Association for the Application of Neuroscientific Knowledge to Social Aims

European Opiate Addiction Treatment Association

World Federation for the Treatment of Opioid Dependence

Basics on Addiction

Training Programme on Opioid Dependence Treatment

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

Contributors

- These slides have been developed by Icro Maremmani (President of EUROPAD) Matteo Pacini (President of EUROPAD-Italia) and Pier Paolo Pani (President of the Italian Society of Addiction Medicine, SITD) on behalf of the Basics on Addiction (BoA) Group:

- Francesco Auriemma (NA)
- Jacopo Bizzarri (BZ)
- Pietro Casella (Roma)
- Lucia D'Ambrosio (MT)
- Giovanna De Cerce (CB)
- Stefano Dell'Aera (EN)
- Fernando Fantini (CH)
- Paola Fasciani (CH)
- Michele Ferdico (AG)
- Giuseppe Filippone (PA)
- Piero Fundone (PT)
- Riccardo Gionfriddo (SR)
- Guido Intaschi (LU)
- Claudio Leonardi (Roma)
- Angelo GI Maremmani (PI)
- Andrea Michelazzi (TS)
- Carlo Minestrini (PG)
- Franco Montesano (CZ)
- Maria Chiara Pieri (BO)
- Vico Rosolino Ricci (SP)
- Francesco Ruffa (FI)
- Alberto Santamaria (BA)
- Carmelo Siragusa (CE)
- Lorenzo Somaini (BI)
- Luigi Stella (NA)
- Enrico Teta (TO)
- Andrea Vendramin (PD)

Acknowledgments

- This initiative was supported by an unrestricted Educational Grant from Reckitt Benckiser to EUROPAD and the 'Association for the Application of Neuroscientific Knowledge to Social Aims' (AUCNS)
- Editorial support was provided by Purple Hat Communications Ltd

Training Programme on Opioid Dependence Treatment

Section A

Neurobiology of opioid dependence

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

Learning objectives

- This section will provide an introduction to opioid dependence. By the end of this section you will be able to describe:
  - Opioids and their mechanism of action
  - Principle effects of opioids, including their action on the reward pathway
  - Opioid classification
  - Neurobiological adaptations to opioids
  - Opioid dependence as a chronic, relapsing brain disorder

What is an opioid?

- Opium is the dried juice of the poppy *Papver somniferum*
- Opioids are substances that have the same effect on the body as opium
- Some opioids derived from opium whilst others are synthetically derived

Ries et al. 2009

Endogenous opioids

- There are at least four classes of endogenous opioids: enkephalins, endorphins, endomorphins, and dynorphins
  - Each class consists of structurally similar molecules
  - Produced in the CNS and various glands
- Endogenous opioids have a range of functions, including:
  - Pain relief
  - Induction of euphoria
  - Regulation of respiration
- Endogenous opioids function as neuromodulators to influence the actions of other neurotransmitters such as dopamine or glutamate

CNS, central nervous system

Simon, 1991

Opioid receptors

Opioid receptor	Distribution	Primary effects
Mu (μ), MOP	Thalamus, various brainstem areas (ventral tegmental area, nucleus accumbens)	Analgesia, euphoria, respiratory depression, sedation
Kappa (κ), KOP	Spinal cord, brainstem areas	Analgesia, dysphoria, miosis
Delta (δ), DOP	Limbic system	Analgesia, reinforcing effects of opioids
NOP	Ubiquitous	Intervenes in the modulation of pain

- Opioid effects are primarily explained by binding to receptors located on neuronal cell membranes
- Four main types have been identified
- The mu opioid receptor is the best-studies and is associated with the rewarding effects of opioids

Chahl, 1996; Rang et al., 2007; Minami and Satoh, 1995; Atweh and Kuhar, 1983; Dhawan et al., 1996

Cellular actions of opioid receptors

- Opioid receptors are G-protein coupled receptors
  - Inhibits adenylate cyclase to reduce intracellular cAMP content
  - Chronic opioid use → reduced inhibition of adenylate cyclase
- Opioids also effect ion channels
  - Promotes opening of potassium channels
  - Inhibits opening of voltage-gated calcium channels
- The overall effect is inhibitory at the cellular level
  - Reduced neuronal excitability
    - Increased potassium conductance → hyperpolarisation
  - Reduced transmitter release
    - Inhibition of calcium entry
- However, opioids increase activity in some neuronal pathways, inhibiting excitation of inhibitory interneurons e.g. inhibition of GABA receptor

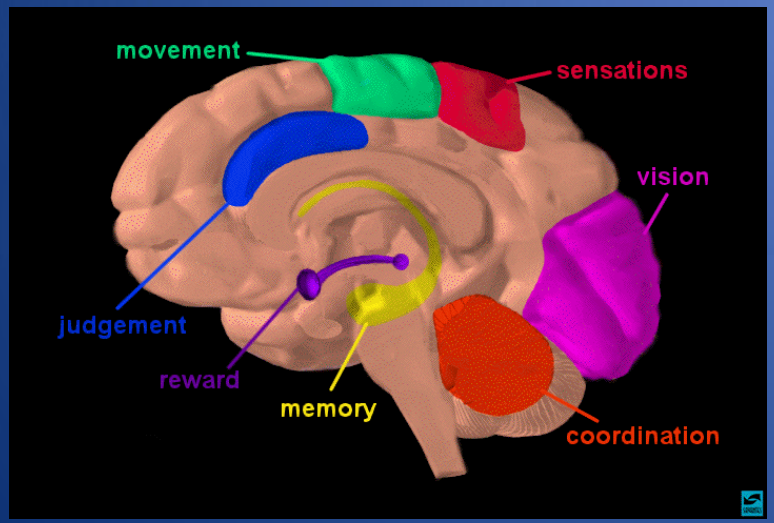
cAMP , cyclic adenosine monophosphate:
GABA, gamma-aminobutyric acid

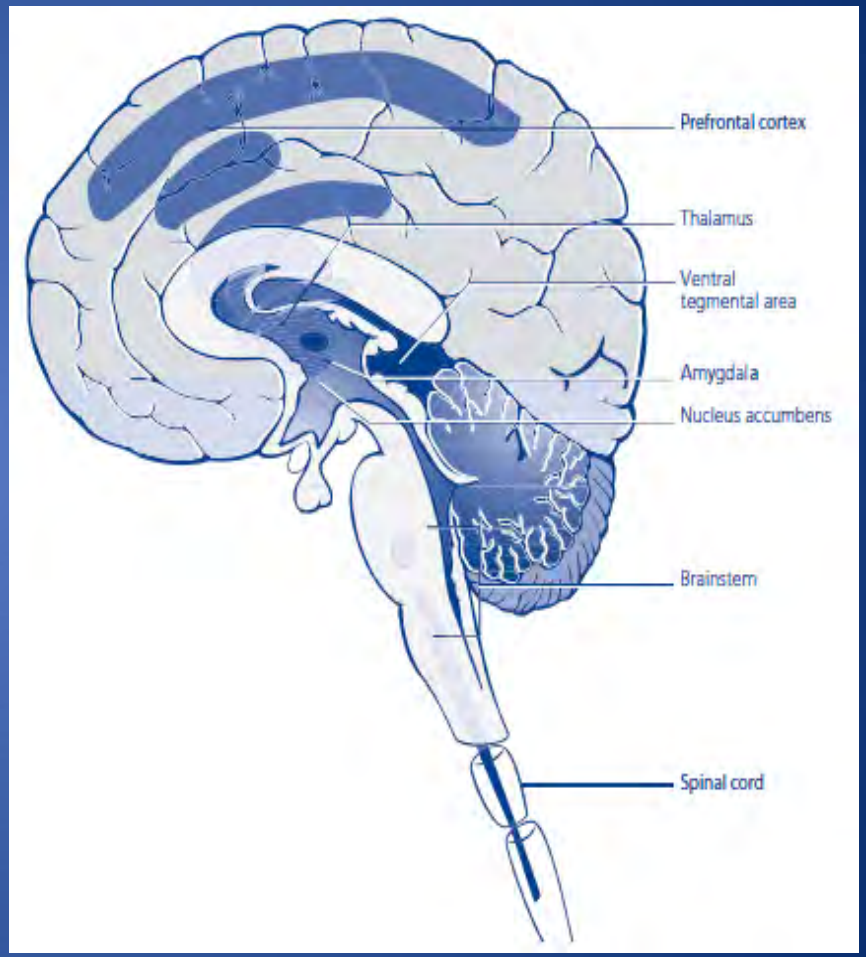
Chahl., 1996; Minami and Satoh, 1995; Atweh and Kuhar, 1983; Dhawan et al., 1996

Opioid sites of action and brain pathways

Opioid receptors are clustered in brain and spinal cord regions that modulate:

- Pain pathway: thalamus, brainstem, and spinal cord
- Reward pathway: ventral tegmental area, nucleus accumbens, and prefrontal cortex
- Emotional states and arousal: amygdala





Yaster et al., 2003; www.drugabuse.gov

The reward pathway

Opioids bind to opioid receptors in the nucleus accumbens (limbic region)

