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Basics on Addiction: a training package for medical practitioners or psychiatrists who treat opioid dependence

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Summary

Opioid dependence is a chronic, relapsing brain disease that causes major medical, social and economic problems to both the individual and society. This seminar is intended to be a useful training resource to aid healthcare professionals – in particular, physicians who prescribe opioid pharmacotherapies – in assessing and treating opioid-dependent individuals. Herein we describe the neurobiological basis of the condition; recommended approaches to patient assessment and monitoring; and the main principles and strategies underlying medically assisted approaches to treatment, including the pharmacology and clinical application of methadone, buprenorphine and buprenorphine–naloxone.

Key Words: Tolerance; physical dependence; addiction; clinical assessment; maintenance pharmacotherapies; methadone; buprenorphine; suboxone.

1. Introduction

Opioid dependence is a chronic, relapsing brain disease that causes major medical, social and economic problems to both the individual and to society. Opioid-dependent individuals are subject to substantial health risks including overdose, transmission of infectious diseases, poor physical and mental health and frequent hospitalization [44]. For society as a whole, opioid dependence incurs a significant economic burden, both in terms of direct healthcare costs (i.e., treatment and prevention services), and in terms of the broader impact on other budgets (e.g., social welfare and criminal-justice services). In addition, opioid dependence affects productivity, due to unemployment, absenteeism and premature mortality [111]. In West and Central Europe, there are estimated to be between 1 and 1.4 million opiate users, corresponding to a prevalence of between 0.4% and 0.5% of the population.

Given the magnitude of these problems, it has become crucial to ensure medical practitioners responsible for treating opioid dependence have access to evidence-based training packages. This supplement is intended to be a useful

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Table 1. Actions of morphine [78]
Central nervous system depression
Respiratory depression (death)
Sleepiness
Analgesia
Euphoria
Cough suppression
Pupillary constriction
Nausea and vomiting
Increased respiratory tract secretions
Constipation
Intense sweating
Itching

training resource to aid healthcare professionals – in particular, physicians who prescribe opioid pharmacotherapies – in assessing and treating opioid-dependent individuals. It is based upon the 'Basics on Addiction' training package developed as a collaborative initiative by leading treatment experts in Italy and led by Professor Icro Maremmani (President of EUROPAD) and Professor Pier Paolo Pani (President of the Italian Society of Addiction Medicine) on behalf of the Basics on Addiction (BoA) Group.

In order to optimally treat opioid-dependent individuals it is first necessary to understand the neurobiological basis of the condition as a chronic, relapsing disorder. The first article in this supplement, 'Neurobiology of opioid dependence', gives an overview of the effects of opioids on the body at the cellular level and the physiological effects of opioids and neurobiological adaptations to opioids (including tolerance, physical dependence, withdrawal, craving and relapse). Effective treatment of opioid dependence requires thorough, ongoing assessment of patients to ensure therapeutic strategies are suited to their individual needs and circumstances. The second article in this supplement describes approaches to clinical assessment and monitoring that should be conducted in drug-dependent individuals to inform choices regarding appropriate treatment. The final article discusses the main principles, goals and strategies underlying medically assisted approaches to opioid-dependence treatment, the unique pharmacological profiles of methadone, buprenorphine and buprenorphine-naloxone, how each of these treatment options can be used to treat opioid dependence and the main efficacy and safety considerations that are relevant to the choice of treatment strategy.

2. Neurobiology of opioid dependence

2.1. Opioids and their mechanism of action

2.1.1. What is an opioid?

Opium has been used for social and medicinal purposes for thousands of years to produce euphoria, analgesia and sleep and to prevent diarrhoea [85]. Several pharmacologically active compounds are derived from the opium poppy *Papaver somniferum*, including morphine, codeine, papaverine, thebaine and noscapine [24]. Opioids is the term given to natural or synthetic drugs that have certain pharmacological actions similar to those of morphine [84] by the interaction with some or all opioid receptors.

2.1.2. Acute opioid effects

Morphine, the archetypal opioid, is a powerful analgesic and narcotic, and remains one of the most valuable analgesics for relief of severe pain [24]. It also induces a powerful sense of contentment and well-being, which is an important part of its analgesic activity, as it reduces the anxiety and agitation associated with a painful illness or injury. Other opioid effects on the central nervous system include respiratory depression, depression of the cough reflex, nausea and vomiting and pupillary constriction [85]. Morphine also acts on the gut wall, reducing intestinal secretion and motility and lengthening gut transit time [21]. The actions of morphine are shown in Table 1.

Following elucidation of the chemical structure of morphine at the beginning of the 20th century [95], many semi-synthetic and totally synthetic opioids have been produced (including methadone, buprenorphine and pethidine) with the aim of harnessing the clinically useful proper-

Table 2: Effects associated with the main types of opioid receptors [85]

Effect	mu (μ, MOP or OP3)	delta (δ DOP or OP2)	kappa (κ, KOP or OP1)
Analgesia			
Supraspinal	+++	−	−
Spinal	++	++	+
Peripheral	++	−	++
Respiratory depression	+++	++	−
Pupil constriction	++	−	+
Reduced GI motility	++	++	+
Euphoria	+++	−	−
Dysphoria	−	−	+++
Sedation	++	−	++
Physical dependence	+++	−	+

+: denotes activity; −: denotes weak or no activity

ties of the opioids without the less desirable side effects (i.e. habit-forming propensity or nausea and vomiting) [24].

2.1.3. Opioid receptors

Pharmacologic studies performed in the 1970s had suggested the existence of three types of classic opioid receptor, termed mu, delta and kappa [68], and this was subsequently confirmed by receptor-cloning studies. Opioid receptors belong to the large family of receptors possessing seven transmembrane domains of amino acids and are coupled to guanine nucleotide-binding proteins known as G-proteins [17]. They reduce the intracellular cyclic adenosine monophosphate (cAMP) content by inhibiting adenylate cyclase and also exert effects on ion channels through a direct G-protein coupling to the channel [85]. The main effects of opioids at the membrane level are thus the promotion of the opening of potassium channels and inhibition of the opening of voltage-gated calcium channels [85]. These membrane effects reduce neuronal excitability as the increased potassium conductance causes hyperpolarisation of the membrane and reduces transmitter release due to inhibition of calcium entry [85]. The overall effect is inhibitory at the cellular level [85]. However, opioids do increase activity in some neuronal pathways by suppressing the firing of inhibitory interneurones [85].

High densities of opioid receptors are present in five areas of the central nervous system (CNS): the brainstem, the medial thalamus, the spinal cord, the hypothalamus and the limbic system. They have also been identified on peripheral sensory nerve fibres and their terminals and on immune cells [36]. Each receptor type is associated with specific functional effects, as shown in Table 2. The best-studied receptor type is the mu receptor (also known as the μ, MOP or OP3 receptor), which is found in both spinal and supraspinal structures as well as in the periphery. It plays an important role in nociception, as well as respiration, cardiovascular function, intestinal transit, feeding, learning and memory, locomotor activity, thermoregulation, hormone secretion, and immune functions [25]. Kappa receptors (also known as κ, KOP or OP2 receptors) have been implicated in the regulation of nociception, diuresis, feeding and neuroendocrine secretion. In addition, as kappa receptor agonists can produce dysphoria in humans [25], they appear to play a role in regulation of mood. The olfactory bulb, neocortex, caudate putamen and nucleus accumbens contain the highest densities of delta (δ, DOP or OP1) receptors, with lower densities in the thalamus, hypothalamus and brainstem [25]. A fourth opioid receptor has been discovered more recently, the NOP receptor (formerly referred to as opiate receptor-like 1 [ORL1], LC132 or OP4). Pharmacologically this is not a classical opioid receptor, as non-selective opioid antagonists (e.g., naloxone) display negligible affinity; the International Union of Basic and Clinical Pharmacology (IUPHAR) database of recep-

Table 3: Selectivity of opioid drugs and peptides for the three main opioid receptors [85]

	mu (μ, MOP or OP3)	delta (δ, DOP or OP2)	kappa (κ, KOP or OP1)
Endogenous peptides			
Beta-endorphin			
Leu-enkephalin	+	+++	–
Met-enkephalin	++	+++	–
Dynorphin	++	+	+++
Opiate drugs			
Pure agonists			
Morphine, codeine, oxymorphone, dextropropoxyphene	+++	+	+
Methadone	+++	–	–
Pethidine	++	+	+
Etorphine, bremazocine	+++	+++	+++
Fentanyl, sufentanil	+++	+	–
Partial/mixed agonists			
Pentazocine, ketocyclazocine	x	+	++
Nalbuphine	x	+	(++)
Nalorphine	xx	–	(++)
Buprenorphine	(+++)	–	xx
Antagonists			
Naloxone	xxx	x	xx
Naltrexone, diprenorphine	xxx	x	xxx

+: agonist activity; (): partial agonist activity; x: antagonist activity; −: weak or no activity

tors proposes that the NOP receptor is considered as a non-opioid branch of the opioid receptor family [27].

2.1.4. Agonists and antagonists

The overall effect of an opioid depends on its activity at each of the opioid receptors; some opioids act as agonists on one type of receptor and antagonists or partial agonists at another. Agonist potency depends on two parameters: i) the affinity of the agonist for the receptor, that is, its tendency to bind to the receptor; and ii) the efficacy (commonly indicated as intrinsic activity) of the agonist, that is, its ability to initiate changes which lead to effects once bound. Full agonists (which can produce maximal effects) have high efficacy whereas partial agonists (which can produce only submaximal effects) have intermediate efficacy [87]. The relationship of a drug with its receptor is often likened to that of the fit of a key into its lock – the drug represents the key and the receptor represents the lock (Figure 1). Hormones, neurotransmitters, drugs or intracellular messengers may all interact with receptors in this way [13]. The classification of opioid drugs and endogenous peptides in terms of their agonist, partial agonist or antagonist activity and their selectivity for the three main opioid receptors is shown in Table 3.

2.1.5. Endogenous opioids

The search for endogenous compounds that mimicked the actions of morphine in the 1970s led to the discovery of the endogenous opioids [43]. Four classes of endogenous opioids have now been identified: endorphins, enkephalins, dynorphins and endomorphins [56]. Endogenous opioids function as neuromodulators to influence the actions of other neurotransmitters such as dopamine or glutamate [94]. The endogenous opioid system has been found to be important in the modulation of pain, mood, blood-pressure regulation and other cardiovascular functions, control of respiration, appetite, thirst and sexual activity [94]. There are high concentrations of receptors for endorphins and enkephalins in many areas of the CNS, particularly in the periaqueductal grey matter of the midbrain, in the limbic sys-

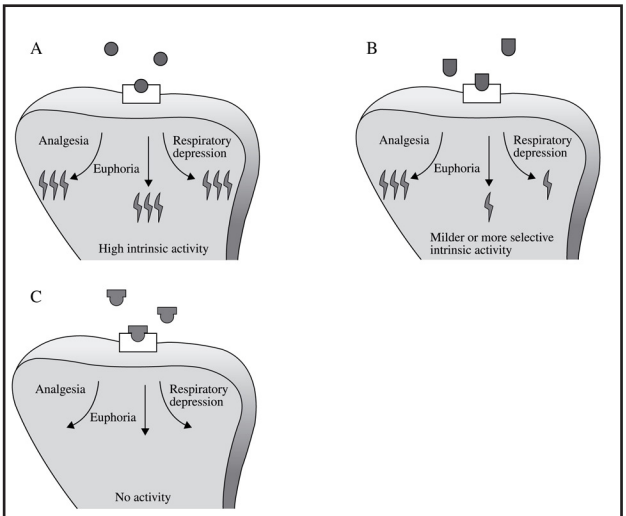

Figure 1: Action of opioid agonists, antagonists and partial agonists. A: Opioid agonist; B: Opioid partial agonists; C: Opioid antagonists

tem and at interneurones in the dorsal horn areas. These areas are involved in pain transmission or perception and the endogenous opioids are thought to be the body's natural pain-relieving chemicals, which act by enhancing inhibitory effects at opioid receptors. Opioid drugs elicit their effects by mimicking the actions of the endogenous opioids on opioid receptors [13].

