



METHADONE  
MAINTENANCE  
TREATMENT UNDER  
NATIONAL AIDS  
CONTROL  
PROGRAMME  
PRACTICE GUIDELINE



NATIONAL AIDS CONTROL ORGANISATION

# **Opioid Substitution Therapy under National AIDS Control Programme – Clinical Practice Guidelines for treatment with Methadone**

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## Foreword

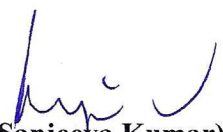
India is implementing Harm Reduction Programme for Injecting Drug Users (IDUs) through the National AIDS Control Organisation (NACO). This Harm Reduction Strategy is a part of National AIDS Policy and includes preventive strategies like Needle Syringe Exchange Programme (NSEP), abscess management and prevention, condom promotion, behaviour change communication, HIV testing and ART, linkages, referral, etc.

Under the National AIDS Control Programme, Opioid Substitution Therapy (OST) was initiated for the first time in NACP III as was planned in the strategy-cum-implementation document for NACP III. The OST strategy was implemented after obtaining due endorsement from other ministries, including Ministry of Social Justice and Empowerment, Ministry of Home, Narcotics Control Board and the Director General of Health Services.

At present, OST is being provided in 215 OST centres covering more than 22,000 clients adopting two models, namely Non-Governmental Organisation (NGO) model and Collaborative model which is implemented through a partnership of Public Health Setting and Injecting Drug Users (IDU) Targeted Interventions.

NACO has recently introduced Methadone Maintenance Therapy (MMT) in Imphal, Manipur which is being implemented by Regional Institute of Medical Sciences (RIMS). The Clinical Practice Guidelines have been developed by NACO in technical consultation with AIIMS supported by Nossal Institute of Global Health (NIGH), University of Melbourne, Australia to guide the clinic staffs in MMT implementation across the country.

I am confident that these practice guidelines on MMT will help all stakeholders to ensure quality service delivery thereby preventing HIV transmission among IDU and enhance better health seeking behaviour leading to better quality of life among IDU.

  
(Sanjeeva Kumar)

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अपनी एचआईवी अवस्था जानें, निकटतम सरकारी अस्पताल में मुफ्त सलाह व जाँच पाएँ

Know your HIV status, go to the nearest Government Hospital for free Voluntary Counselling and Testing

## PREFACE

Though globally, methadone is the most commonly used medication for Opioid substitution therapy (OST), India initiated OST with buprenorphine due to non-availability of methadone in the 1980s. Methadone made its entry in India only recently. To begin with, methadone treatment was piloted at five Government hospitals, through a collaborative project between National Drug Dependence Treatment Centre, AIIMS, New Delhi and UNODC, Regional Office for South Asia. . This project provided important insights for the country, which have proved useful for incorporating methadone maintenance treatment for HIV prevention among Injecting Drug Users under the National AIDS Control Programme, as well as for scaling-up methadone treatment services in other health programmes.

As of now, very few health care providers in India have any experience or expertise with providing methadone treatment. Thus, these clinical practice guidelines on methadone has been developed to assist the medical staff of OST centres; however the language has been kept simple to also benefit the non-medical staff working in OST centres. The present document borrows heavily from the practice guidelines on buprenorphine based OST developed by the authors for NACO in 2015, as NACO currently follows similar operational procedures for buprenorphine and methadone based OST. The authors are thankful to NACO, Emmanuel Hospitals Association and Public Health Foundation of India for their support towards development of this document. We also acknowledge feedback from Dr Michelle Kermode and Dr David Jacka in finalisation of the guideline. It is hoped that these guidelines will be helpful to the staff of OST centre for providing methadone treatment services in the OST centres with a reasonable degree of standard and quality. Indeed, health-care providers working outside the National AIDS Control Programme, may also find the document useful.

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Atul Ambekar  
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## ABBREVIATIONS

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

## INTRODUCTION

It is estimated that there are 177000 Injecting Drug Users (IDUs)<sup>1</sup> in India. The distribution of Injecting Drug Use (IDU) population is not uniform throughout the country. As of 2014, there are some states that have high number of Injecting Drug Users (IDUs) including, Manipur, Nagaland, Punjab, Mizoram and Delhi. IDU is an important factor in the transmission dynamics of HIV epidemic in India. HIV in India is a concentrated epidemic – concentrated in certain geographical areas and among certain population groups. These population groups, designated as High Risk Groups (HRGs), have much higher prevalence of HIV as compared to the general population. As per the data from the Integrated Bio-Behavioural Study, 2015, HIV prevalence among IDUs is 9.9% nationally, which is the highest among any population group. However, some states have much higher HIV rates among IDUs.

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

### A. NATIONAL STRATEGY FOR HIV PREVENTION AMONG IDU POPULATION

Globally, the “harm reduction” strategy is employed to manage HIV prevention among IDUs. Harm reduction strategy is based on the premises that it is as important to focus on addressing harms associated with drug use as it is to help them give it up. The strategy offers an effective alternative approach for continuous engagement and HIV prevention among drug users, especially those who are unable or unwilling to give up drug use through other abstinence-oriented approaches. Priority is accorded to immediate, easily preventable harms of public health importance. HIV prevention becomes an important focus of harm reduction. A number of interventions have been found to be useful and effective for HIV prevention among IDUs. WHO, UNAIDS and UNODC, together, have proposed nine interventions for HIV prevention, care and treatment of IDUs which, when implemented together, are called the “comprehensive package of interventions” for HIV prevention among IDUs. The core interventions among these include – Needle Syringe Programme (NSP), Opioid Substitution Therapy (OST), and Anti-Retroviral Treatment (ART).

#### COMPREHENSIVE PACKAGE OF INTERVENTIONS

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

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

<sup>1</sup> The preferred terminology to refer to this population is People Who Inject Drugs (PWIDs). In order to maintain uniformity with other documents of National AIDS Control Programme, Government of India, the term Injecting Drug Users (IDUs) has been used throughout the document, without any intended pejorative connotation.



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

As in 2017, there are more than 300 core IDU TIs throughout the country, reaching out to more than 80% of the IDU population. Thus, there is a saturation of the coverage of IDUs with HIV prevention services in India. Programmatic data also shows that there has been a significant increase in commodity distribution, number of needle/syringes distributed per IDU, referrals for HIV testing, etc.

## **B. OPIOID SUBSTITUTION THERAPY UNDER NATIONAL AIDS CONTROL PROGRAMME**

OST as a HIV prevention strategy among IDUs was formally integrated into the National AIDS Control Programme (NACP) in 2007, during its third phase. Before formal integration, OST for HIV prevention among IDUs was being implemented in India by some NGOs. After a formal approval for OST implementation, besides putting in place mechanisms for financial support to the NGOs implementing TI projects, a number of documents for standardisation and quality assurance have been developed by NACO, including *practice guidelines for buprenorphine*, *standard operating procedures* and *quality assurance manual*. The NGO OST centres were also accredited through an independent accreditation agency, following which they started receiving support from NACO. In this NGO-based model of OST, the OST centres located within the Drop-in-Centre (DIC) of an IDU TI are managed by the staff implementing the IDU TI. A part-time doctor, a full time nurse, a counsellor/ANM, programme manager and outreach workers are part of the team delivering OST services.

To further expand the OST programme, since 2010, Government hospitals have also been involved in the provision of OST services through a collaborative public health model. In this model, the OST centre is located within the government hospital and is manned by full-time staff comprising of a doctor, a nurse, a counsellor and a data manager. The staff of the OST centre work under the direct supervision of a designated ‘nodal officer’, who is a full-time employee of the hospital. The OST centre is linked with an IDU TI located in the vicinity of the hospital for initial referral of IDU clients to the centre, as well as field-based follow-up and advocacy. Currently, as of July 2016, there are about 210 OST centres in the country supported by NACO, operating through either the NGO or the collaborative public health model, catering to more than 20,000 IDUs. There is a plan to establish about 350 OST centres and increase the OST coverage to 35000 – 40000 IDUs during NACP IV.

