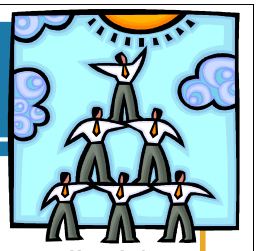
Volume C, Module 2 Leader's Guide
Opioids: Basics of Addiction; Treatment with Agonists, Partial Agonists, and Antagonists

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

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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

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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?

15 minutes

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Workshop 1: Opiates

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

5

Pre-assessment

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

(Your responses are strictly confidential.)

10 minutes

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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

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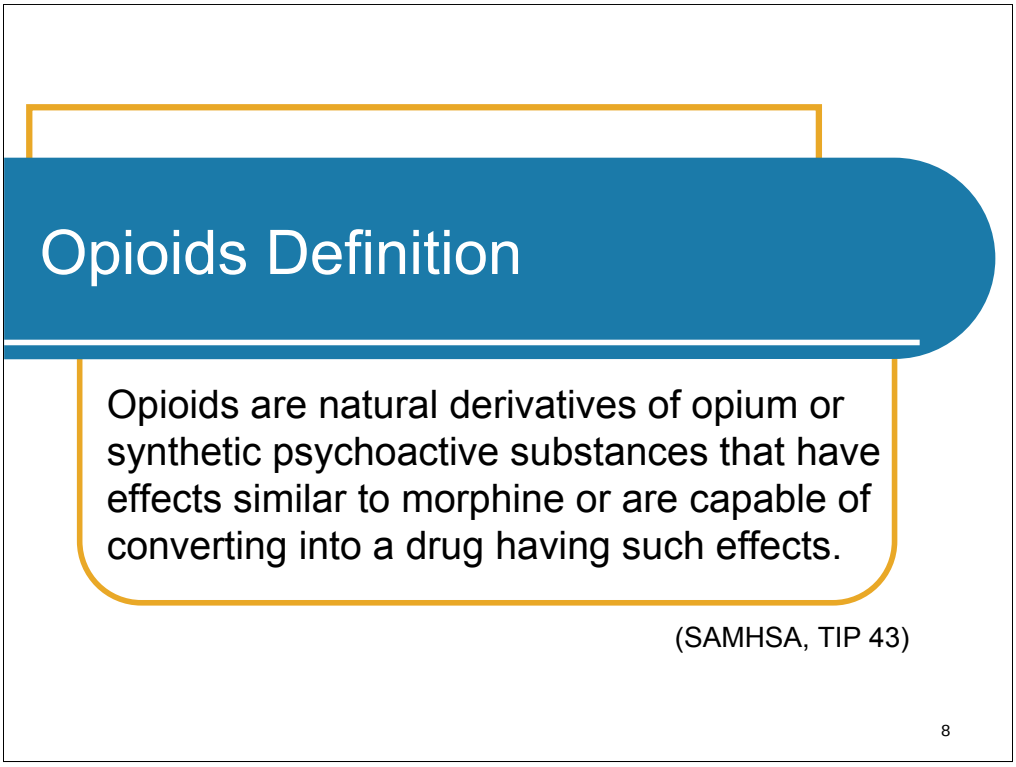


Notes:

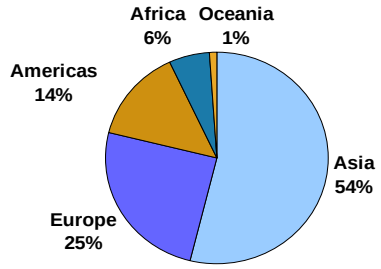
(source: U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs: TIP 43. Available at www.samhsa.gov)

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.

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Notes

Proportions of heroin abuse vary by region:

-Almost all of opiate consumers in Africa are reportedly abusing heroin.

-2/3 of opiate abusers consume heroin in Asia. Uuse of opium is still widespread in a number of countries.

-Asia & Europe together account for 80% of the world's heroin abusers.

Annual Prevalence of Opiate Abuse, 2003 - 2005

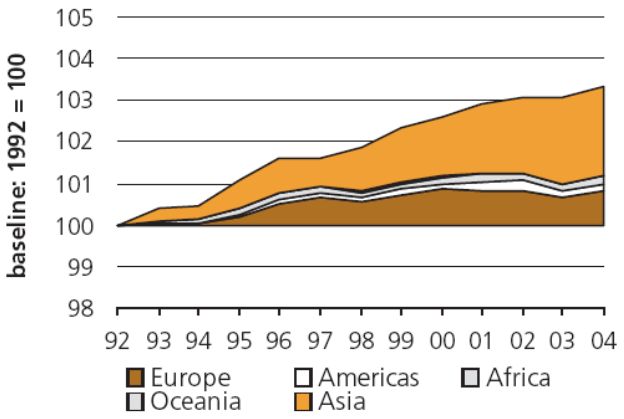
	Abuse of opiates		of which abuse of heroin	
	Number of abusers	in % of population age 15-64	Number of abusers	in % of population age 15-64
EUROPE	4,030,000	0.7	3,340,000	0.6
West & Central Europe	1,565,000	0.5	1,445,000	0.5
South-East Europe	180,000	0.2	175,000	0.2
Eastern Europe	2,285,000	1.6	1,720,000	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**

Above global average
Around global average
Below global average

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.

Notes

Opiate Abuse Levels

- **Rising in Asia**, **mainly among countries close to Afghanistan, though falling in East & South East Asia** (reflecting the strong declines of opium production in Myanmar & Lao PDR).

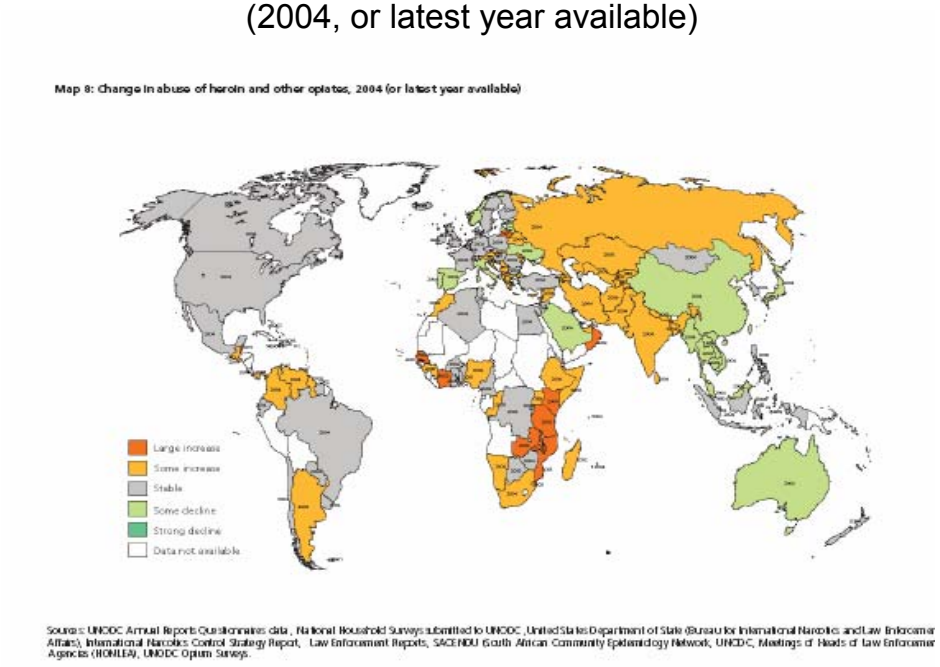
- **Stable decline in West & Central Europe; rising in East Europe** (Eastern Europe suffering from the supply push of Afghan opiates).

- Stable decline in Americas (Falling opium production levels in Latin America & South-East Asia, the two main traditional supply lines for the North American market, may have contributed to this.

-**Oceania continues to remain below levels recorded in 2000** (major heroin shortage in 2001, prompted by the dismantling of some major heroin trafficking networks).

-Opiate use in Africa starts rising (upward trend is particularly noted in South Africa, where heroin used to account for less than 1% of treatment demand; by the first two quarters of 2005, this proportion had increased to 7%.

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, SACENDU (South African Community Epidemiology Network, UNODC, Meetings of Heads of Law Enforcement Agencies (HONLEA), UNODC Opium Surveys.

Opioids

Opiate (n)

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

Ambrose Bierce
The Devil's Dictionary (1906)

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Notes

Opium is the milky juice or dried exudate of the opium poppy. In the week after the flowers fall off, the pod, if cut, will excrete a tar-like substance. The tar is brown in colour, and has an unpleasant odour and bitter taste. The gum is drained, dried, boiled in water and filtered to produce opium paste. Two additional products can then be isolated (morphine and codeine).

Heroin (diacetylmorphine), a semi-synthetic substance, is the result of a chemical process that combines opium with two additional molecules.

Opium contains around 1–15% morphine, 1–2% codeine, and 75–80% substances which have little or no pharmacological activity (Victoria Police, 2001).

Opium poppies are grown in the Middle East, Asia, China, Afghanistan, and increasingly, the Americas.

Sources: Kahan, M. & Marsh, D. 2000, 'Intoxication, Overdose and Withdrawal' in Brand, B. (ed.), *Management of Alcohol, Tobacco and Other Drug Problems*, Centre for Addiction and Mental Health, Toronto.

Medicine in Quotations Online www.acponline.org/cgi-bin/medquotes

Ryder, D., Salmon, A. & Walker, N. 2001, *Drug Use and Drug Related Harm,* IP Communications, Melbourne.

Opioid-related problems

- Most prominent problems are associated with heroin dependence
- Not all users of heroin develop dependence. Between 1 in 4 to1 in 3 regular users develop dependence
- Development of heroin dependence usually requires regular use over months (or longer, when use is more irregular)

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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.

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Notes

Heroin dependence is a chronic, relapsing–remitting condition. Long-term follow-up of those entering treatment suggests:

–Only 10% of heroin users will become and remain abstinent in the first year after treatment

–Approximately 2%–3 % of people who use heroin will achieve abstinence and remain abstinent in each subsequent year.

Source: NCETA 2004, 'Heroin and other Opioids' *Alcohol and Other Drugs: A Handbook for Health Professionals*., ch. 9, Australian Government Department of Health & Ageing, Canberra.

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

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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

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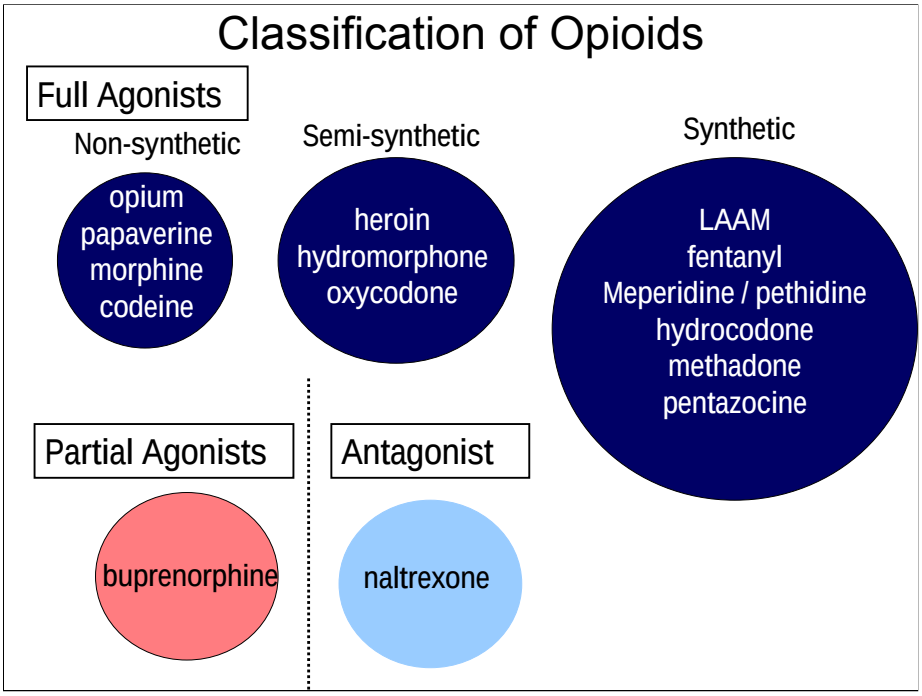


Notes

Pure opioid agonists: of 20 naturally occurring alkaloids, only morphine and codeine have analgesic properties.

Semisynthetics: e.g., heroin and "homebake" (morphine made out of codeine by a home-made method) are chemical derivatives of morphine.

Synthetics: e.g., methadone and dextropropoxyphene, share a common structure that enables interaction with opioid receptors. These entirely artificial drugs have been synthesised without commencing the process with a naturally occurring opioid.

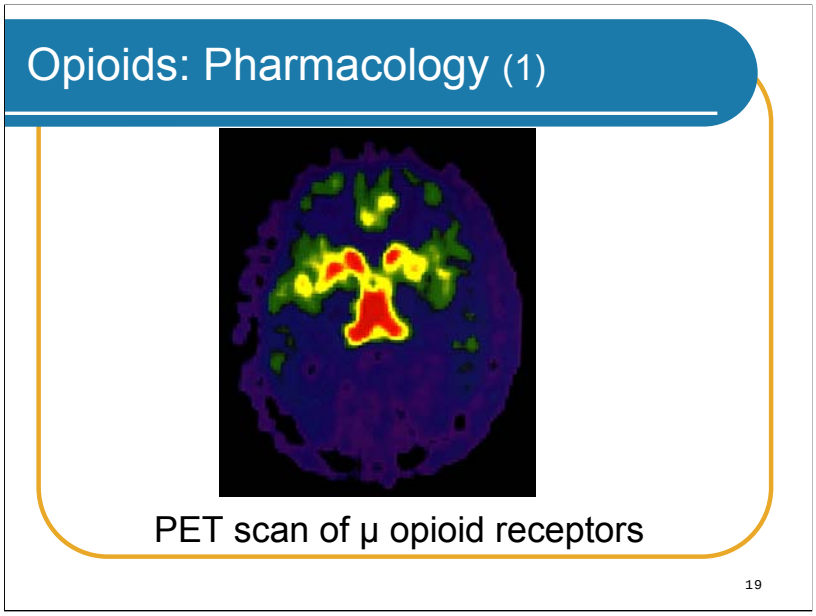
Commonly used opioid-based preparations include:

- heroin/homebake
- morphine/morphine-based medications such as Pethidine
- codeine phosphate and codeine based preparations, e.g., cough mixtures, and preparations such as 'Codral Forte', 'Panadeine Forte', 'Mersyndol Forte'
- methadone
- oxycodone-based medications such as 'Endone' and 'Prolodone'
- dextropropoxyphene contained in medications such as 'Digesic', 'Doloxene'and dextromoramide (Palfium).

Sources: Brands, B. 2000, *Management of Alcohol, Tobacco and Other Drug Problems*, Centre for Addiction and Mental Health, Toronto.

Victoria Police 2002, *Custodial Drug Guide: Medical Management of People in Custody with Alcohol and Drug Problems*, Custodial Medicine Unit, Victoria Police, Mornington, Victoria.

Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.



Notes

Refer also to next slide.

Three main types of opioid receptors in the CNS and periphery have been identified – ќ, б and ц. It is also believed that there are several other subtypes whose characteristics are yet to be determined. There are also four groups of endogenous peptides (enkephalins, endorphins, dynorphins, and endomorphins) produced by peptidases that cleave inactive precursor peptides. Opioid peptides and their receptors are widely distributed through the CNS and non-neuronal tissues, such as the GI tract. Opioid receptors, acting via G-proteins, are inhibitory. They inhibit adenylate cyclase, open potassium channels, and block voltage-gated calcium channels, therefore reducing neurotransmitter release (5-HT, acetylcholine, glutamate and GABA) (Young et al., 2002, p. 80).

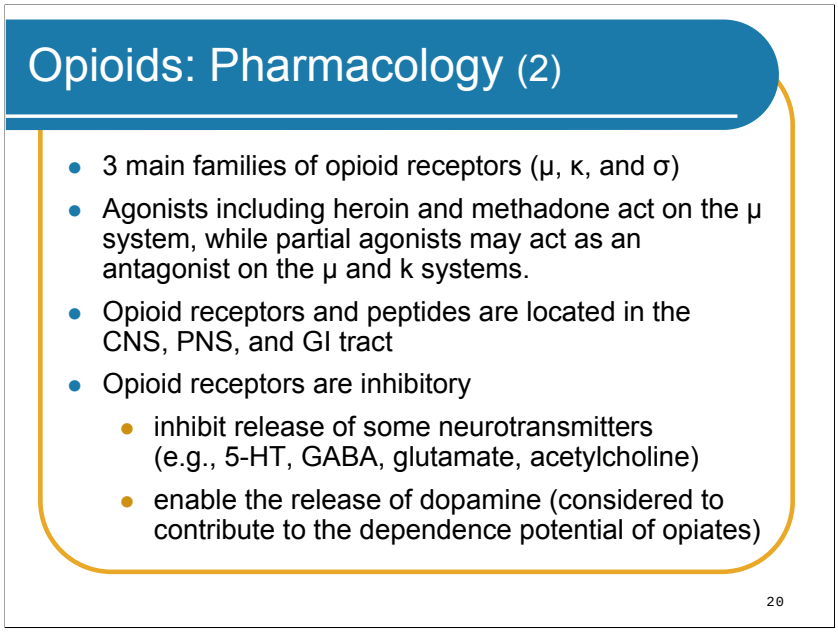
Sources: Victoria Police 2002, *Custodial Drug Guide: Medical Management of People in Custody with Alcohol and Drug Problems*, Custodial Medicine Unit, Victoria Police, Mornington, Victoria.

Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.

Picture: Society for Neuroscience
http://apu.sfn.org.content/publications/BrainBriefings/addition.html#fullsize

Notes:

"PET" stands for "Positron Emission Tomography."



Pharmacodynamics

Opioids act on 3 main families of opioid receptors (μ, κ and σ). Endogenous opioid peptides (e.g. enkephalins, endorphins, dynorphins, endomorphins) produced by peptidases also bind with opioid receptors. Both the opioid peptides and receptors are located in the brain, spinal cord, and periphery (including non-neuronal pathways in the GI tract), resulting in effects such as cough and respiratory suppression, reduced GI motility (hence nausea and vomiting), miosis, and urinary retention (from increased bladder and urethral tone). Effects exerted through the limbic system produce changes in emotions, such as the euphoric high.

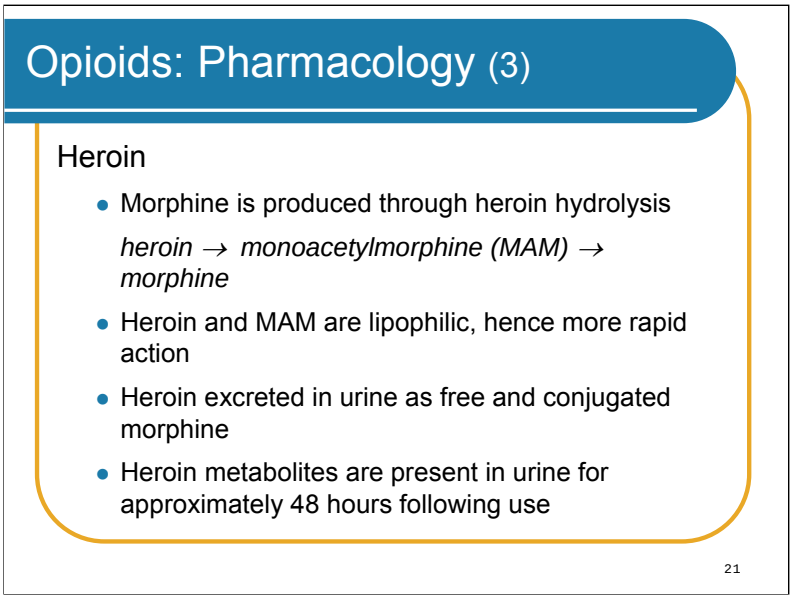
Opioid receptors are inhibitory and act via G-proteins. They inhibit adenylate cyclase, open potassium channels and block voltage-gated calcium channels thereby inhibiting the release of neurotransmitters such as 5-HT, GABA, glutamate and acetylcholine (Young et al., 2002, p. 80).

The endogenous opioid system is activated by stress. It can modulate pain perception, mood and physiological systems (e.g., the respiratory or immune systems) (Young et al., 2002, p. 81).

All prescription opioids produce morphine-like effects but rather than removing pain, they alter perceptions of the pain so that it is more tolerable and less aversive. Although cognition is impaired, consciousness and coordination are generally intact at low doses. Opioids produce analgesia and euphoria, decrease muscle tone, slow movement of the digestive tract, may alter hormonal balance and have a role in regulating immune function. Inhibition of the respiratory system and potential for overdose occur due to the brainstem response to carbon dioxide

Opioids are distinguished from sedative hypnotics through their powerful analgesic, anti-diarrhoeal, and cough suppressant properties.

Source: Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.



Notes

Pharmacokinetics

The variety of chemical structures in the opioid class result in important differences in their pharmacokinetics. Although most are metabolised by oxidation, morphine and buprenorphine are conjugated with glucuronic acid in the liver. As morphine is rapidly metabolised by the liver after oral administration, only a small amount reaches systemic circulation (Young et al., 2002, p. 81).

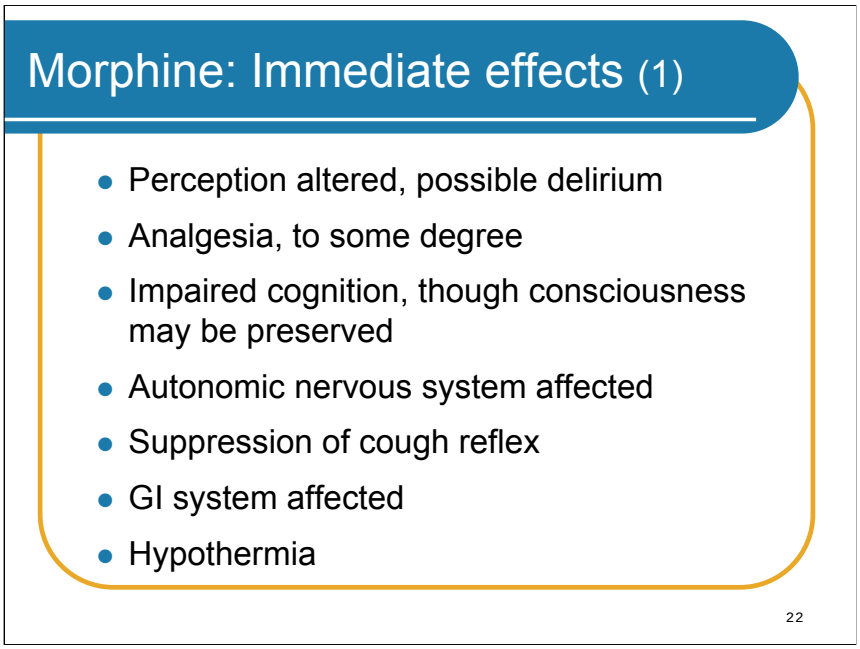
Heroin (diacetylmorphine) is hydrolysed firstly to monoacetylmorphine (MAM), then to morphine. As heroin and MAM are more lipophilic than morphine, they cross the adult blood-brain barrier more rapidly than morphine, resulting in feelings of euphoria.

