UNODC
United Nations Office on Drugs and Crime

OPIOID SUBSTITUTION TREATMENT (BUPRENORPHINE)

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INTERVENTION TOOLKIT

PREVENTION OF TRANSMISSION OF HIV AMONG DRUG USERS IN SAARC COUNTRIES (RAS/H13)

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Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
COWS	Clinical Opiate Withdrawal Scale
CTN	Clinical Trial Network
DOT	Direct Observation Treatment
HIV	Human Immunodeficiency Virus
ICD	International Classification of Disease
ICTC	Integrated Counselling and Testing Centre
IDU	Injecting Drug User
LAAM	Levo Alpha Acetyl Methadol
MSJE	Ministry of Social Justice and Empowerment
NACO	National AIDS Control Organisation
NGO	Non-Governmental Organization
ORW	Outreach Worker
OST	Opioid Substitution Treatment
PE	Peer Educator
PM	Project Manager
SAARC	South Asian Association for Regional Cooperation
SHG	Self-Help Group
TI	Targeted Intervention
UNODC ROSA	United Nations Office on Drugs and Crime Regional Office for South Asia
WHO	World Health Organization

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BACKGROUND

The project *"Prevention of transmission of HIV among drug users in SAARC countries"* (Project RAS/H13) is executed by UNODC as part of a joint UN initiative between UNODC, UNAIDS and WHO in South Asia. The overall goal of this project is to reduce the spread of HIV among drug using populations in SAARC countries. In doing so, the project assists governments and communities to scale-up comprehensive prevention and care programs for drug users, especially injecting drug users (IDUs), and their regular sex partners.

Under its current phase (Phase II), the project is designed to demonstrate the effects of comprehensive harm reduction interventions which were initiated in Phase I and place the evidence for consideration by national governments to scale up programs for significant coverage with quality services. The project is presently working in seven countries (Bangladesh, Bhutan, India, Nepal, Maldives, Pakistan and Sri Lanka) and has four key components:

1) Advocacy to support change in policy and practice

2) Demonstrate the effectiveness of comprehensive risk reduction approaches to reduce HIV transmission among drug users, especially IDUs, and their sex partners

3) Scaled up risk reduction approaches to reduce HIV transmission among drug users, especially IDUs, and their regular sex partners and

4) Efficient project management

A number of tools have been developed by UNODC to build the capacities of service providers, institutions, as well as policy makers on various aspects linked to HIV prevention among drug users. The tools have been tailor-made, keeping in mind the strategic gaps in capacities and service delivery, to ensure quality, and to ensure standardization of services which are cost-effective and can be replicated.

Accordingly, a set of six intervention toolkits were developed by UNODC during Phase I of the project. These toolkits were field tested through implementation at the demonstration sites developed under the project's Phase I (2003-2007). They have been extensively used by the countries and finalized drawing from the implementation experiences.

Two toolkits on Opioid Substitution Treatment (OST) i.e., one each on buprenorphine and methadone substitution have been of particular significance in this context and specially in assisting countries with their scale-up plans. Since the inception of the project and development of the toolkits, four out of the seven SAARC countries have initiated OST. The choice of medicines has been different in different countries. While Bangladesh and Maldives have initiated Methadone maintenance treatment alone, India and Nepal have initiated OST with both Buprenorphine and Methadone. Bhutan too has demanded the initiation of OST interventions. The rich experiences gained over the years on OST implementation in the SAARC region have been drawn upon to revise and update this intervention toolkit on OST (Buprenorphine).

This toolkit therefore has been developed with the aim of assisting policy makers and program implementers to initiate, strengthen and scale-up OST interventions for opioid dependent drug users (and specially those who inject drugs) based on lessons learnt elsewhere and the cumulative weight of scientific evidence.

1

INTRODUCTION

In South Asia, opioid use, and in particular heroin use, is on the increase. The diffusion of injecting drug use is causing concern in the region (UNODC & MSJE, 2004). Heroin and other opioid dependence cause significant morbidity and mortality; it is a chronic and enduring condition that often requires long-term treatment and care. Adequate access to a range of treatment options should be offered to respond to the varying needs of people with heroin/opioid dependence.

Substitution maintenance treatment is an efficacious, safe and cost-effective modality for the management of opioid dependence. Such treatment is a valuable and critical component of the effective management of opioid dependence and the prevention of HIV among IDUs. Scientific evidence suggests that substitution treatment can help reduce criminality, infectious diseases and drug-related deaths as well as improve the physical, psychological and social well-being of dependent users (Gibson et al. 1999). Provision of substitution maintenance treatment should be integrated with other HIV preventive interventions and services, as well as with those for treatment and care of people living with HIV/AIDS (WHO, UNODC & UNAIDS, 2004). A review recommended that the provision of substitution treatment for opioid dependence should be supported both in countries with emerging HIV and injecting drug use problems as well as those with established populations of injecting drug users (IDUs) (Gowing et al. 2004).

Pharmacological agents used as substitution substances in the management of opioid dependence are: methadone, buprenorphine, levo alpha acetyl methadol (LAAM), dihydrocodeine and tincture of opium (laudanum).

Drug substitution means replacing, under medical supervision, the drug, which the drug user is taking with a similar substance. It may also mean using the same drug but taking it in a different way, for example, sublingual buprenorphine to replace injecting of buprenorphine. Substitution treatment comes either with or without psychosocial support.

Methadone is the most employed agent in substitution treatment around the world. There have been increasing doubts about the safety of LAAM because of the related cardiac risk. Buprenorphine is emerging as a useful complementary or alternative option to methadone.

The partial opioid-receptor agonist profile of buprenorphine is attractive, and this drug can be used to suppress heroin craving and antagonize heroin effects, while having a limited potential for dose escalation and toxicity. Buprenorphine is efficacious in comparison with other available options as shown by individual comparative studies of buprenorphine in heroin dependence (Johnson et al. 1992; Strain et al. 1994; Ling et al. 1996; 1998; Johnson et al. 2000; Pani et al. 2000) and meta-analyses (West et al. 2000; Barnett et al. 2001). Observational data from France where buprenorphine substitution is widely used lend support to the notion of reduced toxicity (Auriacombe et al. 2001). Since it is a partial agonist, buprenorphine can be especially useful for patients who need only a limited degree of agonist action. The one-year retention rate

for buprenorphine substitution combined with psychosocial care was 75 per cent compared with 0 per cent for a placebo group in Sweden; and the treatment was safe and efficacious for heroin dependence (Kakko et al. 2003).

Buprenorphine also has an important role to play in the control of HIV infection among and from IDUs. However, the impact of buprenorphine on HIV infection in this population has been less researched than methadone. Findings from India demonstrate the potential of buprenorphine treatment in reducing injecting drug use, decline in HIV related risk behaviours among heroin users and improved retention in treatment (Kumar et al. 2003; Kumar et al. 2009; Armstrong et al, 2010; Kumar & Agrawal, 2012). As buprenorphine reduces the number of injecting episodes, it is likely to have an effect similar to methadone on reducing the spread of HIV. Recently published work from Buprenorphine-HIV Evaluation and Support (BHIVES) Collaborative indicates that integrated buprenorphine and HIV treatment is feasible and successful. Both providers and patients are satisfied with the integrated models of care. The multi-study demonstrated that the integrated model has the potential to improve access to ART and reduce morbidity and mortality among HIV-infected opioid-dependent patients who have traditionally been less likely to access and adhere to ART. Additionally, the integration is likely to increase receipt of high-quality HIV care by ameliorating some of the adverse effects of opioid dependence on quality of life indicators (Altice et al. 2011).

Buprenorphine, in sublingual tablet form (in doses of 0.4 mg and 2 mg), has been licensed in India for the management of opioid dependence, including maintenance and detoxification, at specified drug treatment centres approved by the Ministry of Social Justice and Empowerment (MSJE), Government of India (GoI). This preparation is effective in the long-term as a maintenance treatment program, and in the short-term for treatment of heroin withdrawal. Following support from National

Buprenorphine Substitution

- As efficacious as other available options
- Reduced toxicity
- Better retention in treatment
- Potential for reducing HIV among heroin injectors

AIDS Control Organisation (NACO), there has been a significant attempt to lay a good foundation for the scale-up of opioid substitution treatment (OST) in India. OST has been included in National AIDS Control Programme-III (NACP III) as an intervention component, and it is planned to scale up OST services through NGOs working in the drug treatment sector as well as through government hospitals. Two documents, namely, 'Substitution Treatment with Buprenorphine for Opioid Injecting Drug Users – Practice Guidelines' and 'Standard Operating Procedure for Oral Substitution Treatment with Buprenorphine' have been developed by NACO (NACO, 2007; NACO, 2008). The supply-chain mechanism in place is fully functional.

To assist in the safe and effective implementation of buprenorphine treatment in India and other countries of the SAARC region, a protocol was developed by the All India Institute of Medical Sciences, New Delhi. The practice of substitution maintenance treatment must be guided by clinical modules and supported by adequate training and evaluation. Possible adverse consequences need to be minimized by adhering to best clinical practices, monitoring treatment quality and outcomes, and instituting adequate control measures and regulations to avoid diversion of the medicines into illicit channels. Hence, this module on buprenorphine substitution has been developed to guide maintenance programs us-

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AIM

The aims of the buprenorphine module are:

- To outline the safety and effectiveness of buprenorphine in the management of heroin and other opioid dependence.
- To describe the guidelines and procedures for opioid substitution treatment (OST) with buprenorphine.
- To discuss issues relating to buprenorphine administration and a rollout plan for buprenorphine substitution clinics.
- To understand the quality assurance indicators in the operation of the buprenorphine clinics.

