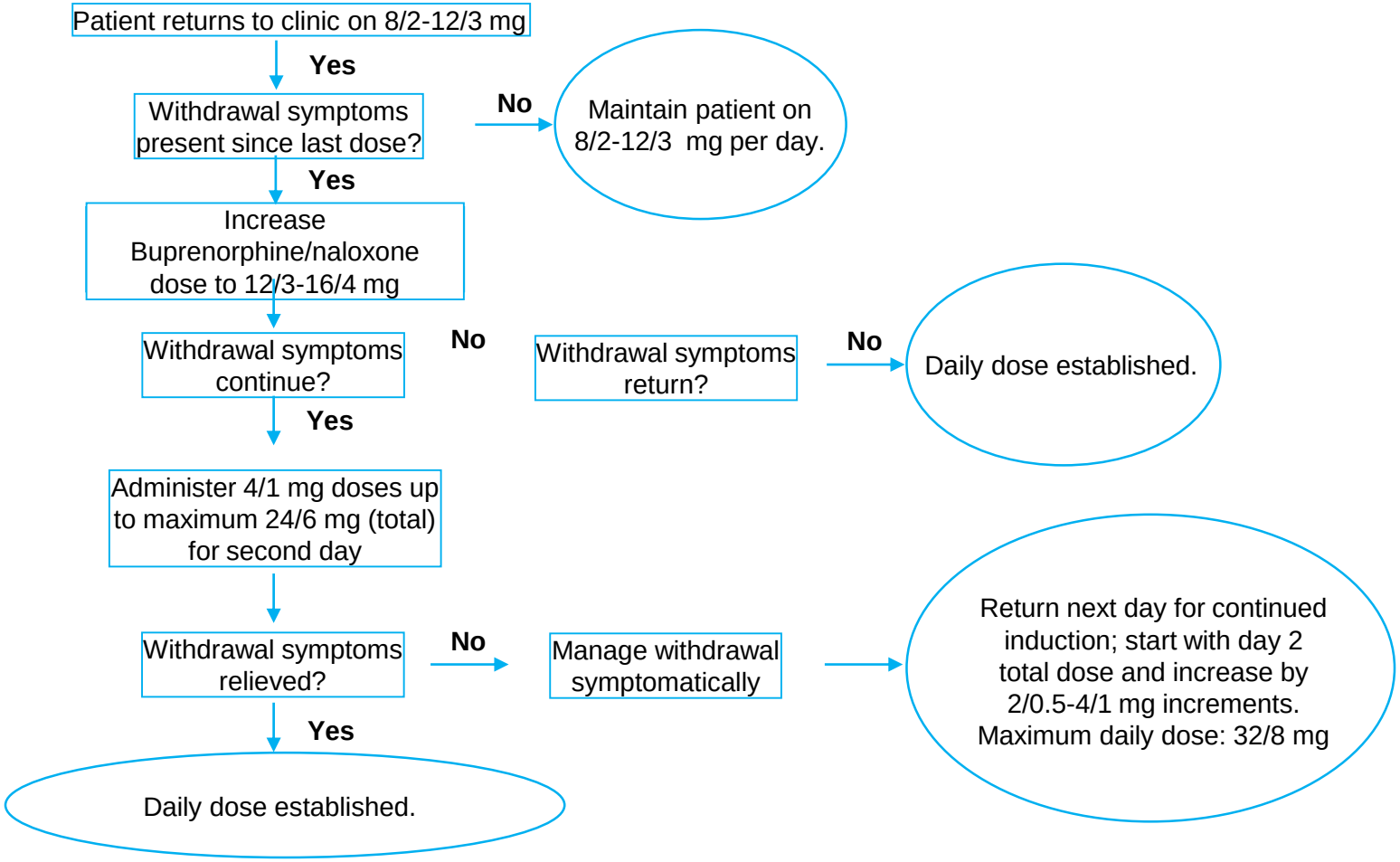
- On day 2, have the patient return to the clinic if possible for assessment and dosing
- Assess if patient has used opioids since they left the clinic, and adjust dose according to the patient's experiences after first-day dosing

Buprenorphine induction

Days 2-7

- Dose subsequently increased to achieve symptomatic relief:
  - Buprenorphine 2-4 mg each day or
  - Suboxone 2/0.5 - 4/1 mg increments/day
- Target dose of 12-16 mg/day to be achieved in 1st week, unless side effects occur
- Increase Buprenorphine rapidly if patients have persistent withdrawal or craving, up to 24 mg otherwise patients may drop out
- Once target dose is achieved, induction phase ends and stabilisation begins

Induction: patient physically dependent on short- or long-acting opioids, Days 2+