NACO now plans to expand the menu of options available for OST in terms of medications. Methadone which has been widely used as an OST globally was introduced in India through a collaborative project between UNODC and National Drug Dependence Treatment Centre (NDDTC), All India Institute of medical Sciences (AIIMS) in 2012. The project was successful in establishing the feasibility of methadone for use in long term treatment of opioid dependence. The project also demonstrated the

effectiveness of methadone in reducing opioid use, injecting behaviour, and improvement in quality of life among those retained on methadone.

## About the document...

- *The clinical practice guidelines are intended to be used by the staff implementing OST interventions supported under the National AIDS Control Programme.*
- *While this document is of interest to all staff members (including those of linked IDU TIs) they 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 relied on scientific evidence-base, especially from India, other similar guidelines published for India, the training manuals and operational procedures developed for OST, as well as their own clinical and Programmatic experience.*

# BACKGROUND

## UNDERSTANDING INJECTING DRUG USE AND INJECTING DRUG USERS

### A. DEFINITION OF 'INJECTING DRUG USER'

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

### B. DRUGS INJECTED BY IDUs IN INDIA

Though theoretically, as per the definition, an IDU may use any psychoactive substance through injecting route, research conducted thus far has shown that in India, **a vast majority of the IDUs use opioids as their primary drug of choice**. These opioids include heroin (pure or the impure – 'smack' / 'brown sugar') as well as pharmaceutical opioids such as buprenorphine, pentazocine and dextro-propoxyphene. The opioids may be injected either alone or in combination with other substances which include benzodiazepines such as diazepam, or antihistamines such as chlorpheniramine<sup>2,3</sup> or promethazine. The other substances are combined with opioids to enhance the pleasure of opioids or due to some perceptions existing among IDUs regarding their positive effects.

#### OPIOIDS

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



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

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

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

<sup>2</sup> The commonly available brands of the pharmaceutical substances are –

Buprenorphine: Norphine, Lupigesic, Tidigesic, Sangesic, etc.; Dextropropoxyphene: proxyvon, SP, spasmoproxylon, etc.; Pentazocine: Fortwin; Chlorpheniramine: Avil; Promethazine: Phenargan  
(Disclaimer: Use of the brand names above are in no way pejorative, or incriminatory of a particular brand.)

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

### C. SUBSTANCE USE DISORDERS

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

- **Harmful use:** A pattern of substance use, in which a user experiences physical or psychological harms by substance use, and despite such harms, continues to use the substance.

During harmful use, though the user is not dependent on the particular substance, he/she still suffers from adverse consequences related to the use of the substance and continues the substance even though he experiences these harms. The user may or may not be using the substance on a daily basis.

- **Dependence:** This is a pattern of substance use in which the substance is used on a daily/almost daily basis, and the substance use and associated behaviour takes precedence over other behaviours/activities that were important to the individual. In this pattern of substance use, a number of symptoms generally appear in the physical, psychological and social domains that form the diagnostic criteria of dependence.

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

### DEPENDENCE SYNDROME

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

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

*(Adapted from ICD-10 guidelines)*

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

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



#### **D. OPIOID DEPENDENCE SYNDROME**

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

- **Acute Withdrawals:** Opioids as a group produce typical physical withdrawal syndrome on a short term basis, upon reducing or stopping or even delaying the intake of the usual amount of opioid drugs. These withdrawal symptoms include *lacrimation* (tears from the eyes), *rhinorrhoea* (running nose), *yawning*, *diarrhoea*, *muscle cramps*, *sweating*, *muscle aches and pains*, etc. Along with these symptoms, other symptoms include *anxiety*, *restlessness*, *insomnia* (not able to sleep), *irritability*, as well as an *intense urge* (craving) to consume opioids. These 'acute' withdrawal symptoms are usually self-limiting in nature, i.e., they usually rise up to a peak level and subsequently subside on their own even without any intervention/help. However, these acute

withdrawal symptoms are very distressing and disabling for the client, and often a cause for the client to restart or continue his/her opioid use. In most of the cases, once opioid use has stopped, the acute withdrawal symptoms would last for about two to three weeks before subsiding, provided the user has not resumed using opioid drugs.

- **Protracted withdrawals:** In some clients, even after the acute withdrawals have been resolved, some symptoms may persist for a longer period of time, i.e. up to four to six months. These include: *mild aches and pains, loss of interest in pleasurable activities, premature ejaculation, sleep disturbances, and craving*. These symptoms are also some reasons for relapse in a number of opioid users.
- **Relapsing nature of illness:** As is true of other substance use disorders, especially dependence syndromes, ODS is also characterized by repeated relapses and remissions. An individual may restart using opioids after a period of abstinence. Such relapses and remissions are a feature of Opioid Dependence Syndrome especially among those who have used them for prolonged periods (years).
- **High risk behaviours:** Opioid use may be associated with various behaviours associated with high risk of transmission of blood-borne viruses such as HIV. As discussed above, opioids can be used through an injecting route, and a number of IDUs resort to sharing of needles/syringes or other injecting equipment. Injecting is a very efficient means of transmission of blood borne viruses, including HIV, Hepatitis B and C, as a result of which HIV prevalence among IDUs is very high. Additionally, individual users may also have high risk sex behaviours resulting in transmission of HIV through the sexual route to their female partners and the sex workers.
- **Multiple harms:** An opioid dependent user may incur harms in multiple domains of life. There may be family complications in terms of broken families, family fights, domestic violence, etc.; legal complications may include involvement in illegal activities like stealing, drug peddling, petty thefts, and incarceration, etc.; social complications may include loss of reputation/social status, being a social outcast, ridicule from society, sometimes even inhuman treatment/physical torture.

## E. INJECTING DRUG USERS – RISK AND VULNERABILITY

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

the IDUs suffer from harms resulting from opioid dependence in addition to the above-mentioned injecting and sex-related risks. An additional vulnerability of concern among IDUs is of 'overdose'. If a person takes a heavier dose of drugs than he is accustomed to, this may result in serious intoxication and overdose, which is a potentially fatal, medical emergency.



## OPIOID SUBSTITUTION THERAPY – BASIC CONCEPTS AND PRINCIPLES

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

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

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

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

centres/hospitals free of cost, the client does not have to resort to illegal means. This helps in reducing legal complications faced by the clients and also reduces instances of petty crimes like thefts, etc. in the society.

- During the illicit drug use phase, IDUs are often branded as anti-social or criminal by the families and the society. When on OST, such IDUs are seen as sufferers and 'patients'. This renewed status helps the clients to seek help for other problems as well and makes them amenable to other help that can be provided.