3

WHAT NEEDS TO BE IN PLACE BEFORE INITIATING BUPRENORPHINE SUBSTITUTION

Policies and procedures for buprenorphine clinics to be established prior to initiating opioid dependence treatment

- Establish policies and procedures for buprenorphine treatment (outpatient delivery in supervized settings – directly observed treatment)
- Plans for staff education and training
- Backup coverage in case of absence or leave of the medical doctor/core team
- Assurance of privacy and confidentiality of addiction treatment information
- Linkages with other drug treatment services, who will accept referrals for other forms of treatment (e.g., abstinence-oriented approaches; psychosocial interventions)
- A referral network of medical specialists
- Timely physical examinations
- Linkages with medical treatment facilities including HIV treatment and care
- Linkages with addiction and psychiatric treatment programs (e.g., detoxification centres, psychiatric clinics)
- Listing of community referral resources, including specific self-help groups who would welcome patients on buprenorphine substitution

Buprenorphine is listed under Schedule III of the 1971 Convention on Psychotropic Substances. Given the lax drug control measures in South Asia, there is a fear that buprenorphine used in drug maintenance treatment may be diverted to the black market. Reduction in the diversion of buprenorphine to the black market can be achieved by observing certain procedures strictly. Currently, the drug is licensed and can be prescribed for heroin dependence in India by specified drug deaddiction centres notified by the MSJE, GoI. Procedures have been laid down for procuring, storing and documenting the distribution of medication. It is essential that the agencies responsible for buprenorphine treatment are

completely aware of the legal and regulatory procedures related to this drug in their respective countries and strictly adhere to them.

Assessment of the capacity of the agencies

The capacity of the agencies that will be establishing the buprenorphine clinic has to be assessed. Given the nature of the treatment and the regulatory procedures, it is important that, to begin with, the services are provided by clinics that have received accreditation. For example, in India, an independent National Accreditation Committee has been constituted to evaluate the OST centres and to provide accreditation, and only centres that received accreditation can provide OST to IDUs with support from NACO. It is worthwhile to set up buprenorphine clinics at medical colleges, university hospitals, major government hospitals and recognized drug treatment centres.

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IMPLEMENTATION

The implementation of buprenorphine substitution is organized into five subsections. Subsection 4.1 on 'clinical pharmacology' provides information on the safety and effectiveness of buprenorphine. Subsection 4.2 deals with the assessment of opioid dependent individuals for buprenorphine treatment. Subsection 4.3 describes the guidelines and procedures for maintenance treatment with buprenorphine. Subsection 4.4 discusses the issues relating to the administration of buprenorphine and the roll-out plan for delivering buprenorphine to the patients. The final subsection 4.5 focuses on the training needs and ongoing support.

- Clinical pharmacology
- Assessing patients for treatment with buprenorphine
- Guidelines and procedures for maintenance treatment
- Roll-out plan for buprenorphine administration
- Training and support

4.I Clinical Pharmacology

In this subsection, the following will be discussed:

i) About buprenorphine

ii) Onset and duration of response to buprenorphine

iii) Buprenorphine withdrawal syndrome

iv) Side-effects

v) Safety

vi) Drug interactions

vii) Properties and their clinical implications

viii) Buprenorphine formulations

ix) Comparison between buprenorphine and methadone

i) About buprenorphine

Buprenorphine is a semi-synthetic opioid derived from the morphine alkaloid the baine. It has low intrinsic activity[1] and high affinity at the opioid receptors responsible for some properties of opioids like analgesia and euphoria[2].

Buprenorphine suppresses the craving for heroin and also blocks the effect of additional heroin and other opioid use.

ii) Onset and duration of response to buprenorphine

Buprenorphine has poor gastrointestinal bioavailability but has a fair sublingual bioavailability. It is easily absorbed within 5-10 minutes. It has a mean elimination half-life from plasma of 37 hours.

The reasons for the extended action of buprenorphine are:

- Tight binding at opioid μ receptors and slow dissociation

[1] Buprenorphine is a partial agonist and has both agonist (opiate like) and antagonist (blocking the action of opioids) activity at the opioid receptors.

[2] Several opioid receptor subtypes have been described and characterized. μ receptors: Classic opioids like morphine bind here preferentially. They are believed to be responsible for most of analgesic properties of opioids, as well as for euphoria, sedation, constipation, respiratory depression and dependence.

Effects & Duration of Buprenorphine

Effects	Duration
Onset of effects	30-60 minutes
Peak clinical effects	1-4 hour
Duration of effects	8-12 hours at low dose (e.g. < 4 mg) 24-72 hours at high dose (e.g. >16 mg)

Higher dosage has prolonged duration of response

- Very slow release of low levels of buprenorphine from the fat stores

Extended duration of action helps a daily dose or thrice a week dose

iii) Buprenorphine withdrawal syndrome

Whereas the withdrawal effects from full agonists like heroin, morphine or methadone are marked, only mild withdrawal effects is observed when buprenorphine is abruptly withdrawn. In fact, there may not be significant withdrawal symptoms for almost 72 hours following cessation of the drug. Its partial agonist properties, along with its slow dissociation from opioid receptors, are thought to explain why opioid withdrawal syndrome is milder.[3]

iv) Side-effects

The medical effects of acute buprenorphine administration are similar to those of opioid agonists. Opioid dependent individuals show tolerance to many of these effects. Since sublingual buprenorphine tablets dissolve readily in water, they can be injected. The use of combination tablets of buprenorphine and naloxone[4] (in doses of 2 mg of buprenorphine and 0.5 mg naloxone)[5] will help mitigate the potential diversion and abuse. This combination will also permit sublingual therapeutic use without precipitating withdrawals, as naloxone has poor sublingual bioavailability. When the combination is injected, naloxone precipitates an opioid withdrawal syndrome in persons with opioid dependence. Though the withdrawal is distressing, it is not life-threatening and a medical emergency.

There does not appear to be an increase in the QTc interval associated with buprenorphine use.

Precipitated withdrawal: A potential adverse effect of buprenorphine is precipitated withdrawal associated with the first dose of buprenorphine. Its likelihood is generally increased if the first dose is high (>4-8 mg), if the person has a high level of physical dependence on opioids, and if the time interval between the last dose of full opioid agonist and the first dose of buprenorphine is short (<2 hours). To minimize this risk of precipitated withdrawal, the first dose is best administered at the time of opioid withdrawals.

v) Safety

Buprenorphine exerts a "ceiling effect"; as the dose of buprenorphine increases, the agonist effect reaches a peak and then reduces in

Side-effects

- Constipation
- Disturbed sleep
- Drowsiness
- Increased sweating
- Headaches
- Nausea

[3] Treatment with opioid antagonists (e.g., naltrexone) can be commenced within days of the cessation of low-dose buprenorphine treatment without precipitating severe opioid withdrawal. This enables patients to transfer promptly to naltrexone treatment, and avoid relapse and treatment dropout.

[4] Naloxone is an opioid antagonist (preventing activation of opioid receptor by an opioid); it is short acting; used in the treatment of overdose; 10-20 times more potent by injection than by sublingual route.

[5] The combination tablet is available in some states of India.

magnitude. In contrast to full opioid agonists, overdose of buprenorphine (by itself) does not appear to cause lethal respiratory depression in non-compromised individuals.

Overdose of buprenorphine (by itself) does not appear to be fatal

Deaths have been associated with injecting buprenorphine in combination with benzodiazepines and/or other central nervous system depressants. Therefore, use of sedative-hypnotics is a relative contraindication to treatment with buprenorphine. If treatment with both drugs is required, the doses of both medications may need to be lowered.

Hepatic safety is not compromised with buprenorphine in opioid dependent persons.

vi) Drug interactions

Drugs	Drug interactions
Sedatives(Benzidiazepenes)	Additive sedative effects Deaths reported with combinations
Opioid antagonists	High doses of naloxone required for treating overdose Naltrexone can precipitate a delayed withdrawal syndrome
Opioid agonists	Difficult to achieve analgesia with short-term opioid agonists in patients maintained on buprenorphine
Hepatic enzyme inhibitors[6]	Drugs to treat HIV like Atazanavir (ATV); Ritonavir (RTV); Saquinavir (SQV); Tipranavir (TPV); Antifungal drug, Ketoconazole[7]
Hepatic enzyme inducers[8]	Drug to treat HIV – Efavirenz (EFV)[9]

vii) Properties of buprenorphine and their clinical implications

Property	Clinical implication
Opioid effects	Reduces cravings for heroin
Partial agonist	Less sedating than full agonists (heroin, morphine or methadone)
Prevents or alleviates heroin withdrawal symptoms	Can be used for maintenance or withdrawal treatment of heroin dependence
Diminishes the effects of additional opioid use (e.g. heroin)	Diminishes psychological reinforcement of continued heroin use.
Long duration of action	Allows for once a day to three-times-a-week dosing schedules.
Ceiling on dose response effect	Higher doses prolong the duration of action but safer in overdose.
Preparation (sublingual)	Poorly absorbed orally. Accidental poisoning by children may not be fatal. More time required for directly observed treatment (DOT).
No severe withdrawal precipitated by opioid antagonists	Treatment with naltrexone can be commenced within days of buprenorphine.

[6] Buprenorphine is metabolized by the hepatic enzyme system (cytochrome P450 3A4). Medications that inhibit this enzyme system may potentially increase blood levels of buprenorphine. As yet, no controlled studies have examined the pharmacokinetic interactions.

[7] Interactions clinically not significant.

[8] Medications that induce the enzyme system may potentially decrease the blood levels of buprenorphine. As yet, no controlled studies have examined the pharmacokinetic interactions.

[9] Interactions clinically not significant.