2.2. Chronic opioid use: tolerance, physical dependence and addiction

2.2.1. Effects of chronic opioid exposure

Although possessing valuable properties (e.g., analgesia), repeated and chronic exposure to opioids can lead to development of tolerance and physical dependence. The rate of development of tolerance varies from one opioid to another.

Tolerance describes the need to progressively increase the drug dose to produce the effect originally achieved with smaller doses, following repeated exposure to opioid agonists. It may develop at different rates for the different effects of opioids and can occur over days, weeks or years [90]. Tolerance develops to the analgesic and euphoric effects of opioids, and to some of the adverse effects such as respiratory depression, nausea and sedation, but does not fully develop for effects such as constipation and miosis [85].

Table 4: Clinical features of opioid intoxication and withdrawal (55)

Intoxication
Drowsiness, stupor or coma
Symmetric, pinpoint, reactive pupils
Hypothermia
Bradycardia
Hypotension
Decreased peristalsis
Skin cool and moist
Hypoventilation (respiratory slowing, irregular breathing, apnea)
Pulmonary oedema
Seizures
Reversal with naloxone
Withdrawal
Anxiety, restlessness
Insomnia
Chills, hot flushes
Myalgias, arthralgias
Nausea, anorexia
Abdominal cramping
Vomiting, diarrhoea
Yawning
Dilated pupils
Tachycardia, hypertension (mild)
Hyperthermia (mild), diaphoresis, lacrimation, rhinorrhoea
Piloerection
Spontaneous ejaculation

When the drug is stopped or when its effect is counteracted by a specific antagonist [80], unpleasant physical effects occur, which indicates the occurrence of the withdrawal (abstinence) syndrome. Withdrawal symptoms generally represent physiologic actions opposite to the acute actions of opioid drugs. For example, pupillary constriction and constipation occur with opiate use, whereas pupillary dilatation and diarrhoea occur in the withdrawal state [54]. The most common symptoms of opioid intoxication and withdrawal are shown in Table 4. Individuals who abruptly stop taking morphine are extremely restless and distressed and have a strong craving for the drug. Although not life-threatening, opioid withdrawal is associated with severe psychological and moderate physical distress [54]. The onset of withdrawal symptoms typically

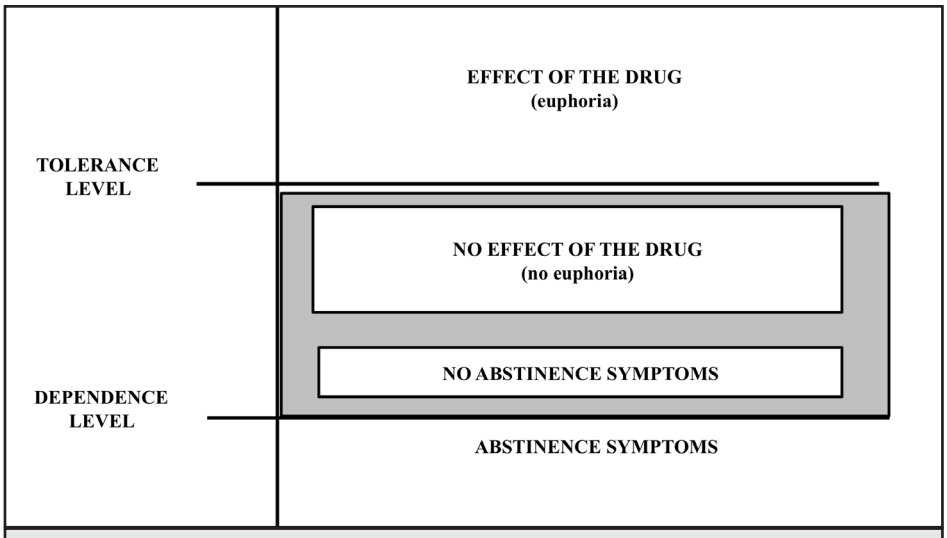

Figure 2: Experience of the opioid-dependent individual depending on opioid concentrations in the body. Reproduced with permission from Newman et al., 1995 [78]

occurs 8–16 hours after cessation of the use of heroin or morphine, with autonomic symptoms appearing first. By 36 hours, severe restlessness, piloerection, lacrimation, abdominal cramps and diarrhoea become apparent. Symptoms reach their peak intensity at 48–72 hours and resolve over 7–10 days [54]. However, negative mood states and craving may persist for up to 2 years after abstinence [37, 69]. Symptoms experienced by the opioid-dependent patient depend on the concentration of opioids in their body and their own individual levels of tolerance: the patient will experience euphoria when the concentration of opioids in the body exceeds the tolerance level and will experience withdrawal symptoms when the concentration of opioids in the body is below the dependence level. When the opioid concentration is in between these two levels the opioid-dependent patient will look and feel normal (Figure 2) [78]. Evidence of tolerance/withdrawal is termed 'physical dependence', although it is not a constant or exclusive feature of addiction. Addiction manifests with a persistent change in reward-seeking behaviour, with an irresistible desire to repeat the drug experience or to avoid the discontent of not having it. Such an instinctual drive is contrary to the person's declared intentions and underlies recidivism. It is the key aspect of addiction, and it is also referred to as 'psychological dependence' [86].

2.2.2. Criteria for opioid dependence/addiction

The key criteria indicating that an individual is addicted is when they no longer have control over their drug use and demonstrate a persistent change in reward-seeking behaviour, with an irresistible desire to repeat the drug experience or to avoid the discontent of not having it. Such an instinctive drive is contrary to the person's declared intentions and underlies relapsing behaviour (recidivism). It is the key aspect of addiction, and is also referred to as 'psychological dependence' [86]. A joint statement by the World Health Organization (WHO), the United Nations Office on Drugs and Crime (UNDOC) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) defines the key elements of opioid dependence as follows: a strong desire or sense of compulsion to take opioids; difficulties in controlling opioid-taking behaviour; a withdrawal state when opioid use has ceased or been reduced; evidence of tolerance, such that increased doses are required to achieve effects originally produced by lower doses; progressive neglect of alternative pleasures or interests; and persistence with opioid use despite

clear evidence of overtly harmful consequences [113].

2.2.3. Neurobiology of opioid- and drug-addiction

Advances in knowledge of the neurobiological processes that occur following acute and chronic opioid administration have helped to improve scientific understanding of how drug addiction develops, including the role of the specific neuronal circuits in mediating the reinforcing effects of opioids and the development of uncontrolled use and craving.

2.2.3.1. The reward pathway

Increased dopamine activity in the mesocorticolimbic system (Figure 3) is intimately involved in eliciting and reinforcing responses to natural stimuli (e.g., food, drink and sex), which is important to drive behaviour necessary for survival and reproduction [55]. From an evolutionary point of view, the capacity to seek rewards as goals is essential for the survival and reproduction of mobile organisms [35]. Drugs of abuse mediate their acute reinforcing effects by enhancing dopamine activity in this neural network, which consists of dopamine projections from cell bodies in the ventral tegmental area to limbic structures and cortical areas of the brain [35]. It has been proposed that a network of four circuits within the mesolimbic system are involved in drug abuse and addiction: the nucleus accumbens and the ventral pallidum, which are associated with reward; the orbitofrontal cortex and the subcallosal cortex, which are associated with motivation/drive; the amygdala and the hippocampus, which are associated with memory and learning; and the prefrontal cortex and the anterior cingulate gyrus, which are associated with control [101]. These four circuits receive direct innervations from dopamine neurones but are also connected with one another through direct or indirect projections (mostly glutamatergic), confirming observations from preclinical studies indicating that modifications in glutamatergic projections mediate many of the adaptations observed with addiction [101]. As may be expected from such a complex system,

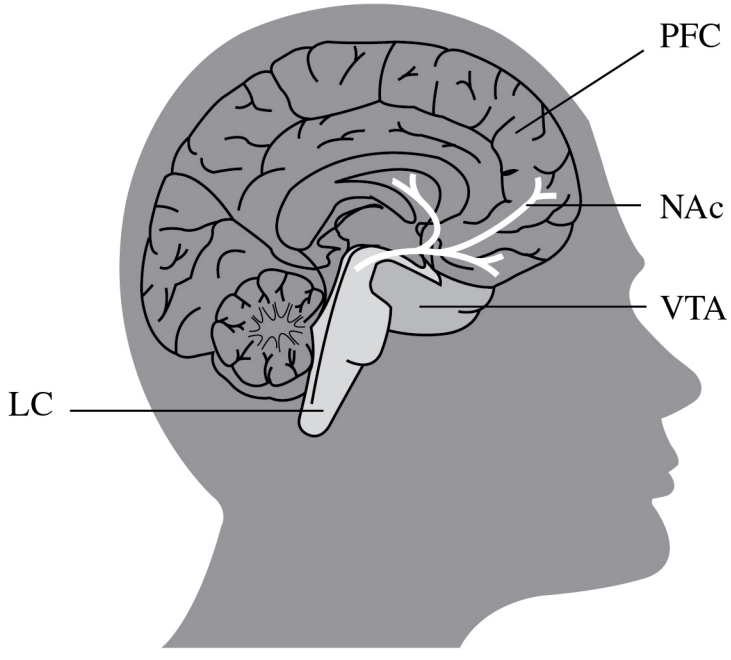

Figure 3: The mesolimbic reward system. Reproduced with permission from Kosten and George, 2002 [57]

other brain regions are thought to be involved in these circuits (e.g., the thalamus and insula), one region may participate in more than one circuit (e.g., the cingulate gyrus plays a role in both control and motivation/drive circuits) and other brain regions (e.g., the cerebellum) and circuits (e.g., attention and emotion circuits) are likely to be affected in drug addiction [101]. In the case of addiction to opioids it is predominantly the interaction of opioids with mu receptors in the mesocorticolimbic system that appears to mediate the behavioural and reinforcing properties [35].