## BENEFITS OF OPIOID SUBSTITUTION THERAPY

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

### BENEFITS OF OPIOID SUBSTITUTION THERAPY

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

### OST-RELATED OUTCOMES – GLOBAL EVIDENCE

- A Cochrane review conducted by Mattick et al, 2009, concluded that OST using methadone was more effective (in a statistically significant manner) as compared to non-pharmacological treatment in retaining patients undergoing treatment and in suppression of heroin use.
- A Cochrane review conducted by Mattick et al, 2008, concluded that buprenorphine is an effective maintenance agent for heroin dependence, but not more effective than methadone.
- Large prospective cohort studies conducted over 18 months found that the odds of HIV infection were 5.4 times greater among those who were not in maintenance treatment compared with those who were in treatment (Metzger et al, 1993).
- A report by World Health Organisation, 2005, reviewed many studies conducted in different parts of the world and concluded that substitution treatment is a critical component of HIV prevention, and helps in reducing opioid dependency and HIV infection rates.
- A systematic review and cost effectiveness by Connock in 2007 reported the following:
  - All doses of methadone or buprenorphine were more effective in retention as compared to placebo or no therapy.
  - OST using methadone or buprenorphine in higher dose was more effective in reducing illicit opioid use.
  - A meta-analysis of observational studies spanning publications of 21 years showed that patients on OST using methadone were four times less likely to die than those not in treatment.
  - OST using methadone significantly improved HIV-related outcomes (HIV risk behaviours, number of sex partners, frequency of unprotected sex, and rates of seroconversion).
- A joint position statement of WHO, UNODC and UNAIDS, 2004 described the cost effectiveness of OST as: "According to several conservative estimates, every dollar invested in opioid dependence treatment programmes may yield a return of between \$4 and \$7 in reduced drug-related crime, criminal justice costs and theft alone. When savings related to health care are included, total savings can exceed costs by a ratio of 12:1".

### **OST-RELATED OUTCOMES–INDIAN EVIDENCE**

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

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

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

### **KEY CHARACTERISTICS OF OPIOID SUBSTITUTION THERAPY**

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

- **OST is primarily a medical intervention.** The medical staff (doctor and nurse) play a lead role in OST intervention. The doctor conducts the assessment and diagnosis, plans and initiates treatment, monitors the progress and side effects, manages comorbidities and terminates treatment. The nursing personnel dispense the medications, and supervise the administration of OST medicines. Thus, the OST intervention is essentially a medical intervention led by the medical team and supported by the psychosocial team.
- **Adequate dose of medicines is one of the most crucial determinants of a good outcome.** The dose of medicines used for OST needs to be adequate and optimum. In general, the studies have found that the higher the dose, the better the retention in treatment and ultimate outcome.
- **Long duration of retention in continuous treatment is essential for a good outcome.** OST, as a medical treatment, is expected to last for a long duration, ranging from months to years. The OST medicines help the clients to stabilise their chaotic lifestyles associated with drug use and assists them to improve other areas of functioning, such as familial, social and occupational. As the clients settle down in their functioning and are ready, the treatment can

be tapered in consultation with the clients and their family members. In many instances, the treatment needs to be continued over years to maintain the benefits accrued by the clients. Thus, there is no fixed formula for determining the optimum duration of treatment of OST; the key factor in determining the duration is 'attainment of treatment goals' viz., achieving a lifestyle free from illicit substance use, optimum psycho-social functioning and reintegration into the society.

- **Combining psychosocial interventions along with dispensing of medicines forms the complete treatment package.** OST works best if psychosocial interventions are combined along with OST medicines. Psychosocial interventions help in improving retention, and minimise drop-out, assisting the clients in regaining family and social ties and in gainful employment.
- **Involving the clients at all the treatment stages is crucial for success.** OST works best if clients are involved in the decision-making process of OST intervention. Thus, the clients need to be involved in setting treatment goals, deciding the dose of treatment, the duration of treatment and the endpoint of treatment. These decisions, if taken along with client, help in improving client retention and outcome on OST.

## OPIOID SUBSTITUTION THERAPY MEDICINES

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

- Have **action similar to the illicit opioid** used by the clients. This is essential to effectively suppress the craving and withdrawals associated with cessation of opioid use. This means that an OST medicine should also be an agonist on the OPIOID receptors.
- Have **lesser addiction potential** as compared to the illicit opioid being consumed by the client. Any OST medicine will have some liability to result in addiction, as it is an opioid. However, its street value should be much less than the illicit opioids, i.e. users should not prefer the OST medicine over illicit opioids for their addiction/intoxication.
- Be **easy to administer** i.e. the medicine should be effective when administered orally or sublingually.
- Have **action lasting for at least 24 hours**, so that the frequency of administration should be once a day at the maximum.

### Pharmaceutical compounds commonly used as OST medicines

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

- Be **well tolerated**. The side effects should be minimal so that the clients find it acceptable to continue OST medicines for a long period of time.
- Be **cheaper, easily available, easily stored and transported**, so as to provide for a large number of clients with minimal financial or logistic constraints.

In India, methadone, buprenorphine and slow release oral morphine have been used as OST medicine. However, the use of buprenorphine exceeds that of the other two; OST programme under NACP currently uses buprenorphine as the OST medicine, and hence buprenorphine has been discussed in detail in subsequent sections. Methadone based OST is also being implemented at five sites in India, though not as a part of National AIDS Control Programme.

## STATUS OF OPIOID SUBSTITUTION THERAPY IN INDIA

As per the Global status of Harm Reduction report, 2016, OST is currently available in 80 countries; of these, most countries use methadone as the OST medicine, followed by buprenorphine. In India, OST has been available since the early nineties, when buprenorphine started being used in some Government hospitals as well as in some NGO settings. While the OST was available uninterruptedly in a few Government hospitals for both IDU as well as non-IDU opioid dependent users, the availability in NGOs was dependent upon funding from donor partners and restricted to only IDU population (as a HIV prevention tool). The NGO OST centres were subsequently supported under NACP, while the Government centres continued to provide OST for opioid dependent individuals through funding from the Ministry of Health and Family Welfare. Additionally, there are anecdotal reports of OST being provided through private drug treatment centres.

The large scale expansion of the OST programme began with the transition of existing OST interventions for HIV prevention by NACP in 2008, after its formal incorporation in 2007. Initially, the existing NGO OST centres were evaluated and accredited, and those which were found eligible were provided support by NACO. A total of 55 such centres have been provided continued support for OST implementation among IDUs. To further expand the OST programme, existing government hospitals at district and sub-district levels were included, and OST was initiated through the collaborative public healthcare model. Thus, currently (in 2016) there are two models of OST being implemented under NACP.

| <u>NGO OST CENTRES</u>                                                                                                                                                                                                                                                                      | <u>PUBLIC HEALTH OST CENTRES (COLLABORATIVE MODEL)</u>                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Part of IDU TI set-up. Staff largely shared with the IDU TI intervention</li> <li>• OST centre located within the DIC of the IDU TI</li> <li>• Medical intervention delivered by a trained part-time doctor and full-time nursing staff</li> </ul> | <ul style="list-style-type: none"> <li>• OST intervention jointly between the Government hospital and nearby IDU TI</li> <li>• OST centre located in Government hospital (Medical College/District Hospital/CHC/PHC)</li> <li>• Separate staff at OST centre for medical and psychosocial intervention</li> </ul> |

## METHADONE – BASIC PHARMACOLOGY

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

### CLASSIFICATION BASED ON THE ACTIONS ON OPIOID RECEPTORS

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

Methadone is a long-acting synthetic opioid developed initially as an analgesic. Methadone fulfils most criteria of an ideal medicine for opioid dependence treatment.

### EFFECTS OF METHADONE

It is a full-agonist at mu opioid receptor. Its action is similar to other opioid agonists such as morphine and heroin.

- Opioid effect on Central Nervous System (CNS):
  - **Analgesia:** Opioid agonists relieve pain. The pain relief is selective; other sensory modalities are not affected. Not only is the pain relieved, opioids help in making the pain more bearable, i.e. they change the way in which an individual perceives pain sensation.
  - **Euphoria:** Opioids elevate the mood and make the person calm. However, methadone produces significantly less euphoria compared to heroin.
  - **Sedation:** Opioids are not typical 'sleep inducing' agents. They produce dullness and stupor, also called as narcosis, and hence opioids are labelled as 'narcotics'.
  - **Miosis:** Opioids produce constriction of pupils. At toxic doses, the constriction is marked such that the pupils appear like a pin point. The pin point pupils are indicative of opioid toxicity/overdose, along with other features such as coma and respiratory depression.

