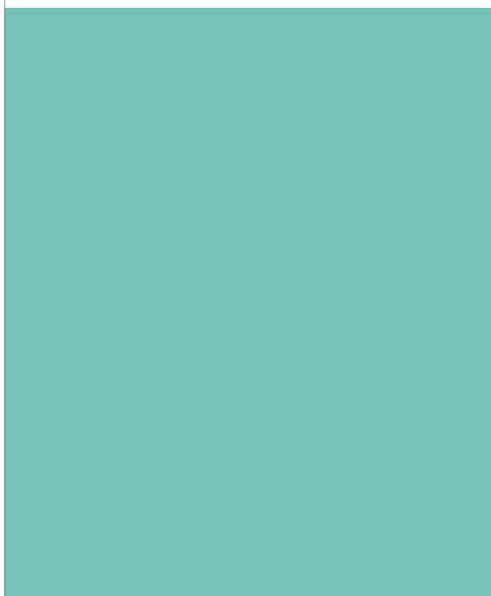
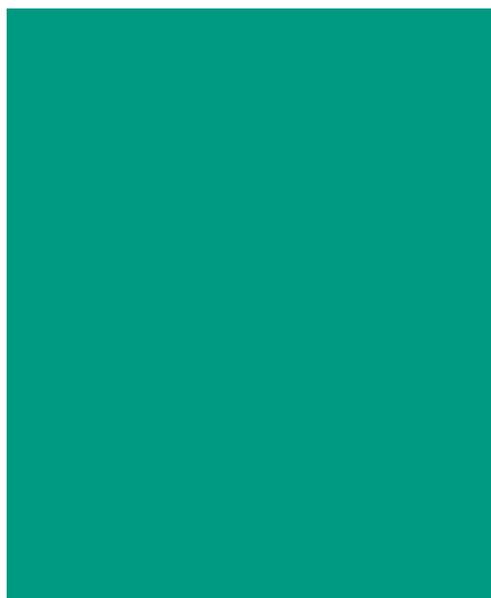




Opioid Substitution Therapy Under National AIDS Control Programme

Clinical Practice Guidelines for Treatment with Buprenorphine



Opioid Substitution Therapy Under National AIDS Control Programme

Clinical Practice Guidelines for Treatment with Buprenorphine



PUBLIC
HEALTH
FOUNDATION
OF INDIA

YEAR OF PUBLICATION: 2014

Authors: Ravindra Rao*, Alok Agrawal*, Atul Ambekar*

* National Drug Dependence Treatment Centre (NDDTC),

All India Institute of Medical Sciences (AIIMS), New Delhi

Copyright: Department of AIDS Control, Ministry of Health and Family Welfare, Government of India, New Delhi

Possible Citation: Rao R, Agrawal A, Ambekar A. (2014). Opioid Substitution Therapy under National AIDS Control Programme: Clinical Practice Guidelines for treatment with Buprenorphine. Department of AIDS Control, Ministry of Health and Family Welfare, Government of India, New Delhi



सत्यमेव जयते

डॉ. वि. के. सुब्बुराज, भा.प्र.से
सचिव
Dr. V.K. SUBBURAJ, IAS
Secretary



भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
एड्स नियंत्रण विभाग
राष्ट्रीय एड्स नियंत्रण संगठन
6वां तल, चन्द्रलोक बिल्डिंग, 36 जनपथ, नई दिल्ली - 110001
Government of India
Ministry of Health & Family Welfare
Department of AIDS Control
National AIDS Control Organisation
6th Floor, Chandralok Building, 36 Janpath, New Delhi - 110001

Message

India has made significant achievements in containing Human Immunodeficiency Virus (HIV) infection. India is one of the few countries across the globe that has been able to bring about reduction in the incidence of HIV in the country. Additionally, HIV prevalence among certain high risk groups such as female sex workers has also been reduced. This has been possible due to massive efforts from all the stakeholders concerned, including the civil society, affected communities, technical experts, as well as the various divisions working within the Department of AIDS Control (DAC).

While there is much to celebrate, certain high risk groups continue to show high prevalence of HIV. Injecting Drug Users (IDUs) is one such group that has more than 5% HIV prevalence consistently across various rounds of sentinel surveillance. Efforts have been made in the third phase of the National AIDS Control Programme (NACP) to scale up HIV prevention services for IDUs, mainly with respect to Needle syringe programmes. There are more than 280 targeted interventions (TIs) working exclusively for IDUs, covering more than 80% of the IDU population in the country. Opioid Substitution Therapy (OST) is another important element of HIV prevention among IDUs. The process of initiating OST within the HIV programme began during NACP III, and a number of quality assurance mechanisms were built in the programme. Newer models of OST delivery were also tested and found to be equally feasible. There are currently about 150 OST centres in the country catering to about 15000 IDUs.

OST remains an important intervention strategy in the NACP IV, and DAC is committed to scale up the OST intervention, so that a greater number of IDUs would benefit from this intervention strategy. The revised clinical practice guidelines document is in tune with this commitment. I am given to understand that the experience accumulated so far in OST implementation under NACP has been made use of to modify the document. I am sure that this revised guideline from DAC would help the service providers to provide optimum care and treatment for the IDUs. I wish the stakeholders all the best for their endeavours.

 28/7/2014

Secretary
Department of AIDS Control

6th Floor Chandralok Building, 36 Janpath New Delhi – 110001, Phones. 011-23325331, Fax 011-23731746

E-mail : secydac@gmail.com

अपनी एचआईवी अवस्था जानें, निकटतम सरकारी अस्पताल में मूलत सलाह व जाँच पाएँ
Know your HIV status, go to the nearest Government Hospital for free Voluntary Counselling and Testing

The present document is a revision of the document “Substitution Therapy with Buprenorphine for Opioid Injecting Drug Users – Practice Guidelines” that was developed by National AIDS Control Organisation in 2008 for guiding the implementation of NACO supported Opioid Substitution Therapy (OST) programmes in India. The current revision of the document has been made taking into consideration a number of developments. OST programme in India has progressed to a great extent through National AIDS Control Programme (NACP) since 2008. The NACO OST programme was in its nascent stages in 2008, with handful of centres as well as limited capacities to implement OST services. Today, the OST programme is functional in at least 150 centres, and NACO has more than six years of experience in supporting the training, monitoring and supervision of these centres. Apart from initial trainings conducted, a number of other activities such as refresher trainings, quality assurance visits, accreditation and supervisory visits by NACO officers have been conducted. This has led to a deeper understanding of the problems faced by the service providers in the day-to-day implementation of OST programme. The existing document was found inadequate to guide the service providers, especially the clinical staff working in OST centres, which form the backbone of the intervention implementation.

There have been a number of changes made in the document. A detailed background section is now provided that provides a conceptual understanding of the need for OST for injecting drug users (IDUs). The section on clinical practices has been expanded and the specific goal, objectives and practices thereof for the particular stage of the OST implementation has been added. Finally, the section on special clinical situation has been introduced for the first time that deals in detail with day-to-day problems encountered by clinicians in OST implementation. Special issues such as adolescence and pregnancy have been dealt with in greater detail.

The primary audience for the document remains the medical and paramedical staff working in the NACO-supported OST centres. However, the writing style has been kept simple so that even other staff can benefit from the document. It is hoped that the document helps in improving the quality of OST interventions in the country. The authors are thankful to the reviewers for providing feedback on the document. Special thanks also to NACO TI division for their encouragement and feedback on the document. Finally, thanks are also due to the various OST centre staff as well as the service recipients who have provided greater understanding of the OST programme that has made this revision possible.

Ravindra Rao

Alok Agrawal

Atul Ambekar

Table of Contents

ABBREVIATIONS	08
INTRODUCTION	09
BACKGROUND	13
Understanding Injecting Drug Use and Injecting Drug Users	15
Opioid Substitution Therapy – Basic Concepts and Principles	19
Buprenorphine – Basics of Pharmacology	25
CLINICAL PRACTICE GUIDELINES	31
Assessment and Diagnosis	34
Determining Suitability of Clients for Opioid Substitution Therapy	37
Preparing Clients for Opioid Substitution Therapy	39
Buprenorphine Based Opioid Substitution Therapy	40
Management of Common Clinical Situations	48
Management of Special Clinical Conditions	50
CONCLUSIONS	53
REFERENCES	54
ANNEXURES	55

Abbreviations

ANM	Auxiliary Nurse Midwifery
ART	Anti-Retroviral Treatment
CHC	Community Health Centre
DAC	Department of AIDS Control
DIC	Drop-in Centre
DOTS	Daily Observed Treatment Strategy
HIV	Human Immunodeficiency Virus
HRGs	High Risk Groups
ICTC	Integrated Counselling and Testing Centre
IDU	Injecting Drug Use
NACP	National AIDS Control programme
NAS	Neonatal Abstinence Syndrome
NDPS	Narcotic Drugs and Psychotropic Substances
NGOs	Non-Governmental Organisations
NSP	Needle Syringe Programme
ODS	Opioid Dependence Syndrome
OST	Opioid Substitution Therapy
PHC	Primary Health Centre
SACS	State AIDS Control Society
STI	Sexually Transmitted Infection
TB	Tuberculosis
TI	Targeted Intervention
UNAIDS	Joint UN Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organisation

It is estimated that there are 177000 IDUs in India. The distribution of Injecting Drug Use (IDU) population is not uniform throughout the country. As of 2014, there are some states that have high number of Injecting Drug Users (IDUs) including, Manipur, Nagaland, Punjab, Mizoram and Delhi. IDU is an important factor in the transmission dynamics of HIV epidemic in India. HIV in India is a concentrated epidemic – concentrated in certain geographical areas and among certain population groups. These population groups, designated as High Risk Groups (HRGs), have much higher prevalence of HIV as compared to the general population. As per the latest HIV sentinel surveillance report, HIV prevalence among IDUs is 7.2% nationally, which is one of the highest among any population group. However, some states have much higher HIV rates among IDUs; for e.g. HIV prevalence among IDUs is 21% in Punjab, 18% in Delhi and around 12% in Manipur and Mizoram.

Thus, there is considerable variability among IDUs in terms of their numbers, their choice of drugs for injecting, their socio-demographic characteristics, and HIV prevalence among the group.

A. NATIONAL STRATEGY FOR HIV PREVENTION AMONG IDU POPULATION

Globally, the “harm reduction” strategy is employed to manage HIV prevention among IDUs. Harm reduction strategy is based on the premises that it is as important to focus on addressing harms associated with drug use as it is to help them give it up. The strategy offers an effective alternative approach for continuous engagement and HIV prevention among drug users, especially those who are unable or unwilling to give up drug use through other abstinence-oriented approaches. Priority is accorded to immediate, easily preventable harms of

public health importance. HIV prevention becomes an important focus of harm reduction. A number of interventions have been found to be useful and effective for HIV prevention among IDUs. WHO, UNAIDS and UNODC, together, have proposed nine interventions for HIV prevention, care and treatment of IDUs which, when implemented together, are called the “comprehensive package of interventions” for HIV prevention among IDUs. The core interventions among these include – Needle Syringe Programme (NSP), Opioid Substitution Therapy (OST), and Anti-Retroviral Treatment (ART).

In India, the harm reduction strategy is endorsed in the National AIDS Prevention and Control Policy (NAPCP), 2002. Department of AIDS Control (DAC) is the nodal agency responsible for HIV prevention, care and treatment in India. DAC follows a ‘targeted intervention (TI)’ approach for HIV prevention among all HRGs, including IDUs. The targeted intervention approach entails providing interventions specifically aimed at HRGs through outreach and peer-based delivery. In the ‘outreach’ model, services are

COMPREHENSIVE PACKAGE OF INTERVENTIONS

1. Needle syringe programmes
2. Opioid Substitution Therapy
3. Anti-retroviral therapy
4. Counselling and testing for HIV
5. Prevention and treatment for Sexually Transmitted Infections (STIs)
6. Condom programme for Injecting Drug Users and their partners
7. Targeted Information, Education and Communication
8. Prevention, diagnosis and treatment of Tuberculosis
9. Prevention, diagnosis and treatment of Viral Hepatitis

delivered at places where the HRGs are most likely to be found, using their own peers as primary agents of service delivery (peer-based service delivery). The TI projects are implemented by Non-Governmental Organisations (NGOs) who are able to reach out to HRGs much more efficiently as compared to the traditional service delivery systems. For HIV prevention among IDUs, the TI-based services include – NSP, condom distribution, abscess prevention and management, general medical care, STI prevention and treatment, and behaviour change communication. Additionally, testing for HIV, ART, TB diagnosis and treatment, as well as drug treatment services are provided through referral linkages to the concerned service provider/s.

As in 2014, there are more than 280 core IDU TIs throughout the country, reaching out to about 152000 IDUs, which is more than 80% of the IDU population in the country. Thus, there is a saturation of the coverage of IDUs with HIV prevention services in India. Programmatic data also shows that there has been a significant increase in commodity distribution, number of needle/syringes distributed per IDU, referrals for HIV testing, etc.

B. OPIOID SUBSTITUTION THERAPY UNDER NATIONAL AIDS CONTROL PROGRAMME

OST as a HIV prevention strategy among IDUs was formally integrated in National AIDS Control Programme (NACP) in 2007, during its third phase. Before formal integration, OST for HIV prevention among IDUs was being implemented

in India by some NGOs. After a formal approval for OST implementation, besides putting in place mechanisms for financial support to the NGOs implementing TI projects, a number of documents for standardisation and quality assurance have been developed by DAC, *including practice guidelines for buprenorphine, standard operating procedures and quality assurance manual*. The NGO OST centres were also accredited through an independent accreditation agency, following which they started receiving support through DAC. In this NGO-based model of OST, the OST centres located within the Drop-in-Centre (DIC) of an IDU TI are managed by the staff implementing the IDU TI. A part-time doctor, a full time nurse, a counsellor/ANM, programme manager and outreach workers are part of the team delivering OST services.