2.2.3.2. Uncontrolled use and craving

Tolerance may develop with repeated opioid use to the extent that the user no longer experiences the euphoric effects once achieved with the drug, despite ingesting higher and higher doses of opioids [31]. Chronic opioid users will typically continue to exhibit a strong drive to engage in further drug-seeking and -using behaviours despite developing tolerance to the euphoric effects of opioids. It has been postulated that repeated exposure to drugs of abuse disrupts the function of the striato-thalamo-orbitofrontal circuit. This dysfunction leads to a conditioned response when the addicted subject is exposed to the drug and/or drug-related stimuli that activates the circuit and results in the intense drive to get the drug (consciously perceived as craving) and uncontrolled self-administration of the drug (consciously perceived as loss of control). This model of addiction postulates that the drug-induced perception of pleasure is particularly important for the initial stage of drug self-administration but that with chronic administration, pleasure alone cannot account for the compulsive drug intake. Rather, dysfunction of the striato-thalamo-orbitofrontal circuit, which is known to be involved in perserverative behaviours, accounts for the compulsive intake [100]. During withdrawal and without drug stimulation, the striato-thalamo-orbitofrontal circuit becomes hypofunctional, resulting in a decreased drive for goal-motivated behaviours [100]. For excellent reviews of the neurobiology underpinning addiction, see Felkenstein, 2008 and Volkow, 2003 [35, 101].

2.2.4. Relapse

A defining feature of drug dependence is the incidence of relapse to drug-seeking and drug-taking behaviours following months or years of abstinence [116]. It has been estimated that between 40 and 60% of drug-addicted patients will relapse within a year [72] even though they may have achieved abstinence temporarily alone or through detoxification or environmental interventions. Such a pattern is common to most chronic relapsing disorders, such as diabetes or hypertension. The relapsing course illustrates the chronic nature of opioid addiction and the need for long-term approaches to treatment. An important focus of addiction research has been to identify the behavioural, environmental and neural mechanisms underlying drug relapse. Three types of trigger have been identified to cause craving and relapse following extended periods of abstinence: a small 'priming' dose of the drug; cues previously associated with drug use (e.g., people, places, things, moods); and stress (e.g., stressful life events as well as anger, anxiety and depression) [114]. As opioid-using individuals invariably relapse following opioid withdrawal, detoxification alone does not constitute an adequate intervention for substance dependence; maintenance treatment is a more effective option for opioid-addicted individuals to resume a normal life and achieve a favourable outcome [78]. Detoxification is, however, a first step for many forms of shorter- or longer-term abstinence-based approaches, i.e., those in which no opioid agonist pharmacotherapy is used. Both detoxification with subsequent abstinence-oriented treatment and agonist maintenance treatment are considered essential components of an effective treatment system for people with opioid dependence [113]. Overcoming opioid dependence is not easy: at the cellular level, the pathological changes that occur as a re-

sult of drug use can persist even after drug use has ceased [45, 51] and the likelihood of relapse actually increases during a period of abstinence (a process called 'incubation') as a result of the neuroadaptations that occur in drug dependence [40, 93]. Pharmacotherapies should ideally be accompanied with motivation, social support, and positive coping strategies to fully achieve rehabilitative goals [61].

2.2.5. Stages of addiction

The development of addiction may be considered to consist of three stages: (1) acute (immediate) drug effects; (2) transition from recreational use to patterns of use consistent with addiction; and (3) end-stage addiction, which is characterised by an overwhelming desire to obtain the drug, a diminished ability to control drug seeking and reduced pleasure from biological rewards [52]. These stages are associated with neurobiological adaptations, including a switch from dopamine- to glutamate-based behaviour as different parts of the neural circuitry play the key role [52]. The first stage of addiction, acute drug effects, is caused by supraphysiological levels of dopamine being released throughout the motive circuit which induces changes in cell signalling. These changes lead to short-term neuroplastic changes, persisting for a few hours or days after drug intake, which initiate cellular events involved in the process of addiction. The second stage of addiction, the transition from recreational drug use to addiction, is associated with changes in neuronal function that accumulate with repeated drug use and diminish with drug discontinuation over days or weeks. There are also alterations in the content and function of various proteins that are involved in dopamine transmission (e.g., tyrosine hydroxylase, dopamine transporters, RGS9-2 and D2 autoreceptors) that persist for a few days after drug discontinuation. However, these changes appear to be compensatory and may not directly mediate the transition to addiction. End-stage addiction is characterised by vulnerability to relapse and results from enduring cellular changes. Changes in protein content and/or function often become greater with increasing periods of withdrawal, which is consistent with the possibility that the more temporary changes in protein expression that mediate the transition to addiction may induce changes in protein expression that convert vulnerability to relapse from a temporary and reversible phase into permanent features of addiction [52].

2.2.6. Risk factors for opioid dependence

Dependence is not an inevitable consequence of opioid use, as demonstrated by their widespread use as a treatment for chronic pain [79]. It has been proposed that addictive disease does not begin with the onset of substance use, but that an individual's complex history of risk and protective factors increase or decrease the likelihood of their developing an addictive disorder when they use a substance for the first time [12]. A large number of risk and protective factors have been identified, the most important of which is genetics, with some research suggesting that between 40% and 60% of the vulnerability to addictive disease is accounted for by genetic factors [60]. However, exposure to certain substances can be sufficient to induce dependence in the absence of risk factors. Associations have been found between substance abuse and polymorphisms in genes encoding opioid (*OPRM1* and *OPRK1*), serotonin (5-hydroxytryptamine-1B [*HTR1B*] and melanocortin (*MC2R*) receptors, endogenous opioids (prodynorphin [*PDYN*]) and neurotransmitter enzymes (catechol-*O*-methyltransferase [*COMT*] and tryptophan hydroxylase [*TPH*]) [115]. Other factors known to play a role in the development of addictive disorders include an individual's temperament, psychopathology, attitudes and perceptions. Society, including family, peer group, school and community, also have important implications for the development of addictive disease [12]. Prevention strategies have been demonstrated to play an important part in

reducing the risk of opioid dependence among vulnerable groups [76].

2.2.7. Opioid dependence as a chronic, relapsing brain disorder

Individuals who are drug dependent have historically been considered to be 'bad', 'weak' people who are unable to control their behaviour and do not deserve treatment. Among the scientific community, however, advances in our understanding of the neurobiology of addiction, the pharmacology of opioids and their receptors, and the discovery that some individuals may be particularly susceptible to drug dependence have led to greater appreciation of the condition being a chronic, relapsing brain illness. In addition, the substantial changes in brain structure and function observed in drug dependence that persist after individuals have stopped drug use provide further evidence that the condition should be considered a medical condition rather than a moral weakness. Viewing drug dependence as a chronic illness akin to diabetes or chronic hypertension changes the way in which treatment success is recognised. In the case of diabetes, for example, complete cure is not currently a feasible outcome and a decrease in blood glucose would therefore be indicative of treatment success. Considering dependence in the same way, treatment success may be defined as a decrease in drug use with only occasional relapses or abstinence from drug use with only occasional relapses rather than total abstinence. Total abstinence develops gradually, is rarely achieved soon after initiating treatment, and depends on ongoing treatment rather than being self-maintaining in the absence of chronic treatment.

Optimal management of opioid dependence requires a multi-faceted approach in order to address the neurobiological, social, behavioural and psychological aspects of the condition [62]. The pharmacotherapy of opioid dependence will be discussed in more detail in Part 3 of this supplement.

2.3. Conclusion

An understanding of the mechanisms responsible for opioid addiction is critical for optimal treatment of this chronic brain condition. Improvements in our understanding of the cellular processes responsible for opioid dependence, addiction and relapse have helped to inform the now widespread view that opioid dependence is a chronic disease requiring medical treatment rather than a purely moral or social problem that can be 'cured' by criminal-justice solutions. Ulti-

Key learning points

- Opioids are drugs that share some of the pharmacological effects of opium
- Opioid receptors are widely distributed in the nervous system
- Mu-receptor activation produces direct opioid effects, including euphoria
- Opioids promote the release of dopamine in the reward pathway (ventral tegmental area, nucleus accumbens, prefrontal cortex)
- Opioids are classified as agonists (complete, partial) or antagonists according to their intrinsic activity at different receptors
- Neuroadaptations that occur in response to chronic opioid lead to:
  - Tolerance: reduced effect of drug for a given dose
  - Withdrawal: emergence of withdrawal syndrome upon abstinence or reduced drug levels
  - Cravings and vulnerability to relapse
- Opioid dependence is a chronic, relapsing brain disorder
- Relapse is a symptom of the disorder and not a sign of abstinence failure

mately, increased understanding of the neurobiology of addiction should help to optimise the way we manage drug-dependent individuals with the treatment options we currently have at our disposal and also inform the development of new treatment approaches.

3. Clinical assessment of opioid dependence

Effective management of opioid dependence includes a comprehensive patient assessment. The goals of the assessment are to confirm a diagnosis of opioid dependence, determine the appropriate course of therapy and identify any co-existing physical or psychosocial conditions that may affect treatment outcomes [108, 111]. As the number of options to treat opioid addiction increases across a range of clinical settings, it becomes possible and desirable to tailor therapy to individual needs [111]. Furthermore, the heterogeneity of the opioid-dependent population makes treatment standardisation implausible [108]. A comprehensive, long-term treatment plan should be developed based on a multi-factorial assessment and the best available clinical evidence. All decisions should be made in concert with principles of medical ethics and consideration of patient preferences [111].

3.1. Key components of patient assessment in opioid dependence

A detailed patient assessment should consider specific physical, psychological and social factors, in addition to past and current drug use, in order to assess the patient's condition and treatment options (Table 5). Psychological assessment of patients is critical as psychosocial factors, including co-existing psychiatric disorders and cognitive impairment, patient readiness and motivation for treatment, contribute to non-com-

Table 5: Key features of patient assessment [108, 111]

Physical/Biological assessment	Patient history	Demographics and family history Medical history Psychiatric history Past and current drug use Past treatment experience
	Clinical examination	Assessment of intoxication/withdrawal Injection marks Presence of opportunistic infection(s) Presence of co-morbidities
	Lab investigation(s)	Urine and plasma drug screen, LFTs, HIV, hepatitis B and C, CBC,TB
Co-existing conditions	Pregnancy	
	Infectious diseases	HIV, hepatitis C and B, sexually-transmitted diseases, TB
	Other substance abuse	Alcohol, benzodiazepines, stimulants, barbiturates, cocaine, marijuana, hallucinogens
	Psychiatric disturbance	Depression, anxiety, personality disorders, cognitive impairment
Psychological/Social assessment	Living conditions	Extent of integration into drug community, homelessness
	Legal/criminal issues	Past/present involvement with legal system and incarceration
	Occupational situation	Current and past employment
	Social/cultural factors	Language barriers, education level, religion
	Support network	Support for treatment and avoidance
	Patient motivation	Short-term and long-term goals, and reason for seeking treatment

LFT: liver function tests; TB: tuberculosis; CBC: complete blood count; HIV: human immunodeficiency virus

pliance and treatment failure [108].

