National AIDS Control Organisation

India's response to HIV & Sexually Transmitted Infections

Ministry of Health & Family Welfare, Government of India

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CLINICAL PRACTICE GUIDELINES FOR

Buprenorphine based Opioid Substitution Therapy under NACO

THIRD EDITION

Opioid Substitution Therapy (OST) under National AIDS Control Programme – Clinical Practice Guidelines for treatment with Buprenorphine

THIRD EDITION

Third Edition

YEAR OF PUBLICATION: 2021

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TABLE OF CONTENTS

ABBREVIATIONS

ANM	Auxiliary Nurse Midwifery
ART	Anti-Retroviral Treatment
CHC	Community Health Centre
DAA	Directly Acting Antiviral
DIC	Drop-in Centre
DOTS	Daily Observed Treatment Strategy
HIV	Human Immunodeficiency Virus
HRGs	High Risk Groups
ICTC	Integrated Counselling and Testing Centre
PWID	People Who Inject Drugs
MAT	Medication Assisted Treatment
NACP	National AIDS Control programme
NAS	Neonatal Abstinence Syndrome
NDPS	Narcotic Drugs and Psychotropic Substances
NGOs	Non-Governmental Organisations
NSP	Needle Syringe Programme
OAT	Opioid Agonist Maintenance Therapy
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 Organization

INTRODUCTION

Drug use by injection route is an important factor in the transmission dynamics of HIV epidemic in India. HIV in India is a concentrated epidemic, i.e., concentrated in certain geographical areas and among certain population groups. These population groups, designated as High-Risk Groups (HRGs), have a much higher prevalence of HIV as compared to the general population. As per the last HIV sentinel surveillance report 2017, HIV prevalence among People Who Inject Drugs (PWIDs)[1] is 6.26 % nationally, which is the highest among any of the high risk groups [1].It is to be noted that this highest HIV prevalence in PWID compared to other HRGs has been present consistently since the past till now [1,2]. The latest HIV estimations Report (2019) also reports HIV incidence rates to be high among PWID. The incidence of HIV among PWID is highest in Uttar Pradesh (16.4%), followed by Bihar (9.7%), Maharashtra (3.71%), Delhi (3.61%), Haryana (3.51%) and Jharkhand (3.04%)[3]. Drug use by injection route not only increases the risk of acquiring HIV infection, but it can also adversely affect the course of the HIV infection. Active drug use is associated with delayed initiation of HIV treatment as well as reduced treatment adherence to anti-retroviral treatment, and lower retention in treatment. All of these in turn can lead to lower rates of viral suppression.

There are an estimated 8.5 lakhs PWID in India according to the recently reported National Survey on the magnitude of substance use in India. The highest number of PWID population live in Uttar Pradesh (1,00,113), Punjab (88,165), Delhi (86,909), Andhra Pradesh (69,916) and Telangana (64,000). PWID in India predominantly use opioids(96%) by the injection route, with heroin and pharmaceutical opioids being the most common opioids being injected[4].

Thus, there is a substantial burden of injecting drug use in the country. PWIDs have the highest prevalence of HIV compared to other HRGs. Injecting drug use not only increases the risk of HIV transmission, but also leads to adverse effect on HIV treatment adherence and retention.

A. NATIONAL STRATEGY FOR HIV PREVENTION AMONG PEOPLE WHO INJECT DRUGS

Globally, “harm reduction” approach is employed to manage HIV prevention among PWIDs. Harm reduction approach is based on the premise that it is more important to focus on reducing the harms associated with drug use as compared to quitting drug use. The strategy offers an effective alternative approach for continuous engagement and HIV prevention among PWIDs, especially among 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, thus, becomes an important focus of harm reduction.

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 of Sexually Transmitted Infections (STIs)
6. Condom programme for People Who Inject Drugs and their sexual partners
7. Targeted Information, Education and Communication
8. Prevention, diagnosis and treatment of Tuberculosis
9. Prevention, vaccination, diagnosis and treatment of Viral Hepatitis
10. Prevention of overdose deaths

Various interventions are found to be useful and effective for HIV prevention among PWIDs. The WHO and UNODC have recommended a set of interventions called as the ‘Comprehensive Package of Interventions’ or

the 'Comprehensive package of Health Services' that are found to be effective and necessary for the HIV prevention, treatment and care of PWID[5,6]. The core interventions among these include – Needle Syringe Exchange Programme (NSP), Opioid Agonist Maintenance Therapy (OAT) also called as 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 as well as by the National Narcotic Drugs and Psychotropic Substances (NDPS) policy 2012. National AIDS Control Organisation (NACO) is the nodal agency responsible for implementing and coordinating HIV prevention, care, and treatment response in India. NACO follows a 'targeted intervention (TI)' approach for HIV prevention among all HRGs, including PWIDs. The targeted intervention approach entails providing specific interventions aimed at HRGs through outreach and peer-based delivery. In the 'outreach' model, services are 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 reach out to HRGs much more efficiently as compared to the traditional service delivery systems. For HIV prevention among PWIDs, 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 per the status in April 2021, there are a total of 327 PWID TIs throughout the country reaching out to 1.49 lakh PWIDs. Programmatic data shows that there is a substantial increase in commodity distribution, number of needle/syringes distributed per PWID, referrals for HIV testing, etc.

B. OPIOID SUBSTITUTION THERAPYUNDER NATIONAL AIDS CONTROL PROGRAMME

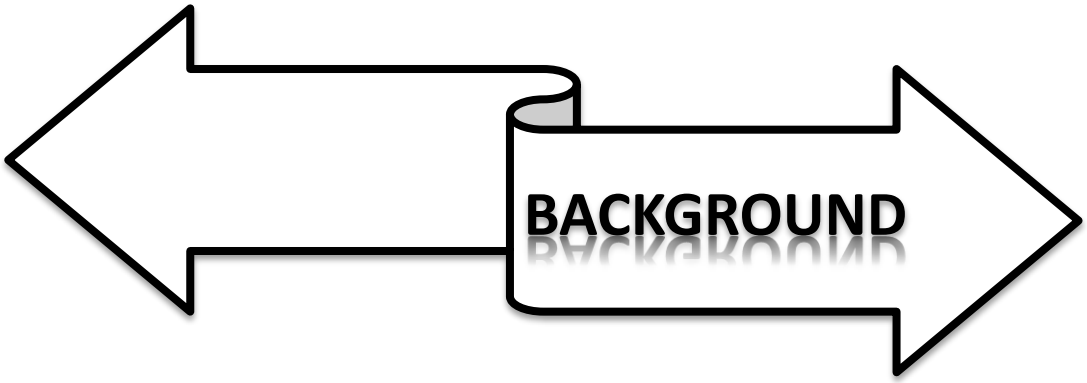
OST as a HIV prevention strategy among PWIDs was formally integrated in National AIDS Control Programme (NACP) in 2007. Before formal integration, OST for HIV prevention among PWIDs was implemented in India by some NGOs. After a formal approval for OST implementation was obtained, mechanisms for financial support to the NGOs implementing TI projects were set up. Various documents for standardisation and quality assurance have been developed by NACO, including *Clinical Practice Guidelines for Buprenorphine (current document)*, *Standard Operating Procedures, Training Manual* and *Quality Assurance Manual*. Currently, two models of providing OST services exist under the NACP. In the NGO-based model of OST, the OST centres located within the Drop-in-Centre (DIC) of an PWID TI are managed by the staff implementing the PWID 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. As of April 2021, 46 OST centres are operational within this model.

Since 2010, the predominant model of OST delivery under the NACP is the collaborative Government hospital – NGO model. In this model, the OST centre is located within the government hospital and is managed by a full-time staff comprising of a doctor, nurse, counsellor, and a data manager. The staff of the OST centre works under the direct supervision of a designated 'nodal officer', a senior doctor (usually a psychiatrist) who is a full-time employee of the hospital. The OST centre is linked with an PWID TI located in the vicinity of the hospital for initial referral of PWID clients to the centre, as well as field-based follow-up and advocacy. Currently, there are 187 OST centres in the country operating through the collaborative model. Apart from these, there are around 58 Satellite OST centres as well. Satellite OST centres have been established to improve the access of OST services to PWIDs who are staying at places far away from the existing OST centres. Satellite centres have also been established in areas where the main OST centre has high client load, to

decongest the main OST Centres. Satellite OST Centres are not stand-alone centres but are always established in link with a main OST Centres.

About the document...

- *The clinical practice guidelines are intended to be used by the staff implementing OSTinterventions supported under the National AIDS Control Programme.*
- *This edition of the Clinical Practice Guidelines supersedes the earlier edition, published in 2015.*
- *While all staff members (including those of linked PWID 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 NACO.*
- *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 NACO.*
- *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 the clinical and programmatic experience from India.*


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 PWID. Some researchers opine that a person who has injected even once in his/her lifetime is an PWID, while others define an PWID as someone who has injected at least once in the past 12 months. In India, for programmatic purposes, **NACO defines an PWID 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 on the recommendation of experts working in the field in India.

B. DRUGS INJECTED BY PWIDs IN INDIA

Though theoretically, as per the definition, an PWID may use any psychoactive substance through injecting route, research conducted thus far has shown that in India, **a vast majority of the PWIDs inject 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 till the recent past, 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 chlorpheniramine[2,3] or promethazine. The other substances are combined with opioids to enhance the pleasure of opioids or due to perceptions existing among PWIDs regarding their positive effects.

OPIOIDS

Opioids are a group of psychoactive substances that are similar in actions 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, Pentazocine

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

[2]The commonly available brands of the pharmaceutical substances are –
Buprenorphine: Norphine, Lupigesic, Tidigesic, Sangesic, etc.; Pentazocine: Fortwin; Chlorpheniramine: Avil; Promethazine: Phenergan

[2](*Disclaimer: Use of the brand names above are in no way pejorative, or incriminatory of a particular brand.)*

The choice of opioids for injecting differs from one region to another. Overall, at the national level, almost half of PWIDs prefer injecting heroin while the rest prefer injecting one of the pharmaceutical opioids (predominantly, injection buprenorphine). Regarding the regional variations, in the north-eastern region, heroin (known locally as 'number four') (and till recently 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 Punjab and adjoining areas of northwest India, heroin (known locally as 'chitta') appears to be the preferred substance among PWIDs. In states such as Karnataka, Andhra Pradesh, Chhattisgarh, etc., pentazocine is commonly injected. 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 and pentazocine) which are also manufactured and sold in pharmacies/chemist shops due to their medicinal value. Notably, buprenorphine is mostly injected in its injectable form; the practice of injecting crushed, sublingual tablets of buprenorphine, appear to be uncommon, so far, but does exist[7].

C. SUBSTANCE USE DISORDERS

It must be remembered that 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 PWID must be dysfunctional enough to warrant a medical diagnosis for which a treatment needs to be advised. Under the International Classification of Diseases – 11th revision (ICD-11), there are three distinct diagnostic entities of dysfunctional use of substances:

- **Single episode of harmful use of substance**: A single episode of use of substance that has led to damage to a person's physical or mental health or has resulted in behaviour leading to harm to the health of others.
- **Harmful pattern of use of substance:** A pattern of use of substance over a period of at least 12 months, that has led to damage to a person's physical or mental health or has resulted in behaviour leading to harm to the health of others.
- **Substance dependence:** Substance dependence is a disorder of regulation of substance use arising from repeated or continuous use of substance. The characteristic feature is a **strong internal drive** to use substance, which is manifested by **impaired ability to control use**, **increasing priority given to use** over other activities, and **persistence of use despite harm or negative consequences**. These experiences are often accompanied by a subjective sensation of **urge or craving** to use substance. Physiological features of dependence may also be present, including **tolerance** to the effects of substance, **withdrawal symptoms** following cessation or reduction in use of substance, or repeated use of substance or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. The features of dependence are usually evident over a period of **at least 12 months**. However, the diagnosis may be made if substance use is continuous (daily or almost daily) for at least one month.