To further expand the OST programme, since 2010, Government hospitals have also been roped in for providing OST services through a collaborative public health model. In this model, the OST centre is located within the government hospital and is manned by a full-time staff comprising of a doctor, a nurse, a counsellor and a data manager. The staff of the OST centre works under the direct supervision of a designated ‘nodal officer’, who is a full-time employee of the hospital. The OST centre is linked with an IDU TI located in the vicinity of the hospital for initial referral of IDU clients to the centre, as well as field-based follow-up and advocacy. Currently, there are about 150 OST centres in the country supported by DAC, operating through either the NGO or the collaborative public health model, catering to about 15000 IDUs. There is a plan to establish about 350 OST centres and increase the OST coverage to 35000 – 40000 IDUs during NACP IV.

About the document...

- The clinical practice guidelines are intended to be used by the staff implementing OST interventions supported under the National AIDS Control Programme.
- This edition of the Clinical Practice Guidelines supercedes the earlier edition, published in 2008.
- While all staff members (including those of linked IDU TIs) would be benefitted, these guidelines are especially relevant for doctors and counsellors working in these centres. The guidelines aim to provide guidance mainly on the clinical practices related to OST implementation supported by DAC.
- These guidelines are not a substitute to formal training programmes, which each staff is expected to undergo. The guidelines are complementary to the “standard operating procedures” for OST implementation approved by DAC.
- For preparing the document, the authors have heavily relied upon scientific evidence-base, especially from India, other similar guidelines published for India, the training manuals and operational procedures developed for OST, as well as their own clinical and Programmatic experience.

Background

Understanding Injecting Drug Use and Injecting Drug Users

A. DEFINITION OF 'INJECTING DRUG USER'

Different definitions have been used for identifying who is an IDU. Some researchers opine that a person who has injected even once in his/her lifetime is an IDU, while others define an IDU as someone who has injected at least once in the past 12 months. In India, for programmatic purposes, **DAC defines an IDU as a person 'who has used any psychoactive substance through injecting route for non-medical purpose at least once in the last three months'**. This definition is based upon the recommendation of experts working in the field of IDU in India.

B. DRUGS INJECTED BY IDUs IN INDIA

Though theoretically, as per the definition, an IDU may use any psychoactive substance through injecting route, research conducted thus far has shown that in India, **a vast majority of the IDUs use opioids as their primary drug of choice**. These opioids include heroin (pure or the impure – 'smack' / 'brown sugar') as well as pharmaceutical opioids such as buprenorphine, pentazocine and dextro-propoxyphene. The opioids may be injected either alone or in combination with other substances which include benzodiazepines such as diazepam, or antihistamines such as chlorpheniramine¹ or promethazine. The other substances are combined with opioids to enhance the pleasure of opioids or due to some perceptions existing among IDUs regarding their positive effects.

OPIOIDS

Opioids are a group of psychoactive substances that are similar in action to that of opium poppy. Opium is a plant product, extracted from the plant *Papaver Somniferum*.

Opioids act specifically on a set of receptors in humans, named as opioid receptors. Some of the common opioids include:

- **Natural derivatives:** Morphine, codeine
- **Semi-synthetic:** Buprenorphine, Heroin
- **Synthetic:** Methadone, Dextropropoxyphene, Pentazocine



The opioids used for injection in India are: Heroin ("No. 4"), "Smack" (impure heroin), buprenorphine, dextropropoxyphene and pentazocine.

¹ The commonly available brands of the pharmaceutical substances are –
Buprenorphine: Norphine, Lupigesic, Tidigesic, Sangestic, etc.; Dextropropoxyphene: proxyvon, SP, spasmoproxyvon, etc.;
Pentazocine: Fortwin; Chlorpheniramine: Avil; Promethazine: Phenargan
(Disclaimer: Use of the brand names above are in no way pejorative, or incriminatory of a particular brand.)

The choice of opioids for the purpose of injecting differs from one region to another. In the north-eastern region, heroin and dextropropoxyphene are the most commonly used opioids; impure heroin, known as smack, and buprenorphine are the most commonly used opioids in metropolitan cities such as Delhi, Mumbai, Chennai and Kolkata. In states such as Karnataka, Andhra Pradesh, Chattisgarh, etc., pentazocine is the most commonly injected opioid. In the states of Punjab and Haryana, buprenorphine is the choice of opioid injectors. Thus, the opioids injected are either heroin or its impure variety, that is manufactured and sold illegally only for the purpose of abuse, or pharmaceutical opioids (such as buprenorphine, dextropropoxyphene and pentazocine) which are also manufactured and sold in pharmacies/chemist shops due to their medicinal value.

C. SUBSTANCE USE DISORDERS

It must be remembered that the mere presence of behaviour of 'injecting drug use' does not qualify for a diagnosis of substance use disorder. The pattern of drug use of an individual must be dysfunctional enough to warrant a medical diagnosis for which a treatment needs to be advised. Under the International Classification of Diseases – 10th revision (ICD-10), given by the World Health Organization (WHO), two distinct diagnostic entities exist, as below:

- **Harmful use:** A pattern of substance use, in which a user experiences physical or psychological harms by substance use, and despite such harms, continues to use the substance.
During harmful use, though the user is not dependent on the particular substance, he/she still suffers from adverse consequences related to the use of the substance and continues the substance even though he experiences these harms. The user may or may not be using the substance on a daily basis.
- **Dependence:** This is a pattern of substance use in which the substance is used on a daily/almost daily basis, and the substance use and associated behaviour takes precedence over other behaviours/activities that were important to the individual. In this pattern of substance use, a number of symptoms generally appear in the physical, psychological and social domains that form the diagnostic criteria of dependence.

DEPENDENCE SYNDROME

For making a diagnosis of dependence syndrome for a given substance, the following criteria should be fulfilled for at least three months in a one-year period:

- Use of substance in high amounts over a long period of time
- Need to increase the quantity of substance to get the same pleasure (tolerance)
- Appearance of specific physical and/or psychological symptoms upon stopping or reducing the amount / use of substance (withdrawal symptoms)
- Intense desire to consume the substance (craving)
- Continued use of the substance despite harm
- Significant socio-occupational dysfunction due to substance use
- Significant time spent in procuring / using / recovering from the substance in a day

(Adapted from ICD-10 guidelines)

The withdrawal symptoms differ from one chemical class of substance to another. Thus, for example, a typical withdrawal syndrome for any alcoholic beverage (whiskey, vodka, gin, beer, wine, rum, etc.) would be sleeplessness, anxiety, restlessness, tremors, palpitations, etc. On the other hand, stimulant withdrawals may produce excessive sleep, lethargy, irritability, sadness, etc. A typical feature of withdrawal syndromes is that they tend to immediately subside once the individual re-starts using the same (or similar) substance. Thus, an alcohol dependent person experiencing withdrawal would start feeling better after drinking and an opioid dependent person would feel relieved after taking the next dose of opioids.

In case of use of more than one substance simultaneously, it is not necessary for the user to be dependent on all the substances; he/she may be dependent on one substance, while he/she may have harmful use of another substance. For e.g., an individual using opioids as well as alcohol may be dependent on opioids, while he may be using alcohol in a 'harmful use' pattern.

Usually, an individual progresses from the stage of use and harmful use before going on to develop dependence on the substance in question. As stated earlier, the stages of 'harmful use' and 'dependence' are clearly morbid and are diagnostic entities. The time taken to progress from one stage to another is different for different persons and substances consumed. For example, an opioid user usually progresses rapidly within weeks from first use to dependence.



D. OPIOID DEPENDENCE SYNDROME

Opioid dependence syndrome (ODS) is a pattern of opioid drug use in which an individual uses opioids on a daily/almost daily basis and fulfils the criteria for dependence on opioid drugs. Some features of opioid dependence syndrome are as follows:

- **Acute withdrawals:** Opioids as a group produce typical physical withdrawal syndrome on a short term basis, upon reducing or stopping or even delaying the intake of the usual amount of opioid drugs. These withdrawal symptoms include *lacrimation* (tears from the eyes), *rhinorrhoea* (running nose), *yawning*, *diarrhoea*, *muscle cramps*, *sweating*, *muscle aches and pains*, etc. Along with these symptoms, other symptoms include *anxiety*, *restlessness*, *insomnia* (not able to sleep), *irritability*, as well as an *intense urge* (craving) to consume opioids. These 'acute' withdrawal symptoms are usually self-limiting in nature, i.e., they usually rise up to a peak level and subsequently subside on their own even without any intervention/help. However, these acute withdrawal symptoms are very distressing and disabling for the client, and often a cause for the client to restart or continue his/her opioid use. In most of the cases, once opioid use has stopped, the acute withdrawal symptoms would last for about two to three weeks before subsiding, provided the user has not resumed using opioid drugs.
- **Protracted withdrawals:** In most clients, even after the acute withdrawals have been resolved, some symptoms may persist for a longer period of time, i.e. up to four to six months. These include: *mild aches and pains*, *loss of interest in pleasurable activities*, *pre-mature ejaculation*, *sleep disturbances*, and *craving*. These symptoms are also some reasons for relapse in a number of opioid users.
- **Relapsing nature of illness:** As is true of other substance use disorders, especially dependence syndromes, ODS is also characterized by repeated relapses and remissions. An individual may restart using opioids after a period of abstinence. Such relapses and remissions are a feature of Opioid Dependence Syndrome especially among those who have used them for prolonged periods (years).

- **High risk behaviours:** Opioid use may be associated with various behaviours associated with high risk of transmission of blood-borne viruses such as HIV. As discussed above, opioids can be used through an injecting route, and a number of IDUs resort to sharing of needles/syringes or other injecting equipment. Injecting is a very efficient means of transmission of blood borne viruses, including HIV, Hepatitis B and C, as a result of which HIV prevalence among IDUs is very high. Additionally, individual users may also have high risk sex behaviours resulting in transmission of HIV through the sexual route to their female partners and the sex workers.
- **Multiple harms:** An opioid dependent user may incur harms in multiple domains of life. There may be family complications in terms of broken families, family fights, domestic violence, etc.; legal complications may include involvement in illegal activities like stealing, drug peddling, petty thefts, and incarceration, etc.; social complications may include loss of reputation/social status, being a social outcast, ridicule from society, sometimes even inhuman treatment/physical torture.

E. INJECTING DRUG USERS – RISK AND VULNERABILITY

- **Injecting-related risky behaviours:** IDUs are vulnerable to sharing of needles, syringes and other injecting paraphernalia. The sharing related behaviour may be due to a number of factors, such as non-availability of needles/syringes, non-affordability of needles/syringes or due to prevalent practices in group/peer norms, etc. Apart from sharing, there may be reuse of needles/syringes. These behaviours lead to a number of complications including abscesses, blocked veins, and transmission of blood-borne viruses such as hepatitis C, B and HIV.
- **Sex-related risky behaviours:** IDUs also engage in high risk sex behaviours including sex with female sex workers, sex without condoms, and sex with multiple partners. They may also sell sex in exchange for drugs or money. These behaviours put IDUs at risk for acquiring and transmitting HIV as well as other sexually transmitted infections to not just other injecting drug users but also to the general population.
- **Drug-related vulnerabilities:** As mentioned above, almost all IDUs in India use opioids as the primary drugs for injecting; studies also show that **almost all IDUs are opioid dependent**. In dependence syndrome, the use of drugs and injecting does not remain a matter of choice for the user; drug use becomes a compulsion – in the absence of drug use, the user suffers from withdrawal symptoms that compel him/her to continue/restart the use of drugs. As a result, the IDUs suffer from harms resulting from opioid dependence in addition to the above-mentioned injecting and sex-related risks. An additional vulnerability of concern among IDUs is of ‘overdose’. If a person takes a heavier dose of drugs than he is accustomed to, this may result in serious intoxication and overdose, which is a potentially fatal, medical emergency.

Opioid Substitution Therapy

– Basic Concepts and Principles

Various terminologies have been used to describe the clinical practice of maintaining opioid dependent drug users on opioid medicines over a long period of time. These include–oral substitution treatment, opioid substitution treatment, oral substitution–buprenorphine, medication assisted treatment, buprenorphine maintenance treatment, methadone maintenance treatment, etc. All these terminologies describe the same practice. Under the National AIDS Control Programme, the term ‘Opioid Substitution Therapy’ (OST) is currently in use.

OST is a process in which opioid-dependent injecting drug users are provided with long acting opioid agonist medications for a long period of time under medical supervision along with psycho-social interventions. Short term treatment of opioid dependence lasting for a couple of weeks called ‘detoxification’ which involves management of acute withdrawals alone, is associated with very high rates of relapse. Long term treatment is hence necessary for opioid dependence. OST is one such long-term treatment option.

The lives of IDUs revolve around illicit opioid use. Most of their day is spent in procuring the drugs, using them and/or recovering from the effects of the drugs. Withdrawals and craving associated with opioid use compel them to consume opioids repeatedly. As the opioid drugs usually have short-term effects, the drug using population needs to inject them multiple times throughout the day. As a result, they are not able to concentrate on other aspects of their life, including their work, family and social roles/responsibilities. They are also forced to indulge in illicit activities to finance their drug use. OST addresses a number of such issues faced by the IDU clients:

- The **opioid medicines used for OST relieve drug-related withdrawals and craving and do not lead (when used in appropriate doses) to acute intoxication** (which is seen with use of illicit opioids). Thus, the client is maintained in a state which produces neither intoxication nor withdrawals, nor craving. Due to this, the client does not need to use opioids to produce relief of withdrawals or craving.
- As compared to the illicit opioids that act quickly and for a short period of time, **opioid medicines used for OST act slowly and for a long period of time (for at least 24 hours)**. As a result, the client does not have to spend time on procuring or using opioids frequently in a given day and can focus on other important activities like occupational and family responsibilities.
- The illicit opioids used by the clients are taken by routes that are potentially harmful. Many harmful effects faced by IDUs are due to the injecting route of administration. On the other hand, **opioid medicines used for OST are administered orally or sublingually, which is a much safer route**. This saves the client from incurring harmful effects of opioid use.
- As the IDUs procure the opioids mostly through illegal channels, they are often not aware of the purity of the opioid product they inject. This is especially true for heroin and its impure form, smack. The purity of street heroin varies across different time periods as well as across the drug suppliers. This may result in life-threatening overdose situations if the heroin is purer than usual. On the other hand, the **potency and purity of opioid medicines used for OST is known**; this helps in averting overdose situations.