Codeine is also converted to morphine via demethylation by the enzyme CYP2D6.

For the 8–10% of Caucasians and 2% of South-East Asians who do not have the enzyme CYP2D6, codeine will have no analgesic effect.

Source: Gill, T. & Evans, M. 1996, 'Methadone in the Treatment of Opioid Dependence' *GP Drug and Alcohol Supplement No.2.* Central Coast Area Health Service, New South Wales.

Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.



Notes

Perception: euphoria, flushing, sense of tranquillity, peace or contentment**.**

Analgesia: pain is not removed but perception of pain altered so that the experience is no longer aversive.

Impaired cognition: consciousness and coordination intact at low doses.

Autonomic nervous system: reduced brainstem response to CO_2 inhibits respiratory system; low blood pressure.

Suppression of cough reflex, nausea and vomiting: opioids stimulate the chemoreceptor trigger zone in medulla.

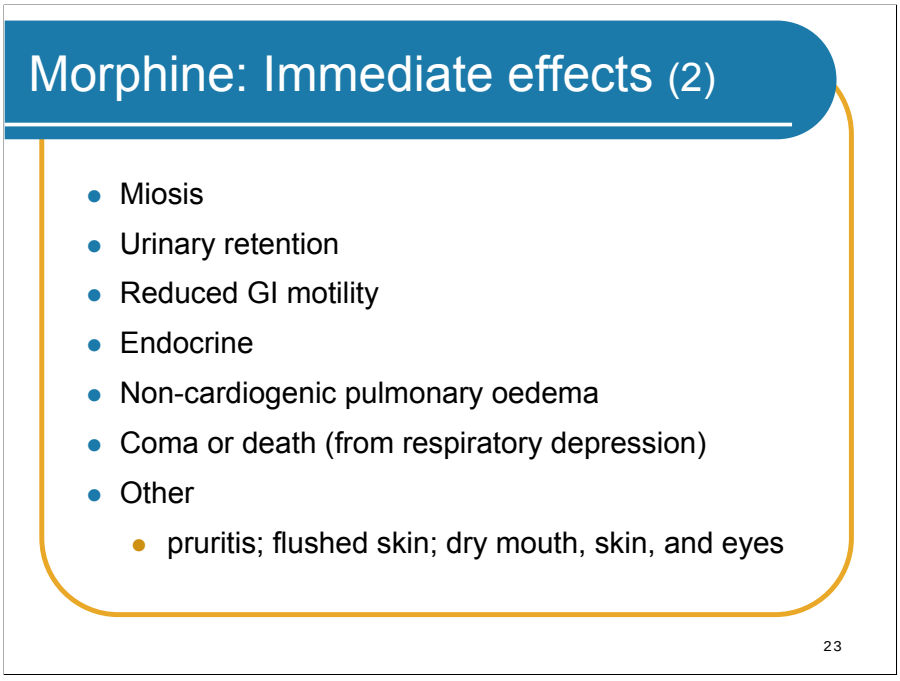
Through activation of the μ receptors in the mesolimbic reward pathway, morphine increases the release of dopamine through inhibiting GABA interneurones. The release of dopamine is believed to contribute to the dependence-producing potential of opioids. The euphoric effects of opioids, especially when injected, can be highly reinforcing to vulnerable individuals. Effects such as euphoria, flushing and the abdominal 'buzz' (described by many as akin to orgasm) are specific to recreational experiences and are not generally seen when opioids are used in clinical situations.

All opioids exert a morphine-like effect, producing drowsiness, clouding of sensorium and perception, mood changes (usually euphoria or contentment), analgesia and respiratory depression.

The CNS depressant effects can be reversed by the opioid antagonist naloxone.

At high doses, the muscle tone of the large trunk and intercostal muscles may increase (tighten), hence further impairing breathing.

Source: Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.



Notes

Miosis: due to increasing parasympathetic tone in the pupil.

Urinary retention: increased urethral and bladder tone.

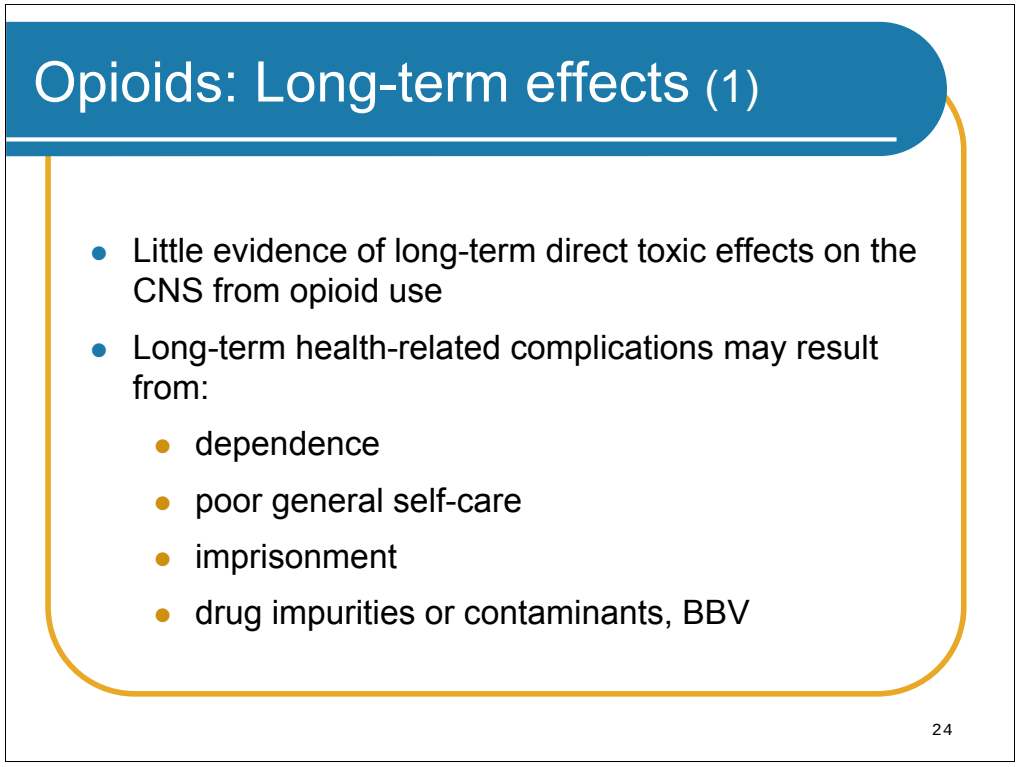
Reduced GI motility: opioid receptors are present in GI tract. Reduced GI motility can result in constipation. Opioids increase muscle tone, specifically affecting the Sphincter of Oddi (increasing the muscle tone).

Endocrine: changes sex hormones in women – decreased follicle-stimulating hormone (FSH) and lutenising hormone (LH); raised prolactin resulting in menstrual changes, reduced libido, galactorrhoea; reduced testosterone in men with reduced libido. Also increases ADH, decreases ACTH.

Tolerance to opioids develops rapidly, commencing with the first dose and involves:

- down-regulation – reduced number of receptors
- desensitisation – diminished response to receptor action.

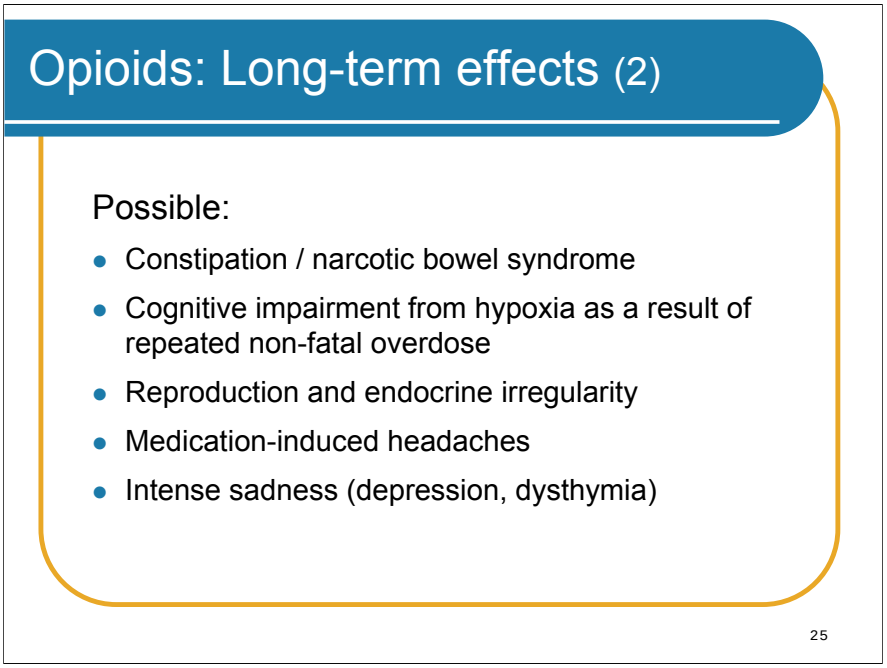
Source: Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.



Notes

There is little evidence of long-term direct toxic effects on the CNS from using opiates. (See next slide for chronic use complications).

Source: Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.



Notes

There is little evidence of long-term direct toxic effects on the CNS from using opioids. However, the following complications may result from long-term chronic opioid use.

Narcotic bowel syndrome

- Characterised by bloating, vague abdominal discomfort
- Physical examination and investigations are negative though patients may have a dilated bowel (with no obstruction)
- Intervention – taper to discontinue the drug use.

Medication induced headaches

- This condition generally refers to patients who are not regular heroin users but who are receiving mixed opioid/non-opioid analgesics such as paracetamol with codeine for management of migraine. Patients may report increased headache frequency since commencing the use of opioid-based medications which stop on cessation of analgesia.

Depression

- Changing drug-use behaviours requires significant social change. It is not unusual for patients to experience depression or sadness in the face of significant change and take time to adjust to a different lifestyle. Ongoing assessment is important to ensure adequate support is provided and for detecting the possible emergence of any mental health problems.

Sources: Kahan, M. & Marsh, D. 2000, 'Intoxication, Overdose and Withdrawal' in Brand, B. (ed.), *Management of Alcohol, Tobacco and Other Drug Problems*, Centre for Addiction and Mental Health, Toronto.

Victoria Police 2002, *Custodial Drug Guide: Medical Management of People in Custody with Alcohol and Drug Problems*, Custodial Medicine Unit, Victoria Police, Mornington, Victoria.

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)

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Notes

This slide highlights areas of special consideration when assessing or treating an injecting drug user who uses opioids.

It is advisable to prescribe methadone for opioid-using pregnant patients. Cessation of opioids is not recommended because of risks to the fetus from withdrawal. Refer patients to an authorised methadone prescriber.

Urinalysis:

•may be valuable in confirming drug use history, although this is an expensive process and the results are not immediately available

•indicates evidence of recent use but does not identify dependence, nor does it indicate problem areas

•does little to assist in building rapport with patient.

Source: NCETA 2004, 'Heroin and other Opioids' *Alcohol and Other Drugs: A Handbook for Health Professionals*, ch. 9, Australian Government Department of Health & Ageing, Canberra.

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

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Notes

Note that track marks are not always in the obvious locations and some injecting drug users will go to considerable lengths to use sites that are less obvious and less easy to detect on examination, e.g. soles of the feet.

Complications from use

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

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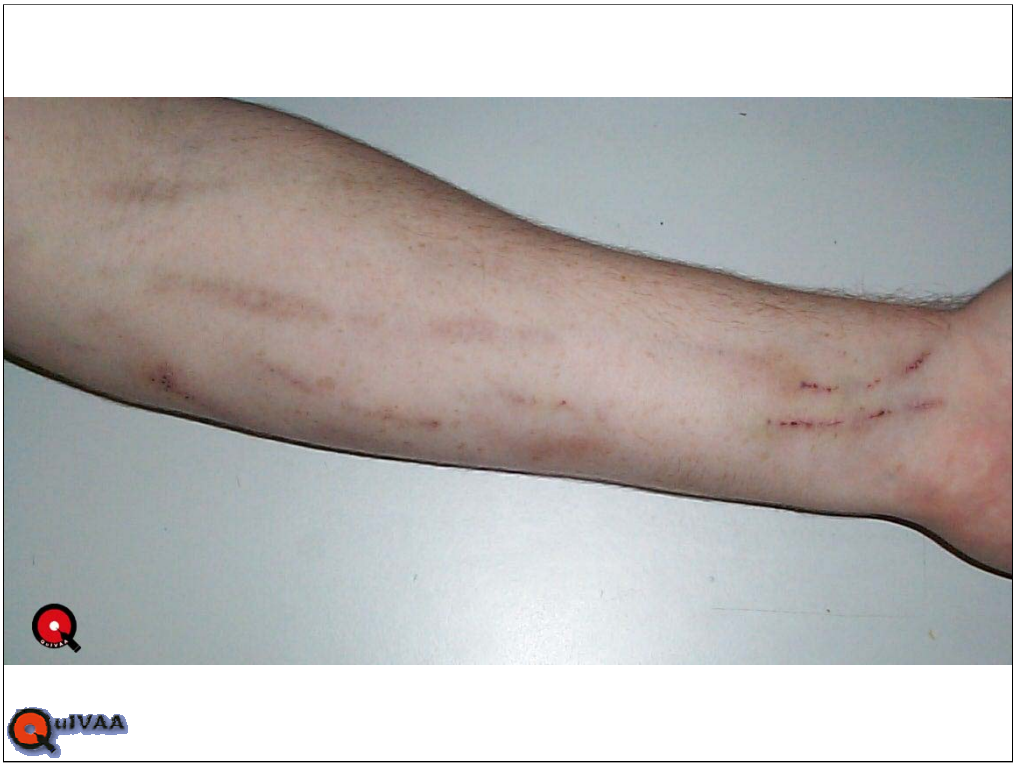
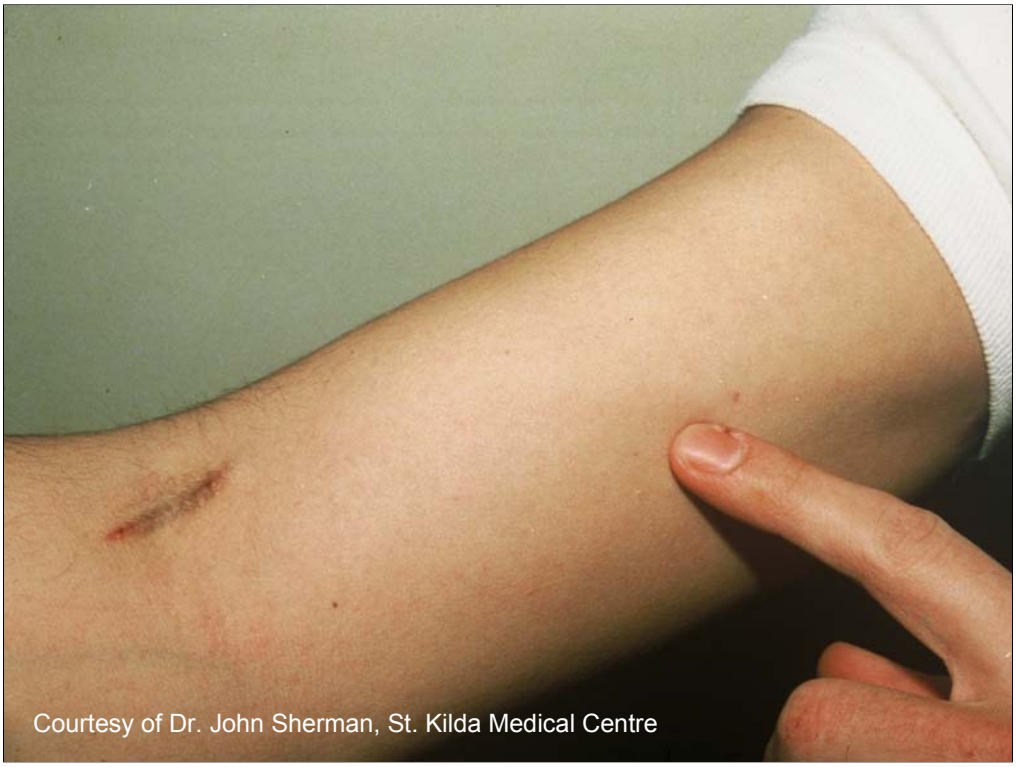


Notes

Extensive “track marks” – IV drug use.

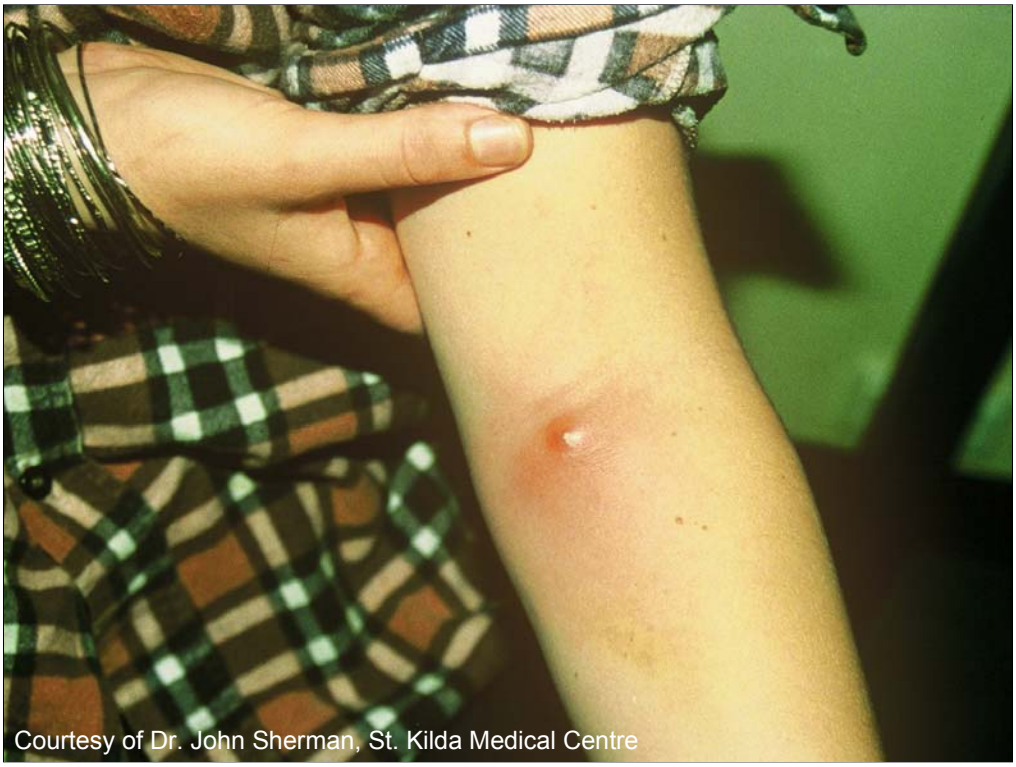


Notes

A typical track mark due to IV heroin use.

The person is pointing to slight inflammation (red line) up the arm. This is thrombophlebitis – inflammation of the vein.

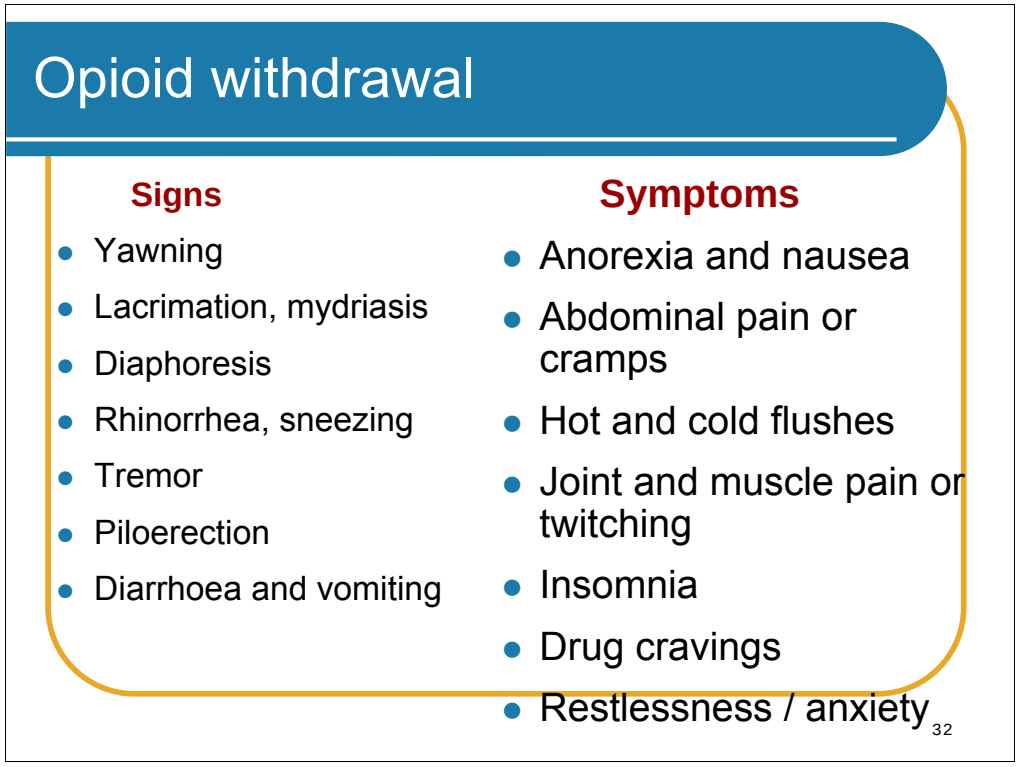
Plastic surgery can remove the track so it is less obvious.



Notes

Venous abscess – IV drug user.

Infections may also include septicaemia or a septic joint in IV drug users. Hot, painful joints should be assumed to be septicaemia until proven otherwise.



Notes

People using opioids may experience a moderate to severe but not life-threatening withdrawal syndrome.

The onset and duration of withdrawal varies according to the half life of the drug used, e.g., withdrawal symptoms from heroin (usually manifest in a marked drive to obtain and use the drug) may commence 6–12 hours after the last dose, and may last for 5–7 days. With methadone, withdrawal may not commence for 2–3 days after most recent dose and last for up to 3 weeks.

Knowledge of the half-life of the drugs used (methadone vs. heroin) and the time for likely onset of withdrawal after the last dose can assist in predicting, identifying, and managing opioid withdrawal.

Signs and symptoms of opioid withdrawal may be mistaken for a bad dose of the 'flu'.

Despite depictions of heroin withdrawal in popular culture, opioid withdrawal is rarely, and is unlikely to be, fatal.