↓

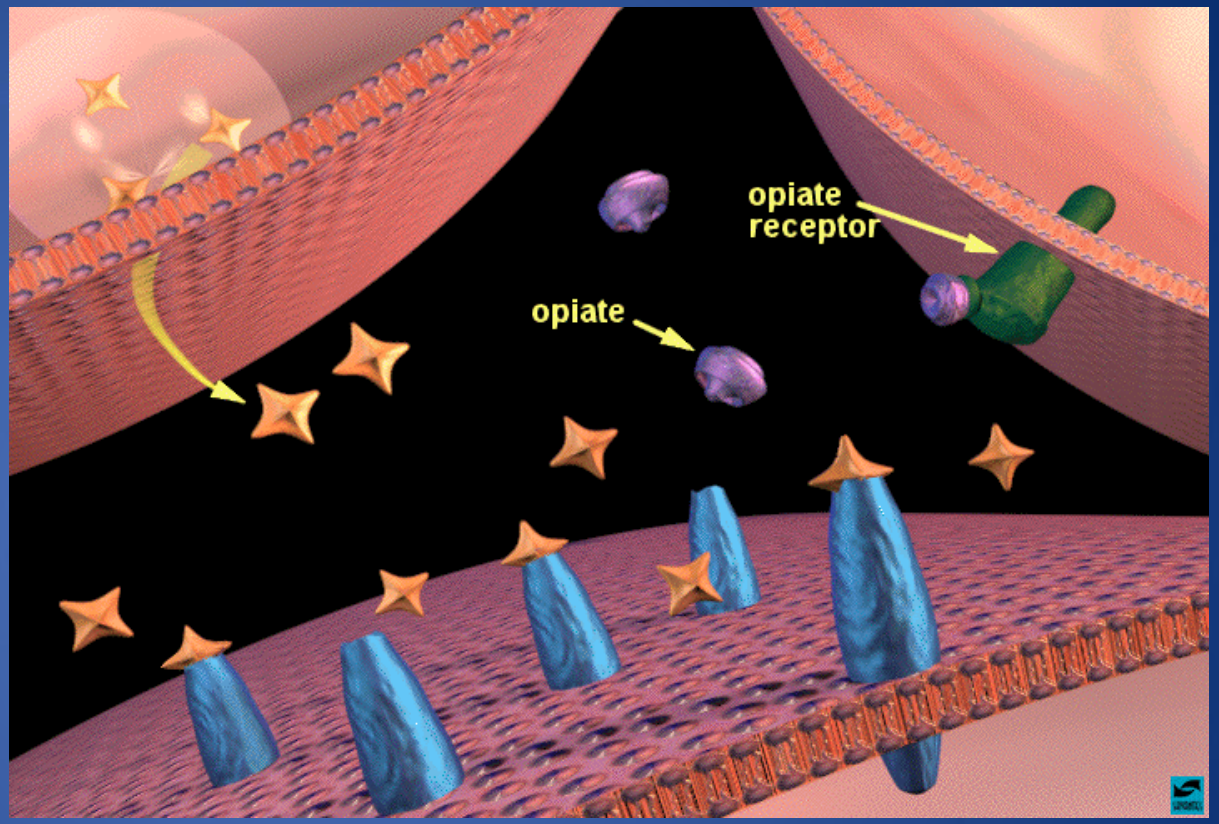
Decreases GABA

↓

Increased dopamine

&

Activation of reward pathway



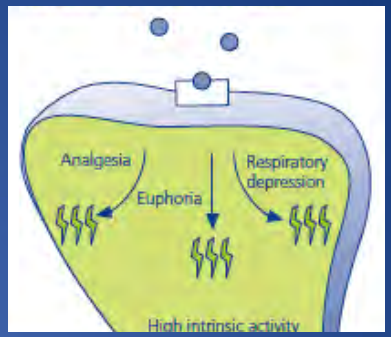
The illustration describes the action of the mu opioid receptor. This is a simplified model.

Moss and Dyer, 2010; National Institute on Drug Abuse (*http://www.drugabuse.gov/index.html*); Rang et al., 2007

Agonists and antagonists

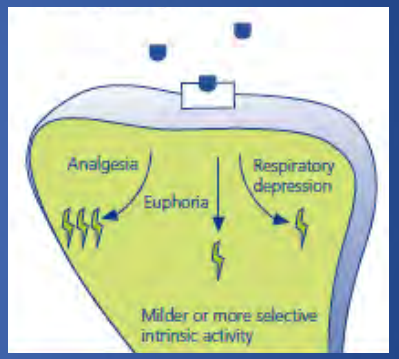
Full agonists

- Bind to a receptor and activate it fully



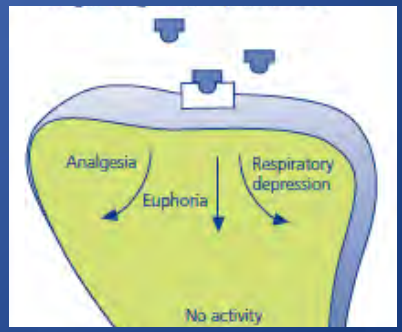
Partial agonists

- Bind to a receptor and activate it partially or in an attenuated way



Antagonists

- Bind to a receptor but do not activate it



Opioid classification

	Natural	Semi-synthetic	Synthetic
Full agonists	Morphine Codeine	Heroin Hydromorphone Oxymorphone Oxycodone	Fentanyl Methadone Propoxyphone
Partial agonists		Buprenorphine	Butorphanol
Antagonists		Naloxone Naltrexone Nalmefene	

Opioid effects

Euphoria	• Mediated through mu receptor • Degree can depend on psychological status and environment • Associated with the release of dopamine in the limbic region
Analgesia	• Inhibited neurotransmitter release from the spinal cord primary afferent terminals • Activation of descending inhibitory controls in the midbrain • Activity in the limbic region reduces the affective (mood) pain component
Respiratory depression	• Mediated through mu receptor • Dose dependent decrease in tidal volume and increase arterial CO_2 • Diminished sensitivity to rising CO_2; no depression of medullary centres
Nausea and vomiting	• Direct stimulation of chemoreceptor trigger zone in the medulla • Tolerance develops quickly
Gastro-intestinal tract	• Decreased gastric acid secretion, increased tone and reduced motility • Acetylcholine-mediated responses increased during withdrawal • Increase tone of sphincter muscles and decreased voiding reflexes
Histamine release	• Leads to bronchoconstriction and hypotension • Skin rash and itching
Pupil constriction (miosis)	• Centrally mediated stimulation of oculomotor nucleus • Important diagnostic feature of use/overdose (pin point pupils) • Tolerance does not develop

Jaffe and Martin, 1992

Summary of key points

- Opioids are drugs that have similar effects to opium
- Opioid receptors are widely distributed in the nervous system
- mu receptor activation produces direct opioid effects including euphoria
- Opioids promote the release of dopamine in the reward pathway (ventral tegmental area, nucleus accumbens, prefontal cortex)
- Opioids are classified as agonists or antagonists according to their intrinsic activity at different receptors

Tolerance and withdrawal

- Neuroadaptations in response to repeated opioid use over time lead to phenomena of tolerance and withdrawal

Tolerance	Withdrawal

• Continued use leads to diminished response to a given dose
• Increased dose needed to achieve the same level of effect
• Does not develop to the same degree or at same speed for different effects
  • May develop for anagelsia and euphoria
  • Does not develop for constipation or miosis
• Cross-tolerance normally seen within classes of the same drug
	• Continued use leads to physical dependence
	• Abstinence or reduced drug blood level results in withdrawal symptoms
	• Withdrawal symptoms are typically opposite of drug effects
	• Onset and duration of withdrawal syndrome will vary according to the opioid used
	  • More severe for full agonist vs partial agonist
	  • Longer duration for drugs with long half-lives
	• Reversible with opioid agonist

Meehan and Adelman, 2010; Newman, 1995

Symptoms and duration of heroin withdrawal

- Symptoms begin toward end of heroin effect (6h) and peak after 2 days
- The first symptoms include craving, negative mood states, excessive sweating, runny eyes and nose, and frequent yawning
- The heroin withdrawal syndrome is not normally life threatening, but can be risky when associated with other comorbidities
- Negative mood states and craving may persist for up to two years after abstinence

Autonomic symptoms	• Diarrhoea • Rhinorrhea • Diaphoresis, • Lacrimation • Shivering • Nausea • Emesis • Piloerection
Central Nervous System Arousal	• Sleeplessness • Restlessness • Tremors • Craving a
Pain	• Abdominal cramping • Bone pains • Muscle aching

Meehan and Adelman, 2010; Moss and Dyer, 2010; Rang et al., 2007

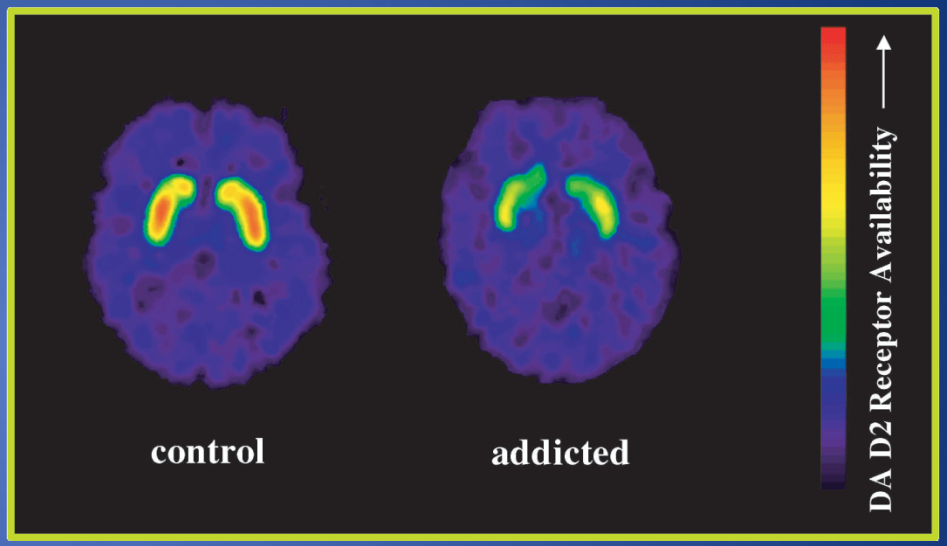
Cravings and relapse

- Even after withdrawal and sustained abstinence, long-term changes in brain responsivity are apparent
- Re-exposure to the drug or to environmental cues associated with the drug can trigger craving and relapse
- Drug- and cue-induced cravings are associated with activation of critical brain regions
  - Orbitofrontal cortex, nucleus accumbends, anterior cingulate, ventral tegmental area
- Relapse is recognized by treatment professionals as a part of the disease of substance dependence and should not be seen as a sign of treatment failure

Hommer, 1999; Volkow and Fowler, 2000

Compulsive drug-seeking

- Opioid dependence can cause drug-seeking behavior
- The brain's reward circuit has evolved to positively reinforce behaviors essential to survival
- Drugs of abuse, such as opioids, manipulate the reward circuit, causing the person to believe that they are necessary for survival



Positron emission tomography showing the effects of heroin dependence on brain dopamine D_2 receptors