- As the street opioid drugs are costly, IDUs often resort to illegal activities to finance their drug use. However, as the opioid medicines used for OST are available in government supported centres/ hospitals free of cost, the client does not have to resort to illegal means. This helps in reducing legal complications faced by the clients and also reduces instances of petty crimes like thefts, etc. in the society.
- During the illicit drug use phase, IDUs are often branded as anti-social or criminal by the families and the society. When on OST, such IDUs are seen as sufferers and ‘patients’. This renewed status helps the clients to seek help for other problems as well and makes them amenable for other help that can be provided.

BENEFITS OF OPIOID SUBSTITUTION THERAPY

The benefits accrued from OST range from HIV prevention to treatment of opioid dependence, and from individual level to family and society level. The benefits of OST go beyond HIV prevention alone. A large body of literature is available globally that has documented the benefits and outcomes of OST. Substantial research has also been conducted in India on the use of OST in Indian settings. Evidence globally as well as locally shows that OST leads to improved retention and benefits detailed in the preceding section.

OST has been endorsed and recommended as the most effective and first-line treatment option for long-term pharmacotherapy of opioid dependence.

BENEFITS OF OPIOID SUBSTITUTION THERAPY

- Reduction in injecting behaviour
- Improved adherence for other treatment, especially treatment for HIV, tuberculosis and viral hepatitis
- Reduction in opioid use
- Reduced overdose related deaths
- Reduction in criminality
- Reduction in domestic violence
- Improved child care and family ties
- Improved productivity

OST-RELATED OUTCOMES – GLOBAL EVIDENCE

- A Cochrane review conducted by Mattick et al, 2009, concluded that OST using methadone was more effective (in a statistically significant manner) as compared to non-pharmacological treatment in retaining patients undergoing treatment and in suppression of heroin use.
- A Cochrane review conducted by Mattick et al, 2008, concluded that buprenorphine is an effective maintenance agent for heroin dependence, but not more effective than methadone.
- Large prospective cohort studies conducted over 18 months found that the odds of HIV infection were 5.4 times greater among those who were not in maintenance treatment compared with those who were in treatment (Metzger et al, 1993).
- A report by World Health Organisation, 2005, reviewed many studies conducted in different parts of the world and concluded that substitution treatment is a critical component of HIV prevention, and helps in reducing opioid dependency and HIV infection rates.

Contd...

- A systematic review and cost effectiveness by Connock in 2007 reported the following:
 - All doses of methadone or buprenorphine were more effective in retention as compared to placebo or no therapy.
 - OST using methadone or buprenorphine in higher dose was more effective in reducing illicit opioid use.
 - A meta-analysis of observational studies spanning publications of 21 years showed that patients on OST using methadone were four times less likely to die than those not in treatment.
 - OST using methadone significantly improved HIV-related outcomes (HIV risk behaviours, number of sex partners, frequency of unprotected sex, and rates of seroconversion).
- A joint position statement of WHO, UNODC and UNAIDS, 2004 described the cost effectiveness of OST as: “According to several conservative estimates, every dollar invested in opioid dependence treatment programmes may yield a return of between \$4 and \$7 in reduced drug-related crime, criminal justice costs and theft alone. When savings related to health care are included, total savings can exceed costs by a ratio of 12:1”.

OST-RELATED OUTCOMES – INDIAN EVIDENCE

As buprenorphine has been in use most commonly in India, much of the evidence in India exists for buprenorphine; some evidence exists for slow release oral morphine, and recently, for methadone.

- Dorabjee and Samson, 1998, describing their experience of implementing buprenorphine-based OST in a community setting in New Delhi reported that 33% of 447 IDUs on buprenorphine stopped injecting, and 35% of those injecting had reduced their frequency of injecting and sharing while on treatment.
- Kumar MS, 2009 reported that OST intervention implemented in Manipur and Nagaland covered 1200 IDUs and was found to be acceptable to the clients, their families, the general community, religious leaders as well as militant groups.
- A study by Armstrong et al, 2010, conducted on OST clients in Manipur and Nagaland showed that the retention rates on OST was about 73% at 3 months and 63% at 6 months. Statistically significant improvements were observed in relation to sharing of needles, unsafe sex, detention incidents, and quality of life measures.
- A multi-site study by Dhawan et al, 2010 showed that retention rates on OST were about 70% at the end of 9 months. The study showed significant decrease in opioid use, high risk behaviours, addiction severity and improvement in quality of life.
- A study conducted across 42 centres by Rao et al, 2012, showed that OST was being implemented in accordance with the DAC prescribed guidelines; a majority of the clients reported satisfaction with their treatment.
- Studies on SROM conducted in New Delhi have shown that SROM was associated with decrease in illicit opioid use, improved functioning and reduction in illegal activities (Rao et al, 2005, 2012).
- A research on methadone implementation across five centres in India showed that it is feasible to implement methadone for IDUs in India, and is associated with improved functioning and reduced opioid use (Dhawan et al, 2013).

KEY CHARACTERISTICS OF OPIOID SUBSTITUTION THERAPY

The practice of OST is based on a number of principles:

- **OST is primarily a medical intervention.** The medical staff (doctor and nurse) plays a lead role in OST intervention. The doctor conducts the assessment and diagnosis, plans and initiates treatment, monitors the progress and side effects, manages comorbidities and terminates treatment. The nursing personnel dispense the medications, and supervise the administration of OST medicines. Thus, the OST intervention is essentially a medical intervention led by the medical team and supported by the psychosocial team.
- **Adequate dose of medicines is one of the most crucial determinants of a good outcome.** The dose of medicines used for OST needs to be adequate and optimum. In general, the studies have found that the higher the dose, the better the retention in treatment and ultimate outcome.
- **Long duration of retention in continuous treatment is essential for a good outcome.** OST, as a medical treatment, is expected to last for a long duration, ranging from months to years. The OST medicines help the clients to stabilise their chaotic lifestyles associated with drug use and assists them to improve other areas of functioning, such as familial, social and occupational. As the clients settle down in their functioning and are ready, the treatment can be tapered in consultation with the clients and their family members. In many instances, the treatment needs to be continued over years to maintain the benefits accrued by the clients. Thus, there is no fixed formula for determining the optimum duration of treatment of OST; the key factor in determining the duration is 'attainment of treatment goals' viz., achieving a substance-free lifestyle, optimum psycho-social functioning and reintegration into the society.
- **Combining psychosocial interventions along with dispensing of medicines forms the complete treatment package.** OST works best if psychosocial interventions are combined along with OST medicines. Psychosocial interventions help in improving retention, and minimise drop-out, assisting the clients in regaining family and social ties and in gainful employment.
- **Involving the clients at all the treatment stages is crucial for success.** OST works best if clients are involved in the decision-making process of OST intervention. Thus, the clients need to be involved in setting treatment goals, deciding the dose of treatment, the duration of treatment and the endpoint of treatment. These decisions, if taken along with client, help in improving client retention and outcome on OST.

OPIOID SUBSTITUTION THERAPY MEDICINES

The medicines used in OST should have certain properties that help the clients obtain the benefits discussed above. The OST medicine should:

- Have **action similar to the illicit opioid** used by the clients. This is essential to effectively suppress the craving and withdrawals associated with cessation of opioid use. This means that an OST medicine should also be an agonist on the OPIOID receptors.
- Have **lesser addiction potential** as compared to the illicit opioid being consumed by the client. Any OST medicine will have some liability to result in addiction, as it is an opioid. However, its street value should be much less than the illicit opioids, i.e. users should not prefer the OST medicine over illicit opioids for their addiction/intoxication.
- Be **easy to administer** i.e. the medicine should be effective on oral or sublingual administration.

- Have **action lasting for at least 24 hours**, so that the frequency of administration should be once a day at the maximum.
- Be **well tolerated**. The side effects should be minimal so that the clients find it acceptable to continue OST medicines for a long period of time.
- Be **cheaper, easily available, easily stored and transported**, so as to provide for a large number of clients with minimal financial or logistic constraints.

In India, methadone, buprenorphine and slow release oral morphine have been used as OST medicine. However, the use of buprenorphine exceeds that of the other two; OST programme under NACP currently uses buprenorphine as the OST medicine, and hence buprenorphine has been discussed in detail in subsequent sections. Methadone based OST is also being implemented as a pilot at five sites in India.

PHARMACEUTICAL COMPOUNDS COMMONLY USED AS OST MEDICINES

- **Methadone:** Methadone was the first and currently, the most common opioid used as an OST medicine globally. Methadone is a pure opioid agonist, available for oral use either as a liquid or as a tablet.
- **Buprenorphine:** Buprenorphine is a partial opioid agonist available for use as a sublingual tablet. It is the second most commonly used OST medicine worldwide.
- **Slow Release Oral Morphine:** Morphine is a pure opioid agonist and commonly used in cancer patients for alleviation of pain. The slow release formulation is available as a tablet.

STATUS OF OPIOID SUBSTITUTION THERAPY IN INDIA

OST is currently available in 77 countries; of these, most countries use methadone as the OST medicine, followed by buprenorphine. In India, OST has been available since the early nineties, when buprenorphine started being used in some Government hospitals as well as in some NGO settings. While the OST was available uninterruptedly in a few Government hospitals for both IDU as well as non-IDU opioid dependent users, the availability in NGOs was dependent upon funding from donor partners and restricted to only IDU population (as a HIV prevention tool). The NGO OST centres were subsequently supported under NACP, while the Government centres continued to provide OST for opioid dependent individuals through funding from the Ministry of Health and Family Welfare. Additionally, there are anecdotal reports of OST being provided through private drug treatment centres.

The large scale expansion of the OST programme began with the transition of existing OST interventions for HIV prevention by NACP in 2008, after its formal incorporation in 2007. Initially, the existing NGO OST centres were evaluated and accredited, and those which were found eligible were provided support by DAC. A total of 55 such centres were provided continued support for OST implementation among IDUs. To further expand the OST programme, existing government hospitals at district and sub-district levels were roped in, and OST was initiated through the collaborative public healthcare model. Thus, currently there are two models of OST being implemented under NACP.

NGO OST CENTRES

- Part of IDU TI set-up. Staff largely shared with the IDU TI intervention
- OST centre located within the DIC of the IDU TI
- Medical intervention delivered by a trained part-time doctor and full-time nursing staff
- Outreach and follow-up by the outreach staff of the IDU TI

COLLABORATIVE PUBLIC HEALTH OST CENTRES

- OST intervention jointly between the Government hospital and nearby IDU TI
- OST centre located in Government hospital (Medical College/District Hospital/CHC/PHC)
- Separate staff at OST centre for medical and psychosocial intervention
- Outreach and follow-up by the IDU TI

Buprenorphine

– Basics of Pharmacology

As described above, the opioid family consists of a number of substances that act like opium (hence called opioids as they are similar in action to opium). The opioids have an effect mainly through their actions on the opioid receptors situated in the brain and other organ systems. There are three types of opioid receptors in the human body: mu, kappa and delta; out of these, the main action is produced by action on mu receptors. The opioids are classified as agonists, partial agonists and antagonists based on the nature of action produced on opioid receptors.

Buprenorphine is a semi-synthetic opioid derived from thebaine, an alkaloid of opium. As an analgesic, buprenorphine is 25 – 50 times more potent than morphine. Used intravenously, 0.3 mg of buprenorphine is equivalent to 10 mg of morphine.

CLASSIFICATION BASED ON THE ACTIONS ON OPIOID RECEPTORS

- **Agonists:** Opioid agonists bind to and activate the mu receptors, thereby exerting 100% action-producing opioid-like effects. Examples of agonists include: morphine, codeine, dextropropoxyphene, heroin and methadone.
- **Partial agonists:** Partial agonists exert less than 100% action on the mu receptors producing opioid-like effects, but less than opioid agonists. Example of partial agonist includes buprenorphine.
- **Antagonists:** Antagonists bind to the mu receptors, but do not produce any actions by themselves. However, once they are bound to the receptors, they do not allow the opioid agonists to occupy and act on the receptors, thus blocking the opioid actions. Additionally, if the opioid agonists are already present at the receptors, they displace the agonists, thereby producing opioid withdrawal syndrome. Examples of antagonists include Naloxone and Naltrexone.

PHARMACOLOGY

The pharmacological properties of buprenorphine and its clinical implications are described below.

- Buprenorphine is a **partial agonist of mu receptors** and an antagonist of kappa receptors. With lower doses, the action of a partial agonist is similar to that of a full agonist. As the dose increases, the effects of both the partial agonist and the full agonist are increased. However, beyond a certain dose-point, further increase in buprenorphine dose does not increase the opioid effect. This is called as '**ceiling effect**'. The figure below illustrates the point.

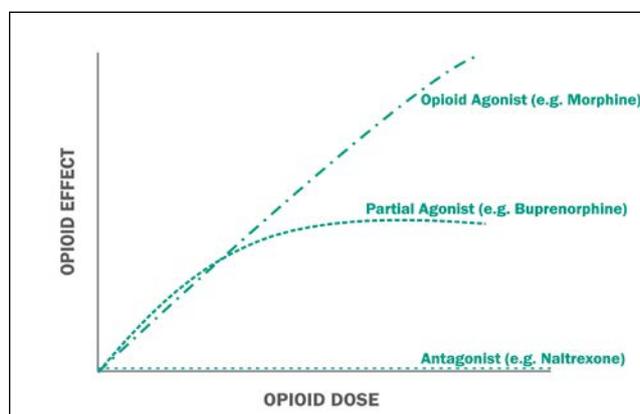


Fig: Ceiling effect of Buprenorphine

Clinical implication: The chances of overdose-related respiratory depression and consequently death are minimal with higher doses of buprenorphine. This is unlike pure agonists, where higher doses can result in overdose-related deaths due to respiratory depression.