- **Respiratory depression:** Opioids in large doses reduces the rate and volume of respiration. This is due to direct effect of methadone on brainstem respiratory centre receptors.
- **Cough:** Opioids act on the cough centre in the medulla and suppress cough reflex. This property makes opioids a very effective antitussive agent.
- **Nausea and vomiting:** opioids act on the chemoreceptor trigger zone and cause nausea and vomiting, especially in new users.
- **Opioid effect on other systems**
  - **Gastrointestinal system:** the most prominent effect on GI system is reduction in bowel movements and constriction of anal sphincter, resulting in constipation.
  - **Skin:** opioids cause vasodilation and results in flushing. Pruritus (itching) is a common complaint, especially among new users.
  - **Urinary bladder:** opioids increase the tone of the sphincter, sometimes, resulting in urine retention. Tolerance develops to this opioid property.
  - **Ejaculation:** Opioids do not have an effect on penile erection; they delay ejaculation. Many opioid users initiate opioids due to this property of opioids.
  - **Endocrine system:** Opioids inhibit hypothalamic release of gonadotropin releasing hormone, resulting in reduced levels of follicle stimulating hormone and luteinizing hormone. Tolerance often develops to this opioid property.

### **Methadone in opioid dependence**

Methadone helps in opioid dependence in the following ways:

- At lower doses, methadone helps in suppressing the withdrawal symptoms produced by sudden stopping of opioids. Methadone being a full agonist controls all the opioid withdrawal symptoms, thereby bringing enormous relief to the opioid dependent user.
- At intermediate doses, methadone also controls the craving related to opioids.
- At high (and optimal) doses, methadone also produces 'cross-tolerance' also called as 'narcotic blockade'. Methadone in high doses produces opioid tolerance to such an extent that other short acting opioids are not able to produce their effect. Thus, if an individual is on sufficient dose of methadone, he would not get opioid related 'high', even if he consumes street heroin/smack over and above his methadone dose. This cross-tolerance property makes methadone an ideal opioid agonist maintenance agent.

### **Pharmacokinetics of methadone**

- It is rapidly absorbed from the GI tract. The onset of effect of methadone is within 30 minutes, while the peak effects after an oral dose is about three hours.
- It is fat-soluble and binds to various body tissues. The concentration of methadone in body tissues is much higher than in the blood, and there is a slow transfer of methadone between the body stores and the blood. The half-life of the first dose of methadone is 12-18 hours, with a mean of 15 hours. With daily administration of methadone, the half-life is extended to 13-47 hours, with a mean of 24 hours. As a result, methadone can be taken once a day. It takes about 5 – 10 days of treatment to reach the steady state.



- Methadone is primarily broken down in the liver via cytochrome P450 enzymes. Only 10% of methadone is excreted unchanged. The metabolites of methadone are inactive and are excreted in the urine and faeces.

## SIDE EFFECTS AND SAFETY PROFILE

Used as an agent for long term maintenance, methadone is by and large, tolerable. Most unwanted effects reported by patients are related to the dose of methadone.

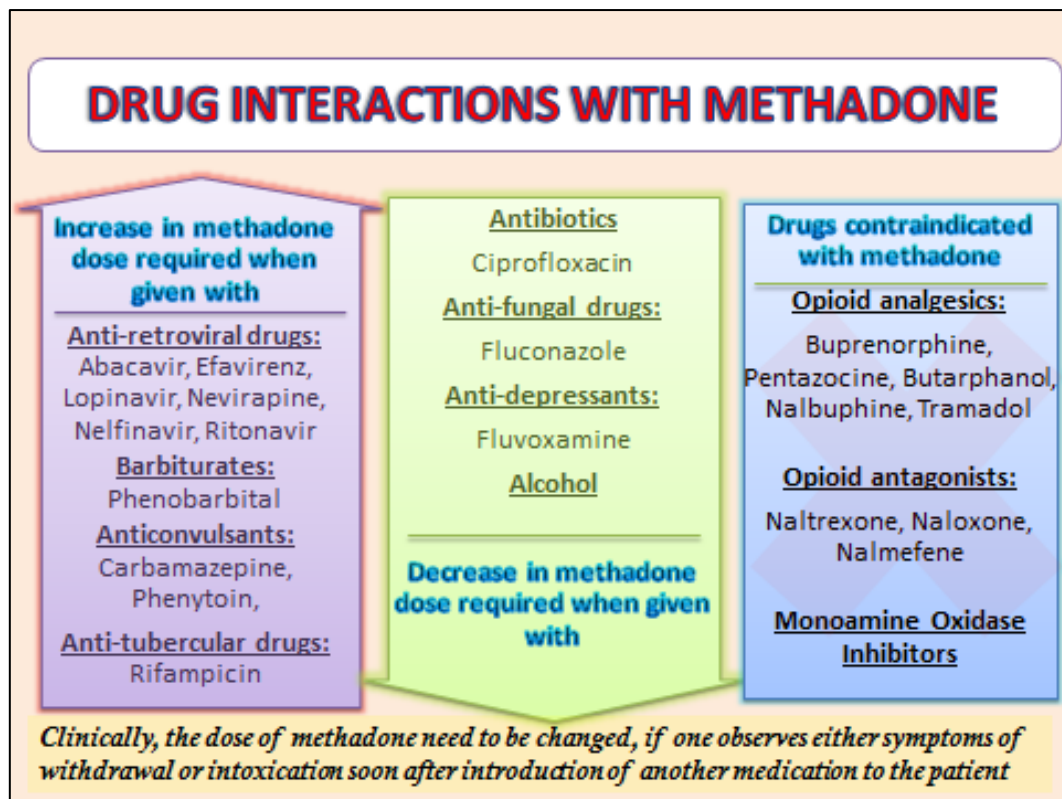
- **Somnolence:** caused by increased dose of methadone; tolerance develops to this effect.
- **Respiratory depression:** develops at very high dose of methadone. This is an emergency and needs to be managed by giving naloxone injections.
- **Sleep disturbance:** methadone interferes with deep sleep, and the patient may not feel refreshed despite spending enough time asleep.
- **Nausea and vomiting:** seen in the initial phase of methadone initiation. The management strategy is discussed in detail in the later section.
- **Cognitive disturbance:** patient may subjectively feel slowness in his thinking processes. Tolerance develops to this effect. Long-term use of methadone does not lead to impairment of driving or other motor skills.
- **Constipation:** patients on methadone may have chronic constipation. Tolerance does not develop to this side effect. Patients with intractable constipation may require reduction in doses of methadone.
- **Sweating:** excessive sweating is seen with methadone, which may not remit in some patients.
- **Sexual dysfunction:** may be seen in up to 20% of patients, which may not necessarily be due to methadone. Men may complain of decreased libido and orgasmic dysfunction, while women may additionally complain of oligomenorrhea.

## DRUG INTERACTIONS

As mentioned in the section on pharmacokinetics of methadone above, methadone is metabolised by cytochrome P450 group of enzymes. Other drugs that alter the cytochrome P450 enzymes can potentially affect the levels of methadone due to enhancement or inhibition of its metabolism in liver. In such cases, the dose of methadone may need to be altered. However, the most important indicator of such change is appearance of clinical symptoms or signs of methadone withdrawal or intoxication. Close follow-up and monitoring of those methadone maintained patients in which drugs with potential interactions are initiated should be done.

The figure below provides a tentative list of drugs with potential interaction with methadone. It should be remembered here that this is not an exhaustive list.





## ABUSE LIABILITY

Being an opioid, methadone can be abused. A person who has not used opioids before (opioid-naïve individual) will experience intoxication and other acute opioid effects on consumption of methadone. A dose of less than 20 mg of methadone per day is considered safe for a 70 kg individual even if opioid naïve, as this is the lowest dose as which toxicity is observed. Administration of higher dose can lead to overdose and death.