Two primary features of buprenorphine are particularly relevant to its use as an opioid dependence treatment medication:

Buprenorphine acts as an agonist at the μ opioid receptor: It is a partial agonist, with effects very similar to full agonist at the lower end of a dose-response curve. It suppresses spontaneous opioid withdrawal, ensuring that the patients who are in the opioid withdrawal stage when they take their first dose of buprenorphine do not suffer from the withdrawal symptoms. In addition, given regularly as a maintenance drug, it generally decreases craving for illicit opioids in persons who are physically dependant on opioids. Finally, occupancy at the μ receptor provides blockade, so a subsequently administered dose of another μ opioid receptor agonist such as heroin is not experienced to the same degree as would occur if no buprenorphine were present.

Buprenorphine has a bell-shaped dose-response curve: As the dose of buprenorphine is increased, there is an increase in a measured effect (analgesia, respiratory depression) until a maximum effect is achieved, then the measured effect decreases at even higher doses. This means that there is a lower risk of respiratory depression associated with an overdose of the drug.

viii) Buprenorphine formulations

The formulations approved for clinical use in opioid dependence are:

a) Sublingual buprenorphine tablet available as 0.2, 0.4 and 2 mg tablets

b) Buprenorphine-naloxone tablet in the ratio 4:1, available as 2mg buprenorphine/ 0.5 mg naloxone.

The injectable form of buprenorphine is not approved for the treatment of opioid dependence.

ix) Comparison between Buprenorphine and Methadone

Comparative trials have compared the efficacy of buprenorphine with methadone as a maintenance drug. Studies indicate that high dose buprenorphine is equal in efficacy to methadone as a maintenance agent. Buprenorphine is a partial agonist and has a greater safety profile than full agonists. Apart from low acute toxicity, it has adequate safety margins for chronic toxicity. Its slow receptor kinetics (tightly binds to the receptors and dissociates from receptors slowly) accounts for longer duration of action and low levels of dependency. Due to its pharmacological profile, the drug

Buprenorphine	Methadone
Partial agonist and produces only mild euphoria.	Full agonist and can produce significant intoxication.
Has low dependence potential compared to full opioid agonists.	Potential to produce significant dependence. As tolerance increases, dose increases over time are required.
Abstinence leads to mild withdrawal symptoms.	Abstinence leads to marked withdrawal symptoms.
At high doses, there is a ceiling effect. The risk of fatal respiratory depression by overdose of buprenorphine by itself is minimal. But when combined with benzodiazepines (diazepam), alcohol and other CNS depressants, respiratory depression has been reported.	Risk of fatal overdose by respiratory depression.
Sublingual tablets are effectively absorbed. It is not orally active. Sublingual tablets can be crushed, easily dissolved and injected.	Orally active.
Relatively expensive	Cheaper

is thus very safe and can be used on alternate days or thrice weekly, reducing the number of clinic visits. Buprenorphine has low abuse potential. Even though buprenorphine abuse is reported, it is mostly for the parenteral (injectable) preparations. The withdrawal symptoms are milder and are not distressing unlike those of heroin withdrawal. The withdrawal symptoms do not appear until 72 hours after the last dose of buprenorphine. Patients administered on buprenorphine can discontinue the drug easily. The withdrawal symptoms are mild but can be prolonged after discontinuation due to slow receptor kinesis.

There is increasing evidence that buprenorphine can be safely administered to opioid dependent pregnant women. In addition, the incidence of neonatal withdrawal syndrome is low in buprenorphine treated pregnant women. Moreover, recent studies indicate that buprenorphine is the ideal substitution drug for adolescents and younger persons who require OST.

4.2.Assessing Patients for Treatment with Buprenorphine

To determine the appropriateness of buprenorphine substitution treatment, a comprehensive assessment of the patient is essential. To be eligible for buprenorphine treatment, one should have an objectively ascertained diagnosis of opioid dependence. In this subsection, how to assess and diagnose opioid dependence through history, examination and laboratory investigations is outlined, followed by the criteria to determine the suitability of patients for buprenorphine maintenance treatment. Additional information on appropriateness of buprenorphine treatment is found in the Annexure.

i) How to assess and diagnose opioid dependence?

A) History of substance use:

Reason for presentation

- In crisis (health or economic or legal crisis)
- Brought in by a concerned parent/relative/spouse/employer/friend/outreach worker
- Want help for their drug use and motivated to change their behaviour
- Usual source of drugs not available
- Referred by another medical practitioner
- Pregnant

Past and current drug use (last 4 weeks)

- The age of starting drug use (including alcohol and nicotine)
- Types and quantities of drugs taken (including concomitant alcohol misuse)
- Frequency of use, including routes of administration
- Experience of overdose
- Periods of abstinence
- What triggers a relapse?
- Symptoms experienced when unable to obtain the drugs

History of injecting and risk of HIV and hepatitis

- Past history
- Present usage and why patient changed to injecting?
- Supply of needles and syringes
- Sharing habits, including lending and borrowing injection equipment/paraphernalia
- Does the patient know how to inject safely?
- How does the patient clean equipment?
- How does the patient dispose of the used equipment?

- Has the patient thought or tried any other method of use?
- Knowledge of HIV, hepatitis B and C issues and transmission
- Use of condoms

Medical history

- Complications of drug use – abscesses, thromboses, viral illnesses, chest problems
- Hepatitis B, C status, if known
- HIV status, if known
- History and/or diagnostics for STIs
- Last menstrual period
- Operations, accidents and head injury
- Any current medication?

Psychiatric history

- Any psychiatric consultations?
- Any overdoses (accidental or deliberate)?
- Forensic history
- Any outstanding charges?
- Past imprisonment?
- Past custodial lock-ups?

HISTORY

Tip: TRAPPED

Treatment History

Route of administration

Amount of drug used

Pattern of use

Prior abstinence

Effects (medical, psychiatric, social)

Duration of use

Welsh, 2003

Social history

- Family situation
- Employment situation
- Housing situation
- Financial situation including debts

Past contact with treatment services

- Previous efforts to reduce or stop taking drugs
- Contacts with doctors, addiction services, social services, community services
- Previous admissions, how long they lasted and the cause of relapse(s) if any

B) Assessing motivation for change

Is the patient motivated to stop or change his/her pattern of drug use or to make other changes in life? Patients have different levels of motivation for changing their substance use.

Stages of Change

1. Precontemplation: "I don't desire to stop"
2. Contemplation: "I may want to think about stopping, some day"
3. Preparation (determination): "I am planning to stop soon"
4. Action: "I have just stopped using drugs"
5. Maintenance: "I have been away from substances (drugs) for several months"

Prochaska and DiClemente, 1983

C) Examination

- Assessing general health
- General – Anaemia, nutritional status, dentition and overall hygiene
- Skin – Needle marks, tattoo, skin abscesses and open wounds
- Route specific – Injecting (abscesses, cellulitis)
- Drug related – *(See Annexure for assessing medical syndromes associated with opioid use)*
  - Side-effects (e.g. constipation)
  - Overdose (e.g. respiratory depression)
  - Withdrawal (e.g. irritability, pain) – *(See Annexure for opiate withdrawal scale)*
- Current medication – What drugs? If HIV status known, whether on HIV drugs?
- Mental status examination – Co-existing psychiatric problems

D) Special investigations with full-informed consent

- Haematological investigations
  - Haemoglobin
  - Liver function tests
  - HIV
  - Hepatitis B and C

Urine assessment: Opioids persist in the urine for up to 24 hours

Diagnosis

The International Classification of Diseases -10 (ICD-10) provides criteria for establishing the diagnosis of substance dependence.

After completing a comprehensive assessment of a candidate for treatment, the physician should be prepared to

- Establish the diagnosis or diagnoses
- Determine appropriate treatment options
- Make initial treatment recommendations
- Formulate an initial treatment plan
- Plan for engagement in psychosocial treatment

Dependence Syndrome

Presence of 3 or more of the following, during the past 12 months:

1. Evidence of tolerance
2. A physiological withdrawal state when substance use has ceased or reduced
3. A strong desire or sense of compulsion to take the substance
4. Difficulty in controlling substance-taking behaviour in terms of its onset, termination or levels of use
5. Progressive neglect of alternative pleasures or interests
6. Persisting with substance use despite clear evidence of overtly harmful consequences

- Ensure that there are no absolute contraindications to the recommended treatments
- Assess other medical/psychiatric conditions that need to be addressed

The physician then decides about the appropriateness of buprenorphine treatment for the patient. *(See Annexure for buprenorphine treatment appropriateness checklist)*

Criteria to determine suitability for treatment with buprenorphine

Patient Selection Criteria

- Age ≥ 15 years
- Injecting opioid (heroin and/or buprenorphine) users or opioid dependent users (non-injecting)
- Willing to take sublingual buprenorphine (provide informed consent for treatment)

Contraindications

- Patients with serious medical conditions like acute respiratory failure, acute hepatic disease, acute alcoholism, and delirium tremens
- Patients below 15 years of age
- Known hypersensitivity to buprenorphine

Precautions

- Co-morbid dependence on high doses of benzodiazepines or other central nervous system depressants (including alcohol)
- Significant untreated psychiatric co-morbidity
- Significant medical complications

The inclusion criteria can vary from country to country as decided by the national protocols.

Intake Process

(see figure below)

4.3 Guidelines and Procedures for Maintenance Treatment

Physicians who use buprenorphine to treat opioid dependence must consider the entire process of treatment, from induction to stabilization and then maintenance. At each stage of the process, many different factors must be considered if the physician is to provide comprehensive and maximally effective opioid dependence care.