Tomkins et al., 2003; Wang et al., 1997; Camí and Farré, 2003

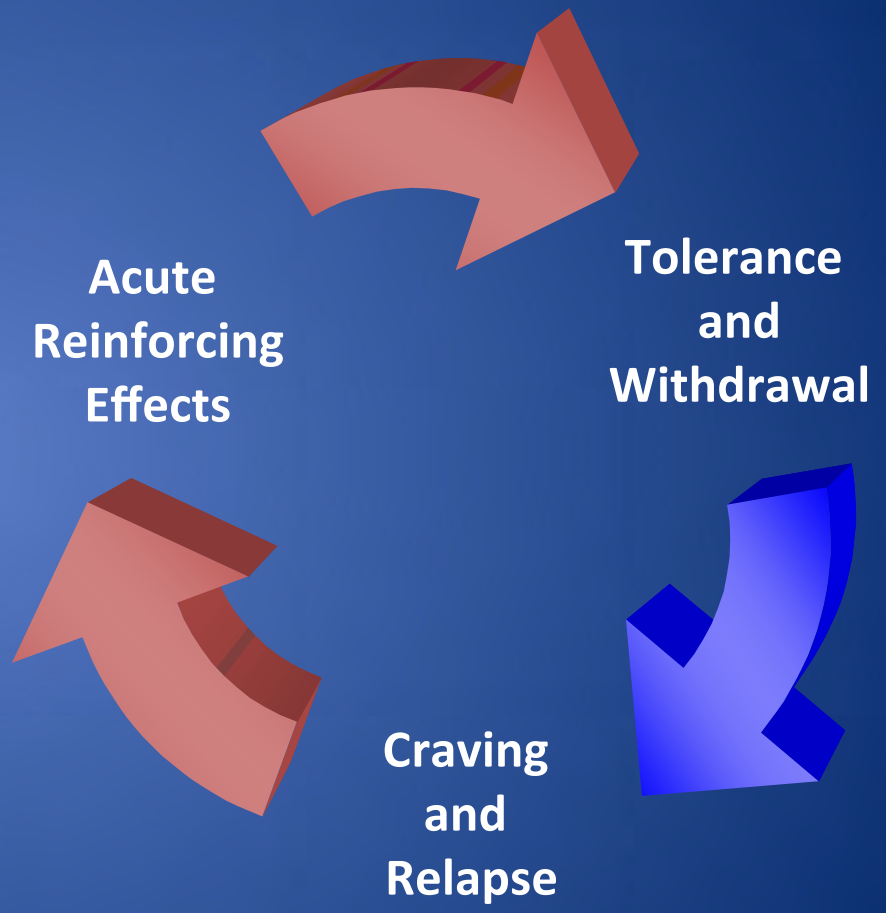
Risk factors for opioid dependence

- Patient populations most at risk include those with
  - A family history of opioid dependence or substance abuse
  - A continued need for opioid analgesics despite resolution of pain
  - Psychiatric disorders (depression, anxiety disorder, or bipolar disorder)
  - A history of recreational drug use
  - Easy access to prescription drugs among healthcare professionals
- Emerging research indicates that some patients may be genetically vulnerable to opioid dependence

Brooner et al., 1997; Center for Substance Abuse Treatment 2004; Kopsten and George, 2002; Yuferov et al, 2010

Stages of drug dependence

- Stage 1: acute rewarding drug effects mediated by dopamine release
- Stage 2: transition to addiction involving neuroadaptations to repeated use such as tolerance and withdrawal
- Stage 3: end-stage addiction and vulnerability to relapse mediated by enduring cellular changes and cravings



Koob and Le Moal, 2001; Kalivas and Volkow, 2005

Opioid dependence as a chronic brain disorder

- Two types of drug dependence:
  - Psychological – compulsion and craving
  - Physical – drug withdrawal syndrome

- Opioid dependence is considered a chronic, relapsing brain disorder associated with:
  - Pervasive changes in cognitive and drug-rewarding circuits of the brain
  - Significant alterations at the neurochemical, molecular, and cellular levels
  - Changes to the brain structure that persist after drug use has ceased
  - Compulsive drug-seeking and craving

World Health Organization; Cami and Farre, 2003; Moss and Dyer, 2010; Leshner,1997

Summary of key points

- Neuroadaptations that occur in response to chronic opioid lead to:
  - Tolerance: reduced effect of drug for a given dose
  - Withdrawal: emergence of withdrawal syndrome upon abstinence or reduced drug levels
  - Cravings and vulnerability to relapse
- Opioid dependence is a chronic, relapsing brain disorder
  - Relapse is a symptom of the disorder and not a sign of treatment failure

Training Programme on Opioid Dependence Treatment

Section B

Clinical assessment of opioid dependence

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

Learning objectives

- This section will provide an introduction to the clinical assessment of opioid dependence. By the end of this section you will be able to describe:
  - The therapeutic importance of patient assessment
  - Key components and methodologies for conducting patient assessments

Opioid abuse and dependence

- Drug dependence can be considered a chronic, relapsing disorder characterized by impulsive drug-seeking and by long-lasting chemical changes in the brain
- Key features are:
  - Chronic
  - Progressive
  - Relapsing
  - Impulsive
  - Continued drug use despite physical or psychological problems

Robinson and Berridge, 1993; O'Brien and McLellan, 1996; McLellan et al, 2000; American Psychiatric Association: DSM-IV-TR, 2000

Diagnosis and assessment

- Involves establishing a relationship between the patient and the treatment staff, based on free exchange of information
- Key components of the assessment include:
  - Past and current drug use
  - Determining the physical, psychological and social health-care needs of the patient
  - Other factors that may influence drug use, such as past treatment experiences, living conditions, legal issues, occupational situation, and social and cultural factors
  - Assessing the reasons for seeking treatment

World Health Organization Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, 2009

Substance abuse: definitions

DSM-IV: Substance abuse*	ICD-10: Harmful use†
A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring at any time in the same 12-month period: •Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home •Recurrent substance use in situations in which it is physically hazardous •Recurrent substance-related legal problems •Continued substance use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	A pattern of psychoactive substance use that is causing damage to physical or mental health; adverse social consequences are also common, but not sufficient to establish a diagnosis of harmful use.
In addition, the symptoms must never have met the criteria for substance dependence for the substance in question	

*American Psychiatric Association. Desk Reference to the Diagnostic Criteria from DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000;
†World Health Organization. Lexicon of alcohol and drug terms. Available at www.who.int. Accessed March 2010

Substance dependence: definitions

DSM-IV *	ICD-10 †
A maladaptive pattern of substance use leading to clinically significant impairment or distress. Three (or more) of the following, occurring at any time in the same 12-month period: • Tolerance • Withdrawal • Taking the substance in larger amounts or over a longer period than was intended • Persistent desire or unsuccessful efforts to cut down or control substance use • Spending a great deal of time in activities necessary to obtain, use, or recover from the substance • Giving up or reducing important social, occupational, or recreational activities because of substance use • Continued use despite knowledge of having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by the substance	A cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. Three or more of the following have been present together at some time during the previous year: • Strong desire or compulsion to take the substance • Difficulty controlling substance use (onset, termination, or levels of use) • A physiological withdrawal state when substance use is stopped or reduced • Evidence of tolerance (increased doses are required in order to achieve the effects originally produced by lower doses) • Progressive neglect of alternative pleasures or interests because of time spent to obtain, use, or recover from the substance • Persisting with substance use despite clear evidence of overtly harmful consequences

*American Psychiatric Association. Desk Reference to the Diagnostic Criteria from DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000;
†World Health Organization. Dependence syndrome. Available at www.who.int. Accessed March 2010

Signs of withdrawal or intoxication

- Signs of intoxication or withdrawal should be interpreted in combination with the stated time of last use
- Multi drug abuse is common, therefore it is advised to investigate intoxication by drugs other than opioids

Signs of opioid intoxication	Signs of opioid withdrawal
• Drooping eyelids • Donstricted pupils • Sedation • Reduced respiratory rate • Head nodding • Itching and scratching • Dry mouth and nose	• Yawning • Anxiety • Muscle aches and abdominal cramps, • Headache • Dilated pupils • Difficulty sleeping • Vomiting and diarrhoea • Piloerection (gooseflesh) • Agitation and restlessness • Myoclonic jerks • Delirium • Seizures • Elevated respiratory rate, blood pressure and pulse

World Health Organization Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, 2009

Examination of injecting sites

- Provides useful information on the timing and duration of injecting drug use
  - New injection marks are typically small and red, and are sometimes inflamed or surrounded by slight bruising
  - Old injection sites are usually not inflamed, but may show pigmentation changes (either lighter or darker), and the skin may have atrophied (appears sunken)
- A combination of recent and old injection sites would normally be seen in an opioid dependent patient with current neuroadaptation

World Health Organization Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, 2009

Infectious disease screening

- HIV, hepatitis C and common infectious diseases
  - Voluntary testing should be offered as part of an individual assessment
  - Counselling should be offered before and after the test
  - HIV testing should be encouraged in high prevalence areas
- Hepatitis B
  - Serology testing and vaccination for hepatitis B is recommended
  - In some circumstances it may be more effective to vaccinate before testing for hepatitis B and to use accelerated vaccination schedules
- TB and sexually transmitted diseases should also be considered during assessment

World Health Organization Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, 2009

Pregnancy

- Pregnancy testing should be offered to all women, particularly those contemplating opioid withdrawal, because it may influence the choice of treatment

World Health Organization Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, 2009

Psychiatric disturbance

- Comorbid mood disturbances and other psychiatric disorders are common
- Approximately 40–80% of opioid-dependent patients have a psychiatric co-morbidity
- Common disorders include depression, anxiety, antisocial and other personality disorders
- Acute mood disturbances (depressed mood, anxiety) are also apparent during opioid withdrawal

Dyer, 2005; Dyer et al., 2001; Jaffe, 2000; Pani et al., 2010

Urine drug screening

- Urine drug screening (or using another biological sample) should be routinely conducted at the start of treatment
  - Tests should be positive for opioids if the person is to be eligible for treatment
  - A negative urine drug screen in the absence withdrawal symptoms should prompt caution in the use of opioids and other sedative medication
  - Dependence should not be diagnosed on urine drug screening alone
- Interpretation of urine test results should account for the following factors
  - Knowledge of the specific commercial test or reagents used
  - False positives can [**be**] be caused by large amounts of poppy seeds.
  - Heroin is metabolised to 6-monoacetylmorphine (6-MAM), then to morphine and then to codeine; thus, 6-MAM is usually specific for recent heroin use
  - Morphine, with or without small amounts of codeine, can indicate either heroin or morphine use in the last few days
  - Small amounts of morphine in the presence of large amounts of codeine can suggest intake of high doses of codeine, since codeine can also be metabolized to morphine

World Health Organization Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, 2009

Standardised questionnaire tools

- Standardised questionnaires to measure drug dependence include:

- Severity of Opioid Dependence Questionnaire
  - Measures physical aspects of opioid dependence

- Severity of Alcohol Dependence Questionnaire
  - Measures physical aspects of alcohol dependence

- The Symptom Check List (SCL-90) and the General Health Questionnaire (GHQ)
  - Global assessment of mental health

Jarvis et al., 1994

Summary

- Drug dependence is a chronic, relapsing medical disorder characterized by impulsive drug-seeking and abuse and by long-lasting chemical changes in the brain
- A comprehensive assessment enables appropriate treatment planning
  - It should include drug use and dependence, physical and mental health status, and psychosocial functioning
- Ongoing assessment during treatment permits the evaluation of treatment effectiveness

Training Programme on Opioid Dependence Treatment

Section C

Maintenance pharmacotherapies: treatment principles and clinical application

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

Learning objectives

- This section will provide an introduction to opioid dependence. By the end of this section you will be able to describe:
  - The main principles, goals and strategies underlying medically-assisted approaches to opioid dependence treatment
  - The unique pharmacological profiles of methadone, buprenorphine and buprenorphine-naloxone and how each of these treatment options can be used to treat opioid dependence
  - The main efficacy and safety considerations that are relevant to the choice of treatment strategy

