INTRODUCTION

The problem of drug abuse is in existence in most of the societies over the world since the time Immortal. However, the problem has become more complex and alarming in the recent years. (Gautam S et al 2000). Of the various substance use disorders, opioid dependence syndrome has a significantly major impact on mortality and morbidity.

Over the past few years, scientific progress has changed our understanding of the nature of opioid dependence and its various possible treatments. Drug dependence is a chronic illness treatable if the treatment is well delivered and tailored to the needs of the particular patient. There is indeed an array of treatments that can effectively reduce drug use, help manage drug cravings, prevent relapses and restore people to productive social functioning. The treatment of drug dependence will be part of long-term, medical, psychological, and social perspectives. (Baltieri et al. 2004).

There are historical reports on the use of opioid such as those descriptions of Assyrian ‘poppy’ art dating from 4000 BC and from studies of Egyptian, Greek, and Persian cultures. The term opium derives from the Greek word for ‘juice’ and refers to juice from the poppy plant Papaver somniferum (Gold MS, 1993).

In the nineteenth century, millions of Chinese people became addicted to opium after smoking, eating, drinking, or sniffing it. Purified derivatives of poppy latex, such as morphine, were available. Named after Morpheus, the Greek god of dreams, morphine was isolated from opium in 1806 by Sertturner. In rapid succession, many of 20 distinct alkaloids of opium were isolated, including codeine in 1832 and papaverine by Merck in 1848, with many of these alkaloids continuing to be used and abused.

With the availability of parenterally administered opiates and the invention of the hypodermic syringe, opiate addiction and opiate withdrawal distress became major worldwide public health problems (Fernandez H. 1998). The recent trends show several changes in habits and behavior, including a frightening increase in the use of drugs throughout the world. This has included an increase in opioids as drugs of abuse (Cangenciam MW et al. 2001).

Epidemiology

Use of illicit opioids around the world: In 1994 the United States (U.S.) Office of National Drug Control Policy (ONDCP) reported some key trends in heroin use; more teenagers and young adults and more middle- and upper-middle-class people were using purer heroin, and the proportion of people seeking for treatment continued to increase. Around 2000-2001 the number of opium or heroin abusers was estimated at almost 15 million (0.2%) of the world population.

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In 2002 the main illegal opium producing countries were Afghanistan (76%), Myanmar (18%), Laos (2%) and Colombia (1%).

In spite of scant data, prevalence rates for alcohol and illicit drug abuse among doctors seem to be similar to those in the general population. As regards prescription drugs, like benzodiazepines, amphetamines and opioids, however prevalence among doctors is apparently higher than in the general population, due to easier access to these drugs.

Consumption within the country and its implications (Indian Data)

According to UNDCP report that the prevalence rate of opiate user is 0.4% for India. While this is in itself highly improbable, here an attempt is made to address this within a different context.

The total population of India, for 2002 is 1,027,015,247. From this the male population being 531,277,078, as the separate figures is available for those above 60 years, which is 32,407,901, then the male population to be considered is 498,869,177. Considering prevalence to be 0.4% then the users are around 1,995,476.

Drug Abuse Monitoring Systems data on profile of drug users (Siddiqui, 2002) indicate that among drug users from Rajasthan, 39.8% use opium and heroin is used by 30.45% of the person who seek treatment. Seeking care for opium use became significant in Rajasthan after enforcement of NDPS Act and the Government’s unplanned systematic reduction of legal outlets for distribution of opium. Other studies do indicate that the cultural practice of opium use in Rajasthan and Gujarat existed for centuries. In Gujarat it has been given as a drink to greet guest, to celebrate marriage or seal a business deal. The quantity consumed is very small but refusal can be seen as an insult (Masihi et al., 1994). The age of those who seek treatment after the implementation is above fifty years, this is an indication that use has not led to major consequence as in the case of heroin where the age of those seek care are from lower age group.

Drug Abuse Monitoring Systems (DAMS) (Siddiqui, 2002) collected data from 203 treatment centres from 23 States, two union territories and Delhi, the national capital. The total sample of users is 16942. According to the study the mean average age is 35.3 years, 97.2% of the users are male and number of respondents for the study were equally distributed between rural (51.7%) and urban (48.3%) areas. Female users were reported from three states and their state wise data showed for Andra Pradesh 10.5%, Manipur 9.8% and Mizoram 6...9% were women.

The Rapid Assessment Survey of Drug Abuse (Kumar, 2002) the focus was on use of drugs other than alcohol. It was undertaken with specific focus on use of opiates and injecting behaviour for four metropolitan cities (Delhi, Chennai, Mumbai, Kolkata) and Imphal, capital of Manipur state. Among drug users 71.1% is heroin consumers, 25.8% users of other opiates and 1.3% take sedatives.

Creation of guidelines

This guideline aims at providing guidance to psychiatrists and other mental health professionals who treat patients with Opioid Dependence Syndrome. It comments on the somatic and psychosocial treatment that is used for such patients, and reviews scientific evidences and their strength.

The terminology used in this guideline is consistent with the ICD-10 and DSM-IV Classification of Mental and Behavioral Disorders.

The reader is encouraged to consult this guideline and the accompanying references when specific treatment recommendations are sought for. However, this text is not intended to stand by itself, as data are subjected to change as scientific knowledge and technology advances.
**Definition of terms**

(i) **Opioid Physical Dependence** - demonstrated by the presence of opioid withdrawal on cessation of/or a marked reduction in opioid use, or on the acute administration of an opioid antagonist. The signs and symptoms of opioid withdrawal have been well characterized, and include features such as rhinorrhea, gooseflesh, and mydriasis.

(ii) **Opioid Dependence Syndrome (Addiction)** - characterized by a clustering of signs and symptoms associated with pathologic use of opioids; an alternative term that can be used for syndromic opioid dependence is opioid addiction. One feature of this syndrome of dependence can be physical dependence, along with the presence of physical dependence is not required for the diagnosis of syndromic dependence. Criteria for syndromic dependence, such as those found in the DSM-IV-American Psychiatry Association - are widely used.

(iii) **Tolerance** - Tolerance develops when after repeated administration, a given dose of a drug produces a decreased effect, or conversely, when increasingly larger doses must be administered to obtain the effects observed with the original dose.

(iv) **Relapse** - The recurrence on discontinuation of an effective medical treatment of the original condition from which the patient suffered.

(v) **Withdrawal** - The psychological and physiological reductions to abrupt cessation or reduction of the drug dose.

**Opioid Classification**

- **Narcotic agonist**: include natural opium alkaloids (e.g. Morphine, Codeine), Semi-synthetic analogs (e.g. Hydromorphone, oxymorphone, oxycodone), and synthetic compounds (e.g. Mepridine, levorphanol, Methadone, Sulfentanil, alfentanil, fentanyl, remifentanil, and levomethadyl).

- **Mixed agonist-antagonist drugs** (e.g. Nalbuphine, pentazocine) have agonist activity at some receptors and antagonist activity at other receptors: also included are the partial agonists (e.g. butorphanol, buprenorphine).

- **Narcotic antagonists**: Narcotic antagonists (e.g. Naloxone) do not have agonist activity at any of the receptor sites. Antagonists block the opiate receptors, inhibit pharmacological activity of the agonist, and precipitate withdrawal in dependent patients.

**Opioid Receptors**

The word opioid is assigned to any substance, whether endogenous or synthetic, that presents, to a varying degree, morphine-like properties. The term opiate is frequently used to refer to synthetic opioids (Baltieri DA, 2001).