- Buprenorphine has a **high affinity for opioid mu receptors**. Buprenorphine binds to the opioid receptor much more tightly than other full agonists such as morphine, heroin or methadone. Thus, buprenorphine displaces morphine and other full agonists if it is administered to individuals whose opioid receptors are occupied by the full agonists. Conversely, if the opioid receptors are already occupied by buprenorphine, it is difficult for full agonists to displace buprenorphine.

Clinical implication: Buprenorphine can displace illicit opioids from the opioid receptors; however, as buprenorphine is a partial agonist, while illicit opioids such as heroin are full agonists, there is a net decrease in the opioid actions. This results in '**precipitated withdrawals**' in the individual, if a sufficient gap between the last dose of illicit opioids consumed by the patient and the first dose of buprenorphine is not maintained. Conversely, once buprenorphine occupies the receptors, it is difficult for full agonists such as heroin to displace buprenorphine from the receptors, and produce their own actions. Thus, buprenorphine creates an **opioid blocking effect**. However, this blocking effect is dose-dependent – higher dose of buprenorphine blocks opioid receptors more effectively than lower doses of buprenorphine.

- Buprenorphine **dissociates from opioid receptors slowly** as compared to other opioids. Thus buprenorphine is a long-acting opioid with terminal elimination half-life of 24 to 37 hours. Peak clinical effect occurs one to four hours after sublingual administration. The duration of the effect depends on the dose administered: a low dose of 2 mg of buprenorphine produces clinical effect for up to 12 hours while higher doses of 16 mg can produce effects lasting up to 48 hours.

Clinical implication: At the right doses, buprenorphine can be administered at a frequency of less than once per day. It is possible for buprenorphine to be administered every alternate day and in some cases, once in three days too.

- Buprenorphine undergoes extensive metabolism in the liver, and is converted into nor-buprenorphine and other products through the cytochrome P450 3A4 enzyme. The metabolites do not have a major effect on the brain due to their poor penetration. Most of the metabolites are excreted through faeces, and some through urine.

Clinical implication: Due to high first-pass metabolism, buprenorphine has poor oral bioavailability, less than 10% compared to that when given intravenously. Hence, buprenorphine is not clinically effective when given orally. Buprenorphine should be **administered sublingually** to bypass the high first-pass metabolism. The bioavailability by the sublingual route is about 50-60%.

As buprenorphine is metabolised through the liver, **care should be taken in those individuals who have deranged liver functioning**. This is true in cases of alcohol or viral hepatitis-induced hepatic insufficiency. The metabolism of buprenorphine becomes erratic in such cases, and dose titrations may be required.

As buprenorphine is poorly absorbed orally, its **effect would be milder if it is accidentally ingested**. The ceiling effect adds to its safety in accidental ingestion.

SIDE EFFECTS AND SAFETY PROFILE

Buprenorphine is generally well-tolerated by drug-using individuals. Serious side effects are rare. Common side effects are generally related to the therapeutic dose (please see the accompanying box). Due to partial agonist and 'ceiling effect' property, buprenorphine does not result in respiratory depression even if it is administered at higher than therapeutic doses. In this regard, buprenorphine scores over other opioid agonists used in substitution therapy such as methadone and oral morphine. However, respiratory depression can occur even at low doses, if buprenorphine is combined with other brain depressants such as alcohol or sedatives.

COMMON SIDE EFFECTS

- Constipation (can be due to higher dose)
- Sedation (can be due to higher dose)
- Sleep disturbances
- Body aches/pains (features of withdrawals; can be due to lower dose)
- Nausea/Vomiting
- Itching (in few cases and in the initial days)
- Dizziness
- Headache
- Sweating

Buprenorphine has no major effect on hepatic functioning. Buprenorphine does not have any major effect on psychomotor functioning as compared to opioid agonists. Thus, individuals can continue to engage in potentially hazardous work such as driving or operating machinery. Precautions need to be taken mainly during the initial few days during dose induction or during increase in doses.

DRUG INTERACTIONS

Drug interactions with buprenorphine can occur due to the action of buprenorphine on opioid receptors or due to the metabolism of buprenorphine.

- **Sedatives:** The brain depressant effect of buprenorphine is additive to concomitant use of sedatives. These sedatives include benzodiazepines, barbiturates, and alcohol. While buprenorphine by itself does not cause respiratory depression, respiratory depression can occur even with lower doses of buprenorphine if high doses of sedatives and alcohol are concomitantly used with buprenorphine. This is particularly a concern among those drug users who have decreased respiratory reserves due to comorbid conditions such as chronic obstructive pulmonary disease (COPD), pneumonia, etc.
- **Opioid agonists:** Buprenorphine prevents other opioid agonists from exerting their effect due to strong affinity to opioid receptors; conversely, buprenorphine displaces opioid agonists resulting in precipitated withdrawals, as described above.
- **Hepatic enzyme inducers or inhibitors:** As mentioned above, buprenorphine is metabolised in the liver through the cytochrome p450 3A4 enzymes. As a result, medications that induce cytochrome p450 3A4 enzymes can lower the blood levels of buprenorphine, thereby requiring an increase in the dose of buprenorphine. Conversely, medications that inhibit cytochrome p450 3A4 enzymes can increase the blood levels of buprenorphine, thereby requiring a decrease in the dose of buprenorphine. In both scenarios, clinicians need to monitor for the emergence of opioid withdrawal or intoxicating symptoms and decide on dose titration accordingly.

COMMON MEDICATIONS INDUCING CYTOCHROME P450 3A4 ENZYMES

(Buprenorphine dose may have to be increased)

- **Anti-epileptics:** Carbamazepine, Phenobarbital, Phenytoin
- **Anti-tubercular drugs:** Rifampicin
- **Anti-retrovirals:** Efavirenz, Nevirapine

COMMON MEDICATIONS THAT INHIBIT CYTOCHROME P450 3A4 ENZYMES

(Buprenorphine dose may have to be decreased)

- **Anti-fungals:** Fluconazole, ketoconazole
- **Antibiotics:** Erythromycin
- **Anti-depressants:** Fluoxetine, Fluvoxamine, Paroxetine
- **Anti-retrovirals:** Indinavir, Ritonavir, Saquinavir

CONTRAINDICATIONS

The only **absolute contraindication** for buprenorphine is **known hypersensitivity to buprenorphine**.

PRECAUTIONS

In some conditions, the clinician has to assess the primary conditions and use buprenorphine cautiously depending upon the status of the primary condition. Some of these conditions include:

- **Respiratory conditions:** Asthma, chronic obstructive pulmonary disease, kyphoscoliosis, etc.
- **Hepatic conditions:** Alcoholic liver diseases, viral hepatitis B and C,
- **Abdominal conditions:** Irritable bowel syndrome and other colonic conditions
- **Urological conditions:** Conditions causing urinary retention
- Pheochromocytoma
- Hypothyroidism

However, it should be noted that mere presence of the conditions mentioned above should not preclude use of buprenorphine in an opioid dependent individual.

ABUSE LIABILITY

As buprenorphine is an opioid mu receptor agonist (though partial agonist), it is liable to be abused. In individuals who are not dependent on opioids, buprenorphine use through sublingual route produces euphoria and other opioid-like effects, thus increasing the likelihood that buprenorphine tablets can also be abused. Among drug users, buprenorphine is often the preferred opioid used for injecting in India. As sublingual buprenorphine is easily dissolvable in water, it can be diverted for injection purposes. Thus, one should exercise caution in dispensing of buprenorphine to opioid dependent individuals, and hence in the NACP, buprenorphine is almost always dispensed as Directly Observed Treatment (described later). However, it must be remembered that abuse liability of buprenorphine is significantly lower as compared to full agonists like heroin, morphine and methadone.

FORMULATIONS AND LEGAL STATUS IN INDIA

Currently, in India, buprenorphine is available both in injectable and sublingual tablet form. The injectable form is commonly available as 2 ml ampoules with each ml containing 0.3 mg of buprenorphine. The injectable form is used as an analgesic. The sublingual tablets of buprenorphine are currently available in three strengths – 0.2 mg, 0.4 mg, and 2 mg.

Buprenorphine is classified as a ‘psychotropic’ under the Narcotic Drugs and Psychotropic Substances (NDPS) Act. Under the NDPS act, narcotics and psychotropics can be used for medical and scientific purposes. However, these medications should be prescribed by a doctor, and can be made available only in Government-recognised centres. The injectable form and the 0.2 mg tablet is available in pharmacies, where these formulations can be sold upon availability of a valid prescription for the same. However, the higher strengths of buprenorphine, i.e. 0.4 mg and 2 mg have been approved only for the purpose of treatment of opioid-dependent individuals and can be made available only in Government-recognised drug treatment/de-addiction centres. Both these strengths are available for use in the OST programme supported by NACP.

**Clinical Practice
Guidelines
for OST Centres under NACP**

Clinical Practice Guidelines for OST Centres under NACP

The opioid substitution therapy (OST) intervention under NACP is conceptualised as follows:

OST INTERVENTION UNDER NATIONAL AIDS CONTROL ORGANISATION

- OST is a strategy for prevention of HIV among IDUs
- OST is to be provided to Injecting drug users (as defined by DAC) who are opioid dependent
- Currently, the only medicine available for OST is buprenorphine
- OST is a medical intervention in which a doctor initiates OST and a nurse dispenses the medicines
- Buprenorphine is to be dispensed on a daily basis as a 'Daily Observed Treatment' regimen

This section would describe the clinical practices involved in OST implementation as guided under DAC. The areas covered in this section include:

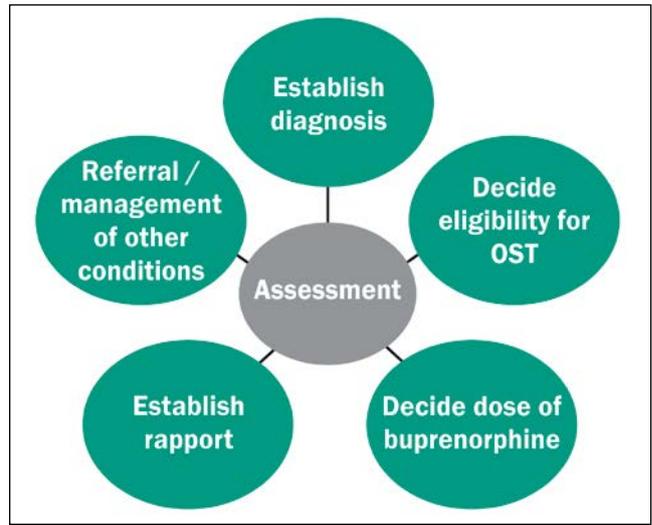
- Assessment and diagnosis
- Determining client suitability for buprenorphine-based OST
- Preparing client for OST
- Initiating buprenorphine (induction phase)
- Continuation on buprenorphine (maintenance phase)
- Terminating buprenorphine (termination phase)
- Managing common side effects of buprenorphine
- Special clinical situations

Psychosocial interventions provided along with OST are not described in this document. It is felt that the discussion on psychosocial interventions warrant a separate document altogether.

Assessment and Diagnosis

Initial assessment of the client is an essential prerequisite in OST intervention. The assessment helps the service provider in making appropriate decisions on the client requirement with regard to OST, including whether OST should be initiated, as well as the dosing requirements. Assessment has multiple purposes that go beyond mere OST consideration.

Assessment is to be carried out **both by the counsellor as well as the doctor** of the OST centre, though the doctor takes a larger role, since OST is a medical intervention. While the counsellor would focus on the psychosocial aspects of the client's drug use history, the doctor would focus on the clinical/medical aspects pertaining to the client's drug use and medical history. During assessment, the counsellor and doctor must attempt to answer the following questions:



- What are the various psychoactive substances consumed by the client till date?
- What is the pattern of use of various psychoactive substances consumed by the client?
- Does the client fulfil the criteria for opioid dependence syndrome?
- Does the client fulfil the criteria for dependence/harmful use of other substances?
- What is the current pattern of use of various psychoactive substances consumed by the client?
- What are the various complications in the client's life/functioning due to substance use (including physical, psychological, familial, social, legal, occupational and financial areas)?
- What are the high risk behaviours practiced by the client (including injecting and sex-related high risk behaviours)? What is the level of knowledge of the client regarding HIV and other consequences of high risk behaviours?
- What has been the nature of previous attempts by the client to stop injecting/opioid use? What kind of help was received by the client during these previous attempts?
- What are the major facilitating factors and barriers in the recovery for the client?
- Does the client match the inclusion and exclusion criteria laid down in the programme for initiating OST?
- Does the client have any medical condition that makes him/her unfit for OST?
- What is the motivation level of the client to stop injecting and initiate OST?
- What is the level of psychosocial support currently available to the client for OST initiation and continuation?

To answer the above questions, the assessment can be conducted using various modalities covering the following areas:

ASSESSMENT MODALITIES

- Interaction with the client
- Interaction with family members (if present during assessment)
- Interaction with other individuals associated with the client (client's friends/peers, staff of the IDU TI project, if present during assessment)
- Review of previous treatment records, if available
- Observation and physical examination of the client

ASSESSMENT AREAS

- Socio-demographic details
- Psychoactive substance use details
- Complications due to substance use
- Injecting and other high risk behaviours
- Past abstinence attempts
- History of medical illnesses
- Current psychosocial support and living arrangement
- Current status of occupational and family functioning
- Evidence of current opioid withdrawals/intoxication
- Evidence of injection/other physical consequences of substance use (injection marks, abscesses, scars, etc.)

(Note: Specific formats exist for recording the information collected during assessment. These formats ("Intake Forms") are prescribed by DAC and provided by the respective SACS to all the OST centres.)