Treatment principles, goals and strategies

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

Basic principles of medically-assisted treatment

- Opioid dependence is a chronic and relapsing medical disorder with a well-established neurobiological basis
- The status of opioid dependence as a chronic medical condition is endorsed by the WHO
  - Buprenorphine and methadone on essential medications list
  - Medical use of treatments is indispensable
  - Medical, economic and social benefits
  - Treatment works and is evidence-based
  - Controls during treatment should NOT restrict availability
  - Access to essential medicines is a fulfilment of the human right to health (International law)
  - Joint initiatives involving WHO, UNODC, UNAIDS, AUSAID

WHO, World Health Organization; UNODC, United Nations Office on Drugs and Crime; UNAIDS, United Nations Programme on HIV and AIDS; AUSAIDS, Australia's AIDS Program; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome

Fiellin et al., 2006; Davies et al, 2009; Gowing et al, 2001; World Health Organization, 2009

Fundamental principles of drug dependence treatment (Part 1 of 2)

1. Drug dependence is a complex but treatable disorder affecting brain function and behaviour
2. No single treatment is appropriate for everyone
3. Treatment needs to be readily available
4. Effective treatment attends to multiple needs of the individual, not just drug abuse
5. Remaining in treatment for an adequate period of time is critical
6. Behavioural/counselling therapies are critical components of the treatment process
7. Pharmacotherapy (e.g., methadone, buprenorphine or buprenorphine-naloxone), especially in combination with psychosocial therapy, is proven to help opioid users stabilise their lives and reduce drug use

National Institute of Drug Abuse, 2009

Fundamental principles of drug dependence treatment (Part 2 of 2)

8. An individual's treatment plan must be continually assessed and modified to ensure it meets his or her changing needs
9. Patients with concomitant mental disorders should receive treatment for these underlying disorders as well
10. Medical detoxification must be followed by some type of maintenance or stabilisation treatment to change long term drug use
11. Patients should be monitored during treatment for continuing drug use
12. Treatment programmes should also encompass therapy for concomitant infections such as HIV and hepatitis C

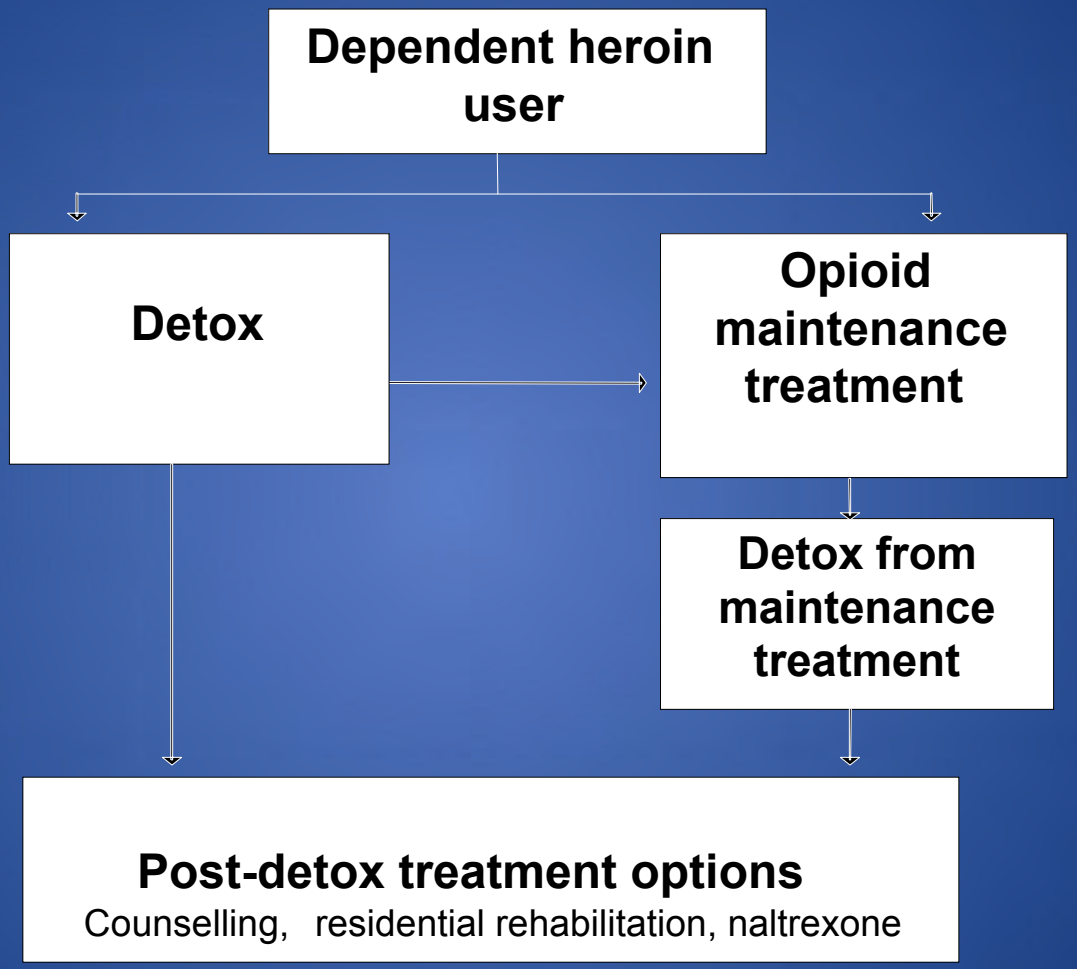
National Institute of Drug Abuse, 2009

Objectives of treatment for opioid dependence

- To reduce harm arising from opioid use to individuals and community, by reducing:
  - Harms to the individual
    - Opioid use
    - Infectious disease transmission
  - Harms to society
    - Health problems and health service costs
    - Opioid-related mortality
    - Crime
    - The negative psychosocial impact of drug dependence

Maremmani, 2010; Mattick et al., 2009; World Health Organization, 2009

Treatment pathways for heroin dependence



Gowing et al., 2001; Maremmani, 2010; Marlatt and Gordon, 1985; World Health Organization, 2009

Agonist maintenance treatment options

- Agonist maintenance therapies
  - Primary options: methadone, buprenorphine, buprenorphine-naloxone
  - Infrequently used: heroin, slow release morphine, codeine
- Maintenance treatment is more effective than:
  - No treatment
  - Drug-free counselling and rehabilitation
  - Placebo medication
  - Detoxification / medical withdrawal
- Evidence of effectiveness in reducing harm
  - Reductions in heroin use, criminality, morbidity, mortality and spread of blood borne diseases
  - Treatment is evidence based (e.g., Cochrane library)
  - An abundance of evidence exists on positive outcomes

Davies et al., 2009; Gowing et al., 2001; Mattick et al., 2009; World Health Organization, 2009

Detoxification and naltrexone

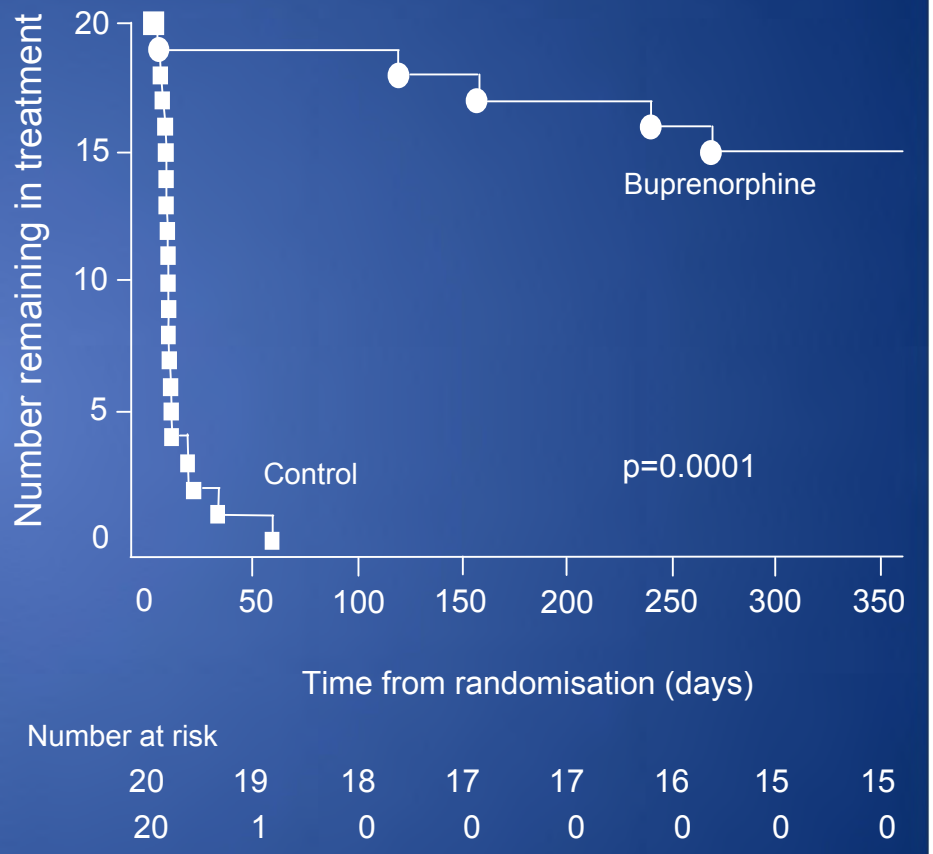
- Detoxification/medical withdrawal
  - Heroin/methadone dose reduction
  - Clonidine/lofexidine (withdrawal suppressants)
  - Benzodiazepines
  - Ultra-rapid detox (sedation/anaesthesia + opioid antagonist)
  - Herbal/local medicines

  Detoxification alone does not improve outcomes compared with not entering treatment (Mattick et al., 2009)
- Naltrexone (antagonist) maintenance
  - With/without naltrexone long term outcomes the same (90–95% relapse)

Gowing et al., 2001; Mattick et al., 2009; World Health Organization, 2009

Maintenance versus detoxification

- 40 subjects randomised :
  - 20/20: 1-week detox/1-year buprenorphine maintenance
  - Cognitive behavioural therapy + counselling for 1 year
- Heroin use
  - Placebo = all relapsed
  - Buprenorphine maintenance = 75% retention + opiate negative
- Mortality (p=0.015)
  - Placebo 4/20 (20%)
  - Buprenorphine maintenance 0/20