  The withdrawal symptoms differ from one chemical class of substance to another. Thus, for example, a typical withdrawl syndrome for any alcoholic beverage (whisky, 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 syndromeis that they tend to immediately subside once the individual re-starts using the same (or similar) substance. Thus, an alcohol dependent person experienceing withdrawal would start

feeling better after drinking and an opioid dependent person would feel relieved after taking the next dose of opioids.

DEPENDENCE SYNDROME

For making a diagnosis of dependence syndrome for a given substance, the following features should be **present over a period of at least 12 months (diagnosis can also be made if substance use is continuous for at least a month):**

- Characteristic feature: Strong internal drive to use substance manifested by
  - Impaired ability to control use
  - Increasing priority given to use over other activities
  - Persistence of use despite harm or negative consequences

- Accompanied by
  - Subjective sense of urge or craving
  - Tolerance to the effects of substance
  - Withdrawal symptoms

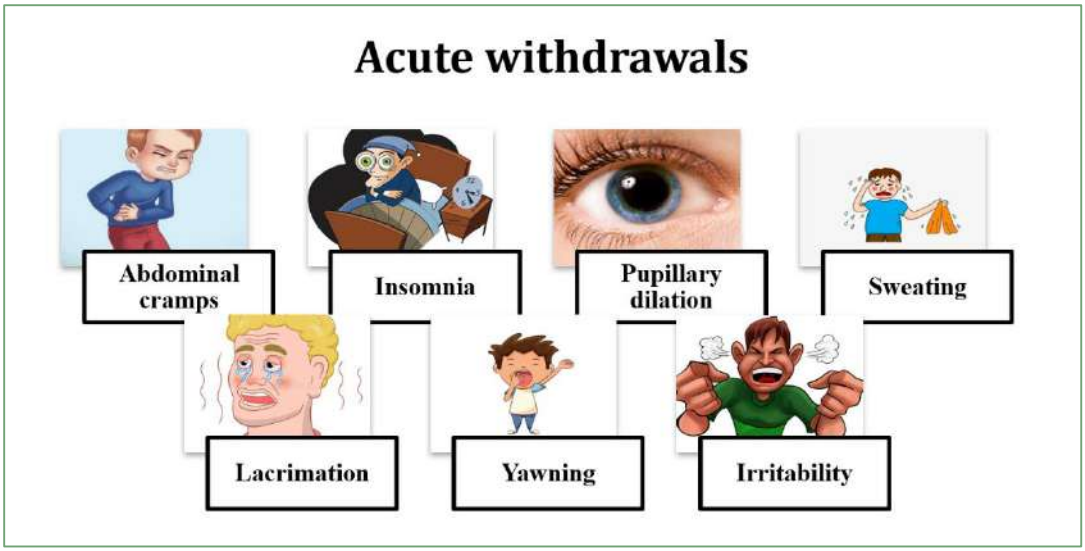
(Adapted from ICD-11 guidelines)

In case of use of more than one substance simultaneously, it is not necessary for the user to be dependent on all the substances; the user may be dependent on one substance, while at the same time, not have dependence on another substance. For e.g., an indivPWIDal using opioids as well as alcohol may be dependent on opioids, while using alcohol in a non-dependent pattern.

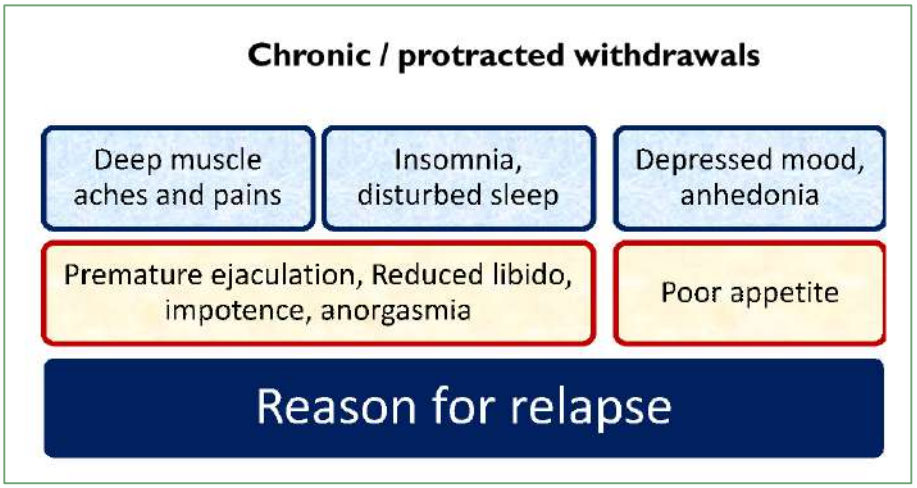
D. OPIOID DEPENDENCE SYNDROME

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

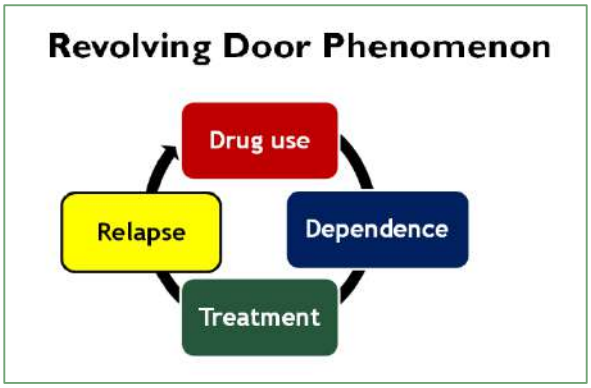
- **Acute withdrawal:** Opioids as a group produce a typical physical withdrawal syndrome on a short-term basis, upon reducing or stopping or even delaying the intake of usual quantity of opioid drugs. These withdrawal symptoms include *lacrimation* (tears from the eyes), *rhinorrhoea* (runny nose), *yawning, diarrhoea, muscle cramps, sweating, muscle aches and pains*, etc. Along with these symptoms, other symptoms include *anxiety, restlessness, insomnia* (inability to sleep), *irritability* as well as *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 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 does not resume using opioid drugs.



- **Protracted withdrawal:** In most patients with opioid dependence, even after the acute withdrawals have 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 the reason of relapse in a number of opioid users.

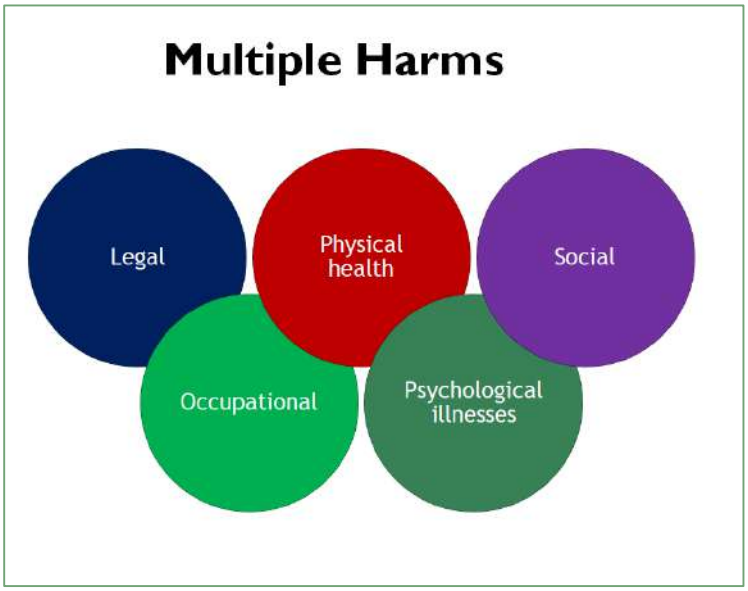


- **Relapsing nature of illness:** As is true of other substance use disorders, especially dependence syndromes, ODS is also characterized by repeated relapses and remissions. An individual may restart using opioids after a period of abstinence. Such relapses and remissions are a feature of Opioid dependence 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 earlier, opioids can be used through injecting route, and many PWIDs resort to sharing of needle/syringes or other injecting equipment. Injecting is a well-documented means of transmission of blood borne viruses, including HIV, Hepatitis B and C, as a result of which the prevalence of HIV and Viral Hepatitis among PWIDs is very high. Additionally, individual users may also have high risk sexual behaviours resulting in transmission of HIV through sexual route to their sexual partners.

- **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 inhumane treatment / physical torture.



E. INJECTING DRUG USERS – RISK AND VULNERABILITY

- **Injection-related risky behaviours:** PWIDs are prone to sharing needles, syringes, and other injecting paraphernalia. The sharing related behaviour may be due to several factors, such as non-availability of needles/syringes, non-affordability of needles/syringes or due to prevalent practices in their group/peer norms, etc. Apart from sharing, there may be reuse of needles/syringes. These behaviours

lead to various complications including abscesses, blocked veins, and transmission of blood-borne viruses such as hepatitis C, B and HIV.

- **Sex-related risky behaviours:** PWIDs also engage in high-risk sexual behaviours including sex with sex workers, sex without condoms, and sex with multiple partners. They may also sell sex in exchange for drugs or money. These behaviours put PWIDs 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 PWIDs in India use opioids as the primary drugs for injecting; studies also show that **almost all PWIDs 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 or craving that compel him/her to continue / restart the use of drugs. As a result, the PWIDs suffer from harms resulting from opioid dependence in addition to the above-mentioned injection and sexual practices related risks. An additional vulnerability of concern among PWIDs is of 'Overdose'. If a person takes a heavier dose of drugs than what the person is accustomed to, this may result in serious intoxication and overdose, which is a potentially fatal, medical emergency.

F. MANAGEMENT OPTIONS OF OPIOID DEPENDENCE

Opioid dependence is a chronic, relapsing disorder where a patient undergoes multiple relapses and remissions, similar to that for other non-communicable diseases like Diabetes, Hypertension, etc.[8] Opioid detoxification provides only short-term treatment of opioid dependence and helps to manage the acute withdrawal symptoms. However, it is associated with high rates of relapse. Long term treatment is hence necessary for management of opioid dependence. The two long term treatment options currently are opioid antagonist maintenance and opioid agonist maintenance therapy.

In opioid antagonist maintenance therapy, an opioid antagonist (Naltrexone) is provided for long period of time. As the antagonist occupies the opioid receptors, it blocks the action of opioid agonists (for example, illicit

opioids like Heroin) taken by the patient. As a result, patient does not get to feel the euphoria or intoxicating effects of opioids. This in turn, reduces the likelihood of the individual using illicit opioid again and thus, prevents relapse. However, antagonist treatment is not effective in controlling the craving to opioids[9] as well as in managing protracted withdrawals. As a result, there is a high degree of non-compliance and drop out from treatment. Antagonist maintenance is suitable for patients with shorter duration of opioid use (less than one year of use), those who do not have any major medical or psychiatric comorbidity and have high level of motivation (as they need to withstand opioid craving and protracted withdrawals) and have good psychosocial support.