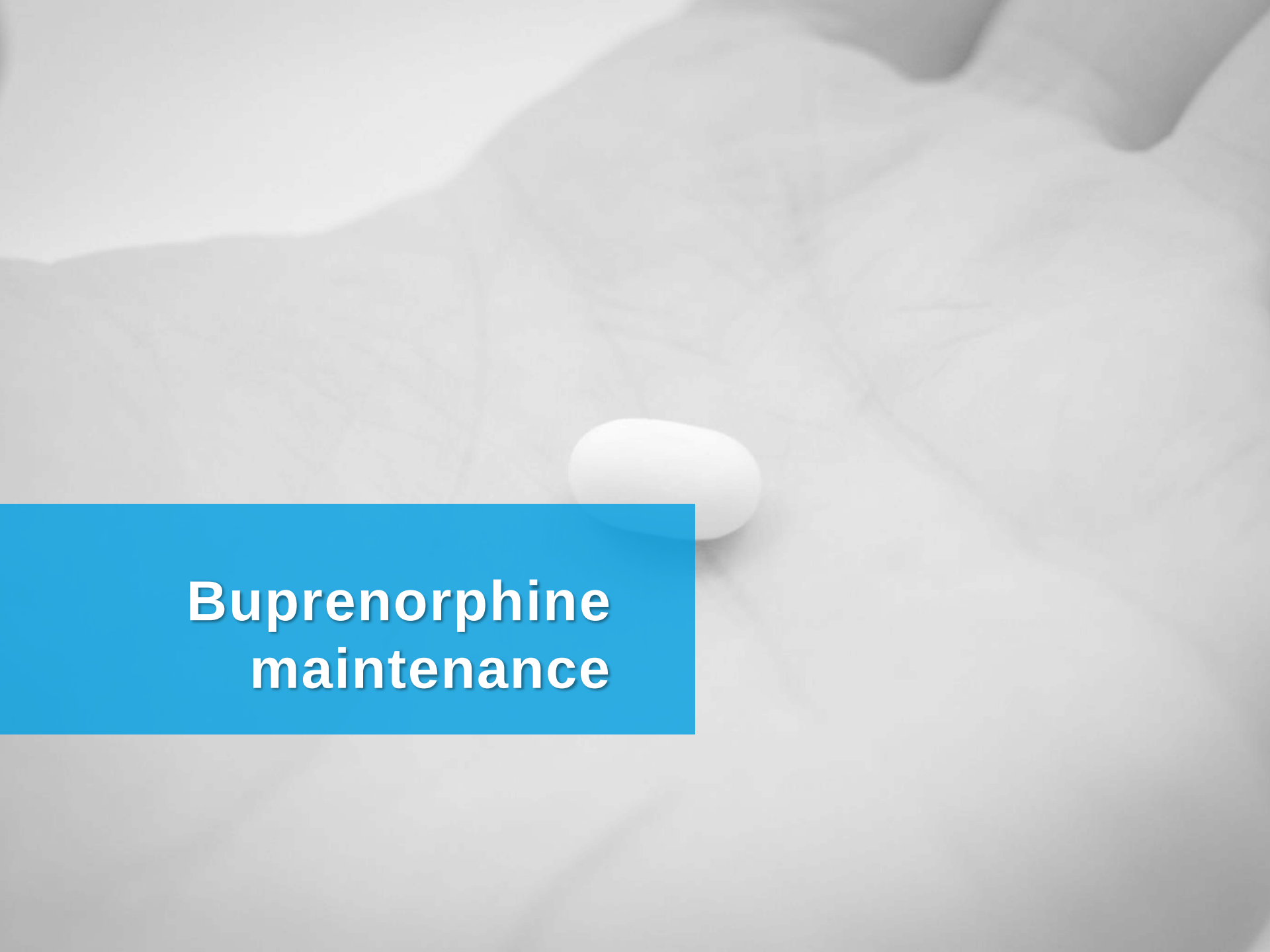
Buprenorphine stabilisation

Buprenorphine stabilisation

- The stabilization phase has begun when
  - Drug of abuse discontinue or greatly ↓
  - Patient has no more cravings
  - Patient has few or no side effects
- Stabilise on daily sublingual dose
- The Buprenorphine dose may need to be ↑ by 2-4 mg/week till stabilization achieved
- Nearly all patients will stabilize on 16–24 mg/day
  - Some may require up to 32mg

Buprenorphine stabilisation

- Once stabilized, patient should be monitored daily. If daily administration is not feasible, alternate dosing can be used (every other day)
- Increase dose on dosing day by amount not received on other days (e.g., if on 8 mg/d, switch to 16/16/24 mg MWF)
- Higher daily doses more tolerable if tablets are taken sequentially rather than all at once

