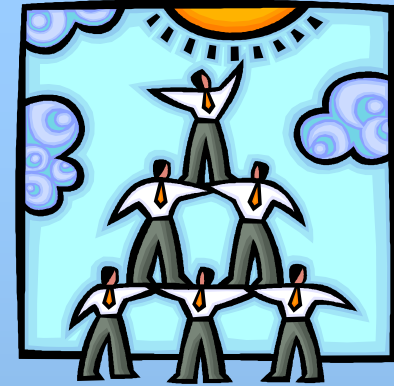


Volume C, Module 2

Opioids: Basics of Addiction; Treatment with Agonists, Partial Agonists, and Antagonists



Module 2: Training goals



To describe the:

- Key components of opiate addiction and its medical / psychiatric consequences
- Benefits and limitations of methadone as a pharmacotherapy for opiate dependence
- Benefits and limitations of buprenorphine as a pharmacotherapy for opiate dependence
- Benefits and limitations of narcotic antagonists for overdose (naloxone) and relapse prevention (naltrexone) for opiate dependence

Module 2: Workshops

Workshop 1: Opiates: What they are, problems associated with their use, and medical treatment implications

Workshop 2: Opiate addiction treatment with methadone

Workshop 3: Opiate addiction treatment with buprenorphine

Workshop 4: Opiate Antagonist Treatment: Naloxone for overdose, Naltrexone for relapse prevention

Icebreaker:

Opiate medication in my country



Does your country use opiate medications, and if so, what type of medication?



What are the main problems in your country regarding the use of these medications?

Workshop 1: Opiates

What they are, problems associated with their use, and medical treatment implications

Pre-assessment



Please respond to the pre-assessment questions in your workbook.

(Your responses are strictly confidential.)



Training objectives



At the end of this training you will understand the:

- 1. Epidemiology of opiate addiction worldwide and its relationship to infectious diseases**
- 2. Basic neurobiology of opiate addiction**
- 3. Medical / psychiatric co-morbidities and treatment strategies for these disorders used with opiate addicts**
- 4. Key issues in engaging opiate addicts into treatment with low threshold approaches**

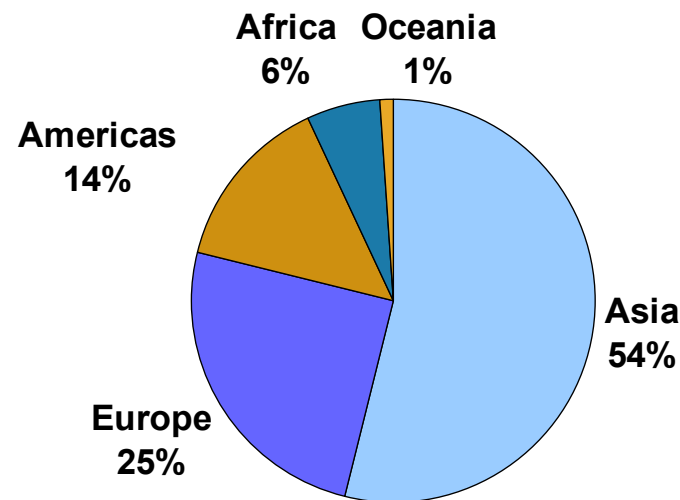
Introduction

Global abuse of opiates

Overview:

- Sixteen million (0.4%) of world's population aged 15-64 abuse opiates
- Heroin abusers make up about 71% of opiate abusers
- Opiates account for 2/3 of all treatment demands in Asia and 60% of treatment demand in Europe

Regional Breakdown of Opiate Abusers



Sources: UNODC, Annual Reports Questionnaire Data, Govt. reports, reports of regional bodies, UNODC estimates.

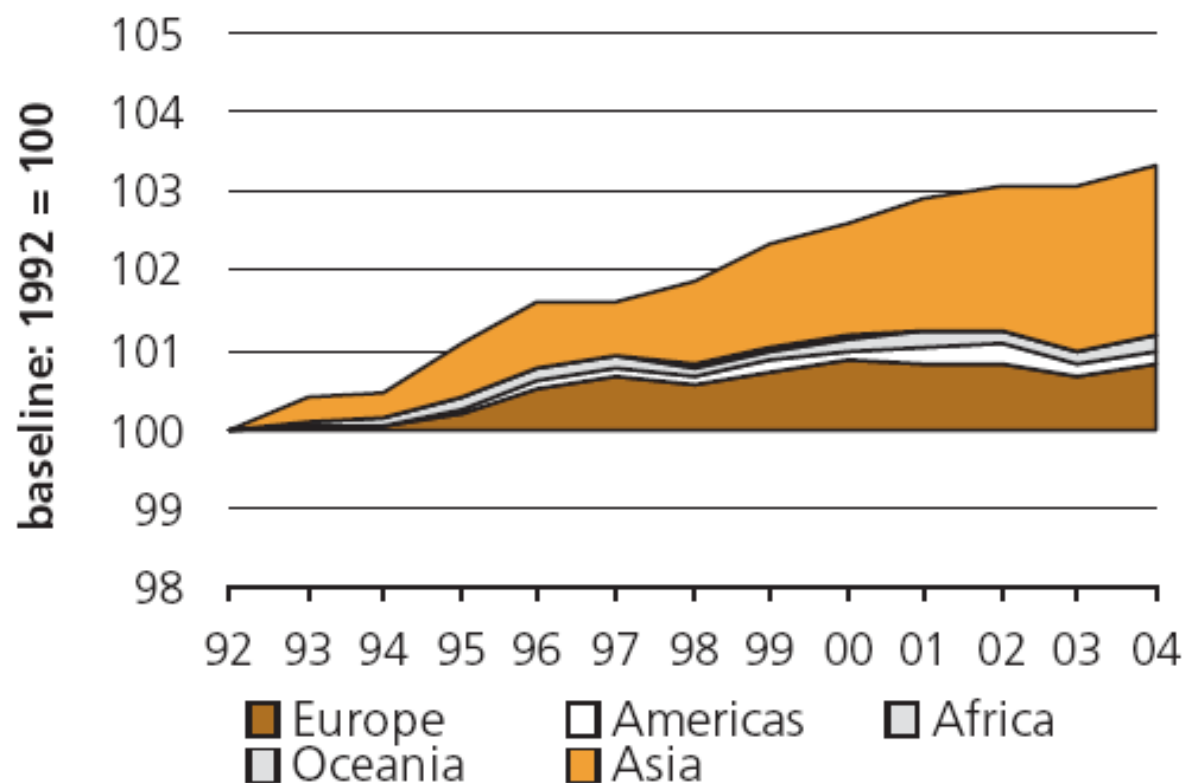
Annual Prevalence of Opiate Abuse, 2003 - 2005

	Abuse of opiates		of which abuse of heroin	
	Number of abusers	in % of population age 15-64	Number of abusers	in % of population age 15-64
EUROPE	4,030,000	0.7	3,340,000	0.6
West & Central Europe	1,565,000	0.5	1,445,000	0.5
South-East Europe	180,000	0.2	175,000	0.2
Eastern Europe	2,285,000	1.6	1,720,000	1.2
AMERICAS	2,280,000	0.4	1,540,000	0.3
North America	1,300,000	0.5	1,240,000	0.4
South America	980,000	0.3	300,000	0.1
ASIA	8,530,000	0.3	5,430,000	0.2
OCEANIA	90,000	0.4	30,000	0.2
AFRICA	910,000	0.2	910,000	0.2
GLOBAL	15,840,000	0.4	11,250,000	0.3
<div> <div></div> Above global average <div></div> Around global average <div></div> Below global average </div>				

Sources: UNODC, Annual Reports Questionnaire data, various Govt. reports, reports of regional bodies, UNODC estimates.

Trends in Opiate Use

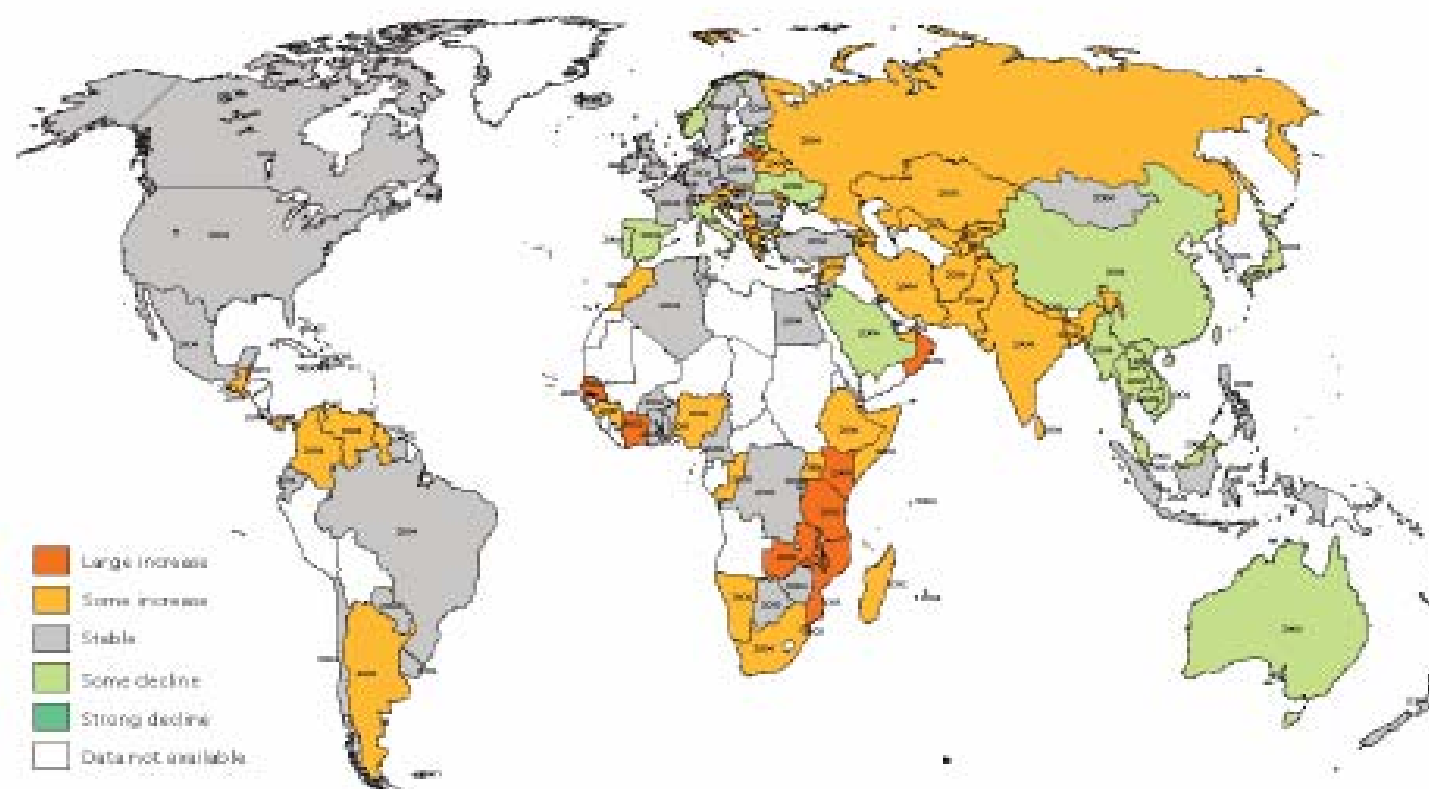
Fig. 46: Twelve-year drug use trends as perceived by experts: opiates



Sources: UNODC, Annual Reports Questionnaire Data, Government reports, UNODC Field Offices, UNODC's Drug Abuse Information Network for Asia and the Pacific (DAINAP), EMCDDA, CICAD, HONLEA reports and local studies.

Change in Abuse of Heroin and Other Opiates (2004, or latest year available)

Map 8: Change in abuse of heroin and other opiates, 2004 (or latest year available)



Sources: UNODC Annual Reports Questionnaires data, National Household Surveys submitted to UNODC, United States Department of State (Bureau for International Narcotics and Law Enforcement Affairs), International Narcotics Control Strategy Report, Law Enforcement Reports, SACENOU (South African Community Epidemiology Network), UNODC, Meetings of Heads of Law Enforcement Agencies (HONLEA), UNODC Opinion Surveys.

Opioids

Opiate (n)

“An unlocked door in the prison of identity. It leads to the jail yard.”



Opioid-related problems

- **Most prominent problems are associated with heroin dependence**
- **Not all users of heroin develop dependence. Between 1 in 4 to 1 in 3 regular users develop dependence**
- **Development of heroin dependence usually requires regular use over months (or longer, when use is more irregular)**

The revolving door



- Heroin dependence is a chronic, relapsing disorder. It is a dependency that is very difficult to resolve.
- Relapse is extremely common. It is part of the process of resolving the dependence – much like giving up tobacco.
- A principle health care objective is to get the patient into treatment, help keep them in treatment, and return them to treatment when relapse occurs.

Polydrug use: Patterns and risks

- **Polydrug use is the norm among drug users**
- **Most people who use illicit drugs use a variety of different drugs**
- **Heroin users also are heavy users of alcohol and benzodiazepines**
- **As CNS depressants, these combinations are especially dangerous and known to be significant contributors to overdose**
- **Patients should be advised against the use of these combinations and told of the risks involved**

Detecting opioid dependence



Look for a pattern (not an isolated event):

- In which a patient frequently runs out of scripts for a prescribed opioid
- In which a patient is on a high and increases the dose of prescribed opioids
- In which a patient injects oral medications
- Of observed intoxication or being in withdrawal
- Which presents plausible conditions that warrant prescribed opioids, but with specific requests for medication type and amount
- In which the patient threatens or harasses staff for a fit-in appointment
- In which a patient alters, steals, or sells scripts
- In which a patient is addicted to alcohol or other drugs

Classification of Opioids

Pure Opioid Agonists Semi-synthetic

opium
papaverine
morphine
codeine

heroin
hydromorphone
oxycodone

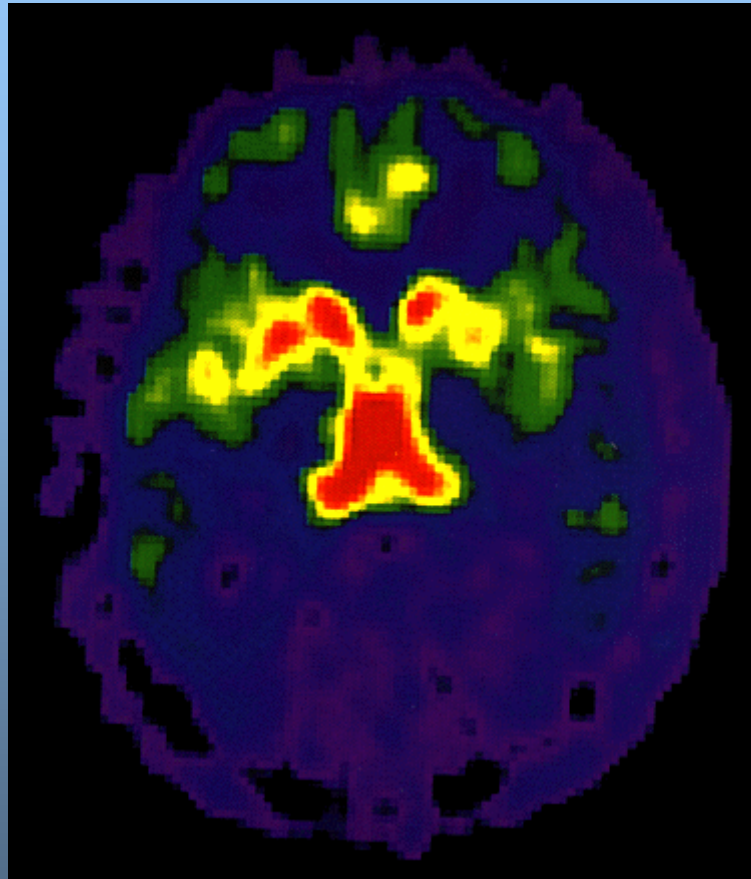
Synthetic

LAAM
fentanyl
meperidine
hydrocodone
methadone
pentazocine
pethidine

Partial Agonists/Antagonists

naltrexone
buprenorphine
LAAM

Opioids: Pharmacology (1)



PET scan of μ opioid receptors

Opioids: Pharmacology (2)

- 3 main families of opioid receptors (μ , κ , and σ)
- Agonists including morphine and methadone act on the μ system, while partial agonists, including buprenorphine, also act at that site but have less of a maximal effect as the dose is increased.
- Opioid receptors and peptides are located in the CNS, PNS, and GI tract
- Opioid receptors are inhibitory
 - inhibit release of some neurotransmitters (e.g., 5-HT, GABA, glutamate, acetylcholine)
 - enable the release of dopamine (considered to contribute to the dependence potential of opiates)

Opioids: Pharmacology (3)

Heroin

- Morphine is produced through heroin hydrolysis
heroin → monoacetylmorphine (MAM) → morphine
- Heroin and MAM are lipophilic, hence more rapid action
- Heroin excreted in urine as free and conjugated morphine
- Heroin metabolites are present in urine for approximately 48 hours following use

Morphine: Immediate effects (1)

- **Perception altered, possible delirium**
- **Analgesia, to some degree**
- **Impaired cognition, though consciousness may be preserved**
- **Autonomic nervous system affected**
- **Suppression of cough reflex**
- **GI system affected**
- **Hypothermia**

Morphine: Immediate effects (2)

- **Miosis**
- **Urinary retention**
- **Reduced GI motility**
- **Endocrine**
- **Non-cardiogenic pulmonary oedema**
- **Coma or death (from respiratory depression)**
- **Other**
 - **pruritis; flushed skin; dry mouth, skin, and eyes**

Opioids: Long-term effects (1)

- Little evidence of long-term direct toxic effects on the CNS from opioid use
- Long-term health-related complications may result from:
 - dependence
 - poor general self-care
 - imprisonment
 - drug impurities or contaminants, BBV

Opioids: Long-term effects (2)

Possible:

- **Constipation / narcotic bowel syndrome**
- **Cognitive impairment from hypoxia as a result of repeated non-fatal overdose**
- **Reproduction and endocrine irregularity**
- **Medication-induced headaches**
- **Intense sadness (depression, dysthymia)**

Opioids: Drug Interactions

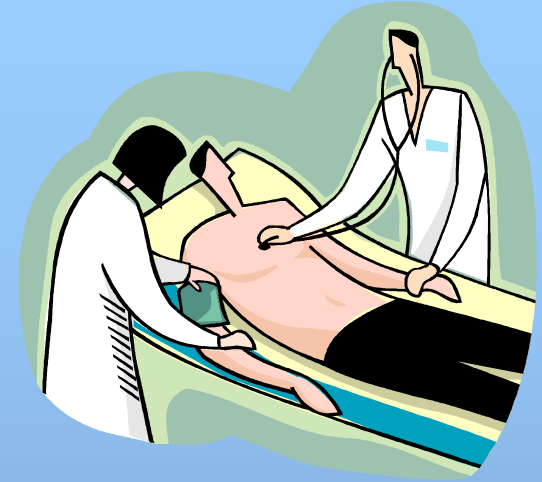
	Respiratory depression	Toxicity/ risk of death	Hypotension	Coma
CNS Depressants	✓		✓	✓
MAOIs	✓		✓	✓
TCAs	✓	✓		
Betablockers		✓		
BZDs	✓			

Opioids: Considerations for assessment

- Pregnancy
- Infectious Diseases
- Polydrug dependence
- Opioid-related overdose
- Major or pre-existing medical conditions (e.g., liver, cardiac)
- Major psychiatric / mental health issues (e.g., psychosis, depression, suicide)



Physical exam



Signs of opioid dependence:

- Needle marks on wrists, antecubital fossa, legs (inner thighs), feet, hands, neck
- Intoxication: pinpoint pupils, “nodding off,” drowsiness, sweating
- Withdrawal: restlessness, “goosebumps,” sweating, increased bowel sounds, lacrimation, “sniffles,” dilated pupils, muscle tenderness, tachycardia, hypertension

Complications from use

The following slides depict complications from use, dependence, and overdose.