## FORMULATIONS AND LEGAL STATUS IN INDIA

Methadone is listed as a narcotic under the Narcotic Drugs and Psychotropic Substances (NDPS) act. Methadone has also been approved to be used for treatment of opioid dependence by the office of the Drug Controller General (India). The earlier provisions in the act were much stricter in terms of storage and transport of methadone. The last amendment of the act in 2014 has made the storage and transport of methadone easier. Methadone is now classified as an 'Essential Narcotic Drug'. The administrative department in charge of the licensing and reporting is now the State Drug Controller's office of each state where the MMT centre will operate. A centre working in Government hospital is now exempt from being recognised as 'Recognised Medical Institution'. The centre will not require a transport license to import methadone. The centre, however, has to furnish the required amount of methadone for the next financial year in advance as well as report the consumption incurred at the end of the financial year.

# CLINICAL PRACTICE GUIDELINES

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

#### **OST INTERVENTION UNDER NATIONAL AIDS CONTROL ORGANISATION**

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

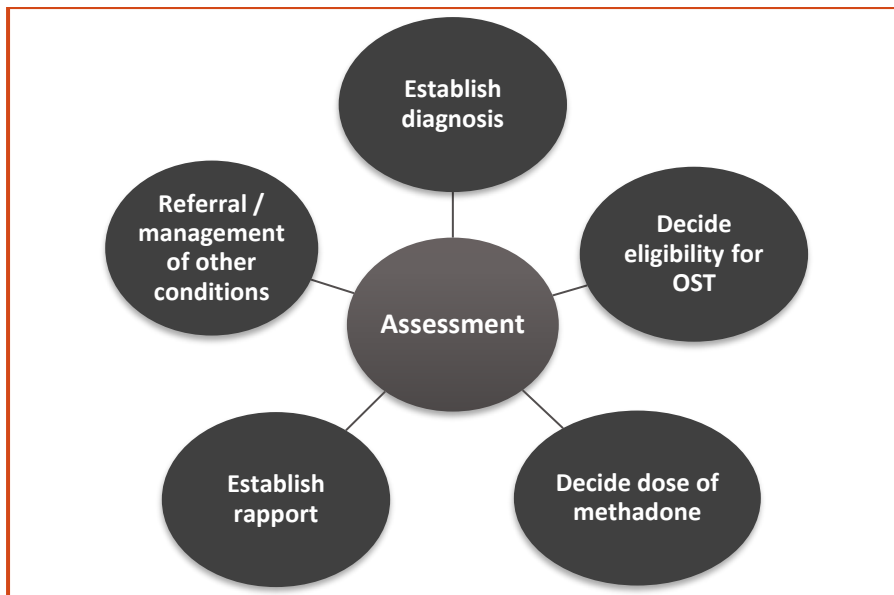
This section describes the clinical practices involved in OST implementation as guided under NACO. The areas covered in this section include:

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

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

## **ASSESSMENT AND DIAGNOSIS**

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



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

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

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

#### ASSESSMENT MODALITIES

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

#### ASSESSMENT AREAS

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

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

- **Socio-demographic details** including the client's name, age, sex, marital status, educational status, occupational and employment status, and current contact information are required.
- **Psychoactive substance use details** including chronological order of initiation of substance use, and for every substance, the age of initiation, progression, frequency of use, mode of intake of substance, any dependence features, usual dose, and last dose of intake have to be noted.
- **Complications due to substance use** can be psychological (guilt, shame, depression, anxiety, etc.), financial (loss of money, debts, etc.), familial (fights, violence, neglect, homelessness, etc.), social (outcast, ridicule, discrimination, etc.), occupational (loss of job, irregular in work, frequent change of job, etc.), and legal (thefts, robbery, drug dealing/peddling, imprisonment, etc.).
- **High risk behaviours:** Both injecting (sharing, reuse of needle/syringes or other paraphernalia) and sex-related (sex with female sex workers, multiple sex partners, sex in exchange of drugs/ money, sex under the influence of substances, non-use of condoms) are high risk behaviours.
- **Abstinence attempts:** Any attempts to give up psychoactive substance use should be noted. For every significant attempt, the duration of attempt, reason for abstinence, type of help received, reason(s) for relapse should be tracked. An abstinence attempt may be considered as significant if the client was able to completely stop substance use for a duration of one month or more.

- **Psychosocial support:** The nature of relationship with family members particularly spouse, the nature of relationship with non-drug-using friends, attitude of family/friends towards client's drug use, possibility of involvement in treatment process, etc.
- **Current living arrangement:** Type of accommodation, family members sharing accommodation, etc.
- **Evidence of injection:** Any needle track marks, scarring of tissue, abscesses, ulcers, etc.
- **Evidence of current intoxication:** Slurring of speech, altered sensorium, change in rate of speech, disinhibition, gait disturbance, etc.
- **Evidence of current withdrawals:** Specific to the substance of use.  
For opioids: Lacrimation, rhinorrhoea, yawning, dilated pupils, increased sweating, restlessness, palpitations, increased respiratory rate;  
For alcohol/benzodiazepines: Anxiety, restlessness, tremors of hands, increased respiratory rate, palpitations, sweating, etc.

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

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

## DETERMINING SUITABILITY OF CLIENTS FOR OPIOID SUBSTITUTION THERAPY

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

### ESSENTIAL CRITERIA FOR OST INITIATION:

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

1. **DIAGNOSIS OF OPIOID DEPENDENCE SYNDROME:** A diagnosis of opioid dependence syndrome is essential as OST is a specific medical treatment for this condition. Mere use of street opioids or injecting drug use is not sufficient to consider OST. Hence, before starting treatment, the doctor should carefully assess the pattern of opioid use by the client and consider OST only if the client meets the criteria for opioid dependence discussed above.
2. **CURRENT IDU:** The client should meet the operational criteria for IDU established under NACP i.e. he/she must have injected a psychoactive substance **at least once in the past three months** for non-medical purposes.
3. **ABSENCE OF MEDICAL CONTRAINDICATIONS:** The client must not suffer from such medical disorders that prevent him/ her from being initiated on OST. Severe respiratory and hepatic dysfunctions are contraindications to start methadone treatment. Mild respiratory or hepatic insufficiencies are relative contraindications and do not preclude the use of methadone.
4. **HYPERSENSITIVITY TO METHADONE:** Clients who have been exposed to methadone in the past and experienced hypersensitive reactions should not be initiated methadone.
5. **INFORMED CONSENT:** The client must have the mental capacity to provide informed consent, and be willing to start on OST after understanding the implications, requirements, safeguards to be taken, etc. Under NACP, written informed consent is a must before OST can be prescribed to any IDU.
6. **Client's willingness to come daily to receive treatment:** At the time of initial assessment, the client should be educated about the need to come to the OST centre every day to receive treatment under supervision. Only those clients who agree to adhere to this mechanism should be initiated on treatment after duly signing the informed consent.

### DESIRABLE CRITERIA FOR OST INITIATION

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

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

dependence in a given client as well as lesser chances of recovery with other shorter duration treatments like detoxification.

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

## CONDITIONS REQUIRING SPECIAL CONSIDERATIONS FOR OST INITIATION

There are certain conditions in which caution should be exercised while prescribing OST to IDU clients.