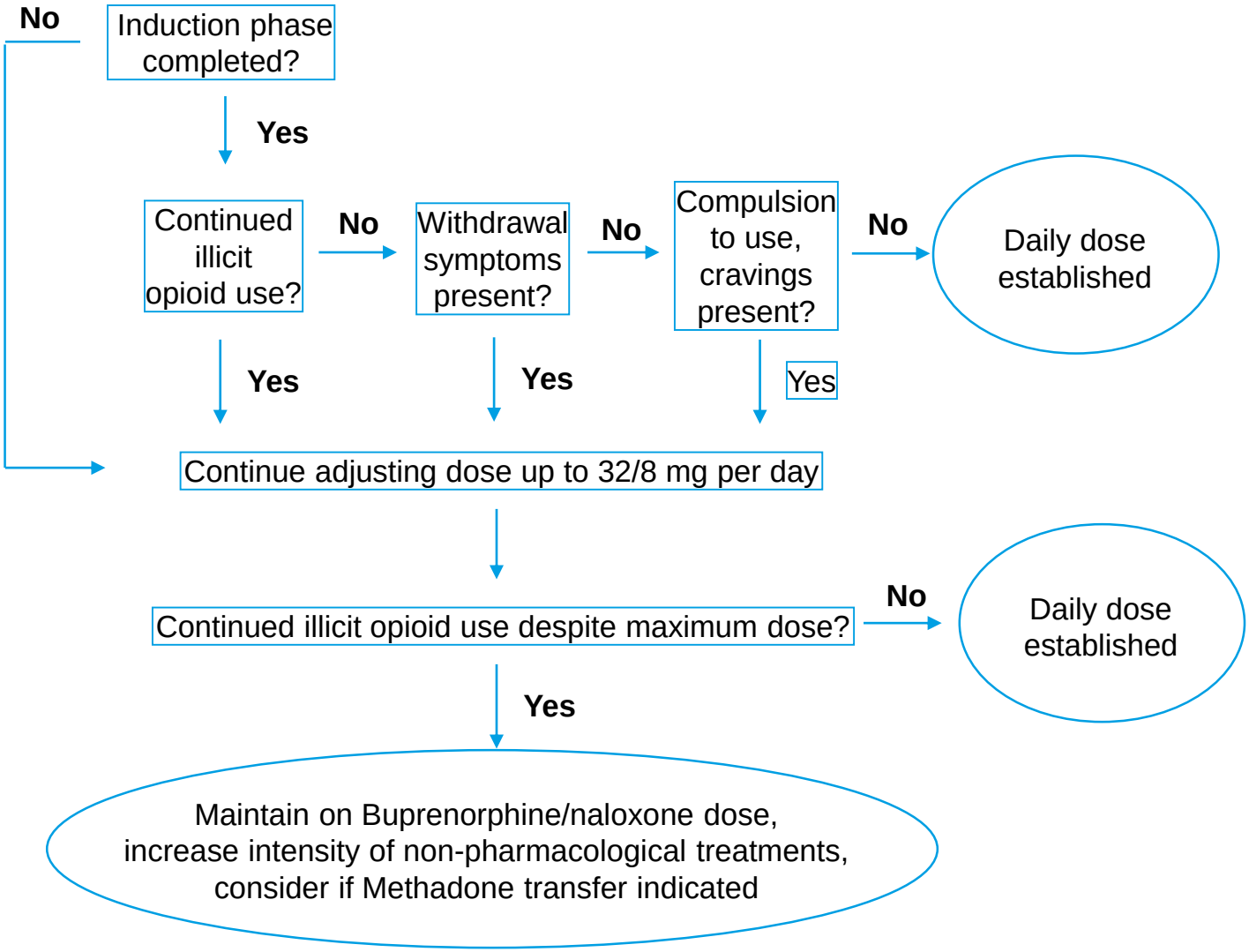


Buprenorphine maintenance

Buprenorphine maintenance

- The maintenance phase is reached when the patient is doing well on a steady dose of Buprenorphine
- Maintenance dose is between
  - 8- 32 mg of Buprenorphine
  - 8/2- 32/8 mg of Buprenorphine + Naloxone
- The duration of maintenance phase is individualized for each patient and may be indefinite
- The alternative to going into (or continuing) a maintenance phase, once stabilization has been achieved, is medically supervised withdrawal

Buprenorphine maintenance

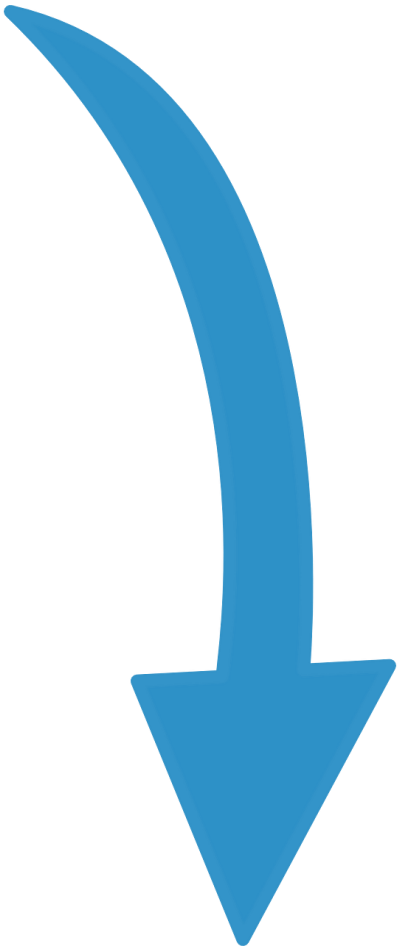


Buprenorphine for opioid detoxification

Buprenorphine for assisted withdrawal

- After a period of maintenance phase or as an alternative to maintenance phase, withdrawal with Buprenorphine can be instituted
- Reduce Buprenorphine 2mg to 4mg every 3-4 days or longer
- Once the daily dose has reached 8mg, choose from the following 2 options:
  - Gradual withdrawal
  - Rapid withdrawal

Buprenorphine rapid dose reduction



Rapid dose reduction can be achieved over a 12-day period.