Opioids act in the central nervous system (CNS) and in peripheral organs, such as bowels. There are at least four types of specific receptors for opioids, situated primarily in the sensory, limbic and hypothalamic areas, amygdala and periaqueductal sylvius.

Mu (m) – subtype 1 accounts for the symptoms of analgesia, elation and respiratory depression; subtype 2 mediates gastrointestinal (GI) effects, like constipation;

Kappa (k) – mediates analgesia, sedation, miosis, dysphoria and psychotomimetic symptoms as depersonalization and derealization;
Delta (d) – mediates analgesia and may be associated with mood changes;
Epsilon (e) – may be associated with sedation.

Opioids – Neurobiologic aspects

Despite the use of opium for thousands of years, it was only in the 1970s that the existence of opioid receptors became a reality and subsequently endogenous opioids were identified. Although opioid receptors' biology is well known, the physiological systems regulated by opioids and responsible for the analgesic effects and for other actions are partially known (Dickenson, AH, 2001).

The opioid receptors are coupled to G° and G1 proteins and the inhibitory actions of opioids occur from the closing of calcium channels (in the case of kappa receptor) and the opening of potassium channels (for mu and delta receptors). These actions either result in reduction in transmitters' release or depression of neuronal excitability depending on the pre- or postsynaptic location of the receptors.

Acutely, opiates inhibit Locus coeruleus (LC) via activation of an inward rectifying K+ channel and inhibition of an inward Na+ flow. Chronically, LC neurons develop tolerance to these acute inhibitory action of opiates, as neuronal activity recovers toward pre-exposure levels. Abrupt cessation of opiate treatment, for example, causes a marked increase in neuronal firing rates above pre-exposure levels (Nestter EJ et al. 1993).

Located in the dorsolateral pontine tegmentum of all mammals, the nucleus LC is the largest grouping of norepinephrine-containing neurons in the brain. It has been suggested that a single LC cell probably projects to the brain, hippocampus, and cerebellum simultaneously, forming a tree of collateral axons. The LC hyperactivity seen during opioid withdrawal is responsible for many symptoms of the opioid withdrawal syndrome (Krupitsky et al. 2002).

Increasing evidence indicates that the mesolimbic dopamine system – consisting of dopaminergic neurons in the ventral tegmental area (VTA) and their projection regions, most notably the nucleus accumbens (Nac) – plays in important role in mediating the reinforcing actions of opiates on brain function (Nestler EJ, 1997).

Based on the heterogeneous distribution of opioid receptors in the brain, many neurons and pathways are affected by different opioid agonists.

It has been postulated that many opioid receptors are located in the post-synaptic region. Thus, opioids modulate the release of neurotransmitters such as acetylcholine, serotonin, epinephrine and other peptides, like p substance. Some studies however, suggest the possibility of different neuromodulations, according to the type of receptor stimulated. For instance, the activation of Mu type (m) receptors in cortical regions of rats induces the inhibition of norepinephrine release, while the stimulation of kappa type (k) receptors inhibits striate dopamine release and the activation of Delta (s) receptors inhibits acetylcholine release (Semon EJ, 1991; Narita M, 2001).

Opioids – Clinical aspects

Opioids are centrally activating at low dosages and sedating at higher dosages. They are important and valuable drugs used in medicine.

1. Clinical syndromes associated with opioid use: There are three pathological clinical syndromes associated with opioid use: Intoxication, Abuse and Dependence (or what can also be referred to as Addiction). In addition, Opioid Withdrawal is a common clinical syndrome typically associated with the abrupt cessation or marked decrease in opioid use by a person physically dependent upon opioids. Syndromes according to DSM IV are:-

(16)
(a) **Opioid intoxication**: Opioid intoxication is characterized by analgesia, feelings of euphoria or dysphoria, feelings of warmth, facial flushing, itchy face, dry mouth, and pupil constriction. Intravenous use of an opioid can cause lower abdominal sensations described as an organ-like 'rush'. This is followed by a feeling of sedation (called the 'nod') and dreaming. Severe intoxication may cause respiratory suppression, areflexia, hypotension tachycardia, apnea, cyanosis, and death. This clinical picture may be treated in clinical emergency services. The relationship between the symptoms of Opioid intoxication and dose of opioid can vary as a function of the person's level of physical dependence, history of opioid use, and the acute dose and route of administration of the opioid ingested.

(b) **Opioid abuse**: According to DSM-IV-TR, Opioid Abuse is a maladaptive pattern of opioid use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(i) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home;

(ii) Recurrent substance use in situations in which it is physically hazardous;

(iii) Recurrent substance-related legal problems;

(iv) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by effects of the substance.

The symptoms of Opioid Abuse have never met the criteria for substance dependence for this class of substance (APA, 2000).

(c) **Opioid dependence**: The opioid dependence syndrome is characterized by a clustering of signs and symptoms associated with pathologic use of opioids. It is defined as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(i) Tolerance, as defined by either of the following:

- A need for markedly increased amount of the substance to achieve intoxication or desired effect:
- Markedly diminished effect with continued use of the same amount of the substance.

(ii) Withdrawal syndrome.

(iii) The substance is often taken in larger amounts or over a longer period than was intended;

(iv) There is a persistent desire or unsuccessful effort to cut down or control substance use;

(v) A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects;

(vi) Important social, occupational, or recreational activities are given up or reduced because of substance use;
(vii) The substance use is continued despite knowledge of having a persistent or recurrent
physical or psychological problem that is likely to have been caused or exacerbated
by the substance (APA, 2000).

(d) **Opioid withdrawal**: Symptoms of opioid withdrawal can include hyperalgesia, photophobia,
goose flesh, diarrhea, tachycardia, increased blood pressure, gastrointestinal cramps, joint
and muscle pain, anxiety and depressed mood.

**THE ICD- 10 CLASSIFICATION OF MENTAL AND BEHAVIOUR DISORDER DUE TO USE OF
OPIOIDS:**

**Diagnostic criteria for research**

**F-11.0**  Acute intoxication due to use of opioids

A. The general criteria for acute intoxication (F1x.0) must be met.

**F1x.0 Intoxication**

G1. There must be clear evidence of recent use of a psychoactive substance (or substance) at
sufficiently high dose levels to be consistent with intoxication.

G2. There must be symptoms or sign of intoxication compatible with the known actions of the particular
substance (or substance), as specified below, and of sufficient severity to produce disturbances
in the level of consciousness, cognition perception, affect or behaviour that are of clinical
importance.

G3. The symptoms or signs present cannot be accounted for by a medical disorder unrelated to
substance use, and not better accounted for by another mental or behavioural disorder.

Acute intoxication frequently occurs in person who have more persistent alcohol or drug-related
problems in addition, where there are such problems, e.g harmful use (F1x.1), dependence
syndrome (F1x.2), or psychotic disorder (F1x.5), they should also be recorded.

The following five- character code may be used to indicate whether the acute intoxiachion was
associated with any complication:

**F1x0.00** Uncomplicated: Symptoms varying severity, usually dose-dependent.

**F1x0.01** With trauma or other bodily injury

**F2x0.02** With other medical complications: Examples are haematemesis, inhalation of vomit.

**F1x0.03** With delirium

**F1x0.04** With perceptual distortions

**F1x0.05** With coma

**F1x0.06** With convulsions

**F1x0.07** Pathological intoxication: Applies only to alcohol.

B. There must be dysfunctional behaviour, as evidenced by at least one of the following:

1. apathy and sedation
2. disinhibition
3. psychomotor retardation
4. impaired attention
(5) impaired judgement
(6) interference with personal functioning

C. At least one of the following signs must be present
(1) drowsiness
(2) slurred speech
(3) pupillary constriction (except in anoxia from severe overdose, when pupillary dilatation occurs)
(4) decreased level of consciousness (e.g. stupor, coma).