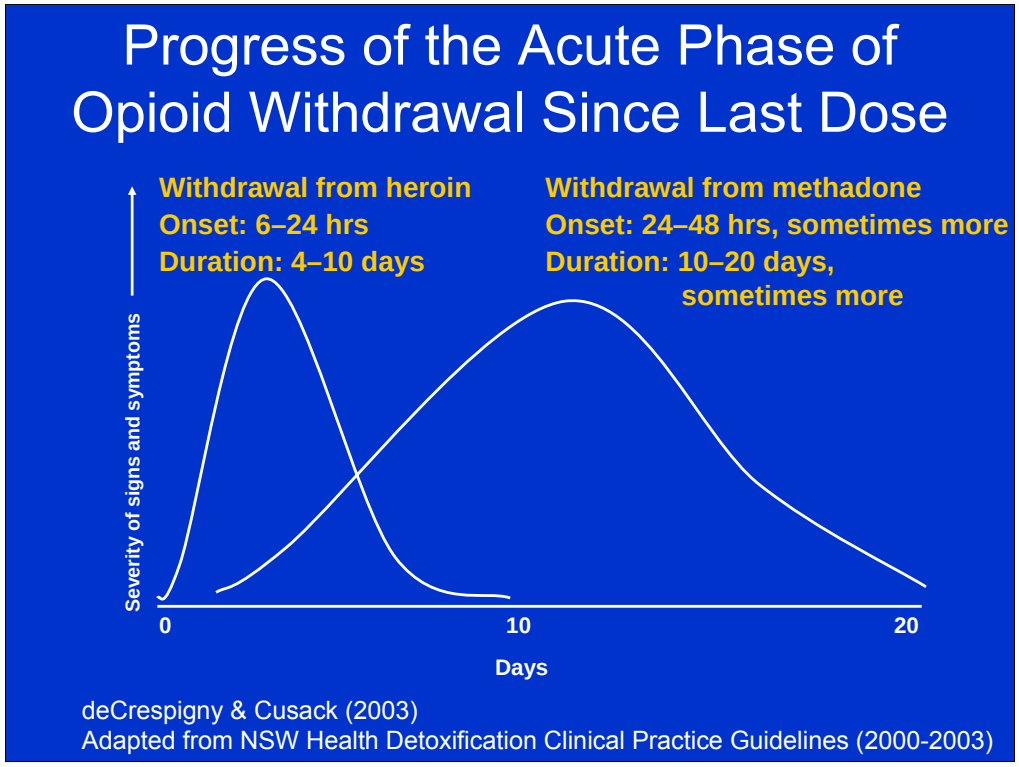
Withdrawal (and the culture or lifestyle associated with use, or withdrawal from that lifestyle) may precipitate dysthymia or depression.

Source: deCrespigny, C., Talmet, J, Modystack, K., Cusack, L. & Watkinson, J. 2003, *Alcohol, Tobacco and Other Drugs Guidelines for Nurses and Midwives: Clinical Guidelines*, Flinders University and Drug and Alcohol Services Council (DASC), Adelaide.

Notes

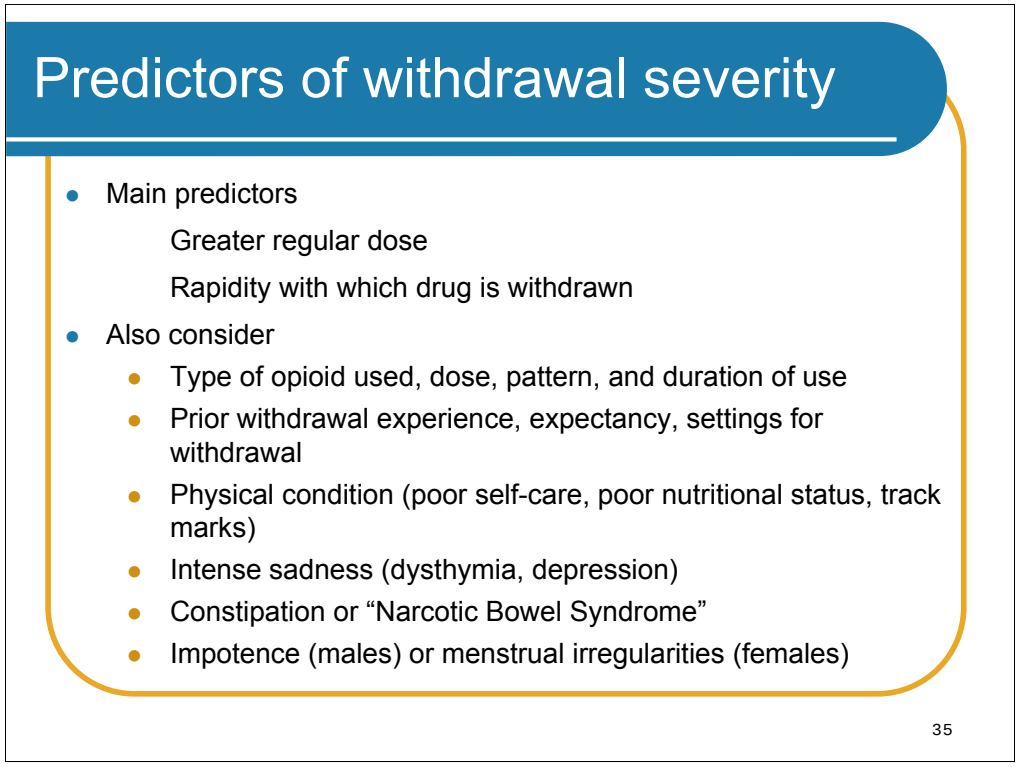
Dilated pupils – opiate withdrawal.

Pupils will be constricted when intoxicated.



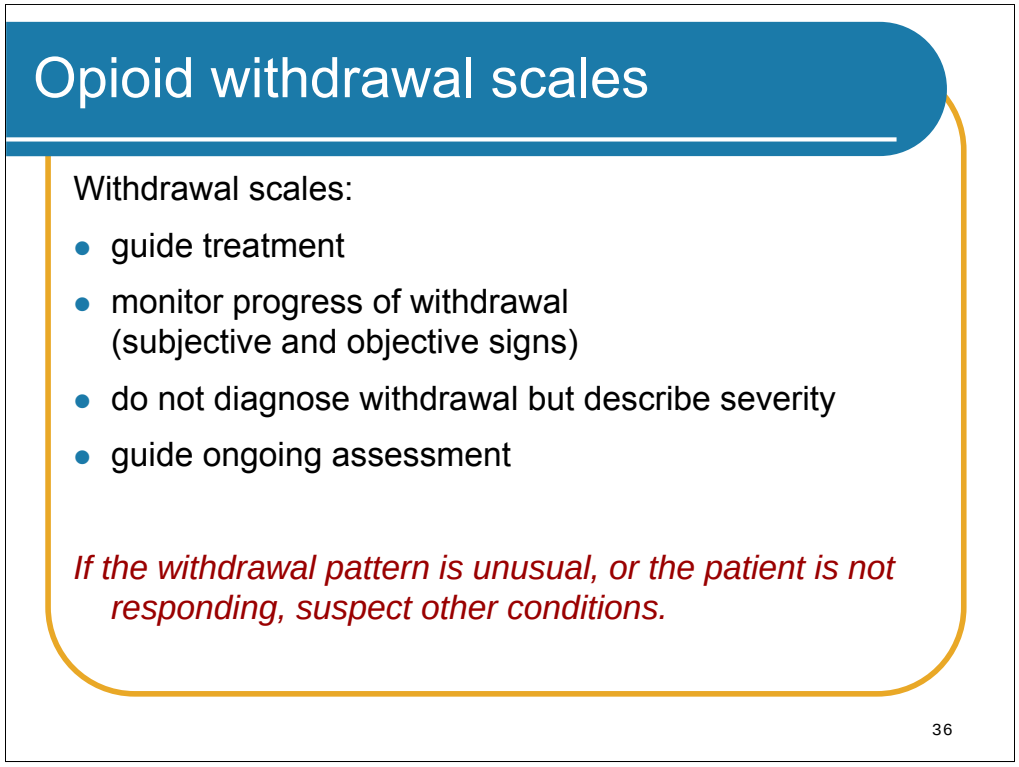
Source: deCrespigny, C., Talmet, J, Modystack, K., Cusack, L. & Watkinson, J. 2003, *Alcohol, Tobacco and Other Drugs Guidelines for Nurses and Midwives: Clinical Guidelines*, Flinders University and Drug and Alcohol Services Council (DASC), Adelaide.

NSW Department of Health 1999, *NSW Detoxification Clinical Guidelines*, NSW Department of Health, Sydney.



Notes

Signs on the slide are indicative of long-term use and may predict severity of withdrawal. Despite potential severity, opioid withdrawal does not present a risk for fatality, except in the neonate or when other significant medical conditions are present.



Tools

The Subjective Opioid Withdrawal Scale (SOWS) (See Handouts).

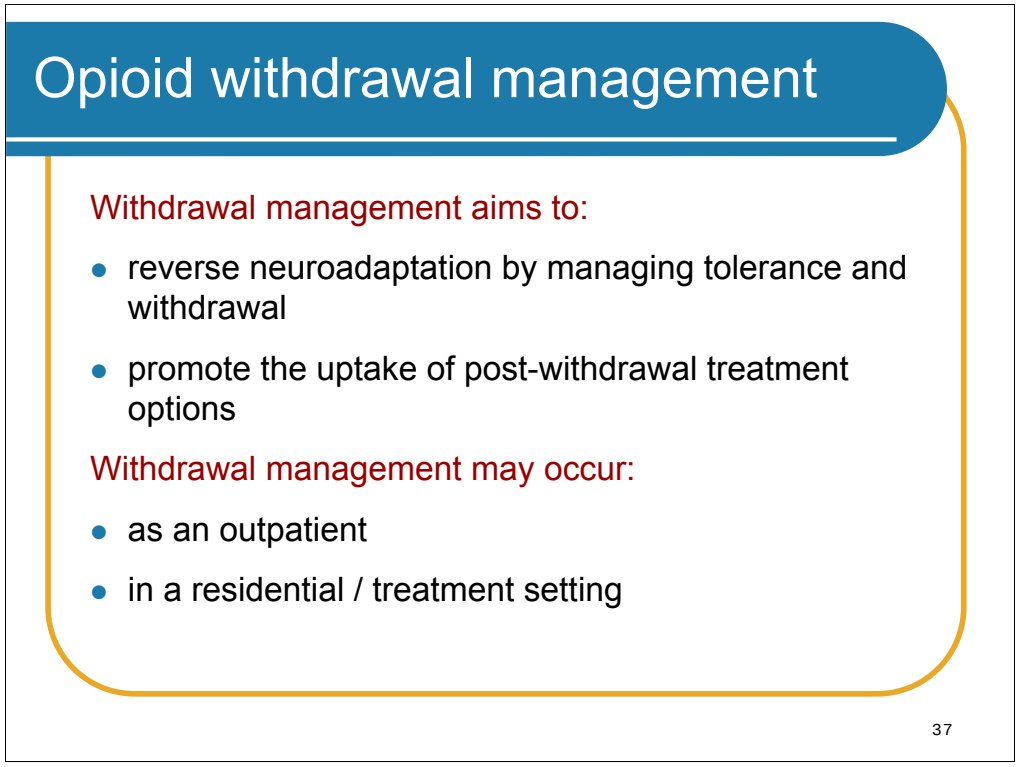
The Objective Opioid Withdrawal Scale (OOWS) (See Handouts).

Use of the SOWS during assessment enables patients to be involved in their own care, and can assist in reducing their anxiety.

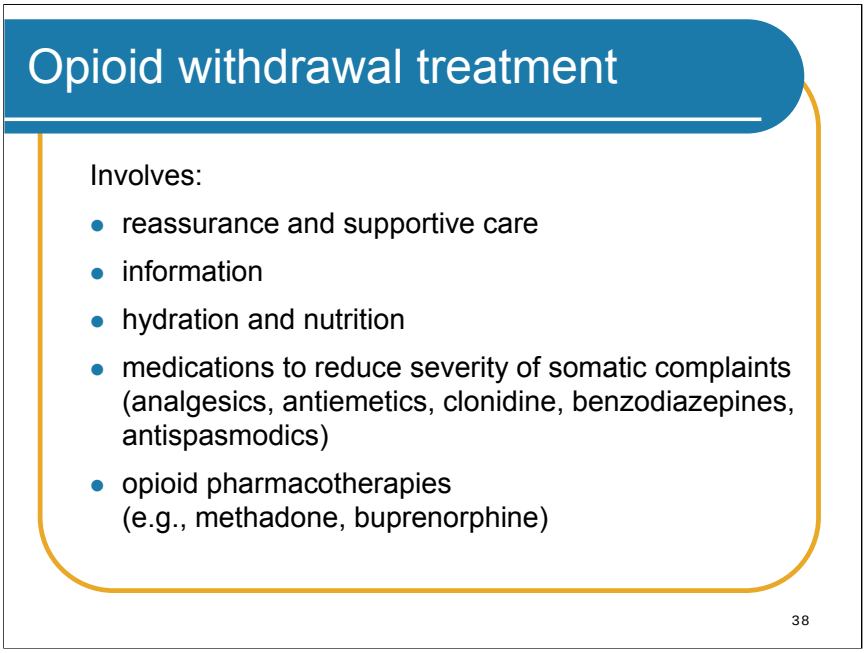
Sources: deCrespigny, C., Talmet, J, Modystack, K., Cusack, L. & Watkinson, J. 2003, *Alcohol, Tobacco and Other Drugs Guidelines for Nurses and Midwives: Clinical Guidelines*, Flinders University and Drug and Alcohol Services Council (DASC), Adelaide.

Lintzeris, N., Clark, N., Muhleisen, P., Ritter, A., Ali, R., Bell, J., Gowing, L., Mattick, R., Monheit, B., Newton, I., Quigley, A. Whicker, S., White, J. & Henry-Edwards, S. 2001, *National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence,* National Drug Strategy, March 2001, cited in CDHA (Commonwealth Department of Health and Ageing) 2002 *Illicit Drug Training for Pharmacists*, CDHA, Canberra, pp. 67–68.

Victoria Police 2002, *Custodial Drug Guide: Medical Management of People in Custody with Alcohol and Drug Problems*, Custodial Medicine Unit, Victoria Police, Mornington, Victoria, pp. 4-9–4-10.



Source: Palmer, B. 2001, *Alcohol and Drug Withdrawal: A Practical Approach. A Manual for Doctors to Assist in the Treatment of Patients Withdrawing from Alcohol and Other Drugs,* Next Step Specialist Drug and Alcohol Services, Mt Lawley, Perth, Western Australia, www.nextstep.health.wa.gov.au.



Notes

Reassurance, arranging supportive care, insuring adequate hydration and nutrition, and providing accurate information about withdrawal (what to expect) for patients and their caregivers can significantly reduce anxiety and assist in the effective management of the patient.

A range of medications can assist in reducing the severity of somatic complaints and increase the comfort of the patient.

Buprenorphine is increasingly used for withdrawal management, as it:

- offers less intense withdrawal compared with methadone tapering
- has fewer side-effects when compared to clonidine.

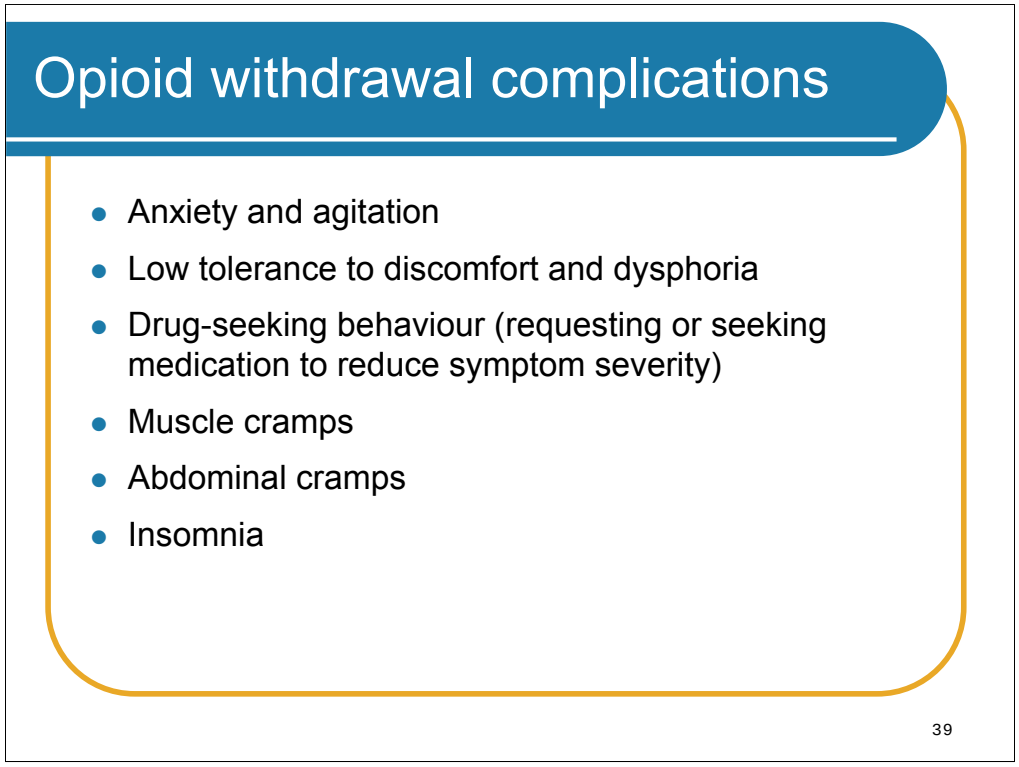
The main complications from opioid withdrawal are not life-threatening.

Sources: Lintzeris, N., Clark, N., Muhleisen, P., Ritter, A., Ali, R., Bell, J., Gowing, L., Mattick, R., Monheit, B., Newton, I., Quigley, A. Whicker, S., White, J. & Henry-Edwards, S. 2001, *National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence,* National Drug Strategy, March 2001, cited in CDHA (Commonwealth Department of Health and Ageing) 2002 *Illicit Drug Training for Pharmacists*, CDHA, Canberra, pp. 39, 41.

Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne,
pp. 79–99.

Notes:

Opioid detoxification by itself should not be considered "treatment" for heroin addiction.



Source: deCrespigny, C., Talmet, J, Modystack, K., Cusack, L. & Watkinson, J. 2003, *Alcohol, Tobacco and Other Drugs Guidelines for Nurses and Midwives: Clinical Guidelines*, Flinders University and Drug and Alcohol Services Council (DASC), Adelaide, p. 93.

Opioid withdrawal

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

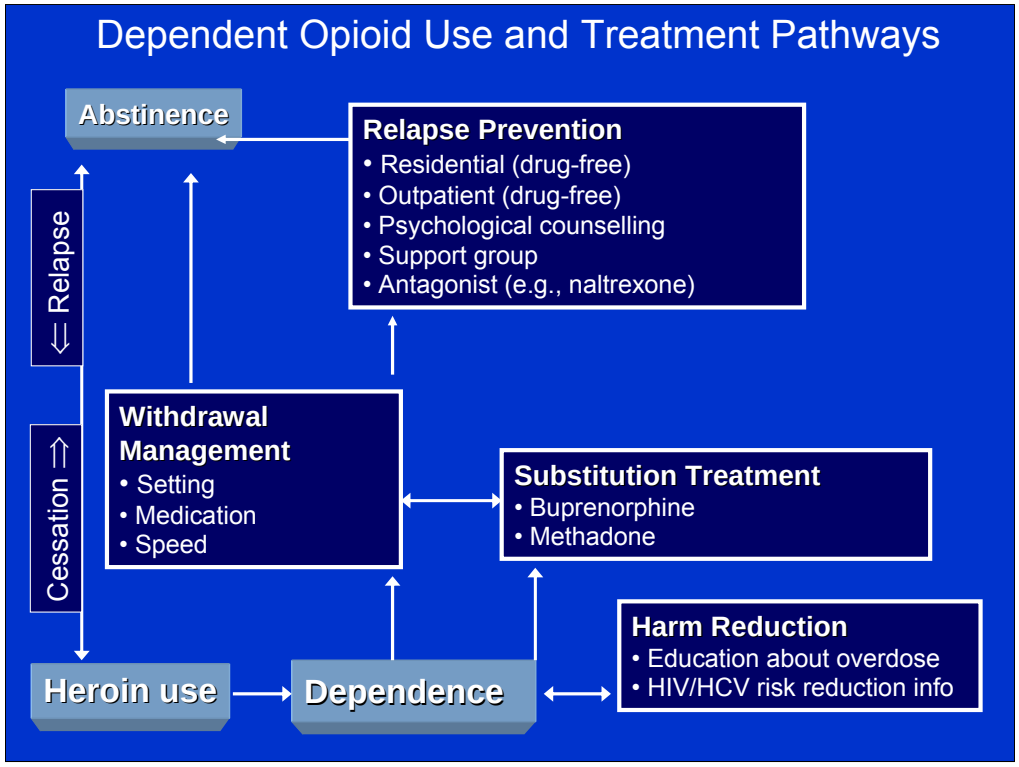
There is increasing recognition of the existence of a protracted phase of withdrawal lasting some weeks or months, characterised by reduced feelings of wellbeing, insomnia, dysthymia, and cravings.

40

Notes

Protracted phase – monitor for dysthymia/depression, which may need to be treated.

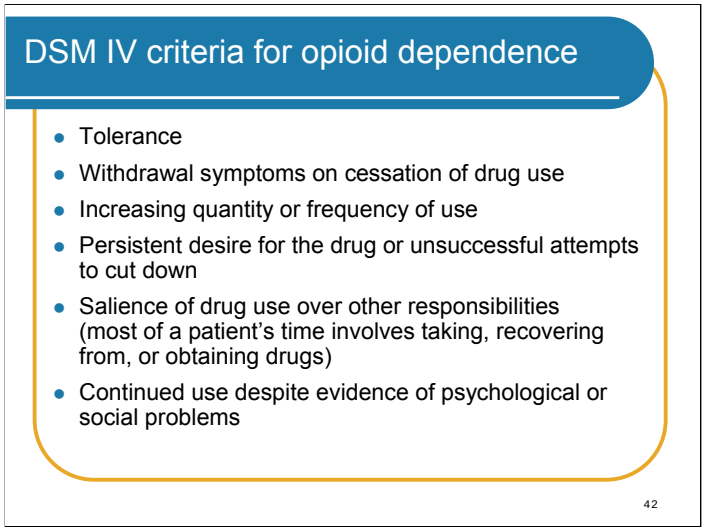
Note: hallucinations and seizures are not features of heroin withdrawal except in neonates. Assess for other conditions.



Notes

This slide depicts the various treatment options and pathways available for dependent patterns of opioid use and the role of harm reduction and relapse prevention strategies as valuable components of the model.