Kakko et al., 2003

Properties of maintenace pharmacotherapies

- Properties of drugs that are suitable for use as maintenance therapy are [WHO/UNODC/UNAIDS position paper 2004]
  - Opioid properties in order to prevent withdrawal symptoms and reduce craving
  - Affinity for opioid receptors in the brain in order to diminish or blockade the effects of heroin or other opioids
  - Longer duration of action than abused opioid drugs to delay the emergence of withdrawal and reduce the frequency of administration
  - Oral administration to reduce the risk of infections associated with injections

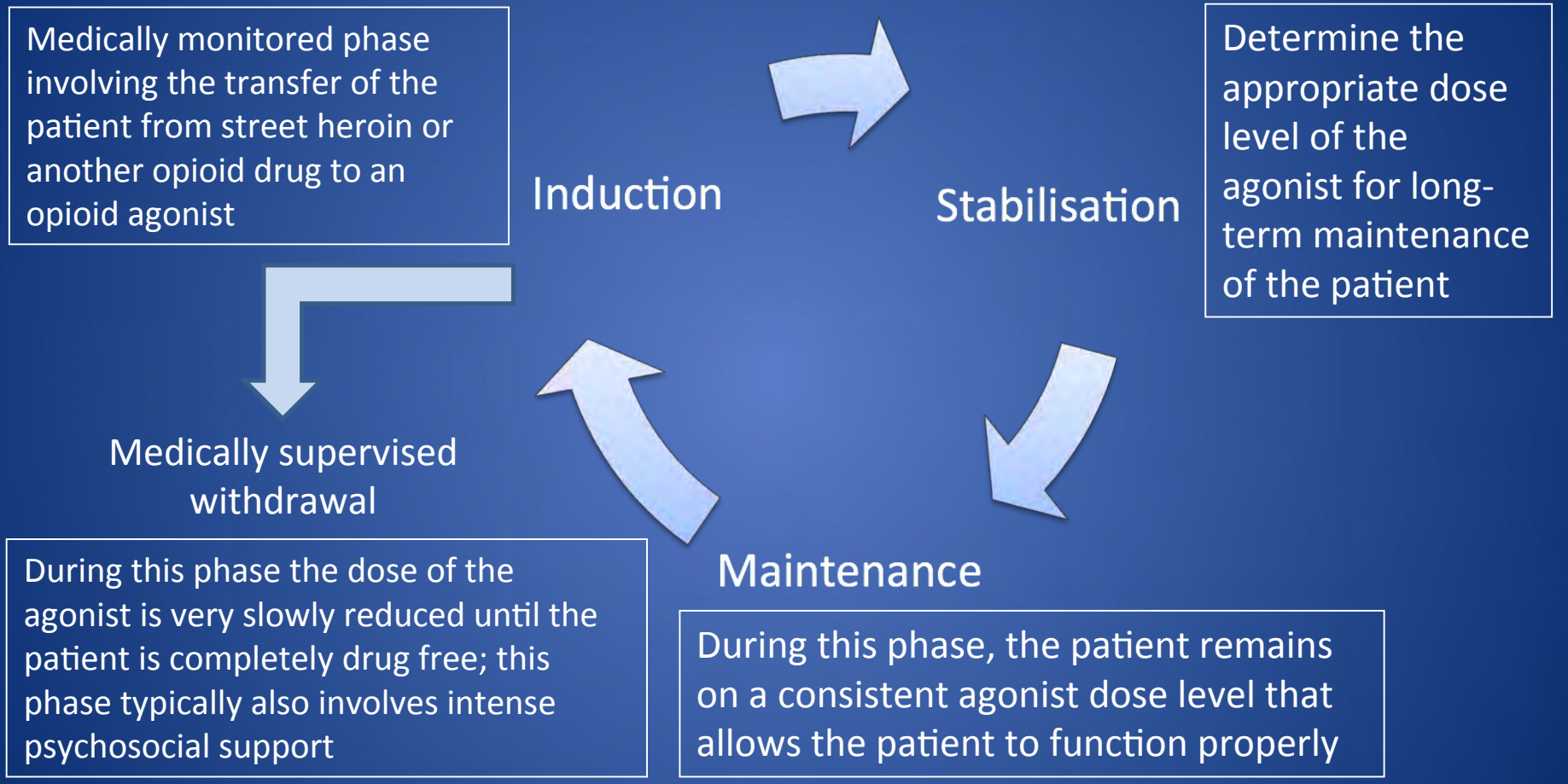
World Health Organization; United Nations Office on Drugs and Crime; United Nations Programme on HIV and AIDS 2004

Principles of effective maintenance treatment for individual patient outcomes

- Long duration of treatment
- Adequate doses of medication
- Psycho-social support of the patient
- Regular review, monitoring and support
- Quality of therapeutic relationship
- Attend to co-morbidities

Maremmani et al., 2010; Mattick et al., 2010; World Health Organization, 2009

Phases of treatment



Gowing et al., 2001; Mattick et al., 2009; World Health Organization, 2009

Adjunct treatment

- Facilitating access to additional psychosocial services can assist in responding to the broader aspects of addiction
  - Referral to vocational, financial, housing and family assistance can improve treatment outcome
  - Access to counselling services can assist with greater retention in treatment and reduced illicit drug use
  - Motivational Interviewing and Social Skills Training have been associated with improved methadone treatment outcome

Henry-Edwards et al., 2003; Jarvis et al., 1995; Ward et al., 1998

Summary

- Opioid dependence is a medical condition with complex biological, sociological and individual determinants
- Effective treatment
  - Is accessible for as many people as possible
  - Involves a set of pharmacological and psychosocial interventions
  - Aims to reduce or cease opioid use; prevent harms associated with opioid use; improve quality of life for the patient and benefit the wider community
- Opioid agonist maintenance treatment is the most cost-effective form of treatment
  - Primary options are methadone, buprenorphine and buprenorphine-naloxone
  - Access to psychosocial interventions can significantly enhance success
- The benefits of maintenance programmes increase the longer the person remains in treatment
  - For many people they may need to receive treatment for a number of years

Methadone:
Pharmacology and Clinical Application

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

Methadone pharmacology

- Synthetic mu receptor agonist with similar affinity to heroin
- Well absorbed orally (40–100% bioavailability)
- Long acting: effects for 20–40 hrs (t½=13–35 hrs)
  - Onset effects: 0.5–2 hrs
  - Peak: ~2–4 hrs after dose
- In general, plasma methadone concentrations rise for 3–4 hrs following oral ingestion and then decline gradually
- Time to reach stabilisation: 3–10 days

Dyer et al., 1999; Henry-Edwards et al., 2003; Mitchell et al., 2006

Methadone safety

- Most patients will not experience significant side effects
  - No damage to any major organs or systems of the body
  - Tolerance will develop such that cognitive skills and attention are not impaired
  - Tolerance will not fully develop to some symptoms (e.g., constipation, sexual dysfunction, miosis and occasionally increased sweating), but these may become less with time
- The primary hazard is the risk of overdose, particularly in the absence of opioid tolerance and in combination with other sedatives

Dyer and White, 1997; Henry-Edwards et al., 2003

Methadone dose considerations

- In heroin dependent individuals
  - 20–50mg prevents withdrawal
  - >60mg is usually needed to block effects of additional heroin use

- In non-tolerant / opiate naïve people
  - 1 dose of 20mg can kill a child
  - repeated doses 30–40mg can kill an adult
  - 1 dose 70mg can kill an adult

Henry-Edwards et al, 2003

Pharmacokinetic drug interactions with methadone

- Metabolized by CYP 3A4, 2B6, 2D6 to EDDP (inactive)
- Other drugs that inhibit these enzymes will increase methadone plasma levels
- Other drugs that induce these enzymes will reduce methadone plasma levels & can cause withdrawal

CYP, cytochrome; EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene

Henry-Edwards et al, 2003; McCance-Katz et al., 2010

Assessment for methadone treatment

- A comprehensive assessment should be conducted and documented

- Specific attention should be directed to:
  - Opioid and other drug use, current and past
  - Health and psychosocial status
  - Past treatment experience
  - Motivation for treatment and stage of change
  - Physical examination
  - Urine drug analyses and investigations for HIV and hepatitis B/C

HIV, human immunodeficiency virus

Henry-Edwards et al., 2003; Maremmani, 2010; World Health Organization, 2009

Induction to methadone treatment

- Primary objectives are to retain in treatment by reducing the signs and symptoms of opioid withdrawal and ensuring patient safety

- First dose
  - Determined on basis of level of opioid tolerance
  - A dose of 20mg for a 70kg patient can be presumed safe
  - Caution should be exercised with doses of 30mg or more
  - Extreme caution and specialist involvement is advisable for 40mg or more

Henry-Edwards et al., 2003; Ward et al., 1998

Induction to methadone treatment

- Stabilisation on a daily methadone dose can be achieved over first two weeks
- Patients should be observed daily prior to dosing
  - Assess for signs of intoxication or withdrawal
- Consider dose increments of 5–10mg every 1–3 days subject to assessment

Henry-Edwards et al., 2003; Ward et al., 1998; World Health Organization, 2009

Induction to methadone treatment: transfers from other pharmacotherapies

- Transfer may be appropriate when another therapy has failed
- Seek specialist advice if patient transferring from pharmacotherapies with which you are unfamiliar
- Buprenorphine
  - Patients should be stabilised on 16mg/day or less
  - Commence methadone 24h after last buprenorphine dose
  - Initial methadone dose should not exceed 40mg
- Naltrexone
  - Do not administer methadone for at least 72h after last naltrexone dose
  - Treat as if the patient opioid naive

Henry-Edwards et al., 2003; Ward et al., 1998

Safe methadone induction

- Induction: usually commence 20–30mg initial dose
- Only increase dose after review of patient
  - Increase by 5–10mg every 2–3 days as required
  - Do not increase by more than 30mg/week
- Greatest risk period for methadone overdose is first 2 weeks of treatment: typically days 3–7
- Usually takes 2–6 weeks to reach maintenance dose
- Maintenance dose: 60–120mg optimal dose for most patients
- Supervised dosing recommended

Methadone maintenance dosing

- Doses should be individually determined to alleviate withdrawal without significant opioid effect
  - Methadone doses in excess of 60mg/day are associated with higher retention rates and less heroin us
    - A daily methadone dose of 60mg/day or greater should be sufficient to ensure a substantial level of tolerance to effects of heroin in the majority of individuals
  - Maintenance doses higher than 120mg/day may be necessary for some patients, but there is no evidence that doses above this level produce additional benefits for the majority of patients
  - Similarly, doses less than 60mg/day may be sufficient for some patients

Caplehorn et al., 1994; Dyer et al., 1999; Henry-Edwards et al., 2003

Methadone maintenance dosing

- Patient input to determination of maintenance dose level can enhance the therapeutic relationship
  - Identify a maintenance dose that alleviates opioid withdrawal without producing euphoria
- Daily administration of methadone is required to ensure plasma levels are maintained
- Monitoring other drug use during maintenance treatment improves clinical management and treatment outcome