1. **SEVERE DEPENDENCE ON ALCOHOL OR BENZODIAZEPINES:** If the clients have concomitant use of alcohol or benzodiazepines, and have higher degree of dependence on these substances through heavy use, OST may not be started in the OST centre itself. Such clients should be referred to a psychiatrist/ drug de-addiction centre before initiating on OST and may require inpatient treatment. Most IDU clients inject a cocktail of opioid drugs (buprenorphine/pentazocine/heroin/d-propoxyphene) along with sedatives (diazepam/pheniramine /promethazine). Such clients are seen as primarily dependent on opioids and can be safely started on OST.
2. **MEDICAL ILLNESSES:** Caution should be exercised if the client is suffering from medical problems such as inflammatory bowel diseases, renal conditions causing urinary retention, biliary colic, and head trauma.
3. **PSYCHIATRIC ILLNESSES:** if client is suffering from a psychiatric illness which impairs his capacity to understand the treatment process and to give informed consent, OST should not be started. Such patient must be referred to a psychiatrist, and opinion sought before starting methadone.



### **LABORATORY TESTS FOR OST:**

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

## PREPARING CLIENTS FOR OPIOID SUBSTITUTION THERAPY

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

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

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

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

## METHADONE-BASED OPIOID SUBSTITUTION THERAPY

OST with methadone 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 methadone is taken
- **Termination phase:** Phase from decision to stop methadone to the last dose of methadone

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

### INITIATING OST WITH METHADONE – 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 methadone 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 methadone, 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 client has at least mild opioid withdrawals. This is important to minimise chances of overdose with methadone.
- The client is not intoxicated with alcohol or benzodiazepines, as these mask opioid withdrawals and it becomes difficult for the clinician to make a judgement about the initiating dose of methadone. The client is also at risk of overdose, if methadone is given over and above the illicit opioids or alcohol/benzodiazepines.

The induction phase for methadone based OST lasts for a period of about 2–3 weeks. The general dictum of methadone induction is “**START LOW AND GO SLOW**”. This is in contrast with buprenorphine induction, where the maintenance dose is reached in 3 – 4 days.

The first dose of methadone usually is 15 – 20 mg. If there is doubt regarding the recent intake of opioids, the client can be started on a lower dose of 10 mg. The client should be assessed 2 – 3 hours after the first dose to observe for the peak effect of methadone. If the client experiences withdrawal even after four hours after the first dose, an additional 5 mg dose can be administered. It is advisable not to administer more than 25-30 mg on day one. As methadone accumulates in the body in the initial 5 – 10 days, the client should be reassured that the same dose of methadone will have greater effect on subsequent days.

The client should be reassessed by the doctor every fourth day to assess the adequacy of the dose of methadone given. The client should not suffer opioid withdrawals and craving for an entire day with the methadone dose provided. In addition, the client should not be intoxicated with methadone after taking his dose. The dose can be increased by 5 – 10 mg every fourth day. The total dose of methadone should not exceed 40 mg/day in the first week. The total dose increase in a week should not exceed 15 mg.

### **METHADONE DOSING DURING INDUCTION**

The goal of treatment in the first 2 – 3 weeks is to ensure that the client does not suffer opioid related withdrawals or craving in between doses. Rapid increase in methadone dosing should not be done, especially in the initial weeks. It is seen that the greatest risk of **OVERDOSE WITH METHADONE IS DURING INDUCTION PHASE**. The guideline for dosing mentioned above should be followed to ensure that clients do not overdose on methadone.

Maintaining clients on appropriate dose of methadone is very important. It should be remembered lower dose of methadone can alleviate withdrawals and craving, while higher doses of methadone is required for achieving 'cross-tolerance' so as to prevent experiencing euphoria from illicit opioids. Achieving this maintenance dose may take 3 – 4 weeks.

While guidelines from western countries recommend a maintenance dose of 60 mg per day of methadone and above, experience from India shows that for optimum outcomes, doses of 40 – 60 mg of methadone per day is sufficient for most clients. For maximum dose too, the guidelines from western countries suggest a maximum of 150 mg/day; however, in India, a dose of 90 – 120 mg per day can be considered as maximum dose. If the clinician feels that the client is not improving despite the maximum dose, the client may be referred to a higher centre specialising in substance use treatment for further management. However, if the client is on concomitant medications that can potentially alter the metabolism of methadone, higher than 90 – 120 mg/day of methadone may be required.

Apart from stabilising the dose of methadone, 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.

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## MAINTAINING CLIENTS ON METHADONE – MAINTENANCE PHASE

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

### GOALS OF MAINTENANCE PHASE

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

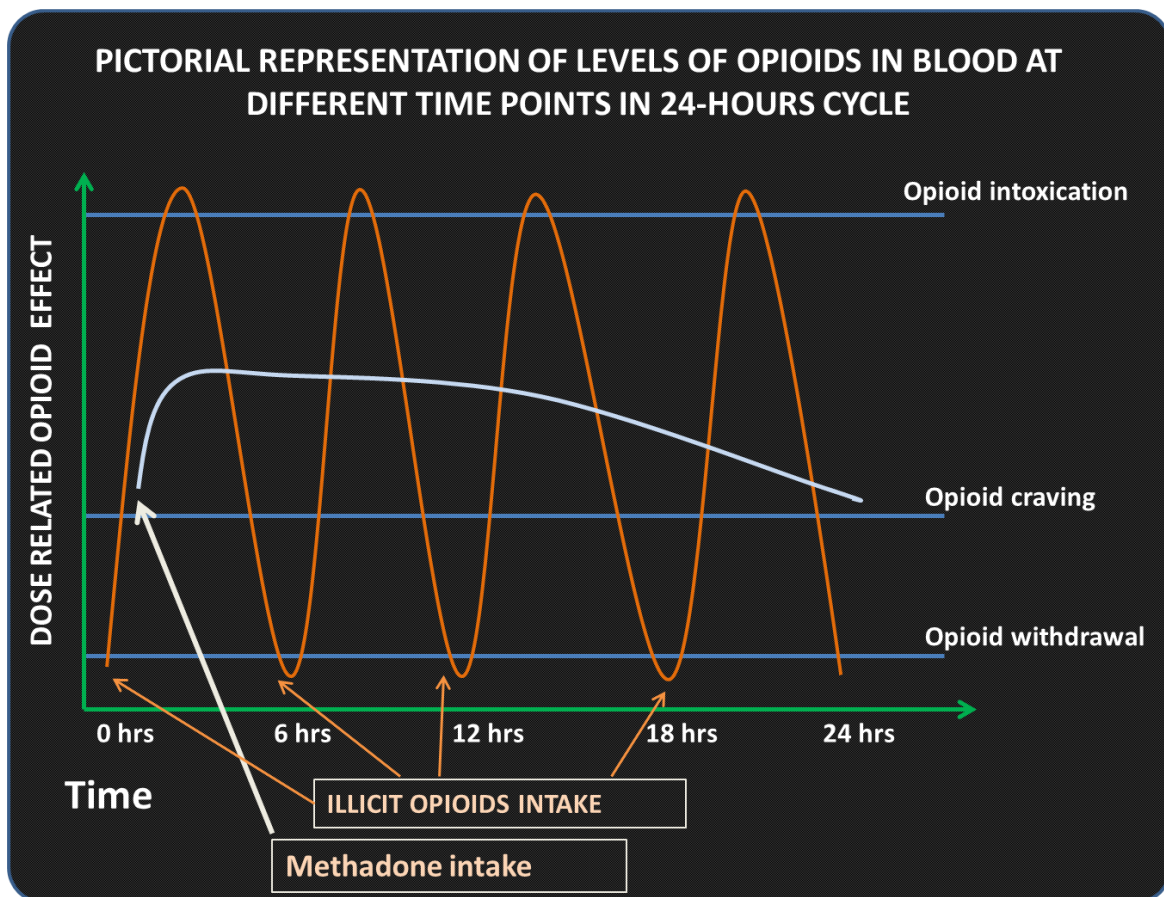
### METHADONE MAINTENANCE DOSE:

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

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

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

If the clients report that they still have (a) withdrawals or (b) craving or that (c) they use injections/ other opioids and experiences euphoria on opioid use, it is an indication to the doctor that the dose of methadone is inadequate. In such cases, the doctor must increase the dose of methadone to an optimum level. Care must also be taken to ensure that the client does not experience opioid intoxication effect due to use of methadone such as sedation, slurring of speech, incoordination, etc. Such effects are related to the peak plasma blood levels of methadone typically seen 2-4 hours after administration of the daily dose. Thus, the dose of methadone must be such that the client neither has a peak effect of intoxication nor has the trough effect of withdrawal/craving. A pictorial representation of difference between the level of illicit opioids such as heroin and methadone is shown below.