The following issues are dealt with in this subsection:

i) Factors that need to be considered before selecting an opioid dependent person for buprenorphine substitution

ii) Induction

iii) Stabilization

iv) Maintenance dosing

v) Frequency of dosing

vi) Missed doses

vii) Pregnancy

viii) Chronic pain disorders

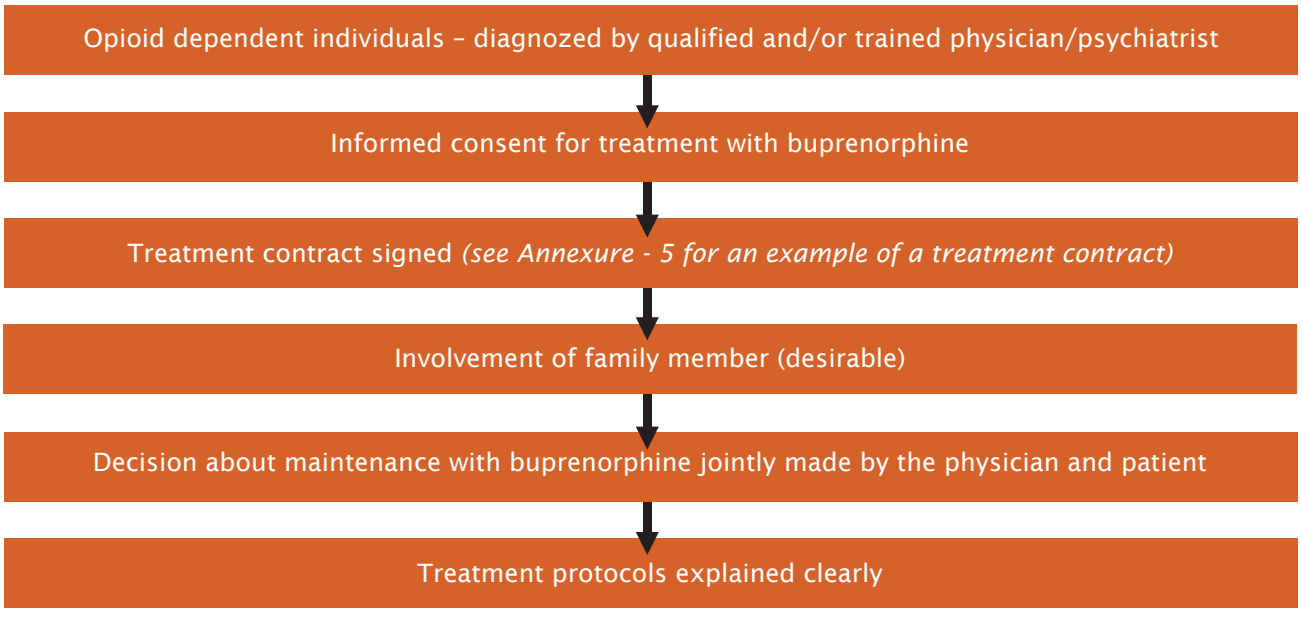
ix) Buprenorphine taper

x) Detoxification with buprenorphine

xi) Transfer of methadone patients to buprenorphine

i) Factors to be considered before selecting an opioid dependent person for buprenorphine substitution

Response to treatment: Treatment goals to be agreed upon by the patient and the provider.



Additional psychosocial support is beneficial for the majority of patients and improves adherence to maintenance treatment.

Adverse effects: People complaining of sedation with methadone prefer buprenorphine.

Logistics of participating in treatments:

- Ease of access for participants
- Frequency of dispensing (alternate day or thrice weekly is attractive for working patients)
- Convenient location of treatment services (located where drug users live; central location; proximity to public transportation)
- User-friendly services
- Costs to patients (free or subsided treatment is most attractive to users)

Ease of withdrawal from maintenance buprenorphine treatment: Though withdrawals are milder compared to methadone, the relapse to heroin following discontinuation of buprenorphine is the same for both drugs.

General expectations from the treatment: Some patients have unrealistic expectations from the treatment; all patients must be told clearly about the treatment benefits and limitations.

Capacity for transfer from methadone maintenance: Patients who cannot reduce methadone[10] below 60 mg are not suitable for transfer to buprenorphine.

Additional psychosocial care with buprenorphine improves treatment adherence

ii) Induction

In settings where both mono and combo (buprenorphine-naloxone) tablets are available, induction is best done for all non-pregnant opioid users with the combo in order to avoid diversion to injecting. In pregnant dependents, mono tablets are preferred. Induction is avoided on weekends unless the setting has personnel to treat the patients during that time.

Initial buprenorphine dose – inducting heroin users

The first dose of buprenorphine should be administered during the time of opioid withdrawal (at least 6 hours after the last heroin use) to reduce the risk of precipitated opioid withdrawal. It should be explained to the patient that buprenorphine is a sublingual tablet, which takes about 5-10 minutes to dissolve. While dissolving the tablet under the tongue, the patient should 1) not talk, 2) not drink, and 3) not chew the tablet until it is completely dissolved. The initial dose usually ranges between 0.4 and 8 mg.[11] Induction is usually done in the first one or two days. The following must be taken into consideration when considering the initial dose:

- The degree of tolerance to opioids:
  - Low or uncertain tolerance to opioids: 0.4 to 4 mg
  - High levels of tolerance: 6 to 8 mg
- Severity of opioid withdrawal[12] experienced by patient at first buprenorphine dose:
  - Moderate to severe opioid withdrawal: 6 to 8 mg
  - Little or no opioid withdrawal: 0.4 to 4 mg, or delay initial dose
- The maximum amount of buprenorphine at the end of first day of induction ranges from 8-16 mg.
- Alcohol, sedative drug (benzodiazepines), or illicit heroin use warrants low initial buprenorphine doses, with frequent reviews
- Medical conditions may warrant the use of lower initial doses

[10]Applicable in countries where both drugs (methadone and buprenorphine) are available for substitution treatment.

[11]Clinical experience in India has indicated this dosage recommendation; however, rigorous studies may be required in the region to establish proper initial doses.

[12]Severity of opioid withdrawal can be determined using the Clinical Opiate Withdrawal Scale included in the Appendix.

Managing precipitated withdrawal

If opioid withdrawal worsens or re-emerges shortly after the first dose of buprenorphine, the medication has most likely precipitated a withdrawal syndrome. Although precipitated withdrawal is not a medical emergency, it is very discomforting to the patient. The preferred strategy is to administer additional doses of buprenorphine, 2 mg every 1-2 hours, attempting to provide enough agonist effect to suppress the withdrawal. Once buprenorphine has precipitated withdrawal, it cannot be withdrawn, therefore, escalating the dosage to achieve an agonist response is the best alternative.

On the second day of induction, the patient's experience following first day dose is reviewed. The dose is increased if withdrawals persist and reduced if adverse effects occur. If the patient continues to experience withdrawal, the full dose of the first day is provided with additional 2 mg increments of buprenorphine. A good night's sleep is a good measure of adequate coverage.

iii) Stabilization

The key principles to stabilizing patients are:

- Review of the patient by the prescribing doctor/members of the treatment team
- Titration of the buprenorphine dose by the reviewing doctor according to:
  - Features of intoxication, withdrawal, cravings over preceding 24 hours
  - Additional drug use (e.g., heroin, sedatives)
  - Side-effects or other adverse events
  - Adherence to dosing regime (attendance at the buprenorphine clinic)
  - Adherence to dosing route (injecting the crushed medicines)
  - Patient satisfaction with buprenorphine dose
- Dose changes:
  - increase by increments of 0.4–2 mg at a time

Patient's experience with an administered dose is relevant to determining proper dosage

At each review, the buprenorphine dose should be titrated in the light of:

- Intoxication, or significant side effects indicate a need to reduce the dose
- Adverse events (such as overdoses) - an indication to reduce the dose
- Cravings for heroin use, use of illicit and other drugs, reported withdrawal symptoms - reasons for increasing the daily dose

The stabilization phase takes 2-8 weeks in general. The goal is to treat the patient with the optimal dose of medication needed to address the target signs and symptoms and so as to give the desired benefits. Once withdrawal and craving are controlled, further dose increases may be done in a conservative manner. It may take 10-14 days to achieve the full benefit of an increased dosage because of the drug's long half life. More frequent dose escalations may be unnecessary.

Adequate and optimal dosing helps to reduce additional illicit drug use and promote adherence to maintenance treatment

Initiating and Maintaining Treatment with Sublingual Buprenorphine – A Tentative Schedule

Before starting

Before administering the first dose of buprenorphine, the patient needs to be in opioid withdrawal. The timing of the last opioid dose before the office visit should be as follows:

- Short-acting opioids -12 hours or more
- Longer-acting opioids - 24 hours or more
- Methadone - 6 hours to 3 days

Initial dose

Day 1: The doctor gives medication under observation. It should be taken sublingually. After the receipt of the tablet of Buprenorphine, the patient should remain in the office for at least one hour to observe for any reaction. The dosage should be slowly stepped up depending on the prevailing withdrawal symptoms. The patient is seen every day for a few days and given medication under the direct observation treatment (DOT).

Administer sublingually 2-4 mg only if the patient has symptoms of withdrawal

2 mg if at higher risk (e.g, older, lower tolerance, taking benzodiazepines)

4 mg for lower-risk patients

Observe for 2 hours, then dispense according to symptoms:

- Withdrawal symptoms resolved

  Request to report the next day

- Withdrawal symptoms only slightly better

  Administer another 2-4 mg

  Maximum first day dose 8 mg (range 8-16mg)

- Withdrawal symptoms substantially worse (precipitated withdrawal)

  Symptomatic treatment or administer 2 mg buprenorphine every 2 hours till symptoms subside

Week 1: Review of the patient's progress by the doctor; relapse if any; adverse effects of the medication.

Week 2-5: Mandatory for patient to meet the doctor every week and more often if necessary.

Week 6: Patient to meet the doctor for review of treatment. The benefits and limitations of treatment are discussed in detail with the counsellor. The patient has been stabilized and is on maintenance dose. This maintenance dose (8-24 mg) will be

contd..

delivered to the patient regularly under DOT by the clinic staff.