Henry-Edwards et al., 2003; Ward et al., 1998

Responding to missed methadone doses

- Patients who miss their daily methadone dose may be engaging in other drug use or are at risk or leaving treatment
- When methadone is missed for 3+ days, tolerance will be significantly reduced
- Following schedule can be considered:
  - 1 day – no change in methadone dose required
  - 2 days – if no evidence of intoxication administer normal dose
  - 3–4 days – assess patient and administer 50% dose
  - 5+ days – regard as a new induction to methadone

Henry-Edwards et al., 2003; Ward et al., 1998

Cessation of methadone treatment: voluntary withdrawal from methadone

- The length of time in treatment predicts improved outcome
  - Patients should be encouraged to remain in treatment for at least 12 months to achieve enduring lifestyle changes
  - Some patients may need to be retained on methadone for considerably longer periods
- Withdrawal should be completed slowly and safely
  - Reduce dose by 10mg/week to a level of 40mg/day, and then reduce by 5 mg/week
- Positive psychosocial function and participation in supportive aftercare can reduce the risk of relapse

Henry-Edwards et al., 2003; Ward et al., 1998

Cessation of methadone treatment: transfer to buprenorphine

- Buprenorphine has higher affinity for mu receptors
- Patients on low methadone doses (<30mg/day) can be transferred to buprenorphine with minimal discomfort
  - Patients on higher methadone doses may find that buprenorphine precipitates opioid withdrawal
- Administer buprenorphine at least 24h after last methadone dose
  - It is strongly recommended that the patient be in moderate withdrawal before commencing on buprenorphine
  - Delaying first buprenorphine dose until signs of withdrawal reduces risk of precipitated withdrawal

Henry-Edwards et al., 2003; Rang et al., 2007; World Health Organization, 2009

Buprenorphine: Pharmacology and Clinical Application

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

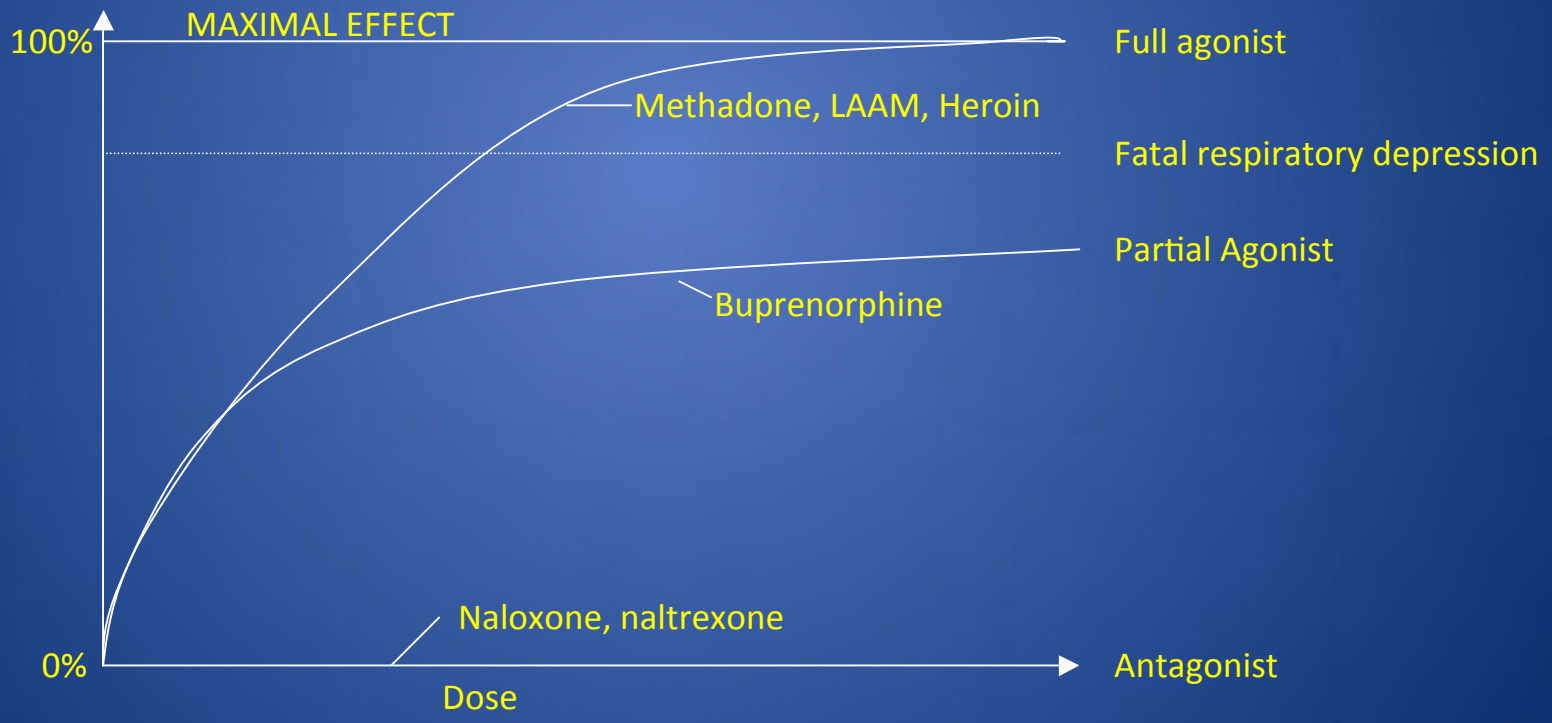
Buprenorphine pharmacology

- Mu receptor partial opioid agonist, kappa receptor antagonist
- High mu receptor affinity and receptor occupancy:
  - Up to 95% at 16mg (Greenwald et al, 2003)
    - Methadone shown to bind to <30%
  - Blockade or attenuated effect of additional opioids
  - Can result in precipitated withdrawal
- Lower intrinsic activity than full agonists:
  - Favourable safety profile (ceiling effect on respiratory depression)
  - Less physical dependence and limited development of tolerance
- Long duration of action (slow dissociation)
  - Longer duration of action
  - Milder withdrawal

Lintzeris et al., 2001; Rang et al., 2007; Walsh, 2003

Respiratory depression: agonists, partial agonists and antagonists

Death by overdose a major problem for heroin and methadone



Buprenorphine efficacy: no ceiling effect

- Higher doses of buprenorphine result in increasing effectiveness
  - Reduced heroin use demonstrated by urine toxicology
  - Improved retention rates
  - Reduced withdrawal and craving

Greenwald et al., 2007; Di Petta and Leonardi, 2005; Ling et al., 1998; Kamien et al., 2009

Optimum use of buprenorphine

- Induction principles and guidelines:
  - Aim to avoid precipitated withdrawal
    - Not to avoid toxicity as for methadone
  - To prevent withdrawal with buprenorphine
    - Administer 1st dose when objective signs of withdrawal are present:-
      - 4-6hrs after last heroin use
      - >24hrs after last low dose methadone use
      - >36hrs after last medium methadone dose
  - Dose titration (start high, go fast):-
    - Initial test dose (2–4mg) then more Day 1
    - Rapid dose increases, target dose by Day 3
    - Optimal dose range 12–24mg
    - Contrast start low, go slow with methadone

Lintzeris et al., 2001; Mattick et al., 2009; World Health Organization, 2009

When does buprenorphine-precipitated withdrawal occur?

- Generally commences 30–90 min after 1st dose
- Generally peaks within 90–180 min after 1st dose
- Minor symptoms may continue after 2nd or 3rd dose
- Symptoms may also persist with continued heroin/opioid use
- Key factors affecting precipitated withdrawal
  - Time since last opioid use
  - Dose of last opioid
  - Dose of buprenorphine

Lintzeris et al., 2001

Pharmacokinetic drug interactions buprenorphophine

- Metabolised by CYP3A4 to norbuprenorphine (active but does not cross blood brain barrier)
- Drugs that inhibit/induce CYP3A4 can theoretically affect buprenorphine levels, but usually not clinically significant due to safety profile of buprenorphine and high opiate receptor affinity
- Buprenorphine is a weak inhibitor of CYP3A4 (rarely clinically active)

CYP, cytochrome

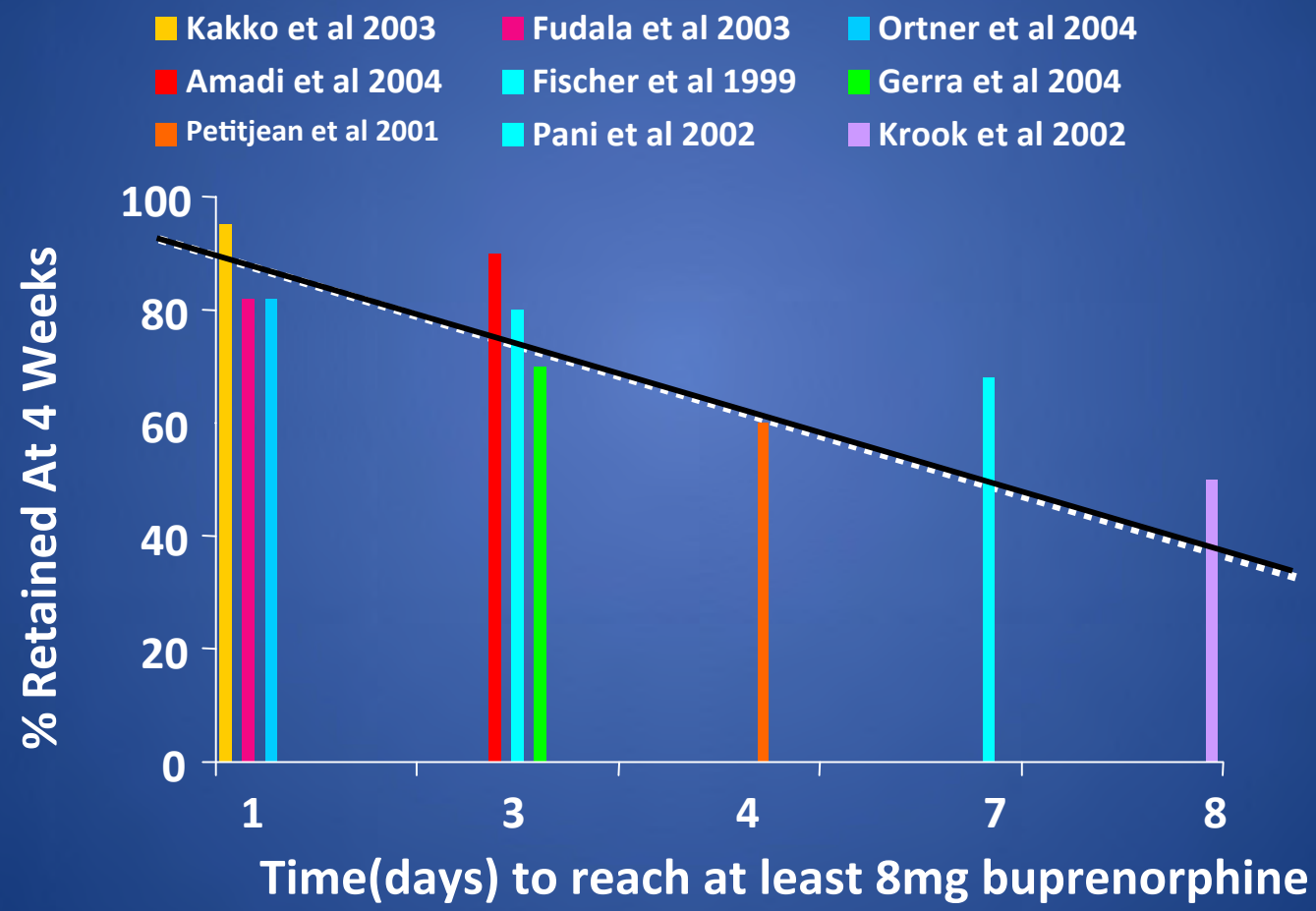
Lintzeris et al., 2001; Rang et al., 2007; Walsh, 2003