Source: Gowing, L., Ali, R. & White, J. 2000, 'The Management of Opioid Withdrawal', *Drug and Alcohol Review*, vol. 19, pp. 309–318.



Notes

About one in three heroin users develops dependence.

Dependence has grades of severity – it is not an "all or nothing" phenomenon.

The most salient feature of the dependence syndrome is loss of control over the use of a drug, with persistent use despite significant harms.

Physical dependence is not a requisite for drug dependence.

Most dependent heroin users describe first using heroin in their late teens to early twenties, with regular use usually commencing several years later.

Heroin dependence is a chronic, relapsing–remitting condition. Long-term follow-up of those entering treatment suggests:

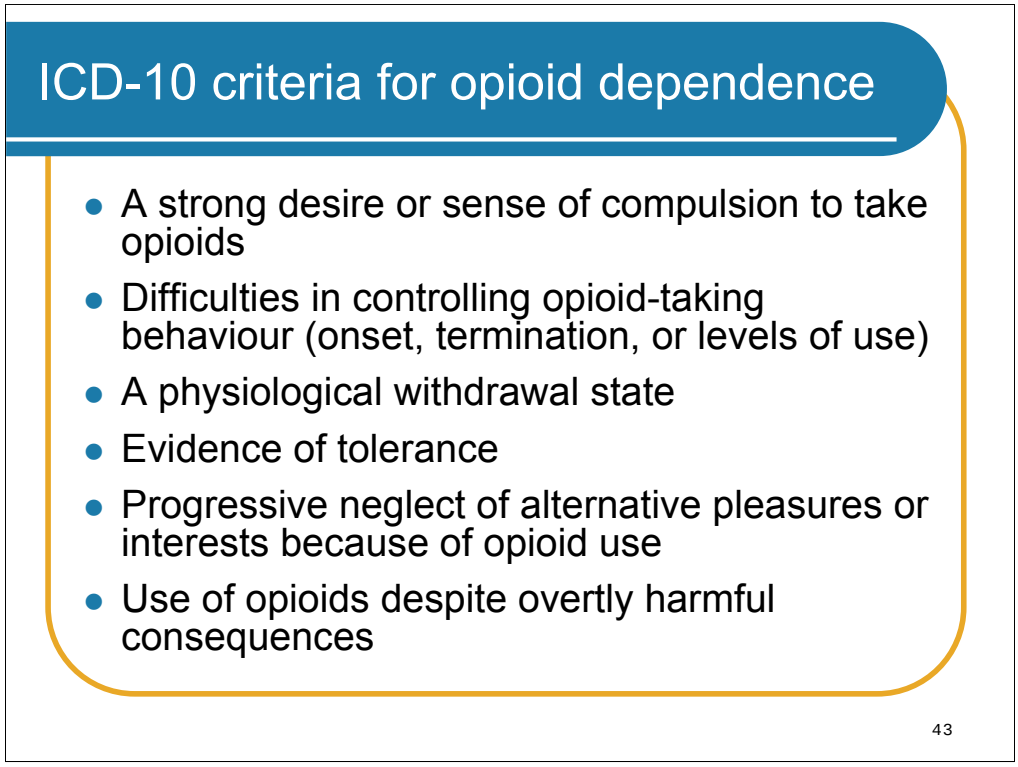
- 10% of heroin users will become and remain abstinent in the first year after treatment
- approximately 2%–3 % of people who use heroin will achieve and remain abstinent in each subsequent year.

Some characteristics of dependent heroin use in Australia

- Dependent heroin use is difficult to sustain for most people.
- Heroin is a short-acting drug: 2 to 4 injections a day is common.
- Illicit heroin has variable concentration and adulterants, and is expensive (costing $50 to $200 per day in 2001).
- Stigma associated with heroin use can deter people from seeking treatment or disclosing their drug use to family, friends, work colleagues, and health workers.

Polydrug use is common: Over half of dependent heroin users use cannabis regularly and approximately one third used benzodiazepines within last month.

Source: NCETA 2004, 'Heroin and other Opioids' *Alcohol and Other Drugs: A Handbook for Health Professionals*., ch. 9, Australian Government Department of Health & Ageing, Canberra.



Additional information on diagnostic guidelines

A definite diagnosis of dependence should usually be made only if three or more of the following have been experienced or exhibited at some time during the previous year:

(a) a strong desire or sense of compulsion to take opioids;

(b) difficulties in controlling opioid-taking behaviour in terms of its onset, termination, or levels of use;

(c) a physiological withdrawal state when opioid use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for opioid; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;

(d) evidence of tolerance, such that increased doses of opioid are required in order to achieve effects originally produced by lower doses (clear examples of this are found in opioid-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users);

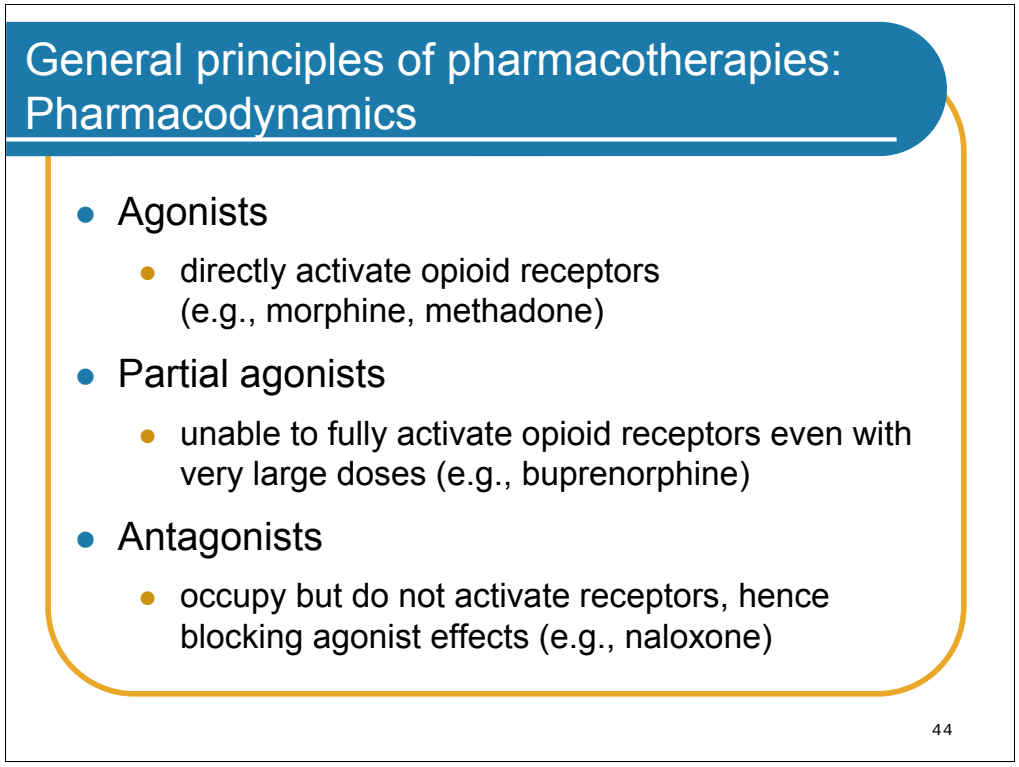
(e) progressive neglect of alternative pleasures or interests because of opioid use, increased amount of time necessary to obtain or take the substance or to recover from its effects;

(f) persisting with opioid use despite clear evidence of overtly harmful consequences, such as depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Narrowing of the personal repertoire of patterns of opioid use has also been described as a characteristic feature.

It is an essential characteristic of the dependence syndrome that either opioid-taking or a desire to take opioids should be present; the subjective awareness of compulsion to use drugs is most commonly seen during attempts to stop or control substance use. This diagnostic requirement would exclude, for instance, surgical patients given opioid drugs for the relief of pain, who may show signs of an opioid withdrawal state when drugs are not given but who have no desire to continue taking drugs.

(Source: ICD-10 World Health Organization. Available at http://azpsychiatry.info/icd/substance/dependence/opioid.htm)



Notes

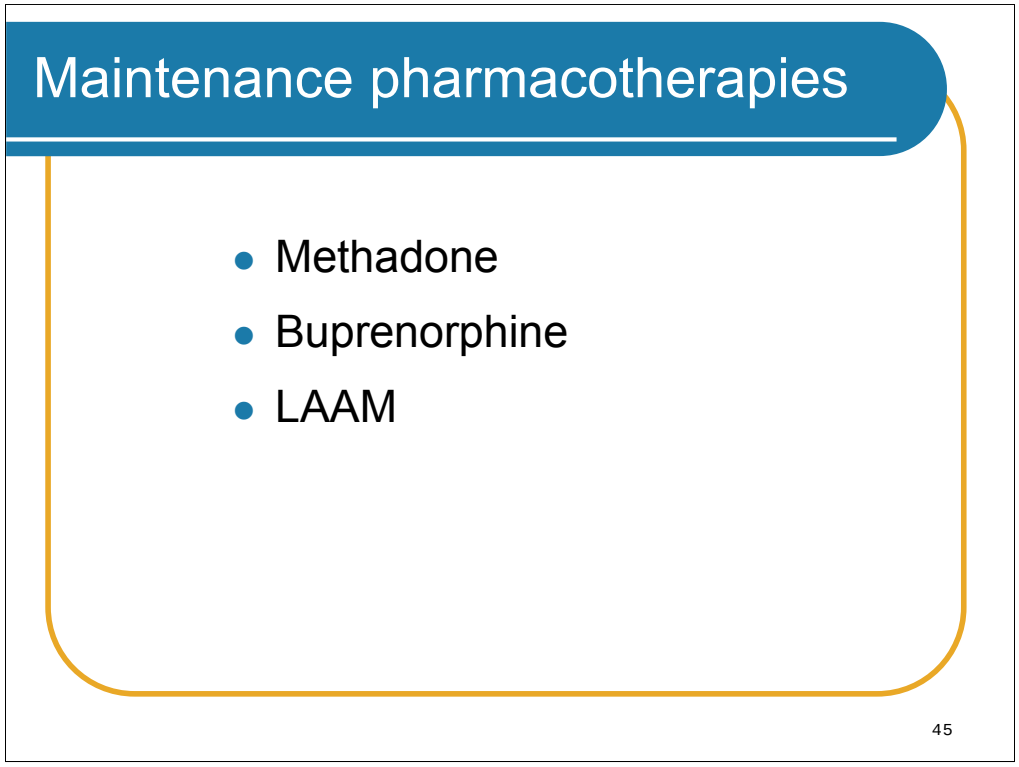
Both agonists and antagonists can demonstrate selectivity for specific receptor sub-types, e.g.:

- as a partial agonist, buprenorphine can block some of the reinforcing effects of full μ agonists
- as a mixed kappa agonist and μ antagonist, pentazocine produces dysphoria rather than euphoria.

Mixed agonist/antagonists may precipitate withdrawal if given to a person who is opioid dependent.

Pure antagonists, e.g., naloxone/naltrexone, have no analgesic or other reinforcing properties, hence they are suitable for maintenance treatment.

Source: Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.



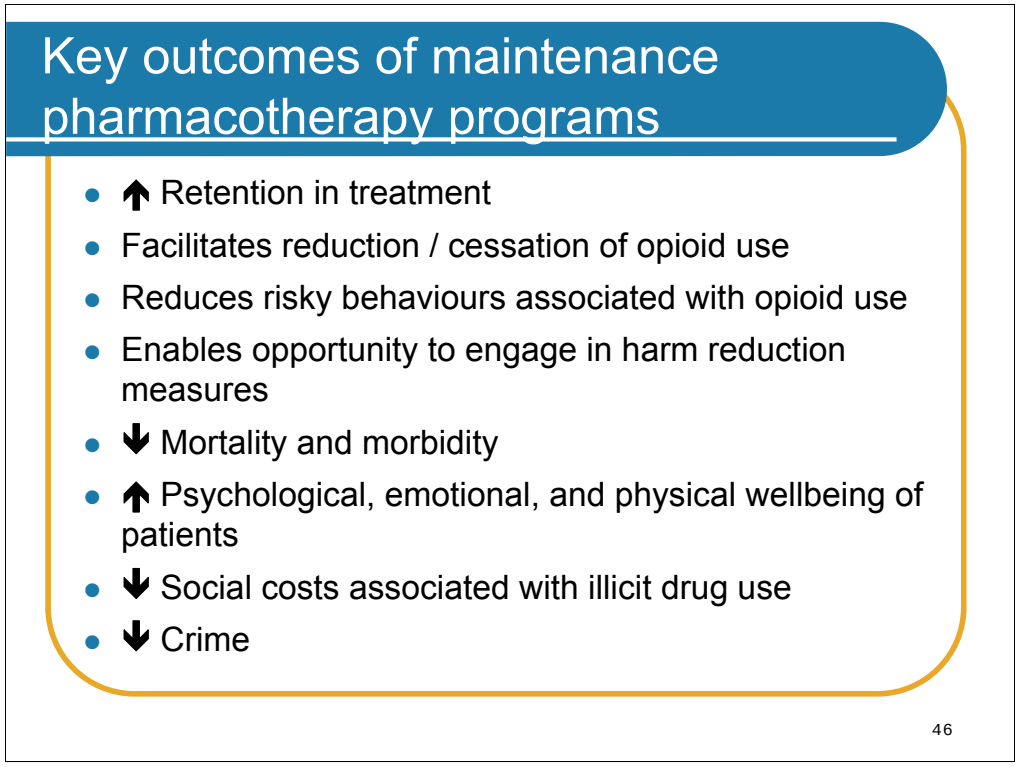
Notes

Until recently, methadone was the most studied treatment modality for responding to opioid dependence. Patients prescribed methadone have been found to:

- reduce their use of drugs
- be more likely to be retained in treatment
- have improved health, social relationships and general functioning, including
  - reduced risk of transmission of BBV through reduced frequency of injecting
  - opportunity to withdraw from drug-using lifestyle
  - stable dosing, which enables stability and development of routine.
- have reduced chance of risky behaviours associated with opioid use and premature death
- have reduced participation in criminal activities.

LAMM has been withdrawn in Europe. LAAM was approved for clinical use in America (1994) and in Europe (1997).

However, LAAM was subsequently withdrawn in Europe after several cases of serious cardiac arrhythmias associated with QT prolongation, torsade de pointes, cardiac arrest, and deaths. In the U.S., the Food and Drug Administration did not completely suspend LAAM, but recommended using other opiate pharmacotherapy first. (Fegus Law



Notes

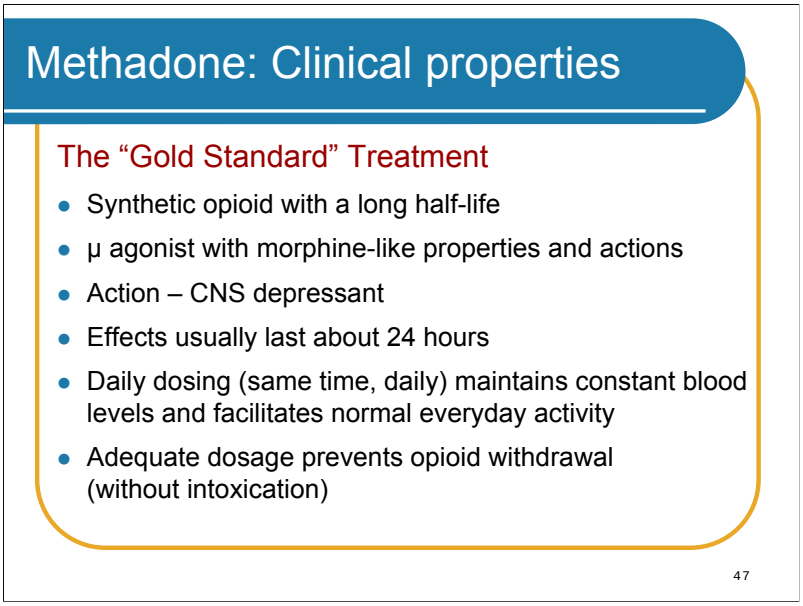
Patients are more likely to cut down or cease use as they age and mature. Retaining them in treatment is the first priority. GPs can greatly assist in initiating and supporting patients' engagement in treatment.

Involvement in a comprehensive treatment program is crucial to insure the provision of patient supports required to adjust to new lifestyles and to take the opportunities afforded by maintenance therapies. The legal, social, health, and lifestyle changes that occurred when a patient was (or is still) using drugs may take considerable time to resolve. Hence, the support offered by members of the health team can significantly assist the patient and the treatment plans.

Harm reduction measures reduce mortality and morbidity rates associated with opioid use.

Pharmacotherapies increase psychological, emotional, and physical wellbeing of patients.

Source: CDHA (Commonwealth Department of Health and Ageing) 2002, *Illicit Drug Training for Pharmacists* [training package], overheads 6.4, 6.6; CDHA, Canberra.



Notes

Methadone is recognised as the “gold standard” of treatment for managing opioid dependence and has been found to be an effective public health and harm reduction measure. Its use is generally restricted to specific medical conditions, such as opioid dependence and the management of chronic pain.

In Australia, methadone is provided by public government services (public programs) and privately through trained GP prescribers.

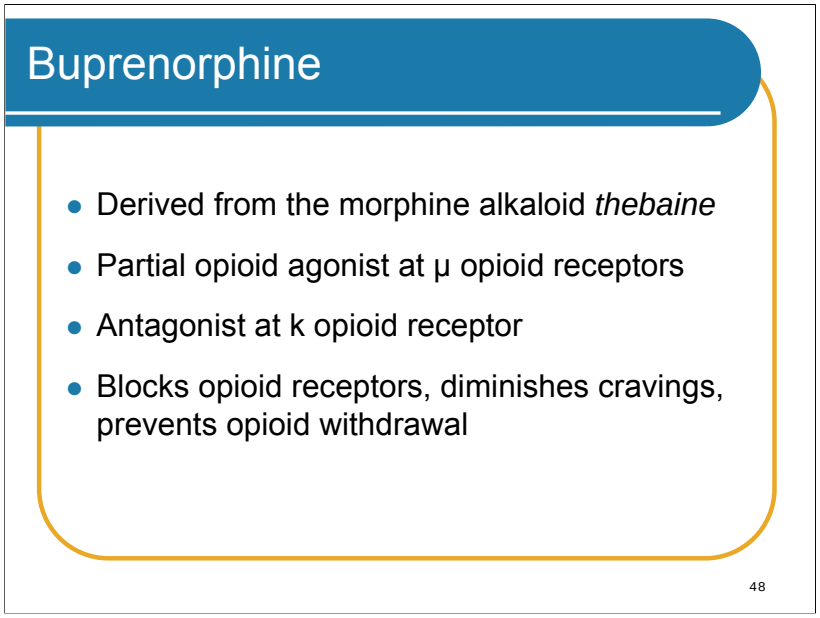
Methadone is highly effective when taken orally. When used repeatedly, such as during maintenance for opioid dependence, its effects persist and the duration of its effect is extended.

Although a potent analgesic for chronic pain, the analgesic effect can lasts for 24 hours (variable) because of its variable half-life.

Methadone:

- is detectable in plasma for 30 minutes following ingestion and it might be detected in plasma for hours to days
- has a peak concentration after about 4 hours
- has a single dose half-life of 15–22 hours (high variability)
- has a maintenance dosing half-life of 22 hours and suppression of withdrawal for 24–36 hours
- stability varies with metabolic rate, which varies according to genetic makeup and environmental and disease-state factors (e.g., pregnancy increases methadone metabolism)
- oral form is only marginally less potent than IM form.

Source: CDHA (Commonwealth Department of Health and Ageing) 2002, *Illicit Drug Training for Pharmacists*, CDHA, Canberra, p.86.



Notes

Blocks opioid receptors (which blocks the effects of extraneous opioids), thereby diminishing cravings for opioids and preventing opioid withdrawal.

Buprenorphine:

–is a partial opioid agonist at μ receptors. It can displace other opioids competing at the same receptor. It may therefore precipitate onset of withdrawal on initial administration. It has an euphoric effect but a less sedating effect than full opioid agonists

–binds strongly to the receptor and is not easily displaced

–also a kappa opioid receptor antagonist

Metabolism occurs through two pathways:

–conjugation with glucuronic acid

–N-de-alkylation

Metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites, mainly in urine and faeces

Pain management: includes post-operative, terminal and chronic pain

Extended duration of action thought to relate to:

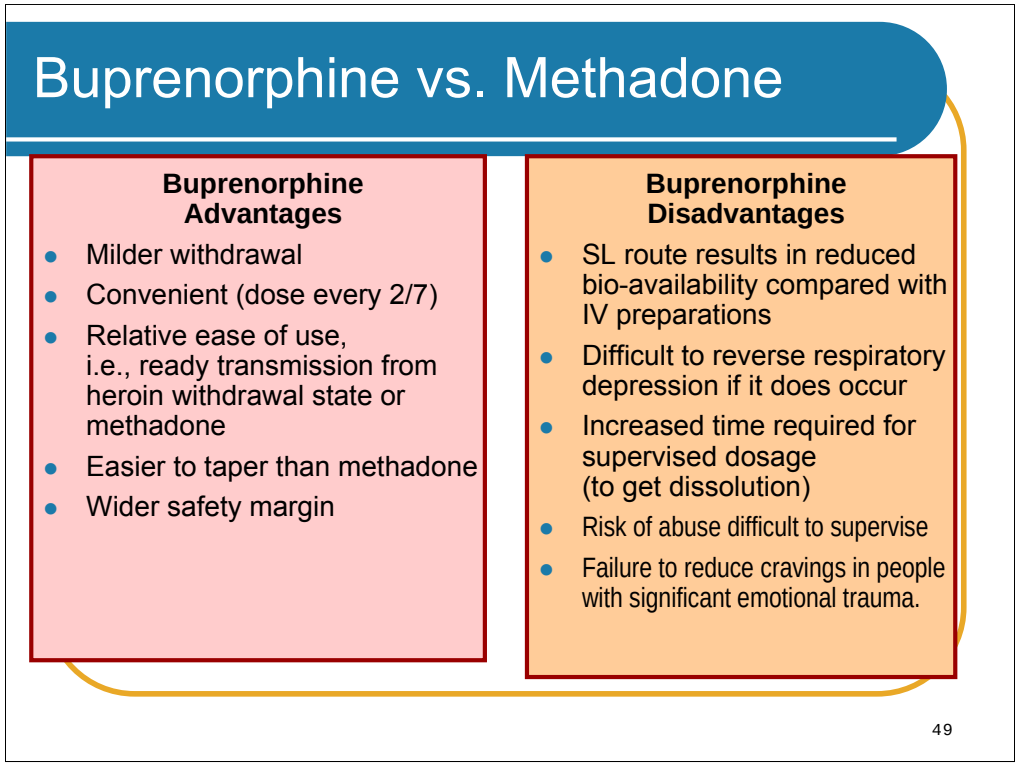
–a high affinity to μ receptors

–high lipophilicity (low levels are released from fat stores with chronic dosing)

–reabsorption after intestinal hydrolysis of conjugated metabolites.