This is appropriate for:

- Patients being discharged from clinic due to lack of treatment benefit
- Those who require a rapid detoxification

Example of Buprenorphine dose reduction Gradual withdrawal

Day	Dose	Day	Dose	Day	Dose	Day	Dose
1	8mg	11	4mg	21	1.6mg	31	800mcg
2	8mg	12	4mg	22	1.6mg	32	800mcg
3	8mg	13	2.8mg	23	1.6mg	33	400mcg
4	8mg	14	2.8mg	24	1.6mg	34	400mcg
5	6mg	15	2.8mg	25	1.2mg	35	400mcg
6	6mg	16	2.8mg	26	1.2mg	36	400mcg
7	6mg	17	2mg	27	1.2mg		
8	6mg	18	2mg	28	1.2mg		
9	4mg	19	2mg	29	800mcg		
10	4mg	20	2mg	30	800mcg		

Consider using additional ancillary medications to assist with symptoms of opioid withdrawal (e.g., medications for arthralgia, nausea, insomnia)

Example of Buprenorphine dose reduction Rapid withdrawal

Day	Buprenorphine Dose
1	8mg
2	6mg
3	6mg
4	4mg
5	4mg
6	4mg
7	2mg
8	2mg
9	800mcg
10	800mcg
11	400mcg
12	400mcg

Buprenorphine for withdrawal from heroin or Methadone

Withdrawal from Methadone ≤ 30mg or heroin ≤ ½ gm daily

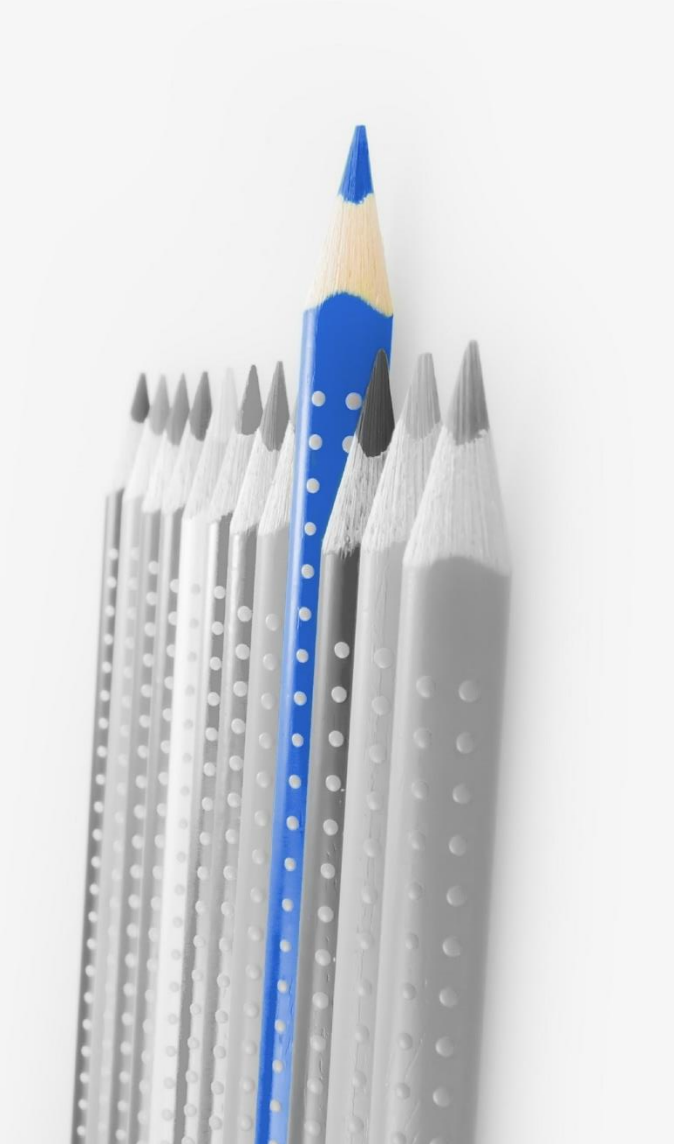
Day	Buprenorphine Dose	Day	Buprenorphine Dose
1	4mg	8	4mg
2	8mg	9	2mg
3	8mg	10	2mg
4	6mg	11	800mcg
5	6mg	12	800mcg
6	4mg	13	400mcg
7	4mg	14	400mcg

Buprenorphine for withdrawal from heroin or Methadone

Withdrawal from Methadone ≥ 30mg or heroin ≥ ½ gm daily

Day	Buprenorphine Dose	Day	Buprenorphine Dose
1	6mg	8	6mg
2	10mg	9	6mg
3	12mg	10	4mg
4	12mg	11	4mg
5	10mg	12	2mg
6	8mg	13	800mcg
7	8mg	14	400mcg

Where are we so far?



- How to conduct Buprenorphine induction and how long does it take?
- What issues may arise during Buprenorphine induction?
- When and how should be Buprenorphine stabilisation begin?
- How can Buprenorphine be used for opioid detoxification?