Buprenorphine induction

- Control physical withdrawal symptoms associated with opioid dependence as quickly as possible
- Begin counselling discussions so patient can prepare for transition to stabilization and maintenance phase
- Buprenorphine induction should proceed rapidly and should reach doses of approximately 12–16 mg within 2 to 4 days

Doran et al., 2005; Lintzeris et al., 2001

Faster buprenorphine induction improves early treatment retention and higher doses reduce craving



Stabilization and maintenance

- Find the appropriate daily dose
  - Dose to clinical effect
    - Achieve reduction / elimination of street heroin use
  - Titrate up or down by 2 to 4mg at a time to find appropriate dosage
  - Recommended target stabilization dosage:
    - 12 to 24mg/day

McLellan et al., 2005; Lintzeris et al., 2001

Transferring between pharmacotherapies

- Based on the scientific literature and clinical experience, the most safe and efficacious treatment model for opioid dependence involves initiating therapy with buprenorphine or buprenorphine-naloxone. This leads to two scenarios:
  - Increasing the dose until a satisfactory clinical effect and well-being of the patient is achieved (stabilisation)
  - Increasing the dose until the maximum dose is achieved without reaching a satisfactory clinical effect and patient well-being; in this case, transfer to methadone should be considered according to the criteria for methadone induction.

Induction from low dose (<40mg) methadone

- Reduce methadone dose to as low as possible
- Cease methadone and commence buprenorphine at least 24h after last methadone dose
  - Preferably wait for signs of early opioid withdrawal
  - Commencement dose between 2 and 4 mg
  - Second day dose between 4 and 8 mg
- Maintain good communication with patient
- Review patient prior to each dose during induction

Lintzeris et al., 2001

Induction from >40mg methadone

- Consider transfer if methadone patient cannot reduce dose below 40mg without instability
- Cease methadone and delay buprenorphine until patient experiences significant opioid withdrawal
  - Generally 2–4 days after last methadone dose
- First dose of 4mg buprenorphine
- Review patient after 3–4 hours:
  - If worsening of withdrawal, provide symptomatic medication
  - If no worsening of withdrawal, provide a further 2–4mg of buprenorphine
- Titrate buprenorphine dose according to response on previous day
  - Usually increase to 6–10mg

Lintzeris et al., 2001

Alternate day dosing

- Buprenorphine dose increases result in increased duration of effects, allowing 48–72 hours between doses
- Not all clients can be stabilised on alternate day dosing
  - Withdrawal discomfort prior to dosing
  - Erratic attendance or requiring regular supervision
- Consider regular days of the week to reduce confusion
  - E.g., Monday – Wednesday – Friday – Saturday
- Attempt after period of stabilisation
- 48 hour dose = 2 x 24 hour dose to a maximum of 32mg
- 72 hour dose = 3 x 24 hour dose to a maximum of 32mg

Lintzeris et al., 2001

Missed buprenorphine doses

- Patients who have missed less than 5 consecutive days must be reviewed prior to dosing
  - If usual 24 hour dose is >8mg, recommence at 8mg
  - If usual 24 hour dose is 68mg, recommence at 4mg
  - If usual 24 hour dose is 2–4mg, recommence at 2mg
- If recommencing a patient after more than 5 days missed doses, recommence on a lower dose (not more than 8mg)

Lintzeris et al., 2001

Health considerations

- Analgesia
  - Non-opioid analgesics or temporary increase in buprenorphine dose are appropriate
- Overdose
  - Buprenorphine is very unlikely to result in overdose
  - Buprenorphine overdose can be reversed with very high doses of naloxone (e.g., 10–15mg)
- Pregnancy
  - The use of methadone and buprenorphine are recommended for opioid pregnant women (MOTHER Trial; unpublished)
  - Do not attempt transfer from methadone to buprenorphine during 1st or 3rd trimester due to risk of precipitated withdrawal

Lintzeris et al., 2001

Medical withdrawal from buprenorphine

- Decision is made by therapeutic team
  - Physician, counselor, patient
- Physician-supervised, slow taper is recommended
  - Better outcomes are achieved with a more gradual reduction
  - Even with a slow taper, reducing the dose past 4mg or 2mg can be difficult
  - If patient feels at risk for relapse, patient can be restabilised
  - Can return to OMT at any time during taper
  - Relapse rates are higher regardless of taper schedule
- Psychosocial counselling should continue and possibly be increased during and after medical withdrawal

Amass et al., 1994; Ling et al., 2009; Becker et al., 2001

Summary: Buprenorphine dose effects

- In heroin dependent individuals
  - 4–8mg prevents withdrawal; >12–24mg for heroin blockade
- Duration of effects: dose-dependent
  - 10mg for 24hrs / 20mg for 48hrs / 30mg for 72hrs
  - No increase in sedation with 2–3x daily dose
- Precipitated withdrawal is possible when there are high levels of circulating opioids
  - Within 3–6 hours of heroin use
  - Within 24 hours of moderate methadone dose (>30mg)
- Transition to buprenorphine
  - Easier from short-acting opioids
  - Easier from lower level of physical dependence
  - Easier if patient is already in withdrawal

Buprenorphine-Naloxone: Pharmacology and Clinical Application

Europad
European Opiate Addiction Treatment Association

AU CNS
FROM SCIENCE TO PUBLIC POLICY

World Federation for the Treatment of Opiod Dependence

Naloxone pharmacology

- Antagonist at mu opioid receptor
  - Blocks actions of most opioids
  - Reverses overdose
  - Precipitates withdrawal (in opioid dependent subjects)
- Not orally available
  - Very poorly absorbed sublingually
- Rapid access to mu receptors (administered intravenously)
- Relatively quick receptor dissociation
  - Short half-life (approx 45 mins)
- Mu receptor affinity:
  - Buprenorphine>naloxone>methadone>heroin

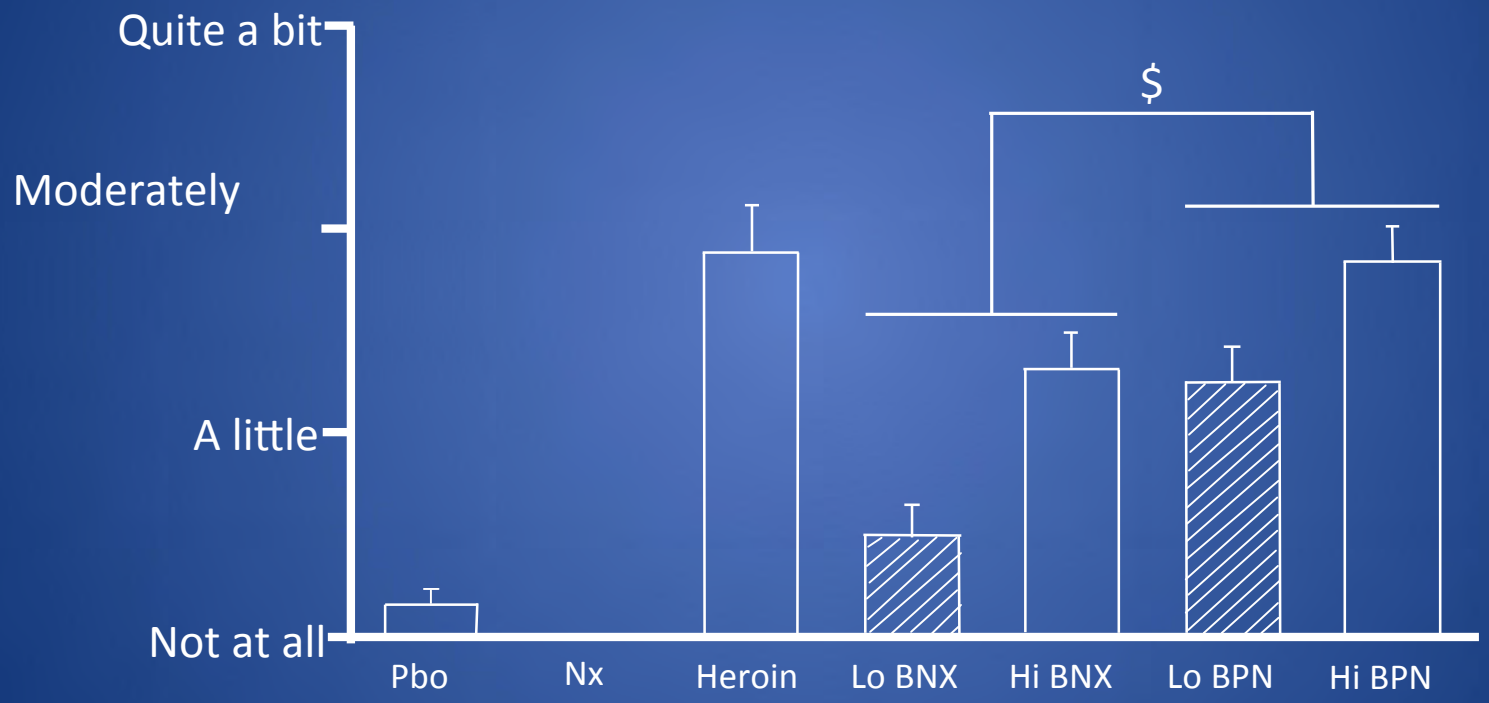
Rang et al., 2007; Walsh, 2003

Buprenorphine-naloxone pharmacology

- Sublingual tablet preparations designed:
  - Buprenoprhine-naloxone: 2mg/0.5mg and 8mg/2mg
- Sublingual administration:
  - Naloxone does not compromise buprenorphine absorption
  - Buprenorphine time of onset and time of peak effect unaltered
  - Duration of buprenorphine action unaltered by naloxone
  - Naloxone plasma levels undetected at 8/2mg dose
- Intravenous administration:
  - Precipitates withdrawal in opioid dependent individuals
  - Blocks the effect of buprenoprhine
- Primary rationale and benefits of combination:
  - Discourages diversion and intravenous use of prescribed medication
  - Reduces abuse potential and street value
  - Allows for safer take-home dosing