- **Socio-demographic details** including the client's name, age, sex, marital status, educational status, occupational and employment status, and current contact information are required.
- **Psychoactive substance use details** including chronological order of initiation of substance use, and for every substance, the age of initiation, progression, frequency of use, mode of intake of substance, any dependence features, usual dose, and last dose of intake have to be noted.
- **Complications due to substance use** can be psychological (guilt, shame, depression, anxiety, etc.), financial (loss of money, debts, etc.), familial (fights, violence, neglect, homelessness, etc.), social (outcast, ridicule, discrimination, etc.), occupational (loss of job, irregular in work, frequent change of job, etc.), and legal (thefts, robbery, drug dealing/peddling, imprisonment, etc.).
- **High risk behaviours:** Both injecting (sharing, reuse of needle/syringes or other paraphernalia) and sex-related (sex with female sex workers, multiple sex partners, sex in exchange of drugs/money, sex under the influence of substances, non-use of condoms) are high risk behaviours.

- **Abstinence attempts:** Any attempts to give up psychoactive substance use should be noted. For every significant attempt, the duration of attempt, reason for abstinence, type of help received, reason(s) for relapse should be tracked. An abstinence attempt may be considered as significant if the client was able to completely stop substance use for a duration of 1 month or more.
- **Psychosocial support:** The nature of relationship with family members particularly spouse, the nature of relationship with non-drug-using friends, attitude of family/friends towards client's drug use, possibility of involvement in treatment process, etc.
- **Current living arrangement:** Type of accommodation, family members sharing accommodation, etc.
- **Evidence of injection:** Any needle track marks, scarring of tissue, abscesses, ulcers, etc.
- **Evidence of current intoxication:** Slurring of speech, altered sensorium, change in rate of speech, disinhibition, gait disturbance, etc.
- **Evidence of current withdrawals:** Specific to the substance of use.
For opioids: Lacrimation, rhinorrhoea, yawning, dilated pupils, increased sweating, restlessness, palpitations, increased respiratory rate;
For alcohol/benzodiazepines: Anxiety, restlessness, tremors of hands, increased respiratory rate, palpitations, sweating, etc.

At the end of assessment, the doctor must be able to make a diagnosis of the client's problem and prescribe appropriate management for the same. The diagnosis should encompass the following:

1. **Diagnosis of Opioid dependence:** Use of opioids in large amounts over a long period of time leading to (presence of three or more among the following in the preceding one year):
 - **Tolerance:** Gradual increase in the amount of opioid intake to get the same high; appearance of withdrawals upon decreasing the dose
 - **Withdrawal symptoms:** Lacrimation, rhinorrhoea, yawning, diarrhoea, cramps in abdomen, intense body ache, insomnia
 - **Craving:** Intense urge to consume opioids
 - **Socio-occupational dysfunction**
 - **Increased time spent** in obtaining opioids, consuming opioids or recovering from the effect of opioids
 - **Continued use of opioids despite harms** incurred due to opioid use, such as abscesses, overdose, vein loss, HIV, Hepatitis B/C, respiratory problems, etc.
 - **Persistent efforts to cut down opioid use:** Unsuccessful attempts / desire to give up on opioid use
2. **Diagnosis of other substance use disorders:** Dependence / harmful use of other substances. Special attention should be given to the concomitant use of alcohol and/or benzodiazepines, which are general brain depressants and commonly used by opioid dependent individuals.
3. **Diagnosis of medical comorbidity, if any:** Special attention should be given to liver conditions, and respiratory conditions, which, if severe, may preclude a client from being started on OST.
4. **Psychosocial issues that can influence treatment outcomes:** Extent of family support, presence or absence of a stable job, current involvement in illegal activities, homelessness, HIV, Hepatitis B/C, etc. can influence the retention of the client on OST, and must be addressed during regular follow-up of the client after OST initiation.

Determining Suitability of Clients for Opioid Substitution Therapy

To be initiated on OST, the client must fulfil the suitability criteria mentioned below. Some of these criteria are 'essential' criteria, while others are 'desirable'.

ESSENTIAL CRITERIA FOR OST INITIATION

The client must fulfil each of the essential criteria for OST initiation:

- 1. DIAGNOSIS OF OPIOID DEPENDENCE SYNDROME:** A diagnosis of opioid dependence syndrome is essential as OST is a specific medical treatment for this condition. Merely use of street opioids or injecting drug use is not sufficient to consider OST. Hence, before starting treatment, the doctor should carefully assess the pattern of opioid use by the client and consider OST only if the client meets the criteria for opioid dependence discussed above.
- 2. CURRENT IDU:** The client should meet the operational criteria for IDU established under NACP i.e. he/she must have injected a psychoactive substance at least once in the past three months for non-medical purposes.
- 3. ABSENCE OF MEDICAL CONTRAINDICATIONS:** The client must not suffer from such medical disorders that prevent him/her from being initiated on OST. It must be remembered that the **only absolute contraindication for OST with buprenorphine is known hypersensitivity to the medication**. Other conditions such as respiratory, renal or hepatic insufficiency are relative contraindications and do not preclude the use of buprenorphine for OST. In such instances, the clinician should judge the possible adverse effects associated with starting buprenorphine versus the benefits of treatment and decide on the course of action on a case to case basis.
- 4. INFORMED CONSENT:** The client must have the mental capacity to provide informed consent, as well as he should be willing to start on OST after understanding the implications, requirements, safeguards to be taken, etc. Under NACP, a written informed consent is must before OST can be prescribed to any IDU.
- 5. CLIENT'S WILLINGNESS TO COME DAILY TO RECEIVE TREATMENT:** At the time of initial assessment, the client should be educated about the need to come to the OST centre every day to receive treatment under supervision (DOTS). Only those clients who agree to adhere to this mechanism should be initiated on treatment after duly signing the informed consent.

DESIRABLE CRITERIA FOR OST INITIATION

While the following criteria are desirable, they are not essential for a client to be initiated on OST. These criteria have been included as they increase the likelihood of selecting a suitable client for OST, thereby increasing the confidence of the clinician in prescribing the treatment.

- 1. AGE MORE THAN 18 YEARS.** While it is desirable that the client should be 18 years or above to be initiated on OST, adolescents who are below 18 years of age can also be given OST. Issues to be considered in adolescents receiving OST is discussed in later sections.
- 2. FAILED ABSTINENCE ATTEMPTS.** The client may have attempted to give up opioids in the past through other means, but has failed in doing so. This indicates greater likelihood of opioid dependence in a given client as well as lesser chances of recovery with other shorter duration treatments like detoxification.

3. **LONG DURATION OF OPIOID USE/INJECTING:** A history of long duration of opioid use (more than 3 years) indicates high severity of opioid dependence, particularly if the client has used opioids by the injecting route for most of this duration. As OST is considered the treatment of choice in severe opioid dependence, a client fulfilling this criterion would really require OST to give up drug use.
4. **MOTIVATION TO GIVE UP DRUG USE/INJECTING:** During the pre-treatment assessment, a client with better motivation is more likely to retain in treatment and accrue the benefits of OST. However, motivation is a dynamic phenomenon and often clients with poor motivation to abstain at OST initiation do well with treatment once they experience the effectiveness of OST in alleviating withdrawals and craving.
5. **FEASIBILITY:** It should be feasible for the client to come to the OST centre on a daily basis to take his OST dose. The feasibility here is as per the understanding of the service providers (OST doctor/counsellor). However, in situations where the treating team has a different opinion about the ability of a client to come daily, the client's perception of the same should prevail and treatment should be started.

CONDITIONS REQUIRING SPECIAL CONSIDERATIONS FOR OST INITIATION

There are certain conditions in which caution should be exercised while prescribing OST to IDU clients. Among these, the only absolute contra-indication is known hypersensitivity to buprenorphine. In other cases, the clinician should use his/her clinical judgement before deciding on initiation of buprenorphine.

1. **KNOWN HYPERSENSITIVITY TO BUPRENORPHINE:** Some clients may have had allergic reactions to buprenorphine in the past; such clients should not be given buprenorphine.
2. **SEVERE DEPENDENCE ON ALCOHOL OR BENZODIAZEPINES:** If the clients have concomitant use of alcohol or benzodiazepines, and have higher degree of dependence on these substances through heavy use, OST may not be started in the OST centre itself. Such clients should be referred to a psychiatrist/drug de-addiction centre before initiating on OST and may require inpatient treatment. Most IDU clients inject a cocktail of opioid drugs (buprenorphine/pentazocine/heroin/d-propoxyphene) along with sedatives (diazepam/pheniramine/promethazine). Such clients are seen as primarily dependent on opioids and can be safely started on OST.
3. **SEVERE DEGREE OF HEPATIC IMPAIRMENT:** Alcohol use or infective hepatitis may result in altered metabolism of buprenorphine, leading to erratic blood buprenorphine levels. If there is clinical evidence of hepatic impairment, a liver function test may be advised and based upon the results, the decision regarding OST can be taken. If the derangement is mild-moderate, OST should be initiated, but with careful titration of dosage. OST should be withheld only in case of severe derangement of hepatic function tests / definite clinical evidence of liver failure.
4. **SEVERE DEGREE OF RESPIRATORY PROBLEMS:** In conditions such as severe asthma or chronic airway diseases leading to severe impairment of respiratory functions, OST should be initiated with caution, as it may further aggravate respiratory problems. Such patients should not be prescribed benzodiazepines for sleep disturbances due to their additive depressive effect on brain.

LABORATORY TESTS FOR OST

It is NOT ESSENTIAL to perform any laboratory test, before initiating OST for a client. If the doctor has conducted a clinical examination and has not detected any significant finding, OST can be safely started. It is a good practice to conduct routine laboratory tests (such as hemogram, liver function tests and renal function tests) in the initial days of assessment and treatment as a 'baseline' test. In cases where there are findings present on physical examination, the relevant laboratory tests are warranted.

Preparing Clients for Opioid Substitution Therapy

Once it is decided that the client will be initiated on OST, he/she should be prepared and educated before initiation. This can be done by the counsellor or the doctor. The important issues to be covered in client education:

- **Nature of illness:** The client should be explained that opioid dependence syndrome is a chronic relapsing medical illness similar to other chronic medical illnesses such as diabetes, hypertension and other cardiovascular illnesses. It is not a weakness of will power, or a 'character defect' in the client. Relapse is part of the recovery process and there are strategies available to minimise/prevent relapse.
- **Nature of treatment:** The client should be informed that OST is a long term treatment option; it is important for the client to remain in treatment for at least one year or more for lasting benefits. The medicines would be given as a daily observed treatment supervised by the nursing staff. The medicines would help in controlling withdrawals, and craving, and he would not need to use opioids for at least a 24 hour period after receiving the dose.
Apart from OST medicine, the client also needs to undergo periodic counselling as well as regular follow-up with the service providers. The client needs to follow the rules and regulations established by the OST centre.
- **Need for active involvement:** The client needs to be involved actively in the treatment process. He/she needs to be forthcoming in informing the service providers about his drug using status, benefits of treatment, sufficiency of medicine dose, and overall improvement. Additionally, if family members are involved in treatment, the outcome would be better.

Along with education, the service providers should also dispel common myths/misconceptions associated with OST. Additionally, this also provides the service providers an opportunity to enhance the motivation of the client towards initiation and continuation on OST.

Once the client has clearly understood the implications of being in OST programme and is ready, he/she should be asked to **sign the informed consent form** and OST should be initiated only after the consent form is signed. The consent form should have signatures of client, a witness (family member or staff) and the person who has obtained the consent (doctor or counsellor).

Buprenorphine – Based Opioid Substitution Therapy

OST with buprenorphine can be divided into three phases:

- **Induction phase:** Phase wherein the client is given the first dose and the dose is subsequently adjusted to achieve a stabilisation dose
- **Maintenance phase:** Phase wherein the client is maintained on stabilisation dose till a decision to stop buprenorphine is taken
- **Termination phase:** Phase from decision to stop buprenorphine to the last dose of buprenorphine

Each of these phases of OST treatment has different goals and objectives, management issues, and role of different service providers, etc. Each of these phases is discussed in detail below in different sections.

INITIATING OST WITH BUPRENORPHINE – INDUCTION PHASE

As mentioned above, the induction phase begins when the decision to initiate the client on OST is taken till the point where the stabilisation dose is reached.

GOALS OF INDUCTION PHASE

- To determine the correct dose of buprenorphine for a client to be able to control opioid withdrawal symptoms and craving
- To address any medical or psychosocial crisis faced by the client
- To establish rapport with the client and educate him / her about the treatment process

Before the first dose of buprenorphine, the doctor should ensure that:

- A detailed assessment of the client has been made, and the client fulfils the criteria for OST initiation as laid down by DAC.
- The client has understood the implications and procedures of OST and has signed the informed consent sheet.
- The **last dose of opioid use is at least 6 – 8 hours before the first dose of buprenorphine.**

The first dose of buprenorphine usually ranges from 2 – 4 mg. After the first dose is administered sublingually, the client should be observed after a gap of two hours, when the peak effect of buprenorphine is expected to be observed. If the client still complains of withdrawals/craving, an additional 2 – 4 mg can be given. If the client reports no symptoms of opioid withdrawal or craving, he/she should be asked to return on the next day for his dose. The total dose of buprenorphine must not exceed beyond 8 mg on DAY ONE.

On the second day, enquiry should be made regarding whether the client had any opioid withdrawal and/or craving symptoms anytime in the last 24 hours after the dose of buprenorphine was initiated or whether the client took any other opioid by injecting / non-injecting routes AND was able to achieve its effects. If the client

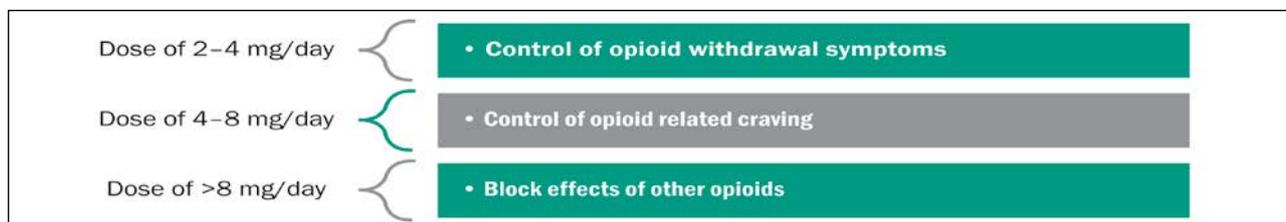
HOW IMPORTANT IS THE TIME GAP BETWEEN LAST DOSE OF ILLICIT OPIOID AND FIRST DOSE OF BUPRENORPHINE?