However, most injection drug users who inject opioids usually have a long history of opioid use as well as develop complications in various domains of life – psychological, physical, social, occupational, etc. by the time they are ready to seek help for their injecting. In such cases, agonist maintenance therapy will be the most effective treatment options. In agonist maintenance therapy, people with opioid dependence are provided with long-acting opioid agonist medications (for example, methadone, buprenorphine and slow-release oral morphine) for a long period of time under medical supervision. The next section will describe in detail the concept behind the Opioid Substitution Therapy (OST).

OPIOID AGONIST 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, opioid agonist 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 people with opioid dependence are provided with long-acting opioid agonist medications for a long period of time under medical supervision and along with psycho-social interventions. Short term treatment of opioid dependence lasting for a couple of weeks known as 'detoxification' which involves management of acute withdrawals alone, is associated with high rates of relapse. Long term treatment is hence necessary for opioid dependence. OST is one such long term treatment option.

The lives of PWIDs who suffer from opioid dependence revolve around illicit opioid use. Most part 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 are usually short acting, 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 illegal activities to finance their drug use. OST addresses many such issues faced by the PWID 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 or craving. Due to these effects, the client does not need to use opioids to produce relief of withdrawals or craving.

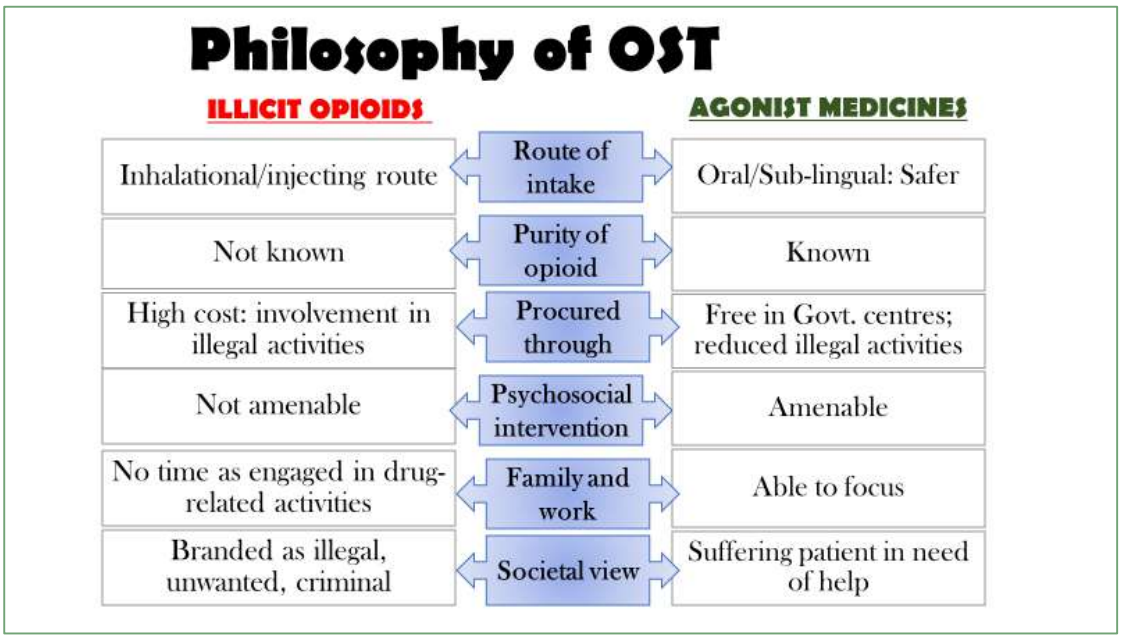
- As compared to the illicit opioids that act quickly and for a short period of time, **opioid medicines used for OST act slowly and for a long period of time (for at least 24 hours)**. As a result, the client does not have to spend time on procuring or using opioids multiple times a day and can focus 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 PWIDs are due to the injecting route of administration. On the other hand, **opioid medicines used for OST are administrated orally or sublingually, which is a much safer route**. This saves the client from incurring harmful effects of opioid use like blood borne infections, abscesses, blocked veins etc.

- As the PWIDs procure the opioids through illegal channels, often, 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, PWIDs 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 as well as reduces instances of petty crimes like thefts, etc. in the society.

- During the illicit drug use phase, PWIDs are often branded as anti-social or criminal by the families and the society. When on OST, such PWIDs are seen as a sufferer and a 'patient'. 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 benefits and outcomes on 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.

BENEFITS OF OPIOID SUBSTITUTION THERAPY

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

OSTRELATED 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 in treatment and in suppression of heroin use[10].
- 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[11].
- 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[12]

- A report by World Health Organisation, 2005, reviewed many studies conducted in different parts of the world and concluded that opioid substitution treatment is a critical component of HIV prevention, and helps in reducing opioid dependency and HIV infection rates.
- A systematic review and Cost effectiveness study by Connock in 2007 reported the following[13]:

  (1) All doses of methadone or buprenorphine were more effective in retention as compared to placebo or no therapy

  (2) OST using methadone or buprenorphine in higher doses were more effective in reducing illicit opioid use compared to lower doses

  (3) A meta-analysis of observational studies spanning publication of 21 years showed that patients on OST using methadone were four times less likely to die than those not in treatment

  (4) 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 cost and theft alone. When savings related to health care are included, total savings can exceed costs by a ratio of 12:1"
- A recent meta-analysis reported that OST was associated with 69% increase in recruitment onto ART, 54% increase in ART coverage, 2-fold increase in adherence, and 23% decrease in the odds of attrition along with 45% increase in odds of viral suppression [14]
- A recent Cochrane review suggested 50% reduction in HCV acquisition risk among those on OST[15]
- Another meta-analysis suggested a reduction in all-cause mortality and overdose mortality among those on Methadone or Buprenorphine assisted treatment[16]
- A recent comparative effectiveness study of 40885 adults with opioid use disorder that compared 6 different treatment pathways (No treatment, inpatient detoxification or residential services, intensive behavioural health, buprenorphine or methadone, naltrexone, or non-intensive behavioural health) reported that only treatment with buprenorphine or methadone was associated with reduced risk of overdose during 3-month and 12-month follow-up period[17]

OSTRELATED OUTCOMES – INDIAN EVIDENCE

As buprenorphine has been the most common OST medication used in India, much of the evidence in India exists for buprenorphine; some evidence exists for slow-release oral morphine, and recently for methadone also.

- A study which described the experience of implementing buprenorphine-based OST in a community setting in New Delhi, reported that 33% of 447 PWIDs on buprenorphine

stopped injecting, and 35% of those injecting had reduced their frequency of injecting and sharing while on treatment[18].

- A study that reported about the OST intervention implementation in Manipur and Nagaland covering 1200 PWIDs found the OST to be acceptable to the clients, their families, general community, religious leaders as well as militant groups[19].
- A study 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. The study also reported statistically significant improvements in relation to sharing of needles, unsafe sex, detention incidents, and quality of life measures[20].
- A multi-site study 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[21].
- A study conducted across 42 OST Centres s in India showed that OST was being implemented in accordance with the NACO prescribed guidelines and majority of the clients reported satisfaction with their treatment[22].
- Studies on Slow Release Oral Morphine (SROM) conducted in New Delhi have shown that SROM was associated with decrease in illicit opioid use, improved functioning and reduction in illegal activities[23]
- A research on methadone implementation across five centres in India showed that it is feasible to implement methadone for PWIDs in India, and is associated with improved functioning and reduced opioid use[24]
- A study comparing buprenorphine, naltrexone and psychosocial intervention reported buprenorphine maintenance to be 4.5 times more effective than naltrexone maintenance and seven times more effective than psychosocial intervention alone [25].
- A recent study reported 35% retention on buprenorphine at the end of 6 years in a community outreach clinic in New Delhi[26].

OST: AN EVIDENCE-BASED TREATMENT FOR OPIOID DEPENDENCE ROOTED IN HARM REDUCTION

Substance use disorder, including opioid dependence, is a complex disorder that affects various dimensions of life – physical, psychological, social, familial, financial, occupational and legal. Hence, for a person with opioid dependence to overcome all these complications successfully, it typically takes a long period of time (usually in years). Hence, the treatment also is required for a long duration.

'Opioid Substitution therapy', or the 'Opioid Agonist Maintenance therapy' is a treatment modality, where the individuals with opioid dependence are provided with medically supervised long-acting opioid agonist (or partial agonist) for a long period of time, which helps the individuals in controlling their craving and withdrawals to opioids. This, in turn, enables the individuals to be able to remain abstinent from the illicit opioids.

While OST has been largely considered as only a 'Harm reduction' approach among PWIDs in the past, that helps to reduce the harms related to injection drug use, like reduction in transmission of blood borne viral infections including HIV and Hepatitis, emerging evidences and experiences of multiple decades of use of OST around the world have unequivocally proven the effectiveness of this therapy in also reducing and stopping the use of illicit opioids, improving the individual's productivity and improving the individual's quality of life. Hence, OST is increasingly being endorsed and recommended as one of the most effective and first-line treatment options for long-term pharmacotherapy of opioid dependence, beyond being just a harm reduction strategy aimed at HIV prevention[29,30].

While OST is an evidence based and effective long treatment option for opioid dependence for irrespective of the route of intake of opioids, under the National AIDS Control Programme, OST is being provided only to People who inject drugs.

KEY CHARACTERISTICS OF OPIOID SUBSTITUTION THERAPY

The practice of OST is based on various 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 associated 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 higher the dose, 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 assist them to improve other areas of functioning, such as familial, social and occupational. As the clients settle in their functioning and are ready, the treatment can be tapered gradually 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, minimising treatment drop-outs, assisting clients in rebuilding family and social ties and 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, duration of treatment and endpoint of treatment. These decisions, if taken along with client, help in improving client retention and outcome on OST.

OPIOID AGONIST 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 **lower 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 it is possible to administer the medicine once in a day.

- 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 that it is possible to scale-up OST with less financial or logistic constraints.

Pharmaceutical compounds commonly used as OST medicines

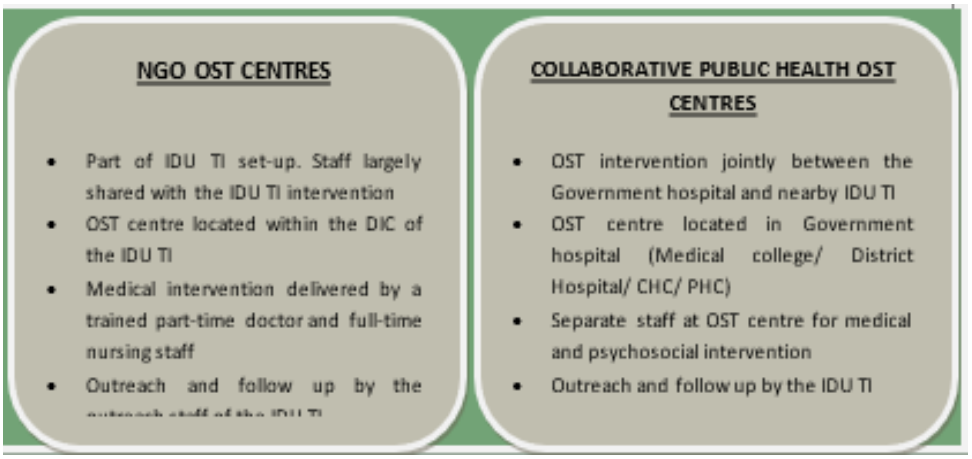
- **Methadone:** Methadone was the first and currently, the most common opioid used as OST medicine globally. Methadone is a pure opioid agonist, available for oral use either as liquid or as tablet.
- **Buprenorphine:** Buprenorphine is a partial opioid agonist available for use usually as a sublingual 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 tablet.
- **Others:** codeine phosphate, tincture of opium

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 at a few sites in India, largely outside the NACP.