Comment: When severe, acute opioid intoxication may be accompanied by respiratory depression (and hypoxia) hypotension, and hypothermia.

F1x.2 Dependence syndrome
Three or more of the following manifestations should have occurred together for at least 1 month or, if persisting for periods of less than 1 month, should have occurred together repeatedly within a 12-month period:
(1) a strong desire or sense of compulsion to take the substance;
(2) impaired capacity to control substance-taking behaviour in terms of its onset, termination, or levels of use, as evidenced by: the substance being often taken in larger amounts or over a longer period than intended; or by a persistent desire or unsuccessful efforts to reduce or control substance use;
(3) a physiological withdrawal state (see F1x.3 and F1x.4) when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance, or by use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms
(4) evidence of tolerance to the effects of the substance, such that there is a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance;
(5) preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time being spent in activities necessary to obtain, take or recover from the effects of the substance,
(6) persistent substance use despite clear evidence of harmful consequences (see F1x.1) as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm.

Diagnosis of the dependence syndrome may be further specified by the following five and six character codes:

F1x.20 Currently abstinent
F1x.200 Early remission
F1x.201 Partial remission
F1x.202 Full remission

F1x.21 Currently abstinent but in a protected environment (e.g. in hospital, in a therapeutic community, in prison, etc.)

F1x.22 Currently on a clinically supervised maintenance or replacement regime (controlled
dependence) (e.g. with methadone; nicotine gum or nicotine patch).

F1x.23 Currently abstinent, but receiving treatment with aversive or blocking drugs (e.g. naltrexone or disulfiram)

F1x.24 Currently using the substance (active dependence)

F1x.240 Without physical features

F1x.241 With physical features

The course of the dependence may be further specified if desired as follows:

F1x.25 Continuous use

F1x.26 Episodic use (dipsomania)

F1x.3 Withdrawal state

G1. There must be clear evidence of recent cessation or reduction of substance use after repeated, and usually prolonged and/or high-dose, use of that substance.

G2. Symptoms and signs are compatible with the known features of a withdrawal state from the particular substance or substances (See below)

G3. Symptoms and signs are not accounted for by a medical disorder unrelated to substance use and not better accounted for by another mental or behavioural disorder.

The diagnosis of withdrawal state may be further specified by using the following five character codes:

F1x.30 Uncomplicated

F1x.31 With convulsions

F11.3 Opioid withdrawal state

A. The general criteria for withdrawal state (F1x.3) must be met. (Note that an opioid withdrawal state may also be induced by administration of an opioid antagonist after a brief period of opioid use.)

B. Any three of the following signs must be present:

(1) craving for an opioid drug;  
(2) rhinorrhoea or sneezing  
(3) lacrimation  
(4) muscle aches or cramps  
(5) abdominal cramps  
(6) nausea or vomiting  
(7) diarrhoea  
(8) pupillary dilatation  
(9) piloerection, or recurrent chills  
(10) tachycardia or hypertension

(11) yawning  
(12) restless sleep

2. Absorption and pharmacokinetics of opioids: The pharmacokinetic properties of different opioids vary widely. Most of them are well absorbed by subcutaneous and intramuscular routes, while gastrointestinal tract absorption varies among different opioids. By virtue of the first-pass effect through the liver, some orally administered opioids become less potent. Hepatic metabolism is the primary method of inactivation of these substances, usually by glucuronide conjugation. Methadone and codeine do not have a significant first-pass effect, justifying their oral administration. (Kaplan HI, 1998).

Morphine, on the other hand, has a slow and erratic absorption by the oral route and is generally administered by the intravenous or intramuscular routes in the management of chronic pain.
### Signs and Symptoms of opioid intoxication and withdrawal

<table>
<thead>
<tr>
<th>INTOXICATION</th>
<th>WITHDRAWAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation or 'rush' (with low dosages) and sedation/ apathy (with high dosages)</td>
<td>Depressed mood and anxiety, Dysphoria</td>
</tr>
<tr>
<td>Euphoria or dysphoria</td>
<td>Craving</td>
</tr>
<tr>
<td>Feelings of warmth, facial flushing, or itching</td>
<td>Piloerection, lacrimation or rhinorrhea</td>
</tr>
<tr>
<td>Impaired judgement, attention or memory</td>
<td>Frequently, &quot;high&quot; attention</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Hyperalgesia, joint and muscle pain</td>
</tr>
<tr>
<td>Constipation</td>
<td>Diarrhea and gastrointestinal cramping, nausea, or vomiting</td>
</tr>
<tr>
<td>Pupillary constriction</td>
<td>Pupillary dilatation and photophobia</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Respiratory-depression, areflexia, hypotension, tachycardia</td>
<td>Autonomic hyperactivity (e.g., hyperreflexia, tachycardia, hypertension, tachypnea, sweating, hyperthermia)</td>
</tr>
<tr>
<td>Apnoea, coma</td>
<td>Yawning</td>
</tr>
</tbody>
</table>

Following table shows a few opioids, with their corresponding administration routes and elimination half-lives.

### Opioids: Aspects of pharmacokinetics and dosing via

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSING ROUTE</th>
<th>PHARMACOKINETIC ASPECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Oral (including the slow-release form), intravenous, intramuscular, intrathecal</td>
<td>Half-life 3-4 hours Converted to active metabolites (morphine-6-glucuronide)</td>
</tr>
<tr>
<td>Heroin</td>
<td>Intravenous, intramuscular, smoked, oral chasing</td>
<td>Half-life &lt;1 hour, Partly metabolized to morphine</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral, intravenous, intramuscular</td>
<td>Half-life &gt; 24 hours, No active metabolite</td>
</tr>
<tr>
<td>Pethidine</td>
<td>Oral, intramuscular</td>
<td>Half-life 2-4 hours, Active metabolite (norpethidine)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Sublingual, intrathecal, subcutaneous, intravenous, intramuscular</td>
<td>Half-life of 12 hours, slow onset of action inactivated by the oral via due to first pass effect</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Intravenous, epidural, transdermal patch</td>
<td>Half-life of 1-2 hours</td>
</tr>
<tr>
<td>Codeine</td>
<td>Oral</td>
<td>Acts as pro-drug Metabolized to morphine and other active opioids.</td>
</tr>
<tr>
<td>Crude opium</td>
<td>Oral (Husk, or as a concoction with tea, or boiled and supernatant consumed.</td>
<td>Varies acc. to concentration</td>
</tr>
</tbody>
</table>
Table: Equivalence of doses among the opioids

<table>
<thead>
<tr>
<th>1 mg of methadone corresponds to;</th>
<th>1-2 mg of heroin;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-4 mg of morphine;</td>
</tr>
<tr>
<td></td>
<td>30 mg of codeine;</td>
</tr>
<tr>
<td></td>
<td>20 mg of meperidine;</td>
</tr>
</tbody>
</table>

Source: Kleber 1994

Review of Management of Opioid Related Disorders

Psychiatric management forms the mainstay in the treatment of opioid related disorders. There are currently a number of effective pharmacological and behavioural therapies for the treatment of opioid dependence, with these two approaches often combined to optimize outcome (Wiley 2000). Review of current interventions in opioid related disorders have been dealt with under the following headings.