Courtesy of Dr. John Sherman, St. Kilda Medical Centre



Courtesy of Dr. John Sherman, St. Kilda Medical Centre

Opioid withdrawal

Signs

- Yawning
- Lacrimation, mydriasis
- Diaphoresis
- Rhinorrhea, sneezing
- Tremor
- Piloerection
- Diarrhoea and vomiting

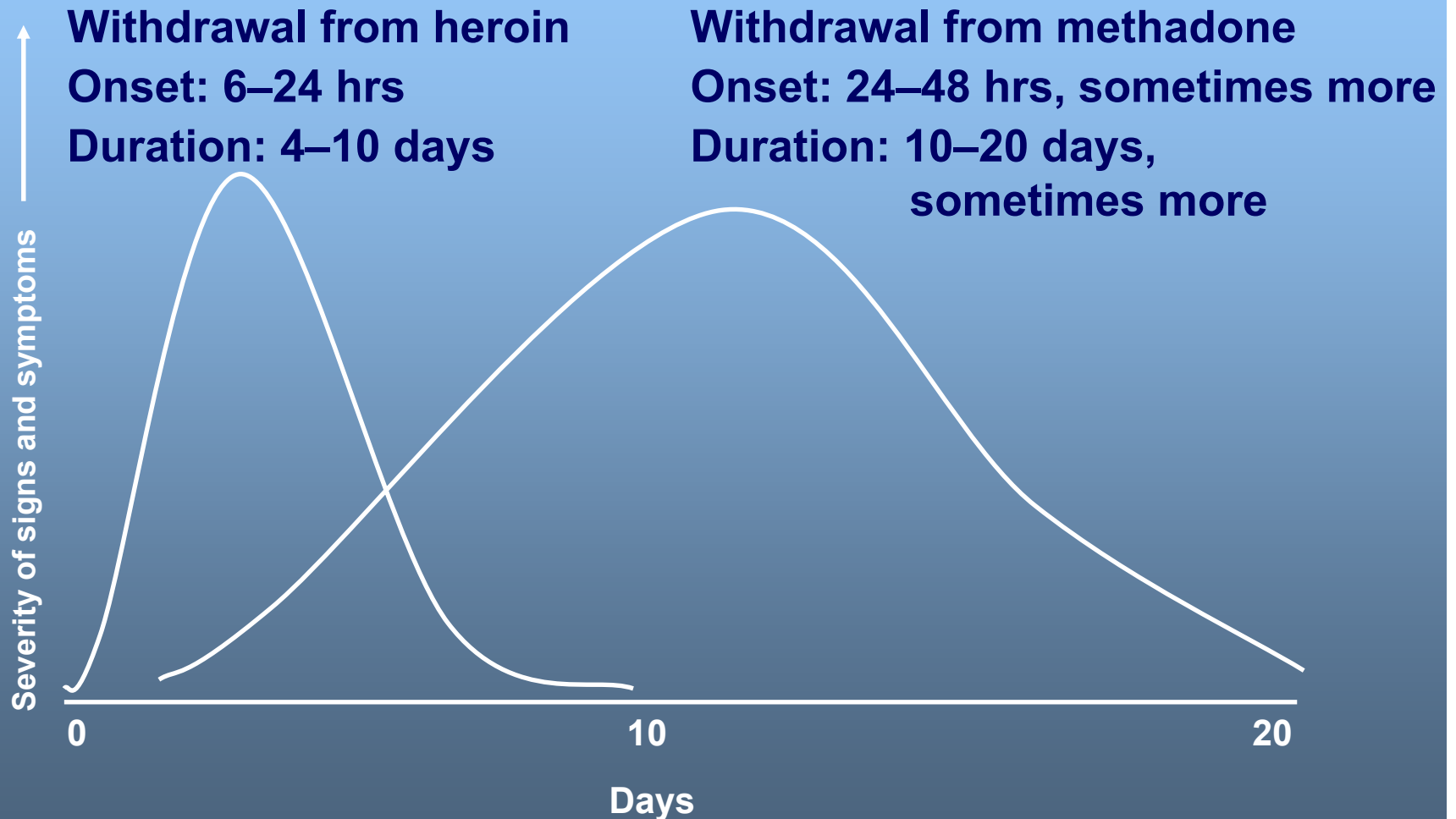
Symptoms

- Anorexia and nausea
- Abdominal pain or cramps
- Hot and cold flushes
- Joint and muscle pain or twitching
- Insomnia
- Drug cravings
- Restlessness / anxiety



Courtesy of Dr. John Sherman, St. Kilda Medical Centre

Progress of the Acute Phase of Opioid Withdrawal Since Last Dose



deCrespigny & Cusack (2003)

Adapted from NSW Health Detoxification Clinical Practice Guidelines (2000-2003)

Predictors of withdrawal severity

➤ Main predictors

- Greater regular dose
- Rapidity with which drug is withdrawn

Greater
withdrawal
severity

➤ Also consider

- Type of opioid used, dose, pattern, and duration of use
- Prior withdrawal experience, expectancy, settings for withdrawal
- Physical condition (poor self-care, poor nutritional status, track marks)
- Intense sadness (dysthymia, depression)
- Constipation or “Narcotic Bowel Syndrome”
- Impotence (males) or menstrual irregularities (females)

Opioid withdrawal scales

Withdrawal scales:

- guide treatment
- monitor progress of withdrawal (subjective and objective signs)
- do not diagnose withdrawal but describe severity
- guide ongoing assessment

If the withdrawal pattern is unusual, or the patient is not responding, suspect other conditions.

Opioid withdrawal management

Withdrawal management aims to:

- reverse neuroadaptation by managing tolerance and withdrawal
- promote the uptake of post-withdrawal treatment options

Withdrawal management may occur:

- as an outpatient
- in a residential / treatment setting

Opioid withdrawal treatment

Involves:

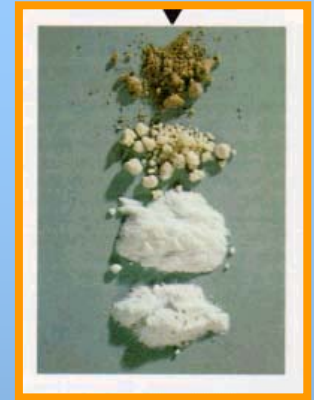
- reassurance and supportive care
- information
- hydration and nutrition
- medications to reduce severity of somatic complaints (analgesics, antiemetics, clonidine, benzodiazepines, antispasmodics)
- opioid pharmacotherapies (e.g., methadone, buprenorphine)

Opioid withdrawal complications

- Anxiety and agitation
- Low tolerance to discomfort and dysphoria
- Drug-seeking behaviour (requesting or seeking medication to reduce symptom severity)
- Muscle cramps
- Abdominal cramps
- Insomnia

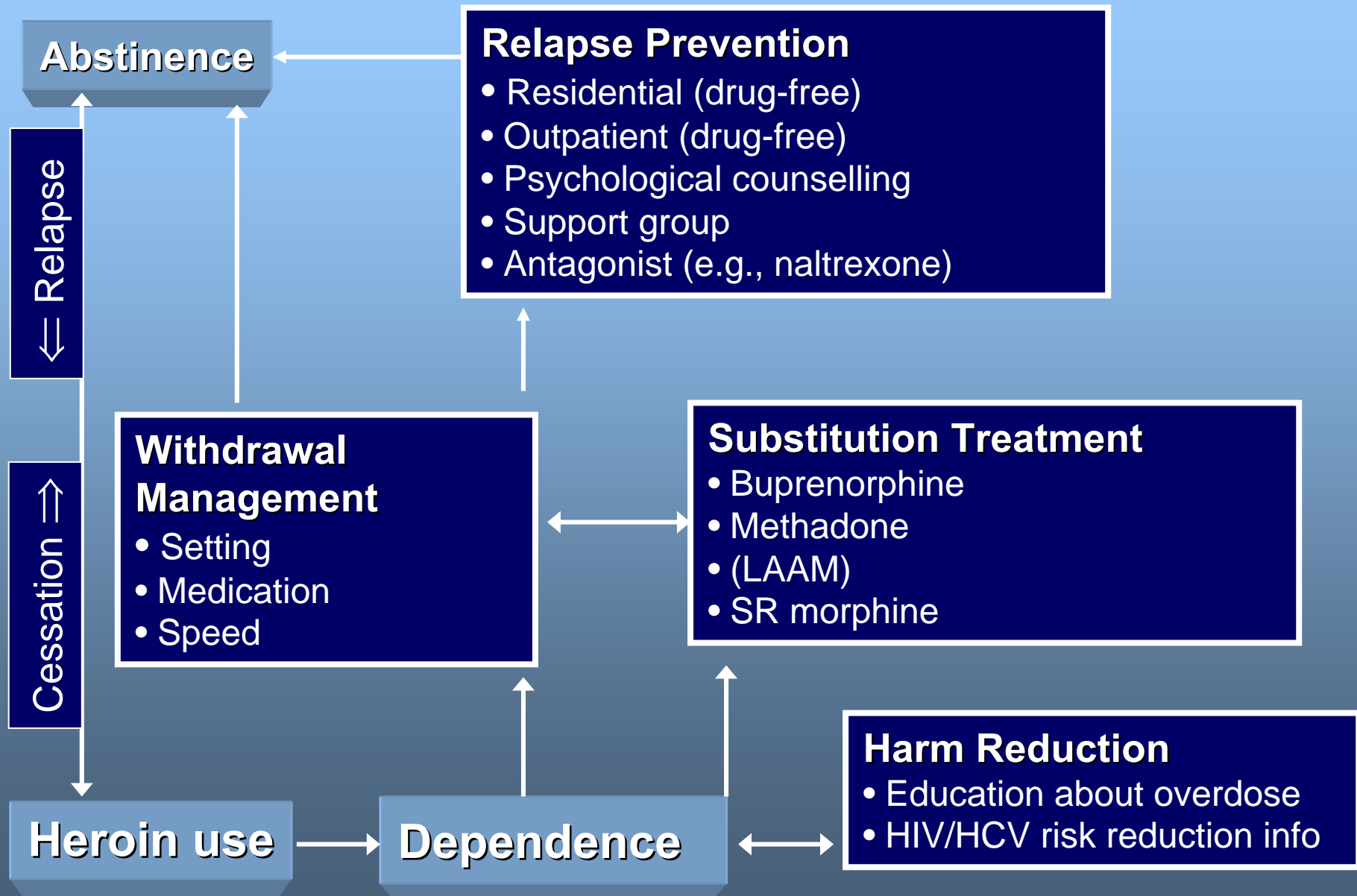
Heroin withdrawal

- Non-life threatening
- Commences 6 – 24+ hours after last use
- Peaks at around 24 – 48 hours after use
- Resolves after 5 – 7 days



There is increasing recognition of the existence of a protracted phase of withdrawal lasting some weeks or months, characterised by reduced feelings of wellbeing, insomnia, dysthymia, and cravings.

Dependent Opioid Use and Treatment Pathways



DSM IV criteria for opioid dependence

- **Tolerance**
- **Withdrawal symptoms on cessation of drug use**
- **Increasing quantity or frequency of use**
- **Persistent desire for the drug or unsuccessful attempts to cut down**
- **Salience of drug use over other responsibilities**
(most of a patient's time involves taking, recovering from, or obtaining drugs)
- **Continued use despite evidence of psychological or social problems**

General principles of pharmacotherapies:

Pharmacodynamics

➤ Agonists

- directly activate opioid receptors (e.g., morphine, methadone)

➤ Partial agonists

- unable to fully activate opioid receptors even with very large doses (e.g., buprenorphine)

➤ Antagonists

- occupy but do not activate receptors, hence blocking agonist effects (e.g., naloxone)

Maintenance pharmacotherapies

- **Methadone**
- **Buprenorphine**
- **Buprenorphine + Naloxone combination product**
- **Naltrexone**
- **LAAM**
- **Slow-release oral morphine**
- **Depot naltrexone**

Key outcomes of maintenance pharmacotherapy programs

- **↑ Retention in treatment**
- **Facilitates reduction / cessation of opioid use**
- **Reduces risky behaviours associated with opioid use**
- **Enables opportunity to engage in harm reduction measures**
- **↓ Mortality and morbidity**
- **↑ Psychological, emotional, and physical wellbeing of patients**
- **↓ Social costs associated with illicit drug use**
- **↓ Crime**

Methadone: Clinical properties

The “Gold Standard” Treatment

- Synthetic opioid with a long half-life
- μ agonist with morphine-like properties and actions
- Action – CNS depressant
- Effects usually last about 24 hours
- Daily dosing (same time, daily) maintains constant blood levels and facilitates normal everyday activity
- Adequate dosage prevents opioid withdrawal (without intoxication)

Buprenorphine

- Derived from the morphine alkaloid *thebaine*
- Partial opioid agonist at μ opioid receptors
- Antagonist at κ opioid receptor
- Blocks opioid receptors, diminishes cravings, prevents opioid withdrawal

Buprenorphine vs. Methadone

Buprenorphine Advantages

- Milder withdrawal
- Convenient (dose every 2/7)
- Better receptor blocker
- Relative ease of use, i.e., ready transmission from heroin withdrawal state or methadone
- Easier to taper than methadone
- Wider safety margin

Buprenorphine Disadvantages

- SL route results in reduced bio-availability compared with IV preparations
- Difficult to reverse respiratory depression if it does occur
- Increased time required for supervised dosage (to get dissolution)

Rationale for opioid agonist / partial agonist treatment

Advantages of opioid agonist / partial agonist medication over heroin

- **Non-parenteral administration**
- **Known composition**
- **Gradual onset and offset**
- **Long-acting**
- **Far less reinforcing than heroin**
- **Medically supervised**

Rationale for opioid agonist treatment (1)

Opioid agonist treatment

- Most effective treatment for opioid dependence
- Controlled studies have shown that with long-term maintenance treatment using appropriate doses, there are significant:
 - Decreases in illicit opioid use
 - Decreases in other drug use

Continued

Rationale for opioid agonist treatment (2)

Opioid agonist treatment (*continued*)

- Decreases in criminal activity
- Decreases in needle sharing and blood-borne virus transmission (including HIV)
- Improvements in pro-social activities
- Improvements in mental health

Injecting Drug Use and HIV/AIDS

Estimated number of deaths from
AIDS up till now: 25 million

Estimated number of people with
HIV infection in 2002/2003: 42
million

Estimated number of additional
HIV infections till 2010: 45
million.

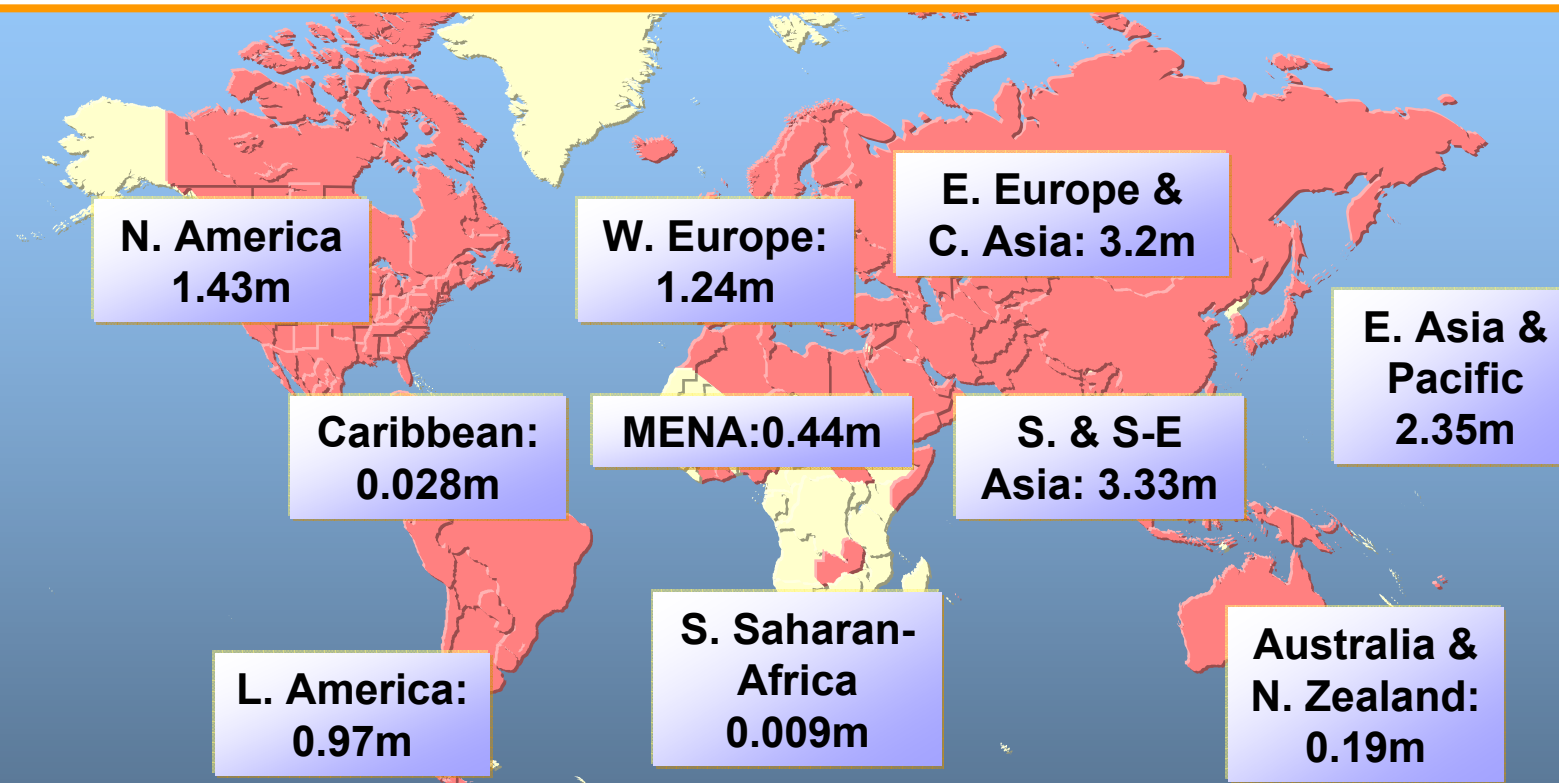
The threat from HIV / AIDS

By 2010, AIDS will have caused more deaths than any disease outbreak in history.

Injecting drug use is an important contributor to the spread of HIV.



Estimated Size of IDU Population (1998/2003)



10.3m (78%) in developing / transitional countries

91% of the world adult population (4 billion) is covered by the data.
Information unavailable for 119 countries.

UN Reference Group on HIV/AIDS prevention and care among IDU
www.idurefgroup.org

The global response: UN support for good treatment

WHO / UNODC / UNAIDS position paper: *Substitution Maintenance Therapy in the Management of Opioid Dependence and HIV/AIDS Prevention*

“Substitution maintenance treatment is an effective, safe and cost-effective modality for the management of opioid dependence. Repeated rigorous evaluation has demonstrated that such treatment is a valuable and critical component of the effective management of opioid dependence and the prevention of HIV among IDUs.”

Availability of Substitution Treatment

95% + methadone is consumed in developed countries (2002)

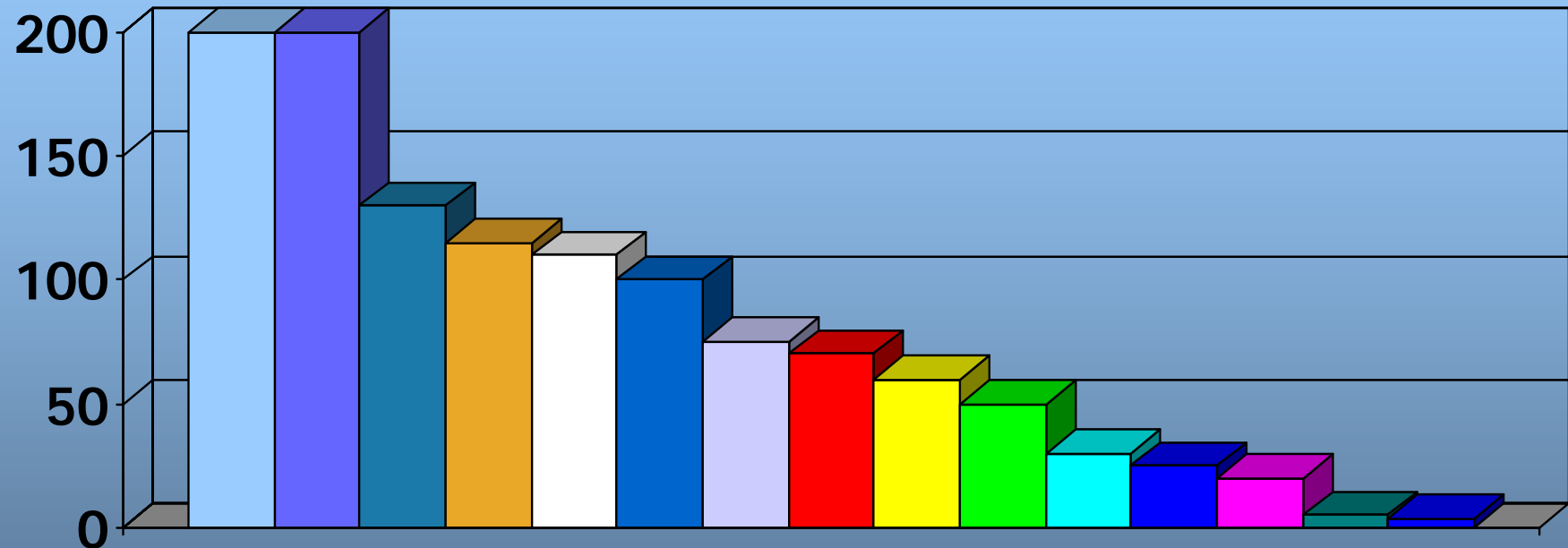
Substitution treatment is available in few countries outside Europe, North America, and Australia, including:

- Argentina
- China
- Croatia
- India
- Indonesia
- Iran
- Kyrgystan
- Malaysia
- Moldova
- Nepal
- Singapore
- Thailand
- Ukraine

Thanks to Gerry Stimson

US	53%	8.7 tons
Spain	11%	1.8 tons
Germany	6%	916kg
Italy	5%	812kg
UK, Canada, Australia, Switzerland, France, Denmark and Belgium,	18%	
Most of the rest consumed by 8 other countries, mostly in Europe, and Australia		

Estimated Opiate-Dependent Drug Users in Substitution Treatment per 100,000 Population



Naltrexone

- Morphine antagonist, true blockade
- No direct psychoactive effect
- No withdrawal experienced upon cessation
- Reported to reduce cravings in some people

Naltrexone: Mechanism of action

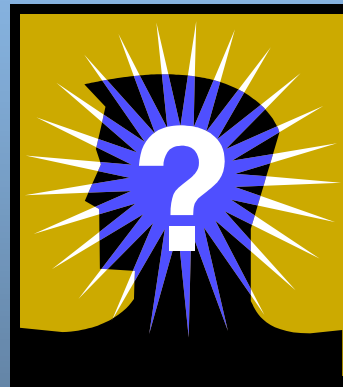
- Fully blocks μ receptors, preventing euphoria from opioid use; therefore
“drug money spent = money wasted”
- Allows extinction of Pavlovian-conditioned response to opiate cues
- Prevents reinstatement of opioid dependence, but does not reinforce compliance

Naltrexone: Indications for use

- Prescribed for the management of opioid dependence by registered prescribers
- Primary role = relapse prevention
- Abstinence-based treatment option
- Non-dependence inducing
- Commenced at least 1 week after cessation of heroin use
- Optimally effective with motivated individuals who have higher levels of psychosocial functioning and family support



Questions?