Break

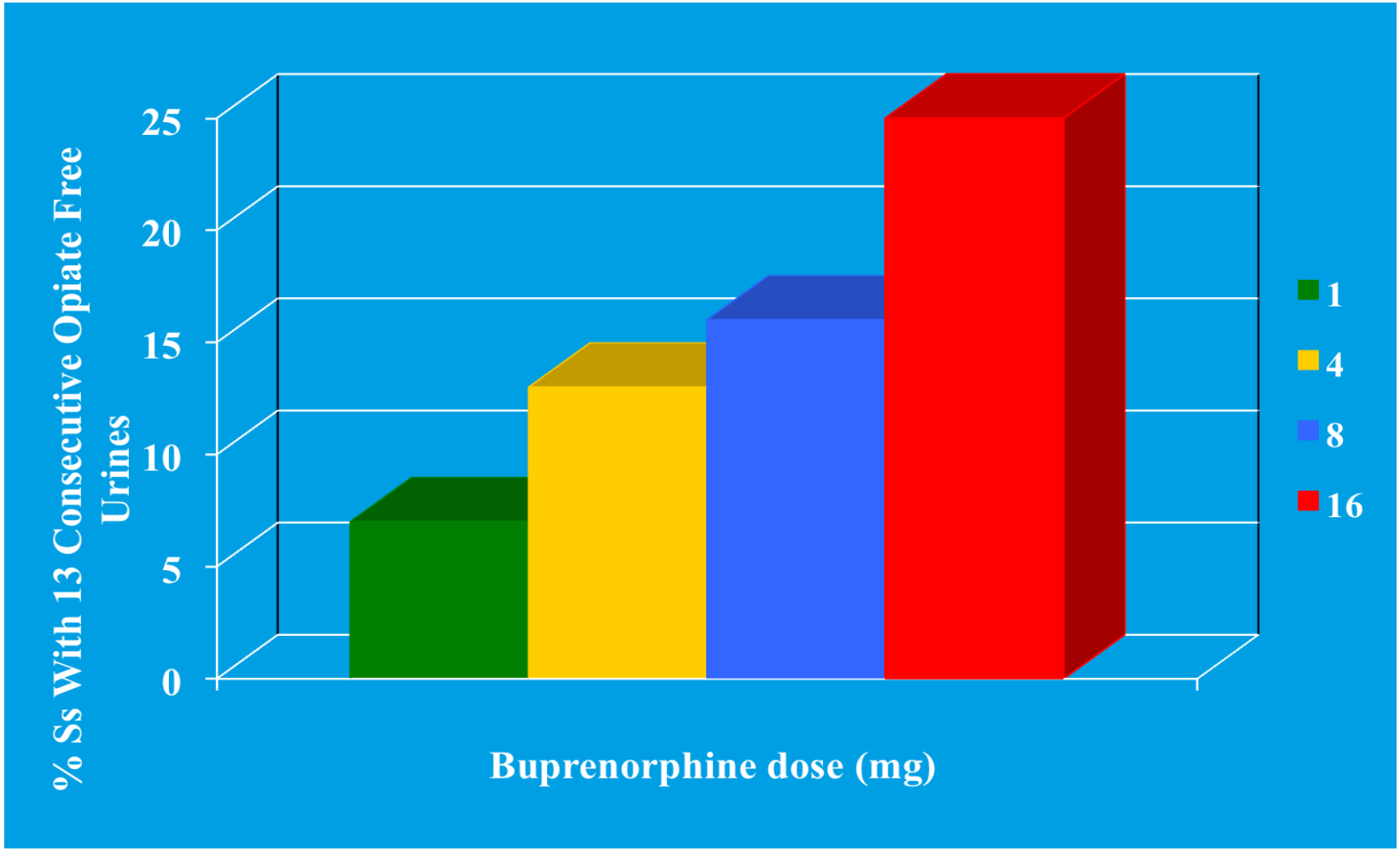
Buprenorphine for opioid dependence treatment: Evidence