3.2. Diagnosis of opioid dependence

As of 1964, the World Health Organization has recommended the term 'substance addiction' be replaced by the term 'substance dependence' [111] (www.who.int). The term 'substance dependence' is somewhat ambiguous, however, as it does not distinguish addictive use from therapeutic dependence on prescribed drugs. We use the term dependence here to mean addiction (i.e., a persistent change in reward-seeking behaviour, with an irresistible desire to repeat the drug experience or avoid the discontent of not having it, which is contrary to the person's declared intentions). Differentiating between opioid use, abuse and dependence is critical to establishing the

Table 6: Definitions of substance abuse and dependence [2,109]

Substance abuse (DSM-IV-TR)(2)/**Harmful use** (ICD-10) (109)	
DSM-IV-TR	ICD-10
A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring at any time in the same 12-month period: Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home Recurrent substance use in situations in which it is physically hazardous Recurrent substance-related legal problems Continued substance use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance In addition, the individual must never have met the criteria for substance dependence for the substance in question	A pattern of psychoactive substance use that is causing damage to physical or mental health; adverse social consequences are also common, but not sufficient to establish a diagnosis of harmful use
Substance dependence	
DSM-IV-TR	ICD-10
A maladaptive pattern of substance use leading to clinically significant impairment or distress. Three (or more) of the following, occurring at any time in the same 12-month period: Tolerance Withdrawal Taking the substance in larger amounts or over a longer period than was intended Persistent desire or unsuccessful efforts to cut down or control substance use Spending a great deal of time in activities necessary to obtain, use, or recover from the substance Giving up or reducing important social, occupational, or recreational activities because of substance use Continued use despite knowledge of having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by the substance	A cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. Three or more of the following have been present together at some time during the previous year: Strong desire or compulsion to take the substance Difficulty controlling substance use (onset, termination, or levels of use) A physiological withdrawal state when substance use is stopped or reduced Evidence of tolerance (increased doses are required in order to achieve the effects originally produced by lower doses) Progressive neglect of alternative pleasures or interests because of time spent to obtain, use, or recover from the substance Persisting with substance use despite clear evidence of overtly harmful consequences
DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; ICD, International Classification of Diseases	

most effective course of treatment, if any. A diagnosis of any opioid disorder is made using criteria similar to other substance abuse disorders [108]. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) [2] describes two distinct categories for substance-use disorders: abuse and dependence (Table 6).

The most important feature that differentiates substance abuse from dependence is a loss of control (e.g., persistent or strong desire to take the substance, unsuccessful efforts to cut down or control substance use, continued usage despite knowledge of harmful consequence and neglect of other activities). It should be noted that tolerance and withdrawal are included in the potential criteria for substance dependence in both DSM-IV-TR and ICD definitions but neither tolerance nor withdrawal are required to establish the diagnosis of abuse or dependence [2, 109]. Conversely, the sole presence of tolerance and withdrawal in the absence of other criteria, may indicate what might be termed a 'normal', medical status corresponding to habitual, controlled use of a tolerance-inducing substance (e.g., nicotine or alcohol) or therapeutic dependence on a tolerance-inducing prescribed drug (e.g., methadone or buprenorphine). The DSM-IV-TR requires the clinician to specify whether the substance dependence is with or without physiological dependence (manifested by evidence of tolerance or withdrawal) [2].

A diagnosis of abuse is subordinate to that of dependence: in other words, all dependent patients are also abusers, whereas abusers can be assessed as such after ruling out a diagnosis of dependence. Furthermore, patients who do not meet the criteria for abuse may fall into a category of non-pathologic use, comprising irregular or habitual use, with possible features of tolerance and dependence. Typically, dependence is the culmination of a pattern of abuse which starts with occasional, social or recreational drug use or as part of a legitimate medical regimen, such as with the treatment of pain [1]. Abuse is, however, often a temporary stage of opioid usage; dependence develops rapidly as a result of the powerful reinforcing qualities of the opioid and the emergence of tolerance [28, 108].

Notably, the DSM-IV-TR requires criteria for dependence to be fulfilled within a 12-month period, although possibly on different occasions. In other words, a diagnosis can be based on a relatively recent period of physical dependence (e.g., in the past month) evidenced by signs of withdrawal and tolerance, as long as features of previous escalating substance use or abuse have occurred in the same 12-month period. In addition, even if the pattern of use is not currently problematic, the recurrence of problems within the same 12-month period is (from a diagnostic perspective) considered equivalent to a constant problematic pattern of use. Conceptually, a diagnosis of substance dependence can also be made for a past period, although the patient may be undergoing a remission phase. Therefore, a prognosis of long-lasting remission in the presence of a retrospective diagnosis of drug addiction is unrealistic.

3.3. Assessing opioid intoxication and withdrawal

The documentation of the signs of opioid intoxication or withdrawal is part of establishing a diagnosis of opioid dependence (Table 7). The degree of opioid intoxication or withdrawal should be evaluated with the reported time of last use.

Clinical assessment is complicated by the fact that opioid users commonly abuse several substances including alcohol, benzodiazepines, stimulants, marijuana, cocaine and nicotine, which may result in additional symptoms such as tremors, delirium or seizures [1]. Care must be taken to make a differential diagnosis against other conditions that may share similar symptoms [108], such as panic attack, gastroenteritis, peptic ulcer and pancreatitis.

Injection sites are valuable indicators when determining the chronology of drug use [111]. The most common sites for injection include

Table 7: Signs of opioid intoxication and withdrawal [108, 111]

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

the cubital fossa (area on the inside of the elbow joint) and the groin although superficial veins in the extremities and neck are also used [28, 111]. Recent injection marks are usually small and red and are sometimes inflamed or surrounded by slight bruising. Older injection sites are usually not inflamed, but may show pigmentation changes (either lighter or darker) and the skin may have atrophied. A combination of recent and old injection sites would normally be seen in an opioid-dependent patient with current neuroadaptation. The visible injection sites should be consistent with the reported history [111].

3.4. Assessment of co-existing conditions

Physical and biological assessment of the patient not only confirms dependence, but also provides important information on their overall health, fitness and willingness to undertake treatment. A trusting relationship between clinician and patient is valuable to establish the free flow of information. A non-judgemental and affirming approach can help to alleviate the sense of shame and diminished self-esteem many patients feel that often leads to the withholding of critical information [38, 111]

Although important, self-reporting by patients often results in questionable validity and reliability [111]. As a result, drug screens, using some form of immunoassay, are generally recommended before making treatment decisions. Gas–liquid chromatography (GLC) and gas chromatography–mass spectrometry (GC–MS) are very sensitive and specific tests, but are labour intensive and expensive and are thus often reserved for confirmation of other forms of testing, such as urinalysis [98, 108].

Urinalysis is an inexpensive, although not sensitive, form of screening for opioids and other substances of abuse. Interpretation of urinalysis results requires knowledge of the specific test or reagents used as well as the pharmacokinetics of the substance or substances being tested [98, 111]. Heroin is metabolised to 6-monoacetylmorphine (6-MAM), then to morphine and eventually to codeine. Therefore, the presence of 6-MAM is usually specific for recent heroin use. Morphine, with or without small amounts of codeine, can indicate either heroin or morphine use in the last few days. However, small amounts of morphine in the presence of large amounts of codeine can suggest intake of high doses of codeine, as codeine is also metabolised to morphine [111].

A positive urine test for opioids must be judged cautiously. Although patients are usually required to test positive for opioids in order to be offered treatment, the presence of opioids indicates recent use, but not necessarily abuse or dependence [111]. On the other hand, the absence

of opioid does not exclude either abuse or addiction, but merely indicates that the individual has not used opioids in the previous week. Conversely, positive findings are possible after ingestion of large amounts of poppy seeds [111] or for people exposed to prescribed opioids. Urinalysis results should therefore always be used in the context of a more comprehensive patient assessment to confirm a diagnosis of opioid dependence.

Further serum testing can detect the presence of other substances of abuse (e.g., alcohol), HIV, hepatitis C and other common infectious diseases. Voluntary testing for HIV and hepatitis C should be offered as part of an individual assessment, with counselling offered before and after the test. In particular, HIV testing should be routinely offered to patients in areas with high HIV incidence rates, particularly if they fall into multiple risk categories. Research suggests opioid-dependent HIV patients have decreased access to quality HIV care and medication, and are more likely to be non-compliant with treatment [111]. Serology testing and vaccination for hepatitis B is recommended for all patients. To offset the risk of patients neglecting to return for repeated treatments to complete a hepatitis B vaccination program, vaccination could commence before serology testing, and accelerated vaccination schedules should be considered [111]. As part of a complete assessment, screening for tuberculosis and sexually transmitted diseases should also be considered [38, 111]. A pregnancy test for women with reproductive potential should be offered, as early as possible in the course of treatment [108, 111].

3.5. Psychiatric co-morbidities

In addition to physiological symptoms, assessment of a patient's behaviour, psychology and cognitive functioning is important in the diagnosis of opioid dependence. Psychological assessment includes determining the presence of co-existing psychological conditions, cognitive impairment, and consideration of the patient's motivation to treatment and short- and long-term goals.

Several large-scale epidemiologic studies indicate approximately 50% of patients with drug or alcohol dependency also have psychiatric distress [82]. Mood and anxiety disorders are common in the opioid-dependent population, in addition to antisocial behaviour and other personality disorders, all of which affect treatment choices and outcomes [33]. It has been estimated that up to 16% of opioid dependents suffer from major depression, which is more commonly associated with poly-drug use. Chronic, episodic low-grade depression or dysthymia can progress to full-blown depression as a result of the stress and trauma associated with opioid dependence [28, 82]. Acute mood disturbances (depressed mood, anxiety) are also apparent during opioid withdrawal [46]. Consequently, when assessing patients, it is important for clinicians to establish any pre-existing psychological conditions and recognise that the short- and long-term effects of opioids, their withdrawal symptoms and the trauma of addiction, can all produce symptoms that are similar to those that characterise many mental disorders [82]. Nevertheless, clinicians should be

Table 8. Examples of standardised questionnaires for patient assessment [6,48]

Questionnaire	Measurement
Severity of Opioid Dependence Questionnaire (SODQ)	Physical aspects of opioid dependence
Severity of Alcohol Dependence Questionnaire (SADQ-C)	Physical aspects of alcohol dependence
The Symptom Check List (SCL-90) and General Health Questionnaire (GHQ)	Global assessment of mental health
The Psychiatric Research Interview for Substance and Mental Disorders (PRISM)	Substance-induced major depression

aware of unusual opioid-related symptoms, such as psychosis or mania, which may require acute treatment.

The presence of psychiatric conditions also has important implications for treatment choices and medication management. Pharmaceutical agents such as methadone and buprenorphine have been shown to have a beneficial effect on mental disorders as well as addiction [82].

3.6. Patient assessment tools

Several instruments and questionnaires have been developed to assist in the patient assessment process when substance abuse is suspected (Table 8). Standard questionnaires can be a useful adjunct to the assessment process, provided they are delivered in the context of a relaxed patient interview [48]. The use of structured and semi-structured interviews and standardised assessment tools has also improved the reliability of co-morbid psychiatric diagnoses [82]. In every case, the results should be interpreted in combination with a complete clinical assessment.

The tools for gathering social and cultural information are not as well developed or widely available as for physical assessment. Although there is a lack of assessment tools, available research suggests that social assessment, e.g., patients' living conditions, occupational situation and legal issues, needs to be an on-going process, beyond the scope of a single interview [108].

3.7. Conclusion

A diagnosis of opioid dependence is contingent on an individualised, comprehensive patient assessment, which considers the particular risks of this patient population. When considered collectively, the information gained from a complete physical and psychosocial examination and history will help to differentiate between substance use, abuse or dependence, and identify the best course of treatment.