Strain et al., 2004

Reduced abuse liability for buprenorphine-naloxone vs. buprenorphine

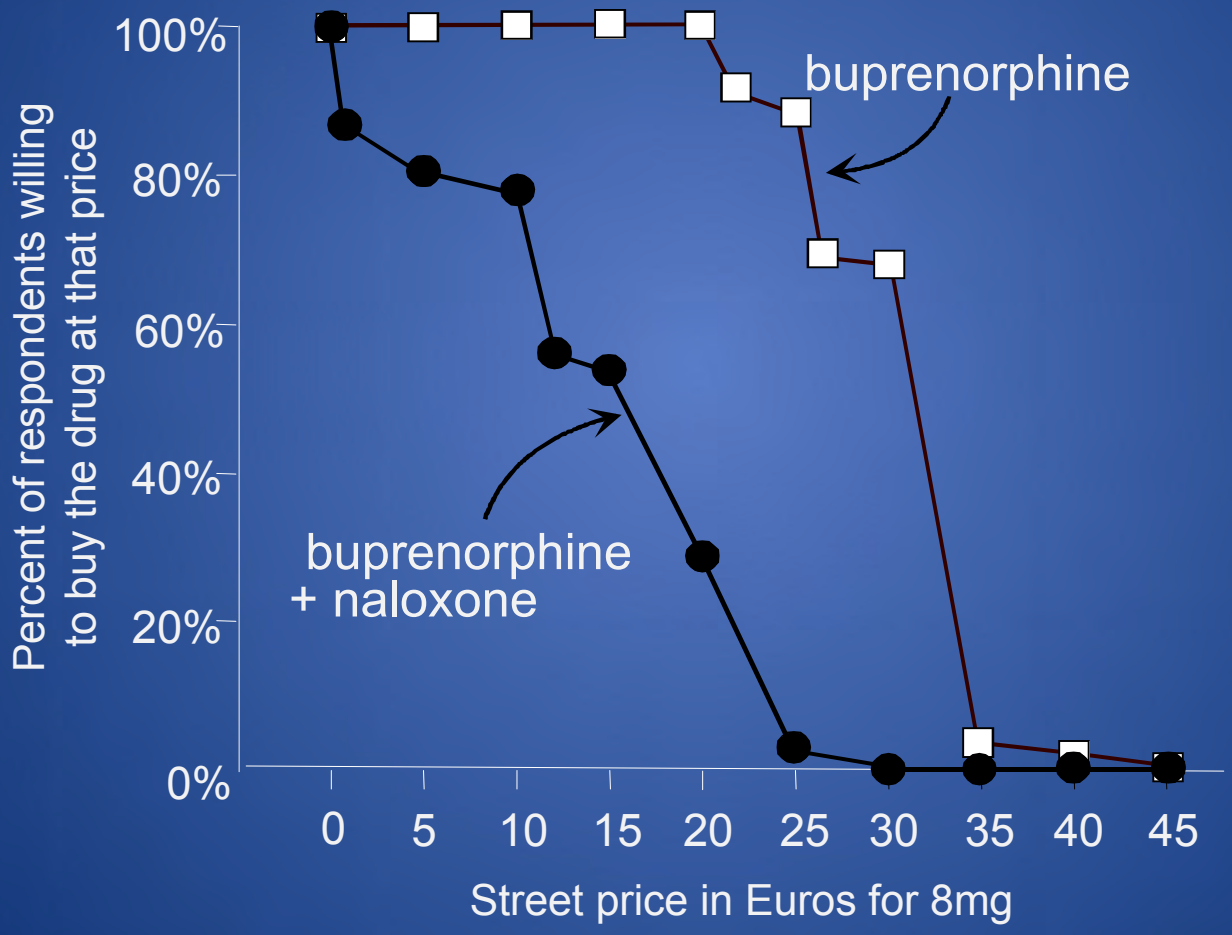


$ Significant difference between BNX and BPN (p=0.0001)

BNX, buprenophine-naloxone ;BPN, buprenorphine

Comer et al.. 2010

Reduced abuse liability for buprenorphine-naloxone vs buprenorphine



Alho et al.. 2007

Direct buprenorphine-naloxone induction from short-acting opioids

- Multiple open-label, randomised clinical trials have now established that direct induction with buprenoprhine-naloxone from short-acting opioids is safe and effective
  - NIDA CTN studies: CTN 001/002 comparing buprenoprhine-naloxone vs. clonidine for detoxification
    - Most patients (83%) received 8 mg buprenorphine-2 mg naloxone on the first day
    - 90% successfully completed induction and reached a target dose of 16mg buprenorphine-4 mg naloxone in 3 days
  - NIDA CTN 003 comparing buprenoprhine-naloxone vs clonidine for detoxification
    - Significantly more patients on buprenorphine-naloxone were retained on days 13/14 and provided urines free of illicit opioid metabolites vs. clonidine (77% vs. 22%)

NIDA CTN, National Institute on Drug Abuse Clinical Trials Network

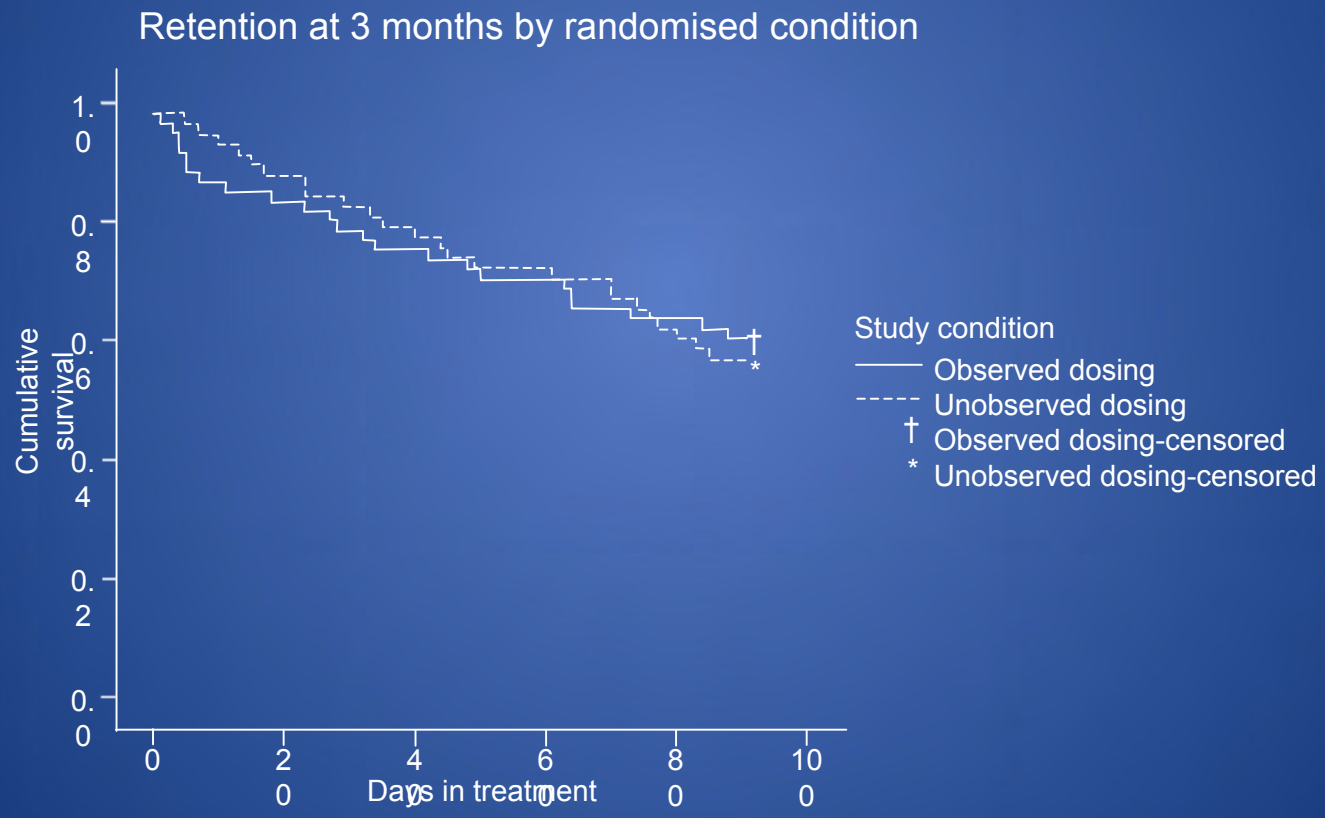
Amass et al., 2004; Ling et al., 2005

Induction: patient physically dependent on short-acting opioids

- The rationale for induction onto buprenorphine-naloxone is similar to that of buprenorphine
- The first dose of suboxone is delayed by 12–24 hours from last opioid use, upon presentation of observable withdrawal signs

Buprenorphine-naloxone and take-home dosing

- Buprenorphine-naloxone could help to alleviate pressure on resources by allowing safe take-home dosing



Bell et al., 2007

Summary of profiles for methadone, buprenorphine and buprenorphine-naloxone

- Broadly comparable retention and effectiveness in reducing opioid use
- Buprenorphine preferred for detox/short term programs
- Methadone associated with specific side effects
  - Respiratory depression, QT prolongation
- HAART fewer drug interactions with buprenorphine
- Methadone greater overdose risk with benzodiazepines
- Buprenorphine–naloxone associated with least abuse potential
- Regular monitoring allows the clinician to evaluate and adapt therapy to meet the needs of the patient

Under the patronage of

Association for the Application of Neuroscientific Knowledge to Social Aims
info@aucns.org - www.aucns.org

European Opiate Addiction Treatment Association
europad@wftod.org - www.europad.org

World Federation for the Treatment of Opioid Dependence
NGO with Special Consultative Status with Economic and Social Council (ECOSOC)
info@wftod.org - www.wftod.org

Maremmani I., Pacini M., Pani P. P., On Behalf of the 'Basics on Addiction Group' (2011): Basics on Addiction: a training package for medical practitioners or psychiatrists who treat opioid dependence. *Heroin Addiction and Related Clinical Problems*. 13(2): 5-40.