Sources: adapted from CDHA (Commonwealth Department of Health and Ageing) 2002, *Illicit Drug Training for Pharmacists*, CDHA, Canberra, pp. 89–90.

Lintzeris, N., Clark, N., Muhleisen, P., Ritter, A., Ali, R., Bell, J., Gowing, L., Mattick, R., Monheit, B., Newton, I., Quigley, A. Whicker, S., White, J. & Henry-Edwards, S. 2001, *National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence,* National Drug Strategy, March, cited in CDHA (Commonwealth Department of Health and Ageing) 2002 *Illicit Drug Training for Pharmacists*, CDHA, Canberra.



Notes

As a partial agonist, buprenorphine induces a lower level of dependence, hence withdrawal is significantly easier.

Buprenorphine is convenient – patients able to travel short distances (with weekend pickup) and takeaways, decrease chemist contact.

Less likely to be diverted or sold on the streets, as it may precipitate withdrawal in opioid-dependent people.

Safer in accidental overdose (e.g., children) because of poor oral absorption (therefore less respiratory depression).

Initially the pharmacists' practice of crushing tablets was intended for those suspected of diversion. However, recent changes in practice suggest that crushing is increasingly common, and that both pharmacists and patients prefer the tablets crushed as this enables the patient to feel the tablet dissolving and reduces the time spent in the pharmacy. Few people report problems with crushed tablets. Others suggest that crushing decreases the bio-availability of buprenorphine. Further research is needed on this.

Source: Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.

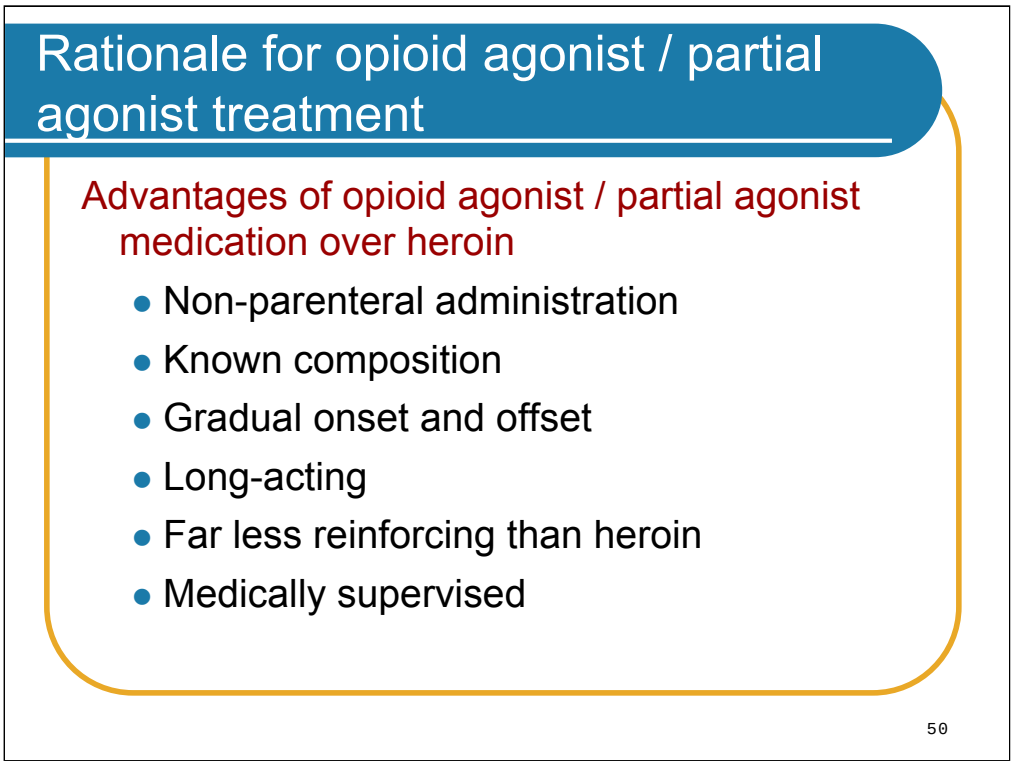
Notes:

Dosing every two days may not be suitable for a proportion of patients.

The main disadvantages of buprenorphine are as follows:

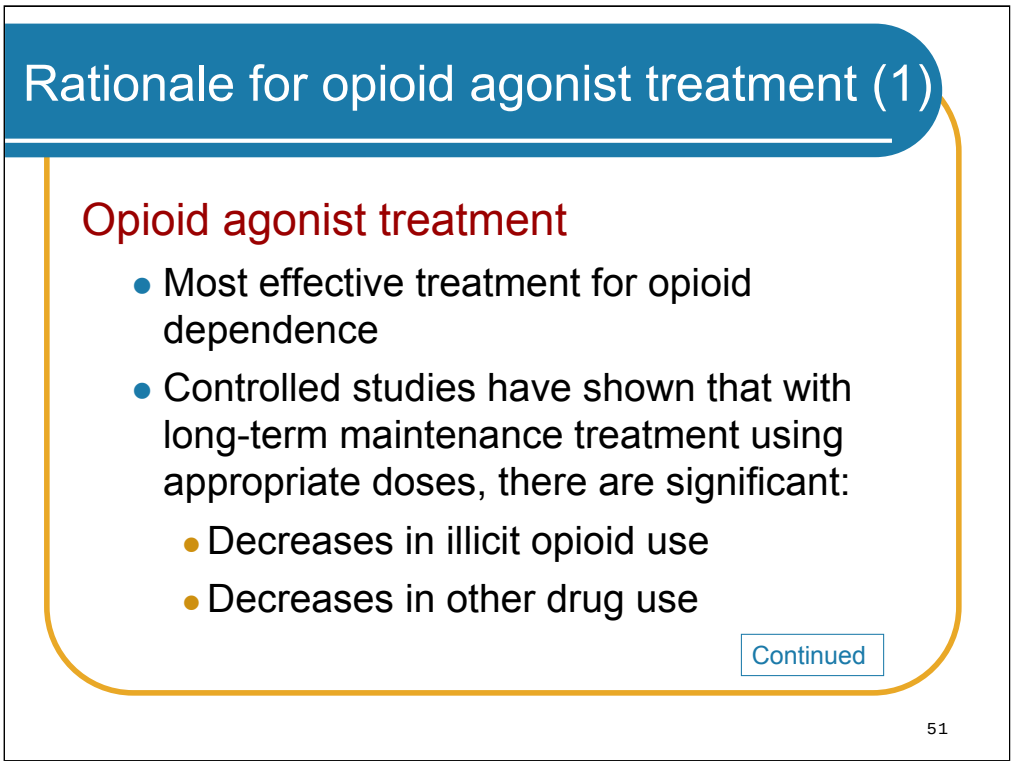
(1) risk of abuse, as it is difficult to supervise

(2) failure to reduce cravings in some people with significant emotional "trauma"



Notes

Medications such as methadone, LAAM, and buprenorphine have several advantages over heroin. They can be administered by safer routes (oral or sublingual, rather than by injection); they are long-acting (so that dosing is daily or several times per week, rather than several times per day); they have known composition (so that dosing can be quantified and constant, and so that contaminants are eliminated and there is a known level of purity); their onset of action is gradual and their effects are mildly reinforcing (insuring compliance in taking the medication while decreasing abuse potential); and they are managed under medical supervision.



Notes

The prototypic opioid agonist maintenance medication is methadone. Controlled studies have shown that methadone, when delivered properly, can be a highly effective medication. Improvements among opioid-dependent patients treated with methadone are not limited to decreases in illicit opioid use. Methadone treatment can result in significant decreases in other drug use, and improvements in other areas (such as employment). Further information about methadone (and LAAM) will be provided in a later section.

References:

Ball J.C., Ross A. The Effectiveness of Methadone Maintenance Treatment. Springer-Verlag, New York, 1991; pages 166-168; 181-182.

Caplehorn J.R.M., Bell J., Kleinbaum D.G., Gebski V.J. Methadone dose and heroin use during maintenance treatment. Addiction 88:119-124, 1993.

Ling W., Charuvastra C., Kaim S.C., Klett J. Methadyl acetate and methadone as maintenance treatments for heroin addicts. Arch Gen Psychiatry 33:709-720, 1976.

Simpson D.D., Sells S.B. Opioid Addiction and Treatment: A 12-Year Follow-up. Robert E. Krieger Publishing Company, Malabar, Florida, 1990.

Strain E.C., Stitzer M.L. Methadone Treatment for Opioid Dependence. Johns Hopkins University Press, Baltimore, Maryland, 1999.

Strain E.C., Stitzer M.L., Liebson I.A., Bigelow G.E. Randomized controlled trial of moderate versus high dose methadone in treatment of opioid dependence. JAMA 281:1000-1005, 1999.]

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

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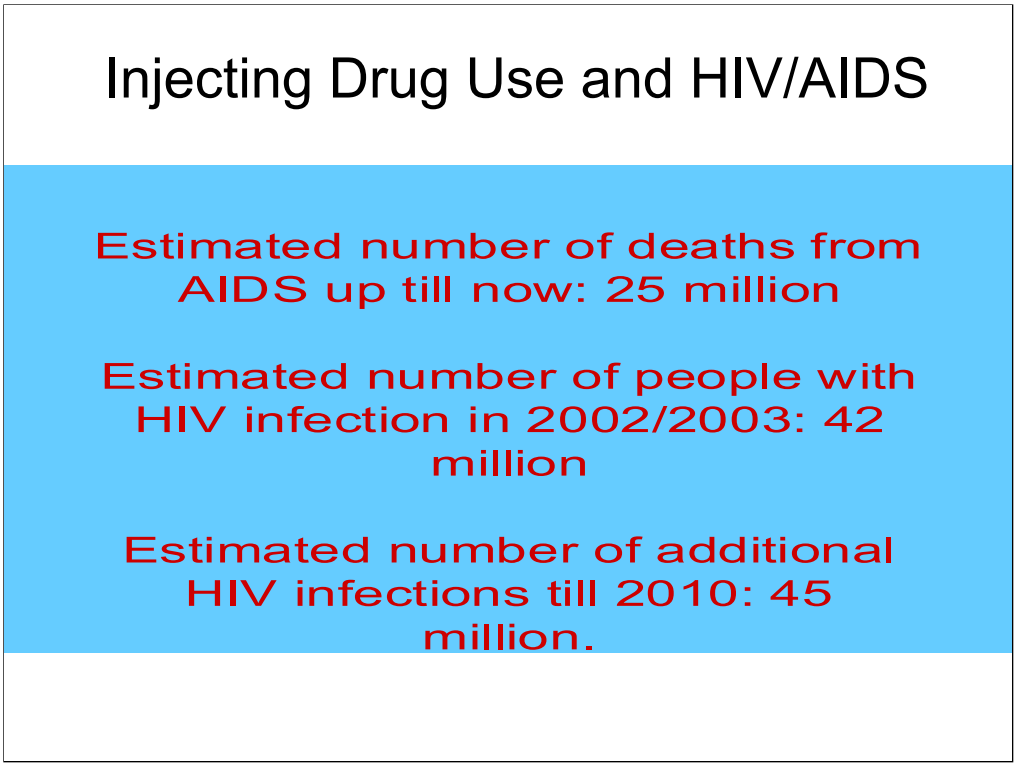

Notes

Injecting drug use is a major form of transmission of HIV/AIDS. Anyone engaging in injecting behaviour should be counselled about risks and illicit drug users advised to use safer routes of administration. Further information on harm reduction strategies (preventing HIV, etc.) is available in Volume D Topic 4 (*Harm Reduction and HIV Risk Reduction Strategies*) of the training materials.

Source: WHO (World Health Organization) 2003.

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.

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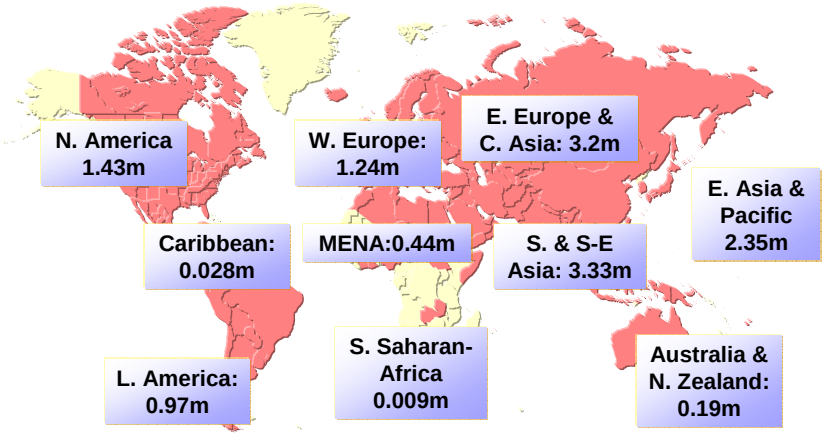
Estimated Size of IDU Population (1998/2003)



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."

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Notes

The position paper *Substitution Maintenance Therapy in the Management of Opioid Dependence and HIV/AIDS Prevention* is available online at:

http://www.who.int/substance_abuse/publications/en/PositionPaper_English.pdf

Availability of Substitution Treatment

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

Substitution treatment is also available in the following countries:

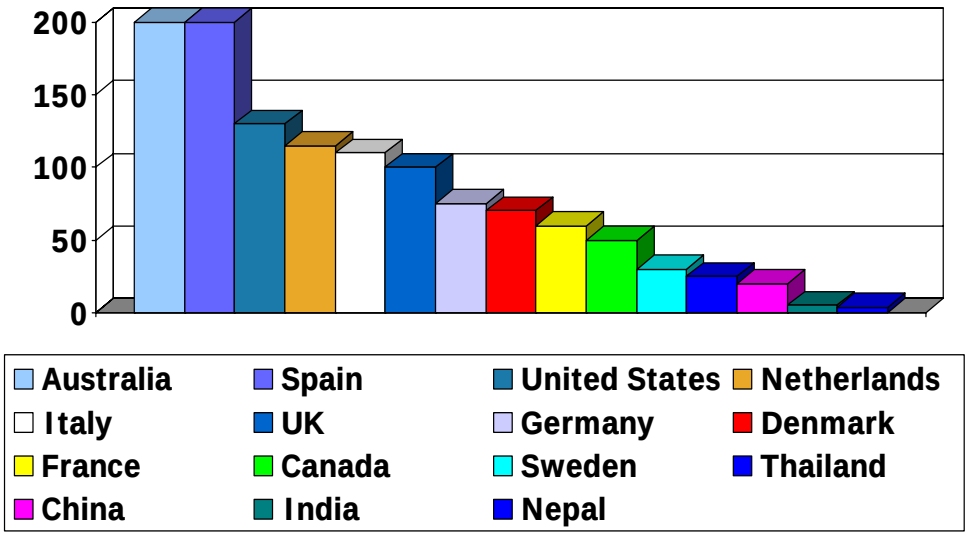
- Argentina
- China
- Croatia
- India
- Indonesia
- Iran
- Kyrgystan
- Malaysia
- Moldova
- Nepal
- Singapore
- Thailand
- Ukraine

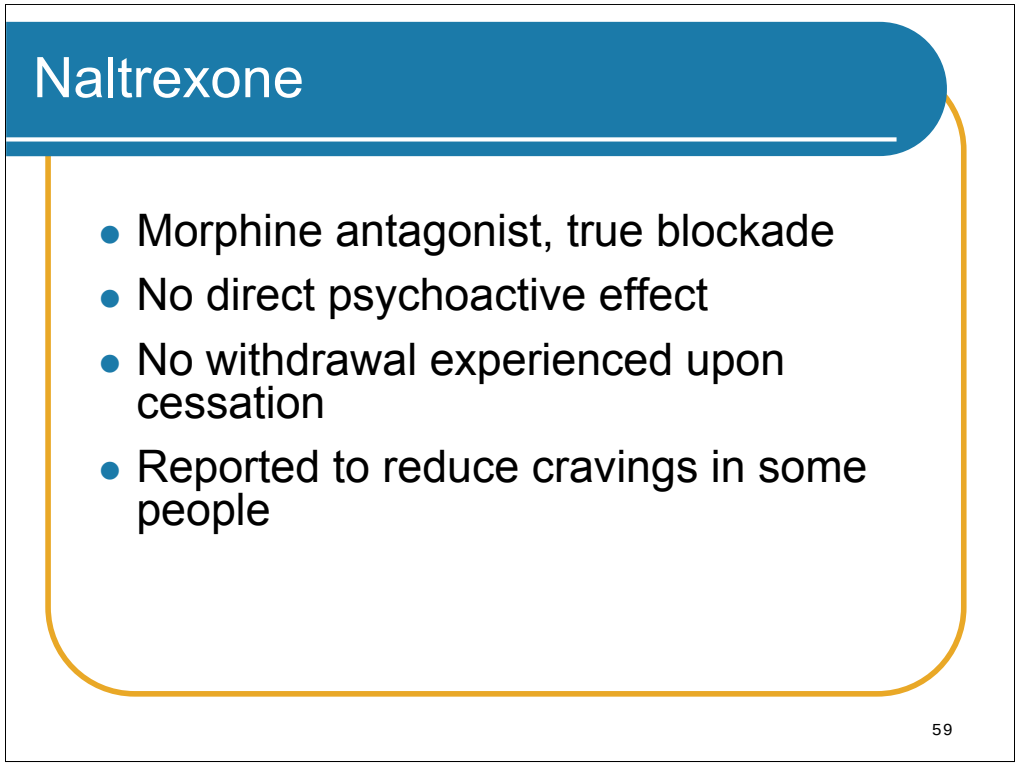
US	**53%**	**8.7 tons**
Spain	**11%**	**1.8 tons**
Germany	**6%**	**916kg**
Italy	**5%**	**812kg**
UK, Canada, Australia, Switzerland, France, Denmark and Belgium,	**18%**	
Most of the rest consumed by 8 other countries, mostly in Europe, and Australia		

Notes:

Acknowledgments: Thanks to Gerry Stimson.

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





Notes

Because of the lack of psychoactive effect, naltrexone is not self-reinforcing.

Naltrexone: Mechanism of action

- Fully blocks u 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

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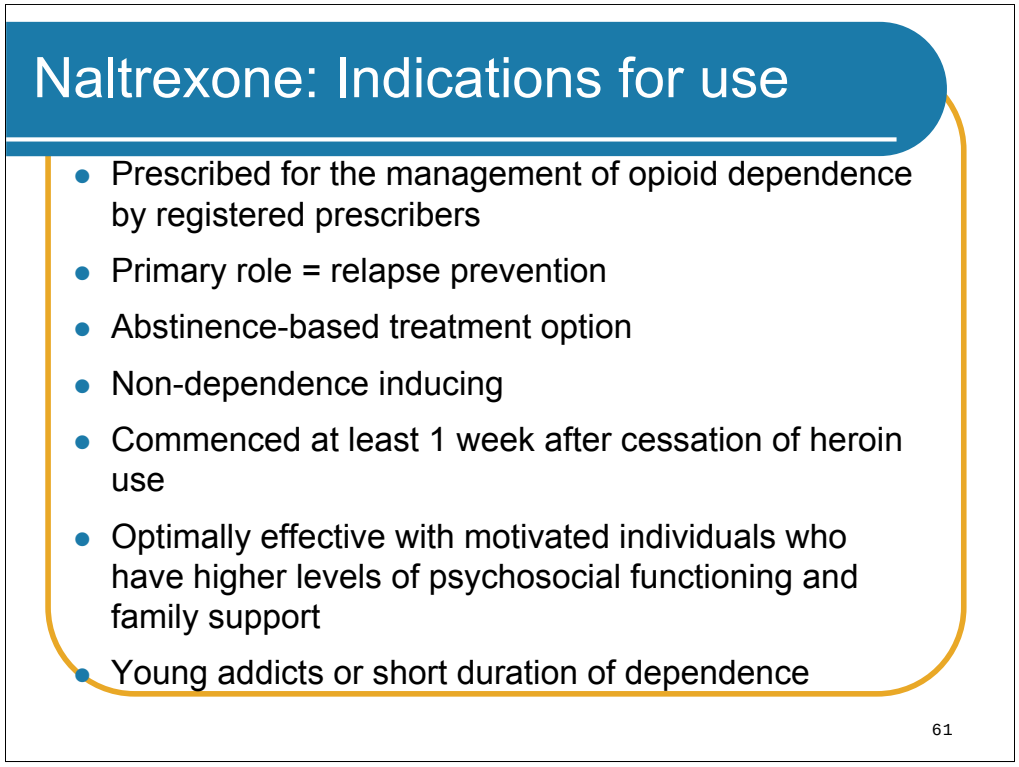

Additional information on Naltrexone:

Because of the potential to induce severe withdrawal, naltrexone should only be commenced after the patient has been at least:

- 7 days heroin-free
- 10 days methadone-free.

Because Naltrexone does not have narcotic effect, it does not produce any withdrawal symptoms. Despite its potential advantage, it has little impact on the treatment of opioid addition in the U.S. because of poor patient compliance.

It is important to mention that some researchers advise of the risk of heroin overdose due to the fact that patients may stop using naltrexone and relapse to heroin. However further research is needed to validate this concern.

(Source: U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment. *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs: TIP 43*. Available at www.samhsa.gov)

Questions?

Comments?

62

Thank you for your time!

End of Workshop 1

Workshop 2:
Opiate Addiction Treatment with Methadone

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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

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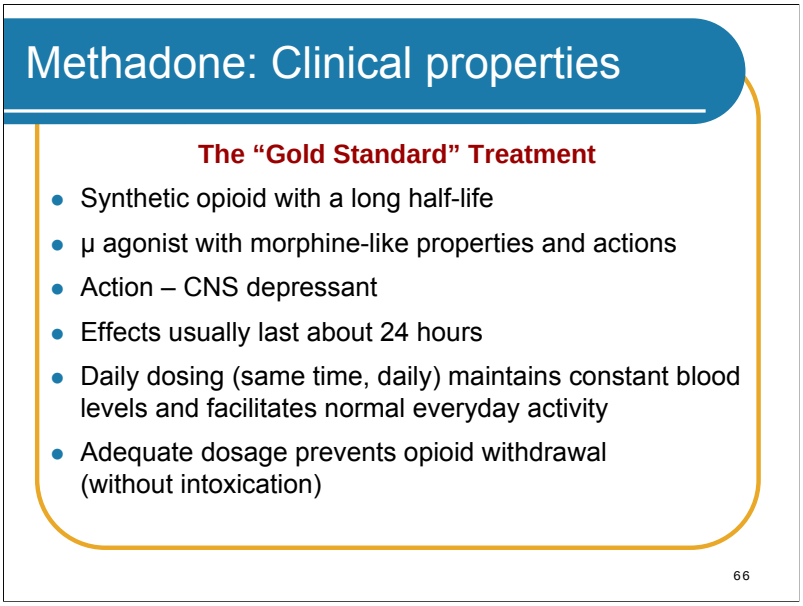


Notes

Methadone is recognised as the "gold standard" of treatment for managing opioid dependence and has been found to be an effective public health and harm reduction measure. Its use is generally restricted to specific medical conditions, such as opioid dependence and the management of chronic pain.