STATUS OF OPIOID AGONIST THERAPY IN INDIA

In India, OST has been available since the early nineties, when the use of buprenorphine began in some Government hospitals as well as in some NGO settings. While the OST was available uninterruptedly in few Government hospitals for both PWID as well as non-PWID opioid dependent users, the availability in NGOs was dependent upon funding from donor partners and restricted to only PWID population (as a HIV prevention tool). The NGO OST Centres s were subsequently supported under NACP, while the Government centres continued to provide OST for individuals with opioid dependence through funding from Ministry of Health and Family Welfare.

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



Drug Treatment Clinics (DTC) under Drug De-Addiction programme of Ministry of Health and Family Welfare have also established centers providing buprenorphine maintenance in government healthcare facilities. More recently, Addiction Treatment Facilities (ATF) are being established by Ministry of Social Justice and Empowerment in Government Health care settings, where buprenorphine maintenance treatment will be provided for people with opioid dependence along with treatment for other substance use disorders. Similarly, the Punjab government has also established Out-patient Opioid Assisted Treatment (OOAT) centers in government healthcare facilities. Finally, quite a few private sector facilities, including some psychiatrists running their clinics, also provide OST with buprenorphine.

BUPRENORPHINE – BASIC PHARMACOLOGY

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

CLASSIFICATION BASED ON THE ACTIONS ON OPIOID RECEPTORS

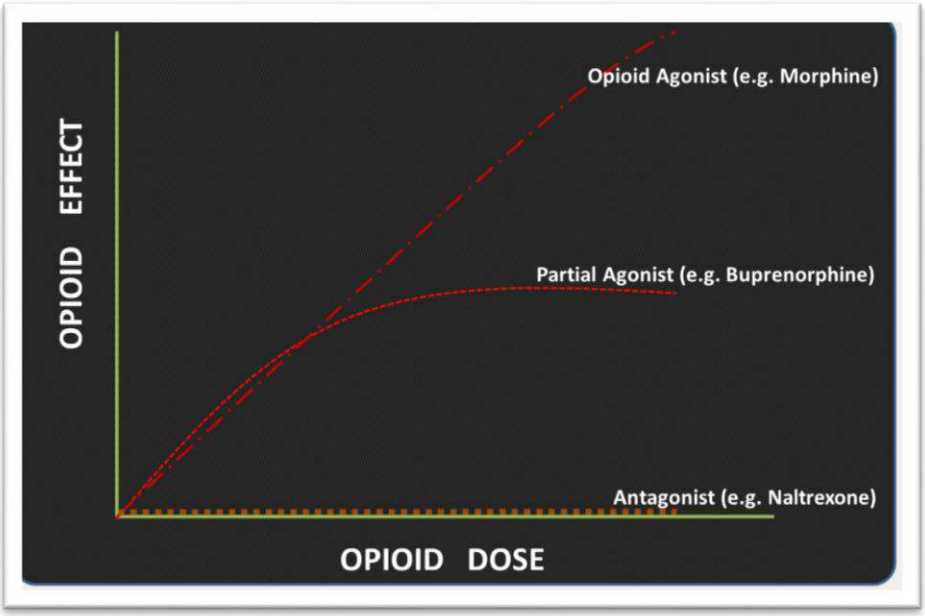
- **Agonists:** Opioid agonists bind to and activate the mu receptors, thereby exerting 100% action producing opioid-like effects. Examples of opioid agonists include: morphine, codeine, heroin, and methadone.
- **Partial agonists:** Partial agonists exert less than 100% action on the mu receptors producing 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. Examples of antagonists include Naloxone and Naltrexone.

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.

PHARMACOLOGY

The pharmacological properties of buprenorphine and 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 partial agonist is similar to that of full agonist. As the dose increases, the effects of both partial agonist and full agonist are increased. However, beyond a certain dose-point, further increase in buprenorphine dose not increase opioid effect. This is called as ***'ceiling effect'***. The figure below illustrates the point.
  Clinical implication: *The chances of overdose-related respiratory depression and death are minimal with higher doses of buprenorphine. This is unlike pure agonists, where higher doses can result in overdose related death due to respiratory depression.*



- Buprenorphine has **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 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 effect depends on the dose administered: lower doses of 2 mg of buprenorphine produces clinical effect for up to 12 hours while higher doses of 16 mg can produce effect lasting up to 48 hours.
  Clinical implication: *At appropriate 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 liver, and is converted into nor-buprenorphine and other products through the cytochrome P450 3A4 enzyme. The metabolites do not have 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 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 accidently 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 adjoining 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 initial days)
- Dizziness
- Headache
- Sweating

Buprenorphine has no major effect on hepatic functioning. Buprenorphine does not have 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 initial few days during dose induction or during increase in doses.

DRUG INTERACTIONS

Drug interactions with buprenorphine can occur due to action of buprenorphine on opioid receptors or due to 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 COPD, pneumonia, etc.

- **Opioid agonists:** Buprenorphine prevents other opioid agonists from exerting their effect due to its strong affinity to opioid receptors; conversely, buprenorphine displaces the other opioid agonists resulting in precipitated withdrawals, as described above.

- **Hepatic enzyme inducers or inhibitors:** as mentioned above, buprenorphine is metabolised in 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 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)***	**COMMON MEDICATIONS INHIBIT CYTOCHROME P450 3A4 ENZYMES** ***(Buprenorphine dose may have to be decreased)***
• **Anti-epileptics:** Carbamazepine, Phenobarbital, Phenytoin • **Anti-tubercular drugs:** Rifampicin • **Anti-retrovirals:** Efavirenz, Nevirapine	• **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, Hepatitis B and C
- **Abdominal conditions:** irritable bowel syndrome and other colonic conditions
- **Urological conditions:** conditions causing urinary retention
- **Others:** Pheochromocytoma, Hypothyroidism

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

ABUSE LIABILITY

As buprenorphine is an opioid receptor partial agonist, it is liable to be used in the non-medical, recreational context. In individuals who are not dependent on opioids, buprenorphine use through sublingual route produces euphoria and other opioid like effects, thus increasing the abuse liability of buprenorphine tablets. Among many drug users, buprenorphine (injectable) is often the preferred opioid used for injecting in India. As sublingual buprenorphine tablets are easily dissolvable in water, they 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 dispensed as Directly Observed Treatment only unless the person fulfils the eligibility criteria for take home dispensing. However, it must be remembered that abuse liability of buprenorphine is significantly lower as compared to full agonists like heroin or morphine.

DIFFERENT FORMULATIONS OF BUPRENORPHINE SUBLINGUAL TABLETS IN INDIA

As sublingual tablets, buprenorphine is available in strengths of 0.2 mg, 0.4 mg and 2 mg. Another sublingual formulation of buprenorphine available is in a fixed dose combination of 4:1 with naloxone. Buprenorphine-Naloxone (BPN-N) sublingual tablets are available in strengths of 0.4mg/0.1 mg (i.e., 0.4 mg Buprenorphine + 0.1mg Naloxone) and 2 mg/0.5 mg (i.e., 2 mg Buprenorphine+0.5 mg Naloxone) in India.

When taken sublingually, naloxone is not active and hence, BPN-N tablets will produce same effects like the plain buprenorphine tablet formulation. However, when BPN-N tablet is injected, naloxone will, most likely, produce a clinically significant effect. As naloxone is an opioid receptor antagonist, it can attenuate the effects of buprenorphine in the short term, and may even produce withdrawal symptoms which can deter the patient from injecting BPN-N tablets and prevent diversion of the tablets to injection route. Thus, BPN-N sublingual tablets are expected to have a lesser risk of diversion for use through injection route compared to plain buprenorphine tablets.

It is important to note that both these formulations contain same amount of Buprenorphine at the same strength. Thus, the formulations of buprenorphine and BPN-N sublingual tablets are clinically interchangeable (thus, any patient on plain buprenorphine sublingual tablet can be shifted to BPN-N sublingual tablet of same strength at any time without a need for dosage adjustment and vice versa).

OTHER FORMULATIONS OF BUPRENORPHINE IN INDIA

Currently in India, apart from the sublingual tablet formulations mentioned above, buprenorphine is also available in injectable and transdermal patch forms. The injectable form is commonly available as 2 ml ampoules with each ml containing 0.3 mg of buprenorphine. The transdermal patches are available as 5 mg, 10 mg and 20 mg patches, which release buprenorphine at rates of 5mcg, 10 mcg and 20 mcg per hour respectively, over a period of seven days. The injectable form and transdermal forms are predominantly used as analgesics.

LEGAL STATUS OF BUPRENORPHINE IN INDIA

Buprenorphine is classified as a ‘psychotropic’ under Narcotic Drugs and Psychotropic Substances (NDPS) Act. Under NDPS Act, narcotics and psychotropics can be used for medical and scientific purposes. Buprenorphine is covered under Schedule H1 in the Drugs and Cosmetics Act 1940, and Drugs and Cosmetic Rules 1945 which means that it can be sold by pharmaceutical chemists only on production of a valid prescription. The chemist will maintain a register with details of patient, contact details of doctor and the dispensed quantity of drug

and the register has to be retained for at least three years. Earlier, the higher strengths of the sublingual tablet formulations of buprenorphine (both the buprenorphine and BPN-N) were approved for supply only to designated de-addiction centres recognised as such by the government. However, these restrictions have been eased recently. In 2019, the Central Drugs Standard Control Organisation (CDSCO) issued a notice to all state /UT drugs controllers, allowing the supply of sublingual buprenorphine and BPN-N tablets to psychiatric clinics and hospitals also, in addition to the above facilities.

Thus, the plain buprenorphine sublingual tablets (0.4 mg and 2 mg tablets) and BPN-N tablets (2/0.5 mg) formulations are approved for the purpose of treatment of opioid dependence and are made available only in Government recognised drug treatment/de-addiction centres or in psychiatric clinics and hospitals.


CLINICAL
PRACTICE
GUIDELINES
FOR OST CENTRES S
UNDER NACP

The Opioid Substitution Therapy(OST) intervention under NACP is conceptualised as follows:

OSTINTERVENTION UNDER NATIONAL AIDS CONTROL ORGANISATION

- OST is a strategy for prevention of HIV transmission among Injecting drug users (PWIDs) with opioid dependence.
- Currently, the predominant medicine available for OST is buprenorphine.
- OST is a medical intervention in which a doctor initiates OST and nurse dispenses the medicines.
- Buprenorphine is to be dispensed initially on daily basis as a 'Daily Observed Treatment' regimen. Once the clients reach clinical stability, they may be allowed carry-home buprenorphine.
- Fixed dose combination of Buprenorphine+ Naloxone sublingual tablets can be dispensed as take-home medications.