This is extremely important, especially in cases where the client uses pure opioid agonist such as heroin as the illicit opioid. If the time gap is not maintained, buprenorphine would displace the illicit opioids from the receptors and precipitate opioid withdrawal symptoms, which would be extremely distressing for the client.

However, some doctors have a myth that if the client has already taken an opioid drug (like heroin) a short while ago, the first dose of buprenorphine will result in added intoxication (and risk of overdose). This is a misconception. The gap must be ensured primarily to avoid the precipitated withdrawal and not overdose.

reports so, the dose of buprenorphine should be increased in increments of 2 mg. The maximum dose of buprenorphine on DAY TWO should be about 12 mg. If the client does not report of any withdrawals or craving for an entire period of 24 hours following dose administration, the client would have achieved his stabilisation dose.

Most clients reach their stabilisation dose in three to four days, maximum by day seven. Apart from control of craving and withdrawal, the stabilisation dose should also be able to block the euphoric effect produced by illicit opioid use. It must be remembered here that lower doses (of up to 2–4 mg) would be able to control withdrawal symptoms, while slightly higher doses (of up to 4–8 mg) would be able to take care of craving. The opioid blocking effect would be produced only at even higher doses (of 8–12 mg). Additionally, the higher the dose of buprenorphine, the longer is the effect of buprenorphine – i.e. a higher dose would enable the client to be without any discomfort or need for additional opioids for longer duration of at least 24 hours duration. Hence, the clinician's efforts must be to ensure that all the three objectives of OST dose – stopping withdrawals, control craving and produce opioid blocking effect – are achieved with the adequate dose of buprenorphine.

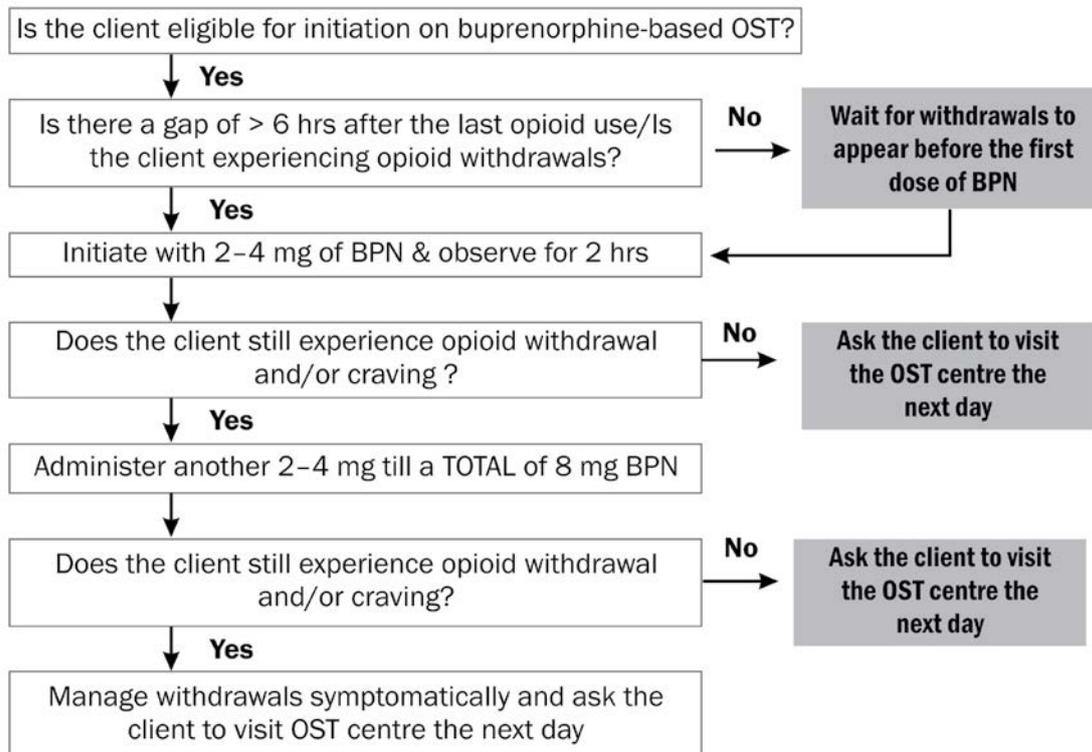


While guidelines from western countries recommend a maintenance dose of 12–16 mg of buprenorphine per day, experience from India shows that for optimum outcomes, doses of 8–12 mg of buprenorphine per day is sufficient for most clients. For maximum dose too, the guidelines from western countries suggest a maximum of 32 mg/day; however, in India, a dose of 20–24 mg per day can be considered as maximum dose. If the clinician feels that the client is not improving despite the maximum dose, the client may be referred to a higher centre specialising in substance use treatment for further management.

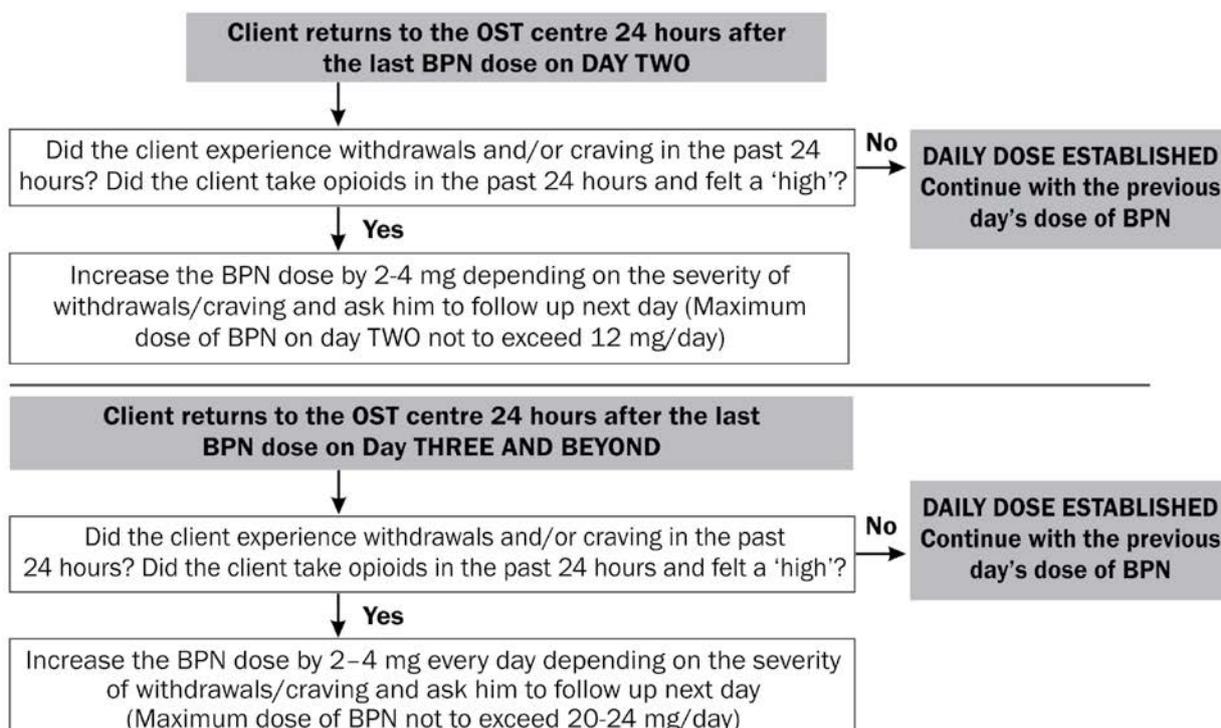
Apart from stabilising the dose of buprenorphine, the service providers also need to work on the following areas of the client's life during induction phase:

- Enhance the client's motivation to stop/reduce injecting and continue OST
- Address any medical priorities. These may include conditions such as an open abscess, active tuberculosis, or any acute comorbid medical problem faced by the client.
- Address any psychosocial crisis. This may include conditions such as recent homelessness, impending legal crisis, etc.

**FLOW-CHART ON INDUCTION PHASE FOR BUPRENORPHINE (BPN)
BASED OPIOID SUBSTITUTION THERAPY: DAY ONE**



**FLOW-CHART ON INDUCTION PHASE FOR BUPRENORPHINE (BPN)
BASED OPIOID SUBSTITUTION THERAPY: DAY TWO AND BEYOND**



DOSE INCREMENTS FOR BUPRENORPHINE

To the extent possible, dose increments should be in round figures, preferably in multiples of 2. Thus, if a client is not comfortable on 4 mg, the next dose should be 6 mg. The fractions (using 0.2 and 0.4 mg tablets) should be limited to only those rare cases where (say) 6 mg is an inadequate dose while (say) 8 mg is perceived as a higher dose. Additionally, the use of fractions can be considered while tapering the dose for the purpose of termination of treatment (described later).

MAINTAINING CLIENTS ON BUPRENORPHINE – MAINTENANCE PHASE

The maintenance phase begins with the client achieving his stabilisation dose till the time a decision is made to stop OST for the client.

GOALS OF MAINTENANCE PHASE

- To maintain the client on adequate doses of buprenorphine
- To address other substance use by the client, if any
- To motivate and refer the client for other services, including HIV diagnosis and treatment
- To help the client in regaining occupational, financial and familial stability
- To retain the client in treatment, adhere to treatment regimen and help prevent relapse to opioid use (through injecting or other route)
- To help the client prevent shifting to another substance use

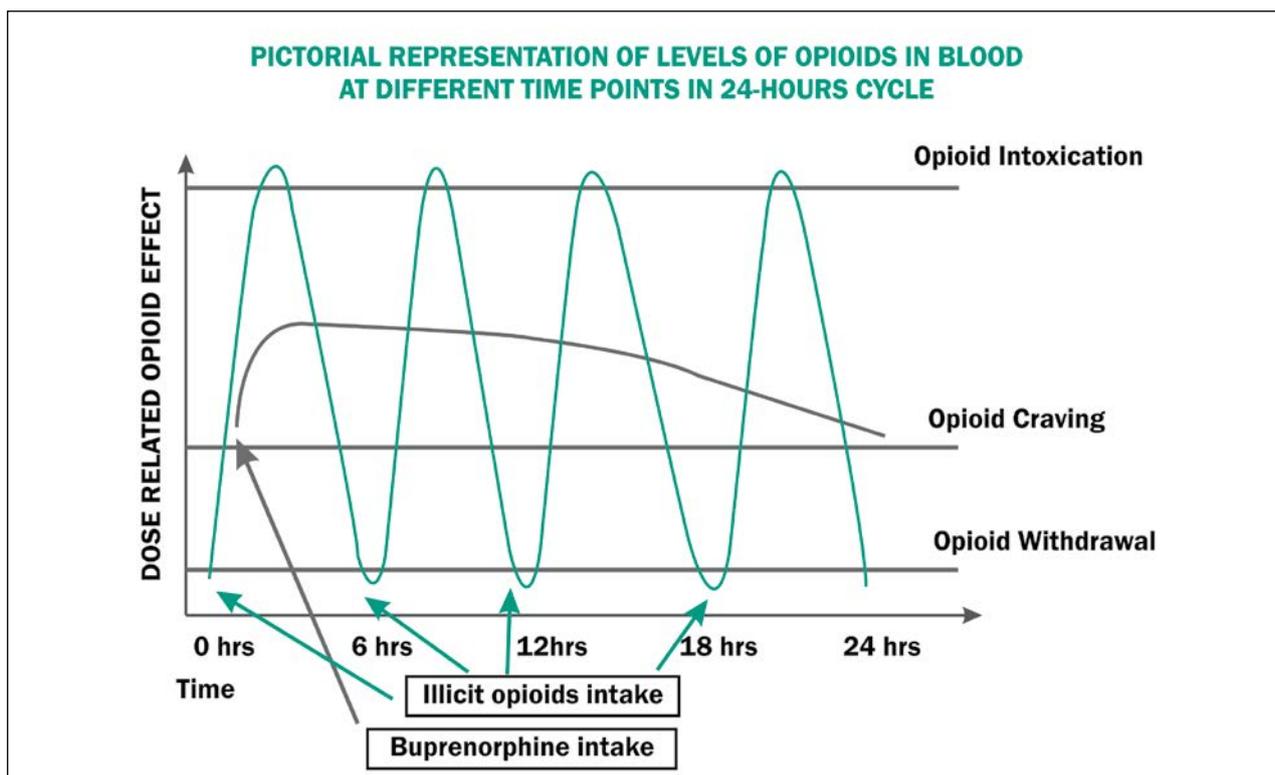
BUPRENORPHINE MAINTENANCE DOSE

The clinician should continue the same dose of buprenorphine as used in the induction phase for stabilisation. Any temptation to reduce the dose of buprenorphine must be avoided, unless specifically warranted. Furthermore, the doctor must make enquiries on the following issues during every follow up:

- Does the client have withdrawals/craving despite his current buprenorphine dose?
- Has the client used any other opioids/injections while on his current buprenorphine dose?
- Does the client experience euphoria while using other opioids/injections?

The information regarding the above can be elicited by interviewing the client, his family members/significant others and staff of the TI linked with the centre.

If the clients report that they still have (a) withdrawals or (b) craving or that (c) they use injections/other opioids and experiences euphoria on opioid use, it is an indication to the doctor that the dose of buprenorphine is inadequate. In such cases, the doctor must increase the dose of buprenorphine to an optimum level. Care must also be taken to ensure that the client does not experience opioid intoxication effect due to use of buprenorphine, such as sedation, slurring of speech, incoordination, etc. Such effects are related to the peak plasma blood levels of buprenorphine typically seen 1-3 hours after administration of the daily dose. Thus, the dose of buprenorphine must be such that the client neither has a peak effect of intoxication nor has the trough effect of withdrawal/craving. A pictorial representation of difference between the level of illicit opioids such as heroin and buprenorphine is shown below.