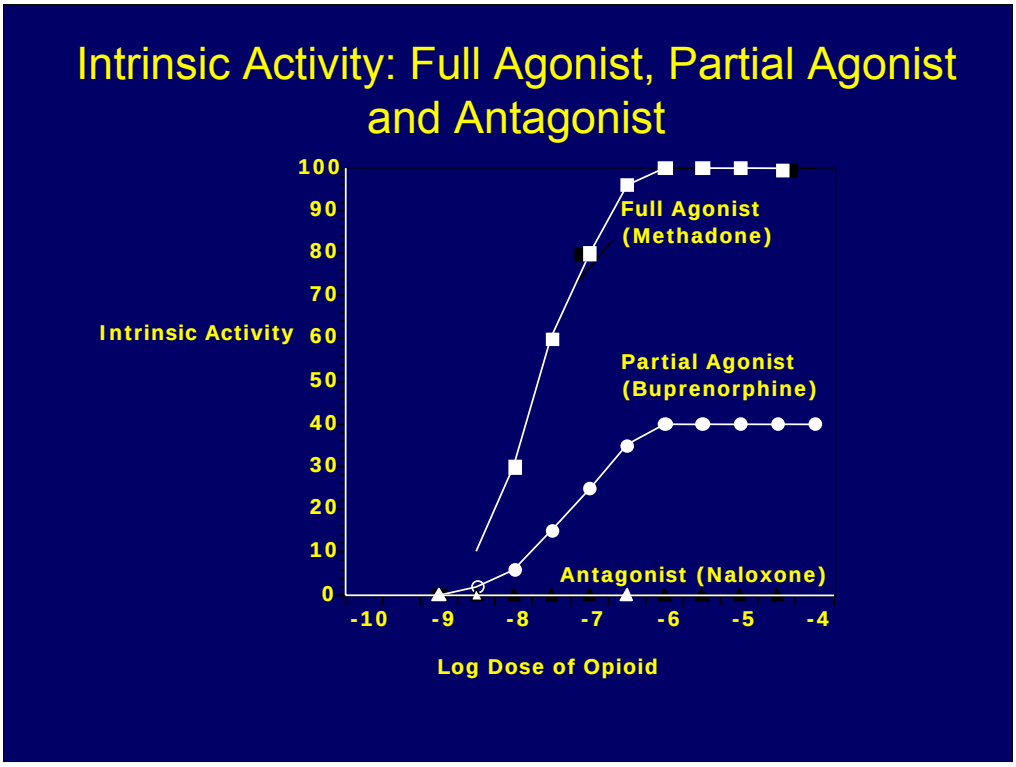
Methadone is highly effective when taken orally. When used repeatedly, such as during maintenance for opioid dependence, its effects persist and the duration of its effect is extended.

Although a potent analgesic for chronic pain, the analgesic effect lasts for less than 24 hours because of its variable half-life.

Methadone:

- is detectable in plasma for 30 minutes following ingestion
- has a peak concentration after about 4 hours
- has a single dose half-life of 15–22 hours (high variability)
- has a maintenance dosing half-life of 22 hours and suppression of withdrawal for 24–36 hours
- stability varies with metabolic rate, which varies according to genetic makeup and environmental and disease-state factors (e.g. pregnancy increases methadone metabolism)
- oral form only marginally less potent than IM form.

Source: CDHA (Commonwealth Department of Health and Ageing) 2002, *Illicit Drug Training for Pharmacists*, CDHA, Canberra, p.86.



(Source: Drug and Alcohol Dependence 70 (Suppl.) Johnson et al. *Buprenorphine: How to use it right*. 59-77, 2003)

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

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Pharmacodynamics

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

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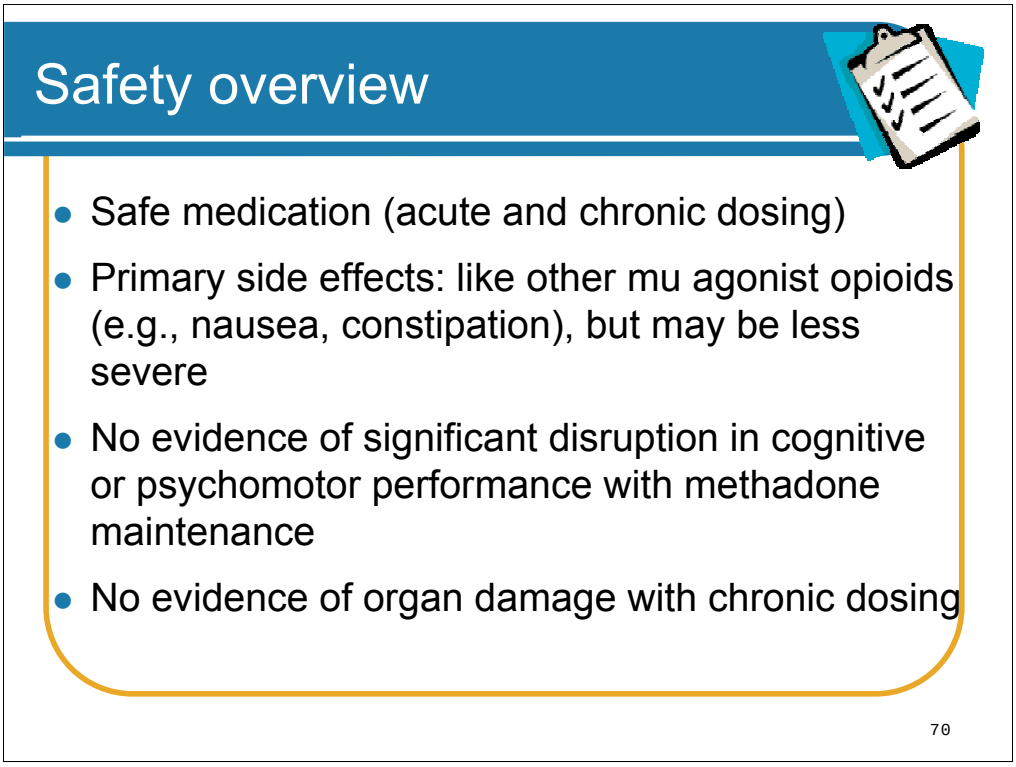


Notes

1. Buprenorphine is a highly safe medication for use in patients with opioid dependence.

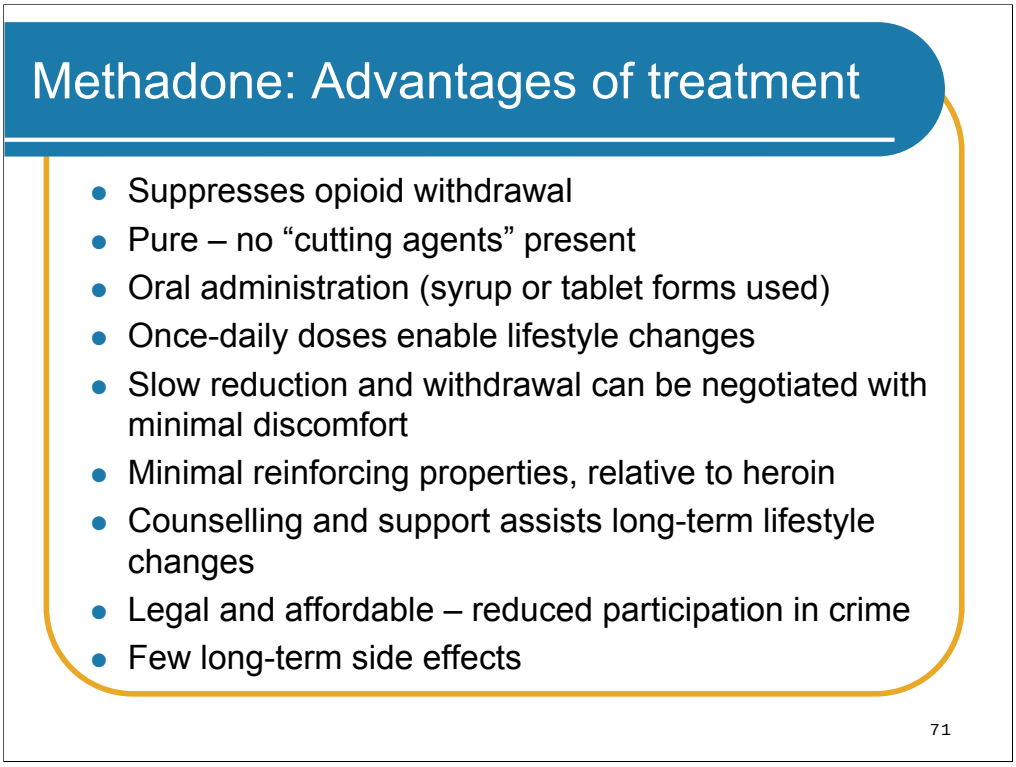
2. Note that it is also safe if inadvertently taken by a person who is not physically dependent on opioids (such as a child). In such a case, it is most likely the person would swallow the tablet and experience virtually no opioid agonist effect because of the poor oral bioavailability. Even if the person sucked on the tablet, there is a low likelihood that they would experience serious adverse effects. This is because buprenorphine is a partial opioid agonist, and there is a ceiling in the maximal effects produced.

3. Clinical trials with buprenorphine have found no significant organ damage associated with chronic dosing. However, buprenorphine may be associated with increases in liver function tests, and this may be especially true for patients with a history of hepatitis prior to the onset of buprenorphine treatment. Increases in liver function tests appear to be mild, and it is important to keep in mind that other factors commonly found in opioid-dependent patients (such as hepatitis and alcohol abuse) can lead to elevations in liver function tests.

References:

Petry, N. M., Bickel, W. K., Piasecki, D., Marsch, L. A., Badger, G. J. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. Am J Addict 9:265-9, 2000.

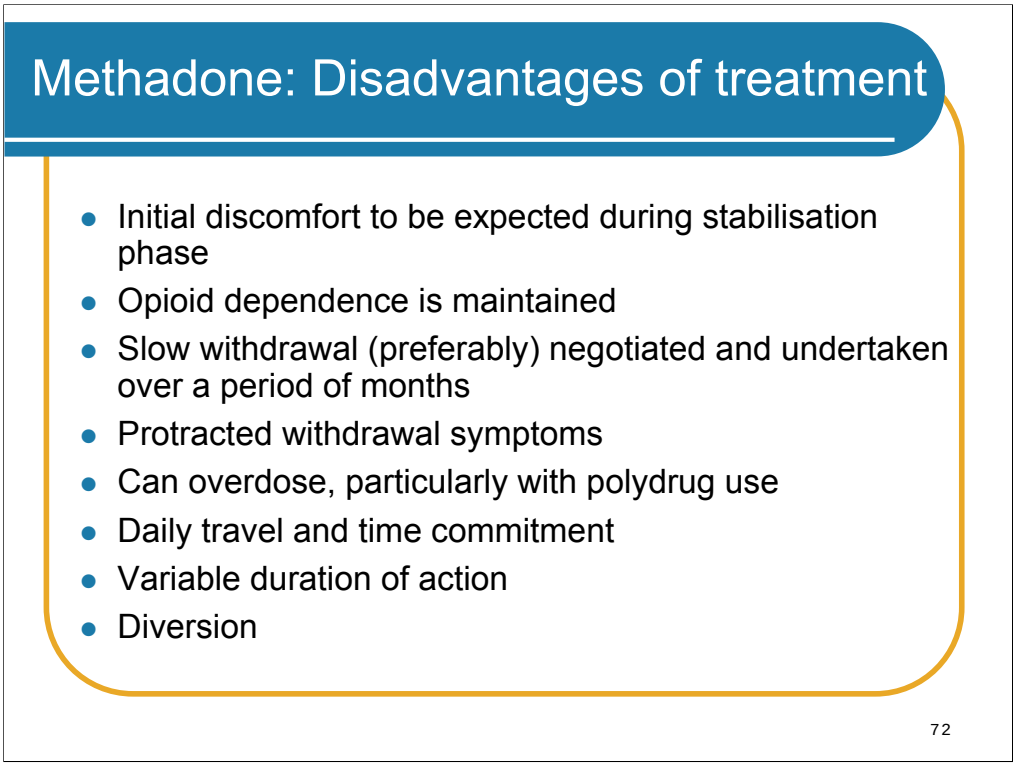
Lange W.R., Fudala P.J., Dax E.M., Johnson R.E. Safety and side-effects of buprenorphine in the clinical management of heroin addiction**.** Drug Alcohol Depend 26:19-28, 1990.]



Notes

There are a few long-term health effects from use of methadone. Those known include:

- weight gain, possibly influenced by fluid retention and dietary changes
- reduced production of saliva – may contribute to dental problems
- endocrine changes – may result in impotence, low libido, disrupted menstrual cycle
- may be harmful in presence of underlying disease, e.g., kidney or liver problems
- some effects disappear when dose is adjusted.



Notes

Committing oneself to methadone maintenance therapy (MMT) can be off-putting to many and interferes with work activities or travel arrangements.

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

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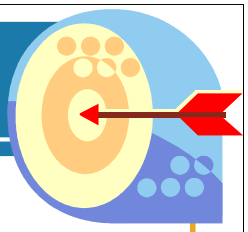
Assessment objectives



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

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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?

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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
- Hepatitis B
- TB
- Pregnancy
- Other major medical conditions
  - Liver
  - Cardiac
- Major psychiatric conditions
  - Depression, suicide, psychosis
- Opioid-related overdose

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Psychosocial

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

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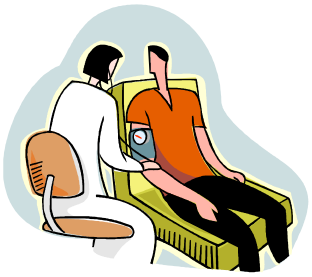
Examination

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



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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

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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

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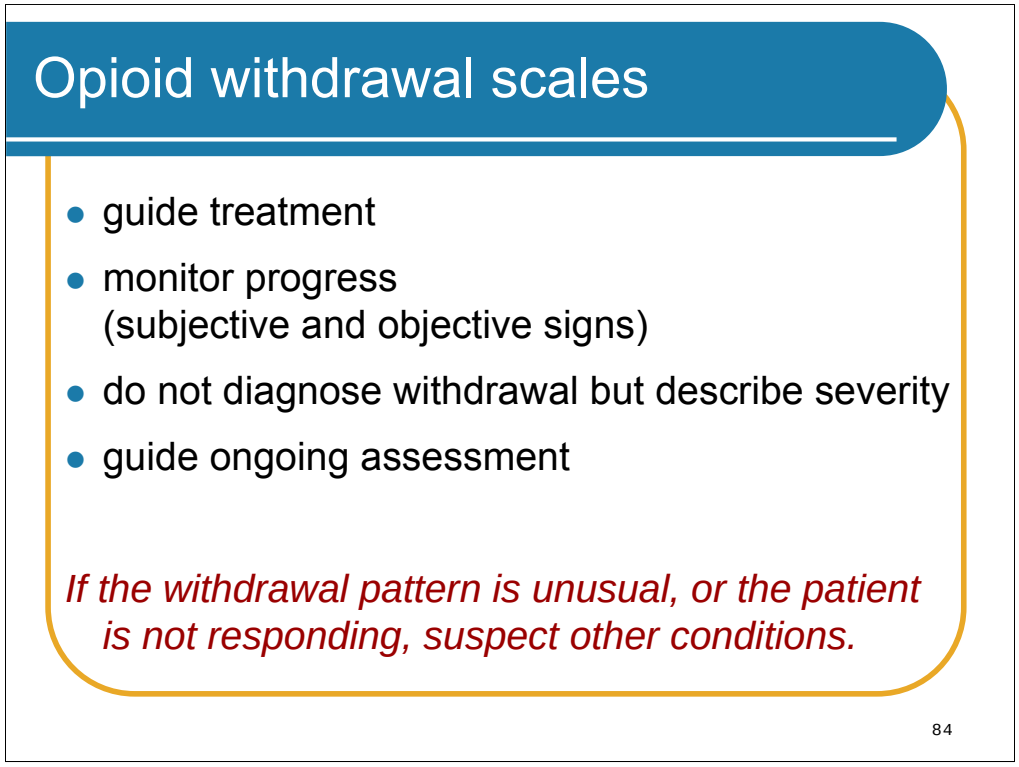
Methadone: Initial Effects and Side-Effects

- 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.

Notes

Effects may vary according to the individual, level of neuroadaptation, dosage, frequency taken, etc.



Notes

Tools

The Subjective Opioid Withdrawal Scale (SOWS; see Handouts).

The Objective Opioid Withdrawal Scale (OOWS; see Handouts).

Use of the SOWS during assessment enables patients to be involved in their own care and can assist in reducing their anxiety.

Sources: deCrespigny, C., Talmet, J, Modystack, K., Cusack, L. & Watkinson, J. 2003, *Alcohol, Tobacco and Other Drugs Guidelines for Nurses and Midwives: Clinical Guidelines*, Flinders University and Drug and Alcohol Services Council (DASC), Adelaide.

Lintzeris, N., Clark, N., Muhleisen, P., Ritter, A., Ali, R., Bell, J., Gowing, L., Mattick, R., Monheit, B., Newton, I., Quigley, A. Whicker, S., White, J. & Henry-Edwards, S. 2001, *National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence,* National Drug Strategy, March 2001, cited in CDHA (Commonwealth Department of Health and Ageing) 2002 *Illicit Drug Training for Pharmacists*, CDHA, Canberra, pp. 67–68.

Victoria Police 2002, *Custodial Drug Guide: Medical Management of People in Custody with Alcohol and Drug Problems*, Custodial Medicine Unit, Victoria Police, Mornington, Victoria, pp. 4-9–4-10.

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

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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

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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 _____

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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

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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

Continued

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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
- Repeated doses of 30mg can be fatal in adults

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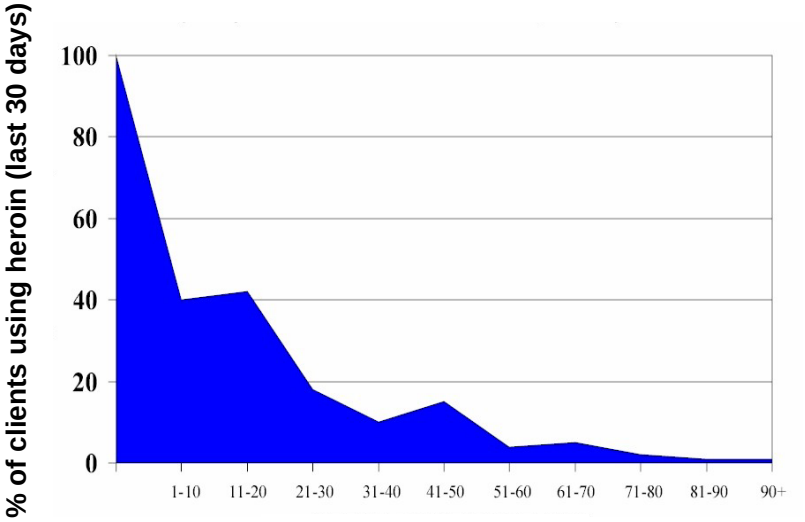
Notes:

Methadone dosage is individualised. 80 mg is the average, but some patients may require lower or higher doses.

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

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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

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Ongoing management issues (1)

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

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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

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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., Nifidepine, etc.

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Questions?

Comments?

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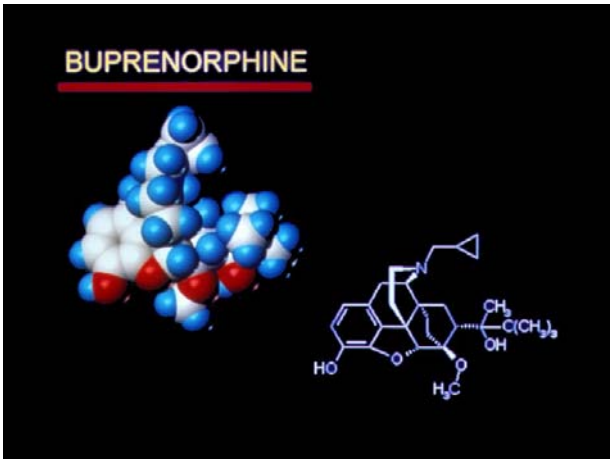
Thank you for your time!

End of Workshop 2

Workshop 3: Opiate Addiction Treatment with Buprenorphine



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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

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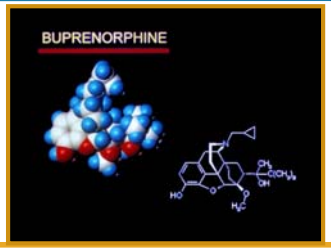
Overview



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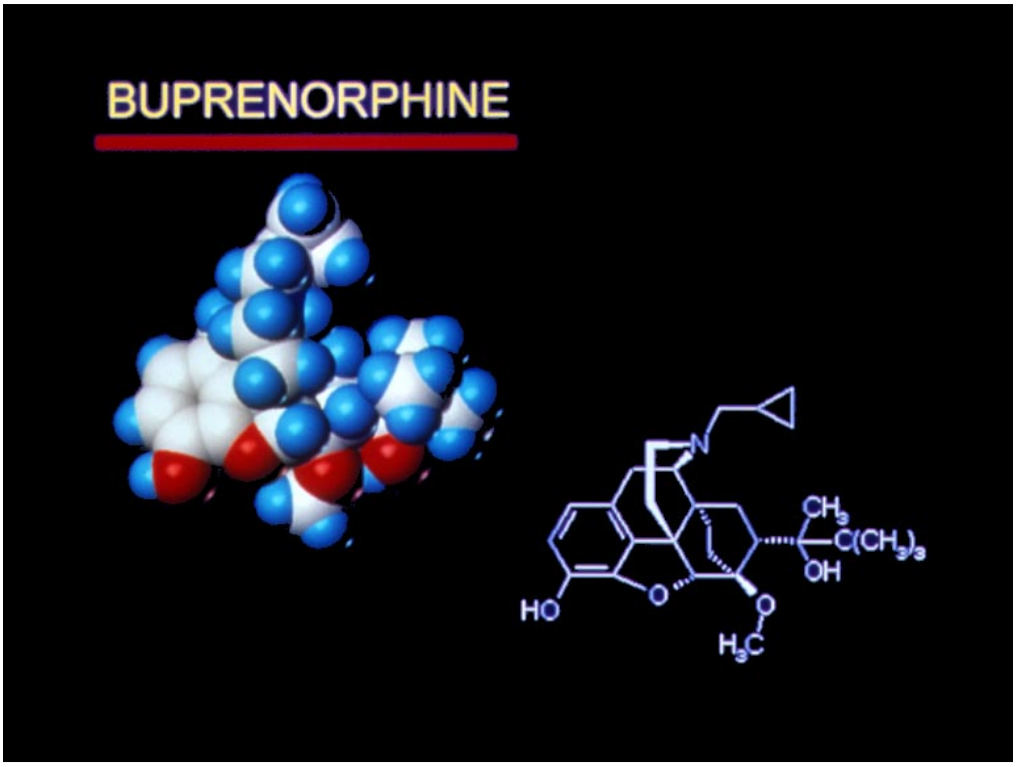
BUPRENORPHINE
HO
O
O
H_3C
N
CH_3
$C(CH_3)_3$
OH

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)
- Available as sublingual tablets (2-8 mg)
- Long duration of action when used for the treatment of opioid dependence contrasts with its relatively short analgesic effects

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Notes

Buprenorphine is a thebaine derivative. This is important, because it leads to buprenorphine's legal classification as an opioid. It has high potency. Buprenorphine has been available for years in the United States as a parenteral analgesic. Typical analgesic doses are 0.3-0.6 mg i.m. or i.v. every 6 (or more) hours.