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

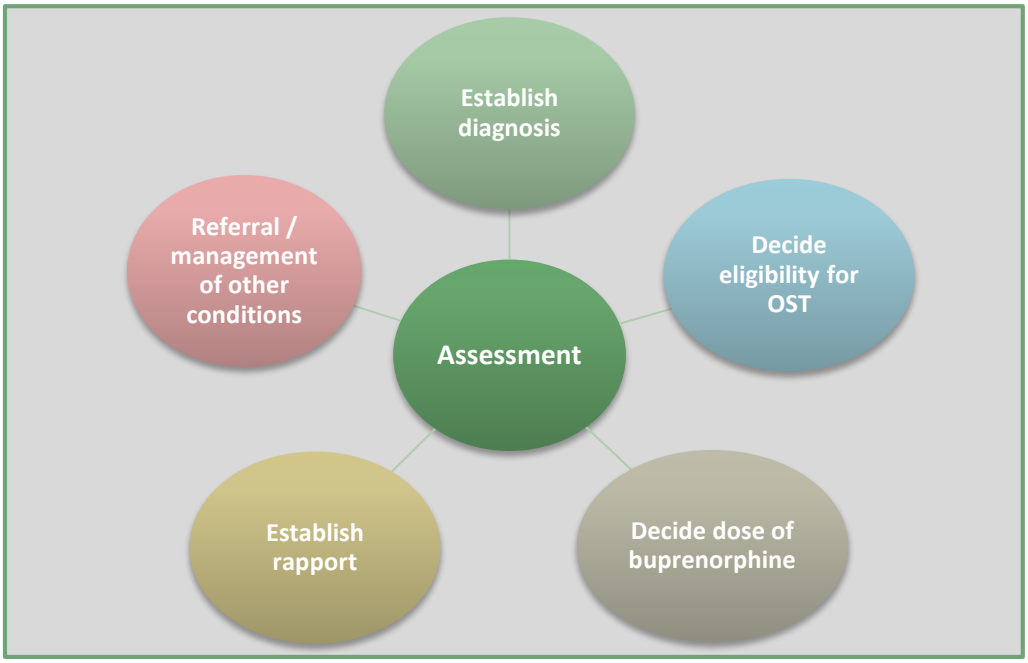
- Assessment and diagnosis
- Determining client suitability for Buprenorphine based OST
- Preparing client for OST
- Initiating Buprenorphine – Induction phase
- Continuation on Buprenorphine – Maintenance phase
- Take home dosing
- Terminating Buprenorphine – Termination phase
- Managing common side 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 requirements with regards 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 Centres, though the doctor assumes a larger role, since OST is a medical intervention. While the counsellor focuses on the psychosocial aspects of the client's drug use history, the doctor focus on the clinical/medical aspects pertaining to the client's drug use and medical history.



During assessment, the counsellor and doctor should 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 pattern of 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 client (including injection and sex related high risk behaviours)? What is the level of knowledge of 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 PWID 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 NACO and provided by the respective SACS to all the OST Centres s.)

- **Socio-demographic details:** including client's name, age, sex, marital status, educational status, occupational and employment status, and current contact information

- **Psychoactive substance use details:** including chronological order of initiation of substance use, and for every substance – age of initiation, progression, frequency of use, mode of intake of substance, any dependence features, usual dose, and last dose of intake

- **Complications due to substance use:** can be physical (overdose, scarring of veins, thrombophlebitis, infections, etc.), 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 injection (sharing, reuse of needle/syringes or other paraphernalia) and sex related (sex with sex workers, multiple sex partners, sex in exchange of drugs/money, sex under influence of substances, non-use of condoms)

- **Abstinence attempts:** Any attempts to give up psychoactive substance use. For every significant attempt – duration of attempt, reason for initiation and maintenance of abstinent attempt, type of

help received, reason(s) for relapse. An abstinence attempt may be considered as significant if the client was able to completely stop substance use for duration of one month or more.

- **Psychosocial support:** nature of relationship with family members particularly spouse, 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 the following in the preceding one year (or present continuously for at least one month):
   - **Loss of control:** Inability / Difficulty in controlling drug use (unsuccessful attempts to stop opioid use, or control the quantity of opioid use or time spent in opioid use)
   - **Increased time spent** in obtaining opioids, consuming opioids or recovering from the effect of opioids leading to neglect of other activities
   - **Continued use of opioids despite harms** incurred due to opioid use such as abscesses, overdose, vein loss, HIV, Hepatitis B/C, respiratory problems, etc.
   - **Tolerance:** gradual increase in 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**

2. **Diagnosis of other substance use disorders:** dependence / harmful pattern of use of other substances. Special attention should be given to 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 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 OSTINITIATION:

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 PWID:** The client should meet the operational criteria for PWID 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 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 PWID.

5. **CLIENTS' WILLINGNESS TO COME DAILY TO RECEIVE TREATMENT THEY MEET REQUIREMENTS FOR TAKE-HOME DOSING:** At the time of initial assessment, the clients should be educated about the need to come to the OST Centres every day to receive treatment under supervision (DOTS) till they meet the requirements for take-home dosing. Also, they should be educated that even initiating take-home dosing, if the doctor requires them to come daily for any reason (for example: dose optimization, monitoring side effects, ensure compliance, restarting medicine after dropped out for some length of time, frequent missing of doses, etc.), they should be willing to come daily. Clients who agree to comply with this arrangement should be initiated on treatment after duly signing the informed consent.

DESIRABLE CRITERIA FOR OSTINITIATION

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.

CONDITIONS REQUIRING SPECIAL CONSIDERATIONS FOR OSTINITIATION

There are certain conditions in which caution should be exercised while prescribing OST to PWID 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 Centres itself. Such clients should be referred to a psychiatrist/drug de-addiction centre before initiating on OST and may require inpatient treatment. MOSTPWID 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, 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 would 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 clients should be informed that OST is a long-term treatment option; it is important for the them 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 unless they are advised take home dosing by the treating doctor. The medicines would help in controlling withdrawals, and craving, and they would not need to use opioids for at least 24 hours 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 Centres .

- **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 the 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, he/she should be requested to **sign the informed consent form** if he is willing for the same. 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, have 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 OSTWITH 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 NACO.
- 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**.

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 withdrawals symptoms, which would be extremely distressing for the client.

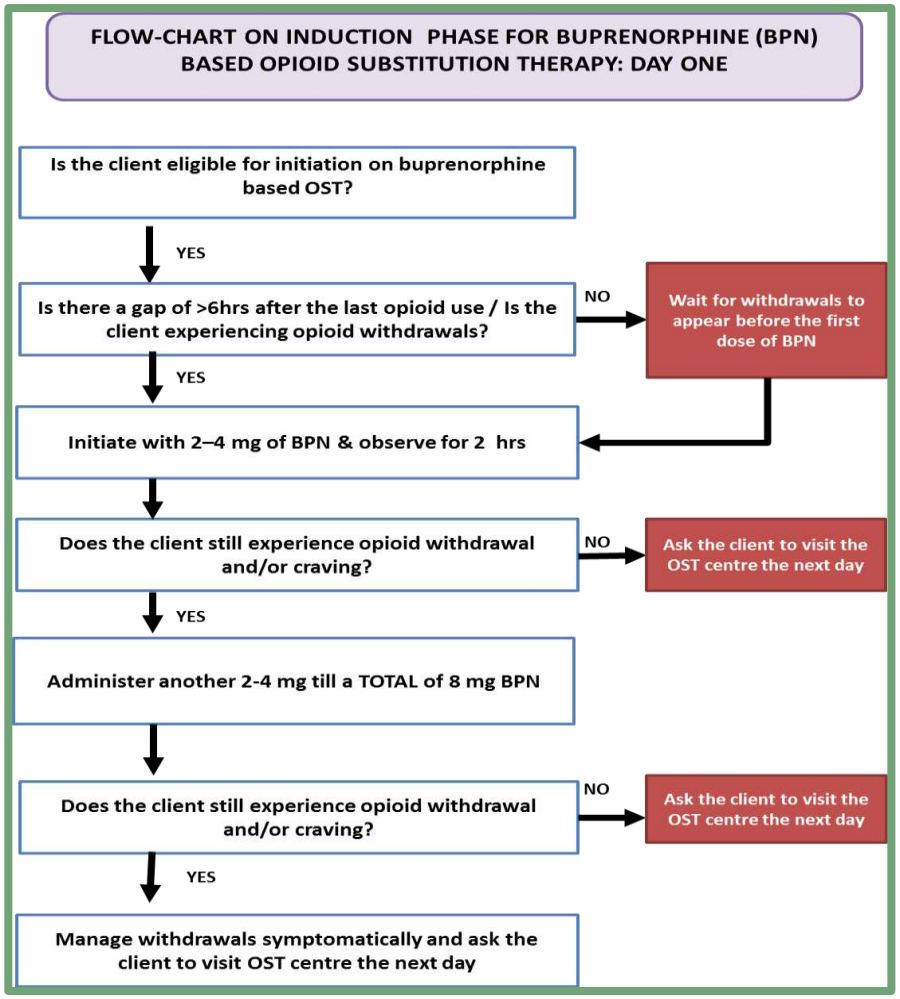
However, some doctors have a myth that if the client has already taken an opioid drug (like heroin) a short while ago, the first dose of buprenorphine will result in added intoxication (and risk of overdose). This is a misconception. The gap must be ensured primarily to avoid the precipitated withdrawal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

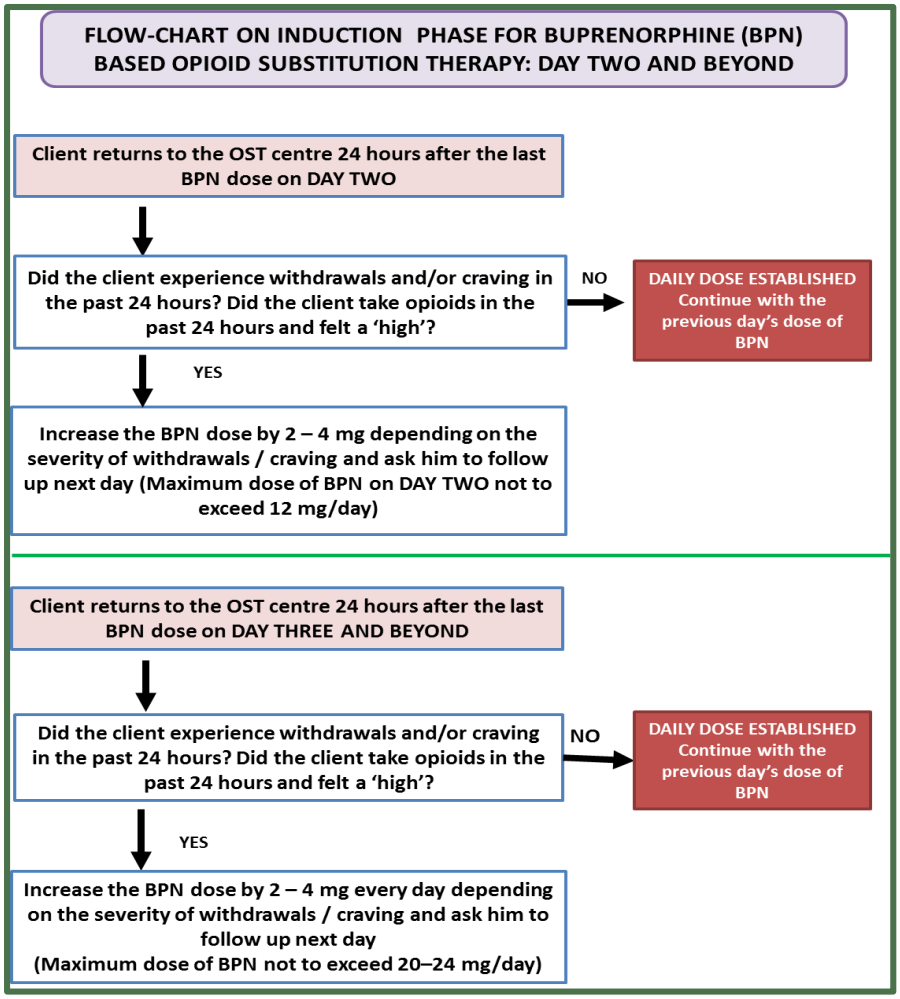
The first dose of buprenorphine usually ranges from 2 – 4 mg. After the first dose is administered sublingually, the clients should be observed after a gap of two hours, when the peak effect of buprenorphine is expected to be observed. If the clients still complain of withdrawals/craving, additional 2 – 4 mg can be given. If the clients report no symptoms of opioid withdrawal or craving, they should be asked to return back on the next day for their 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 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 opioid withdrawals or craving for an entire period of 24 hours following dose administration, the client would have achieved stabilisation dose. The dose increment should continue till the client experiences relief from opioid withdrawals or craving for 24-hour period. Most clients reach their stabilisation dose in three to four days, maximally by day seven.