Key learning points

- A comprehensive and individualised patient assessment is critical for the diagnosis of opioid dependence
- The key components for a comprehensive patient assessment include:
  - Physical/biological evaluation and patient history – drug use, abuse and dependence, health status
  - Co-existing somatic and psychiatric conditions
  - Psychological/social functioning
- The potential for tolerance and withdrawal is common to non-pathologic (controlled) use, abuse and dependence, but is not required to diagnose drug dependence
- Documentation of opioid intoxication or withdrawal is important in diagnosis, and should be made in the context of reported time of last drug usage
- Examination of new and old injection sites aids the determination of drug-use chronology
- Serum and urine testing is recommended to detect opioids and substances of abuse, as well as co-existing infectious diseases and conditions
- A thorough psychiatric assessment is recommended to detect mental symptoms and to identify psychiatric co-morbidities, which affect a substantial proportion of the opioid-dependent population
- Numerous standardised assessment tools and questionnaires are available to assess dependence, physical and mental health

In addition to confirming the presence or absence of opioids and other substances of abuse, clinicians should ensure the necessary serum and urine testing is undertaken to detect co-existing conditions that may affect treatment. Importantly, the patient's psychological health must be considered, given the high incidence of psychiatric co-morbidity and the implications for treatment choice and outcome. A number of standardised patient assessment tools may aid in the assessment and diagnostic process.

As with other chronic conditions, treatment should be structured in such a way as to provide long-term support to patients. Assessment of the patient's response to therapy should be undertaken on a regular basis, with a continued focus on outcome-oriented and individualised treatment.

4. Maintenance pharmacotherapies: treatment principles and clinical application

This section outlines the main principles, goals and strategies underlying medically assisted approaches to opioid-dependence treatment, the unique pharmacological profiles of the therapies available to treat opioid dependence, and the safety and efficacy considerations that are relevant to the use of these pharmacological interventions throughout the different stages of treatment.

4.1. Principles, goals and strategies for treating opioid dependence

4.1.1. Overall aims of drug-dependence treatment

Opioid dependence is a chronic and relapsing medical disorder [62] with consequences that primarily affect the individual but also have broader effects. Harms to the individual include an increased risk of mortality as a result of overdoses, violence, suicide and smoking- and alcohol-related diseases; and an increased risk of HIV and hepatitis C infection through unsafe injection practices [111]. Harms to society associated with opioid dependence include criminal activity and the economic burden associated with healthcare costs (treatment and prevention services, costs incurred due to additional health problems), social welfare and criminal-justice services [111]. The objectives of treatment for opioid-dependent patients are, therefore, to: reduce dependence on abused drugs; reduce the morbidity and mortality caused by the use of opioids of abuse, or associated with their use, such as infectious diseases; improve physical and psychological health; reduce criminal behaviour; facilitate reintegration into the workforce and education system and improve social functioning [113]. Achieving these objectives has clear medical, economic and social benefits [113]. Accordingly, the World Health Organization (WHO) has included the opioid agonists methadone and buprenorphine on their model list of essential medicines as a result of their strong evidence base [112]. Essential medicines are defined as those that satisfy the priority healthcare needs of the population and they are selected with due regard to public-health relevance, evidence on efficacy and safety and comparative cost-effectiveness [112]. Access to essential medicines is considered a fulfilment of the human right to health according to international law [42].

4.1.2. Elements of drug-dependence treatment

Treatment of opioid dependence must address the multiple needs of the patient. Pharmacological treatments (which are discussed in detail here) are the critical component of the treatment process but behavioural interventions and/or counselling therapies to address underlying mental disorders and impaired psychosocial functioning also play a key role [77]. Comprehensive programmes, involving access to psychosocial and counselling services and referral to vocational, financial, housing and family assistance, can help address the broader aspects of addiction. Indeed, combining pharmacological treatments with counselling aimed at promoting treatment adher-

ence and lifestyle change can greatly enhance the effectiveness of treatment [92]. Pharmacological maintenance treatment also helps to initiate and retain contact between patients and substance-abuse specialists, thus enabling these other interventions to be delivered.

Due to the complexity of drug dependence, one treatment approach is not appropriate for every patient. Pharmacological interventions such as opioid agonist treatments should be initiated according to evidence-based quality standards to ensure safety and efficacy. Over time, the appropriate dose and other aspects of treatment can be individualised to the patient's needs, without losing the critical factors of success. Treatment plans must be continually assessed and modified to ensure they meet the patient's changing needs [77].

4.1.3. Overview of treatment pathways

The primary pharmacological approach to treating heroin dependence involves opioid agonist maintenance treatment – also known as medically assisted treatment, and less appropriately as opioid replacement therapy or opioid substitution therapy. Opioid agonist maintenance treatment is defined as the administration of thoroughly evaluated opioid agonists, by accredited professionals, in the framework of recognised medical practice, to people with opioid dependence, for achieving defined treatment aims [110]. The primary aims of maintenance pharmacotherapy are to reduce drug craving and illicit opioid use, and where necessary, to prevent withdrawal symptoms. By reducing the drive to engage in continual addictive-drug-seeking and -using behaviour, maintenance treatment can provide an opportunity to address the broader ramifications of each individual's dependence-related problems (e.g., impaired psychosocial functioning and physical health), reduce associated risks (e.g., overdose mortality, infectious-disease transmission), and minimise the socio-economic burden imposed on wider society (e.g., criminality, lost productivity, healthcare costs of untreated opioid dependence). The medications most frequently used as maintenance therapies are the opioid agonists methadone (typically administered as an oral syrup) and buprenorphine (administered as a sublingual tablet). Buprenorphine is available in two formulations: a monotherapy and a buprenorphine–naloxone (4:1 ratio) combination product designed to reduce the potential for misuse and diversion. Additional op-

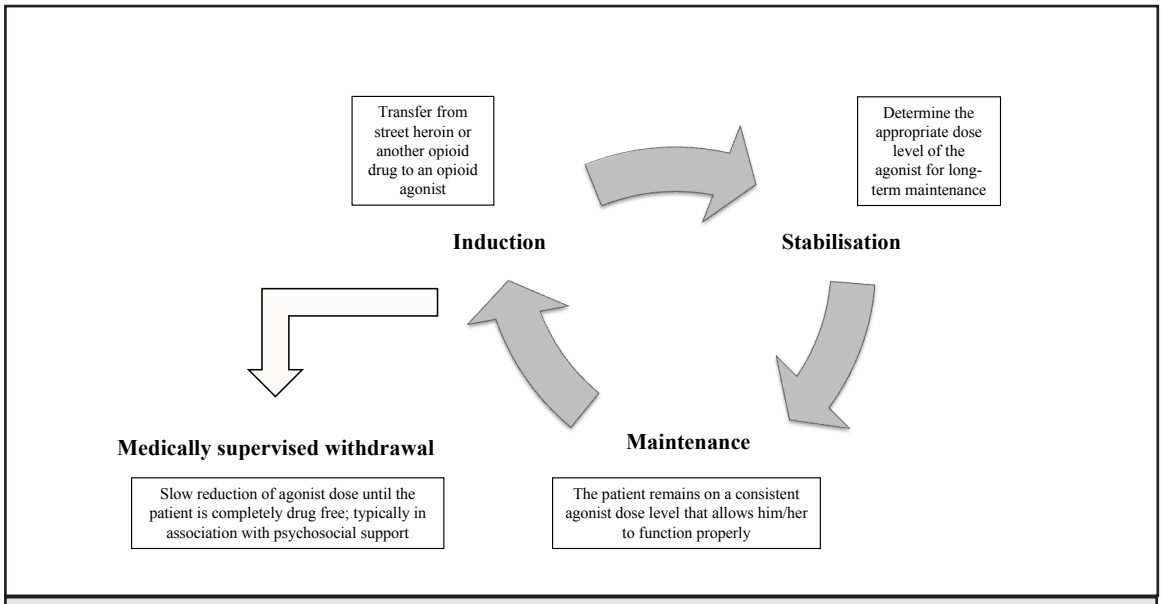

Figure 4. Phases of heroin dependence treatment

tions that are used less frequently and have been less thoroughly evaluated include slow-release oral morphine and injectable therapies including injectable methadone and diamorphine. The main phases of maintenance treatment are summarised in Figure 4. Following induction and stabilisation, patients typically need to be maintained on opioid agonist therapy for at least 12 months in order to achieve enduring positive treatment outcomes [41]. Opioid maintenance treatment is associated with a substantial reduction in the use of heroin and other illicit opioids, crime and the risk of death through overdose. A WHO position paper on maintenance treatment states it to be an effective, safe and cost-effective modality for the management of opioid dependence [113]. Compared to detoxification or no treatment, both methadone and buprenorphine significantly reduce drug use and improve treatment retention [111].

Although maintenance treatment is considered the gold-standard therapeutic strategy (and is the focus of this article), a popular approach is that of assisting opioid-dependent individuals to medically withdraw from opioids, a process also referred to as opioid detoxification (Figure 4). Both methadone and buprenorphine can be used in reducing doses to assist in achieving medical withdrawal from opioids. Gradual dose reductions help to minimise the likelihood of significant withdrawal and allow time for neuronal readaptation. Alpha-2 adrenergic agonists such as clonidine can also be used to reduce the severity of opioid withdrawal symptoms. In non-tolerant patients, the long-acting opioid antagonist naltrexone can be used to prevent relapse to opioids [111]. Both naltrexone and its active metabolite 6-β-naltrexol are competitive antagonists at the mu and kappa opioid receptors, reversibly blocking or attenuating the effects of opioids [91]. As a result, a person maintained on naltrexone will not experience any of the sought-after positive effects of heroin. Naltrexone maintenance may be effective for selected, mildly ill and highly motivated individuals [90]. However, detoxification alone cannot be regarded as a viable treatment approach for drug dependence. Rather than a first step into long-term treatment, it has been likened to a 'revolving door'; many individuals who begin detoxification do not complete it and many individuals who complete detoxification do not go on to more definitive treatment [70]. Results from a placebo-controlled, randomised trial of buprenorphine maintenance *versus* a tapered 6-day regimen of buprenorphine subsequently followed by placebo (individuals in both arms received cognitive behavioural therapy to prevent relapse plus weekly counselling), demonstrated that buprenorphine maintenance was far superior to detoxification (1-year retention rates of 75% *vs* 0% and negative urine screens for illicit opiates, central stimulants, cannabinoids and benzodiazepines in 75% of patients remaining in treatment) [50].

4.2. Maintenance treatment of opioid dependence

There are multiple determinants of the effectiveness of maintenance treatment for opioid dependence, including characteristics of the patient, the medications used and the way treatment is implemented. The primary focus of this educational supplement will be to highlight the basic pharmacological considerations that are relevant in selecting an appropriate medication and implementing this option to achieve the goals of therapy. According to the WHO, the following attributes are essential for treatments to be used as maintenance therapy in opioid-dependent patients [113]:

Opioid properties in order to prevent withdrawal symptoms and reduce craving

Affinity for opioid receptors in the brain in order to diminish or block the effects of heroin or other opioids

Longer duration of action than abused opioid drugs to delay the emergence of withdrawal and reduce the frequency of administration

Oral administration to reduce the risk of infections associated with injections

The following sections present an overview of the basic pharmacological and clinical considerations applicable to the use of the three main maintenance pharmacotherapy options: methadone, buprenorphine and buprenorphine–naloxone. The local manufacturer's prescribing information should be consulted for comprehensive information on dosage, administration, precautions, warnings and contraindications.