Sublingual tablets of buprenorphine with naloxone are also available to reduce the potential for abuse (source: U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction: TIP 40*. Available at www.samhsa.gov)

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)

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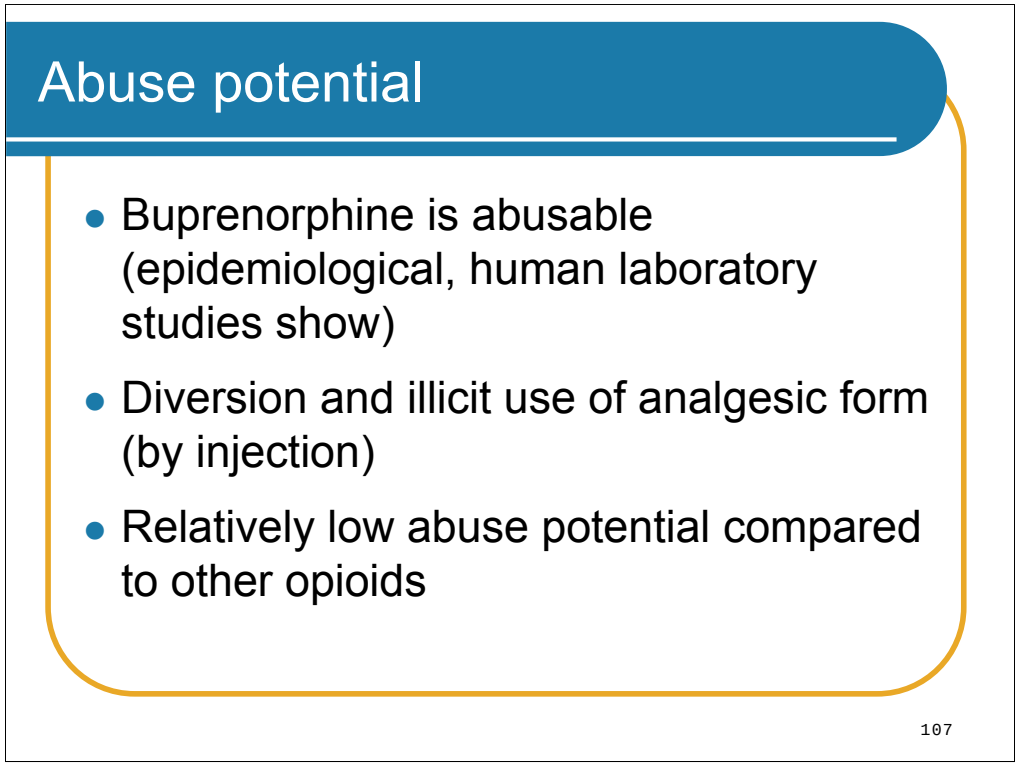
Notes

1. Buprenorphine has high affinity for the mu opioid receptor. This means that it is hard for other opioids with lower affinity to displace buprenorphine from the mu receptor (so it blocks their effects).

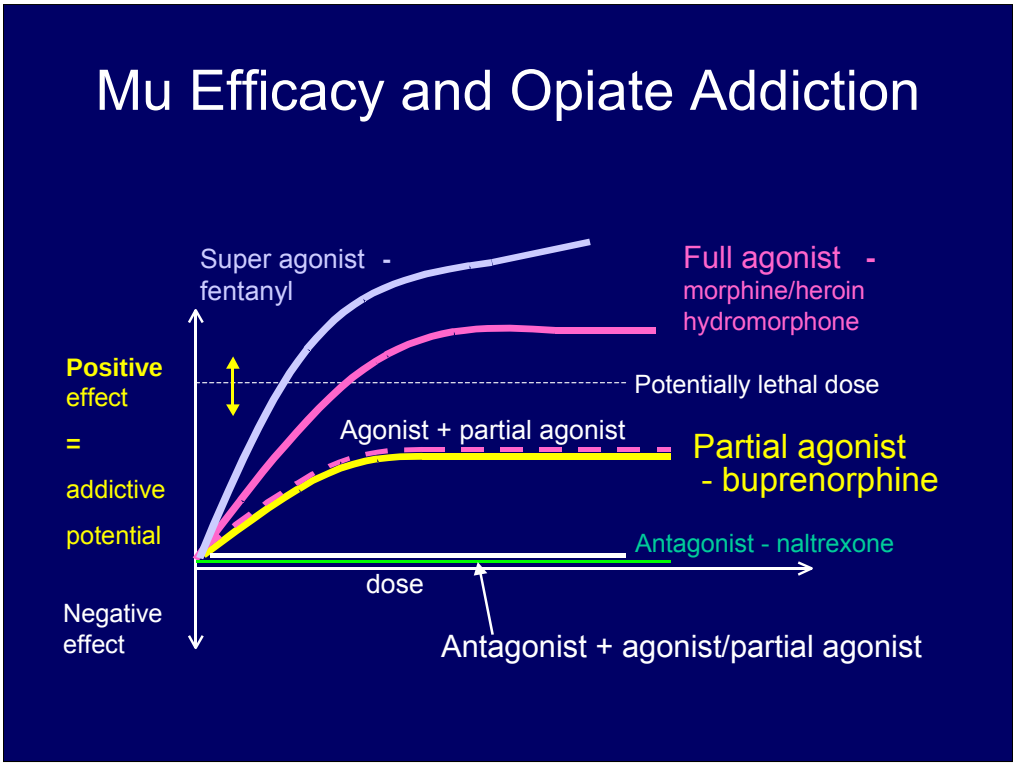
2. Buprenorphine's slow dissociation from the mu receptor results in a prolonged therapeutic effect. Considerable evidence suggests buprenorphine can be given three times per week (rather than daily), and there is some evidence suggesting buprenorphine can be given even less frequently (e.g., two times per week).

3. Buprenorphine's long duration of action when used as a medication for the treatment of opioid dependence contrasts with its relatively short analgesic effects.



Notes:

Abuse potential of buprenorphine is similar to heroin in laboratory studies, but it is safer in overdose.



Notes:

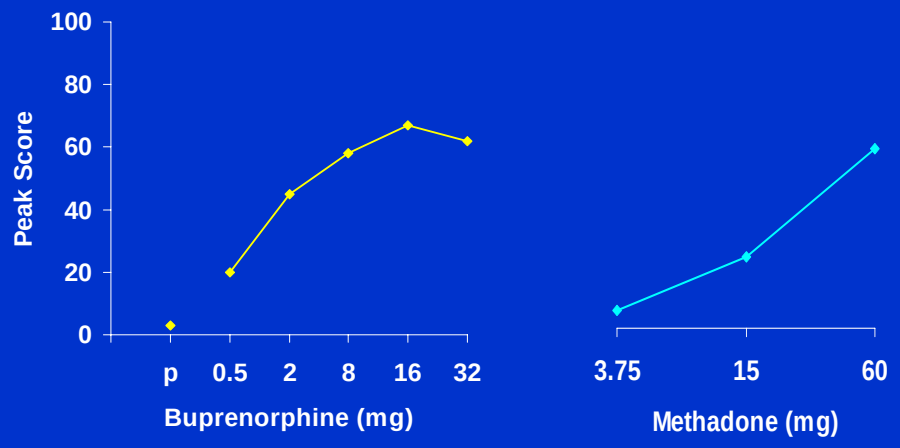
Avoid referring to buprenorphine as an agonist/antagonist. It is confusing. It is sufficient to use the term partial agonist.

Positive effect does not necessarily correspond to the addictive potential. Buprenorphine is as addictive as methadone, if not more so, but it is safer in overdose.

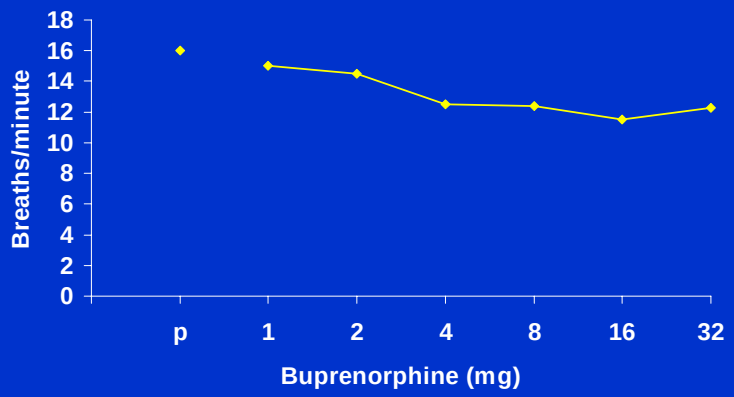
Buprenorphine: Clinical pharmacology

- Partial agonist
  - high safety profile / ceiling effect
- Tight receptor binding at mu receptor
  - long duration of action
  - slow onset mild abstinence
- Antagonist at k receptor

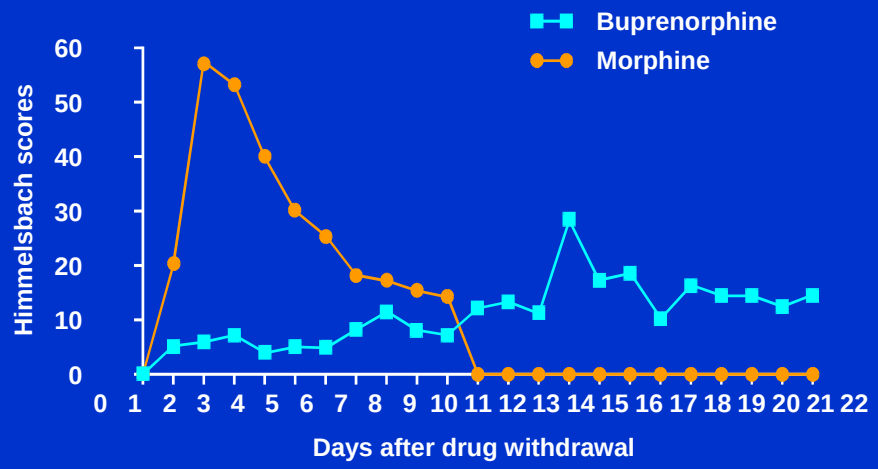
Subjects' Rating of Drugs' Good Effect



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

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References:

Iribarne C., Picart D., Dréano Y., Bail J.-P., Berthou F. Involvement of cytochrome P450 3A4 in *N*-dealkylation of buprenorphine in human liver microsomes. Life Sciences 60:1953-1964, 1997.

Kobayashi K., Yamamoto T., Chiba K., Tani M., Shimada N., Ishizaki T., Kuroiwa Y. Human buprenorphine *N*-dealkylation is catalyzed by cytochrome P450 3A4. Drug Metab Dispo 26:818-821, 1998.]

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

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Patient selection: Issues for consideration (2)

Pregnancy

- Currently buprenorphine is not approved for use during pregnancy.
- However, 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.

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Notes:

There is limited clinical experience with buprenorphine maintenance in pregnant women who are addicted to opioids. There is a need for further studies to determine if it is safe to use buprenorphine during pregnancy.

Patient selection: Issues for consideration (3)

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

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

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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

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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

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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

Continued

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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

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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)

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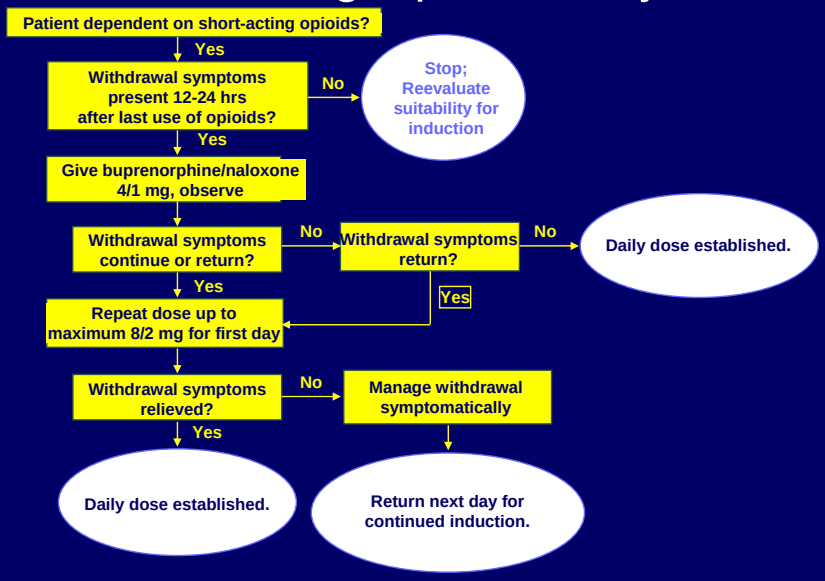
Induction: Patient Physically Dependent on Short-acting Opioids, Day 1



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 <30 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

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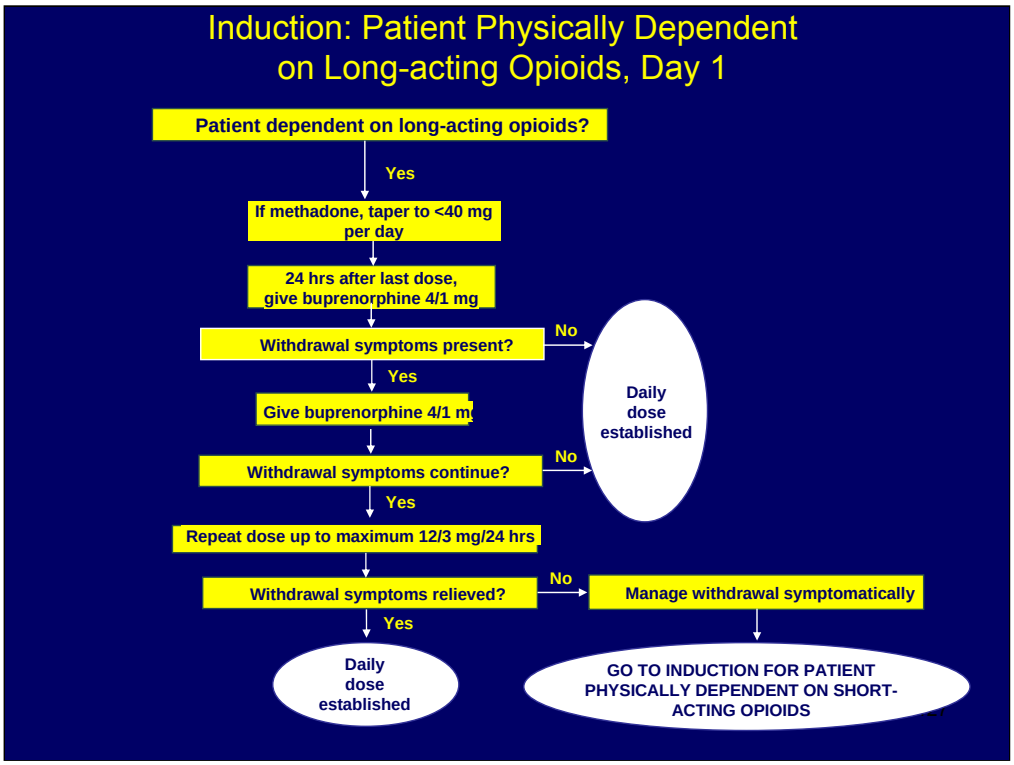
Induction: Patient Physically Dependent on Long-acting Opioids, Day 1
Patient dependent on long-acting opioids?
Yes
If methadone, taper to <40 mg per day
24 hrs after last dose, give buprenorphine 4/1 mg
Withdrawal symptoms present?
No
Daily dose established
Yes
Give buprenorphine 4/1 m
Withdrawal symptoms continue?
No
Yes
Repeat dose up to maximum 12/3 mg/24 hrs
Withdrawal symptoms relieved?
No
Manage withdrawal symptomatically
Yes
Daily dose established
GO TO INDUCTION FOR PATIENT PHYSICALLY DEPENDENT ON SHORT-ACTING OPIOIDS

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, if possible, for assessment and Day 2 dosing
- Assess if patient has used opioids since their last visit, and adjust dose according to the patient's experiences after first-day dosing

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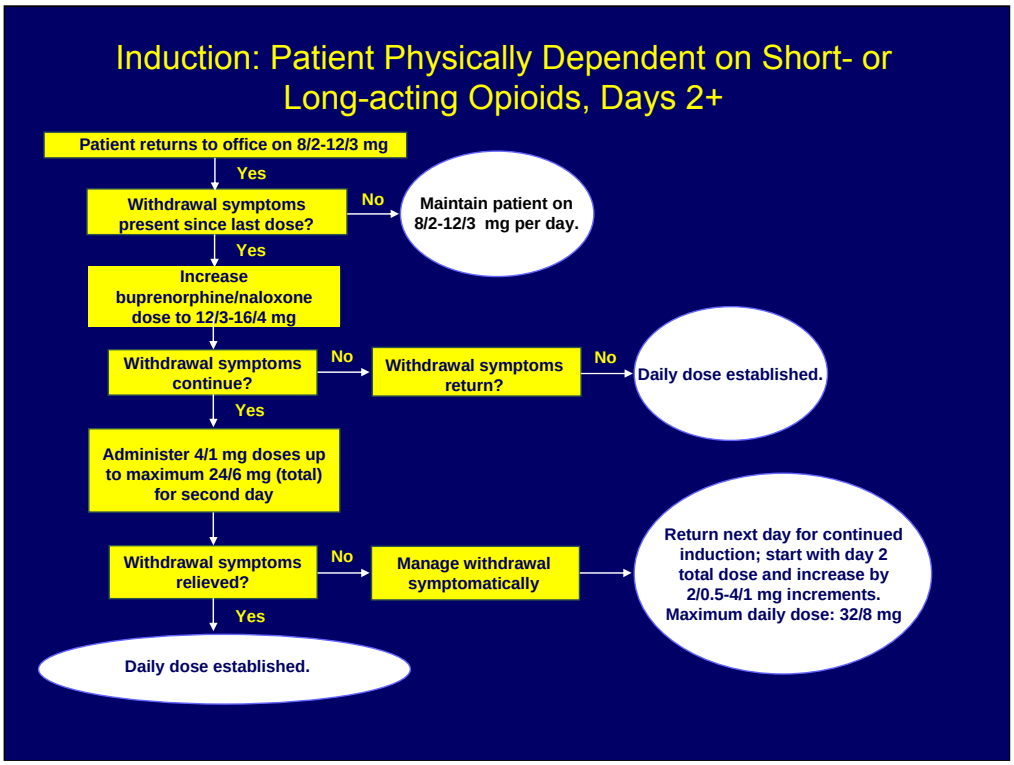

Notes:

Increase the dose if the patient is continuing using heroin or other illicit opioids.

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)

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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
- Higher daily doses more tolerable if tablets are taken sequentially rather than all at once

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Maintenance treatment using buprenorphine

- Buprenorphine more effective than placebo
- Buprenorphine equally effective as methadone. However methadone has better retention rates and probably less heroin use also
- More research needed on 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

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Notes

1. In general, these studies have shown buprenorphine and methadone are equivalent on primary outcome measures (treatment retention, rates of positive urine samples for illicit opioids). However methadone has better retention and probably less heroin use also. There is even less heroin use at higher doses of methadone.

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)

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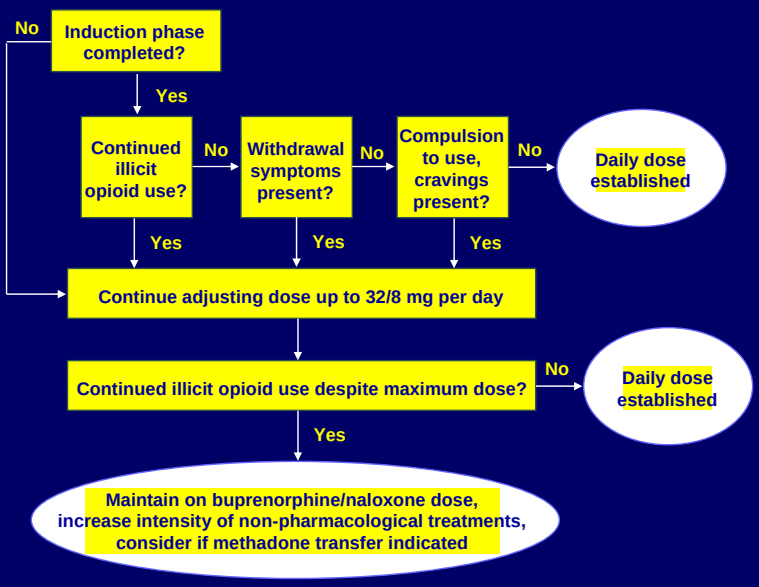
Stabilisation / Maintenance



Withdrawal using buprenorphine (1)

Withdrawal <=7 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 <=7 days

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

Withdrawal <=7 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

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Notes

1. Buprenorphine is a highly safe medication for use in patients with opioid dependence.

2. Note that it is also safe if inadvertently taken by a person who is not physically dependent on opioids (such as a child). In such a case, it is most likely the person would swallow the tablet and experience virtually no opioid agonist effect because of the poor oral bioavailability. Even if the person sucked on the tablet, there is a low likelihood that they would experience serious adverse effects. This is because buprenorphine is a partial opioid agonist, and there is a ceiling in the maximal effects produced.

3. Clinical trials with buprenorphine have found no significant organ damage associated with chronic dosing. However, buprenorphine may be associated with increases in liver function tests, and this may be especially true for patients with a history of hepatitis prior to the onset of buprenorphine treatment. Increases in liver function tests appear to be mild, and it is important to keep in mind that other factors commonly found in opioid dependent patients (such as hepatitis and alcohol abuse) can lead to elevations in liver function tests. Subsequent slides address the effects of buprenorphine on liver function tests.

References:

Petry, N. M., Bickel, W. K., Piasecki, D., Marsch, L. A., Badger, G. J. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. Am J Addict 9:265-9, 2000.