Once the client is maintained on a particular dose of buprenorphine which is comfortable for him/her, the SAME dose should be continued in the maintenance phase. Further changes in dose, especially dose increase, may be required in some conditions. Such conditions may include resumption of work (especially menial jobs such as manual labour, rickshaw pulling, etc.), pain conditions (such as fractures, etc.), re-emergence of craving, psychosocial distress, etc. In such cases, the doctor should re-assess the client and increase the dose as required.

An important issue during maintenance phase is to encourage and motivate clients to continue on OST. Many clients feel that their lives have become normal after 2 – 3 months of OST, as they have stopped opioid and injecting use, and feel that they can now stop OST. This belief is also often supported by family members, who feel that the client should now resume his/her responsibilities, sometimes at the cost of continued OST. The service providers must emphasise on the need for long-term continuation of OST medicines. The principles of motivation enhancement can be applied for encouraging the client to continue OST. Additionally, the family members must also be counselled on the need for continuation on OST.

REDUCTION OF MAINTENANCE DOSE

It is observed that in certain cases, the doctor reduces the dose of buprenorphine despite the fact that there are no side-effects, the client is maintaining well and has not desired for dose reduction. This reduction is done as many doctors and other OST centre staff are under the impression that once the client has stopped using illicit opioids, his dose should be reduced to the minimum possible.

It should be important to note that the **SAME DOSE OF BUPRENORPHINE AS REQUIRED IN THE INITIAL STAGES SHOULD BE CONTINUED**, unless the client reports of any buprenorphine-related side effects. Even if the client requests for dose reduction, he/she should be educated on the need for the same dose. Despite this, if the client demands for dose reduction, then only the dose reduction should be attempted.

BUPRENORPHINE DISPENSING

As per DAC guidelines, dispensing of buprenorphine is to be done on 'Daily Observed Treatment' basis at the OST centre. This means that the client has to come to the OST centre daily and take his medicines in front of the OST nurse. Buprenorphine is to be given through the sublingual route. The tablet should be crushed before administration to prevent diversion of the medicine by the client. The nurse should observe the client for a period of at least 7 – 10 minutes after administering the dose to ensure that the tablets have dissolved. Detailed dispensing procedure is provided in the document on standard operating procedure.

ADDRESSING CO-MORBID SUBSTANCE USE

Once the client is stabilised on OST medicines and he has stopped illicit opioid use, use of other substances may increase or resume. This is mainly because the client attempts to find other sources of pleasure and high. Most commonly, the client may reinstate or increase consumption of other brain depressants such as alcohol, benzodiazepines or cannabis. Some clients may progress on to use of these substances in dependent pattern. Apart from problems due to the substances themselves, use of these substances also affects OST:

- Use of these substances would increase the chance of the client relapsing to opioid use
- Use of high dose of these substances would increase the risk of respiratory depression

The service providers should enquire about other substance use during maintenance phase. In case the client has re-initiated or increased his substance use, the service provider must educate the client about the risks posed, and assist the client in stopping the use of these substances. If required, the client may be referred to a psychiatrist or another specialist dealing with substance use disorder for treatment of these co-morbid conditions.

REFERRAL TO OTHER SERVICES

Once the client is stabilised on OST, he/she becomes more amenable to availing other services required. The client should be motivated to undergo HIV testing and if found HIV positive, should be encouraged to register with an ART centre for further management. Additionally, the client should be clinically screened for other conditions including tuberculosis, hepatitis, abscesses, etc. If the client is found to be suffering from any of these medical conditions, appropriate referral must be made. The client should also be encouraged to adhere to both OST as well as medications prescribed for such co-morbid conditions.

ASSISTANCE IN RE-INTEGRATION

Maintenance phase is an excellent opportunity to motivate the client to repair ties with family, assume family responsibility and regain employment. Such re-integration with work, family and society would further help the client in maintaining abstinence from substance use and help regain the trust of his family members. Occupational rehabilitation makes the client productive once again and helps him/her to have a structured routine as well as earn a livelihood.

During follow-up, the counsellor should explore these areas and assist the client in resuming his work and ties with family. The family members should be involved in these activities, and help from them solicited if required through a home-visit.

TERMINATING CLIENTS ON BUPRENORPHINE – TERMINATION PHASE

The termination phase begins with taking a decision to stop buprenorphine and ends when the last dose of buprenorphine is administered to the client.

GOALS OF TERMINATION PHASE

- To taper and stop buprenorphine medicine
- To ensure that clients have minimal discomfort during tapering of buprenorphine
- To support the client during tapering of buprenorphine and prevent relapse during the same
- To help the client in making decision regarding further treatment after stopping OST
- To motivate the client for continued follow-up after stopping OST

DECISION TO STOP BUPRENORPHINE

A crucial decision in OST management is the decision about stopping buprenorphine treatment. There is no specified time-duration for a client to be maintained on OST. OST may last for months to years. The endpoint is reached upon the client achieving the treatment goals decided mutually by him/her and the service provider during the initiation of OST. The treatment goal is not limited to the client stopping his/her drug use; it also includes successful reintegration of the client in his/her family, society and work. Once these goals are reached, a decision on stopping buprenorphine can be made, if the client wishes to stop buprenorphine.

Some indicators of successful termination can include:

- a) cessation of opioid and injecting use,
- b) cessation of illegal activities,
- c) improved ties with family,
- d) strong psychosocial support,
- e) well-maintained occupational functioning, and
- f) client's readiness to lead a medication-free life.

Despite successful outcomes, clients may still wish to continue OST, as they are not ready or willing to lead a medication-free life, in which case, OST must be continued. Continued drug use, continued perception of risk of relapse, illegal activities, poor occupational functioning, homelessness, and poor family support are the factors which indicate that OST should continue and should not be terminated irrespective of the duration of treatment.

TAPERING BUPRENORPHINE

Before tapering of buprenorphine, the client must be prepared well in advance. The family members should be involved in the decision, and support from them must be solicited. The client must be educated on the possibility of some discomfort and withdrawals during taper and relapse prevention sessions for the client must be conducted.

Buprenorphine must not be stopped abruptly, as otherwise the client would experience withdrawals and there would be the consequent risk of relapse to opioid use. The process of tapering must be gradual. There is no fixed regime for tapering buprenorphine dose; the amount of reduction, time-gap between each reduction and the time taken for the tapering process varies from client to client. For most clients, tapering can be done on an outpatient basis in the centre itself; very few clients may require admission to a hospital for tapering of buprenorphine.

TAPERING TO A LOWER MAINTENANCE DOSE

In clinical practice, a situation is often encountered when during the process of tapering, the dose is lowered (say, from 8 mg per day of maintenance dose to 2.4 mg per day) and any subsequent dose-reduction is met with discomfort. In such cases, clients are continued on this lower maintenance dose for many months or years.

The outpatient taper can be done over 2 – 3 months duration. In outpatient tapering, the tapering can be done in units of 2 mg of buprenorphine every 4 – 7 days, till the client reaches a dose of 2–4 mg of buprenorphine. Further tapering can be done in units of 0.4 – 0.8 mg of buprenorphine every 4 – 7 days. If the client complains of withdrawals or discomfort, the tapering can be more gradual. Inpatient tapering can be faster than outpatient tapering and can be achieved in 2 – 3 weeks' time. In an inpatient setting, the daily dose of buprenorphine can be divided into a thrice-daily regime, and 0.4–0.8 mg of buprenorphine can be reduced daily. Some clients experience greater discomfort as they reach the last few doses of buprenorphine, in which case the minimum dose can be continued for a longer period of time, before finally stopping buprenorphine.

MANAGEMENT AFTER TERMINATION OF BUPRENORPHINE

Following termination of treatment, the client must be educated on the importance of continued follow-up. The follow-up can be frequent initially, once in two weeks or so, and later at a frequency of once in 1–3 months. During such a follow-up, enquiry must be made regarding the client's drug-using status, occupational and familial functioning, as well as re-emergence of withdrawals and craving for opioids. Relapse prevention sessions must be continued during this phase.

Post termination of buprenorphine, the client can remain free of any medication and continue follow-up at the OST centre. In some cases, the client can be started on antagonist maintenance. For antagonist treatment, the tablet naltrexone (at dose of 50 mg/day) should be given once a day. Before starting naltrexone, the client must be free of any opioids for at least 72 hour duration. Unlike buprenorphine or other opioid agonists, naltrexone is not a controlled drug, and can be purchased from local pharmaceutical shops. Antagonist treatment can be continued for a period of 6 – 12 months, during which the client will be fully confident of leading an opioid-free life. The medication can be stopped abruptly and does not require any tapering, unlike the agonist medicines.

If the client relapses at any stage of OST, he/she should be re-initiated on OST after assessment and diagnosis. The principles and practices of OST remain the same as described earlier.

CRITICAL ISSUES IN OST PROGRAMME

- Selection of appropriate clients for OST
- Optimal dosing of buprenorphine
- Proper dispensing procedures
- Attitude of staff: Staff attitude plays an important part in attracting clients to the OST programme and ensuring their retention
- Provision of other services to the OST client
- Stock management: It should be ensured that the stocks of buprenorphine are properly maintained and replenished at regular intervals, so that there is no stock-out situation in the centre
- Record maintenance: The prescribed records should be properly maintained at the OST centre

Further details on the record maintenance and stock management can be found in the document on standard operating procedure

Management of Common Clinical Situations

During OST, a number of clinical situations may be encountered which require management by the service providers of the OST clinic.

VOMITING

Vomiting does not occur commonly with buprenorphine-based OST. Vomiting may occur in the initial period of initiation of buprenorphine, and usually subsides within a few days. The client may be prescribed oral anti-emetics, which can be administered half an hour before taking buprenorphine.

CONSTIPATION

Constipation is a common side effect of buprenorphine-based OST. A client complaining of constipation after buprenorphine initiation should be evaluated to rule out other causes of constipation. If an obvious cause is detected, appropriate treatment should be provided either by the OST doctor or through referral. Enquiry should also be made regarding any symptoms and signs of buprenorphine intoxication, such as increased drowsiness, gait abnormalities, slurring of speech etc. If the symptoms/signs of buprenorphine intoxication are present, a careful reduction in dose may be helpful in relieving constipation. If no organic pathology is detected, conservative measures should be instituted initially. The client may be advised dietary change, increased consumption of water, increased physical activity, etc. If these measures do not improve constipation, the client may be prescribed laxatives. If all of these measures do not help improve constipation, the doctor should then consider decreasing the dose of buprenorphine. In many cases, constipation may be a trade-off – instead of experiencing constipation with the same dose of buprenorphine or undergoing the risk of withdrawal or relapse if the dose is lowered to relieve constipation.

SLEEP DISTURBANCE

Sleep disturbance is common among OST clients, and include delayed initiation in sleep onset, or frequent waking up at nights. Very often, clients inject cocktails of opioids along with other sedative/hypnotics such as chlorphenaramine, promethazine or benzodiazepines. Additionally, the client may be abusing benzodiazepine tablets along with injecting drug use. During OST, while the opioid-related withdrawals are taken care of by administration of buprenorphine, withdrawals related to sedatives are not addressed, which leads to sleep disturbance.

If the client is dependent on benzodiazepines, management of benzodiazepine dependence must be undertaken independent of OST. For sleep disturbance, the client may be educated on sleep hygiene. If these measures fail, the client can be prescribed low dose benzodiazepines (tab. diazepam/nitrazepam 5 – 20 mg at night) or other sleep-inducing medications such as mirtazapine (7.5 – 15 mg at night in tablet form), trazadone (50 mg at night in tablet form), or dothiepin (25 – 75 mg in tablet form). While prescribing benzodiazepines, it must be remembered that clients can also become habituated/dependent on benzodiazepine medications; hence the dose of benzodiazepines must be kept low and should be prescribed for the shortest duration possible.

SLEEP HYGIENE

- Fix the time for going to bed and getting up in the morning
- Avoid afternoon naps
- Have meals 2 hours before sleep
- Avoid stimulants such as coffee, tea or nicotine after sunset
- Avoid stimulating activities such as watching television before going to sleep
- Take light exercise in the evening
- Have a bath with warm water before going to sleep
- Do light reading or listening to music before sleep
- Use the bed only for sleep

MISSED DOSES

As OST is a long-term treatment and requires daily dosing, often clients miss their doses in-between and come back for treatment after a gap of a few days. In such situations, the management will depend on the duration of the missed treatment:

- If the client misses one day's dose of buprenorphine, the client can be given the same dose of buprenorphine as before.
- If the client misses two – three days' dose of buprenorphine, enquiry must be made by the doctor regarding whether the client has consumed any opioids in the intervening period, or whether the client is in withdrawals currently. If the client is in withdrawals, he/she can be given the same dose as before. If the client has consumed any opioids in the intervening period, and he does not have withdrawals currently, the client may be given half the dose of buprenorphine and the dose can be gradually increased depending on the client's response in the subsequent days.
- If the client misses his dose of buprenorphine for more than three days, the same dose of buprenorphine should not be given to the client, as tolerance to opioids can be lost even within three days. The client should be treated as a 'new' client and buprenorphine should be re-inducted, starting from induction phase till the client is stabilised.

Management of Special Clinical Conditions

CO-MORBID HIV INFECTION

Service providers of OST intervention would commonly encounter OST clients who have been diagnosed with HIV infection, and are on ART medications. The following points must be taken into consideration during co-morbid HIV infection:

- All efforts must be made to ensure that every IDU client who is on OST should be referred to ICTC for HIV testing after pre-test counselling. If the client is tested as HIV positive, he/she should be referred to ART centre for registration and for decision on initiation of ART medicines. If the client is HIV negative, he/she should be educated on high risk behaviours and strategies to prevent high risk behaviours as well as HIV prevention during high risk behaviours. The doctor need not wait for the HIV test results before initiation on OST.
- If a client is already diagnosed as HIV positive during the initial assessment, the client can be initiated on OST and referred to ART centre for the initial HIV-related assessment and investigations. The client can be stabilised on OST before initiation on ART, which will help in improved adherence on ART.