4.2.1. Methadone treatment

4.2.1.1. Pharmacology

Methadone was the first widely used opioid-maintenance therapy for the treatment of patients with opioid dependency [29] and its use assisted a shift in treatment targets for opioid dependency from total abstinence to long-term maintenance [106]. Methadone is a synthetic, lipid-soluble, opioid agonist, which acts with similar affinity to heroin at the mu-receptor [47]. Usually administered orally, methadone is readily absorbed via the gastrointestinal tract resulting in a high but variable bioavailability of 40–100% depending on the individual patient [74]. The onset of therapeutic benefit with methadone is within 30 minutes after ingestion, with an average time to peak of 2.5 hours [41, 67]. Plasma-methadone concentrations continue to rise for 3–4 hours following oral ingestion and then decline gradually. With ongoing dosing, the half-life of methadone is extended to 13–47 hours, with a mean of 24 hours [41].

Due to its combination of mu-opioid-receptor-agonist properties, high oral bioavailability and a prolonged half-life, once-daily oral methadone provides effective long-lasting suppression of opioid withdrawal symptoms and cravings for many patients. In addition, as a result of the phenomenon of cross tolerance, tolerance to other opioids is produced. This means that diminished intensity of opioid effects will be observed, which contributes to the reduction in heroin abuse during methadone maintenance [58].

4.2.1.2. Treatment – induction

Induction describes the initial stage of treatment when an individual dependent on street heroin or other non-prescribed opioids is initiated on maintenance treatment. The primary objectives of the induction stage are to ensure safety and to retain patients in treatment by preventing or reducing the signs and symptoms of opioid withdrawal, or preventing relapse in non-tolerant individuals or treatment re-starters in the early phase of use. It is important to carefully explain intoxicating effects and withdrawal symptoms to patients, observe them frequently and ensure safe dosing in seeking to achieve these aims. Once inducted safely, the goal is to achieve an optimal dose for longer-term maintenance that prevents cravings and addictive opioid use.

A comprehensive assessment of patient drug use, medical, psychological and social conditions, previous treatment history and current treatment goals should be conducted and documented prior to initiating therapy. Corroborative evidence of opioid dependence – observed signs of opioid withdrawal or a history of previous treatment for dependence – should be established before initiating treatment. Responses to previous treatments can also guide treatment decisions, forming the basis of the initial treatment plan. Such assessments can also be used to monitor progress during treatment [41, 67].

4.2.1.2.1. Treatment-naïve patients

New patients should be dosed with caution when using methadone in order to safely uptitrate to a satisfactory dose and achieve steady-state plasma concentrations. This approach is necessary to mitigate the risks of methadone accumulation across dosing intervals (due to its prolonged half-life) and consequent toxicity (including respiratory depression and sedation). The first dose should be determined for each patient based on the severity of dependence and level of tolerance to opioids, and, if possible, patients should be ob-

served for 3–4 hours after the first dose. The first 2 weeks of treatment are the greatest risk period for methadone toxicity and overdose. During this time, patients should be observed daily prior to dosing and assessed for signs of intoxication or withdrawal. Deaths in the first 2 weeks have been associated with methadone doses in the range of 25–100mg/day, with most occurring at doses of 40–60mg/day. Whilst therapeutic maintenance doses are typically in the range of 60mg/day or more, the risk of toxicity during methadone induction requires the use of lower starting doses. An initial methadone dose of ≤20mg for a 70kg patient can be presumed safe, even in opioid-naïve users; this dose will alleviate withdrawal symptoms in most patients. Caution should be exercised with doses of 30mg or more, and extreme caution and specialist involvement are advisable for doses of 40mg or more [41, 105]. Dose increments of 5–10mg can be considered every 5–7 days as required, with overall weekly increases no larger than 40mg [41] until a stable maintenance dose is achieved. For individuals starting treatment who are presumed to have no tolerance, or irregular use at time of treatment initiation, dosages should be low, dose increases should take not place more often than weekly (at least until blocking dosages are reached), and overall increases in daily dose should not be more than 10mg. This may be the case for: a) patients who have discontinued treatment recently, and have not yet relapsed into regular drug use; b) patients who have just been returned to their natural environment, with free availability of the opiate of abuse, without having been started on any agonist treatment while in a protected environment; c) patients who are not currently tolerant to opiates, but are willing to start some effective treatment, or who ask for advice about how to prevent relapses (diagnostic criteria should be satisfied).

4.2.1.2.2. Patients transferring from other pharmacotherapies

When another pharmacotherapy has failed, patients may be transferred to methadone treatment. Patients transferring from buprenorphine treatment should be stabilised on 16mg/day or less for several days prior to transfer. Methadone can be commenced 24 hours after the last buprenorphine dose, and the initial methadone dose should not exceed 40mg. Patients transferring from naltrexone should be treated as opioid-naïve, as tolerance to opioids is lost after a few days of naltrexone treatment. Methadone should not be administered for at least 72 hours after the last naltrexone dose, and the commencing dose should be no more than 20mg [41, 105].

4.2.1.3. Treatment – maintenance

Typically, effective methadone maintenance doses are 80–120mg/day. Maintenance doses higher than 120mg/day may be necessary in some patients, such as those who have a fast methadone metabolism or dual-diagnosis patients, while a minority of patients can be maintained effectively on doses less than 60mg/day [15, 32, 41]. Methadone maintenance doses should be determined on an individual basis. Patient input to treatment decisions, including determination of dose levels, helps promote a good therapeutic relationship. The optimal maintenance dose should reduce opioid cravings and use without producing euphoria. Daily administration of methadone is required in order to maintain adequate plasma levels and avoid opioid withdrawal. Monitoring drug use can also help assess treatment progress and may be useful for clinical decision making [41, 105].

Patients who miss their daily methadone dose may be engaging in other drug use or are at risk for leaving treatment. Tolerance to opioids may be reduced after more than 3 days of missed methadone, placing patients at risk of overdose when methadone is reintroduced. If missed for more than 3 days, methadone should be reintroduced at half dose, while for more than 5 days of missed treatment, reintroduction of methadone should be regarded as a new induction [41, 105].

4.2.1.4. Cessation of methadone treatment

Patients should be encouraged to remain in treatment for at least 12 months to achieve enduring lifestyle changes, with some patients requiring considerably longer periods. Beyond this point, no pre-determined treatment-term suits all cases, but benefits are maintained and stability guaranteed by ongoing treatment, while withdrawal from treatment, no matter how gradual, is associated with a higher risk of relapse.

Withdrawal from methadone treatment should be completed slowly and safely, and dose reductions should be made in consultation with patients. Doses should be reduced by 10mg/week to a level of 40mg/day, then by 5mg/week. Signs and symptoms of withdrawal may become apparent as the methadone dose falls below 20mg/day, with a peak at 2–3 days after cessation of methadone. Supportive care reduces the risk of relapse in the short-term and should be offered for at least 6 months post-methadone treatment [41, 105]. Clinical monitoring and follow-up is also advisable in patients who have been drug-free for a long period and are not receiving treatment.

4.2.1.5. Side effects and symptom complaints

Many effects of methadone are similar to those of morphine and other opioid agonists. Tolerance can develop to some side effects, however some side effects (e.g., constipation, increased sweating) can continue to be troubling for some patients for the duration of methadone treatment [3]. The primary hazard of methadone treatment is the risk of overdose, particularly during induction and when used in combination with other sedative drugs. The relatively slow onset of action and long half-life of methadone mean that opioid overdose can be deceptive and toxic effects may become life threatening many hours after ingestion of methadone. Most deaths during the induction period have occurred on the third and fourth day of treatment [41].

Cardiac safety also represents an important safety consideration for methadone given its documented association with QT-interval prolongation. On the basis of available evidence, an expert panel convened by the United States Center for Substance Abuse Treatment developed a series of safety recommendations for physicians prescribing methadone, specifically addressing the need to inform patients about the risk of arrhythmia, assess cardiac history, use electrocardiography for baseline and follow-up assessment, manage risk factors, and be aware of interactions between methadone and other drugs that prolong the QT interval [59].

In addition to direct methadone side effects, some studies have reported that a significant subset of patients (up to a third) may experience symptoms of breakthrough withdrawal during the 24-hour inter-dosing interval [34]. Failure to achieve satisfactory 24-hour withdrawal suppression has been linked to individual variation in methadone pharmacokinetics and the rate of decline in plasma concentrations between peak and trough [32]. Withdrawal symptoms may also indicate that the current dose is inadequate.

4.2.1.6. Drug interactions

Pharmacodynamic and pharmacokinetic interactions can alter the safety and efficacy of methadone for maintenance treatment. Methadone is metabolised in the liver by CYP450 3A4, 2B6 and 2D6. CYP450-inducing drugs reduce plasma methadone levels and can cause withdrawal symptoms; these drugs should be avoided in methadone patients if possible. CYP450 3A inhibitors can decrease the metabolism of methadone and cause overdose; specialist advice should be sought regarding the use of these drugs [41, 71]. Some psychotropic drugs may increase the actions of methadone because they have overlapping, additive effects (e.g., benzodiazepines and alcohol add to the respiratory depressant effects of methadone) [41]. Similarly, given the association between methadone and QT interval prolongation, there is a need for vigilance in prescribing

other agents that have QT prolongation effects in combination with methadone. For details refer to Pacini et al., 2009 [81].

4.2.2. Buprenorphine treatment

4.2.2.1. Pharmacology

During the initial development of buprenorphine as an analgesic in the 1970s its potential utility as a treatment for opioid dependence was recognised [49]. The high-dose sublingual tablet preparation of buprenorphine was introduced in the 1990s and has since been marketed worldwide for the management of heroin dependence.

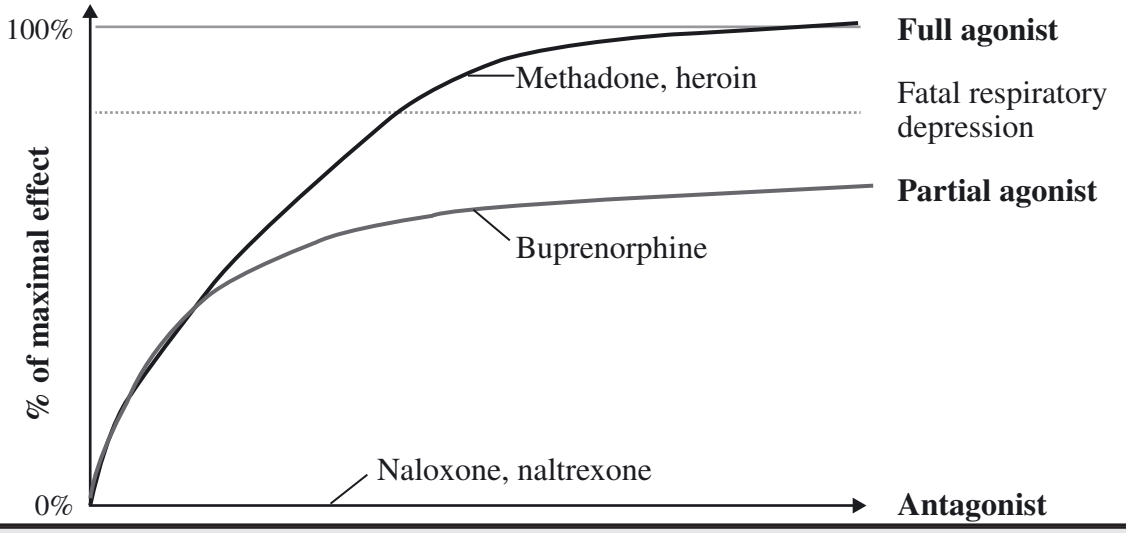

Figure 5. Risk of respiratory depression with opioid agonists, partial agonists and antagonists. Reproduced from Walsh et al., 1994 [104]

Buprenorphine is a highly lipophilic [20] partial agonist at mu-opioid receptors and opioid-receptor-like (ORL-1) receptors and has mixed but primarily antagonistic actions on kappa and delta opioid receptors [99]. Buprenorphine has a high affinity for mu-opioid receptors [11] and dissociates from the receptor slowly [39], thus producing powerful opioid agonist effects whilst also providing blockade against the effects of other opiates in a dose-dependent fashion [102].