Lange W.R., Fudala P.J., Dax E.M., Johnson R.E. Safety and side-effects of buprenorphine in the clinical management of heroin addiction. Drug Alcohol Depend 26:19-28, 1990.

Precipitated withdrawal (1)

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

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Notes

1. The potential for buprenorphine-precipitated withdrawal has been covered elsewhere in the Basic Pharmacology section, and will not be reviewed in detail here.

2. While it is possible for buprenorphine to precipitate withdrawal during buprenorphine induction, and this possibility has received significant attention and review in this curriculum, it is important to keep this potential in perspective. The likelihood for buprenorphine-precipitated withdrawal is low, and even when it does occur, it is mild in intensity and short in duration. The clinician should be aware of the potential, but not allow the potential to deter from the use of buprenorphine.

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

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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).

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Notes

1. The risk of developing clinically significant problems from a buprenorphine overdose is low. Unlike full agonist opioids (such as methadone and heroin), the maximal opioid agonist effect produced by buprenorphine – a partial agonist – is relatively low. The maximal effects of buprenorphine appear to occur in the 8-16 mg dose range for sublingual solution (in non-dependent opioid abusers). This is equal to 16-32 mg of sublingual tablets. This means that higher doses are unlikely to produce greater effects (and may actually produce fewer effects, based on pre-clinical evidence).

2. This ceiling on the effects produced means buprenorphine is less likely to produce clinically significant respiratory depression. However, overdose in situations where buprenorphine is combined with other CNS depressants may be fatal, as reviewed later in this section.

Reference:

Walsh S. L., Preston K.L., Stitzer M.L., Cone E.J., Bigelow G.E. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther 55:569-80, 1994.

Drug interactions with buprenorphine

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

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Benzodiazepines and other sedating drugs (1)

- Reports of deaths when buprenorphine injected along with injected benzodiazepines. Also deaths from non-injection use of both drugs.
  - 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

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Notes

1. It is not clear, based upon the French experience with buprenorphine-related deaths, if any patients have died from use of sublingual buprenorphine combined with oral benzodiazepine. It appears likely that most deaths have been related to injection of the combination of dissolved buprenorphine tablets with benzodiazepine. However, there have been cases of death from non-injection buprenorphine and benzodiazepines.
2. Note that the combination product (buprenorphine with naloxone) is designed to decrease the likelihood that people will dissolve and inject buprenorphine.
3. The mechanism leading to death in these cases is not known.

References:

Reynaud M., Tracqui A., Petit G., Potard D., Courty P. Six deaths linked to misuse of buprenorphine-benzodiazepine combinations. Am. J. Psychiatry 155, 448-449, 1998.

Tracqui A., Kintz P., Ludes B. Buprenorphine-related deaths among drug addicts in France: A report on 20 fatalities. J. Analytic. Tox. 22, 430-434, 1998.

Gaulier J. M., Marquet P., Lacassie E., Dupuy J. L., Lachatre G. Fatal intoxication following self-administration of a massive dose of buprenorphine. J Forensic Sci 45:226-8, 2000.

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.

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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

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Notes

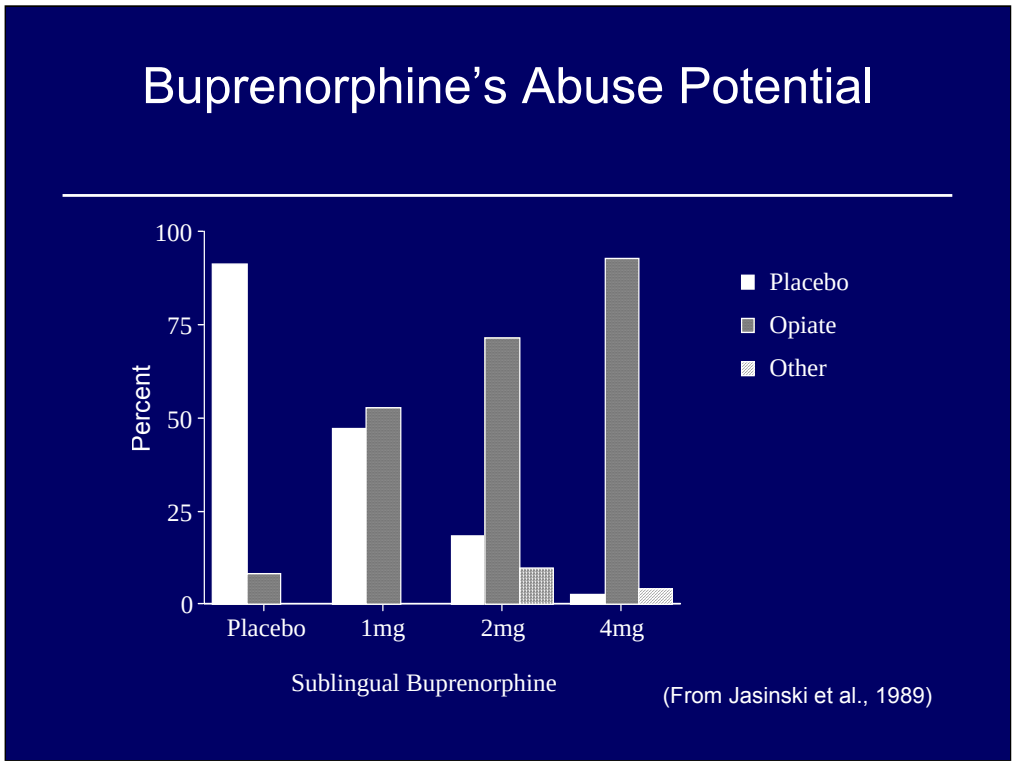
1. Note that there are four possible groups that might attempt to abuse buprenorphine/naloxone.

2. For persons physically dependent on an illicit agonist opioid (like heroin), injection of buprenorphine/naloxone will precipitate withdrawal (or, if the dose is very low – e.g., 1/0.25 mg – it will produce placebo-like effects).

3. For persons physically dependent on a prescribed opioid (like methadone or LAAM), injection of buprenorphine/naloxone will precipitate withdrawal (or, again, if the dose is very low, it will produce placebo like effects).

4. For persons maintained on sublingual buprenorphine/naloxone, injection of buprenorphine/naloxone could produce opioid-agonist-like effects (with no precipitated withdrawal from the naloxone, since high doses of naloxone are needed to precipitate withdrawal in buprenorphine-maintained persons). Note that this is a population that will have access and may be very likely to dissolve and inject buprenorphine/naloxone tablets, since they will have a ready supply of them.

5. For persons not physically dependent on opioids, naloxone will not precipitate withdrawal and it is likely the buprenorphine will produce opioid agonist effects.



Notes

This slide shows results from a study in which persons with a history of opioid abuse, but who were not actively dependent upon opioids, received different doses of sublingual buprenorphine solution. The y-axis shows the percentage of identifications of the buprenorphine as placebo, opiate, or something else. As can be seen, as the dose of sublingual buprenorphine increases, the percent of identifications as opiate-like increases (and the proportion of identifications as something else -- placebo or other, decreases). This illustrates buprenorphine's identification as an opioid-agonist-like drug by persons with a history of opioid abuse.

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

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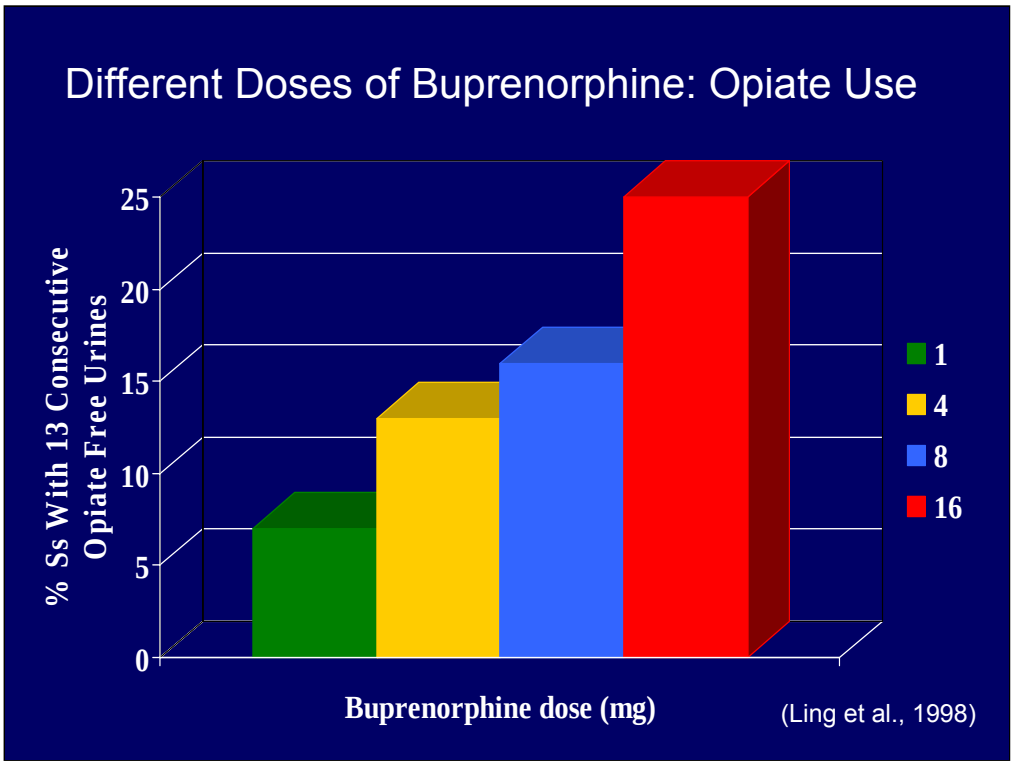
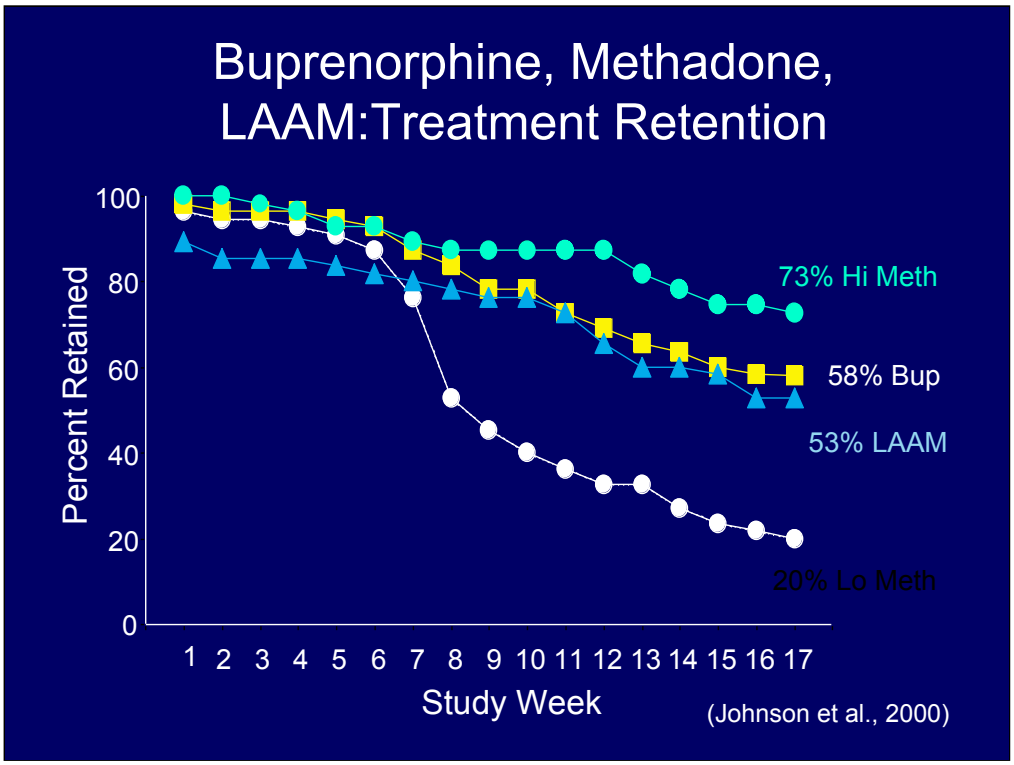
Notes

The next several slides review four of the studies that have examined the efficacy of buprenorphine under different experimental conditions.



Notes

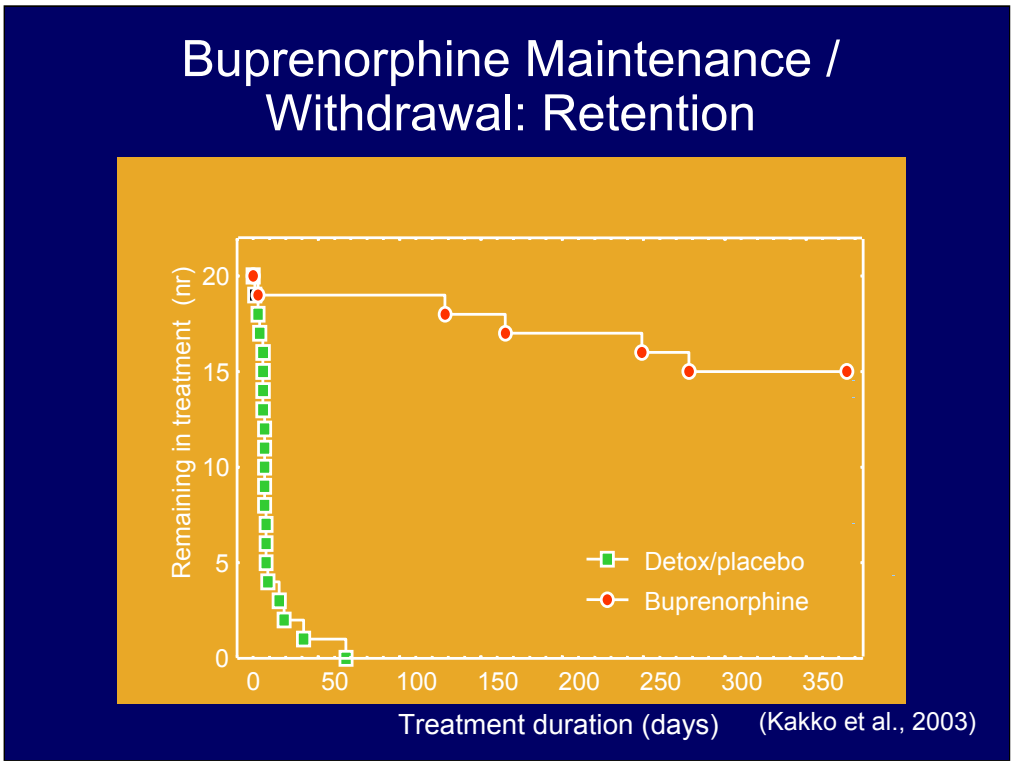
- Dose effects were seen across a number of outcome measures -- for example, the 1 mg group had significantly poorer treatment retention for the 16 weeks (40%) compared to the 8 mg group (52%) and the 16 mg group (61%).
- Similarly, a significantly lower percentage of patients in the 1 mg group achieved 13 consecutive opioid-negative urine samples (18.5%) compared to the 8 mg group (32.9%).



Notes

Treatment retention was significantly better for the LAAM, buprenorphine, and high-dose methadone groups, compared to the low-dose methadone group. (It was also significantly better for the high-dose methadone group, compared to the LAAM group as well.)

Note that the rescue procedure started during week 6 of treatment, and the sharp drop off in treatment retention for the low-dose methadone group represents, in part, the substantial number of participants in this group who were switched to high-dose methadone.



Notes

This figure shows treatment retention, which was significantly better for the maintenance (buprenorphine) vs. control (withdrawal followed by placebo) group. All placebo patients who dropped out did so following relapse to drug use (as determined by urine testing). In the maintenance group, one patient dropped out of treatment, and four were discharged due to relapse in their drug use.

Urine results showed that 74.8% of samples were negative for drugs in the buprenorphine maintenance group over the course of the year.

Buprenorphine Maintenance / Withdrawal: Mortality

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

(Kakko et al., 2003)

Notes

While not the primary goal of the study, the study noted that four of the patients who underwent a withdrawal (which was inpatient, and lasted six days) had died after one year -- compared to none of the patients in the buprenorphine maintenance group.

Questions?

Comments?

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Thank you for your time!

End of Workshop 3

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

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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

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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

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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

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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

Opioid overdose: Steps to take (2)

Assess the client:

If responsive

- 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 ± 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

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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.

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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.

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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.

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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

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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

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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

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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

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Naltrexone for opiate relapse prevention (7)

- Two commonly used agents are lofexidine and clonidine, both a-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.

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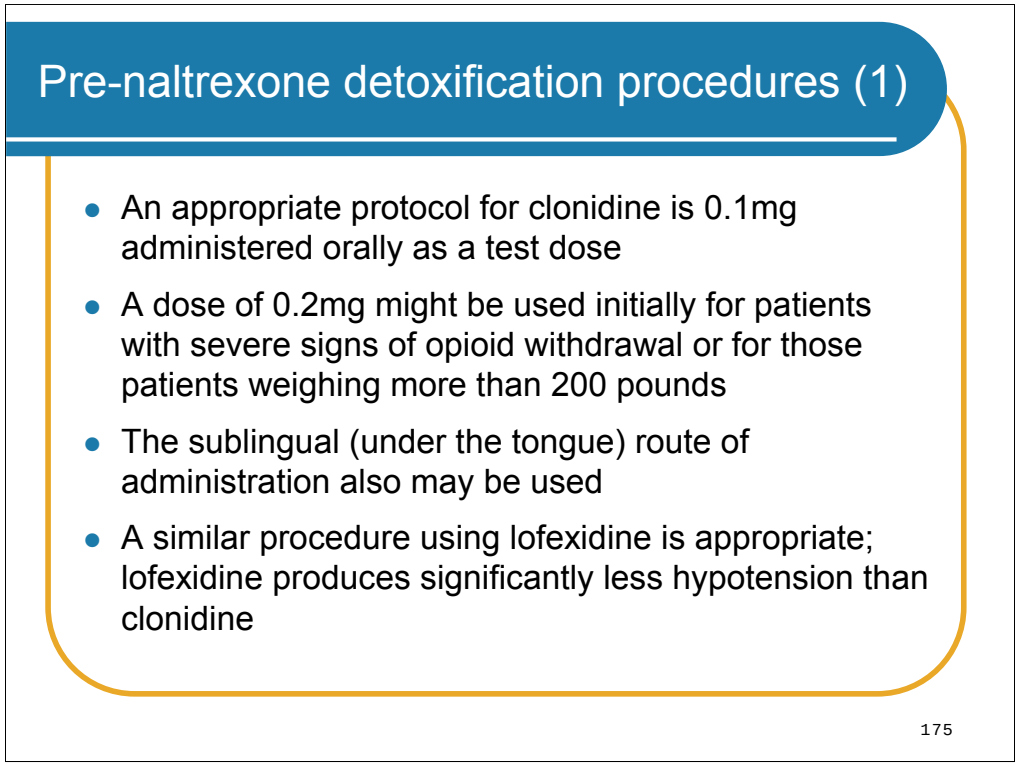

Notes:

In some countries, clonidine is not longer registered (Europe). Buprenorphine can be successfully used for withdrawal management (gradually tapered) and then naltrexone started after 3-5 days for maintenance. This withdrawal procedure might be much more convenient than the use of clonidine, which has a significant effect on blood pressure.

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

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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.

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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**

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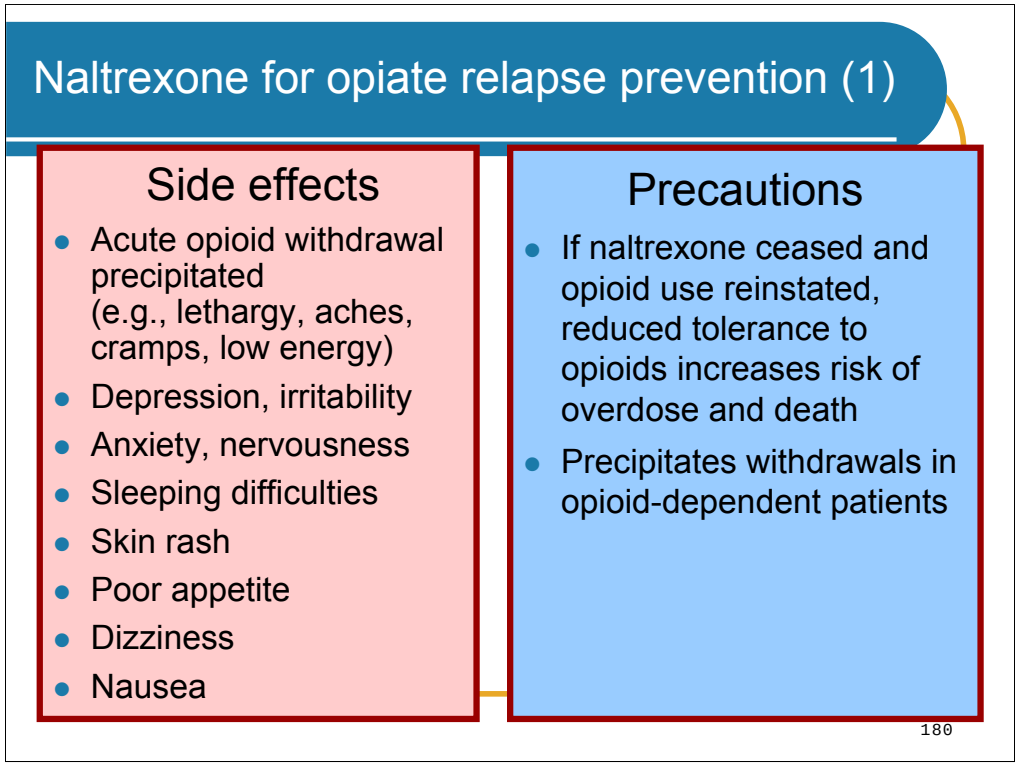

Notes

Depression induced by naltrexone responds rapidly with the use of SSRIs.

Effects last ≤72 hours. During this period there is a gradual reduction in tolerance.

Source: Young, R., Saunders, J., Hulse, G., McLean, S., Martin, J. & Robinson, G. 2002, 'Opioids', in Hulse, G., White, J. & Cape, G. (eds.) 2002, *Management of Alcohol and Drug Problems,* Oxford University Press, South Melbourne, pp. 79–99.

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

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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

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Notes:

It is also important to mention the value of having a caring friend or significant other as a protective factor to increase retention.

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.

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Notes:

Implants have not been registered or tested to date.

Conclusion: Naltrexone for opiate addiction (1)

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

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Conclusion: Naltrexone for opiate addiction (2)

- Treatment with opiate agonists (methadone) or partial agonists (buprenorphine) produces far better retention than does naltrexone
- 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

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Questions?

Comments?

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Post-assessment

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

(Your responses are strictly confidential.)

10 minutes

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Thank you for your time!

End of Workshop 4