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

#### REDUCTION OF MAINTENANCE DOSE

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

It should be important to note that the **SAME DOSE OF METHADONE AS REQUIRED IN THE INITIAL STAGES SHOULD BE CONTINUED**, unless the client reports of any methadone -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 client should now resume his/her responsibilities, sometimes at the cost of continued OST. The service providers must emphasise on the need for long-term continuation of OST medicines. The principles of motivation enhancement can be applied for encouraging the client to continue OST. Additionally, the family members must also be counselled on the need for continuation on OST.

#### METHADONE DISPENSING

As per NACO guidelines, dispensing of methadone is to be done on 'Daily Observed Treatment' basis at the OST centre. This means that the client has to come to the OST centre daily and take his medicines in front of the OST nurse. Methadone is available in liquid to be given orally. Methadone will be available in liquid form in the strength of 5 mg per ml. Further details on the dispensing procedure are provided in the document on standard operating procedure.

#### ADDRESSING CO-MORBID SUBSTANCE USE

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

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

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

#### REFERRAL TO OTHER SERVICES

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



client should also be encouraged to adhere to both OST as well as medications prescribed for such co-morbid conditions.

## **ASSISTANCE IN RE-INTEGRATION**

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

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

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## **TERMINATING CLIENTS ON METHADONE – TERMINATION PHASE**

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

### **GOALS OF TERMINATION PHASE**

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

## **DECISION TO STOP METHADONE**

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

Some indicators of successful termination can include:

- a) cessation of opioid and injecting use,
- b) cessation of illegal activities,
- c) improved ties with family,
- d) strong psychosocial support,
- e) well-maintained occupational functioning, and
- f) client 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 METHADONE

Before tapering off methadone, 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.

### 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 40 mg per day of maintenance dose to 15 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.

**Methadone must not be stopped abruptly**, as otherwise the client would experience withdrawals and there would be the consequent risk of relapse to illicit opioid use. The process of tapering must be gradual. There is no fixed regime for tapering methadone 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 require admission to a hospital for tapering off methadone.

The outpatient taper can be done over 2 – 3 months duration. In outpatient tapering, the tapering can be done in units of 10 mg of methadone every 7 days, till the client reaches a dose of 40 mg of methadone. Further tapering can be done in units of 5 mg of methadone every 7 days till the dose of 20 mg/day is reached. If the client complains of withdrawals or discomfort, the tapering can be more gradual in units of 2.5 mg every 7 days. The final tapering can be achieved in units of 2.5 mg methadone every week. Inpatient tapering can be faster than outpatient tapering and can be achieved in 2 – 3 weeks.

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## MANAGEMENT AFTER TERMINATION OF METHADONE

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

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

### CRITICAL ISSUES IN OST PROGRAMME

- Selection of appropriate clients for OST
- Optimal dosing of methadone
- 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 methadone are properly maintained and replenished at regular intervals, so that there is no stock-out situation in the centre
- Record maintenance: The prescribed records should be properly maintained at the OST centre

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

## MANAGEMENT OF UNIQUE CLINICAL SITUATIONS

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

### VOMITING

Vomiting may be experienced by some clients on methadone, especially in the first few days. Vomiting usually subsides within a few days. The client may be prescribed oral anti-emetics, which can be administered half an hour before taking methadone. In some cases, it may happen that the client has vomited soon after receiving his methadone dose. In such cases, replacement dose may be required for that day. This should be done, if the vomiting is confirmed. The guidelines for replacing the dose of methadone can be as follows:

| SITUATION                                        | REPLACEMENT STRATEGY              |
|--------------------------------------------------|-----------------------------------|
| Vomiting <15 minutes after dose administration   | Consider replacing 50-75% of dose |
| Vomiting 15-30 minutes after dose administration | Consider replacing 25-50% of dose |
| Vomiting >30 minutes of dose administration      | No need for replacement           |

### CONSTIPATION

Constipation can be one of the side effects of methadone-based OST. A client complaining of constipation after methadone 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 methadone intoxication, such as increased drowsiness, gait abnormalities, slurring of speech etc. If the symptoms/signs of methadone intoxication are present, a careful reduction in dose may be helpful in relieving constipation. If no organic pathology is detected, conservative measures should be instituted initially. The client may be advised dietary change, increased consumption of water, increased physical activity, etc. If these measures do not improve constipation, the client may be prescribed laxatives. If all of these measures do not help improve constipation, the doctor should then consider decreasing the dose of methadone. In many cases, constipation may be a trade-off; experiencing constipation with the same dose of methadone or undergoing the risk of withdrawal or relapse if the dose is lowered to relieve constipation.

### SLEEP DISTURBANCE

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

If the client is dependent on benzodiazepines, management of benzodiazepine dependence must be undertaken independent of OST. For sleep disturbance, the

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

### SLEEP HYGIENE

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

### **MISSED DOSES**

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

- If the client misses one day's dose of methadone, the client can be given the same dose of methadone as before.
- If the client misses two – three days' dose of methadone, 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 methadone and the dose can be gradually increased depending on the client's response in the subsequent days.
- If the client misses his dose of methadone for more than three days, the same dose of methadone should not be given to the client, as tolerance to opioids can be lost even within three days. The client should be treated as a 'new' client and methadone should be re-induced, starting from induction phase till the client is stabilised.

## OVERDOSE

As methadone is a mu opioid agonist, the chances of opioid overdose are greater as compared to buprenorphine. Hence, the OST centre providing methadone must be prepared to deal with overdose related emergencies. Each centre must have:

- A. Adequate storage of Naloxone injection
- B. Liaison with a hospital providing emergency services

The risk for methadone overdose is greater during the initial few days during induction phase. In case, the client develops overdose, naloxone must be immediately injected. Naloxone is an opioid antagonist, and is effective through parenteral route. It is a specific antidote to opioid overdose. Though intravenous administration gives the fastest results, the veins may not be easily located. Intramuscular administration is also effective. The dose of naloxone is 0.8 – 1.6 mg. It should be remembered that the effect of naloxone lasts for 60 – 90 minutes only, and hence the client should be monitored even after the symptoms of overdose subside with naloxone injection. After the acute administration of naloxone, the client should be shifted to emergency department of a nearby hospital for continued monitoring. Monitoring should be continued for 24 – 36 hours after overdose.

### Opioid overdose clinical features

- Breathing: Slow and shallow breathing
- Pupils: Pin-point pupils
- Appearing sedated; not responding despite painful stimulus
- Cyanosis: bluish fingernails and lips
- Nausea and vomiting
- Slow pulse
- Snoring
- Coma

## 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 IDU client who is on OST should be referred to ICTC for HIV testing after pre-test counselling. If the client is tested as HIV positive, he/she should be referred to ART centre for registration and for decision on initiation of ART medicines. If the client is HIV negative, he/she should be educated on high risk behaviours and strategies to prevent high risk behaviours as well as HIV prevention during high risk behaviours. The doctor need not wait for the HIV test results before initiation of 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.