Comments?

Thank you for your time!

End of Workshop 1

Volume C, Module 2, Workshop 2:

Opiate Addiction Treatment with Methadone



International network of drug dependence
treatment and rehabilitation resource centres



UNITED NATIONS
Office on Drugs and Crime

Training objectives



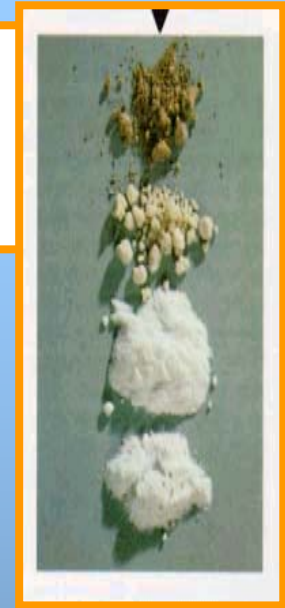
At the end of this training, you will know:

- 1.** The rationale for opiate agonist therapy
- 2.** Medical withdrawal protocols using methadone
- 3.** The basic purpose and background evidence to support the use of methadone for treating opiate dependence
- 4.** The basic principles of maintenance treatment with methadone
- 5.** Effective practices (evaluation, initial dose and management of dose; tapering procedures, etc.) in the implementation of methadone treatment
- 6.** How to address concurrent use of other drugs and alcohol during methadone treatment
- 7.** The contraindications and medical interactions with methadone

Heroin withdrawal

- Non-life threatening
- Commences 6 - 24+ hours after last use
- Peaks at around 24 - 48 hours after use
- Resolves after 5 - 7 days

There is increasing recognition of the existence of a protracted phase of withdrawal lasting some weeks or months, characterised by reduced feelings of wellbeing, insomnia, dysthymia, and cravings.



Opioid withdrawal

Signs

- Yawning
- Lacrimation, mydriasis
- Diaphoresis
- Rhinorrhoea, sneezing
- Tremor
- Piloerection
- Diarrhoea and vomiting

Symptoms

- Anorexia and nausea
- Abdominal pain or cramps
- Hot and cold flushes
- Joint and muscle pain or twitching
- Insomnia
- Drug cravings
- Restlessness / anxiety

Opioid withdrawal complications

- **Anxiety and agitation**
- **Low tolerance to discomfort and dysphoria**
- **Drug-seeking behaviour (requesting or seeking medication to reduce symptom severity)**
- **Muscle cramps**
- **Abdominal cramps**
- **Insomnia**

Predictors of withdrawal severity

➤ Main predictors

- Greater regular dose
- Rapidity with which drug is withdrawn.

} Greater withdrawal severity

➤ Also consider

- Type of opioid used, dose, pattern, and duration of use
- Prior withdrawal experience, expectancy, settings for withdrawal
- Physical condition (poor self-care, poor nutritional status, track marks)
- Intense sadness (dysthymia, depression)

Opioid withdrawal management

Withdrawal management aims to:

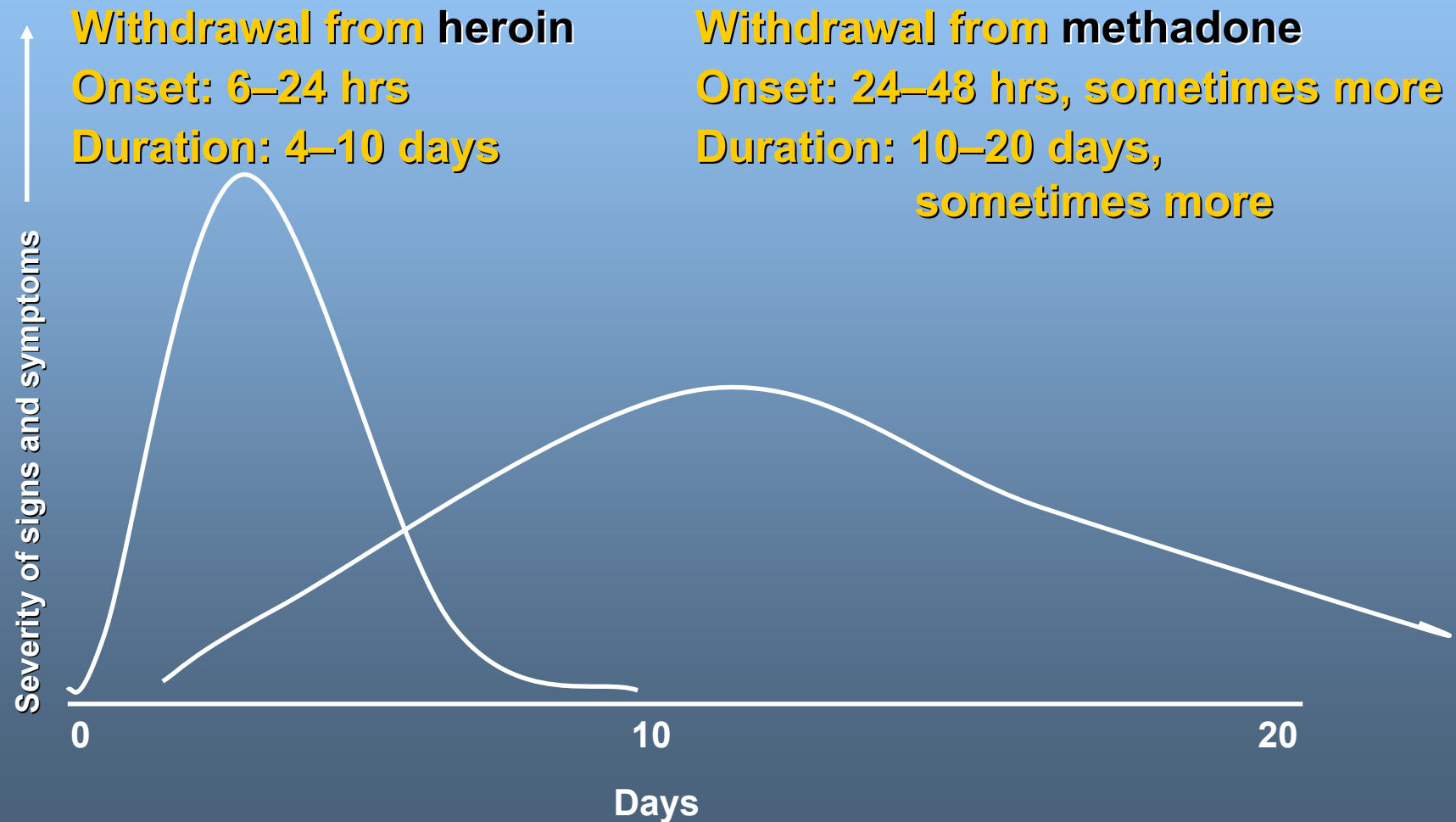
- reverse neuroadaptation by managing tolerance and withdrawal
- promote the uptake of post-withdrawal treatment options

Opioid withdrawal treatment

Involves:

- reassurance and supportive care
- information
- hydration and nutrition
- opioid pharmacotherapies (e.g., methadone)
- medications to reduce severity of somatic complaints (analgesics, antiemetics, benzodiazepines, antispasmodics)

Progress of the Acute Phase of Opioid Withdrawal Since Last Dose

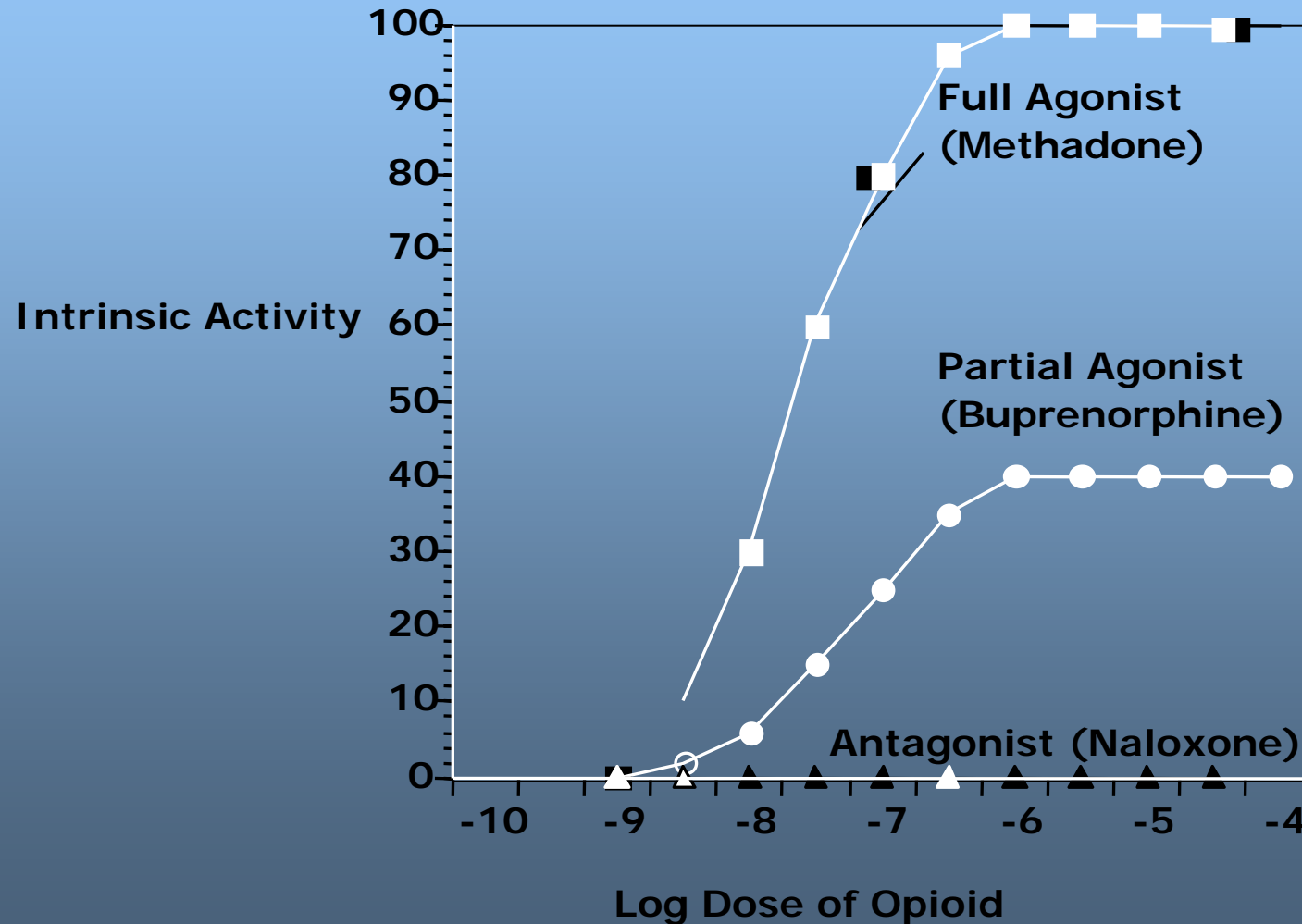


Methadone: Clinical properties

The “Gold Standard” Treatment

- **Synthetic opioid with a long half-life**
- **μ agonist with morphine-like properties and actions**
- **Action – CNS depressant**
- **Effects usually last about 24 hours**
- **Daily dosing (same time, daily) maintains constant blood levels and facilitates normal everyday activity**
- **Adequate dosage prevents opioid withdrawal (without intoxication)**

Intrinsic Activity: Full Agonist, Partial Agonist and Antagonist



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
 - Cytochrome P450 mediated
 - CYP3A4 main
 - also CYP2D6, CYP1A2, CYP2C9 and CYP2C19
 - genetic variability
 - → risk of drug interactions

Pharmacodynamics

➤ Full opioid agonist

- Main action on mu receptors
 - inhibit adenylyl cyclase = ↓ cAMP
 - ↑ potassium channel opening
 - ↓ calcium channel opening
- also inhibit serotonin reuptake
- also non-competitive antagonist NMDA receptor

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 methadone maintenance
- No evidence of organ damage with chronic dosing

Methadone: Advantages of treatment

- **Suppresses opioid withdrawal**
- **Pure – no “cutting agents” present**
- **Oral administration (syrup or tablet forms used)**
- **Once-daily doses enable lifestyle changes**
- **Slow reduction and withdrawal can be negotiated with minimal discomfort**
- **Minimal reinforcing properties, relative to heroin**
- **Counselling and support assists long-term lifestyle changes**
- **Legal and affordable – reduced participation in crime**
- **Few long-term side effects**

Methadone: Disadvantages of treatment

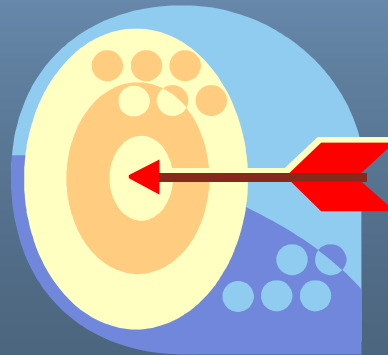
- Initial discomfort to be expected during stabilisation phase
- Opioid dependence is maintained
- Slow withdrawal (preferably) negotiated and undertaken over a period of months
- Protracted withdrawal symptoms
- Can overdose, particularly with polydrug use
- Daily travel and time commitment
- Variable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

Maximising treatment adherence

- **Address psychosocial issues as first priority**
 - emotional stability
 - "chaotic" drug use
 - accommodation
 - income
- **Opioid agonist pharmacotherapy can:**
 - address psychosocial instability
 - increase opportunities to directly observe the administration of various HIV therapies

Assessment objectives

- Clarify nature and severity of problems
- Establish a therapeutic relationship
- Formulate problems into a treatment plan



Core assessment issues



- What does the patient want?
- Is the patient dependent?
- What is their level of tolerance?
- Is the patient using / dependent on other drugs?
- What is their motivation for change?
- What social supports exist?
- Are there other co-existing medical and psychiatric conditions?

Drug use history

➤ Primary drug

- Average daily use (quantity / duration)
- Time last used
- Route of administration
- Age commenced, periods of abstinence
- Severity of dependence
- Previous treatment(s)

➤ Other drugs

- Current and previous
- Dependence

Medical and psychiatric



- **HIV/HCV**
- **Pregnancy**
- **Other major medical conditions**
 - **Liver**
 - **Cardiac**
- **Major psychiatric conditions**
 - **Depression, suicide, psychosis**
- **Opioid-related overdose**

Psychosocial

- Relationship with family
- Relationship with partner
- Education and employment
- Criminal justice
- Living circumstances
- Sources of income

Examination

- **Mental state**
 - Mood
 - Affect
 - Cognition
- **Injection sites**
- **Signs of intoxication / withdrawal**
- **Stigmata of liver disease**
- **Nutritional state**



Induction stabilisation phase (1)

- **Dose adequacy and drug interactions**
 - Signs of intoxication / withdrawal
 - Frequency of drug use
 - Frequency of sharing
- **Case coordination and management**
 - Psychological
 - Social
 - Medical
 - Health / welfare system interaction

Induction stabilisation phase (2)

➤ Risk Assessment

- Drug use practises
 - polydrug
 - OD
 - sharing
- Sexual practises

Safe initial dose

- 20 - 30mg methadone is generally safe
- Deaths have occurred with higher starting doses or polydrug use
- It may be safer to start opioid-dependent polydrug users as inpatients

Methadone: Initial Effects and Side-Effects

- Relief from physical pain
- Feeling of wellbeing
- Constricted pupils
- Vasodilation
- Lowered sex drive
- Nausea and vomiting
- Loss of appetite
- Sweating
- Fluid retention
- Endocrine changes
(loss of libido, menstrual changes)
- Intense constipation
- Lowered temperature
- Bradycardia
- Hypotension
- Palpitations
- Shallow respirations
- Poor circulation
- Itching and skin rashes
- Recurrent dental problems

Polydrug use may cause overdose.

Opioid withdrawal scales

- guide treatment
- monitor progress
(subjective and objective signs)
- do not diagnose withdrawal but describe severity
- guide ongoing assessment

If the withdrawal pattern is unusual, or the patient is not responding, suspect other conditions.

Opiate withdrawal scale

Resting Pulse Rate: _____ beats/minute

Measured after patient is sitting or lying for one minute

0 pulse rate 80 or below

1 pulse rate 83-100

2 pulse rate 101-120

4 pulse rate greater than 120

Sweating: over past ½ hour not accounted for by room temperature or patient activity

0 no report of chills or flushing

1 report of chills or flushing

2 flushed or observable moistness on face

3 beads of sweat on brow or face

4 sweat streaming off face

Restlessness Observation during assessment

0 able to sit still

1 reports difficulty sitting still but is able to do so

3 frequent shifting or extraneous movements of legs/arms

5 unable to sit still for more than a few seconds

Continued

Opiate withdrawal scale

Pupil Size

- 0 pupils pinned or normal size for room light**
- 1 pupils possibly larger than normal for room light**
- 2 pupils moderately dilated**
- 5 pupils so dilated that only the rim of the iris is visible**

Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*

- 0 not present**
- 1 mild diffuse discomfort**
- 2 patient reports severe diffuse aching of joints/muscles**
- 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort**

Runny nose or tearing *Not accounted for by cold symptoms or allergies*

- 0 not present**
- 1 nasal stuffiness or unusually moist eyes**
- 2 nose running or tearing**
- 4 nose constantly running or tears streaming down cheeks**

Continued

Opiate withdrawal scale

GI Upset: over last ½ hr

0 no GI symptoms

1 stomach cramps

2 nausea or loose stool

3 vomiting or diarrhoea

3 multiple episodes of diarrhoea or vomiting

Tremor *observation of outstretched hands*

0 no tremor

1 tremor can be felt but not observed

2 slight tremor observable

4 gross tremor or muscle twitching

Yawning *Observation during assessment*

0 no yawning

1 yawning once or twice during assessment

2 yawning three or more times during assessment

4 yawning several times/minute

Continued

Opiate withdrawal scale

Anxiety or Irritability

0 none

1 patient reports increasing irritability or anxiousness

2 patient obviously irritable or anxious

4 patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh skin

0 skin is smooth

3 piloerection of skin can be felt or hairs standing up on arms

5 prominent piloerection

Total Score _____

The total score is the sum of all 11 items

Initials of persons

Completing assessment _____

Methadone: Inappropriate dosing

Dose too low – Withdrawal

- “Flu-like” symptoms
- Runny nose, sneezing
- Abdominal cramps, diarrhoea
- Tremor, muscle spasm, aches, and cramping
- Yawning, “teary” eyes
- Hot and cold sweats
- Irritability, anxiety, aggression
- Aching bones
- Craving

Dose too high – Intoxicated

- Drowsy, “nodding off”
- Nausea, vomiting
- Shallow breathing
- “Pinned” (pinpoint) pupils
- Drop in body temperature
- Slow pulse, low BP, palpitations
- Dizziness

Stabilisation (1)

Rate of Dose Increase

- Increase 0-10mg methadone per 1-3 days during the first week according to physical assessment and SOWS score
- Maximum increase of 20-25mg over 1st week
- Subsequent dose increases should not exceed 10mg per week