Week 7 and beyond: Since the treatment continues for a longer period, the patient meets the doctor only periodically to assess progress. Encourage participation of the patient in psychosocial intervention programs and self help groups. If the clinic staff members feel that the patient is experiencing any special difficulty, then the patient is asked to be seen by the doctor.

It is important to understand that the first few days of treatment are difficult. Insomnia and restlessness can frequently be experienced; however, they can be reduced to a great extent by reassurance. Craving usually comes in waves and can be triggered by external cues like seeing people using drugs, frequenting places where drugs are used, seeing paraphernalia used and internal cues like stress, anger, depression, anxiety and boredom. In addition, specific strategies to reduce craving can be taught to patients. Advise patient to avoid alcohol or sedating drugs and to avoid driving until tolerant to dose.

iv) Maintenance dosing

Buprenorphine doses should be individually titrated according to the patient's response to the treatment. Effective maintenance doses that result in reduced heroin use and improved treatment retention are achieved with high buprenorphine doses in the range of 8 to 24 mg per day. Little is known regarding the nature of adverse events at maintenance daily doses greater than 32 mg, therefore, the maximum recommended daily dose of buprenorphine is 32 mg. In India, experience in many settings indicates that persons dependent on opioids require a dose of around 8 mg on an average (the daily dose of a majority of patients is in the range of 4–22 mg[13]). For injecting buprenorphine users, the maintenance dose is approximately two to four times the dose that they are regularly administering by intramuscular or intravenous route (given the 42% and 29% buprenorphine bioavailability in sublingual route relative to intramuscular and intravenous route respectively).

In India, a majority of patients require a maintenance dose of about 8 mg every day.

Dosage of Buprenorphine

Purpose	Dose
Managing withdrawal symptoms	0.4 - 4 mg
Craving	4-8 mg
Suppressing further use of heroin/illicit opioids	8 mg and above

v) Frequency of dosing

Daily dosing with buprenorphine is required during induction and stabilization. Once the patient's daily medication dose has been stabilized (usually after 2-8 weeks of treatment) either on alternate days or three times a week, dosing may be instituted as follows:

1. A dose equal to twice the daily dose on alternate days, and not exceeding a maximum of 32 mg.

[13]The suggested dose is based on clinical experience from Punjab, India; and studies are required to determine proper maintenance dose for persons with opioid dependence in the region.

Frequency & Dosage of Bruprenorphine

Daily Buprenorphine dose (mg)	Alternate Day Buprenorphine (mg)	Three times a week Buprenorphine dose (mg)	
		Mon & Wed	Fri
2	4	2	4
4	8	4	8
8	16	8	16
16	32	16	32
20	32	20	32
24	32	24	32

2. A dose equal to twice the daily dose to be given on Mondays and Wednesdays and a dose equal to thrice the daily dose on Fridays, and not exceeding a maximum of 32 mg.

Alternate day dosing and thrice weekly dosing is an option to lessen the number of visits and is usually attractive to working patients. However, some patients (up to 15%) experience craving and return to heroin use if transferred to thrice weekly dosing.

On the other hand, in some cases more frequent dosing may be advised. Twice daily dosing (for example, 4 mg twice daily rather than 8 mg once daily) is a way for some patients to feel psychologically better by mirroring their long-term daily drug use pattern.

vi) Missed doses

It is not uncommon for patients to miss supervised doses of buprenorphine. The reasons may include family or employment commitments or continued drug use and it is often difficult to confirm why doses have been missed. Missing doses, up to one to two a month do not necessarily reflect instability. However, patients who regularly miss one or more doses a week should be reviewed by the treating team. If patients are missing doses to use illicit opioids, the dose of buprenorphine should be increased to suppress the effect of further use of illicit opioids. If the person has missed doses for three days, then the same dose of buprenorphine can be given but if the dose is missed for more than three days, it is better to give half the dose of buprenorphine after review by the treatment team..

vii) Pregnancy

Mono formulation of buprenorphine can be used for pregnant opioid dependent women (risk category C medication). Mono formulation does not contain naloxone, which can cause foetal and hormonal changes. Also, if the patient injects the drug, the medication's potential to cause maternal and foetal withdrawal symptoms is reduced. Recent trials have suggested buprenorphine to be superior in terms of foetal outcomes, with less severe neonatal abstinence syndrome (Jones et al. 2010).

viii) Chronic pain disorders

Buprenorphine can be used for treatment of opioid addiction in chronic non-cancer pain and could be preferable to other options in patients with higher risks of toxicity (e.g., elderly patients, benzodiazepine users), adolescents and young adults, or in communities where methadone is unavailable.

ix) Buprenorphine taper

There is no reason to believe that abstinence following buprenorphine differs greatly from abstinence following methadone. Research evidence confirms that both severity of withdrawal

and relapse post-detoxification[14] are similar for both. Taper from buprenorphine should only be conducted with the consent of the patient; as often taper results in going back to illicit drug use. Graduated reduction over several weeks results in better outcomes. For patients, the dose reduction is 2 mg per fortnight.

Slow Outpatient Taper

- Rate: no faster than 2 mg every 2 weeks
- Put taper on hold or reverse if patient experiences severe withdrawal, cravings, relapse or depression
- Patient should have input into rate of taper

It is important to note that discontinuation of buprenorphine is frequently an ineffective treatment of opioid dependence.

x) Detoxification with buprenorphine

Buprenorphine can be effectively used for detoxification. It is more effective and better tolerated than clonidine for treatment of opioid withdrawal. The Clinical Trials Network (CTN) supported by the National Institute on Drug Abuse had used a 13-day detoxification dosing schedule as shown in the table below.

13-day detoxification dosing schedule

Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Daily dose@	4	8	16	14	12	10	8	6	6	4	4	2	2

@ The drug used is a combination of buprenorphine and naloxone; all doses are in mg

xi) Transfer of methadone patients to buprenorphine

As buprenorphine has a high affinity for the opioid μ receptors, when methadone patients take a dose of buprenorphine, methadone is displaced from the μ receptors, precipitating withdrawal. Patients on low doses of methadone (<30mg) generally tolerate this transfer with minimal discomfort, whereas patients on higher doses of methadone may find that substitution of methadone with buprenorphine precipitates transient opioid withdrawal. Buprenorphine should not be administered within 24 hours of the last methadone dose. The first dose of buprenorphine should be ideally given when there are signs of opioid withdrawal (lacrimation, rhinorrhoea, and piloerection). Increasing the interval between the last dose of methadone and the first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal. It is important that this is explained to the patient and he/she is counselled not to supplement the buprenorphine dose with other opioids (especially heroin) as this will further exacerbate withdrawal.

4.4 Roll-out plan for buprenorphine administration

Buprenorphine is an opioid and its use is regulated. Clinicians should take special precautions while prescribing, handling, dispensing and storing the medication. Certain procedures have to be followed before administering the drug to the patients. It is preferable to

[14]Some patients may prefer to be detoxified with buprenorphine; it is important to transfer them following detoxification to either naltrexone or intensive psychosocial care for relapse prevention. Drug users who have failed with buprenorphine detoxification may be considered for buprenorphine maintenance.

deliver the drug in the substitution programs through directly observed treatment (DOT). Buprenorphine treatment should be part of a comprehensive treatment and care service for opioid dependents. In order to achieve this, government run community based buprenorphine clinics should work in close collaboration with the non-governmental agencies as well as hospitals.

i) Procedures prior to administering the dose of buprenorphine

A psychiatrist at the substitution clinic or a physician trained in buprenorphine treatment shall prescribe the substitution substance buprenorphine. Once the treating physician has stabilized the dose, a pharmacist or a nurse or a community health nurse can administer the drug.

Prior to administering the medication, the clinical staff (e.g., nurse) must:

- Establish the identity of the patient
- Confirm that the patient is not intoxicated
- Check the quantity of the drug in the prescription
- Check for current prescription
- Check that the current day is a dose day on the patient's regime
- Confirm the dose for the current day if it is an alternate-day or three-times-a-week regime
- Record the dose in the recording system

ii) Administering buprenorphine through directly observed treatment (DOT)

After recording dose details in the necessary documentation system, the following procedures should be observed. The drug is preferably given in the substitution clinics by way of DOT. This will ensure that the drug is not taken away, crushed and injected by the patients. There is considerable experience for the provision of buprenorphine through DOT in many centres across India[15].

1) Count the buprenorphine tablets into a dry dosing cup. Double-check the number and strength.

2) Crush the tablets into powder.

3) Place the powder under the tongue of the patient.

4) Give the following instructions:

   a) Do not swallow saliva until the powdered tablets have dissolved (2–5 minutes on an average);

   b) Do not swallow the powdered tablets; and

   c) Once the tablets are given to you, they are your responsibility and will not be replaced.

5) Observe the patient until you are satisfied that the tablets are not divertible (usually >2 minutes).

6) Ask to see "how the powdered tablets are dissolving" enough times for this to become an acceptable part of the patient's delivery routine.

7) Patients should sign/affix thumb impression that they have received their dose. Offer water to rinse the taste out of the mouth.

The doctor should be notified if the dosing administrator has concerns that the patient may be attempting to divert his/her medication.