Drug-drug interactions are observed between methadone and some ART medications, a list of which is provided in the section on pharmacology of methadone. The client should be closely monitored if ART medicines have been initiated, or new ART medicines have been introduced in the ART regimen. For modifying the dose, the doctor should be guided by the clinical presentation. If symptoms of opioid withdrawal are noticed or the client complains of discomfort after initiation of ART during OST

maintenance phase, the doctor should increase and titrate the dose of methadone as per the client's comfort level. Similarly, the dose of methadone 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. The guidelines for dose increase or decrease is the same as mentioned in the induction phase.

## **TUBERCULOSIS**

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

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

## **ADOLESCENTS**

While methadone is considered safe for use in anyone above the age of 12 years, the use of this medication for OST in population aged less than 18 years has not been as systematically studied as for the adult population. Usually, clients from this age-group have short duration of opioid use and even shorter duration of injecting drug use. As a result, a view held commonly by experts is that detoxification followed by antagonist treatment should be tried initially, and if this strategy fails, agonist medications should be considered. However, others are of the view that adolescents also have a high risk of sharing, overdose and other opioid-related complications, and hence, agonist treatment with methadone should be considered for this population. Moreover, detoxification and antagonist treatments are not available everywhere, hence, it is not possible to wait for a trial of such treatments in every opioid-dependent adolescent.

If a client falls in the age group of less than 18 years, OST should not be denied straightaway. A careful assessment of the client's drug use and associated high risk behaviour should be made. Consideration must be given to the duration of opioid use, associated high risk behaviour, especially sharing of injecting equipment and sex-related behaviour. If there is a long history of opioid use (>2 years) along with injecting drug use and associated high risk behaviour, OST with methadone may be considered.

There would be issues around obtaining informed consent, as consent from person less than 18 years old may not be considered valid. Hence, consent from either of the parents, or from a guardian (older than 18 years) may be obtained before initiating OST, besides obtaining the 'assent' from the minor client.

## **FEMALE POPULATION**

There are some special considerations with opioid dependent female patients who inject drugs. Females are more vulnerable to HIV and other complications due to injecting as compared to their male counterparts. More often than not, females have a male partner who is also an IDU, as a result

of which they have to use the injections and injecting equipment after the male uses them. Some female IDUs resort to sex work to support their drug using habit. In addition, they also have to take care of children, which add to their burden. Female IDUs are often looked down upon by the neighbours and the society, resulting in greater stigma and discrimination. Finally, female IDUs have lesser accessibility to general healthcare services as well as HIV prevention programmes or drug treatment services. The staff of OST centre should bear these vulnerabilities in mind when attending to female IDUs who wish to be initiated on OST.

#### Considerations while providing OST intervention to a Female Injecting Drug User

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

## **PREGNANCY AND BREAST-FEEDING**

**OPIOID SUBSTITUTION THERAPY IS RECOMMENDED FOR PREGNANT WOMEN DEPENDENT ON OPIOIDS.** The process of induction and maintenance is the same as for other patients. Care should be taken to ensure that termination of OST is not attempted in the first and the third trimester due to risk of abortion or pre-term delivery. The dose of methadone may need to be increased in the third trimester due to increased volume of water during the third trimester of pregnancy. However, this should be done by clinical assessment of withdrawal. Methadone should be continued throughout the labour. The dose of methadone may need to be reduced after delivery. Methadone should be continued after the delivery. Breast-feeding can be continued, as breast milk contains only small amounts of methadone.

The staff of the OST centre should inform the obstetrician and the neonatologist/ paediatrician about the dose of methadone 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 methadone. After delivery, methadone levels fall in the child's blood due to non-availability of methadone resulting in opioid withdrawals. The clinical features and management of NAS is provided in Annexure B.

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

## **SHIFTING FROM BUPRENORPHINE TO METHADONE**

At times, it may be required to shift clients maintained on buprenorphine to methadone. This may be because of various reasons. Clients may not be benefitting from buprenorphine and may continue to inject or use opioids by other routes despite being on adequate doses. Some clients may have serious and intolerable side-effects with buprenorphine and may want to stop the medicine. In such cases, shifting the client from buprenorphine to methadone can be considered.

Before considering shifting to methadone, the client should be explained the difference between buprenorphine and methadone. This may include increased chance of opioid overdose with methadone, the fact that it takes longer time to build maintenance dose with methadone as compared to buprenorphine or that there is no provision for take-home methadone dose. If the client agrees to switch from buprenorphine to methadone, it should be explained that it will take some days to wean off from buprenorphine and build an adequate methadone dose. The client may experience withdrawals during these days, and he/she should try to remain abstinent during such time, or at least adopt safer ways to use opioids.

There are no fixed guidelines on regimen to switch from buprenorphine to methadone. The treating doctor should be watchful of opioid overdose symptoms during the switch period from buprenorphine to methadone. One way to switch is to reduce the dose of buprenorphine to as minimum dose as sufficient for withdrawal control in a day. Switching is usually not advised at buprenorphine dose of more than 8 mg/day. When the buprenorphine dose of 8mg/day or less is achieved, further dose should be withheld till the client experiences some withdrawal symptoms. It is not necessary for objective withdrawal signs to be present, but the pupils should not be constricted. If the client exhibits withdrawal symptoms/signs, then the first dose of methadone can be administered. The dose of methadone can be 15-20 mg/day on the first day, which needs to be continued for the next 2-3 days. Further increase should be as described in the induction phase above.

## **SWITCHING FROM METHADONE TO BUPRENORPHINE**

Some clients may experience intractable vomiting or severe constipation with methadone. Such clients who would not be able to tolerate methadone may prefer shifting to buprenorphine. It is also possible that some clients may want to shift to buprenorphine after spending some time on methadone. Though the treatment team should dissuade from shifting to buprenorphine in such cases, especially if the client has been maintaining free from opioids while on methadone. However, if the client is not ready to continue methadone despite advice to the contrary, then such a shift can be considered. Similarly, a methadone client may plan moving to a city/town where methadone services are not available, but has access to buprenorphine treatment. In such cases too, a shift from methadone to buprenorphine can be considered.

As mentioned in the preceding section, it will also take some time for the client to adjust to the new medicine and its dose. The treating doctor should be watchful of precipitated opioid withdrawals in the initial period of switch from methadone to buprenorphine. Here too, there are no fixed guidelines on switching from methadone to buprenorphine. However, the dose of methadone should be reduced to the extent that the client does not experience withdrawals with the reduce dose. Switching should not be done at doses of higher than 20 mg/day of methadone. After the methadone dose has been reduced to 15-20 mg per day (or lesser if the client can tolerate) of methadone, further doses of methadone should be withheld and wait for some withdrawals to emerge. It may take more than one day for the withdrawals to emerge in case of methadone. Once the client experiences some withdrawals related discomfort, buprenorphine can be initiated. The first dose of buprenorphine can be 4-6 mg per day, which can be continued for the initial few days before the dose can be increased.

In switch from one medicine to the other, the client should be followed up more closely in the initial few weeks. If the client is not comfortable with his 'new' medicine and wants to switch back to his previous medicine, the same should be allowed.

## CONCLUSIONS

Opioid Substitution Therapy (OST) is an effective treatment option for opioid dependence as well as HIV prevention intervention for opioid dependent IDUs. The clinical practice of methadone-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. Methadone is relatively a safer medicine to use. Appropriate client selection, an adequate dose of methadone as well as for an adequate duration is an important determinant of a successful OST intervention. The attitude of staff towards the clients, combined with other issues such as dispensing hours of the clinic, provision of ancillary services are other important determinants of the success of OST intervention.

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# ANNEXURES

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

Modified Finnegan Neonatal Abstinence Syndrome Score chart for term infants:

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

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

## **Treatment**

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

### ***Pharmacological treatment:***

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

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

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