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
Is the client eligible for initiation on buprenorphine based OST?
YES
Is there a gap of >6hrs after the last opioid use / Is the client experiencing opioid withdrawals?
NO
Wait for withdrawals to appear before the first dose of BPN
YES
Initiate with 2–4 mg of BPN & observe for 2 hrs
Does the client still experience opioid withdrawal and/or craving?
NO
Ask the client to visit the OST centre the next day
YES
Administer another 2-4 mg till a TOTAL of 8 mg BPN
Does the client still experience opioid withdrawal and/or craving?
NO
Ask the client to visit the OST centre the next day
YES
Manage withdrawals symptomatically and ask the client to visit OST centre the next day



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 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

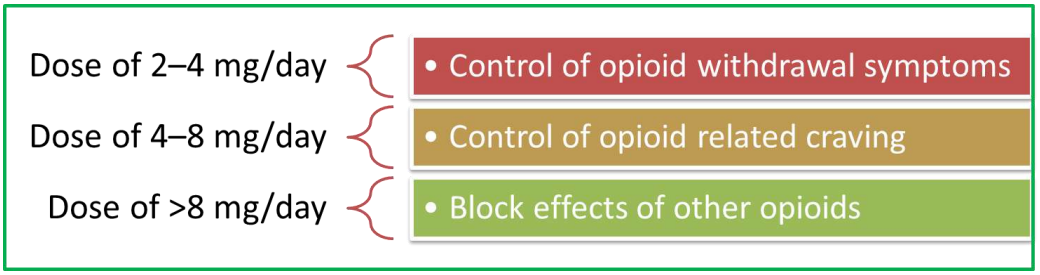
The maintenance phase begins with the clients achieving their stabilisation dose till the time a decision is made to stop OST for the client.

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 another route)
- To help the client prevent shifting to another substance use

BUPRENORPHINE MAINTENANCE DOSE:

While the focus in induction phase is on achieving control of opioid-related craving and withdrawal, the focus in maintenance phase is also 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, higher the dose of buprenorphine, longer is the effect of buprenorphine – i.e., 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 – stoppage of withdrawals, control of craving and production of opioid blocking effect – are achieved with adequate dose of buprenorphine.



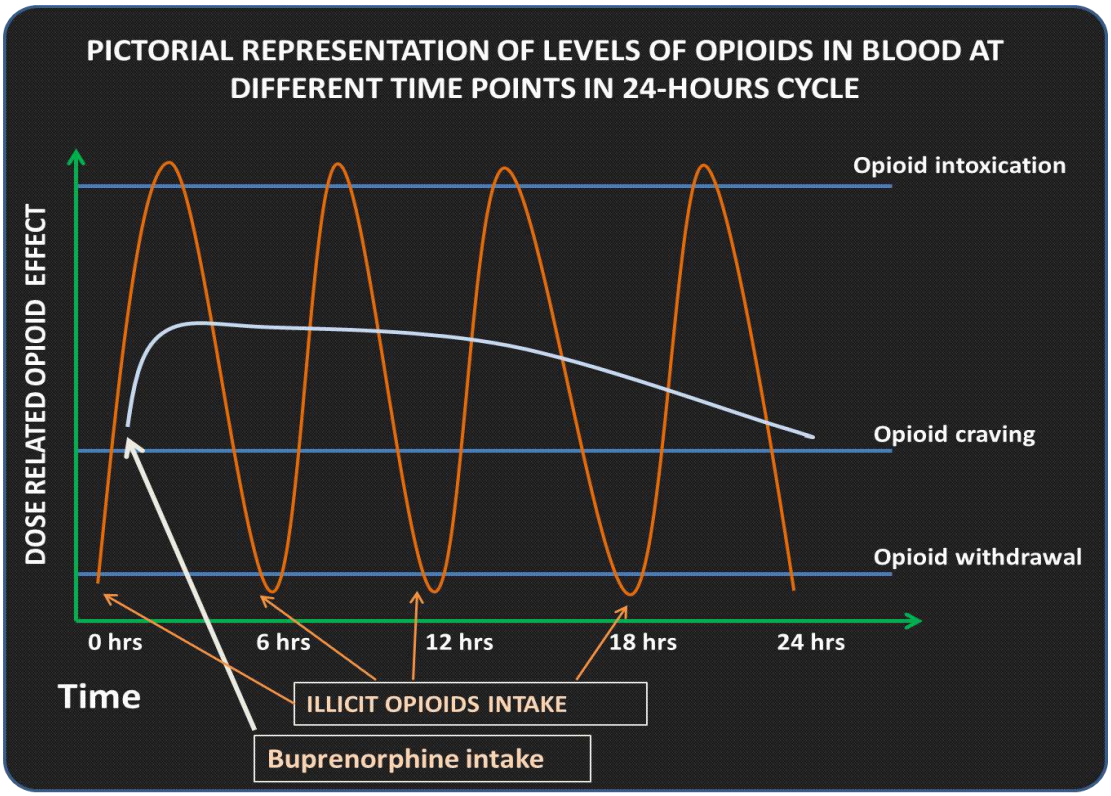
A buprenorphine maintenance dose of usually 8 – 16 mg per day is usually sufficient for most clients. The maximum dose in maintenance phase is up to 28 – 32 mg/day. If the clinician feels that the client is not improving despite the maximum dose, the client may be referred to a higher centre specialising in substance use treatment for further management.

Once the maintenance dose is achieved, the same dose should be continued till a decision to terminate the medication is taken. 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:

- Did the clients have withdrawals/craving despite their current buprenorphine dose?
- Have the clients used any other opioids/injections while on their current buprenorphine dose?
- Did the clients experience euphoria while using other opioids/injections?

The information regarding the above can be elicited by interview with the clients, their 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 experience 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 should 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. Differences between the level of illicit opioids such as heroin and buprenorphine are shown below.



Once the client is maintained on a particular dose of buprenorphine which is comfortable for the client, 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 dose as required.

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, client is maintaining well and has not desired for dose reduction. This reduction is done as many doctors and other OST Centres 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.

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 clients should now resume their responsibilities, sometimes at the cost of continuing 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.

ADDRESSING CO-MORBID SUBSTANCE USE

Once the client is stabilised on OST medicines and 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 reinitiate or increase the consumption of other brain depressants such as alcohol, benzodiazepines or cannabis. Some clients may progress on to the use of these substances in a dependent pattern. Apart from the problems caused due to the substances themselves, use of these substances also affects OST in the following ways:

- Use of these substances would increase the chance of 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 clients have re-initiated or increased their substance use, the service provider must educate them about the risks posed, and assist them 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 clients are stabilised on OST, they become more amenable to availing other services required. The clients 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 clients 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 comorbid conditions.

ASSISTANCE IN RE-INTEGRATION

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

During follow-up, the counsellor should explore these areas and assist the clients in resuming their 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 client during tapering of buprenorphine and prevent relapse during the same
- To help client in making decision regarding further treatment after stopping OST
- To motivate client for continued follow-up after stopping OST

DECISION TO STOP BUPRENORPHINE

A crucial decision in OST management is decision about stopping buprenorphine treatment. There is no specified time-duration for a client to be maintained on OST. OST generally lasts for months to years. The endpoint is reached upon client achieving the treatment goals decided mutually by the client and the service provider during the initiation of OST. The treatment goal is not limited to 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 illicit opioid use and use by injection drug 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 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.

The outpatient taper can be done over 3–6 months duration. In outpatient tapering, the tapering can be done in units of 2 mg of buprenorphine every 7–14 days, till the client reaches a dose of 2 – 4 mg 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.

Further tapering can be done in units of 0.4 – 0.8 mg of buprenorphine every 7–14 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 inpatient setting, the daily dose of buprenorphine can be divided into 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 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 follow-up, enquiry must be made regarding the client's drug use 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.

After termination of buprenorphine, the client can remain free of any medications and continue follow up at the OST Centres. In some cases, the client can be started on antagonist maintenance. For antagonist treatment, tablet naltrexone 50 mg/day should be given once a day. Before starting naltrexone, the client must be free of any opioids for at least 72 - 120 hours 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, the client should be re-initiated on OST after assessment and diagnosis. The practice of OST remains the same as described earlier.

CRITICAL ISSUES IN OSTPROGRAMME

- 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 Centres

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

BUPRENORPHINE DISPENSING

As per earlier guidelines by NACO, dispensing of buprenorphine was to be done strictly on 'Daily Observed Treatment' basis at the OST Centres. This means that the client had to come to the OST Centres daily and take their medicines in front of the OST nurse. The recent COVID-19 pandemic changed this dispensing practice. The COVID-19 pandemic and the subsequent lockdown placed great constraints on the OST clients to come to the OST Centres daily to receive their dose of buprenorphine. There was also greater risk of exposure of the staff of the OST Centres, the clients, and their families to COVID-19 due to daily dispensing. Soon after the onset of pandemic in India, NACO took a decision to initiate take-home dispensing in OST Centres to minimize the possibility of disruption of OST. Take-home dosing was introduced at the OST centers of NACO by the end of March 2020.The experience of take-home dosing during this period showed that it is a feasible option for stable patients on OST, not only during the pandemic, but also beyond that.

DAILY DISPENSING

Daily dispensing of buprenorphine is to be practiced at the initiation of the treatment till the client is stable enough for receiving take-home doses of buprenorphine.

In daily dispensing regimen, plain buprenorphine tablets are administered sublingually to the patient under the direct supervision of the nurse. 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. Care should be taken to ensure that there is nothing in the client's mouth (such as chewing gum or tobacco quid) before administering the medicine. The client should be advised to avoid drinking tea or coffee half an hour before the dose administration. At the end of the observation period of 7 – 10 minutes, the nurse should ensure that the medicine is dissolved sublingually.

Daily dispensing is to be continued for a period till the client meets the requirements for take home dosing (explained in next section). Take-home dosing must be done using BPN-N tablets. It is to be remembered here that the take-home is not a permanent status – if necessary (as assessed by the OST Centres staff), the client may be shifted back to daily dispensing. The clients may be required to be shifted back to daily observed treatment if they lose the clinical stability (as defined in the latter section).