Choice of Treatment Setting

The choice of treatment setting depends on the clinical characteristics and preferences of the patient, the perceived treatment needs and the available alternatives.

Patient should be treated in the least restrictive setting that is likely to prove safe and effectively. Studies comparing the short, intermediate, and long term benefits of treatment in various setting (i.e. inpatient, residential, partial hospital, outpatient suffer from various methodological problems, including heterogeneity of patient populations, high dropout rates, and reliance on patient self reports uncorroborated by data from collateral sources. Stated treatment goals, programme features and outcome measures also varies access studies (Apsler et al. 1991). The treatment settings available are hospitals, residential treatment including therapeutic communities, partial hospitalizations and outpatient settings.

Therapeutic communities have been shown to be effective in the treatment of opioid dependence. Simpson and Sells (157) reported that in a large scale study with a 12 year-follow-up individuals with opioid dependence treated in therapeutic communities had the most favourable outcomes, even after age and demographic variables were controlled for. However these data are tempered by the fact that only 15%- 25% of those admitted voluntarily completed the programme.

Indian Studies

In India, camp detoxification, treatment showed better retention rate, good outcome and no use of illicit drugs during treatment (Gautam S, Shukla GK (1988) Purohit et al. 1988, Ranganathan 1994, Chavan et al. 1999).

Management of Abuse and Dependence

Opioid Agonist Pharmacotherapy

For many patients with chronic relapsing opioid dependence, the treatment of choice is maintenance on long acting opioids. Methadone is the most thoroughly studied and widely used treatment for opioid dependence. (APA Guidelines)
Methadone: Methadone is a μ opioid receptor agonist and produces the typical morphine-like effects in people, including euphoria, drowsiness, analgesia, respiratory depression, nausea, vomiting, constipation, itching, and constriction of pupils. With continued treatment, tolerance develops to most of these effects. Methadone suppresses opioid withdrawal effects (Donny EC et al. 2002).

For maintenance treatment of opioid dependence, the usual starting dose of methadone is 20-30 mg, with 5 to 10 mg increases every other day as tolerated. The goals of Methadone treatment are suppression of opioid withdrawal symptoms and cessation of illicit opioid use. The usual dose of methadone administered in methadone maintenance programs ranges from 30-100 mg. Higher doses (80-100 mg/day) are more effective than moderate doses of methadone (40 to 50 mg/day) in reducing illicit opioid use, but treatment retention is similar for the two groups (Strain et al. 1993). Lower doses of methadone (20 mg) are less effective than the 50 mg dose in treatment retention and illicit opioid use. (Strain et al 1993). Thus 50 mg dose per day is recommended as the minimum target dose and dose up to 100 mg/day should be considered if tolerated. (Strain et al, 1993). Methadone doses over 100 mg may be indicated, especially for those receiving medications that increase the metabolisms of methadone, such as some of the medications used for HIV infection (Bart et al. 2001, Clarke SM et al, 2001), other drugs that increase metabolism of methadone are rifampin, phenytoin, barbiturates, carbamazepine and ethyl alcohol. If higher doses are used, monitoring of plasma methadone concentrations may be useful, with the aim of maintaining minimal levels of 150-200 mg/ml (Kleber et al, 1995).

While methadone is the most researched treatment modality through observational studies examining the effectiveness of methadone maintenance treatment, there have been few controlled experimental studies. Hall et al. (1998) report that only three randomized controlled studies have ever been conducted whereby comprehensive methadone maintenance treatment was compared to a control condition over a considerable period of time. More recently, other randomized controlled trials conducted over short periods of time have compared methadone maintenance treatment to alternative treatments, variations of methadone maintenance treatment (low dose and high dose methadone), and other synthetic opioid treatments (such as LAAM).

Results from randomized controlled trials support the observational studies and indicate that methadone maintenance is associated with a higher treatment retention rates, a reduction in illicit opioid use, a reduction in criminal activity, and a reduction in the mortality rate of users. A reduction in risk related behaviors and improvements in physical and psychological health and improved social and occupational functioning are also demonstrated outcome factors (Newman and Whitehall 1979; Gunne and Gronbladh 1981; Gronbladh and Gunne 1989; Bell et al 1995; Hubbard et al. 1984; Hubbard et al. 1989; Chitwood et al. 1995).

Methadone maintenance treatment has been criticized (Davies, 1986) on the basis that:

- it does no more than maintain a heroin user's addiction and, because of its ready availability, effectively sentences the addict to a lifetime of drug use;
- it is a stronger narcotic than street heroin and is powerfully addictive. Its physiological side effects and problem with withdrawal are substantial; and
- Some methadone patients are maintained in a state of lethargy.

Methadone treatment is only suitable for those patients with a history of illegal opioid dependence usually longer than 12 months. Opioid dependence is characterized by (National Policy on Methadone Treatment 1997).
Doses in excess of 120 mg per day do not confer additional benefit. Long term treatment (i.e. two years or more) is generally more effective (Ward et al. 1998c, 1999f; National Policy on Methadone Treatment 1997).

Discontinuation of Methadone treatment is associated with a high rate of relapse to illicit opioid use. In a review of 14 studies examining planned discontinuation from methadone, over 65% patients relapsed within 6 to 12 months (Milby JB, 1998). A National Mental Health Panel on opioid addiction recommended that most of the patients may require continuous methadone treatment for years and perhaps for life, similar to other chronic medical disorders (NCDP, 1998).

**Levomethadyl acetate (LAAM)** is derivative of methadone. Its long duration of action (48-72 hrs) allows dosing at 48-72 hr interval for opioid maintenance treatment. In clinical trials LAAM was found to be as effective as methadone in reducing illicit opioid use (Ling W, 1976). While treatment with LAAM has been shown to be comparable to methadone treatment with respect to reduction in opioid use, (Rottec et al. 1997) retention rates are reportedly higher for patients treated with 60-100 mg/day of methadone (Ciraulo DA, 1998). In general longer duration of treatment with methadone > 6 months is associated with a better outcome.

Thus LAAM seemed to be a good alternative to methadone, with the advantage of needing less frequent use has been associated with prolongation of the QT internals, torsade de pointes, ventricular tachycardia, angina pectoris myocardial infarction and cardiac asset. (Deamer RA, 2001).

As a result LAAM has been removed from the market in the European Union and is no longer a first line treatment for opioid dependence in the USA. So, treatment needs to be initiated with caution in patients with comorbid cardiac ailments and an ECG should be performed at initiation of therapy to rule out QT prolongation and a repeat ECG should be performed 12-14 days thereafter and periodically during treatment (Deamer et al. 2001).

**Buprenorphine**: Buprenorphine, a derivative of the bain, is a partial m opioid antagonist and a weak k opioid antagonist (78 PCNA). In clinically used doses, buprenorphine effects are similar to full H opioid agonists such as morphine or methadone. At higher doses, however, buprenorphine affects plateau, and it acts like an opioid antagonist. This ceiling effect decreases the risk of overdose, even at high intravenous doses, and limits its abuse liability (Walsh SC 2003). In addition its slow dissociation from the opioid receptors allows flexible dosing ranging from several times a day to three times per week. (Johnson RE, 2003).

Buprenorphine formulated as a sublingual tablet is available alone or in a combination tablet containing Buprenorphine and Naloxone in a ratio of 4:1 on infectible preparation of the combinations (Johnson RE, 2003).