Maintenance treatment using Buprenorphine

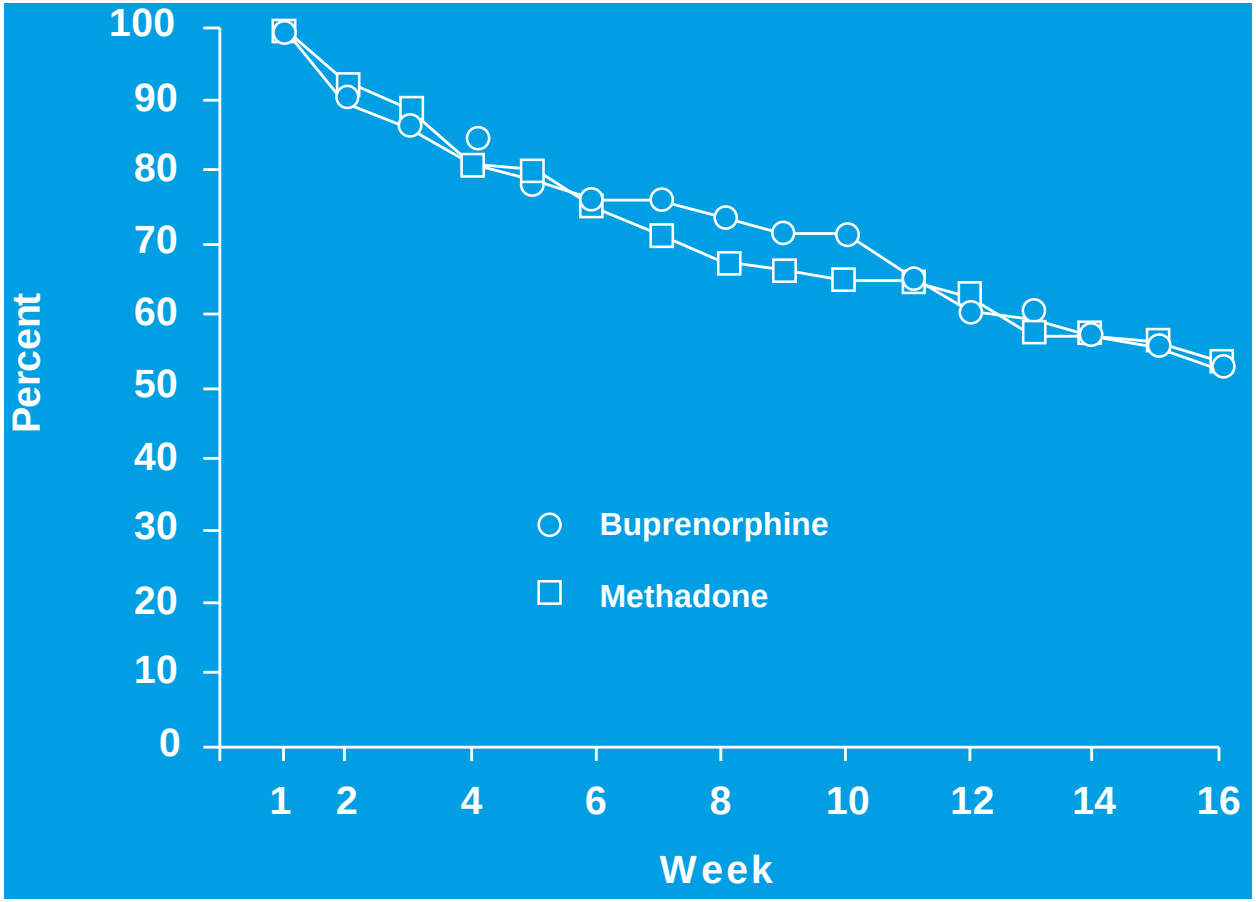
Following slides briefly review representative studies:

- Comparison of different doses of sublingual Buprenorphine
- Buprenorphine-Methadone flexible dose comparison
- Buprenorphine, Methadone, LAAM comparison

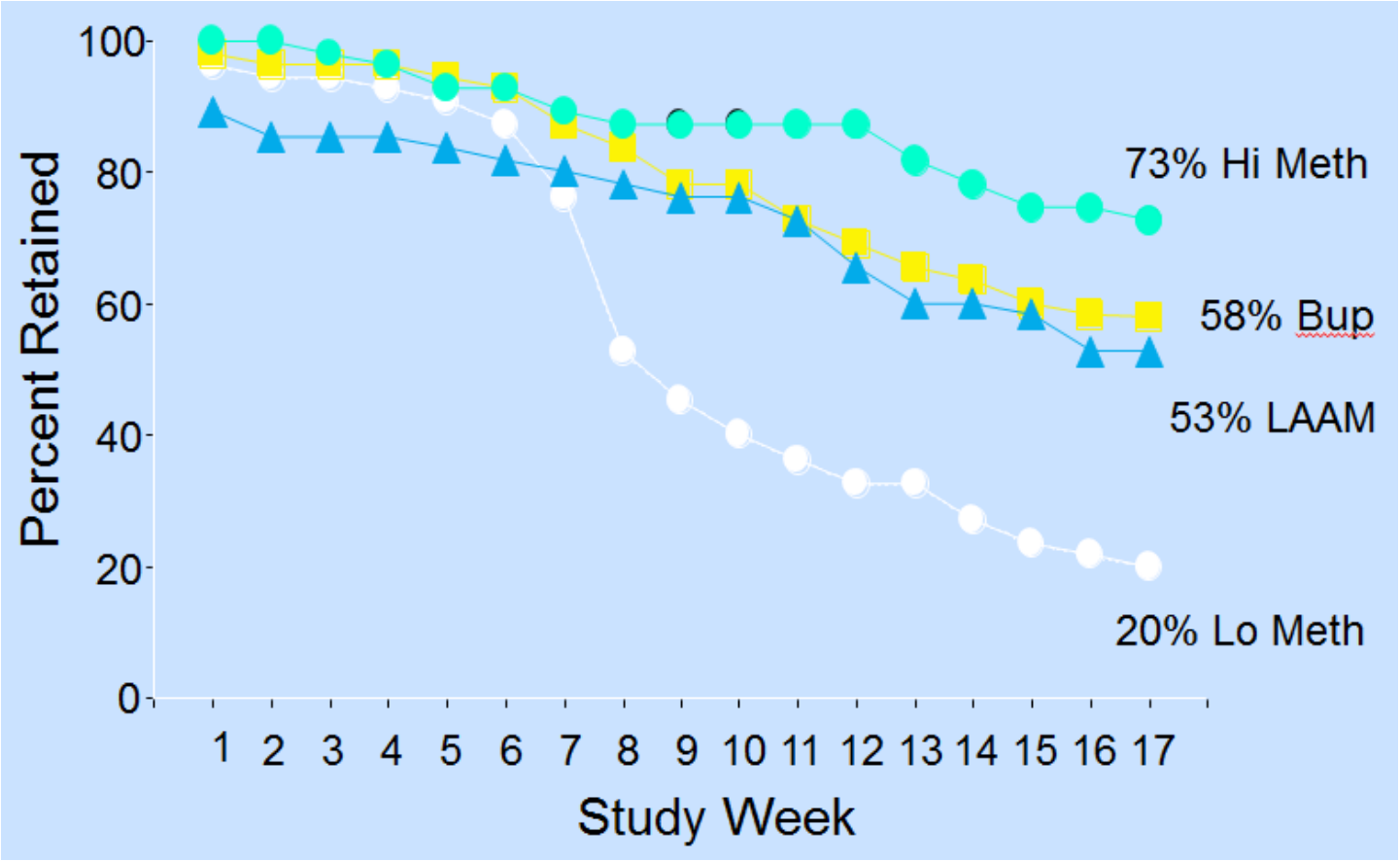
Different doses of Buprenorphine: Opiate use