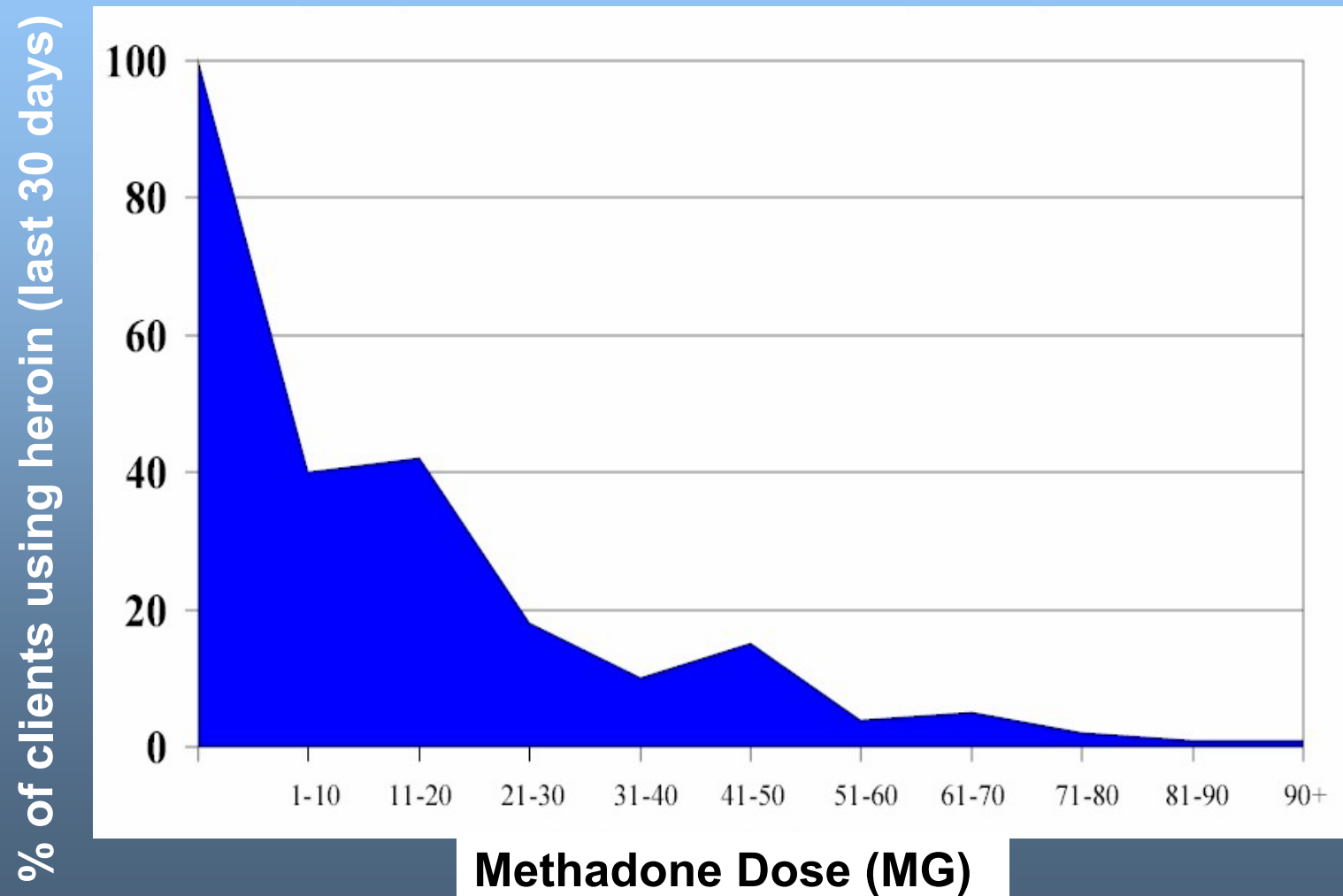
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Stabilisation (2)

Rate of Dose Increase

- gradual increase essential due to long half-life
- Best outcomes from maintenance doses > 60mg
- Lethal dose 20mg for children, as low as 50 mg for opioid-naïve adults

Relationship between Methadone Dose and Heroin Use



(Adapted from Ball and Ross, 1991)

Stabilisation (3)

Frequency of Appointments

- **First 5 -7 days - see every 1-2 days**
- **Write prescription till next appointment only**
- **Always see the patient before increasing the dose**
- **Continue the assessment process, build the therapeutic relationship**

Other treatment issues

- **Promote compassionate opioid analgesia**
 - Health care worker education especially at hospital
 - Role of maintenance treatment in analgesia
- **Encourage good vein care**
 - To maintain venous access
 - Important later, if applicable, in the clinical course of HIV infection

Ongoing management issues (1)

- Monitoring HIV progression
 - Co-infection
 - Cognitive state
- Mental health
 - Depression
 - Suicide ideation
 - ASPD
 - PTSD
- Pain management
- Drug substitution

Ongoing management issues (2)

- Risk exposure
 - dose
 - compliance with program rules
- Cost of medication
- Staff attitudes

Characteristics of effective programs

- **Longer duration (2-4 years)**
- **Higher doses; > 60mg methadone**
- **Accessible prescriber and dispenser**
- **Integrated services**
- **Quality of therapeutic relationship**

Drug interactions-metabolism

➤ Methadone

- Metabolism Cytochrome P450 mediated
 - CYP3A4 main
 - also CYP2D6, CYP1A2, CYP2C9 and CYP2C19, genetic variability
- CYP3A4 breaks down 50% of drugs
 - Methadone mixed inhibitor may increase other drug levels, e.g., Nifedipine, etc.

Opioids: Other Drug Interactions

	Respiratory depression	Toxicity/ risk of death	Hypotension	Coma
CNS Depressants	✓		✓	✓
MAOIs	✓		✓	✓
TCAs	✓	✓		
Betablockers		✓		
BZDs	✓			

Efficacy of methadone concurrent control studies (1)

100 male narcotic addicts randomized to methadone or placebo in a treatment setting.

Both groups initially stabilized on 60 mg methadone per day. Both groups had dosing adjustments:

- Methadone could go up or down
- Placebo – 1 mg per day tapered withdrawal

Outcome measures: Treatment retention and imprisonment

Follow-up <u>Time</u> 2 years	Percent Drug Free "Methadone <u>Group</u> " 71%	Percent Drug Free "No Methadone <u>Group</u> " 6%
-------------------------------------	--	--

Imprisonment rate: Twice as great for placebo group.

Efficacy of methadone concurrent control studies (2)

34 patients assigned to methadone or no methadone at one clinic

Outcomes: Percent drug free

Follow-up <u>Time</u> 2 years	Percent Drug Free "Methadone <u>Group</u>" 71%	Percent Drug Free "No Methadone <u>Group</u>" 6%
--	---	---

Five year follow-up: No methadone group offered methadone

Those choosing methadone: 89%

Those not choosing methadone: 13%

5 died of OD, 2 imprisoned

Evidence for the Efficacy of Methadone Dose Response Studies

- Dose Response Trials
- Retention and illicit opiate use

<u>N</u>	Methadone <u>Doses</u>	<u>Results</u>
212	0,20,50 mg	50 mg > 20 mg > 0

(Strain, E., et al. Ann. Int. Med. 119:23-27, 1993)

<u>N</u>	Methadone <u>Doses</u>	<u>Results</u>
162	20, 60 mg	60 mg > 20 mg

(Johnson RE, Jaffe J, Fudala PJ, JAMA, 267(20), 1992)

Evidence for the Efficacy of Methadone Dose Response Studies

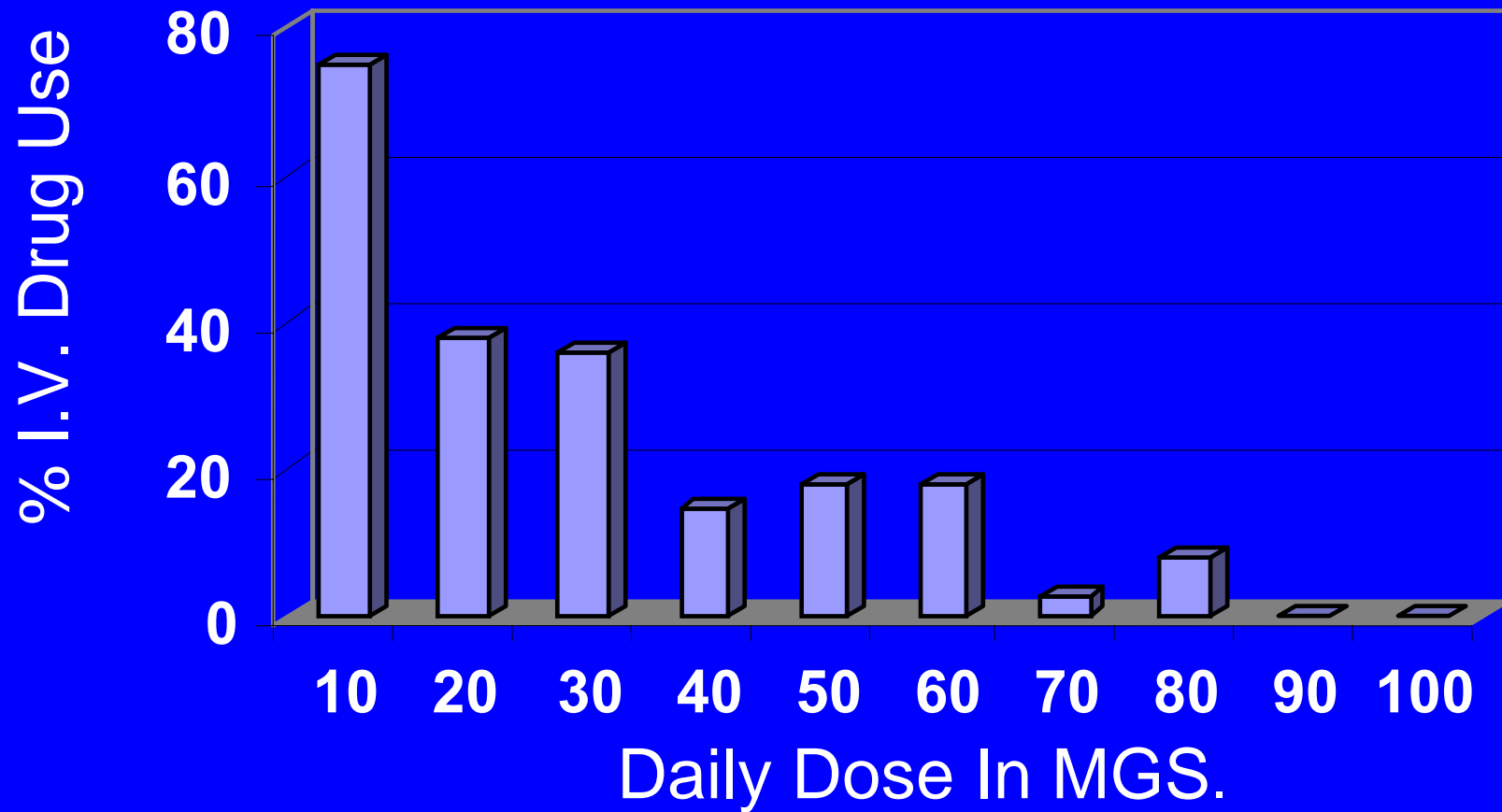
Outcomes: Retention and illicit opiate use

<u>N</u>	Methadone <u>Doses</u>	<u>Results</u>
225	30 and 80 mg	80 > 30 mg
(Ling et al, Arch Gen Psych, 53(5), 1996)		

<u>N</u>	Methadone <u>Doses</u>	<u>Results</u>
140	20 and 65 mg	65 > 20 mg

(Schottenfeld R, et al., 1993)

Heroin Abuse Frequency Vs. Methadone Dose



V.P. Dole, JAMA, VOL. 282, 1989, p. 1881

Evidence for the Efficacy of Methadone

<u>N</u>	<u>Treatment</u>	<u>Annual Death Rate</u>	Age Adjusted <u>Control</u>
4,776	Untreated	7.0	0.6 ¹
100	Treated	3.4	0.3 ²
109	Detox	8.3	³
3,000	MM	0.8	³
368	MM	1.4	0.17 ⁴

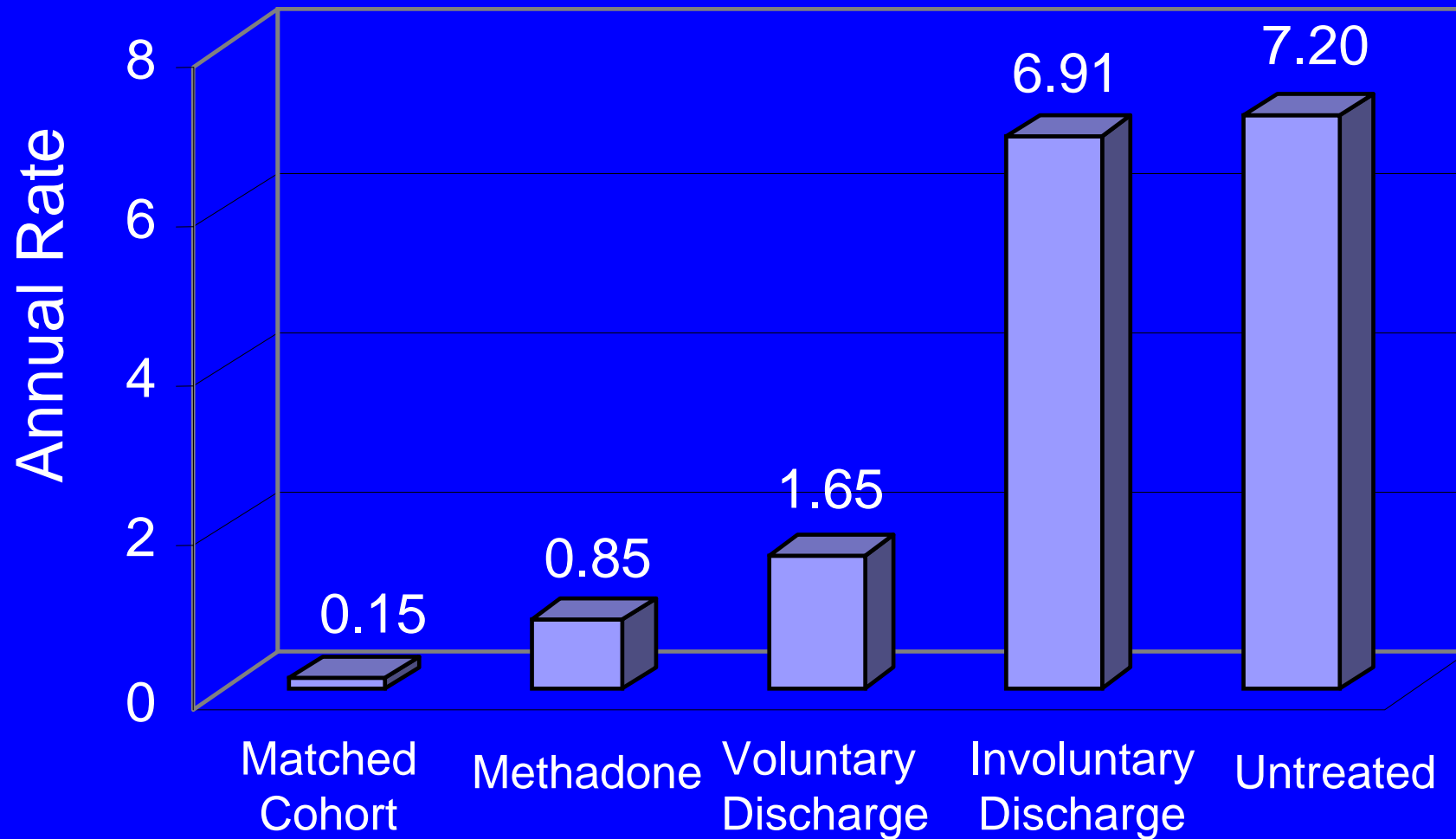
1 Prescore MJ, US Public Health Report, Suppl 170, 1943

2 Valliant GE, Addictive States, 1992

3 Gearing MF, Neurotoxicology, 1977

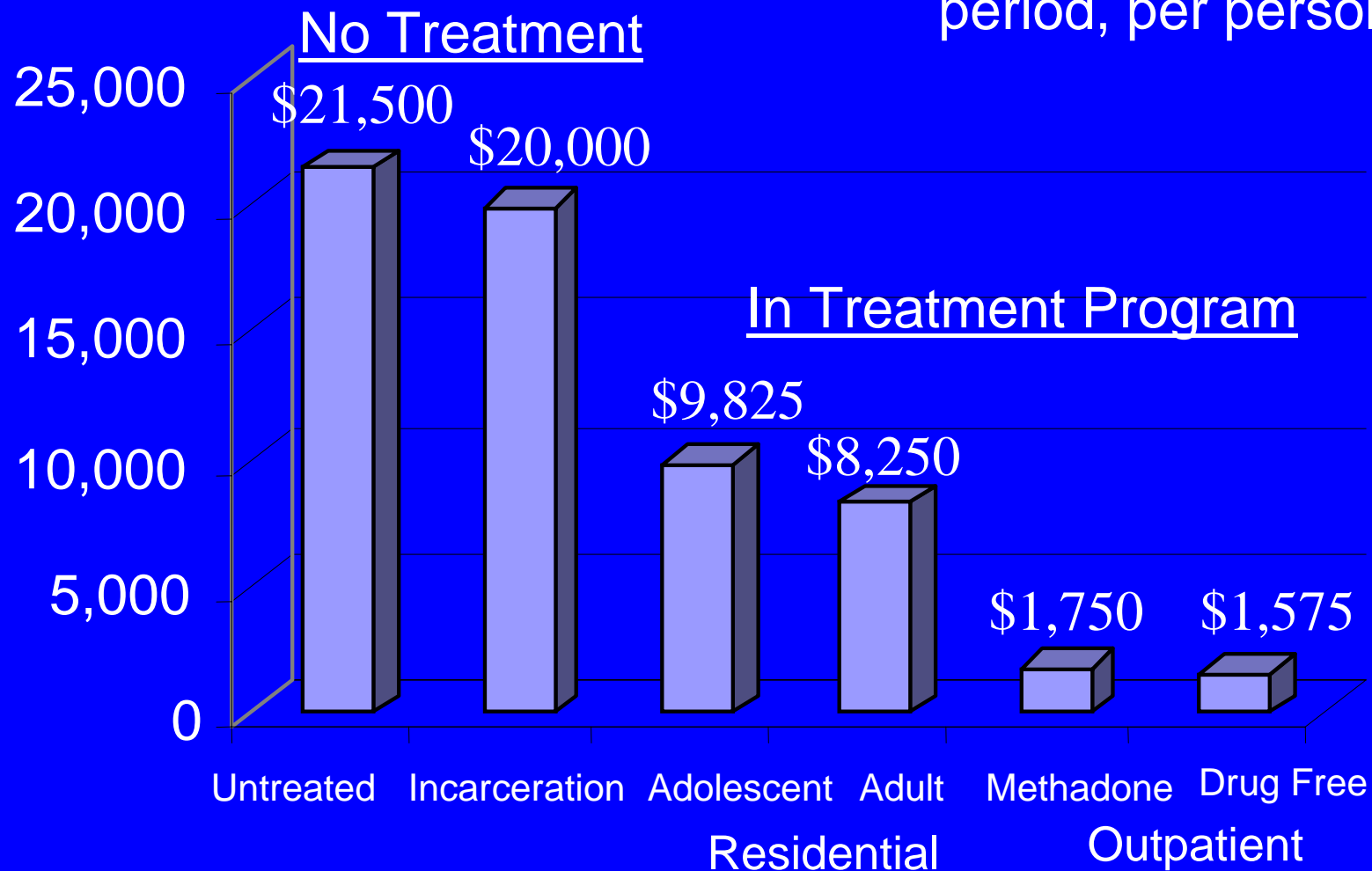
4 Grondblah L, ACTA Psych Scand, 82, 1990

Death Rates in Treated and Untreated Heroin Addicts

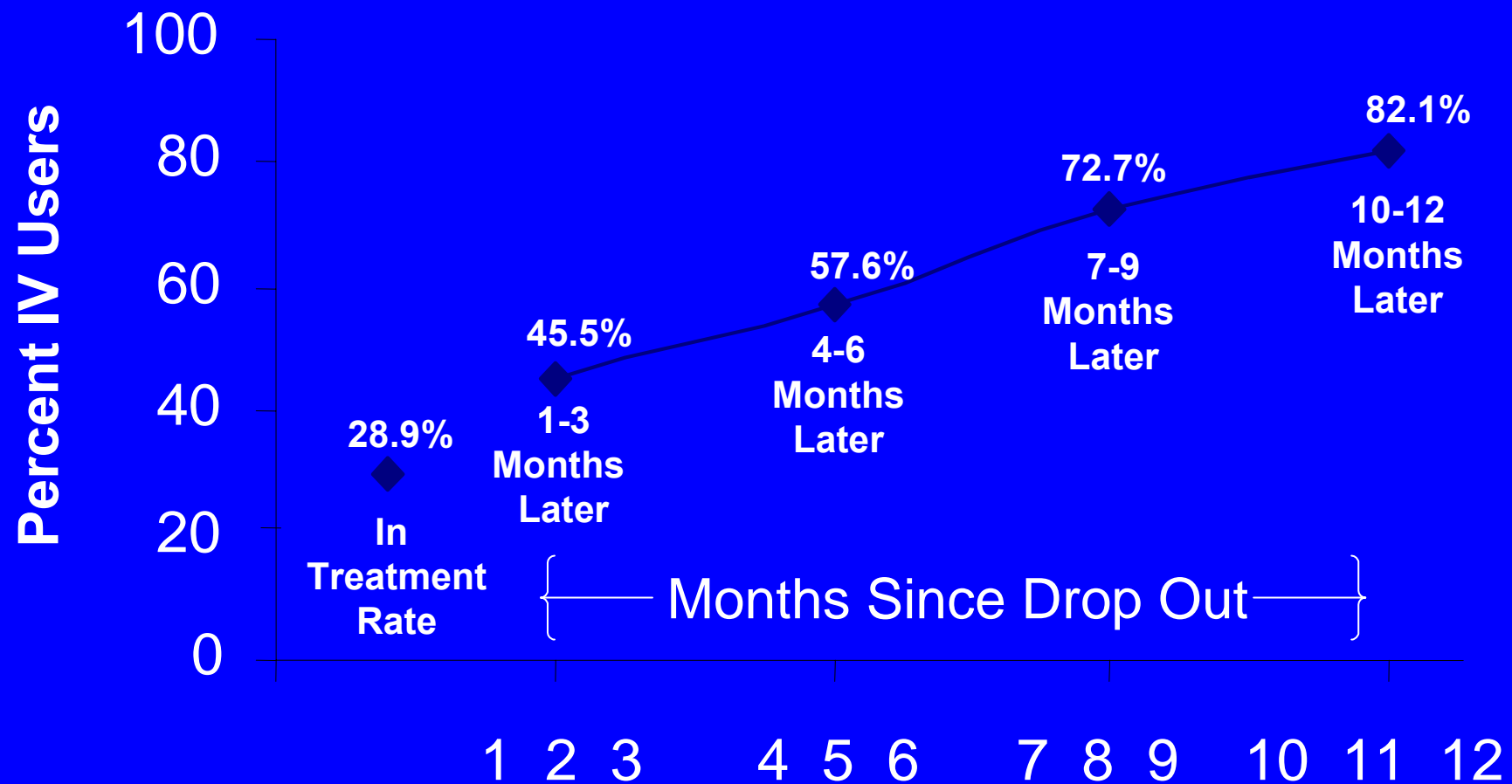


Compare the Costs

Costs are for a 6 month period, per person



Relapse to IV Drug Use After Termination of Methadone Maintenance Treatment



Ball, JC, Ross A. The Effectiveness of Methadone Maintenance Treatment, Springer-Verlag, New York, 1991