[15]Through a European Commission supported program, seven Indian NGOs (from the cities of New Delhi, Mumbai, Kolkata, Chennai and Imphal) provided sublingual buprenorphine substitution through DOT in community based clinics for more than 1,500 injecting opioid/heroin users. Currently more than fifty OST centres are providing buprenorphine through DOT.

iii) Roll-out plan for buprenorphine substitution

The following are required to operate a buprenorphine substitution clinic serving about 300 regular patients with opioid dependence:

1) Program manager

2) Doctor

3) Nurse

4) Counsellor

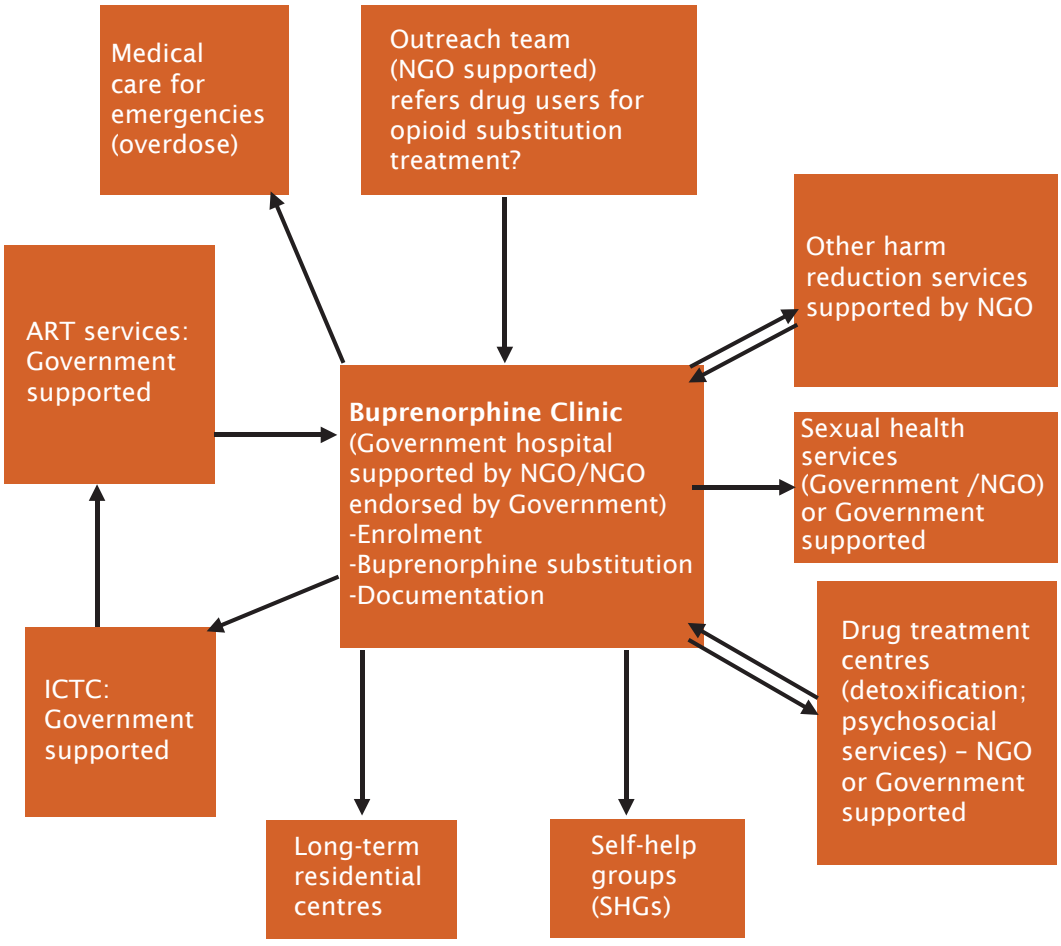
5) Outreach Workers (ORWs)

6) Peer Educators (PEs)

7) Office support staff: guard, office boys, etc.

Apart from the optimal dose, the effectiveness of the substitution treatment is dependent on the length of time in treatment and linkages with other services. In order to ensure that the enrolled patients receive the prescribed medication without interruption, it is important that the substitution programs are supported and endorsed by the respective countries. Sudden interruptions in the supply of maintenance medication can potentially do more harm to the users. Long-term plans should be made for establishing and maintaining substitution programs. Community based clinics are more attractive to drug users and so the Government sponsored buprenorphine clinics should be community based. Both the Government organizations (supply of substitution medication, monitoring of regulatory procedures)

Buprenorphine Clinic – An Integral Component in the Comprehensive Care of Opioid Dependents



and the NGOs involved in community based services, psychosocial care and support services for drug users should become partners in the delivery of treatment. The substitution program should be integrated into the existing drug treatment/rehabilitation services and should be part of a comprehensive continuum of care for the drug users. In places with high potential for HIV transmission among injecting opiate users, substitution treatment should become a key component of HIV prevention strategies for injecting drug users. A broad range of dosages (and if possible, a range of substitution substances – methadone and buprenorphine) should be offered in the clinics to match the profile of the patients. The proportion of problem opioid users to be covered can be reviewed periodically in different geographical locations.

4.5 Training and support

The staff at the clinics need to be trained, and the training should be organized before the clinics become operational. Proper training on the use of buprenorphine will be the key to the successful implementation of buprenorphine substitution. There should be provision for ongoing support for the staff. The training for the staff can be conducted with the help of:

a) A training module

b) 1-5 day training workshops

c) Placement in an existing buprenorphine clinic.

Apart from the initial workshops, there should be provision for follow-up training. A comprehensive training module should be developed, field-tested and widely used in the region. It is likely that pilot projects will be established in many countries in South Asia before large-scale buprenorphine programs supported by the respective Governments become operational. The staff participating in the pilot projects can be brought together for a centralized workshop. The workshop for medical doctors can address issues specifically related to patient assessment for buprenorphine treatment, clinical pharmacology – dosing, drug interactions – and, buprenorphine in the context of dependence care and HIV services. For the core team members from a State/Province, an initial training program conducted centrally within that State/Province can address several issues relating to maintenance treatment, patient care, administrative issues, confidentiality, regulatory issues, documentation, liaison services and linkages. Clinical placements are extremely useful; and even after establishment of projects, there could be exchange visits. Attendance at Harm Reduction Conferences and Drug Treatment Workshops should be encouraged for the buprenorphine clinic team members. The core team members, who have been trained at the State/Province level training workshops, can periodically train new members of the team with the help of local consultants. At the minimum, the program manager, doctor, nurse and the counsellor should have received central training; and the outreach staff should have been trained by the program staff of the OST centre.

The workshops should adopt a participatory training methodology and should be conducted by trainers who are well versed with buprenorphine substitution. The workshop should address practical issues and enhance the skills of the participants.

Topics for a three-day training workshop for the core team

Day 1	Day 2	Day 3
Introduction to the workshop	Assessment of a patient with opioid use and criteria for buprenorphine substitution	Directly observed treatment of buprenorphine
Opioid dependence – concept, course and consequences	Effectiveness of buprenorphine substitution	Enhancing 'quality' in patient care
Effective treatment approaches	Regulatory procedures	Liaison services and linkages
Opioid substitution treatment – definition, benefits and risks	Documentation and record keeping	Visit to a buprenorphine clinic

Topics for a five-day training workshop for the core team

Day 1	Day 2	Day 3	Day 4	Day 5
Overview of drugs and drug use disorders	Opioid Substitution Treatment – overview (including opioid withdrawal, intoxication and other syndromes)	OST with Buprenorphine induction, stabilization, maintenance	Visit to OST clinic	Referral and networking
Drug related problems and harms	Assessment and diagnosis	Special clinical situations – adolescents; women; HIV infected; other medical conditions, dual diagnosis	Program management	Documentation and reporting
General principles of drug treatment and harm reduction	Buprenorphine-pharmacology (including side-effects, drug interactions, contraindications)	Psychosocial interventions	—	—

5

MONITORING AND QUALITY CONTROL OF INTERVENTIONS

Description

Quality improvement is based upon measuring and monitoring the processes and outcomes of treatment, and making use of the information to improve the delivery of care. The practitioner works within a treatment system, and implements quality improvement approaches to ensure that the system delivers care in ways which are effective and accountable.

Important Tasks

- Maintenance of adequate documentation of treatment processes
- Maintenance of clear lines of responsibility and communication between different team members involved in the delivery of care
- Secure storage of patient details and records, accessible only to those who need the information

The project should take the following quality assurance indicators into consideration.

Adequate supply chain mechanisms: An OST centre requires an uninterrupted stock of buprenorphine. The staff should be aware that buprenorphine is a scheduled drug and regulated under national Narcotics Laws. At the OST centre, the medicine stock should be stored in a cupboard which can be securely locked or kept in a safe box attached to the wall. A Central Stock Register should be maintained for buprenorphine. The consumption details should be maintained meticulously by the centre implementing OST. The program manager of the OST centre is responsible for maintaining the supply chain. The nurse(s) should maintain a register documenting the amount of buprenorphine dispensed and consumed daily. The nurse dispenses buprenorphine to patients and enters the dose of every patient in the dispensing register; and keeps a record of amount dispensed and returned each day. The Dispensing Register as well as the Stock Register should be kept in a well secured cupboard.

Accessibility: These programs should be community based to ensure accessibility and to keep the cost low. The NGO collaborating with the clinic can provide the psychosocial support services and the emergency services (e.g., overdose management) should be provided by a hospital.

Safety Guidelines to ensure patient safety should be laid down. Adequate training of staff is required to ensure patient referral in case of an emergency.

Preventing diversion: There is a valid basis for public health concern over inappropriate prescribing, and a need to differentiate between patients who are likely to divert drugs to the black market and those who obtain prescribed opioids for their own use. Towards this end, all the regulatory procedures must be strictly adhered to. To minimize the risks and maximize the benefits of using opioids, they should only be prescribed in the context of a comprehensive assessment and treatment plan, with regular reviews of whether the treatment is proving beneficial. One of the ways of ensuring prevention of diversion by clients is to promote DOT for drug users receiving buprenorphine maintenance. DOT should be recommended for the following:

- Patients who are using street heroin

- Patients with evidence of current injecting drug use
- Patients with continuously escalating dosage requirements
- Patients who appear highly unstable: polydrug use, overdoses
- Patients about whom the doctor has concerns – even if these are non-specific

Efficacy: An adequate dose of medicine should be given. It is to be recognized that a relatively low dose of buprenorphine may be required for some patients in this region. Wherever possible, along with the maintenance drug, low intensity psychosocial intervention should be provided to the patients (three to four sessions in a group setting) with minimal staff investment.