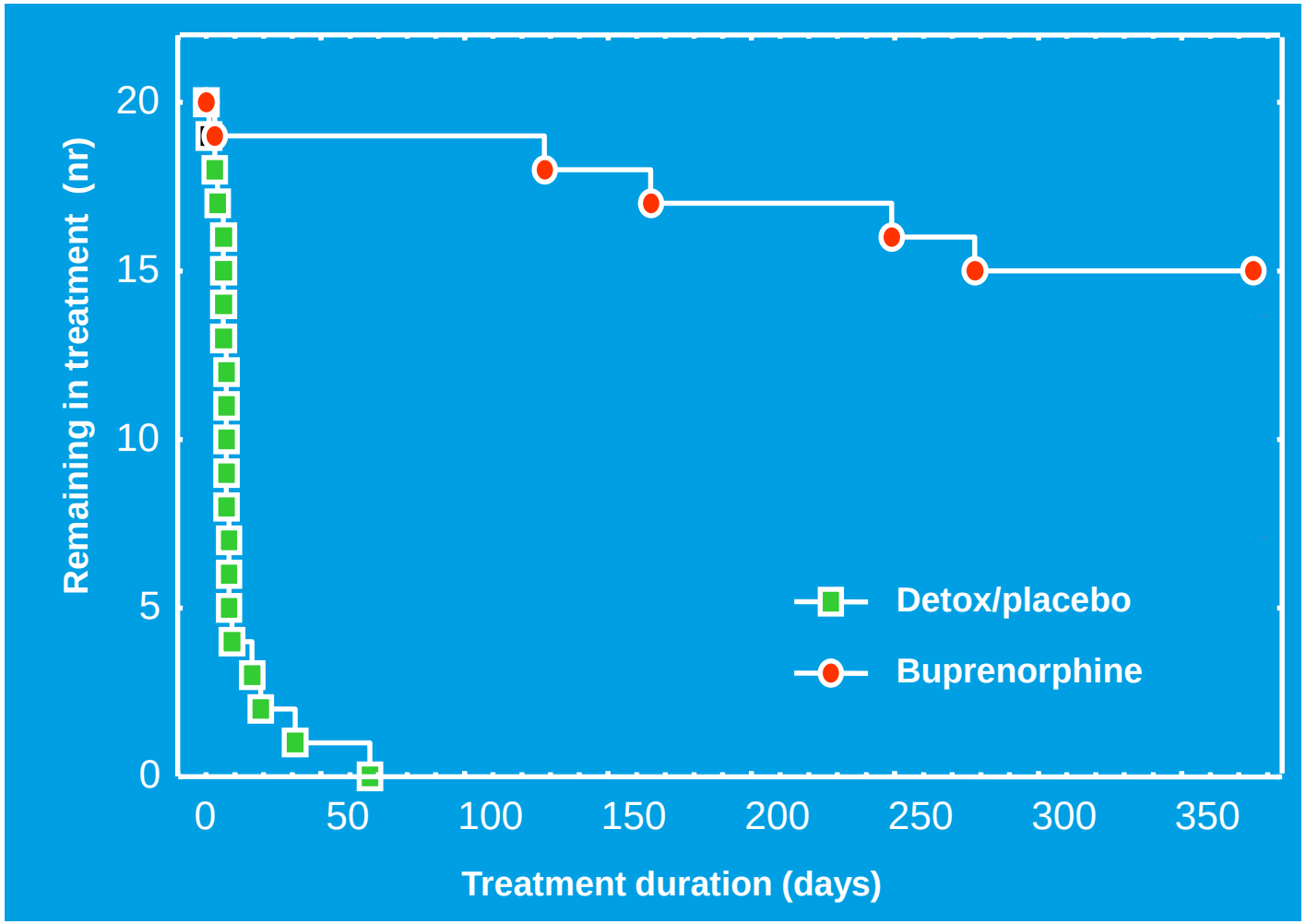
Buprenorphine – Methadone: Treatment retention



Buprenorphine, Methadone, LAAM: Treatment retention



Buprenorphine maintenance / withdrawal: Retention



Buprenorphine maintenance / withdrawal: Mortality

	Detox/Placebo	Buprenorphine	Cox regression
Dead	4/20 (20%)	0/20 (0%)	χ^2=5.9; p=0.015

Buprenorphine: Current evidence base from literature reviews

Buprenorphine maintenance (BMT): Current evidence

- BMT &MMT are effective treatments for opioid dependence
- There is strong evidence that BMT is less effective than MMT in retaining patients in treatment
- BMT is safer during induction
- Risk of cardiac effects (↑QTc) is lower with BMT in comparison to Methadone at doses >100 mg/day