Though some drug-drug interactions are observed between buprenorphine and ART medications, these are often not clinically significant to warrant change in dose of either buprenorphine or ART medicines. The doctor should be guided by the clinical signs and symptoms for changing the dose of buprenorphine. If symptoms of opioid withdrawal are noticed or the client complains of discomfort after initiation of ART during OST maintenance phase, the doctor should increase and titrate the dose of buprenorphine as per the client's comfort level. Similarly, the dose of buprenorphine should be decreased if the client complains of excessive drowsiness, slurring of speech, gait instability or other features of intoxication after initiation of ART medicines. A list of ART medicines that can interact with buprenorphine is provided in Annexure A.

TUBERCULOSIS

Tuberculosis is a common comorbid condition among IDUs. Hence, every client should be clinically assessed for tuberculosis during initiation on OST. If there is clinical suspicion, the client should be referred to a TB centre for sputum testing and chest X-ray. The adherence to TB treatment improves if the client is on OST. Some TB medications can have interactions with buprenorphine. Rifampicin is a cytochrome p 350 enzyme inducer and can increase the clearance of buprenorphine. Isoniazid can cause hepatic damage, which in turn can alter the metabolism of buprenorphine. The doctor should titrate the dose of buprenorphine accordingly.

HOWEVER, SUSPECTED TUBERCULOSIS OR CURRENT ANTI-TUBERCULAR TREATMENT BY THEMSELVES DO NOT PRECLUDE WITHHOLDING OR DELAYING INITIATION OF OST.

ADOLESCENTS

While buprenorphine is now considered safe for use in anyone above the age of 12 years, the use of this medication for OST in population aged less than 18 years has not been as systematically studied as for the adult population. Usually, clients from this age-group have short duration of opioid use and even shorter

duration of injecting drug use. As a result, a view held commonly by experts is that detoxification followed by antagonist treatment should be tried initially, and if this strategy fails, agonist medications should be considered. However, others are of the view that adolescents also have a high risk of sharing, overdose and other opioid-related complications, and hence, agonist treatment with buprenorphine should be considered for this population. Moreover, detoxification and antagonist treatments are not available everywhere, hence, it is not possible to wait for a trial of such treatments in every opioid-dependent adolescent.

If a client falls in the age group of less than 18 years, **OST should not be denied straightaway**. A careful assessment of the client's drug use and associated high risk behaviour should be made. Consideration must be given to the duration of opioid use, associated high risk behaviour, especially sharing of injecting equipment and sex-related behaviour. If there is a long history of opioid use (>2 years) along with injecting drug use and associated high risk behaviour, OST with buprenorphine must be considered. There would be issues around obtaining informed consent, as consent from a person less than 18 years may not be considered valid. Hence, consent from either of the parents, or from a guardian (older than 18 years) may be obtained before initiating OST, besides obtaining the 'assent' from the minor client.

FEMALE POPULATION

There are some special considerations with opioid dependent female patients who inject drugs. Females are more vulnerable to HIV and other complications due to injecting as compared to their male counterparts. More often than not, females have a male partner who is also an IDU, as a result of which they have to use the injections and injecting equipment after the male uses them. Some female IDUs resort to sex work to support their drug using habit. In addition, they also have to take care of children, which add to their burden. Female IDUs are often looked down upon by the neighbours and the society, resulting in greater stigma and discrimination. Finally, female IDUs have lesser accessibility to general healthcare services as well as HIV prevention programmes or drug treatment services. The staff of OST centre should bear these vulnerabilities in mind when attending to female IDUs who wish to be initiated on OST.

PREGNANCY AND BREAST-FEEDING

OPIOID SUBSTITUTION THERAPY IS RECOMMENDED FOR PREGNANT WOMEN DEPENDENT ON OPIOIDS.

The process of induction and maintenance is the same as for other patients. Care should be taken to ensure that termination of OST is not attempted in the first and the third trimester due to risk of abortion or pre-term delivery. The dose of buprenorphine may need to be increased in the third trimester due to increased volume of water during the third trimester of pregnancy. However, this should be done by clinical assessment for withdrawals. Buprenorphine should be continued throughout the labour. The dose of buprenorphine may need to be reduced after delivery. Buprenorphine should be continued after the delivery. Breast-feeding can be continued. Even though buprenorphine is secreted in breast milk, the actual amount of buprenorphine entering the infant's blood may not be high due to high first-pass metabolism.

The staff of the OST centre should inform the obstetrician and the neonatologist/paediatrician about the dose of buprenorphine that the client is on during delivery. The paediatrician should be made aware of the possibility of neonate experiencing opioid withdrawals after delivery, termed as Neonatal Abstinence Syndrome (NAS). NAS occurs due to the fact that the child in the mother's womb is exposed to buprenorphine. After delivery, buprenorphine levels fall in the child's blood due to non-availability of buprenorphine resulting in opioid withdrawals. Recent studies have shown that NAS with buprenorphine occurs in about one-third of all deliveries, and is mild to moderate in most cases. The clinical features and management of NAS is provided in Annexure B.

Medical termination of pregnancy should be offered, in case the client is not desirous of a child.

CONSIDERATIONS WHILE PROVIDING OST INTERVENTION TO A FEMALE INJECTING DRUG USER

- Special efforts must be made to make the female IDU comfortable, as females are often reluctant to access services at places with predominant male IDU clients.
- The doctor and counsellor must ensure that the female IDU is examined and interviewed in the presence of a female staff.
- During assessment, enquiry must be specifically made regarding
 - Signs/symptoms of STI, as well as any high risk sexual behaviour
 - Last menstrual period to rule out pregnancy
 - Child-bearing history
 - Examination to rule out the presence of STI
- Female IDUs must be given priority during follow up and dispensing of OST medicines and not made to wait for their turn
- Presumptive STI treatment must be provided
- Contraceptives must be offered to those female OST clients in the child-bearing period and for those not desirous of having children
- Access to other psychosocial supportive services must be made available to those in need
- If the male partner is also an IDU, efforts must be made to initiate the male partner on OST too

Conclusions

Opioid Substitution Therapy (OST) is an effective treatment option for opioid dependence as well as HIV prevention intervention for opioid dependent IDUs. The clinical practice of buprenorphine-based OST is simple and can be delivered by physicians with adequate training. A proper assessment must be conducted, and screening for OST criteria must be done before initiating a client on OST. Buprenorphine is relatively a safer medicine to use. Appropriate client selection, an adequate dose of buprenorphine as well as for an adequate duration is an important determinant of a successful OST intervention. The attitude of staff towards the clients, combined with other issues such as dispensing hours of the clinic, provision of ancillary services are other important determinants of the success of OST intervention.

References

- Ambekar A, Goyal S. Pharmacological treatment of opioid dependence. In: Basu D, Dalal P (eds.) Indian Psychiatric Society Clinical Practice Guidelines for Substance Use Disorders
- Armstrong G, Kermod M, Sharma C, Langkham B, Crofts N. Opioid Substitution Therapy in Manipur and Nagaland, north-east India: operational research in action. *Harm Reduction Journal*. 2010, 7:29
- Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction - a treatment improvement protocol 40. US Department of Health and Human Service, Substance Abuse and Mental Health Service Administration, Centre for Substance Abuse Treatment, 2004
- Connock M, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technology Assessment*, 2007; vol 11, No. 9
- Dhawan A, Jain R, Chopra A. Opioid Substitution – Buprenorphine in India: A study report. United Nations Office on Drugs and Crime, Regional Office for South Asia, 2010
- Dhawan A, Jhanjee S. Manual for long-term pharmacotherapy. National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, 2013.
- Dorabjee J, Samson L. Self and community based opioid substitution among opioid dependent populations in the Indian sub-continent. *International Journal of Drug Policy*, 1998; 9: 411-416
- Effectiveness of drug dependence treatment in preventing HIV among Injecting Drug Users. World Health Organisation, 2005
- Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. World Health Organisation, 2009
- Kumar MS, Natale RD, Langkham B, Sharma C, Kabi R, Mortimore G. Opioid substitution treatment with sublingual buprenorphine in Manipur and Nagaland in Northeast India: what has been established needs to be continued and expanded. *Harm Reduct J*. 2009 Feb 26;6:4.
- Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008 Apr 16;(2):CD002207.
- Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement for opioid dependence. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD002209.
- Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, DePhilippis D, Stolley P, Abrutyn E. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. *J Acquir Immune Defic Syndr*. 1993 Sep;6(9):1049–1056
- Operational guidelines for the management of opioid dependence in the South-East Asia region”, World Health Organisation, Regional Office for South-East Asia, 2008
- Rao R, Ambekar A, Agrawal A. Opioid substitution therapy under National AIDS Control Programme – A situational Analysis. National Drug Dependence Treatment Centre, All India Institute of Medical Sciences. Prepared for Global Fund Round 9 IDU-HIV grant project ‘Hifazat’.
- Rao R, Ambekar A, Yadav S, Sethi H, Dhawan A. Slow-release oral morphine as a maintenance agent in opioid dependence syndrome: an exploratory study from India. *Substance Use and misuse*, 2012; 17: 294-300
- Ray R, Dhawan A, Ambekar A. Implementing Opioid Substitution Therapy - A training manual for service providers. National AIDS Control Organisation, Government of India, 2011.
- Substance Use Disorders, Manual for Physicians. National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, 2013
- WHO/UNODC/UNAIDS position paper. Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention. World Health Organization, United Nations Office on Drugs and Crime, Joint United Nations Programme on HIV/AIDS, 2004

Annexures

Annexure A: Buprenorphine Interactions with Anti-Retroviral Medicines

Anti-retroviral medicine	Effect on buprenorphine	Buprenorphine effect on ART medicine	Clinical considerations
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
No major interactions: No dose adjustment required			
Non- Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Efavirenz & Nevirapine	Reduced concentration of buprenorphine	No effect	Observation required; may need to increase dose of buprenorphine if opioid withdrawal symptoms/signs observed/reported
Protease inhibitors			
Atazanavir	Increased buprenorphine effects	None	Observation required; may need to decrease dose of buprenorphine if opioid intoxication symptoms/signs observed/reported
Ritonavir, Saquinavir, Indinavir, Tipranavir	Potential for increased buprenorphine effects	None	Observation required; may need to decrease dose of buprenorphine if opioid intoxication symptoms/signs observed/reported
Integrase Inhibitors			
No major interactions observed/reported			

Annexure B: Neonatal Abstinence Syndrome

(Adapted from “Operational guidelines for the management of opioid dependence in the South-East Asia region”, World Health Organisation, Regional Office for South-East Asia, 2008)

CLINICAL FEATURES

Babies born to mothers on buprenorphine should be monitored after delivery. Specific assessment tools can be used to track the signs and symptoms of neonatal abstinence syndrome (NAS). Modified Finnegan Neonatal Abstinence Syndrome Score (NASS) can be used for this purpose. The scoring should be initiated two hours after birth and repeated every four hours. Pharmacological treatment is initiated when three consecutive scores average more than or equal to 8, or when two consecutive scores are more than or equal to 12.

Modified Finnegan Neonatal Abstinence Syndrome Score chart for term infants:

System	Signs	Score	Date and time
Central nervous system disturbances	High-pitched cry	2	
	Continuous high-pitched cry	3	
	Sleeps <1 hour after feeding	3	
	Sleeps <2 hours after feeding	2	
	Sleeps <3 hours after feeding	1	
	Mild tremors, disturbed	1	
	Moderate-severe tremors, disturbed	2	
	Mild tremors, undisturbed	3	
	Moderate-severe tremors, undisturbed	4	
	Increased muscle tone	2	
	Excoriation (specify area)	1	
	Myoclonic jerks	3	
	Generalized convulsions	5	

System	Signs	Score	Date and time
Metabolic/ vasomotor/ respiratory disturbances	Fever (37.3-38.3°C)	1	
	Fever (38.4°C and higher)	2	
	Frequent yawning (3-4 times in a row)	1	
	Nasal stuffiness	1	
	Sneezing (>3-4 times in a row)	1	
	Nasal flaring	2	
	Respiratory rate >60/min	1	
	Respiratory rate >60/min with retractions	2	
Gastrointestinal disturbances	Excessive sucking	1	
	Poor feeding	2	
	Regurgitation	2	
	Projectile vomiting	3	
	Loose stools	2	
	Watery stools	3	
Total SCORE			
Scorer's initials			

TREATMENT

General nursing care should be provided. Keeping the baby warm, close contact with the mother, etc. should be provided to the baby.

PHARMACOLOGICAL TREATMENT

Opioids are the preferred medicines of choice. Morphine elixir 1mg/ml can be used to treat NAS. Initiate with 0.02 mg/kg body weight orally at every 4 – 6 hour interval till the desired response. Maintain the same dose for 3–5 days, and then taper by 10% of the total dose every 2–3 days. Vital signs and oxygen saturation should be monitored during opioid-based treatment. Care should be taken not to induce opioid toxicity/overdose in the neonate due to administration of a higher dose of morphine. Morphine overdose may manifest as narcosis, poor reflexes, decreased suckling, and poor response to pain, and can lead to coma, decreased breathing, hypothermia and bradycardia. In such cases, respiratory support should be provided; naloxone should be avoided as it can cause withdrawal seizures.

Sedatives are the second choice for treatment of NAS. Control of symptoms and seizures are not as effective as with opioids. Phenobarbitone 5 mg/kg/day in two divided doses can be given.

The neonate should be hospitalised till 4 weeks of delivery along with the mother for complete recovery. Breastfeeding must be continued in the meantime.



India's voice against AIDS

Department of AIDS Control
Ministry of Health & Family Welfare, Government of India
www.naco.gov.in