Intake criteria: Specific selection criteria should be laid down.

User participation: The program should be flexible and should involve patient participation at the level of planning and implementation. It should incorporate changes based on the requirements of the patients.

Patient coverage: An outreach team supported by the NGO collaborating with the buprenorphine clinic can facilitate referral of patients to the clinic for assessment relating to suitability for buprenorphine substitution. By publicizing the program, adequate utilization of services can be ensured. Various methods can be used, depending on their suitability for a particular community – street plays, advertising on local cable television or on the radio, distribution of pamphlets etc. Further recruitment can be done with the help of registered drug users using the snowball technique.

Patient retention: This can be enhanced by using adequate doses, empathetic staff, having a program that is receptive to the patients' needs, flexibility in the program, other adjunctive facilities for which liaison with other local NGOs can be done. The retention of patients in a maintenance program is related to its efficacy as well as its "user friendly" attitude.

Training of staff: The staff should be given basic information about opioids; their training should include the concept of use and dependence, complications related to opioid use, history taking, psychosocial assessment, information about effective approaches and buprenorphine maintenance. They should also be trained in identification of complications including intoxication and overdose *(see Annexure),* and should be aware of when to refer a case to the hospital. The training should also address issues relating to patient care – concern, empathy and user friendly services.

6

CHECKLIST FOR MENTOR(S)

- Number of buprenorphine clinics in the City/State or Province/Country
- Location and type of buprenorphine clinic
- Government – NGO partnership
- Community participation
- Training for staff
  - Proportion of trained staff
  - Qualifications/Skills
  - Ongoing training support
- Policy and procedures governing treatment delivery at the clinic in place
- Assessment and intake criteria
  - Criteria for selection defined and transparent
  - No discrimination in selecting patients for treatment
- Operational issues
  - Timing of the clinics
  - Backup coverage (for absence of key staff)
- Consent procedures
  - Informed consent
  - Treatment contracts
- Regulatory procedures
  - Strict adherence to procedures
- Proper accounting of the medicines
  - Safe custody of medicines
- Documentation
  - Patients records (demographic, risk behaviour and treatment characteristics)
  - Confidentiality of information

Buprenorphine delivery

- Range of doses
- DOT
- Alternate dosing schedules
- Other services provided at the clinic
  - HIV prevention education/Overdose prevention education
  - Primary medical care

- Other psychosocial support and care services
- Liaison with other agencies providing a range of services
- Referral networks
- Retention rates
  - Number enrolled for treatment
  - Proportion of regular patients
- User participation in evaluation of services
- Patient satisfaction
- Data gathered on potential outcome indicators
- Crime rates among patients attending services
- Employment among patients attending services
- Risk behaviours (drug use, injection and sex related)
- Community safety

7

INDICATIVE COSTING FOR IMPLEMENTATION OF OST WITH BUPRENORPHINE

Considerations for costing related to initiating and running an OST program is an important issue for policy makers and national program managers of a country. A template for costing along with indicative budgets are provided below, based on UNODC's experience of implementing buprenorphine based OST in the South Asia region. The various heads and sub-heads to be considered in buprenorphine based OST implementation are covered comprehensively. The costing is intended to provide a direction to the countries for tailoring their respective national budgets, taking into consideration the healthcare related systems in the country.

The costs given below are for providing buprenorphine based OST services for 100 clients.

A. Start-up Cost

B. Implementation Cost

A. Start-up Cost

Heads	Details	Cost (in USD)
Sensitisation meeting	A one-day national level sensitisation meeting with the policy makers, service providers, hospital authorities, and community (one time cost)	3,000
Training programme for the service providers	A five-day induction training program for the staff of the OST centre at state/provincial level (one time cost)	4,000
	A three-day refresher training program for the staff of OST centre at state/provincial level (one time cost)	3,000
Feasibility assessment	A one-day feasibility assessment to determine whether it is feasible to implement OST at the proposed centre, as well as to recommend the necessary refurbishment required (one time cost)	2,000
Refurbishment of the proposed OST centre	Necessary infrastructure changes for making the centre ready to initiate OST	5,000
SUB-TOTAL (USD)		**17,000**

B. Implementation Cost (one year)

Heads	Details	Cost (in USD)
1. HUMAN RESOURCE		
1a. Clinical staff		
Medical doctor	One full-time medical doctor for diagnosis and treatment for drug related problems as well as general medical conditions (@ USD 800/month)	9,600
Nurses	Two nursing staff for daily dispensing and stock keeping (@ USD 250/month for 1 nurse)	6,000

Heads	Details	Cost (in USD)
1b. Psychosocial staff[16]		
Counsellor	One full-time counsellor for providing one-to one and group counselling (@ USD 400/month)	4,800
Staff for conducting outreach	Two full-time ORWs and four PEs for bringing the potential clients to the OST centre and conducting follow-ups for the OST clients. (@ USD 400 for 2 ORWs and 4 PEs/month)	4,800
1c. Support staff		
Data manager	One full-time data manager to maintain the records at the OST centre (@USD 200/month)	2,400
Accountant	One part-time accountant (@USD 200/month)	2,400
Other support staff	Three Staff for manning the OST centre (@ USD 150/staff/month)	5,400
2. RUNNING EXPENSES		
Travel-related costs	This is towards travel of the psychosocial staff for outreach and home visits (if required)	1,000
Miscellaneous expenses	Towards purchase of stationery materials and other expenses such as communication and attending meetings	2,000
3. PROCUREMENT EXPENSES		
Procurement of buprenorphine[17]	Costs related to purchase of Buprenorphine tablets (2 mg strength) @ 10–12 mg/client/day	37,000
Equipment and supplies	Purchase of safes (for stock-keeping), dispensing cups, water, etc.	3,000
SUB-TOTAL		**78,400**
Start-up cost (USD)		**17,000**
Implementation cost (USD)		**78,400**
Grand Total (USD)		**95,400**

[16] The psychosocial staff can be part of a separate 'social support unit' SSU created for providing psychosocial services, or they can work as core staff of the OST centre. In case a separate SSU is created, a program manager is also required to oversee the activities of the outreach staff. Alternatively, the services of an NGO working with drug users in the vicinity can also be used for this purpose.

[17] Cost based on UNODC's last procurement of 2mg tablets of buprenorphine.

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ANNEXURES

Annexure 1: Criteria for Opioid Dependence

Annexure 2: Medical Syndromes Associated with Opioid Use

Annexure 3: Clinical Opiate Withdrawal Scale (COWS)

Annexure 4: Buprenorphine Treatment Appropriateness Checklist

Annexure 5: Treatment Contract

Annexure 6: Frequently Asked Questions

ANNEXURE-1

Criteria for Opioid Dependence

Dependence (ICD-10@)	Dependence (DSM-IV-TR±)
Presence of 3 or more of the following in the last 12 months:	*3 or more of the following in the past 12 months:*
1. Evidence of tolerance	1. Tolerance (marked increase in amount; marked decrease in effect)
2. A physiological withdrawal state when substance use has ceased or reduced	2. Characteristic withdrawal symptoms; substance taken to relieve withdrawal
3. A strong desire or sense of compulsion to take the substance	3. Substance taken in larger amount and for longer period than intended
4. Difficulty in controlling substance-taking behaviour in terms of its onset, termination or levels of use	4. Persistent desire or repeated unsuccessful attempt to quit
5. Progressive neglect of alternative pleasures or interests	5. Much time/activity to obtain, use, recover
6. Persisting with substance use despite clear evidence of overtly harmful consequences	6. Important social, occupational, or recreational activities given up or reduced
	7. Use continues despite knowledge of adverse consequences (e.g., failure to fulfil role obligation, use when physically hazardous)

[@] Adapted from WHO ICD 10 diagnostic guidelines for substance use disorders

[±] Adapted from APA DSM-IV-TR diagnostic guidelines for substance use disorders

ANNEXURE-2

Medical Syndromes Associated With Opioid Use

Syndrome (Onset and Duration)	Characteristics
Opiate intoxication	Conscious, sedated, "nodding" Mood normal to euphoric Pinpoint pupils History of recent opiate use
Acute overdose	Unconscious Pinpoint pupils Slow, shallow respiration
Opiate withdrawal Anticipatory* (3-4 hours after last "fix")	Fear of withdrawal Anxiety Drug seeking behaviour
Early (8 – 10 hours after last "fix")	Anxiety Restlessness Yawning Nausea Sweating Nasal stuffiness Rhinorrhoea Lacrimation Dilated pupils Stomach cramps Drug-seeking behaviour
Fully developed (1–3 days after last "fix")	Severe anxiety Tremor Restlessness Piloerection** Vomiting, Diarrhoea Muscle spasm*** Muscle pain Increased blood pressure Tachycardia Fever, Chills Impulse-driven drug-seeking behaviour
Protracted abstinence (indefinite duration, lasting for weeks to months)	Vague muscle aches and pains Difficulty in sleep Loss of interest in pleasurable activities Anxiety, Depression Easily tiredness Irritability

* Anticipatory symptoms occur as the acute effects of heroin begin to subside

** Piloerection has given rise to the term "cold" turkey".

*** The sudden muscle spasms in the legs have given rise to the term "kicking the habit".

ANNEXURE-3

Clinical Opiate Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptoms. Rate only if the symptom has an apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's Name: _____ Date & Time: _____/_____/: _____

Reason for Assessment: _____

1. Resting Pulse Rate: ___
beats/minute

Measured after the patient has been sitting or lying down for 1 minute.