A number of large trials have confined the utility of buprenorphine for agonist maintenance therapy. These studies includes comparisons of buprenorphine to placebo (Johnson et al. 1995, Eudala et al. 1998), a buprenorphine and naloxone combination and placebo (Encleta et al. 1998), and a multiple dose comparison study (Ling et al, 1998). In one of the most recent trials (Johnson et al. 2000) buprenorphine (given three times weekly) was compared with LAAM (given 3 times weekly) and methadone (gives daily) in a 17-week study. Mean retention in treatment was higher for buprenorphine, LAAM and high dose methadone as compared to low dose methadone, and for high dose methadone compared to LAAM. Opioid positive urine samples decreased most for the LAAM treated group and least for low-dose methadone. Patient self reports of opioid use did not differ between the groups, but showed decreases of about 90% over the course of the study.
Buprenorphine has been found to be as effective as methadone treatment in retaining patients in treatment and reducing illicit opioid use (Johnson et al., 1992; Strain et al., 1993; Ritter et al. 1997). Findings of Maticuia et al. (1998) suggests that buprenorphine may be helpful in detoxification, reduces heroin cravings and is safer in terms of potential for overdose.

Buprenorphine has the potential to be abused and can produce addiction, however most patients who abuse buprenorphine initiated opioid use with other drugs. Abuse may take the form of using greater than prescribed dosages for analgesic, using buprenorphine in place of a more desired but less available opioid, or using buprenorphine for its positive reinforcing effects (Baumevielli et al. 1997, Dore et al. 1997). Only one study has characterized the behavioural and physiologic effects of a wide range of buprenorphine analgesic doses in non-users of opioid (Zancy et al. 1997) and the result indicated that buprenorphine given intravenously has a low abuse liability in this population.

Buprenorphine in combination with naloxone, has less potential for abuse than buprenorphine alone (Fudala et al. 1998; Mendelson et al. 1999).

The recommended initial dose of buprenorphine as mentioned in literature available is 4 mg buprenorphine or 4/1 mg buprenorphine/ naloxone followed in 3 to 4 hours with an additional dose of up to 4 mg of buprenorphine (or 4 /mg) if indicated. On the second day; a dose of 1'2 to 16 mg (or buprenorphine / naloxone 12/3 to 16/4 mg per day) may be administered. Once a stable dose of buprenorphineis reached, patient may be switched to a schedule less frequent than daily dosing. Three times weekly dosing as generally recommended (Johnson RE, 2003).

Scenario in India

Out of the three drugs discussed above only buprenorphine is marketed in India and is not in frequent use. There are very few published Indian studies in this regard.

Opioid antagonist pharmacotherapy

Naltrexone, an opioid antagonist blocks opioid receptors competitively. It is orally effective and can block opioid effects for 24 hours when administered as a single daily dose of 50 mg, doses of 100-150 mg can block opioid effects for 48 to 72 hrs. (Conzalez, 1988). Despite a favourable adverse effect profile (Nausea being the commonest side-effect), Naltrexone is generally not favoured by opioid addicts because, unlike opioid agonists and partial agonists, it produces no positive reinforcement effects. Furthermore, it may be associated with the precipitation of an opioid withdrawal syndrome if used too soon after opioid use stops, an effect that can be minimized by administering a naloxone challenge prior to giving the first dose of naltrexone.

To minimize the precipitations of opioid withdrawal, naltrexone treatment should not be initiated until the patient is opioid free for 7 to 10 days. After the initial dose of 25 mg or 50 mg, the following dose schedules have been used for naltrexone: (1) 50 mg daily (2) 100 mg every other day (3) 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday. Although Naltrexone is extremely effective when taken as presented its utility is often limited by the lack of patient compliance and/or low treatment retention. Compliance is improved when drug administration is directly observed and supervised (Meyar RE, 1979). Treatment retention is improved by involving the family in treatment planning and use of behavioural techniques (Anton RF. 1981; Kleber HD, 1989).

Given the poor compliance with oral naltrexone treatment, alternative formulations that allow for less frequent dosing of naltrexone for maintenance treatment of opioid dependence (Moderata Lowe V. 2002).
Another variant on antagonist treatment **Nalmefine**, an orally effective and somewhat longer acting (about 48 hours at doses 50-100 mg/day) opioid antagonist that has been effective for alcohol treatment (Mason et al., 1994) and shows promise as an alternative to naltrexone for opioid dependence (Jones et al., 2000).

**Psychosocial and Behavioural Treatments**

There are numerous psychosocial and behavioural approaches that are currently being used in the management of an opioid dependent individual (Oxford TBP). These include cognitive – behavioural therapy, relapse prevention, and psychotherapy (individual, family and group). The most influential approach in recent years has been the relapse prevention model (29 Oxford), which includes identification of cues or triggers for craving and learning techniques to handle high risk situations. Studies by McLallen et al. (198 APA) have demonstrated the efficacy of these techniques.

Recently, motivational interviewing, based on the work of Muller in the USA, has become increasingly popular. It aims at move the patients along a ‘cycle of change’ (30 Oxford) from pre-contemplation, and then to determinations and action without confrontation.

In case of Psychodynamic therapies, Woody et al. found that supportive-expressive therapy was more effective than drug counselling alone for patients with high levels of other psychiatric symptoms. Rounsaville et al. compared the efficacy of a 6 months course of weekly individual-interpersonal psychotherapy with a low contact comparison condition in individual on full term methadone maintenance programme. He concluded that it was very difficult to engage the opioid dependent patients in individual – interpersonal therapy and that the potential benefit of such treatment is unclear.

Psychodynamically oriented group therapy, modified for substance dependent patients, appears to be effective in promoting abstinence when combined with behavioural monitoring and individual supportive psychotherapy. McAuliffe reported that group relapse prevention based on a conditioning model of addiction, when combined with self help groups, was more effective than no treatment in reducing opioid use, unemployment, and criminal activities in recently detoxified patients.

Self help groups, like Narcotics Anonymous have beneficial for some individuals in providing peer support for continued participation in treatment, avoiding drug-using peers and high risk environments confronting denial and intervening early in pattern of thinking and behaviour that often lead to relapse.

**Treatment of Intoxication**

Acute opioid intoxication of mild to moderate degree usually does not require treatment. However severe opioid overdose, mashed by respiratory depression, may be fatal and requires treatment in a hospital emergency room or inpatient setting. Patients with signs of respiratory depression, stupor or coma need ventilatory assistance. An adequate airway should be established. Aspiration should be prevented.

Naloxone, a pure narcotic antagonist, will reverse respiratory depression and other manifestations of an opioid overdose. The usual dose is .4 mg (1 ml) i.v. A positive response, characterized by increase in respiratory rate and volume, a rise in systolic blood pressure and pupillary dilatation should occur within 2 minutes. If there is no response, similar dose or higher (.8 mg) can be administered twice more at five minutes interval. If there is still no response to naloxone, it suggests a concurrent or a completely different etiology for the problem.
Management of Withdrawal (Detoxification)

The treatment of opioid withdrawal is directed at safely ameliorating acute symptoms of withdrawal and facilitating entry into recovery and/or rehabilitation programmes. The Pharmacologic agents in opioid detoxification are opioid agonists (methadone), partial agonists (Buprenorphine), Antagonists (Naloxone, Naltrexone), Non-opioid alternatives (Clonidine, benzodiazepines, non-steroidal anti-inflammatory drugs); others which include combinations of these drugs and some experimental drugs. The choice of detoxification medication and the duration of the process depend on numerous factors including patient preference, clinicians, expertise and experience, type of treatment facility, and available resources.