As a partial mu-opioid-receptor agonist with lower intrinsic activity than full-agonist opioids but a high binding affinity, buprenorphine competes with other agonists, such as methadone, heroin, morphine and hydromorphone, at the mu-opioid site [10, 49, 103, 107]. As a result, in the short term, it may not produce sufficient compensatory agonist effects, leading to precipitated opioid withdrawal. This can largely be avoided by the use of suitable initial dosing and rapid titration to an appropriate maintenance dose [65]. The lower intrinsic activity of buprenorphine results in a lower level of maximum tolerance, which does not increase over a certain dose threshold (ceiling effect), and its long duration of action leads to milder withdrawal symptoms than those seen with morphine or methadone [49].

Due to its partial agonist action, there is a 'ceiling' effect to the respiratory depression that occurs with buprenorphine; higher doses do not increase respiratory depression to a significant degree [104]. This translates into a lower risk of fatal overdose by comparison with full agonists such as methadone (Figure 5). However, there is no ceiling effect on buprenorphine's clinical efficacy, as higher doses have increasing effectiveness with regard to treatment retention, heroin use

and withdrawal suppression [26, 53, 63]. Availability of mu-opioid receptors is correlated with buprenorphine plasma concentration, withdrawal symptoms and opioid blockade, with 50–60% receptor occupancy required for adequate withdrawal symptom suppression [39] and 80–90% receptor inactivation required for significant reductions in heroin-induced effects [19]. Comer et al. reported that 2, 8 and 32 mg of buprenorphine (using the buprenorphine–naloxone combination) dose-dependently reduced the available mu-receptor population by 74, 83, and 91%, respectively [19]. In addition to buprenorphine dose, receptor blockade also varies with time since administration. Receptor-binding studies conducted using PET scanning at 4, 28, 52 and 72 hours post administration of buprenorphine 16mg to heroin-dependent volunteers demonstrated its duration of action at receptors: 70% of mu-opioid receptors were occupied at 4 hours, 46% at 28 hours, 33% at 52 hours and 18% at 72 hours [39].

Buprenorphine is a long-acting drug with an elimination half-life of 24–36 hours. The onset of effects can be measured within 30–60 minutes of administration and peak clinical effects occur within 1–4 hours. Effects are experienced for up to 12 hours at low doses (2mg) and for as long as 48–72 hours at higher doses (16 or 32mg). The prolonged duration of effect at high doses enables alternate day or three times a week dispensing regimens [9, 83].

4.2.2.2. Treatment – induction

4.2.2.2.1. Treatment-naïve patients

The initial aims of buprenorphine induction are to control possible physical symptoms quickly while avoiding precipitated withdrawal. Successful induction can be achieved by assessing patients for opioid tolerance, observable signs of mild opioid withdrawal, concurrent drug abuse and concurrent medical conditions. To prevent precipitated withdrawal with buprenorphine, the first dose (2–4mg) should be administered at least 6 hours after last opioid use or when objective and clear signs of withdrawal are evident [88]. In contrast with the approach recommended for methadone induction ('start low, go slow'), most guidelines recommend buprenorphine induction should proceed rapidly [16, 23, 65]. It has been shown that faster buprenorphine induction improves early treatment retention in subsequent buprenorphine maintenance treatment and higher doses reduce craving [30] (Figure 6).

4.2.2.2.2. Patients transferring from other pharmacotherapies

Patients can be inducted onto buprenorphine maintenance treatment from either current dependent heroin use, or can transfer from methadone. As methadone and buprenorphine have comparable effectiveness in reducing cravings and illicit opioid use, transfer from methadone to buprenorphine may be appropriate when patients have not met their treatment goals or have developed intolerable side effects to methadone, or in patients who wish to change pharmacotherapies, e.g. to enable reduced-frequency dosing. Patients on low doses of methadone (<40mg) generally tolerate this transition with minimal discomfort. However, patients on higher methadone doses may find that buprenorphine precipitates transient opiate withdrawal [16, 23, 65]. The first buprenorphine dose should be administered at least 24 hours after the last methadone dose to minimise the likelihood of precipitated withdrawal, ideally waiting until patients experience a mild degree of opioid withdrawal symptoms. Patient assessment and communication are important during this phase [65]. The general principle is to cease methadone and delay buprenorphine until patients experience observable withdrawal [16, 23], generally 2–4 days after the last methadone dose. Symptomatic medication may be used to ease withdrawal discomfort.

4.2.2.3. Treatment – maintenance

The aims and principles of buprenorphine

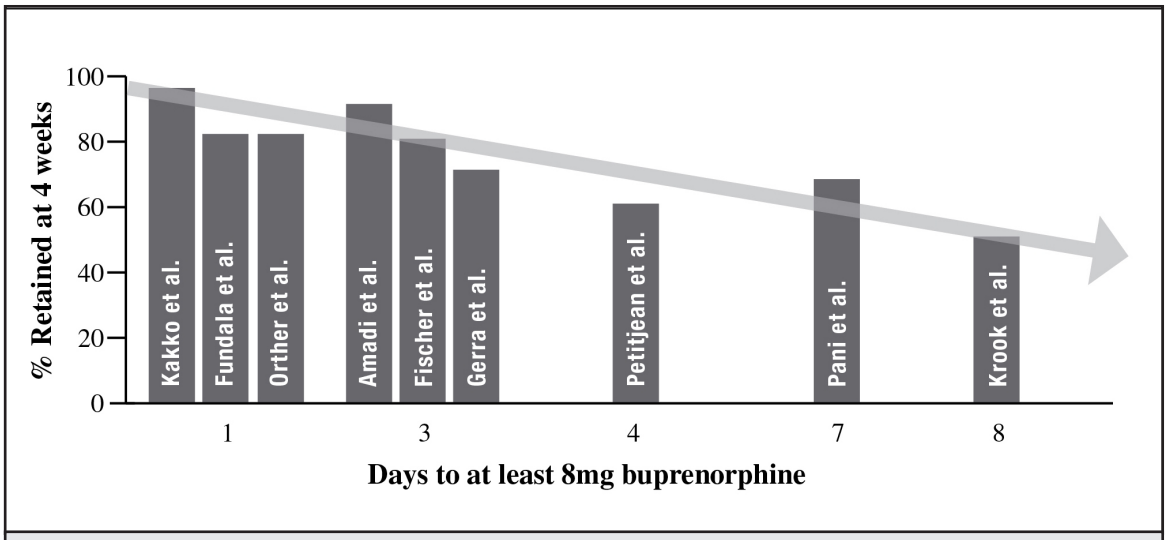

Figure 6. Association of retention rate with intensity of buprenorphine induction. Reproduced from Bacha, Reast and Pearlstone, 2010 [7]

maintenance treatment are generally equivalent to those of methadone maintenance treatment and to addiction treatment in general. The optimal maintenance dose needs to be individualised according to the patient's response to buprenorphine. During the stabilisation phase, buprenorphine doses should be titrated according to clinical effect by increments of 2–4mg, to reach the recommended target dose of 12–24mg/day by the end of the first week. Several guidelines recommend aiming to reach doses of 12–16 mg within 2–3 days, subject to patient response [16, 23]. At each dose review, patients should be assessed for features of intoxication or withdrawal, craving, additional drug use, adverse events, adherence to dosing regimen and satisfaction with buprenorphine treatment [65]. Effective maintenance, resulting in reduced heroin use and improved treatment retention, may be achieved with buprenorphine doses in the range of 8–24mg per day, with a maximum daily recommended dose of 32mg [88].

Alternate-day dosing can be considered in patients who are first stabilised on daily dosing [16, 23, 65]. Duration of buprenorphine effects is dose-dependent, allowing for twice a week or three times a week dosing schedules [9, 83]; however, not all patients can be stabilised on such regimens. The dose dispensed for a 48-hour period is double the normal daily buprenorphine dose, and the dose for a 72-hour period is three times the daily dose, up to a maximum of 32mg at a time [88].

Patients who have missed fewer than 5 consecutive days since their last buprenorphine dose must be reviewed prior to receiving a further dose to ensure safety (i.e., reduction in tolerance may have occurred), while patients who have missed more than 5 days need to recommence treatment at a dose no greater than 8mg [65].

4.2.2.4. Cessation of buprenorphine treatment

The decision to withdraw from opioid maintenance treatment should not be made lightly: relapse to illicit opioid use and treatment dropout is high following interruption of a long-term treatment programme. Patients should be reminded that the ultimate goal of treatment is to continue not to relapse into addictive use and to achieve, maintain and consolidate other life goals (e.g. employment, meaningful relationships) and that there is no restriction to the length of time they can receive maintenance treatment in order to achieve this goal [97].

A gradual process of treatment withdrawal was historically believed to result in better outcomes

[4]; however, a buprenorphine–naloxone tapering schedule of 7 days was reported to be comparable to 28 days in terms of opioid-free urine specimens at 1- and 3-month assessments in a study by the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) [64]. The signs and symptoms of buprenorphine withdrawal are qualitatively similar to withdrawal from other opiates although the withdrawal syndrome experience on cessation of buprenorphine is delayed and may be milder than withdrawal from heroin, morphine or methadone [4]. The onset of symptoms is usually around 24–72 hours after the last dose and the peak is between days 3 and 5 (days 5 and 14 following long-term maintenance treatment).

Frequent monitoring and review, including the use of withdrawal scales, counselling and symptomatic medication should occur regularly during the withdrawal phase. Patients who feel at risk for relapse should be allowed to return to maintenance treatment at any time during taper. Psychosocial counselling should continue and possibly be increased during and after medical withdrawal [65].

4.2.2.5. Side effects and drug interactions

Buprenorphine is principally metabolised by CYP450 3A4. Although buprenorphine metabolism can be influenced by medications that are also metabolised by or alter the activity of the cytochrome P450 system, it is less affected by drug interactions or hepatic disease than other opioids such as methadone. Of particular interest in light of the increased incidence of HIV among injecting drug users, buprenorphine is less likely to be associated with adverse events when given with efavirenz-containing highly active anti-retroviral therapy (HAART) compared with methadone [14]. The combination of buprenorphine with benzodiazepines, alcohol or other sedatives has been associated with fatal overdoses, due to additive effects. Appropriate prescription of these therapeutics, combined with responsible use by patients, is unlikely to lead to adverse consequences [65].