Buprenorphine for opioid withdrawal: Evidence from Cochrane review (2009)

- Buprenorphine equivalent to Methadone in reducing the severity of withdrawal symptoms
- The withdrawal symptoms may resolve more quickly after stopping Buprenorphine
- There was a trend for better completion rates with Buprenorphine

Buprenorphine for opioid dependence: Summary

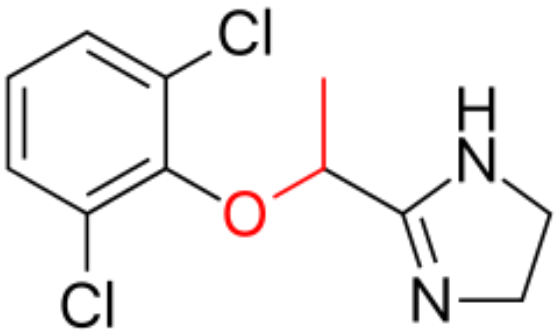
- Buprenorphine has unique pharmacological properties that make it an effective and well tolerated addition to the available pharmacological treatments for opioid addiction
- Its safety profile makes it an attractive treatment for patients addicted to opioids as well as for the medical professionals treating them
- Although Buprenorphine offers special advantages to many patients, it is not for everyone. Care must be taken to assess each patient fully and to develop a realistic treatment plan for each patient accepted for Buprenorphine treatment

Let‘s discuss!

What are the differences between using Methadone and Buprenorphine for meintenance treatment?

Other pharmacotherapy for opioid withdrawal: Lofexidine

Lofexidine for opioid withdrawal



lofexidine

National Institute of Health and Care Excellence, England, guidance:

“Lofexidine may be considered for those who have decided not to use Methadone or Buprenorphine for detoxification, have decided to detoxify within a short time period or have mild or uncertain dependence (including young people)”

Lofexidine pharmacology

- Lofexidine is a non-opioid alpha-adrenergic agonist and is not a controlled drug
- It is authorised for the management of opioid withdrawal
- The treatment is between 7–10 days with doses starting at 800 mcg/day and rising to a maximum of 2.4 mg/day. The dose is then reduced over subsequent days
- It is most likely to be successful for patients with uncertain dependence, young people and shorter drug and treatment histories

Lofexidine side effects & monitoring

- Side effects are dry mouth & mild drowsiness
- Sedation ↑ with concomitant use of alcohol / other CNS depressants
- Hypotension and bradycardia

Daily review in the early stages of treatment to check withdrawal symptoms, BP and to provide general encouragement.

Lofexidine for opioid withdrawal: Advantages

- Lofexidine is a structural analogue of clonidine & effective in ↓ symptoms of noradrenergic hyperactivity of opioid withdrawal
- Effective in ↓ chills, abdominal cramps, diarrhoea, piloerection, pupil dilatation, lacrimation, and yawning
- It offers a non-opioid pharmacological treatment approach to rapid withdrawal from opioids, without the risk of dependency
- It can be used to treat moderate-severe withdrawal symptoms, but is not typically used for mild symptoms.

Lofexidine for opioid withdrawal: Disadvantages

- Additional medications may be needed for other opioid withdrawal Sx, e.g. stomach cramps & diarrhoea
- Patient should be advised to take at least part of their dose at bedtime to offset insomnia associated with opiate withdrawal

Lofexidine for opioid withdrawal: Caution

- A small number of patients experience significant hypotension. It should not be used in conjunction with other medicines that cause hypotension
- It is only partially effective in treating anxiety, insomnia & craving. Other symptomatic medicines may be needed to manage OWS
- Caution in those who have ↑ QTc & those prescribed other drugs known to cause ↑QT

Example of Lofexidine dosage regime

Phase of Lofexidine Detoxification	Moderate Opioid Withdrawal	Severe Opioid Withdrawal	Very Severe Opioid Withdrawal
Induction Phase	Day 1: 0.2mg qds	Day 1: 0.2mg qds Day 2: 0.4mg qds	Day 1: 0.2mg qds Day 2: 0.4mg qds Day 3: 0.6mg qds
Peak Dosing Phase	Day 2 onwards: 0.2mg qds	Day 3 onwards: 0.4mg qds	Day 4 onwards: 0.6mg qds
Early Reduction (ER) Phase ER	ER day 1: 0.2mg qds ER day 2: 0.2mg bd	ER day 1: 0.4mg qds ER day 2: 0.4mg tds ER day 3: 0.2mg qds ER day 4: 0.2mg bd	ER day 1: 0.6mg qds ER day 2: 0.4mg qds ER day 3: 0.4mg tds ER day 4: 0.2mg qds ER day 5: 0.2mg bd
Late Reduction Phase	0.2mg od for 3 days	0.2mg od for 3 days	0.2mg od for 3 days


Questions

Wrap-up

- Why treat opiate dependence with Buprenorphine? What evidence is there?
- Can you give some examples of effective practices of Buprenorphine treatment?
- How can concurrent use of other drugs and alcohol during Buprenorphine treatment be addressed?
- What contraindications and medication interactions with Buprenorphine do you know?

Thank you for your time!

End of workshop 3