TAKE-HOME DISPENSING

A major advantage of daily dispensing supervised by the nurse is that it ensures minimal chances of diversion of buprenorphine tablets by the clients. The clients may divert plain buprenorphine tablet (used in the initial phase) to other clients or may crush the tablet and inject it by mixing with water or other injections such as diazepam or pheniramine. On injecting buprenorphine tablet in this manner, the client will experience euphoria and may continue injecting buprenorphine tablets to get this euphoria. Daily supervised dispensing helps in preventing this likely scenario.

However, many clients may find it difficult to visit the OST Centres daily to receive their medicine. This is especially true for clients who are on maintenance for longer period. These clients may start working and find it difficult to juggle between their daily visit to the OST Centres and their job. This may lead to them dropping out of treatment. Providing take-home doses to the clients can help prevent such outcomes and improve client retention to OST. To prevent diversion to injecting, BPN-N tablets are used for take-home dosing. The naloxone

in BPN-N tablets can help in prevent the euphoria that the client may experience while injecting the tablet and may dissuade the client to inject these tablets in future. However, it is to be remembered here that some clients do experience euphoria injecting the BPN-N tablets as well. Additionally, the clients may still sell or loan their medicines to others. Hence, take-home doses are provided with several caveats as outlined below.

ELIGIBILITY CRITERIA FOR RECEIVING TAKE-HOME BUPRENORPHINE

A client can be considered for take-home buprenorphine if he fulfills the following criteria:

I. Essential Criteria:

- Completed at least three months of supervised buprenorphine dosing from a NACO-supported OST Centres . A client who has taken buprenorphine as daily observed treatment from other government-supported OST Centres s for three months can also be considered for take-home doses provided a credible proof of the same is available.
- Achieved 'clinical stability' defined as
    - Absence of recreational / illicit opioid drug use at least for the last three months
    - No alcohol or benzodiazepines use in dependent pattern at least for the last three months
    - No major changes in the buprenorphine dose during the last two months
    - No or minimal missed doses during the last three months (operationalised as not missed more than **a total of** seven days of doses in the last three months)
    - No opioid withdrawals and craving at the time of assessment
- Regular on follow ups – should have followed up at least once every month in the last three months
- Should be willing to follow the rules and regulations related to take-home dosing

II. Desirable Criteria:

- Has started / resumed his work or school
- Has a stable housing
- Improvement in social relationships

Contra-indications for take-home buprenorphine

Any of the following conditions, if present in a client in the last three months, is an absolute contraindication for take-home dosing:

- History of opioid overdose
- History of diversion of buprenorphine/ BPN-N
- Clients at risk of suicide or self-harm
- Any untoward behaviour in the OST Centres either towards the staff or towards other clients

CLINICAL PROCEDURE FOR PROVIDING TAKE-HOME DOSING:

The decision to allow or stop take-home dispensing to a client should be taken jointly by the doctor and the counsellor. In case of differences of opinion, the opinion of the doctor shall prevail.

Assessment of the client

The client should be assessed by the doctor and the counsellor before deciding take-home dosing. The assessment should determine whether the client fulfils the eligibility criteria for take-home doses. It is useful to corroborate the account provided by the client with their family members as well. The family should also be involved in the take-home process. It is preferable to designate a particular family member who would accompany the client for dispensing and be responsible for custody of medicines and giving it the client under their supervision. The client should be assessed at least once-a-month while receiving take-home doses.

Buprenorphine doses in take-home dispensing

The dose of BPN-N is the same that of plain buprenorphine. There is no need to modify the doses of buprenorphine during shift from buprenorphine to BPN-N and vice-versa. If there is a need to increase the dose of BPN-N during follow up, then the client may be shifted to daily supervised regime for some period (for about two weeks) to observe the client regularly before restarting take-home dispensing.

Take-home dispensing

As mentioned above, only BPN-N tablets should be used for take-home dispensing. The clients can receive take-home BPN-N for a maximum period of six days. In few, exceptional cases, the doctor may extend this to up to 14 days. The doctor may also decide to provide less than six days take home to a given client, depending on the feasibility for the client to visit the centre and collect his medicine. The client will be provided the day's dose on the day they visit the centre for picking up their take-home dose. On the day the client visits the centre to receive their medicine, the nurse should ensure that the client consumes the dose for the day in her presence as is done for supervised dosing.

Other conditions for take-home dosing

Though the client may not fulfil the eligibility criteria laid down for take-home dispensing, take-home doses for a brief period of 5 – 7 days can still be provided in some situations. These could be medical conditions preventing the client from attending the OST Centres daily. These conditions can be, for example, hospitalization for a medical/surgical problem, bone fracture, etc. Similarly, the client may also need to travel outside their city urgently to attend to some family matters such as death of an immediate family member, serious illness in the family, etc. In all such conditions, the doctor and counsellor should ascertain the veracity of the client's claims through examination of medical records or seek confirmation from the client's family. After satisfying themselves, the doctor can allow take-home for a period of up to seven days. As is done for cases of take-home dispensing, only BPN-N tablets are to be provided as take-home.

WITHOLDING TAKE-HOME DOSES

Under certain circumstances, take-home dosing for a client may be stopped temporarily (or even for a longer time) and they would be shifted back to daily supervised regime. Depending on the reasons, the client may be shifted back to daily supervised regime for a period of one to three months. In some cases, this may be done for an indefinite period. Some of these client-related conditions include (but not limited to):

- Found selling/loaning of BPN-N tablet
- Found to be injecting BPN-N tablets

- Using illicit opioids along with BPN-N tablets
- Repeated failure to attend medical or counselor appointments
- Frequent missing of doses while on take-home dosing
- Dropping out of OST for a continuous period of one month or more
- Frequently reaching the clinic in an intoxicated state/drowsy state suggesting the possible use of CNS depressant drugs
- Frequently asking replacement for 'stolen' or 'lost' medications
- Verbal/physical abuse towards the clinic staff (in some cases, stopping the OST may be considered)
- Frequently asking for prescriptions for longer durations without convincing documents / circumstances

It is important to conduct detailed assessment of the clients during follow-up to rule out any conditions that require the client to be shifted back to daily supervised regime. Before initiating take-home dosing, it is also important to inform the client of the potential conditions that could lead to shifting back to daily supervised dosing. Involving family members in treatment also helps prevent any untoward incidents related to take-home dispensing.

MANAGEMENT OF COMMON CLINICAL SITUATIONS

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

VOMITING

Vomiting does not occur commonly with buprenorphine. 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. 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 reliving 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; experiencing constipation with same dose of buprenorphine or undergoing the risk of withdrawal or relapse if 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 chlorpheniramine, 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

SLEEP HYGIENE

- Fix time for going to bed and getting up in 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
- Have light exercise in the evening
- Have a bath with warm water before going to sleep
- Do light reading or music before sleep
- Use bed only for sleep
- Have a glass of warm milk before going to sleep

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), trazodone (50 – 150 mg at night in tablet form), or Dothiepin (25 – 75 mg). 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.

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 few days. In such situations, the management will depend on the duration of the missed treatment:

- If the client misses 1 – 2 day's doses of buprenorphine, the client can be given the same dose of buprenorphine as before
- If the client misses 3 – 5 day's doses 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 dose gradually increased depending on the client's response in the subsequent days.
- If the clients miss their dose of buprenorphine for more than five days, the same dose of buprenorphine should not be given to the client, as the client may have lost tolerance to opioids. The client should be treated as a 'new' client and buprenorphine should be re-inducted starting from induction phase till the client is stabilised.

Missed doses during take-home dosing:

The clients may miss their take-home doses for some time and may contact the centre again for restarting OST. In such cases, if the client has missed their dose for a continuous period of one month, then the client should be shifted back to daily supervised regime for some time.

- In cases where the client has missed their take-home dose for one to two days, they can be continued on take-home dispensing.
- If the client has missed their take-home dosing for three to five days, they should be provided daily supervised dosing for one week before shifting them back to take-home dispensing.
- If the client has missed their take-home dose for more than five days to one month, they should be provided daily supervised dosing for two weeks before shifting them back to take-home dispensing.
- In cases where the client has missed their take-home dose for more than one month but less than six months, then the client should be provided daily supervised dosing for at least one month before shifting them back to take-home dispensing.
- If the client drops out of the OST for continuous period of six months or more, then the client should be on daily supervised dosing of at least three months before shifting to take-home regime.

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:

- Every effort must be made to ensure that every PWID 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, the client should be referred to ART centre for registration and for decision on initiation of ART medicines. If the client is HIV negative, the client 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 withdrawals 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.

CO-MORBID HEPATITIS C VIRUS INFECTION

Hepatitis C virus (HCV) infection is a common comorbid condition among PWIDs. As those living with HCV infection remain symptom free for years, most cases go undiagnosed and therefore untreated. HCV is more readily transmitted through injection as compared to HIV. Unsafe injection practices are responsible for more than 90% new HCV infections. Chronic infection persists in majority of acutely infected clients and around 7% of untreated chronic HCV carriers develop liver cirrhosis within 20 years.

Recently, highly effective treatment options in form of directly acting antivirals (DAAs) have become available for HCV treatment. Because of poor access to treatment, the mortality from untreated HCV infection is high. Hence, all PWIDs, including those on OST, should be tested for co-morbid HCV infection and if detected positive, should be referred for further management. Testing for HCV and the medications are available free of cost under the National Viral Hepatitis Control Program (NVHCP). The program plans to provide free screening, diagnosis, and treatment for hepatitis C at all levels of health care in a phased manner. The common DAAs provided under NVHCP for uncomplicated, non-cirrhotic cases of Hepatitis C are sofosbuvir and daclatasvir.

Pharmacokinetically, there can be changes in the concentration of buprenorphine due to DAAs in the following manner[31,32]:

1) Telaprevir can reduce the serum concentration of buprenorphine as well as naloxone.
2) Daclatasvir can increase the serum concentration of buprenorphine and Nor-buprenorphine.
3) Grazoprevir and Elbasvir does not produce any change in concentration of buprenorphine.

4) Combination regimen of ombitasvir+ paritaprevir + dasabuvir + ritonavir can increase the serum concentration of Buprenorphine as well as Naloxone.

However, these interactions are generally not clinically significant enough to cause changes in the dose of Buprenorphine.

HENCE, DAAs CAN BE USED IN PWIDs CURRENTLY ON BUPRENORPHINE-BASED OSTWITHOUT MAJOR CHANGES IN THE DOSE OF BUPRENORPHINE.

TUBERCULOSIS

Tuberculosis is a common comorbid condition among PWIDs. 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 p450 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 DOES 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 presenting from this age-group have short duration of opioid use and even shorter duration of injection 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 year) along with history of injection 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.

WOMEN WHO INJECT DRUGS

There are some special considerations with opioid dependent women who inject drugs. Women are more vulnerable to HIV and other complications due to injecting as compared to their male counterparts. More often than not, women PWIDs have a male partner who is also an PWID, as a result of which they have to use the injections and injecting equipment after the male uses them. Some women who inject drugs 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. women who inject drugs are often looked down upon by the neighbours and the society, resulting in greater stigma and discrimination. Finally, women who inject drugs have lower accessibility to general healthcare services as well as HIV prevention programmes or drug treatment services. The staff of OST Centres should keep these vulnerabilities in mind when attending to women who inject drugs wishing to be initiated on OST.