Buprenorphine-maintained patients may have a diminished response to opiates prescribed for analgesia [75]. This can be managed by temporarily increasing the buprenorphine dose, using higher potency opioids such as sufentanil (which is approximately 1000 times more potent than morphine) or using non-opioid analgesics [65, 66]. Which option is appropriate depends on the severity, onset and duration of pain. In addition, some options may require management in specialist settings [23; 65].

4.2.3. Buprenorphine–naloxone

4.2.3.1. Pharmacology

Buprenorphine–naloxone (Suboxone®) is a sublingual tablet containing buprenorphine hydrochloride and naloxone hydrochloride dihydrate in a ratio of 4:1. It is available in two dosage strengths: 2mg buprenorphine/0.5mg naloxone, and 8mg buprenorphine/2mg naloxone. The pharmacology of buprenorphine has been described above. Naloxone is a competitive mu-opioid-receptor antagonist, which displaces receptor-bound opioid molecules and produces a rapid reversal of the effects of opioids. The main clinical use of naloxone is to treat respiratory depression caused by opioid overdose [85]. Naloxone has low oral bioavailability but has rapid access to mu receptors if administered intravenously. It is metabolised in the liver, with a short half-life of about 1 hour [85].

The buprenorphine–naloxone combination product was developed to decrease the potential for diversion and abuse of buprenorphine [73]. The presence of naloxone is intended to deter intravenous abuse by persons dependent on other opioids; if administered sublingually, naloxone does not cause significant effects due to the poor absorption of naloxone via this route. However, if the product is used intravenously or nasally, the antagonistic effect of naloxone elicits an acute but non-life-threatening withdrawal syndrome

in opioid-dependent subjects [73]. Therefore, the combination of buprenorphine and naloxone for sublingual administration should diminish the parenteral abuse liability of buprenorphine by opioid-dependent individuals [73]. Notably, buprenorphine time to onset, time to peak effect and duration of action remain unaltered.

4.2.3.2. Reduced abuse liability

Numerous controlled and observational studies have confirmed the reduced abuse liability of buprenorphine–naloxone relative to buprenorphine. The findings of a study in which 12 opioid-dependent volunteers were stabilised on a 60mg daily dose of morphine and then received a series of challenges with buprenorphine alone (2mg intravenous dose), or in combination with naloxone (ratios of 2:1, 4:1 and 8:1) were that buprenorphine alone did not precipitate withdrawal and had similar agonist effects to those of morphine; buprenorphine plus naloxone at ratios of 2:1 and 4:1 produced moderate to high increases in global opiate withdrawal, bad drug effect and sickness; while the 8:1 ratio produced only mild withdrawal symptoms [73]. A study in which opioid-dependent volunteers were maintained on a 40mg dose of hydromorphone and then tested with intramuscular and sublingual buprenorphine/naloxone (1.0/0.25, 2.0/0.5, 4/1, 8/2 and 16/4mg); intramuscular hydromorphone (10mg) and naloxone (0.25mg); both intramuscular and sublingual buprenorphine alone (8mg); and placebo found that the combination produced dose-related opioid antagonist effects when administered intramuscularly but that the same doses produced neither significant agonist or antagonist effects when administered by the sublingual route [96]. Results from a study of 12 intravenous heroin users maintained on each of three different sublingual buprenorphine levels (2, 8 and 24mg) showed that the subjective ratings of 'drug liking' and 'desire to take the drug again' were significantly lower for buprenorphine–naloxone than for buprenorphine or heroin (Figure 7). Similar results were found for the amount of money that participants were willing to pay for each drug. Subjects were most likely to self-administer drug when maintained on the lowest sublingual buprenorphine dose [18]. Retrospective, real-world data collected from interviews with injecting drug users from the Australian Illicit Drug Reporting

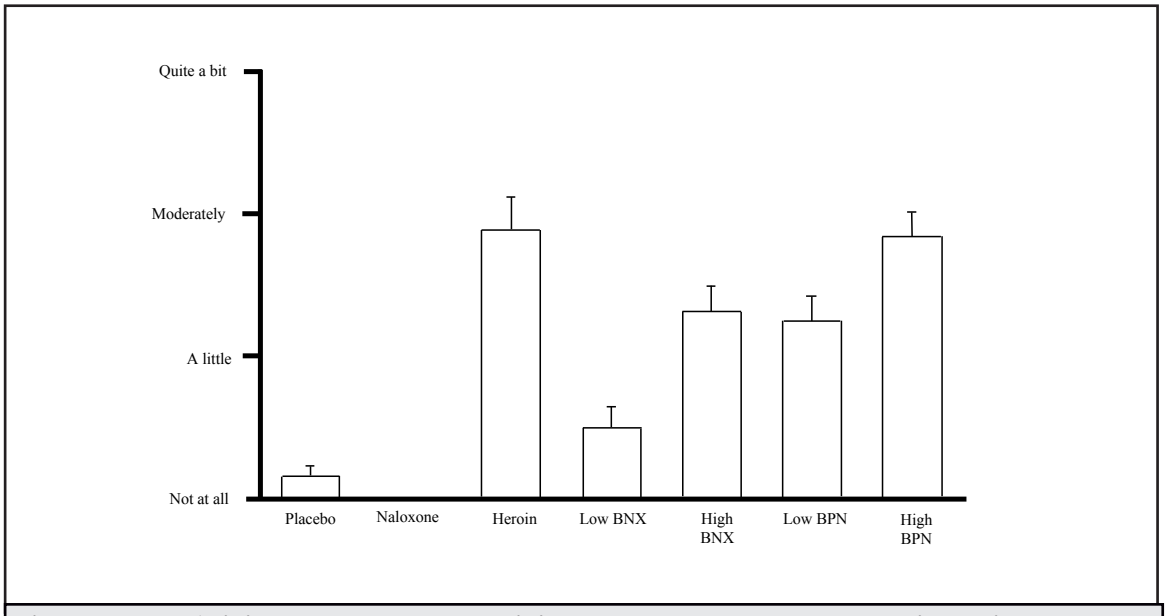

Figure 7. Mean 'willing to take the drug again' responses across all buprenorphine maintenance doses in the study by Comer et al., 2010 [18]

System (IDRS) indicated that buprenorphine–naloxone was less likely to be injected than either methadone or buprenorphine [22].

4.2.3.3. Treatment – induction

The rationale for induction onto buprenorphine–naloxone is similar to that for buprenorphine. To avoid precipitated opioid withdrawal, the first dose of buprenorphine–naloxone is delayed by 12–24 hours from the last opioid use, upon presentation of observable withdrawal signs. Induction on buprenorphine–naloxone from illicit opioid use has been shown to be effective and well tolerated in a NIDA CTN trial of 234 opioid-dependent subjects. The study found that 90% of participants successfully completed the 3-day induction period, reaching the target dose of 16mg buprenorphine/4mg naloxone, and 68% completed the 13-day taper program [5].

4.2.3.4. Treatment – maintenance

EU prescribing information recommends that the dose of buprenorphine/naloxone be increased progressively according to the clinical effect and should not exceed a maximum single daily dose of 24mg/6mg [89], although adopting a best-practice approach by titrating individual doses according to clinical effect means that some patients may require higher or lower dosage for optimum response. As for buprenorphine, patients should be assessed at least weekly during the stabilisation phase to allow assessment of patient response to therapy and appropriate dose adjustment. EU prescribing information states that following satisfactory stabilisation, buprenorphine/naloxone may be administered on alternate days or thrice weekly in some patients (the buprenorphine/naloxone dose given on any 1 day should not exceed 24mg/6mg) [89]. In a 17-week, double-blind, double-dummy trial, daily dosing of buprenorphine–naloxone (8mg/2mg and 16mg/4mg) was compared with methadone (45mg and 90mg) in 268 participants. The percentage of opioid-free urine samples over time did not differ by drug or dosage. The percentage of patients with ≥12 consecutive opioid-negative urine samples did not differ by drug and was significantly greater for patients receiving higher doses of either agent. Induction success, compliance, non-opioid drug use, retention and Addiction Severity Index scores did not differ among the groups [53].

4.2.3.5. Buprenorphine–naloxone and take-home dosing

Due to its favourable safety profile and reduced abuse liability, buprenorphine–naloxone may hold particular value for patients in whom unsupervised ‘take-home’ dosing is used. In an Australian 3-month trial of 119 subjects randomised to observed or unobserved (weekly take-home) administration of buprenorphine–naloxone, retention and heroin use were not significantly different between the two dosing groups. Treatment with close clinical monitoring, but no observation of dosing, was significantly cheaper (AU$ 1663 compared with AU$ 2138) and therefore significantly more cost-effective [8]. Buprenorphine–naloxone might therefore help to alleviate pressure on resources by allowing safe ‘take-home’ dosing.

5. Conclusion

Opioid dependence is a chronic metabolic brain disease manifesting with several biological, sociological and individual effects. Treatment for opioid dependence aims to improve the well-being and social functioning of individuals and to reduce the associated health and social consequences. Given the complexity of this condition, no single treatment approach is effective for all individuals, and people with opioid dependence should therefore be offered access to a range of high-quality treatments to respond to their varying retention and response-related needs [113].

Opioid agonist maintenance treatment has be-

come the first-line treatment for opioid dependence. Agonist maintenance treatment benefits individuals with opioid dependence through reductions in addictive drug use and associated mortality risks, increased stability, improved well-being and social functioning; benefits to society include reductions in the incidence of criminal behaviour, reduced health and criminal-justice costs and increased productivity [113].

In order to realise the full benefits of opioid maintenance treatment, it is necessary that clinicians deliver treatment in a manner that meets certain quality standards, as derived from the available scientific evidence base, while tailoring the treatment to the individual in order to meet the complex and unique needs of different patients. Decisions should be informed by a sound understanding of the basics of addiction, the principles of opioid maintenance treatment, and the clinical application of available options. Whilst treatment with methadone, buprenorphine and buprenorphine–naloxone has the same therapeutic aims, these products/compounds have unique pharmacological properties and safety profiles that need to be considered when formulating treatment plans. This supplement provides an overview of the basic knowledge required to deliver maintenance treatment in a safe and effective manner.

Key learning points

- Opioid dependence is a chronic metabolic brain disease and several biological, sociological and individual factors are implicated in its development
- Effective treatment
  - Is accessible for as many people as possible
  - Involves a set of pharmacological and psychosocial interventions
  - Aims to reduce or cease addictive opioid use, prevent harms associated with opioid use, improve quality of life for the patient and benefit the wider community
- Opioid agonist maintenance treatment is the most cost-effective form of treatment
  - Primary options are methadone, buprenorphine and buprenorphine–naloxone
  - Access to psychosocial interventions can significantly enhance success
- The benefits of maintenance programmes increase the longer the person remains in treatment
  - Many people do need to receive treatment for a number of years
- Methadone, buprenorphine and buprenorphine/naloxone:
  - Are broadly comparable in terms of retention and effectiveness in reducing addictive opioid use or any opioid use
  - Buprenorphine is preferred for detoxification/short-term programmes
  - Methadone is associated with specific side effects
    - Respiratory depression and QT prolongation
  - Fewer drug interactions with buprenorphine and HAART
  - Methadone is associated with greater overdose risk with benzodiazepines
  - Buprenorphine–naloxone is associated with the lowest abuse potential
- Regular monitoring allows the clinician to evaluate and adapt therapy to meet the needs of the patient

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Conflict of interest

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