Opioid detoxification paradigms are frequently categorized according to their duration: long term (typically 180 days), short term (upto 30 days), rapid (typically 3-10 days), and ultra-rapid (1-2 days).

The most common detoxification protocols, and those for which the most data are available, are the long-term (typically 180 days) and short-term (up to 30 days) paradigms involving the use of methadone. Unfortunately, these strategies have not generally been associated with acceptable treatment response using relapse to opioid use as an outcome criterion. For example, one study (Banys et al. 1994) reported that more than half of the individuals participating in a 180 days detoxification program were using opioids illicitly during the medication taper phase. Six month follow-up indicated that 38.5% of the urine samples (n=26) tested negative for illicit opioids, only 3 of 31 patients reported remaining free of illicit opioids for the entire 6 months prior to follow-up, and 22 participated in some other form of treatment (Reilly et al. 1995). Results from more rapid detoxification evaluations using short – or even intermediate term (up to 70 days) medication tapering protocols are even less encouraging and have an unfortunately low success rate. It should be noted, however, that provision of additional services such as counseling, behavioural therapy, treatment of underlying psychopathologies, job skills training, and family therapy to address concomitant treatment needs can improve outcome though success rates remain low, even with these services (Klber 1999).

Rapid detoxification involves the use of an opioid antagonist typically naloxone, in combination with other medications (such as clonidine and benzodiazepines) to mitigate the precipitated withdrawal syndrome. The procedure is intended to expedite and compress withdrawal in order to minimize discomfort and decrease treatment time. Ultra-rapid detoxification also utilizes other medications, along with an opioid antagonist, to moderate withdrawal effects. However, rather than individuals being awake as they are during the rapid detoxification process, they are placed under general anesthesia or alternatively, deeply sedated. A comprehensive review of the rapid and ultra-rapid detoxification literature was recently published (O’Connor and Kosten 1998). Rapid detoxification studies were conducted in inpatient facilities, outpatient substance abuse treatment settings, and outpatient primary care facilities; ultra-rapid ones were confined to inpatient settings. Patients included those who were heroin dependent as well as those in methadone maintenance treatment.

Only four of the ultra-rapid detoxification studies reviewed provided follow-up beyond the initial detoxification. Retention on post detoxification Naltrexone maintenance in one study was 53% at 1 month and 62% in another at 3 months. Only one of the ultra-rapid detoxification studies provided follow-up information indicating that all individuals were taking Naltrexone 30 days post detoxification. A more recently published study (Hensel and Kox 2000) in which ultra-rapid detoxification was followed by Naltrexone maintenance and supportive psychotherapy, indicated that 49 of 72 patients were
opioid abstinent 12 months following detoxification. All of these studies involved self-selected individuals thus making it impossible to know the overall effectiveness of this type of intervention.

A major concern regarding ultra-rapid detoxification is the occurrence of potentially serious adverse effects, such as respiratory distress (San et al., 1995), or other pulmonary and renal complications (Pfab et al. 1999) during or immediately following the procedure. A high frequency of vomiting has also been reported (Cucchia et al. 1998). The degree to which serious adverse events occur has not yet been determined; however, there have been reports of sudden death occurring shortly after the procedure that were not caused by relapse to opioid use and overdose (O'Brien et al. personal communication 2001).

In spite of the emerging evidence about serious adverse events, ultra-rapid detoxification may be appropriate for highly selected individuals based on considerations of previous treatment history, economic factors, and patient choice. However, patients seeking this treatment must be thoroughly informed that serious adverse events, including sudden unexpected deaths, have occurred in association with this procedure and its use should probably be limited to inpatient settings where monitoring by anesthesiologists and other highly trained staff is available.

**Methadone Substitution**

The procedure for opioid detoxification with methadone involves stabilizing the patient on a daily dose of methadone that is determined by the patient’s response to a dose of 10 mg every 2-4 hours as needed (Kleber et al, 1981). During the first 24 hrs 10-40 mg will stabilize most patients and control abstinence symptoms. Once the stabilization dose is determined, the drug can be slowly tapered.

**Buprenorphine**

Buprenorphine a partial opioid agonist when used at low doses (2-4 mg/day sublingually), blocks the signs and symptoms of opioid withdrawal.

Patients treated with low doses may be able to stop taking the drugs abruptly and experience under symptoms of opioid withdrawal than after taking heroin or methadone. Results from inpatient (Cheshin et al. 1994; Passen et al., 1994; Vignau 1998) and outpatient (O’Connor et al, 1997; Diamant et al. 1998) studies have shown that buprenorphine is safe, well tolerated and effective for opioid detoxification. Sachden et al. (2000) found that sublingual Buprenorphine was well tolerated by the subjects undergoing opioid detoxification in the dose range of 4 to 8 mg once daily with minimal side effects.

**Antagonists**

Naltrexone has been used with clonidine (an a2 agonist) for rapidly withdrawing patients from heroin or methadone have found the combination as safe and effective as Naltrexone precipitated withdrawal is avoided by pretreating the patient with clonidine (Vining E, 1988, Charney DS, 1986). O’Cannorla et al reported that 95% of patients successfully completed detoxification with cloindine and Naltrexone on an out-patient basis.

**Others**

Clonidine an a-agonist is a non-opioid antihypertensive drug that has been used successfully to reduce symptoms of opioid withdrawal. It acts by stimulating mid brain a2 adrenergic receptors, thereby reducing the noradrenergic hyperactivity that accounts for many of the symptoms of opioid withdrawn.
Protocols for clonidine detoxifications have been given by Kleler (74). On the first day of treatment, .1 - .3 mg is given in 3 divided doses. The dose is adjusted until withdrawal symptoms are reduced.

Hypotension, a side effect of clonidine has been a limiting factor in its acceptibility, however clonidine is being used more frequently for in patient subjects.

Other Drugs:

Lofexidine, another a2- adrenergic agonist when compared to clonidine has been found to equally suppress autonomic signs and symptoms of opioid withdrawal but with less sedation and hypotension (Kahn et al., 1997, Lin et al., 1997; Carnwath and Hardman 1998). When compared to Methadone dose tapering lofexidine detoxification was associated with opioid withdrawal effects that reached sooner, but resolved to negligible levels more rapidly (Beam et al., 1996).

Data regarding the potential efficacy of guanabenz and guanfacine have also been reported, but further studies are required to assess the potential utility of these medications.

There is a great deal of controversy regarding the use of sedative hypnotics or anxiolytics to treat the insomnia, anxiety, or muscle cramps associated with opioid withdrawal. Some psychiatrists are concerned about the abuse liability of these drugs whereas some advocate that benzodiazepines may be used for a relatively brief period (i.e. 1-2 wks) in carefully selected patients with appropriate monitoring. Diphenhydramine, hydroxyzine and sedating antidepressants (e.g. doxepin, amitriptyline, trazodone) have also been used for this purpose and have a less abuse potential than benzodiazepines.

Acupuncture studies on the efficacy of acupuncture or electro stimulation in the treatment of opioid withdrawal have yielded conflicting findings. Experts remain divided on the efficacy of acupuncture in withdrawal (Elison et al., 1987).

Addressing Comorbidity

Patients with opioid dependence are typically using one or more other substances (Cocaine, alcohol, benzodiazepines, amphetamines, cannabis, etc.) and have additional problems in the psychiatric, medical, family / social, employment or legal areas.