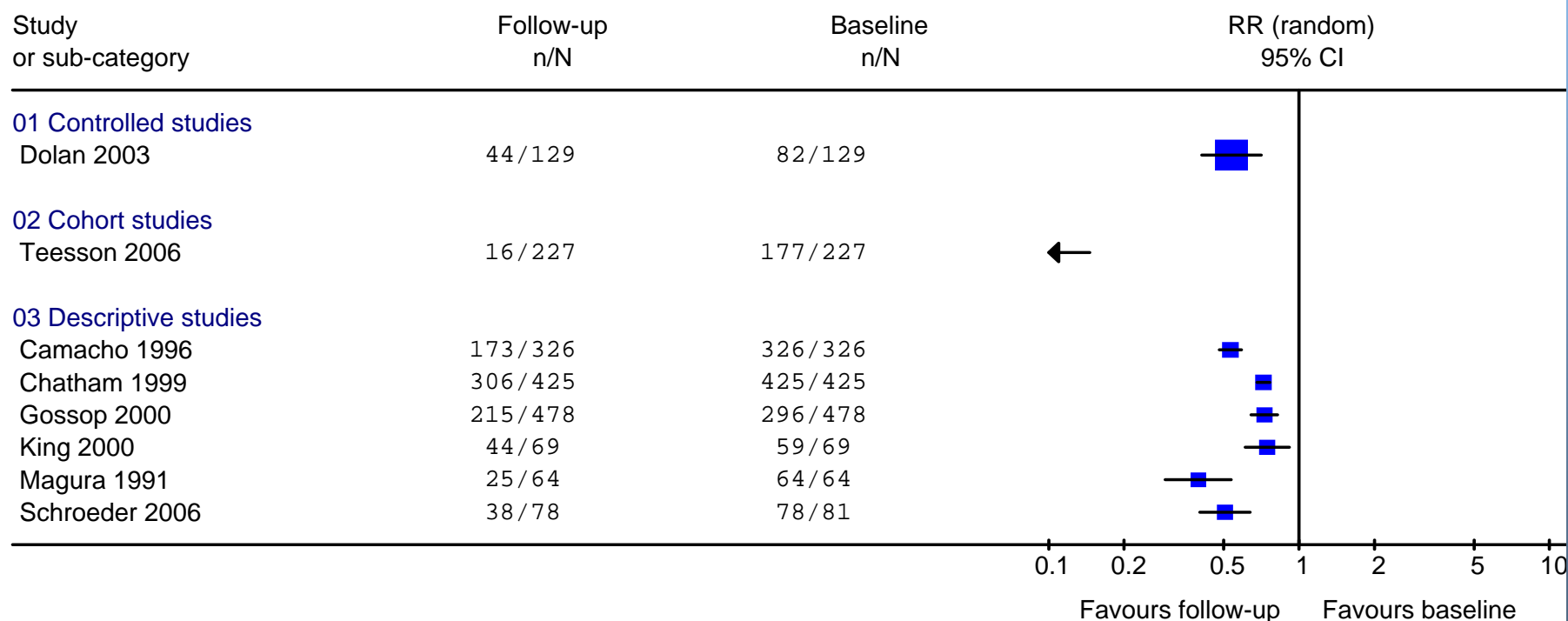
Cochrane Review OST and HIV Prevention

Included studies

- 33 studies involving 10,400 participants
 - Majority not controlled studies
 - 32 studies used methadone
 - 12 reported doses of 60mg/day or more
 - 8 reported doses of 40-60mg/day
 - 12 did not report doses
 - 2 studies provided methadone in the context of detoxification
 - 24 studies were in the context of a specialist drug & alcohol program
 - Most studies at risk of confounding or bias
-

Relative risk of injecting at follow-up compared to baseline

Review: Substitution treatment of injecting opioid users for prevention of HIV infection
 Comparison: 01 Drug use and risk outcomes (follow-up studies)
 Outcome: 01 Proportion reporting injecting use



Gowing L, Farrell M, Bornemann R, Sullivan L, Ali R. Substitution treatment of injecting opioid users for prevention of

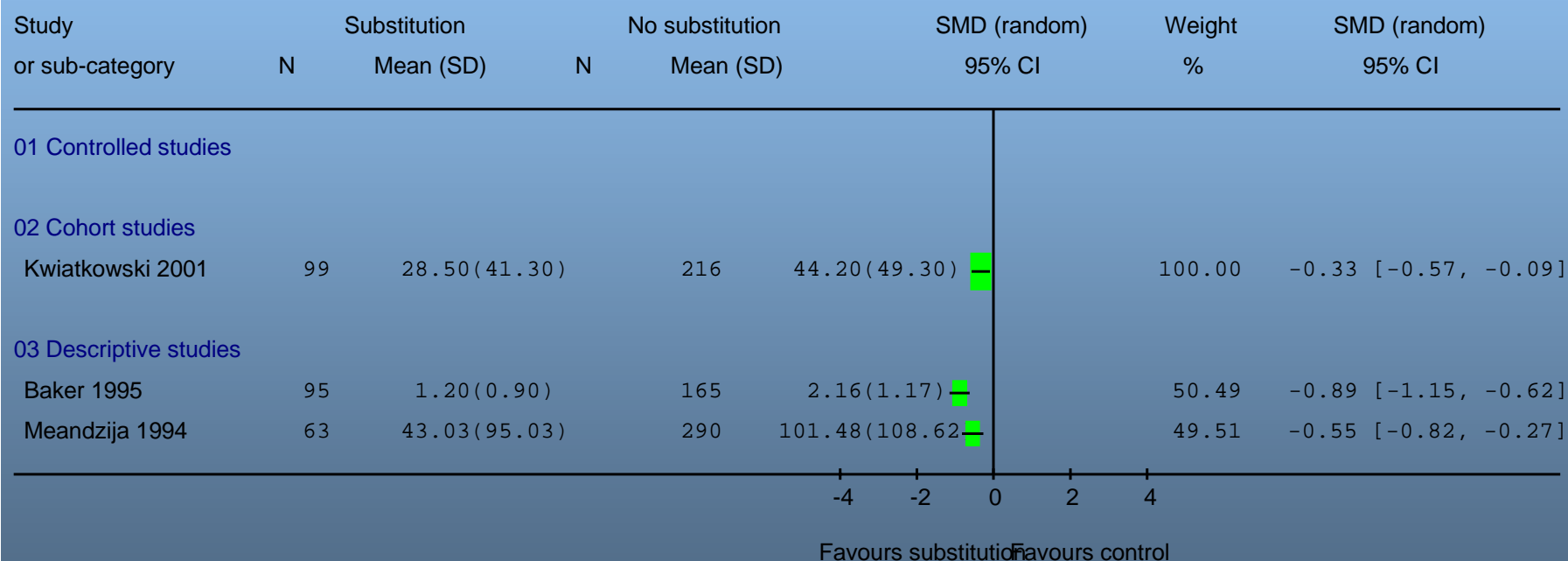
HIV infection. *Cochrane Database of Systematic Reviews* 2008, Issue 2.

Frequency of injecting substitution vs no substitution treatment

Review: Substitution treatment of injecting opioid users for prevention of HIV infection

Comparison04 Drug use and risk outcomes - substitution treatment versus no substitution treatment

Outcome: 02 Frequency of injecting use



Gowing L, Farrell M, Bornemann R, Sullivan L, Ali R. Substitution treatment of injecting opioid users for prevention of

HIV infection. *Cochrane Database of Systematic Reviews* 2008, Issue 2.

Summary of findings on injecting risk

- **Reduction in injecting drug use associated with substitution treatment a consistent finding**
 - **True in terms of:**
 - **proportion of participants reporting injecting drug use and**
 - **frequency of injection**
 - **Benefits may not be sustained after treatment, particularly if treatment cessation is involuntary**
-

Lower Rates of HIV Sero-conversion while in treatment

➤ **Metzger 1993**

- seroconversion 3/100 person years in substitution treatment (10/100 person years not in treatment)

➤ **Williams 1992**

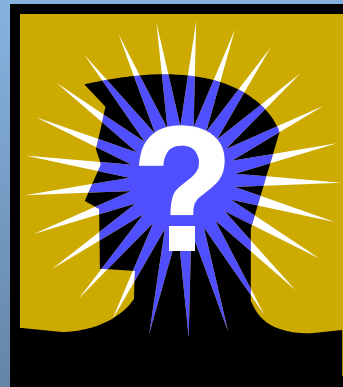
- 0.7/100 person years in substitution treatment (4.3/100 person years not in treatment)

➤ **Moss 1992**

- 1.4/100 person years in substitution treatment (3.1/100 person years not in treatment)
-



Questions?



Comments?

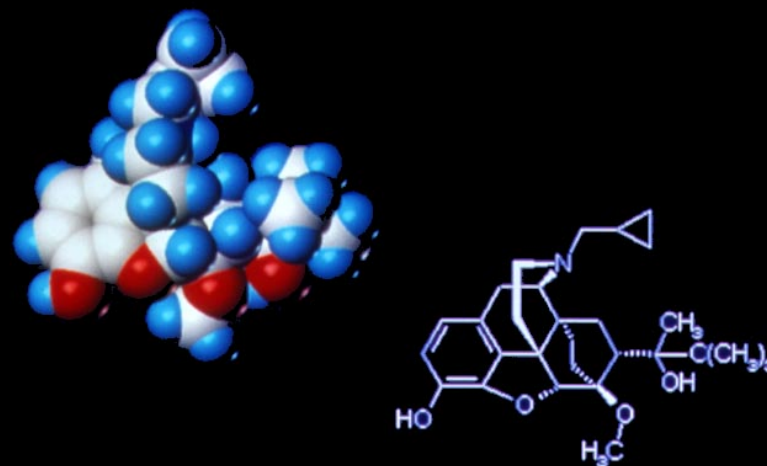
Thank you for your time!

End of Workshop 2

Volume C, Module 2, Workshop 3:

Opiate Addiction Treatment with Buprenorphine

BUPRENORPHINE



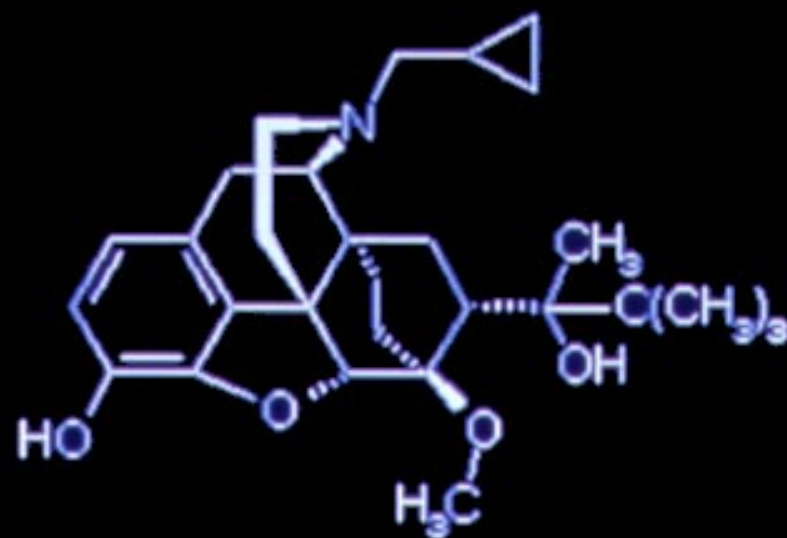
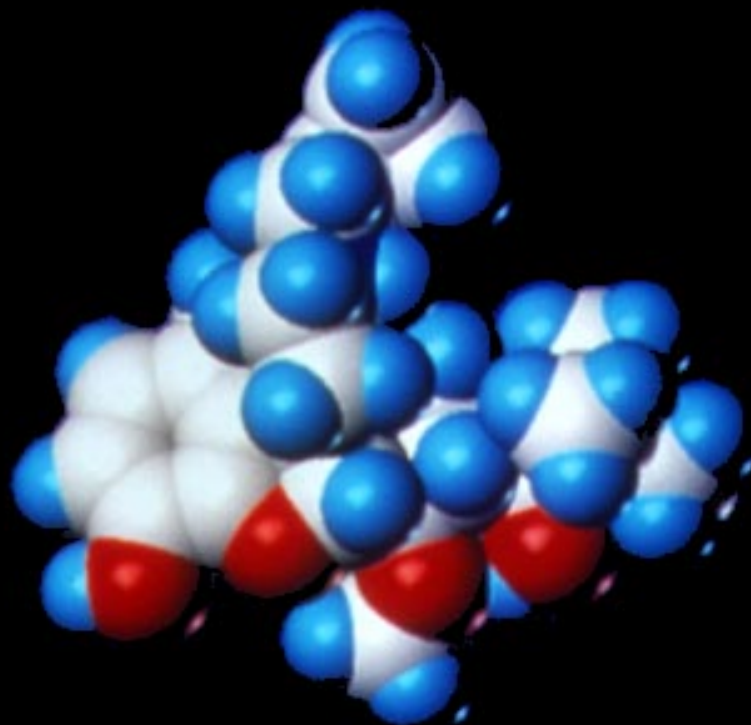
Training objectives



At the end of this training you will:

1. Understand medical withdrawal protocols using buprenorphine
2. Know the basic purpose and background evidence to support the use of buprenorphine for treating opiate dependence
3. Know the basic principles of maintenance treatment with buprenorphine
4. Know effective practises (evaluation, initial dose and management of dose; tapering procedures, etc.) in the implementation of buprenorphine treatment
5. Understand how to address concurrent use of other drugs and alcohol during buprenorphine treatment
6. Know contraindications and medication interactions with buprenorphine

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

Affinity and dissociation

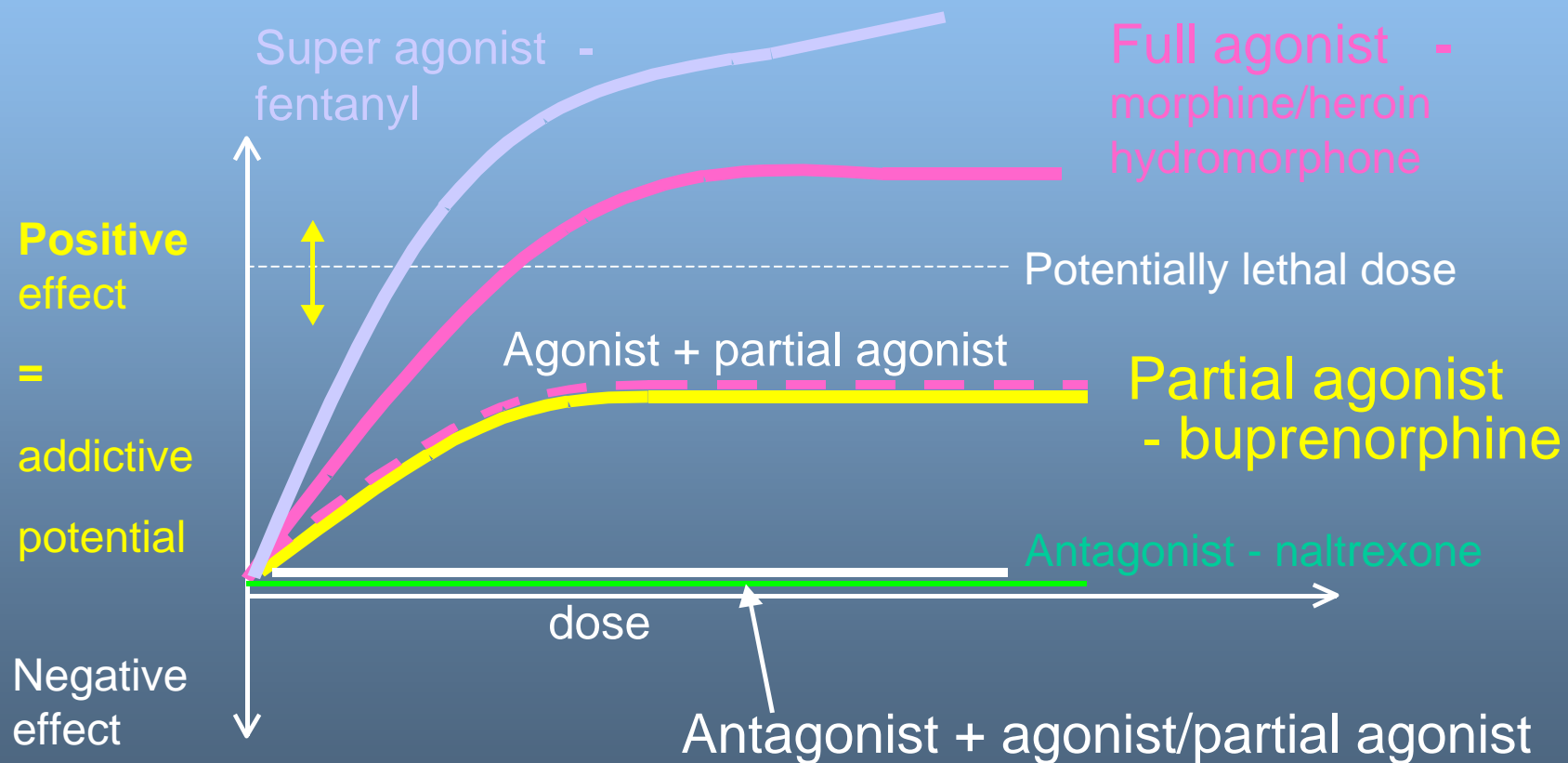
Buprenorphine has:

- high affinity for mu 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)