0 pulse rate 80 or below

1 pulse rate 81 – 100

2 pulse rate 101 – 120

4 pulse rate greater than 120

2. Sweating

Over past ½ hour not accounted for by room temperature or patient activity.

0 no report of chills or flushing

1 subjective report of chills or flushing

2 flushed or observable moistness on face

4 pulse rate greater than 120

3. Restlessness

Observation during assessment

0 able to sit still

1 reports difficulty in sitting still but is able to do so

2 frequent shifting or extraneous movements of legs/arms

5 unable to sit still for more than a few seconds

4. GI Upset

Over last ½ hour

0 no GI symptoms

1 stomach cramps

2 nausea or loose stool

3 vomiting or diarrhoea

4 multiple episodes of diarrhoea or vomiting

5. Tremor

Observation of outstretched hands

0 no tremor

1 tremor can be felt but not observed

2 slight tremor observable

4 gross tremor or muscle twitching

6. Yawning

Observation during assessment

0 no yawning

1 yawning once or twice during assessment

2 yawning three or more times during assessment

4 yawning several times/minute

7. Pupil Size

0 pupils pinned or normal size for room light

1 pupils possibly larger than normal for room light

2 pupils moderately dilated

5 pupils so dilated that only the rim of the iris is visible

8. Bone or Joint Aches

If patient was having pain previously; only the additional component attributed to opiates withdrawal is scored.

0 not present

1 mild diffuse discomfort

2 patient reports severe diffuse aching of joints/muscle

4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

9. Runny Nose or Tearing

Not accounted for by cold symptoms or allergies

0 not present

1 nasal stuffiness or unusually moist eyes

4 nose constantly running or tears streaming down cheeks

10. Anxiety or Irritability

0 none

1 patient reports increasing irritability or anxiety

2 patient obviously irritable/anxious

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

11. Gooseflesh Skin

0 skin is smooth

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

4 prominent piloerection

Total Score ____ The total score is the sum of all 11 items.

Score:
5-12 = mild
3-24 = moderate
25-36 = moderately severe
more than 36 = severe withdrawal

Initials of persons doing the assessment

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ANNEXURE-4

Buprenorphine Treatment Appropriateness Checklist

1. Is the person dependent on opioids?
2. Is the person in opioid withdrawal?
3. Does he/she exhibit signs of opioid intoxication?
4. Are there signs of other drug/alcohol intoxication?
5. Is the patient willing to undergo treatment with buprenorphine?
6. Has the patient been told about the risks and benefits of buprenorphine treatment?
7. Can the patient be expected to attend the OST centre regularly?
8. Is the patient willing to go in for long-term treatment?
9. Is the patient having a psychiatric disorder? Is he/she under treatment? Is he/she mentally stable?
10. Does he/she exhibit active suicidal behaviour?
11. Is the patient currently dependent on or abusing alcohol?
12. Is the patient currently dependent on benzodiazepines or other sedative-hypnotics?
13. Is the patient using other drugs? If yes, list them.
14. Has the patient had prior adverse reactions to buprenorphine?
15. Does he/she have family support?
16. If the patient is a woman, is she pregnant?

Adapted from Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, DHSS, 2004.

ANNEXURE-5

Treatment Contract

As a participant in the buprenorphine for opioid dependence treatment protocol, I freely and voluntarily agree to accept this treatment contract, as follows:

1. I agree to keep, and be on time for, all my scheduled appointments with the doctor and his/her assistant at the clinic/treatment centre.

2. I agree to conduct myself in a courteous manner at the clinic/treatment centre.

3. I agree not to arrive at the clinic/treatment centre intoxicated or under the influence of drugs. If I do, the doctor will not see me and I will not be given any medication until my next scheduled appointment.

4. I agree not to sell, share or give any of my medication to another person. I understand that such mishandling of my medication is a serious violation of this agreement and would result in my treatment being terminated without recourse for appeal.

5. I agree not to deal, steal or conduct any other illegal or disruptive activities in the clinic/treatment centre.

6. I agree that my medication (or prescriptions) can only be given to me at my regular clinic/treatment centre visits. Any missed clinic/treatment centre visits will result in my not being able to get medication until the next scheduled visit.

7. I agree that the medication I receive is my responsibility and that I will keep it in a safe, secure place. I agree that lost medication will not be replaced regardless of the reasons for such loss.

8. I agree not to obtain medications from any physicians, pharmacies or other sources without informing my treating physician. I understand that mixing buprenorphine with other medications, especially benzodiazepines, such as Calmpose or Valium, and other drugs of abuse, can be dangerous. I also understand that a number of deaths have been reported among persons mixing buprenorphine with benzodiazepines.

9. I agree to take my medication as the doctor has instructed and not to alter the way I take my medication without first consulting the doctor.

10. I understand that medication alone is not sufficient treatment for my disease and I agree to participate in the patient education and relapse prevention program, as provided, to assist me in my treatment.

_____	_____	_____
Patient Signature	Witness Signature	Date

ANNEXURE-6

Frequently Asked Questions related to Opioid Substitution Treatment (OST)

Q: What is detoxification?

A: Detoxification refers to the withdrawal over a short period from an opioid or sedative/hypnotic by the use of the same drug or a similar drug in decreasing doses. The objective of detoxification is to assist the patient's transition to a 'drug free' state.

Q: What are the limitations of detoxification?

A: Dependence on heroin and other opioids is a persisting condition and the 'quit' rates following detoxification are alarmingly low. The high relapse rates have nothing to do with being bad or having no will power. A long-term use of illicit opioids such as heroin changes the brain in such a way that the brain continues to need an opioid to function properly. For such people, short-term treatment does not work, and so long-term treatment with OST is necessary.

Q: What is opioid substitution treatment (OST)?

A: Opioid substitution is replacing the illicit drugs the drug user is taking with another drug or a similar drug (e.g., replacing heroin with sublingual buprenorphine). It may also mean using the same drug but taking it in a different way, for example, sublingual buprenorphine to replace injecting of buprenorphine.

Q: What drugs are used in OST?

A: Worldwide the two commonly used drugs for OST are: methadone and buprenorphine. In India, sublingual buprenorphine is available for OST in the public domain.

Q: How is buprenorphine administered in OST?

A: Buprenorphine is available in tablet form. It is crushed into powder, placed under the tongue of the user and allowed to dissolve by itself. This is the only way it will work effectively; consuming the tablet orally is not effective. To prevent diversion of this substance, it is ideal to administer the drug under direct observation of the health worker in the clinic. Patients are advised to sit in the clinic till the drug that was placed under the tongue is fully absorbed (usually about 10-15 minutes). Injecting of the tablet leads to a lot of adverse consequences and hence patients should be advised against injecting.

Q: How to prevent injecting of buprenorphine tablets?

A: Since buprenorphine tablets dissolve readily in water, they can be injected. The use of combination tablets of buprenorphine and naloxone (in doses of 2 mg of buprenorphine and 0.5 mg naloxone) will help reduce the potential diversion and abuse. This combination will permit sublingual use without precipitating withdrawals. This combination of buprenorphine and naloxone is available in India.

Q: When should the initial OST drug buprenorphine be taken?

A: Ideally six to twelve hours after the last illicit heroin intake. Patients in opioid withdrawal (dilated pupils) can safely be given buprenorphine.

Q: What is the right dosage of buprenorphine?

A: The dose can vary from person to person. The correct dose is determined by the healthcare provider (doctor) in consultation with the patient. The doctor will consider several factors before

deciding on the correct dose. It takes a few days before the maintenance dose is finalized for the patient. Usually in Indian settings, the buprenorphine maintenance dose is around 8 mg.

Q: What is the relationship between the buprenorphine dose and its effect?
A: Even a smaller dose of buprenorphine (e.g., 0.4–2 mg) helps to relieve opioid withdrawal symptoms. A moderate dose (usually 4 mg–8 mg) is required to control craving for opioids. A high dose (>8 mg) is needed to suppress the effect of further use of opioids. This means at higher doses of buprenorphine the brain is saturated and if one uses illicit opioids such as heroin, the effect is blocked and the user does not experience the high.

Q: What happens if a person misses a dose of OST drug?
A: If a person has missed taking the OST drug buprenorphine for five days in a row, he/she has to come back to the clinic for a medical examination to decide on the dose. Often they require low doses to begin with; the doctor will decide on this after consultation with the patient.

Q: What are the side effects of buprenorphine?
A: The medical effects of buprenorphine are similar to those of other opioids and include constipation, dizziness, drowsiness, headache, constriction of pupils, nausea, sweating and vomiting. Opioid dependent individuals do not exhibit many of these side effects.

Q: What are the withdrawal symptoms from buprenorphine?
A: The withdrawal effects from drugs such as heroin, morphine or methadone are marked, but only a low intensity of withdrawal effects are observed when buprenorphine is abruptly withdrawn. The withdrawal symptoms appear delayed for 72 hours and include: cold- or flu-like symptoms, headaches, sweating, aches and pains, sleeping difficulties, nausea and loss of appetite.

Q: What are the benefits of buprenorphine substitution?
A: Maintains a majority of patients in treatment
Improves the patients' physical well-being
Decline in the new infections of HIV, Hepatitis B and C
Reduces the criminality significantly
Improves the clients' quality of life
Keeps clients in treatment for longer duration
Causes few side-effects
Patients have only mild withdrawal symptoms
It is not likely that people can overdose on it. Is safe
It is a long acting drug so it does not have to be taken every day; thrice weekly dosing with buprenorphine is possible
It is a good opioid substitution drug for people with mild to moderate opioid dependence
It is an attractive treatment for opioid users