A) Psychiatric Comorbidity

Among the psychiatric disorders seen in persons with opioid dependence, antisocial personality disorder is one of the most common (First and Pincus 2000). Diagnostic studies of persons with opioid dependence have typically found rates of antisocial personality disorder ranging from 20 to 50%, as compared to less than 5% in the general population. PTSD is also seen with increased frequency.

Opioid dependent persons are especially at risk for the development of brief depressive symptoms, and for episodes of mild to moderate depression that meet symptomatic and duration criteria for major depressive disorder or dysthymia. These syndromes represent both substance-induced mood disorders as well as independent depressive illnesses. Brief periods of depression are especially common during chronic intoxication or withdrawal, or in association with psychosocial stressors that are related to the dependence. Insomnia is common, especially during withdrawal; sexual dysfunction, especially impotence, is common during intoxication. Delirium or brief, psychotic-like symptoms are occasionally seen during opioid intoxication (First and Pincus 2000).
Less than 5% of persons with opioid dependence have psychotic disorders such as bipolar illness or schizophrenia. Women with opioid dependence can present special challenges because many have been sexually abused as children, have other psychiatric disorders, and are involved in difficult family/social situations (Blume 1999).

The data on psychiatric comorbidity among opioid addicts and its negative effect on outcome (McLellan et al., 1983) have stimulated research on the effect of combining psychiatric and substance abuse treatment. Studies have shown that tricyclic antidepressants can be useful for chronically depressed opioid dependent persons who are treated with methadone maintenance (Nunes et al. 1998). Two other studies have shown that professional psychotherapy can be useful for psychiatrically impaired, methadone maintained opioid addicts (Woody et al. 1984, 1999), although another found no psychotherapy effect (Rounsavilla et al., 1983). The main result in most pharmacotherapy and psychotherapy studies with methadone maintained addicts has usually been a reduction in psychiatric symptoms such as depression, although some have shown reductions in substance use as well (Nunes et al. 1998, Woody et al. 1985, 1995).

In prescribing medications for comorbid non-substance-related psychiatric disorders, psychiatrists should be aware to the dangers of medications with high abuse potential and to possible drug interactions between opioids and other psychoactive substances (e.g., benzodiazepines) (Kleber, 1989; Woody GE, 1984). In general, benzodiazepines having a rapid onset, such as diazepam and alprazolam should be avoided because of their abuse potential (Sellers EM, 1993).

In patients with psychotic disorders the clinician is faced with a dilemma whether to use antipsychotic drugs or not. Though studies evaluating the outcome of combining opioid agonist treatment with antimanic or antipsychotic medications have not been done, there is little controversy that these medications are useful for persons with opioid dependence and psychiatric disorders.

Combined substance use disorders require special attention, since treatment directed at opioid dependence alone is unlikely to lead to cessation of other substance use. Treatment is generally similar to that for individual substances. Increased frequencies of behavioural monitoring, intensified counselling, contingency contracting, referral to specific self-help groups and specialized pharmacological treatments have all been used with varying degree of success. Two studies suggest that higher methadone doses coupled with intensive outpatient treatment may decrease cocaine use by methadone maintained patients.

Opioid dependent patients who are also dependent on other substances, particularly CNS depressants, should be stabilized with methadone and then gradually withdrawn from other drugs. Efforts to abruptly eliminate all drugs of abuse will not be successful with all patients. In such cases, limitation of the drugs one at a time may be warranted.

**Medical**

Medical comorbidity is a major problem among persons with opioid dependence; HIV infection, AIDS, and hepatitis B and C have become some of the most common problems. Sharing injection equipment including “cookers” and rinse water, or engaging in high-risk sexual behaviors are the main routes of infection.
After rising rapidly in the late 1970s and early 1980s, the incidence of new HIV infections among intravenous drug users, of whom opioid-dependent individuals constitute a large proportion, has decreased (Seage et al. 2001).

Common causes of death are overdose, accidents, injuries, and medical complications such as cellulitis, hepatitis, AIDS, tuberculosis and endocarditis.

Tuberculosis has become a particularly serious problem among intravenous drug users, especially heroin addicts. In most cases, infection is asymptomatic and evident only by the presence of a positive tuberculin skin test. However, many cases of active tuberculosis have been found, especially among those who are infected with HIV.

Pregnancy:

Other medical complications of heroin dependence are seen in children born to opioid-dependent women. Perhaps the most serious is premature delivery and low birth weight, a problem that can be reduced if the mother is on methadone maintenance and receiving prenatal care (Finnegan; 1991).

Opioid use disorders may have adverse effects on the health of the pregnant woman, the course of the pregnancy, fetal development, early child development, and parenting behavior. In pregnant women these effects include (a) poor nourishment, with accompanying vitamin deficiencies or iron and folic acid deficiency anemias; (b) general medical complications from frequent use of contaminated needles (abscesses, ulcers, thrombophlebitis, bacterial endocarditis, hepatitis, urinary tract infections, and HIV infection); (c) sexually transmitted diseases (gonorrhea, chlamydia, syphilis, herpes); and (d) hypertension.

The goals of treatment for the pregnant opioid-using patient include ensuring physiological stabilization and avoidance of opioid withdrawal; preventing further abuse of illicit drugs or alcohol; improving maternal nutrition; encouraging participation in prenatal care and rehabilitation; reducing the risk of obstetrical complications, including low birth weight and neonatal withdrawal, which can be lethal if untreated; and arranging for appropriate postnatal care when necessary.

Pregnant patients who lack the motivation or psychosocial supports to remain drug free should be considered for methadone maintenance regardless of their previous history of treatment. Withdrawal from methadone is not recommended, except in cases where methadone treatment is logistically not possible. In cases where medical withdrawal is necessary, there are no data to suggest that withdrawal in one trimester is worse than in any other. On the other hand, a narcotic antagonist should never be given to a pregnant substance-using patient because of the risk of spontaneous abortion, premature labor, or stillbirth. Data on the safety of clonidine for pregnant patients are not available.

In a randomized comparison of enhanced and standard methadone maintenance for pregnant opioid-dependent women, Carroll et al. found that enhanced treatment-consisting of standard treatment (daily methadone medication, weekly group counseling, and thrice-weekly urine screening) plus weekly prenatal care by a nurse-midwife, weekly relapse-prevention groups, positive contingency awards for abstinence, and provision of therapeutic child care during treatment visits resulted in improved neonatal outcomes (longer gestations and higher birth weights) but did not affect maternal drug use.

Adolescent and Children

Some psychiatrists prefer to avoid methadone maintenance as a first-line treatment for opioid dependence in adolescents since it may become a lifelong therapy. Although therapeutic communities
are sometimes recommended, most adolescents have difficulty tolerating prolonged confinement in such programs unless the programs are specifically tailored to meet the clinical needs of this age group.

**Special Mention**

**Therapeutic Communities (TCs)**

These programs are another approach that has been shown useful for treating opioid dependence, especially patients with a long history of addiction and a strong motivation to become drug-free, either as a result of internal processes or from external pressures such as being given the choice of entering prison for a drug-related crime, or getting treatment in a TC. These programs are very selective, self-governing, and long-term (6 - 18 months). They occur in residential settings where patients share responsibilities for maintaining the treatment milieu (cleaning, cooking, and leading group therapy). Confrontation of denial and behaviors such as lying and “conning”, combined with group support for healthy, positive change are used to restructure character and the addictive lifestyle. Medications such as methadone, LAAM, or Naltrexone are rarely used; however, medications for specific psychiatric or medical conditions are usually available after careful screening and evaluation. Many TCs have large numbers of individuals who have been referred by the criminal justice system including some who have tried but not responded to agonist maintenance on repeated occasions. Though dropout rates are high, studies have shown that over 80% of individuals who complete TCs have a sustained remission, and demonstrate significant improvement in psychiatric symptoms, employment, and criminal behavior (Inciardi et al. 1997, DeLeon 1999).