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**

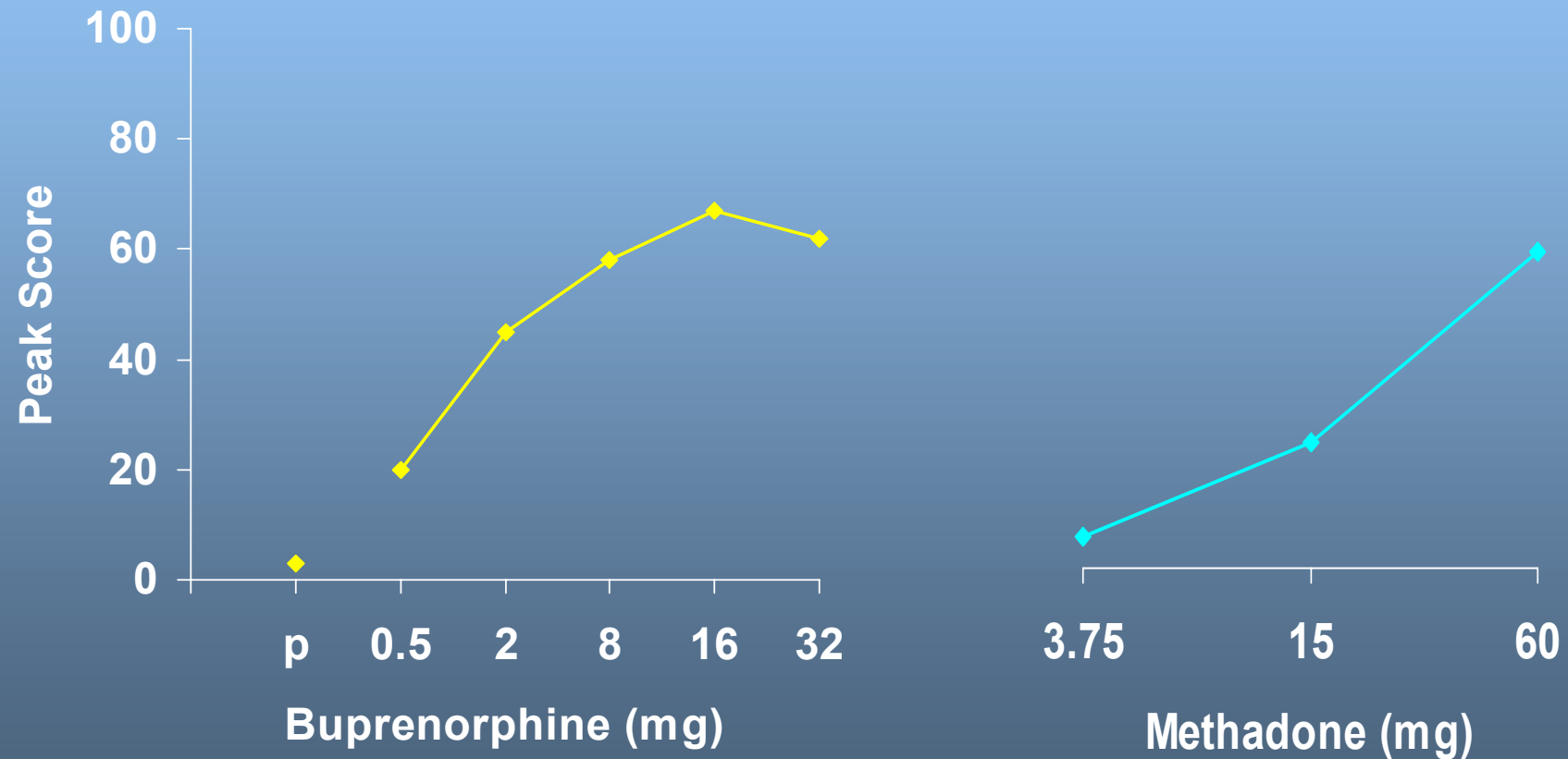
Mu Efficacy and Opiate Addiction



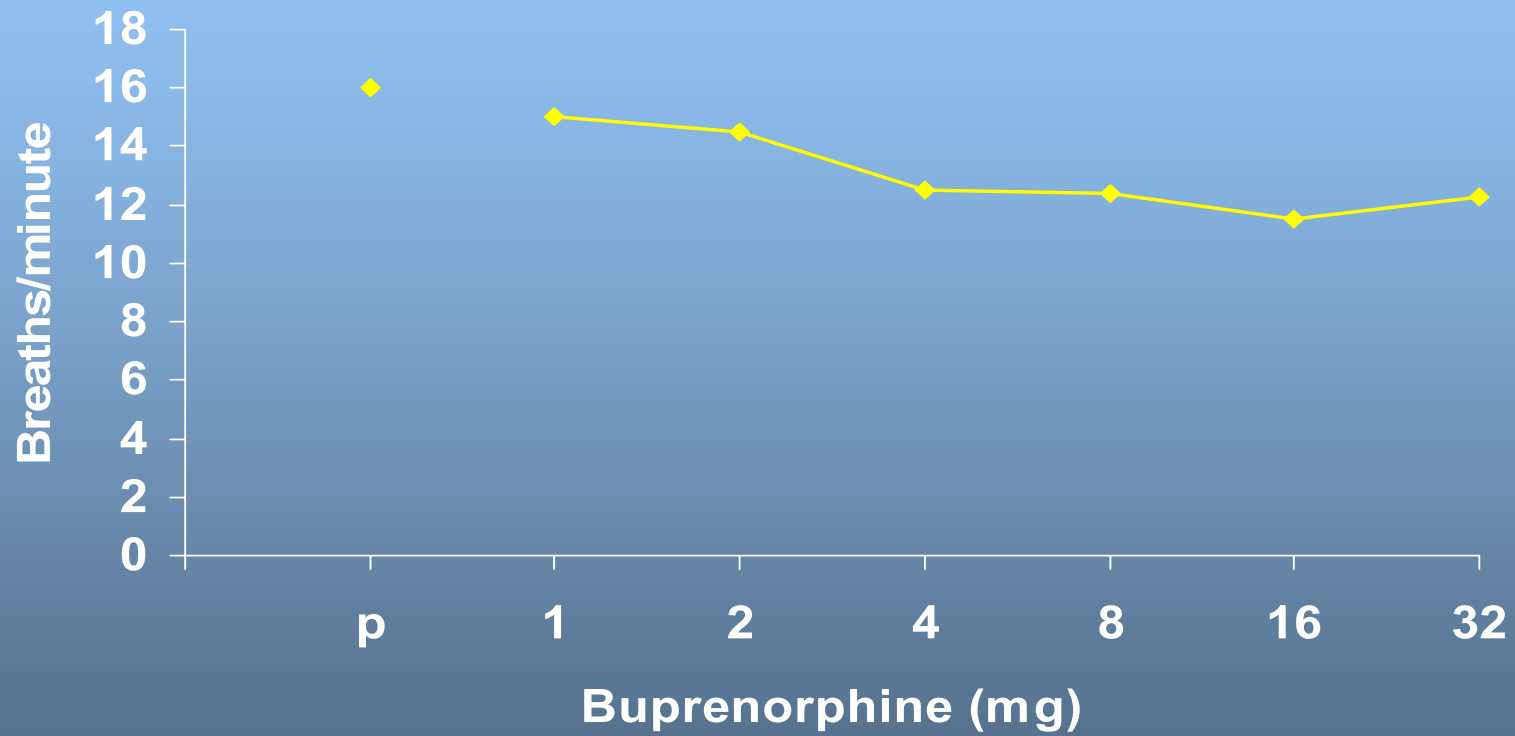
Buprenorphine: Clinical pharmacology

- **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**

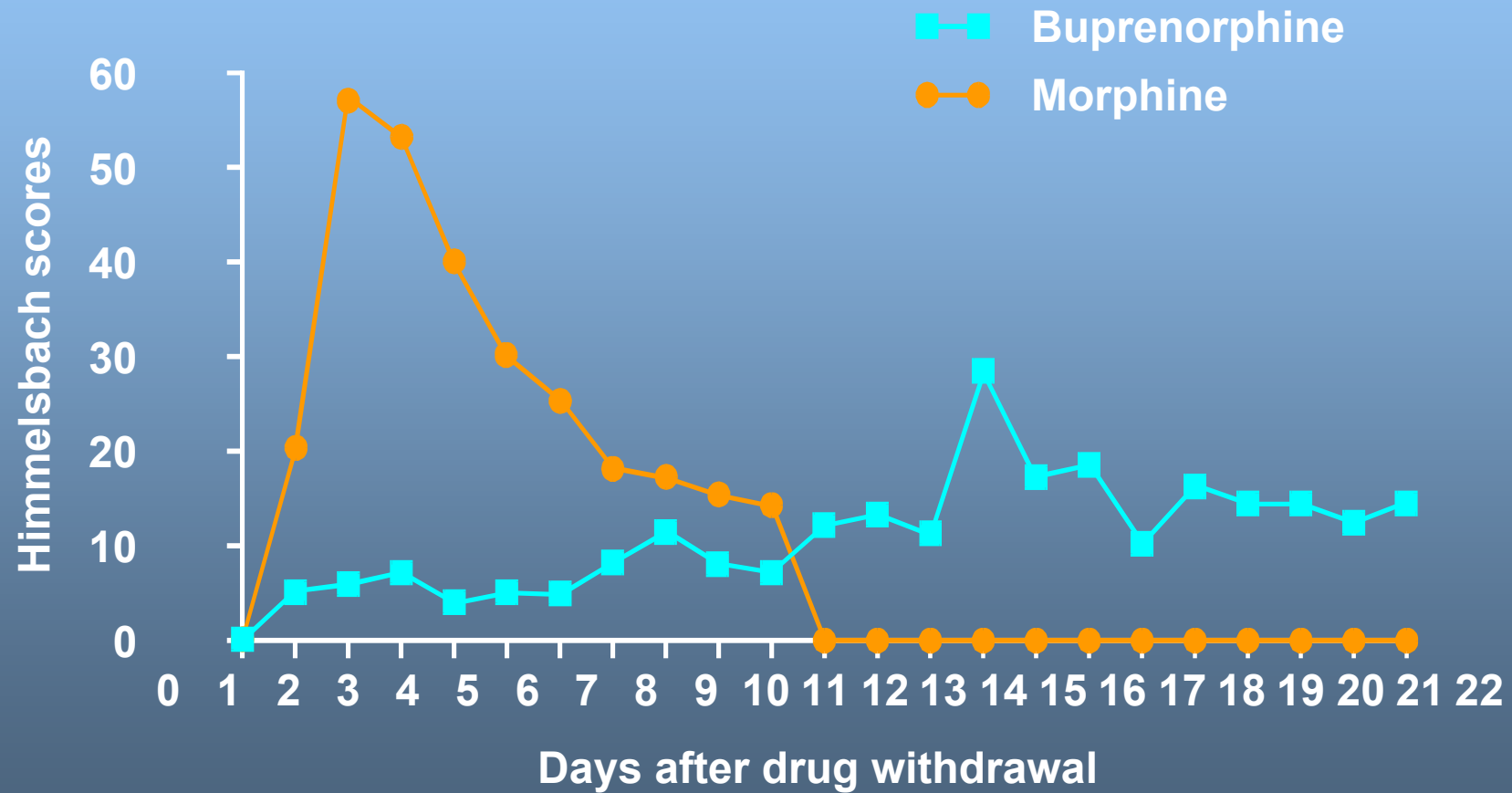
Subjects' Rating of Drugs' Good Effect



Buprenorphine's Effect on Respiration



Intensity of Abstinence Symptoms



Metabolism and excretion

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

Patient selection: Assessment questions (1)



- Is the patient addicted to 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?

Patient selection:

Assessment questions (2)

- **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 office-based buprenorphine treatment?**
- **Are there resources available in the office to provide appropriate treatment?**

Patient selection: Issues for consultation (1)

Several factors may indicate a patient is less likely to be an appropriate candidate, including:

- Patients taking high doses of benzodiazepines, alcohol, or other central nervous system depressants
- Significant psychiatric co-morbidity
- Multiple previous opioid addiction treatment episodes with frequent relapse during those episodes (may also indicate a perfect candidate)
- Nonresponse or poor response to buprenorphine treatment in the past

Patient selection: Issues for consideration (2)

Pregnancy

- Currently buprenorphine is a Category C medication. This means it is not approved for use during pregnancy.
- Studies conducted to date suggest that buprenorphine *may be* an excellent option for pregnant women.
- Randomized trials are underway to determine the safety and effectiveness of using buprenorphine during pregnancy.



Patient selection: Issues for consideration (3)

Patients with these conditions must be evaluated by a physician for appropriateness prior to buprenorphine treatment:

- **Seizures**
- **HIV and STDs**
- **Hepatitis and impaired hepatic function**
- **Use of alcohol, sedative-hypnotics, and stimulants**
- **Other drugs**

Buprenorphine induction

Overview: Goal of induction

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: For short-acting opioids (1)

**Patients dependent on short-acting
opioids (e.g., heroin, oxycodone): Day
1**

**Instruct patients to abstain from any
opioid use for 12-24 hours (so they are
in mild withdrawal at time of first
buprenorphine dose) – may be easiest
to schedule appointment early in day
(decrease risk of opioid use prior to
office visit)**

Continued

Buprenorphine induction: For short-acting opioids (2)

Patients dependent on short-acting opioids (continued)

If patient is not in opioid withdrawal at time of arrival in office, then assess time of last use and consider either having them return another day, waiting in the office until evidence of withdrawal is seen, or leaving office and returning later in the day (with strict instructions to not take opioids while away from the office)

Continued

Buprenorphine induction: For short-acting opioids (3)

Patients dependent on short-acting opioids (continued)

- First dose: 2-4 mg sublingual buprenorphine
- Monitor in office for up to 2 hours after first dose
- Relief of opioid withdrawal symptoms should begin within 30-45 minutes after the first dose

Continued

Buprenorphine induction: For short-acting opioids (4)

Patients dependent on short-acting opioids (continued)

- If opioid withdrawal appears shortly after the first dose, it suggests that the buprenorphine may have precipitated a withdrawal syndrome
- Clinical experience suggests the period of greatest severity of buprenorphine-related precipitated withdrawal occurs in the first few hours (1-4) after a dose, with a decreasing (but still present) set of withdrawal symptoms over subsequent hours

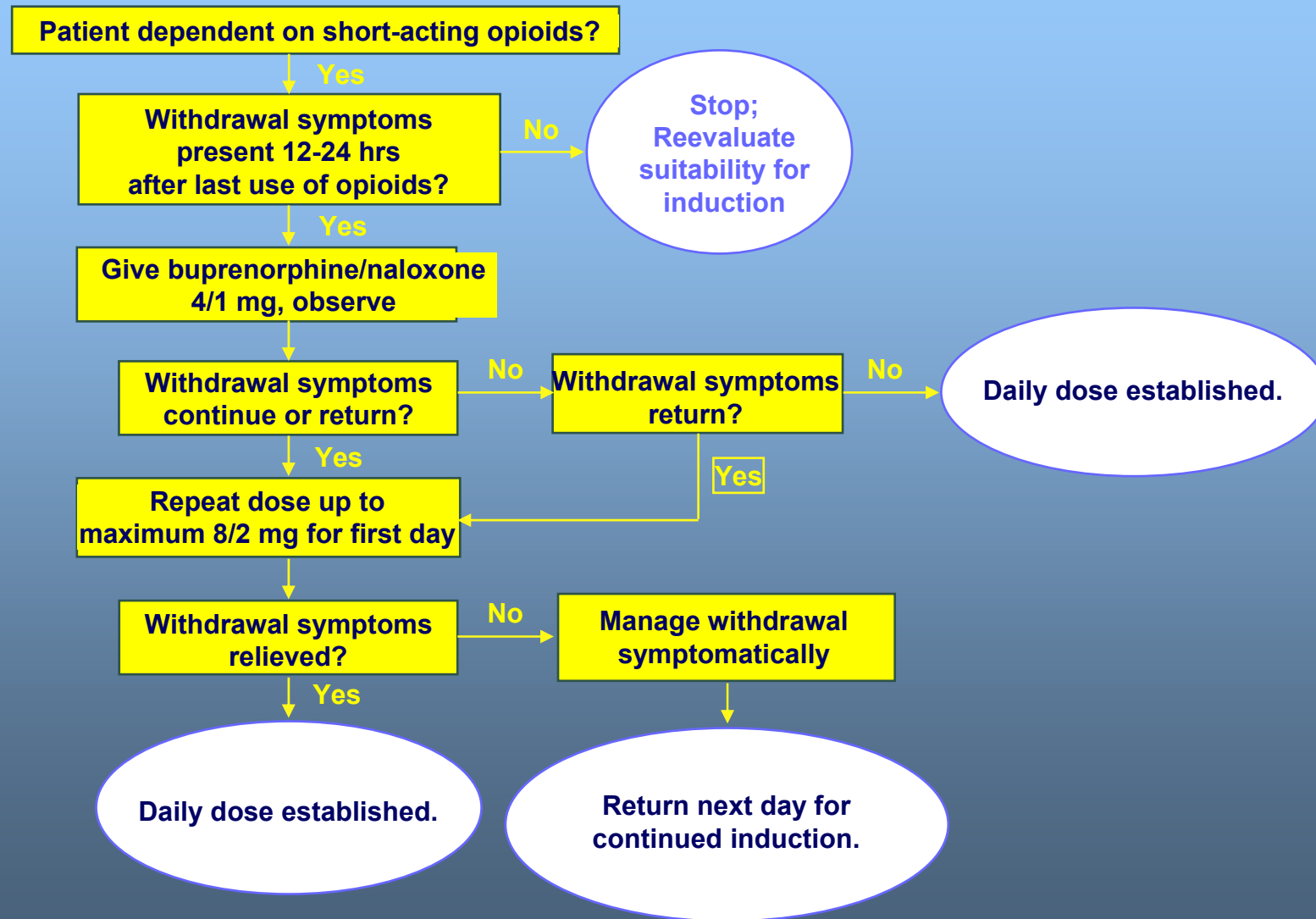
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Buprenorphine induction: For short-acting opioids (5)

Patients dependent on short-acting opioids (continued)

- If a patient has precipitated withdrawal consider:
 - giving another dose of buprenorphine, attempting to provide enough agonist effect from buprenorphine to suppress the withdrawal, or stopping the induction, provide symptomatic treatments for the withdrawal symptoms, and have patient return the next day
- Can re-dose if needed (every 2-4 hours, if opioid withdrawal subsides and then reappears)
- Maximum first-day dose of 8/2 mg buprenorphine / naloxone

Induction: Patient Physically Dependent on Short-acting Opioids, Day 1



Buprenorphine induction: For long-acting opioids (1)

Patients dependent on long-acting opioids

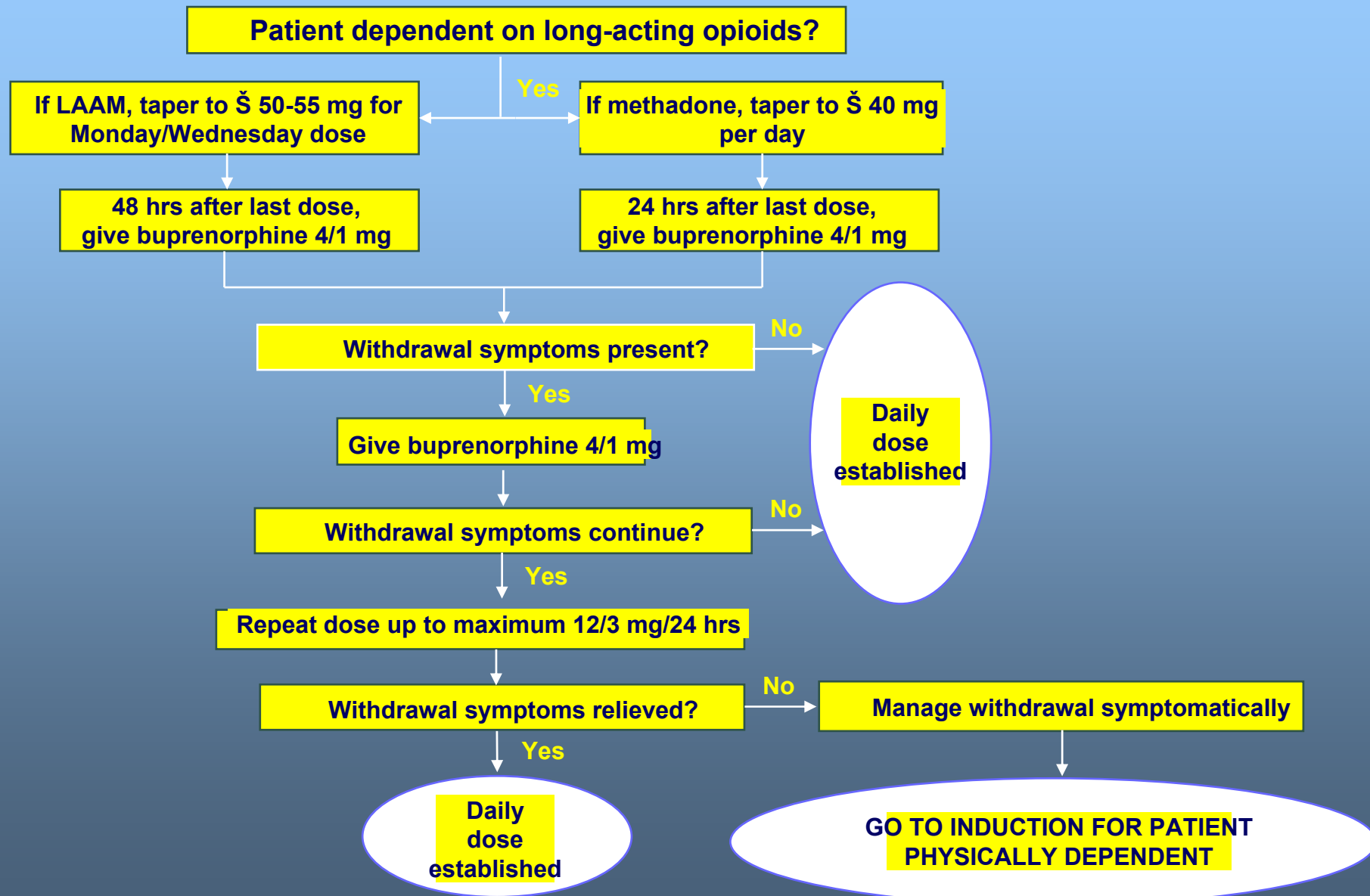
- Experience suggests patients should have dose decreases until they are down to ≤ 40 mg/d of methadone
- Begin induction at least 24-36 hours after last dose of methadone
- Patient should be in mild withdrawal from methadone
- Give no further methadone once buprenorphine induction is started

Continued

Buprenorphine induction: For long-acting opioids (2)

- Use similar procedure as that described for short-acting opioids (i.e., first dose of 4/1 mg of buprenorphine/naloxone)
- Expect total first day dose of 8/2 mg sublingual buprenorphine / naloxone
- Continue adjusting dose by 2-4 mg increments until an initial target dose of 12-24 mg is achieved for the second day
- Continued dose increases are indicated after the second day to a maximum daily dose of 32/8 mg