Considerations while providing OST intervention to a Woman Injecting Drug User

- Special efforts must be made to make the woman PWID comfortable, as females are often reluctant to access services at places with predominant male PWID clients.
- The doctor and counsellor must ensure that the woman PWID 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 presence of STI
- Women PWIDs 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 child bearing period and 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 PWID, efforts must be made to initiate the male partner on OST too

PREGNANCY AND BREAST FEEDING

OPIOID SUBSTITUTION THERAPYIS 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 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 Centres 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 – 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 does not desire a child.

OPIOID OVERDOSE

Another potential challenge with opioid use is overdose. Opioid overdose occurs when the individual consumes opioids over and above their body tolerance to opioid effect. Opioid overdose is associated with high rates of fatality, particularly, when appropriate treatment for opioid overdose is not available. Signs and symptoms of opioid overdose include pinpoint pupils, sedation, 'nodding off', slurring of speech, unsteady gait, dizziness, nausea, snoring, hypotension, bradycardia, hypoventilation, feeling intoxicated, itching, nausea, pulmonary oedema, and coma. The classic triad of opioid overdose includes unconsciousness (coma), pin-point pupils, and slow, shallow breathing. Death generally occurs because of the respiratory depression. In fact, opioid-related overdose is the most common cause of drug-related deaths caused due to illegal drugs worldwide.

Various factors are associated with opioid overdose. This includes use of opioids through injecting route, history of recent imprisonment, forced admission in an addiction treatment facility, opioid antagonist treatment, homelessness, etc. Also, the concomitant use of other brain depressants such as alcohol and benzodiazepines can also increase the risk of opioid overdose. Another important factor is the pharmacological property of the opioid. Full agonists are more liable to cause opioid overdose than partial agonists. Hence, opioids such as heroin and methadone are more likely to be associated with opioid overdose. On the other hand, buprenorphine is less likely to cause opioid overdose due to its partial agonist property. However, there is risk of opioid overdose if buprenorphine is mixed with other brain depressants, particularly, alcohol and benzodiazepines. Hence, OST staff must be aware of opioid overdose and must have adequate knowledge and skills to manage opioid overdose, which is an easily treatable condition.

Opioid overdose is an emergency condition. Opioid overdose must be suspected in any patient presenting with the classic triad of opioid overdose. The management of overdose involves providing airway support, placing the patient in recovery position, and administration of naloxone. Naloxone is an opioid antagonist that acts within minutes of administration. However, its effect lasts for a short duration (30 to 90 minutes). It is effective parenterally and is usually given intravenously or intramuscularly. Intranasal preparations of naloxone are also available elsewhere, but not in India. Naloxone reverses opioid overdose caused by illicit opioids such as heroin almost immediately. However, buprenorphine-associated overdose may take longer to respond to naloxone due to the slow dissociation property of buprenorphine. Higher than usual doses of naloxone may be needed to reverse buprenorphine-associated opioid overdose. The client needs to be monitored for further 12 – 24 hours even after they have recovered from the overdose opioids.

The best way to address opioid overdose is to prevent opioid overdose. The OST client and their family members should be educated on the risk factors of opioid overdose as well as emergency management of opioid overdose.

PATIENTS WITH PAIN:

Management of pain conditions in patients on OST can be a challenge. Even in opioid dependence, the patient may not respond well to opioid analgesic due to tolerance to opioids' effects. Also, there can be an increased sensitivity to pain due to neuroplastic changes caused by opioids. Hence, patients with opioid dependence may experience more pain than those without opioid dependence.

In general, **in any patient presenting with pain, it is necessary to identify the cause for pain and provide suitable treatment for the same**. If it is due to opioid withdrawals alone, OST will be sufficient to manage the same. However, if there is a suspicion that the pain is not only due to withdrawals (for example, pain localised to a specific part of the body), patient should be referred for further investigations and management of the cause of pain. Inadequate pain management can lead to relapse to illicit opioids. **It is necessary to manage both opioid dependence and pain together for optimum outcome.** Buprenorphine, being an opioid, is an analgesic also. However, its **analgesic effects last only for 6 to 8 hours**, even though its effects on craving and withdrawals lasts for around 24 hours. Since buprenorphine is administered in a single dose when used in OST, it may not be sufficient to produce analgesia throughout the day.

- **Mild or Moderate Pain:** Non-opioid analgesics such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) and paracetamol can be added in addition to OST. Non-pharmacological treatment like physical therapies and psychosocial interventions should also be considered for management of pain.
- **Moderate Pain not controlled with non-opioid analgesics or Severe pain: Split the dose of buprenorphine to 3 times daily for a short period** till the acute pain is managed. **Dose of buprenorphine can also be increased if required**, by around 20% to 25% of maintained dose. In cases where buprenorphine is provided as split doses for short duration for management of acute pain, afternoon and evening doses can be provided in the form of BPN-N tablets as take-home medications. Family should be involved in the supervision of medications at home.
- At any time, if the pain is severe, or the pain does not improve, or the pain is prolonged (more than one week), or there are repeated episodes of acute pain, **refer the patient to a medicine or a pain specialist for the management of pain.**

If a client on OST with buprenorphine has severe acute pain refractory to other treatment, short-acting full-agonist opioid can be added to the patient's regular dose of buprenorphine under supervised settings preferably after hospitalization. It should be remembered that in such cases, the dose of full opioid agonist required would be higher than opioid naïve person and hence, it should be preferably administered under inpatient settings.

PERI-OPERATIVE ISSUES:

In case of patients maintained on OST planned for elective surgery / elective procedures, **buprenorphine need not be discontinued. The patient can be given the usual full dose of OST throughout the peri-operative period, including the day of surgery / procedure.** If required, higher potency opioid agonists can be added for analgesia during the peri-operative period on an in-patient basis. In cases, where the treating surgeon and

anaesthetist decide to taper buprenorphine before surgery, the medication can be discontinued on the day of surgery or one day before the surgery. Buprenorphine can be resumed post-operatively when the need for opioid analgesia is over. Buprenorphine can be restarted in the same dose before surgery if buprenorphine has been stopped for less than three days. However, if buprenorphine has been stopped for more than three days, buprenorphine induction should be done as a new patient.

COMORBID PSYCHIATRIC ILLNESS:

Psychiatric disorders are more common in patients with substance use disorders than in the general population. Patients with psychiatric disorders can abuse psychoactive substances as a form of self-medication (for example, to improve mood in depression), or the substances themselves can lead to depression (for example, opioid-induced depression). There may be certain risk factors which are common to both psychiatric illness and substance use disorders (for example, adverse childhood experiences). Irrespective of the reasons for initiation, patients with comorbid opioid dependence and psychiatric illness have worse outcomes, including higher fatality rates associated with suicides. Individuals can also use opioids to die by suicide by overdosing on opioids. These factors equally apply to clients on OST with buprenorphine.

Patients with comorbid psychiatric symptoms should be referred to a psychiatrist for comprehensive assessment and management of the psychiatric illness. As buprenorphine does not interact adversely with the commonly used psychiatric medications, both buprenorphine and the medications for psychiatric illness can be taken together safely. Initiation of OST should not be delayed till psychiatric management is initiated.

HOSPITALIZATION:

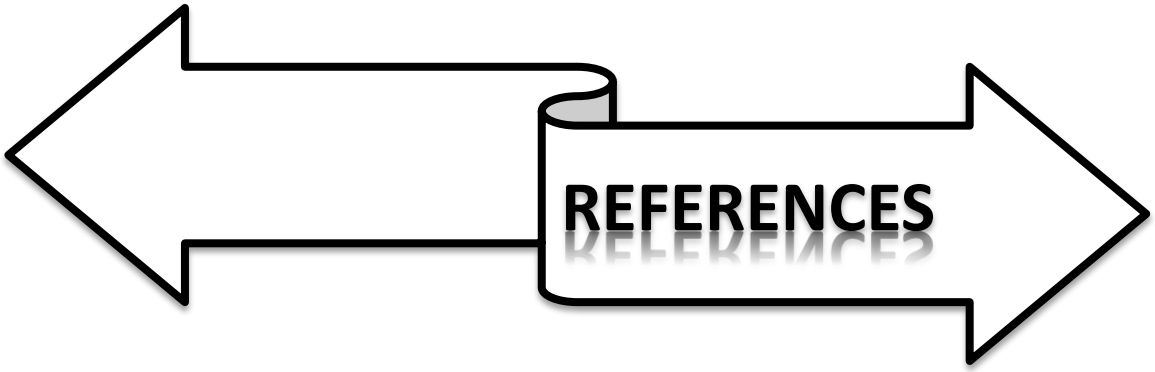
Patients with opioid dependence who have been hospitalized for medical illness can continue their OST in the same dose unless there are any contraindications for continuing the same. As there can be potential drug-drug interactions with other medications prescribed for the medical illness, the treating team should be informed about the medication, preferably by written communication (with the client's permission). During the period of hospitalisation, if the OST medication is continued, BPN-N tablets can be dispensed as take-home to the family members. The duration of take-home dispensing can be up to a maximum period of one week at a time till the time patient is discharged from the hospital. The dose of BPN-N tablets dispensed as take-home is the same as provided to the patient before hospitalisation.

RESTRICTION IN MOVEMENTS/HOME ISOLATION OF PATIENTS DUE TO MEDICAL ILLNESS:

Some patients may not be able to come to the clinic for daily dispensing due to some medical illness (for example, bone fracture in lower limb restricting patient's mobility, home isolation due to coronavirus infection, etc.). In such cases, if the client's family member is willing to supervise the medications, take-home doses of BPN-N on which the client had been stabilised can be provided for the period the patient is in isolation. Proper documentation of the reason for take home dosing and duration of take-home dosing should be recorded in the patients' file.

CONCLUSIONS

Opioid Substitution Therapy(OST) is an effective treatment option for opioid dependence as well as HIV prevention intervention for opioid dependent PWIDs. 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, adequate dose of buprenorphine as well as adequate duration of treatment are important determinants 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.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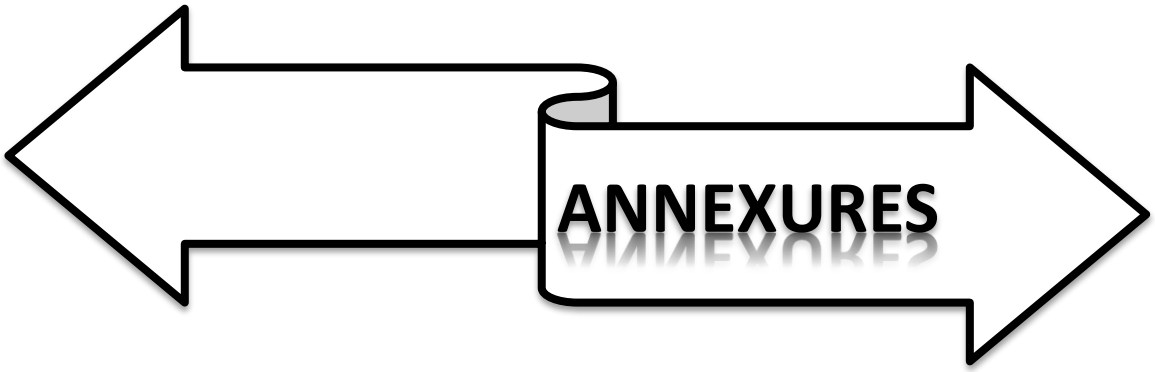
ANNEXURES

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 hours interval till the desired response. Maintain on 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 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 four weeks of delivery along with mother for complete recovery. Breastfeeding must be continued in the meantime.