Induction: Patient Physically Dependent on Long-acting Opioids, Day 1

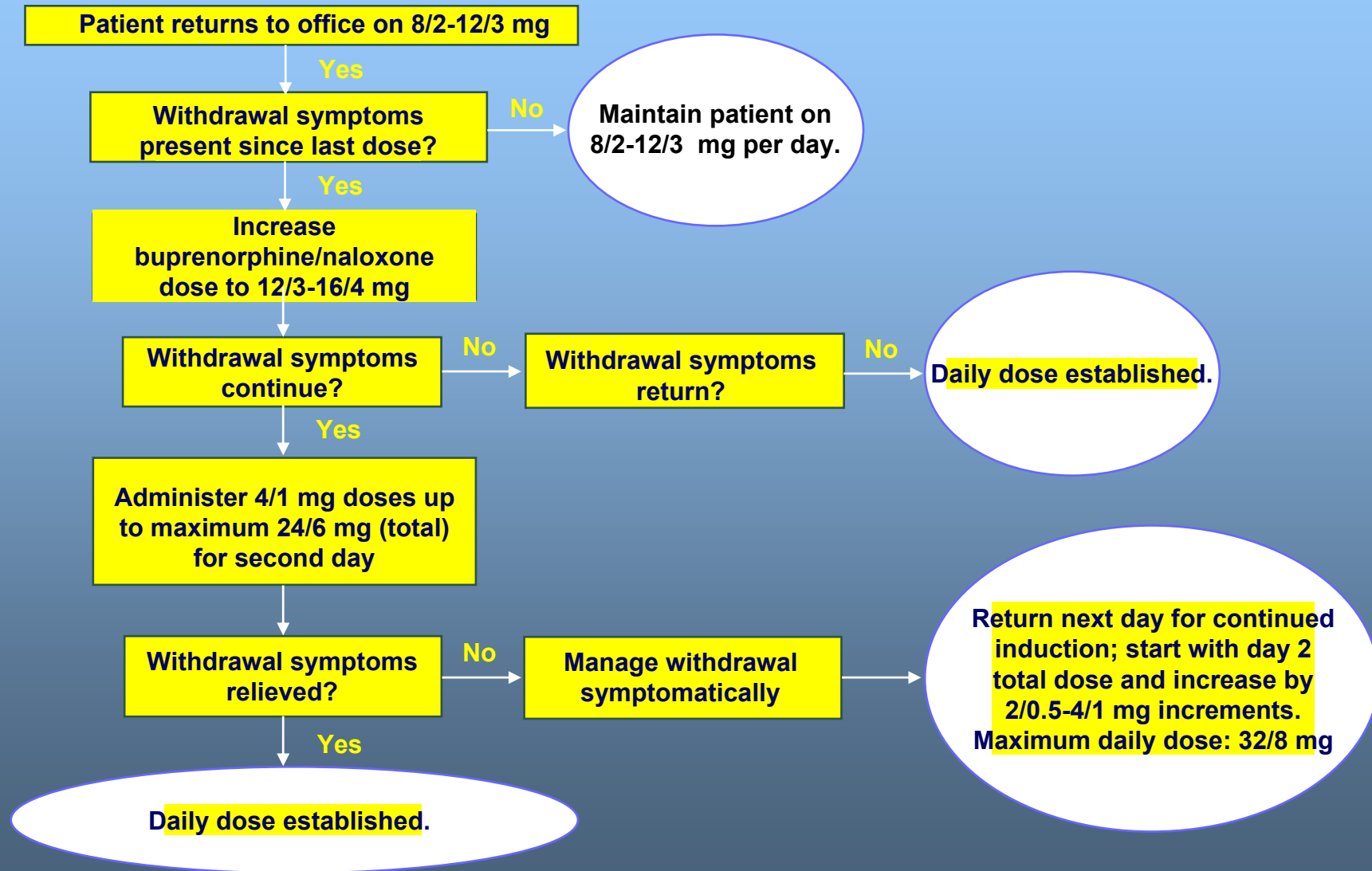


Buprenorphine induction: For short- or long-acting opioids

Patients dependent on short- or long-acting opioids

- After the first day of buprenorphine induction for patients who are dependent on either short-acting or long-acting opioids, the procedures are essentially the same
- On Day 2, have the patient return to the office if possible for assessment and Day 2 dosing
- Assess if patient has used opioids since they left the office, and adjust dose according to the patient's experiences after first-day dosing

Induction: Patient Physically Dependent on Short- or Long-acting Opioids, Days 2+



Buprenorphine stabilisation / maintenance (1)

- **The patient should receive a daily dose until stabilised**
- **Once stabilised, the patient can be shifted to alternate day dosing (e.g., every other day, MWF, or every third day, MTh)**
- **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)**

Buprenorphine stabilisation / maintenance (2)

- **Stabilise on daily sublingual dose**
- **Expect average daily dose to be somewhere between 8/2 and 32/8 mg of buprenorphine / naloxone**
- **Dose may need to be increased if patient continuing to use heroin or other illicit opioids**
- **Higher daily doses more tolerable if tablets are taken sequentially rather than all at once**

Maintenance treatment using buprenorphine

Studies conclude:

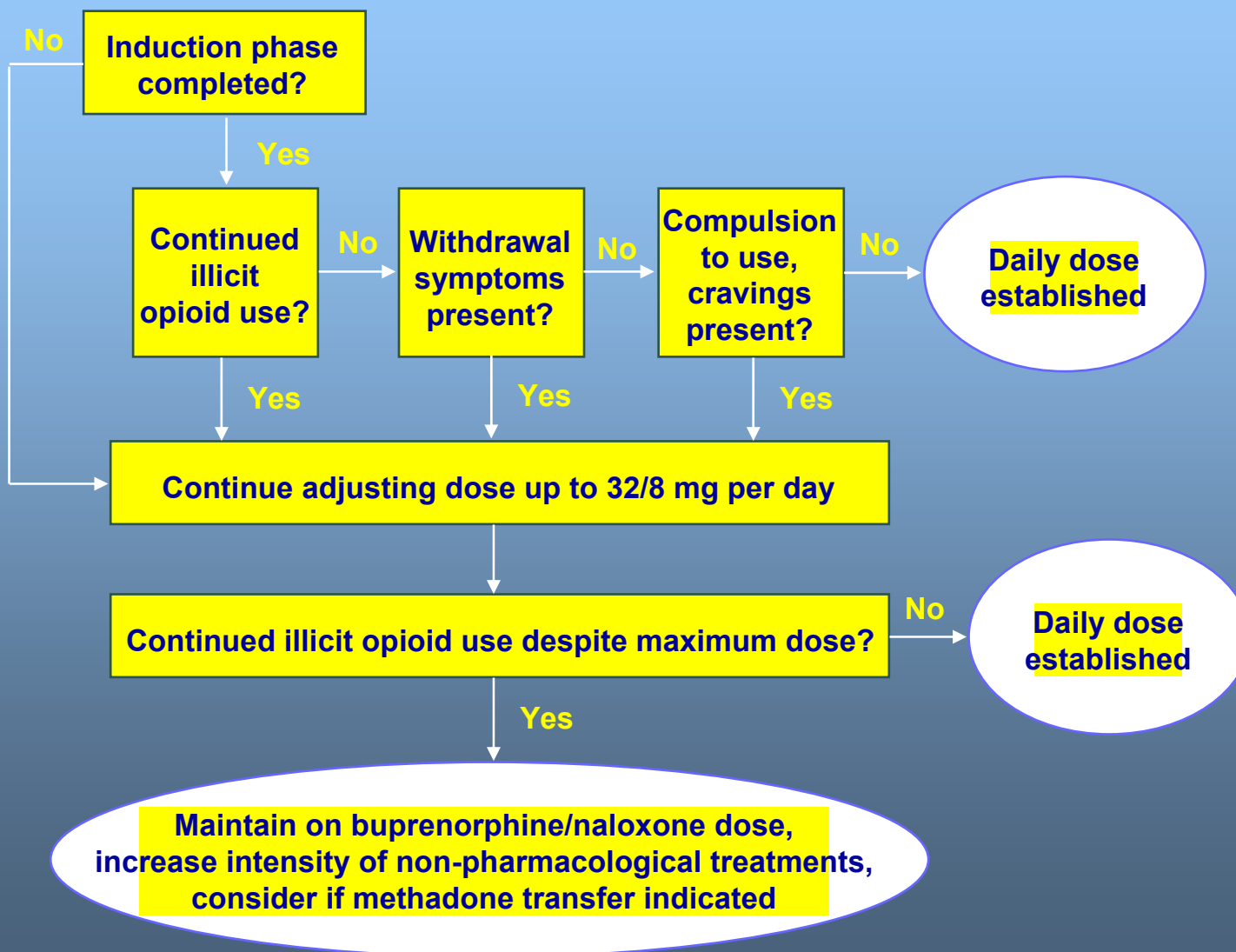
- Buprenorphine more effective than placebo
- Buprenorphine equally effective as moderate doses of methadone (e.g., 60 mg per day)
- Not clear if buprenorphine can be as effective as higher doses of methadone (e.g., 80-100 mg or more per day), and therefore may not be the treatment of choice for some patients with higher levels of physical dependence
- Individuals with better levels of psychosocial functioning and support are optimal candidates for buprenorphine

Buprenorphine maintenance / withdrawal

Comparison of buprenorphine maintenance vs. withdrawal:

Shows both the efficacy of maintenance treatment, and the poor outcomes associated with withdrawal (even when provided within the context of a relatively rich set of psychosocial treatments including hospitalisation and cognitive behavioral therapy)

Stabilisation / Maintenance



Withdrawal using buprenorphine (1)

Withdrawal in ≤ 3 days

- Buprenorphine is effective in suppressing opioid withdrawal symptoms
- Long-term efficacy is not known, and is likely limited
- Studies of other withdrawal modalities have shown that such brief withdrawal periods are unlikely to result in long-term abstinence

Withdrawal in ≤ 3 days

- Reports show buprenorphine suppresses opioid withdrawal signs and symptoms (better than clonidine)

Withdrawal in ≤ 3 days

- Using sublingual tablets:
 - ☐ First day: 8/2-12/3 mg sl
 - ☐ Second day: 8/2-12/3 mg sl
 - ☐ Third (last) day: 6/1.5 mg sl

Withdrawal using buprenorphine (2)

Withdrawal over >30 day (long-term)

- Not a well-studied topic
- Literature on opioid withdrawal can provide guidance; suggests longer, gradual withdrawals more effective than shorter withdrawals

Although there are few studies of buprenorphine for such time periods, buprenorphine has been shown more effective than clonidine over this time period.

Withdrawal using buprenorphine (3)

Regardless of the buprenorphine withdrawal duration:

Consider use of ancillary medications to assist with symptoms of opioid withdrawal (e.g., medications for arthralgias, nausea, insomnia)

Overview of safety and side effects

- ~~Highly safe medication (under both acute and chronic dosing circumstances)~~
- Also safe if inadvertently swallowed by someone not dependent on opioids (because of poor oral bioavailability and the ceiling on maximal effects)
- Primary side effects: like other mu agonist opioids such as methadone (e.g., nausea, constipation)
- Anecdotal reports indicate that symptoms may be less severe

Precipitated withdrawal (1)

- ~~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 (2)

Risk factors that increase the possibility 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**

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 means it is less likely to produce clinically significant respiratory depression. However, overdose in which buprenorphine is combined with other CNS depressants may be fatal (reviewed later in this section).**

Drug interactions with buprenorphine

- 1. Benzodiazepines and other sedating drugs**
- 2. Medications metabolised by cytochrome P450 3A4**
- 3. Opioid antagonists**
- 4. Opioid agonists**

Benzodiazepines and other sedating drugs (1)

- Reports of deaths when buprenorphine injected along with injected benzodiazepines
 - Reported from France, where buprenorphine without naloxone tablets are available (appears patients dissolve and inject tablets)
- Probably possible for this to occur with other sedatives
- Mechanism leading to death in these cases is not known
- Not clear if any patients have died from use of **sublingual** buprenorphine combined with **oral** benzodiazepine. Most deaths appear to have been related to **injection** of the combination of dissolved buprenorphine tablets with benzodiazepine

Benzodiazepines and other sedating drugs (2)

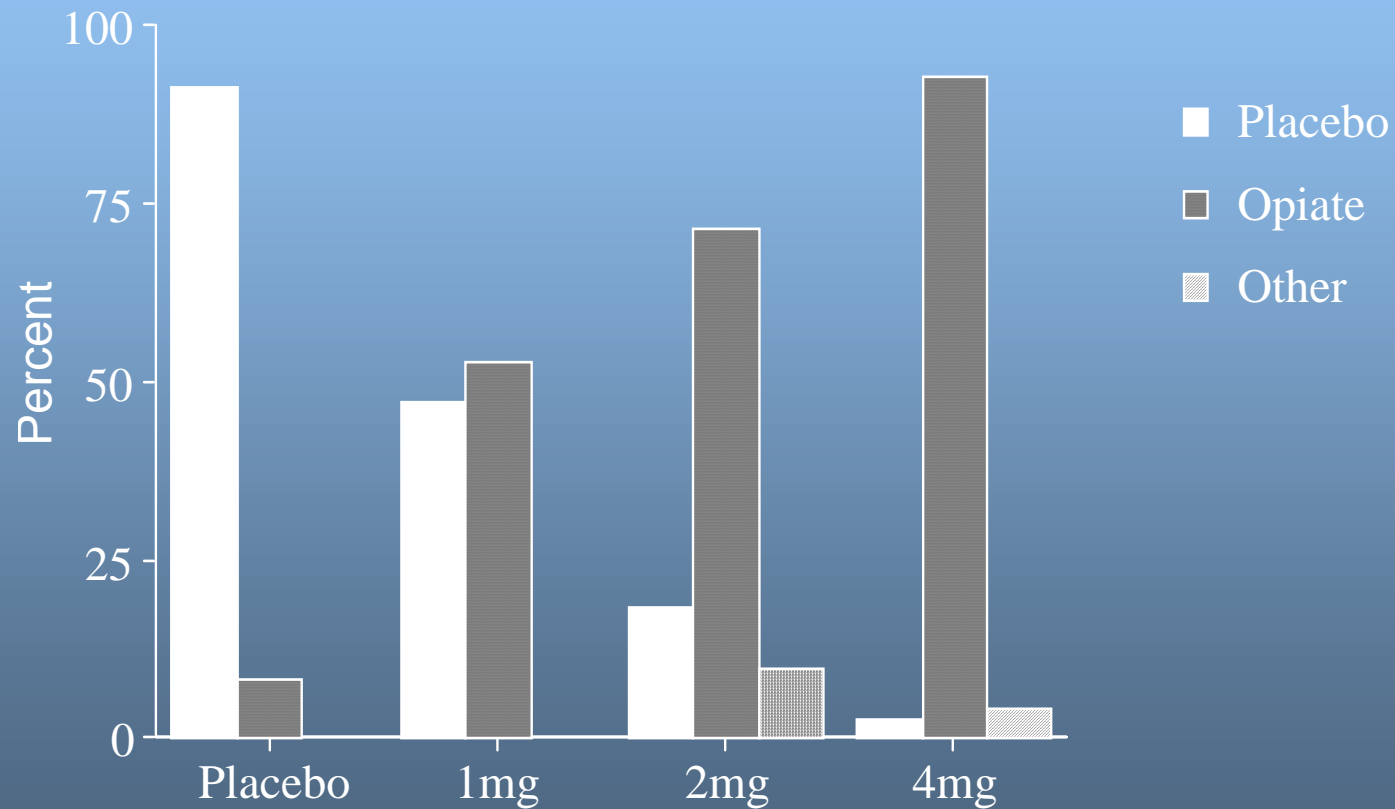
Note that the combination product (buprenorphine with naloxone, Suboxone®) is designed to decrease the likelihood that people will dissolve and inject buprenorphine, so the risk of misuse of buprenorphine with benzodiazepines should be decreased with the availability of buprenorphine / naloxone.

Diversion and misuse

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

- 1. Persons physically dependent on illicit opioids**
- 2. Persons on prescribed opioids (e.g., methadone)**
- 3. Persons maintained on buprenorphine / naloxone**
- 4. Persons abusing, but not physically dependent on opioids**

Buprenorphine's Abuse Potential



Sublingual Buprenorphine

(From Jasinski et al., 1989)

Combination of buprenorphine plus naloxone

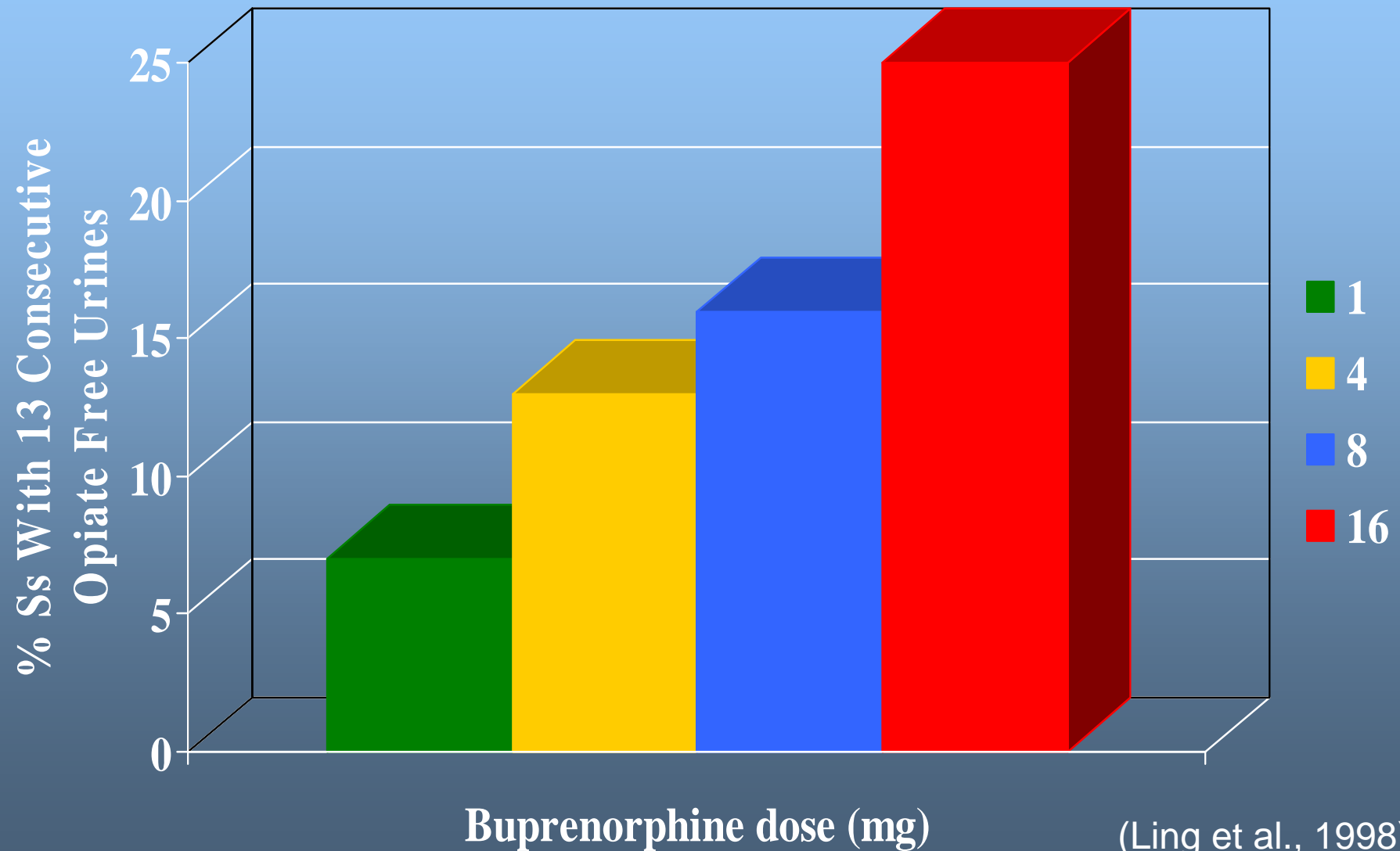
- **Combination tablet containing buprenorphine with naloxone – if taken under tongue, predominant buprenorphine effect**
- **If opioid-dependent person dissolves and injects buprenorphine / naloxone tablet – predominant naloxone effect (and precipitated withdrawal)**

Maintenance treatment using buprenorphine

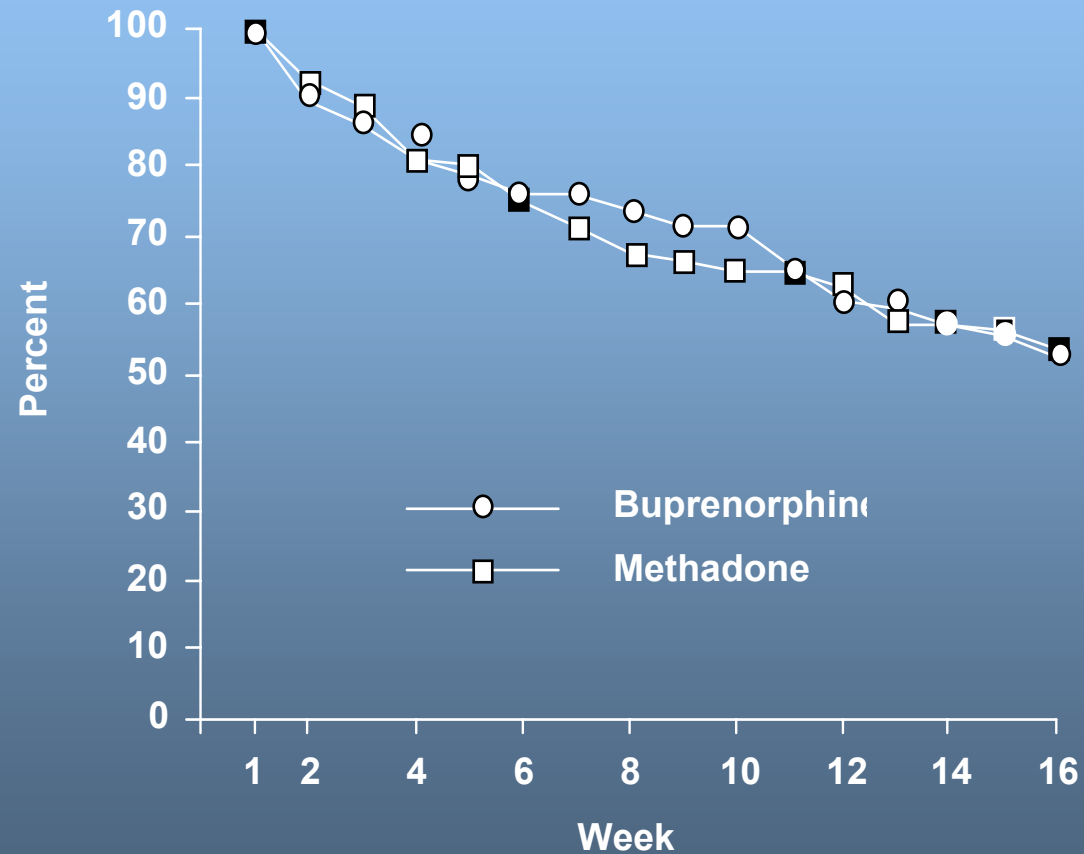
Following slides briefly review representative studies:

- **Comparison of different doses of sublingual buprenorphine**
- **Buprenorphine-methadone flexible dose comparison**
- **Buprenorphine, methadone, LAAM comparison**

Different Doses of Buprenorphine: Opiate Use

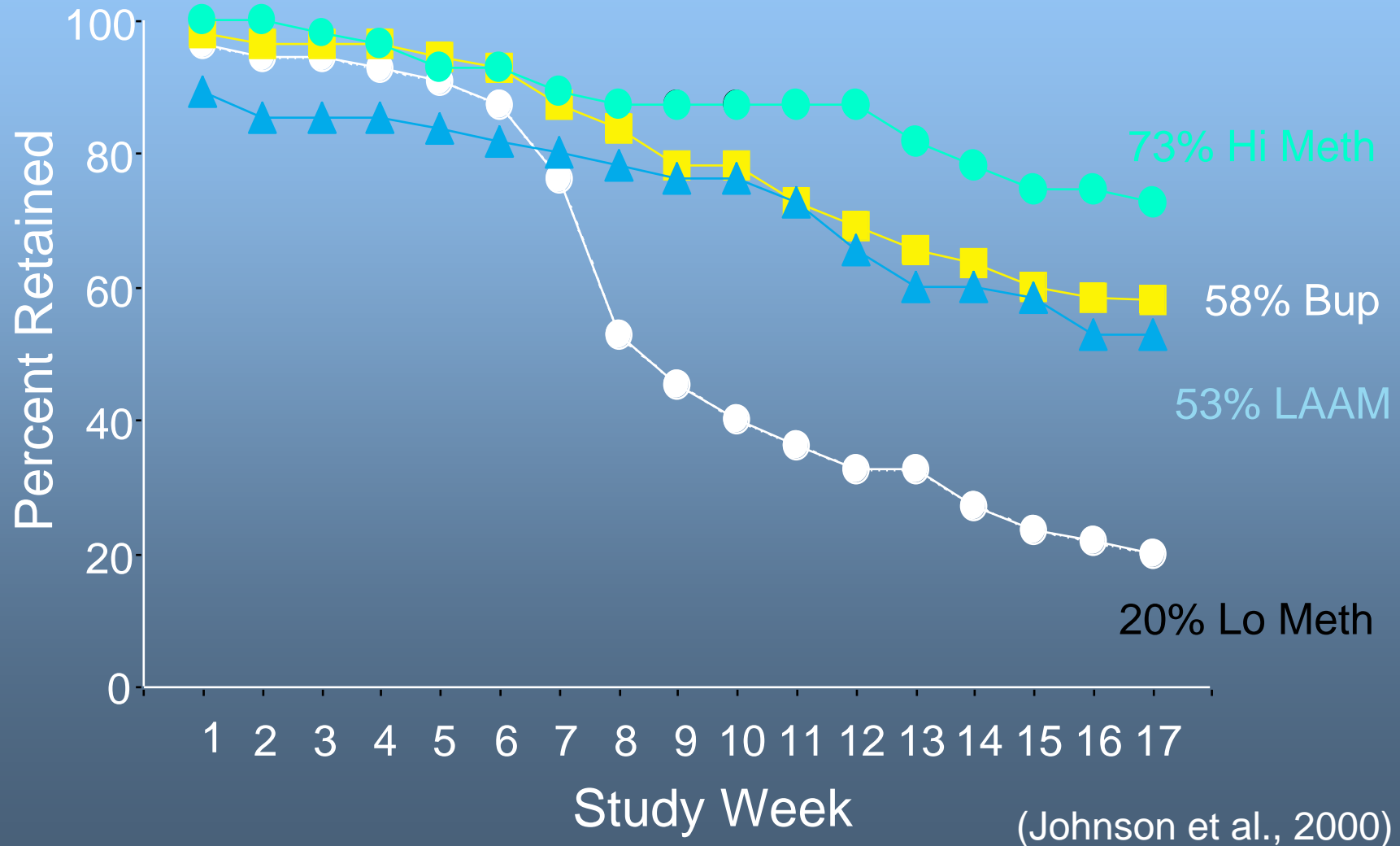


Buprenorphine – Methadone: Treatment Retention

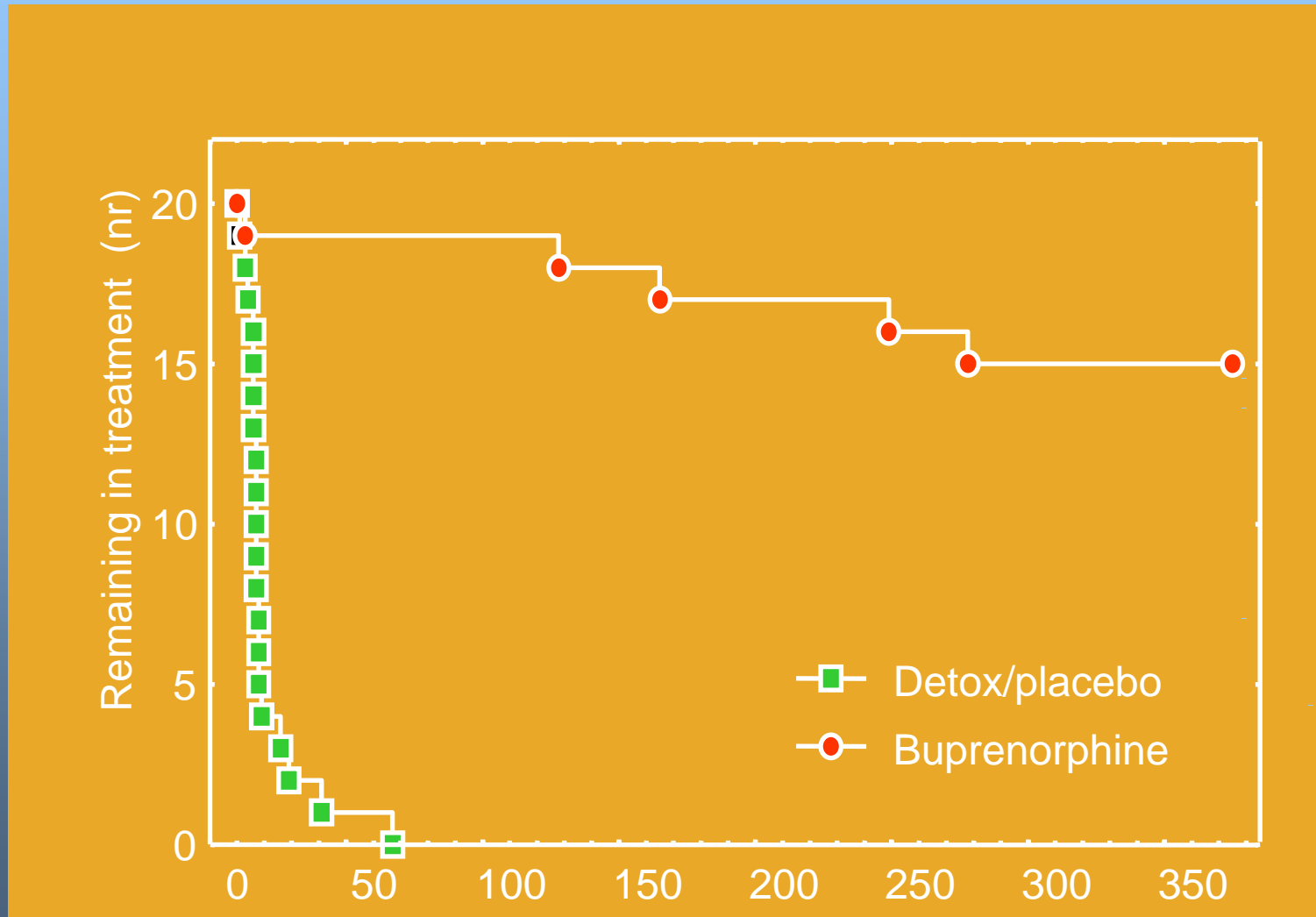


(Strain et al., 1994)

Buprenorphine, Methadone, LAAM: Treatment Retention



Buprenorphine Maintenance / Withdrawal: Retention



Treatment duration (days) (Kakko et al., 2003)

Buprenorphine Maintenance / Withdrawal: Mortality

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

(Kakko et al., 2003)

Questions?



Comments?

Thank you for your time!

End of Workshop 3

Workshop 4: Opiate Antagonist Treatment: Naloxone for Overdose, Naltrexone for Relapse Prevention

Training objectives



At the end of this training you will:

- 1. Understand the neurobiology-conditioning underpinning opiate relapse**
- 2. Understand the rationale for the use of naloxone for opiate overdose**
- 3. Know the protocol for the use of naltrexone for relapse prevention**
- 4. Understand the challenges and limitations of naltrexone treatment**

Naloxone for Opiate Overdose

Naloxone for opiate overdose

- Naloxone is a medication used to counter the effects of opioid overdose, for example heroin and morphine overdose.
- Specifically, naloxone is used in opioid overdoses for countering life-threatening depression of the central nervous system and respiratory system.
- It is marketed under trade names including Narcan, Nalone, and Narcanti.

Continued

Naloxone for opiate overdose

- The drug is derived from thebaine and has an extremely high affinity for μ -opioid receptors in the central nervous system.
- Naloxone is a μ -opioid receptor competitive antagonist, and its rapid blockade of those receptors often produces rapid onset of withdrawal symptoms

Continued

Naloxone for opiate overdose

- **Naloxone is injected, usually initially intravenously for fastest action**

The drug acts after about two minutes, and its effects may last about 45 minutes.

Continued

Signs of opioid overdose

- **Unconscious (does not respond verbally or by opening eyes when spoken to loudly and shaken gently)**
- **Constricted pupils**
- **Hypoventilation (respiration rate too slow or tidal volume too low)**
- **Cool moist skin**

Opioid overdose: Steps to take (1)

If an opioid overdose is suspected:

- Oxygen, if available
- Naloxone – 0.4-0.8mg IV/IMI, (aliquots of 50mcg every 1-2 minutes may be used IV until arousal sufficient for airway maintenance and adequate ventilation). Dose may be repeated after 2 minutes if no response, to a maximum of 10mg
- Call ambulance
- Advise reception of emergency and location
- If client unwilling to attend hospital, you may need to consider need for detention order if concerns for safety of client

Opioid overdose: Steps to take (2)

- **Assess the client**
- **Responsiveness**
- **Airway – open and clear**
- **Breathing – respiratory rate and volume**
- **Circulation – carotid pulse**

Opioid overdose: Steps to take (3)

If unresponsive, respiratory arrest, or hypoventilating

- Call ambulance
- Place in lateral coma position if breathing spontaneously
- Bag and mask, ventilate with oxygen for hypoventilation
- Naloxone 0.4-0.8mg IV (50mcg aliquots every 1-2 minutes) or IM if suspect opioid OD

Opioid overdose: Steps to take (4)

➤ **If response is adequate**

- The patient will be fully conscious, oriented, alert, and responsive

➤ **If response is inadequate or there is no response to naloxone**

- Continue oxygenation
- Keep lateral
- Monitor observations
- Administer further naloxone

Opioid overdose: Steps to take (5)

- Advise client to go to the hospital for observation \pm naloxone infusion
- If refuses, advise no further drugs or alcohol that day
- Stay with a responsible person for > 2 hours
- Provide written information regarding above
- If client at risk (suicide / effects of drugs) consider detention order

Naloxone for opiate overdose

Naloxone has been distributed as part of emergency kits to heroin users, and this has been shown to reduce rates of fatal overdose. Projects of this type are underway in San Francisco and Chicago, and pilot projects started in Scotland in 2006.

Naltrexone for Relapse Prevention

Naltrexone for opiate relapse prevention (1)

- **Naltrexone is an opioid antagonist treatment medication: It is a pure, potent mu antagonist that can be taken by mouth once daily or every other day, and has minimal side effects.**
- **It is neither reinforcing nor addicting and has no potential for abuse or diversion for unprescribed use.**

Naltrexone for opiate relapse prevention (2)

- Naltrexone, and its active metabolite 6- β -naltrexol, are competitive antagonists at μ - and κ -opioid receptors, and to a lesser extent at δ -opioid receptors.
- This blockade of opioid receptors is the basis behind its action in the management of opioid dependence – it reversibly blocks or attenuates the effects of opioids.

Naltrexone for opiate relapse prevention (3)

- **Naltrexone is not a narcotic**
- **It works by blocking the effects of narcotics, especially the “high” feeling that is produced by opiates**
- **It also may block the “high” feeling that is produced by alcohol**
- **It will not produce any narcotic-like effects or cause mental or physical dependence**

Naltrexone for opiate relapse prevention (4)

- **Naltrexone will cause withdrawal symptoms in people who are physically dependent on narcotics**
- **Naltrexone treatment is started after an individual is no longer dependent on narcotics**
- **It is important for an individual to be fully withdrawn from opiates**
- **If naltrexone is taken by individuals who are incompletely detoxified from opiates, it can precipitate a rapid and unpleasant withdrawal syndrome**

Naltrexone for opiate relapse prevention (5)

- **The length of time between the last dose of opiate and the first dose of naltrexone is important**
- **The specific timetable depends on whether the opiate being used was a short-acting opiate (e.g., morphine or heroin) or a long-acting opiate (e.g., methadone) and how long the opiate was used (i.e., days, weeks months)**
- **Before starting naltrexone it is important for the treating physician to have this information**

Naltrexone for opiate relapse prevention (6)

- **When opiate-dependent individuals desire to be inducted onto naltrexone, it is necessary to first detoxify them from opiates to avoid precipitated withdrawal**
- **It is not possible to use the two most effective withdrawal agents, methadone and buprenorphine, because of their agonist properties**
- **Therefore, detoxification methods that do not employ methadone and / or buprenorphine must be used**

Naltrexone for opiate relapse prevention (7)

- **Two commonly used agents are lofexidine and clonidine, both α -adrenergic agonists that relieve most opioid withdrawal symptoms without producing opioid intoxication or drug reward.**
- **Opiate detoxification with these agents is less effective, since they do not relieve many opioid withdrawal symptoms. Therefore, adjunctive medicines often are necessary to treat insomnia, muscle pain, bone pain, and headache.**

Pre-naltrexone detoxification procedures (1)

- **An appropriate protocol for clonidine is 0.1mg administered orally as a test dose**
- **A dose of 0.2mg might be used initially for patients with severe signs of opioid withdrawal or for those patients weighing more than 200 pounds**
- **The sublingual (under the tongue) route of administration also may be used**
- **A similar procedure using lofexidine is appropriate; lofexidine produces significantly less hypotension than clonidine**

Pre-naltrexone detoxification procedures (2)

- **Clinicians should check the patient's blood pressure prior to clonidine administration, and clonidine should be withheld if systolic blood pressure is lower than 90 or diastolic blood pressure is below 60**
- **These parameters can be relaxed to 80/50 in some cases if the patient continues to complain of withdrawal and is not experiencing symptoms of orthostatic hypotension (a sudden drop in blood pressure caused by standing)**

Pre-naltrexone detoxification procedures (3)

- Clonidine (0.1 to 0.2mg orally) can then be given every 4 to 6 hours on an as-needed basis
- Clonidine detoxification is best conducted in an inpatient setting, as vital signs and side effects can be monitored more closely in this environment
- In cases of severe withdrawal, a standing dose (given at regular intervals rather than purely "as needed") of clonidine might be advantageous

Pre-naltrexone detoxification procedures (4)

- The daily clonidine requirement is established by tabulating the total amount administered in the first 24 hours, and dividing this into a three or four times per day dosing schedule.
- Total clonidine should not exceed 1.2mg the first 24 hours and 2.0mg after that, with doses being held in accordance with parameters noted above.
- The standing dose is then weaned over several days.
- Clonidine must be tapered to avoid rebound hypertension.

Naltrexone for opiate relapse prevention

- For *oral* dosage form (tablets):
- For treating narcotic addiction:
 - Adults—25 milligrams (mg) (one-half tablet) for the first dose, then another 25 mg one hour later. After that, the dose is 350 mg a week. This weekly dose should be divided up according to one of the following schedules:
 - ❑ 50 mg (one tablet) every day; or
 - ❑ 50 mg a day during the week and 100 mg (two tablets) on Saturday; or
 - ❑ 100 mg every other day; or
 - ❑ 100 mg on Mondays and Wednesdays, and 150 mg (three tablets) on Fridays; or
 - ❑ 150 mg every three days

Naltrexone for opiate relapse prevention (1)

Side effects

- Acute opioid withdrawal precipitated (e.g., lethargy, aches, cramps, low energy)
- Depression, irritability
- Anxiety, nervousness
- Sleeping difficulties
- Skin rash
- Poor appetite
- Dizziness

Precautions

- If naltrexone ceased and opioid use reinstated, reduced tolerance to opioids increases risk of overdose and death
- Precipitates withdrawals in opioid-dependent patients

Naltrexone for opiate relapse prevention (2)

- Patient non-compliance in part due to the absence of any agonist effects is a common problem. Therefore, a favourable treatment outcome requires a positive therapeutic relationship, careful monitoring of medication compliance, and effective behavioural interventions.
- Effectiveness tends to be dependent on:
 - situation, circumstances, support, commitment of patient
 - inclusion as part of comprehensive treatment program (including counselling)
- Long-term treatment efficacy still under investigation
- While effective for some, inappropriate for others

Naltrexone - psychotherapy research

- Positive results when naltrexone is combined with **cognitive behavioural therapy** and treatment with the **Matrix Model**
- **Contingency management** also produces large increases in retention on naltrexone
- **Family therapy** also promotes successful treatment with naltrexone
- Using **legal pressure** (individuals sentenced to treatment by courts) to mandate people to take naltrexone can greatly increase retention on naltrexone and outcome success

Naltrexone for opiate relapse prevention

- **Naltrexone can also be administered as a low-dose implant. These implants can remain effective for 30-60 days. They dissolve slowly and are usually put in under a local anaesthetic in the left iliac fossa.**
- **This implant procedure has not been shown scientifically to be successful in "curing" the patient of their addiction, although it does provide a better solution than oral naltrexone for medication compliance reasons.**

Conclusion:

Naltrexone for opiate addiction (1)

- **Naltrexone, nonselective opioid antagonist**
- **Induction issues**
- **Retention**
- **Depot preparation**
- **Better outcomes with specific therapies or legal interventions**

Conclusion:

Naltrexone for opiate addiction (2)

- Treatment with opiate agonists (methadone) or partial agonists (buprenorphine) produces far better retention than does naltrexone
 - several studies report by end second week between 39% and 74% left treatment
- Use of these medications has gained far more acceptance by practitioners than has naltrexone treatment
- Psychotherapy can substantially improve outcome with these medications as well

Naltrexone for alcoholism (2)



- Alcohol produces some of its reinforcing properties by releasing the body's own opiate-like substance (endorphin)
- Naltrexone can block endorphin
- An alcoholic who is maintained on naltrexone will not experience endorphin-mediated alcohol-induced euphoria
- Maintenance on naltrexone will reduce alcohol use

Naltrexone for alcoholism (2)

Two landmark studies documented that naltrexone can be an effective treatment for treating alcoholics:

- Volpicelli, W., Alterman, A., Hayashida, M., O'Brien, C. "Naltrexone in the Treatment of Alcohol Dependence". Archives of General Psychiatry 49: 876-880 (1990)
- O'Malley, S., Jaffe, A., Chang, G., Schottenfeld, R., Meyer, R., Rounsaville, B. "Naltrexone and Coping Skills Therapy for Alcohol Dependence". Archives of General Psychiatry 49: 881-887 (1992).

O'Malley et al. demonstrated that if naltrexone is used with coping skills therapy, relapses are reduced and the severity of the relapse is reduced.

Naltrexone for alcoholism (3)

➤ For treating alcoholism:

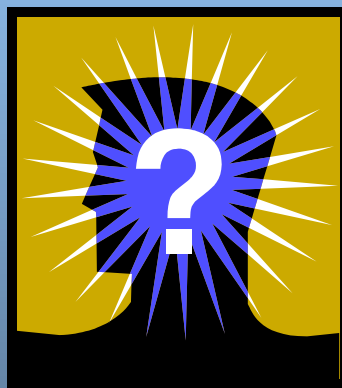
- Adults—The first dose may be 25mg (one-half tablet). After that, the dose is 50 mg (one tablet) every day.
- Children and teenagers up to 18 years of age—Use and dose must be determined by the doctor.

➤ For **injectable** dosage form

➤ For treating alcoholism:

- Adults—380 mg once a month injected into the muscle by a doctor.

Questions?



Comments?

Post-assessment

Please respond to the post-assessment questions in your workbook.

(Your responses are strictly confidential.)

10 minutes



Thank you for your time!

End of Workshop 4