**Harm reduction**

Given the high rates of relapse among patients, and the varying goals patients bring to treatment, attention should be paid to harm reduction strategies in the delivery of all treatment programs. Other contexts for intervention where only brief intervention is possible also need to incorporate harm reduction strategies.

Mattick & Hall (1993) argue that harm reduction can be incorporated into even the most rigid abstinence based programs. Harm reduction strategies aim to reduce problems associated with continuing alcohol and/or other drugs, such as:

* overdose (e.g. avoid mixing drugs, using alone etc);
* family violence (e.g. not to use when you are feeling angry or aggressive or to have an escape plan for potential victims of family violence etc);
* driving under the influence of alcohol and other drugs (e.g. think about alternative methods of transport etc); and
* blood borne viruses (e.g. use clean injecting equipment etc).

Given the high risk of death following opiate overdose, a number of risks have been identified associated with both fatal, and non fatal overdose, as follows;

* general health issues, including malnutrition, HIV, tuberculosis, diarrhoea, malaria and sleep apnoea;
* hepatitis C and other sources of liver damage;
* psychiatric issues, particularly where they might affect the individual’s ability to make rational judgements with respect to dose size or other directly relevant issues;
• drug treatment which may influence vulnerability to overdose on resumption of use;
• tolerance;
• poly drug use;
• rapidity of use and the 'bolus effect';
• 'dirty hits' and other contamination problems;
• location of use, particularly use in non familiar surroundings;
• factors impacting on respiratory function; and
• intervention factors, including the ability of others to recognise that the victim is in danger and act appropriately.

PRACTICE GUIDELINES

These practice guidelines, developed to define the critical and desired elements of substance abuse services, are largely derived from the research literature and recommend interventions with proven efficacy. The guidelines are designed to educate practitioners in best practice models thereby reducing clinical variation across the country and improving outcomes. Treatment should be individualized, clinically-driven and outcomes-driven, assessment-based and allow for a continuum of care with a broad range of services of demonstrated value.

GENERAL TREATMENT PRINCIPLES

A. Assessment. Comprehensive assessment is essential initially and on an ongoing basis throughout treatment. Assessment will determine whether there is, in fact, a substance use disorder: whether the individual's level, pattern or consequence of substance use is medically harmful or meets specified criteria for a substance related disorder. Assessment also describes the individual and the nature of his/her substance use. A multi-dimensional assessment allows for better matching of patient with the appropriate treatment and treatment site.

B. Psychiatric/medical management. The objectives of psychiatric management are as follows:

1. Establishing and maintaining a therapeutic alliance while including reasonable expectations
2. Monitoring the patient's clinical status
3. Managing intoxication and withdrawal states
4. Developing and facilitating adherence to a treatment plan
5. Preventing relapse
6. Providing education about substance use disorders
7. Reducing the morbidity and sequelae of substance use disorders

C. Pharmacologic treatments.

1. To ameliorate the signs and symptoms of drug intoxication or withdrawal
2. To decrease the effect of an abused substance and, more specifically, to decrease its subjective reinforcing effects
3. To make the use of an abused substance aversive by inducing unpleasant consequences through a drug-drug interaction.

(33)
4. To use an agonist substitution strategy to promote abstinence from a more dangerous illicit substance
5. To treat comorbid psychiatric or general medical conditions

D. Psychosocial Treatment:

a) **Addressing motivation.** Ambivalence regarding cessation of drug use is the rule rather than the exception and motivation must be enhanced if the patient is to be an active participant in treatment.

b) **Teaching coping skills.** Treatment must help the patient recognize high risk situations and then develop alternate means of coping.

c) **Changing reinforcement contingencies.** Patients generally need assistance in identifying and developing fulfilling alternatives to substance abuse.

d) **Fostering management of painful affects.** Because dysphoric affects are common reasons for relapse, a critical task in substance abuse treatment is helping patients develop ways of coping with negative affects, feelings, emotions, and craving by enhancing the patient’s ability to identify, tolerate, and respond appropriately.

e) **Improving interpersonal functioning and enhancing social supports.** Many forms of treatment, including family therapy and 12-step approaches, focus on establishing and maintaining a network of positive social supports.

f) **Fostering compliance with and retention in treatment.**

1. Psychosocial therapies play a role in fostering compliance with treatment, including pharmacotherapy.

2. There are many different psychosocial approaches used in the treatment of substance related disorders. The major approaches which have received empirical evaluation have been divided into **low-intensity** and **higher-intensity** interventions.

**LOW INTENSITY INTERVENTIONS**

1) **Brief, Motivational Approaches** consist of 1 to 3 sessions and can be administered in a range of settings. Therapist empathy is emphasized in these approaches. Numerous studies of heavy drinkers have demonstrated that brief interventions are associated with durable reductions in drinking. For certain individuals requiring more intensive treatment, brief therapy may serve as an introduction to treatment. Studies in drug users are ongoing.

2) **Self-Help Groups** (e.g. AA, NA) have played a prominent adjunct role in the treatment of alcohol and opioid related disorders since the 1930’s.

3) **Aftercare**, generally defined as a less intensive level of treatment following an intense treatment intervention, may include partial hospitalization, intensive outpatient, less intensive outpatient or involvement in self-help groups. A more appropriate definition of aftercare probably should focus less on the temporal relationship and more on the focus: namely, relapse prevention. A fully functioning continuum of care must be available to the patient in order to prevent relapse. It is essential that treatment providers in both inpatient and outpatient settings carefully coordinate between the various levels of care well in advance of discharge or transfer in order to link patients with the next step in treatment as seamlessly as possible.
HIGHER-INTENSITY INTERVENTIONS are recommended for patients who do not respond to low intensity interventions or whose substance use is severe.

(1) Behavioral and Cognitive-Behavioral Interventions include a variety of approaches which share a basis in learning and social-learning theories of substance abuse. Cue Exposure, contingency management, and coping skills treatment (also known as relapse prevention therapy) are examples of treatments which have been demonstrated effective. A useful reference is Cognitive Therapy of Substance Abuse by Beck et al.

(2) Marital and Family Therapies. The value of involving the family and important support networks in substance abuse treatment has been shown in multiple studies, with a variety of types of substance abusers and settings. Non-addicted family members are frequently under extreme stress, both financial and emotional. Therapy serves to stabilize the family and assist the entire family in making changes that support the recovery of the patient and all members of the family.

(3) Group Therapy: Styles frequently used include behavioral, cognitive behavioral, interactional (process), and marital group therapies. Patient-matching studies indicate that patients with less sociopathy and those with neurological impairment fare better in interactional therapy while those with higher levels of sociopathy and psychopathology respond better in cognitive behavioral groups.

(4) Short-Term Psychodynamic and Interpersonal Approaches. The empirical evidence for these approaches is mixed.

(5) Case Management. Individuals whose substance use is severe may benefit from case management.

Formulation and implementation of a treatment plan.

The treatment plan should include the following elements:

1. Psychiatric/medical management
2. Strategy for achieving abstinence or reducing the effects or use of illicit substances
3. Efforts to enhance ongoing compliance, prevent relapse, and improve functioning, including addressing psychosocial problems which may be barriers to recovery (e.g. lack of transportation)
4. Additional treatments necessary for patients with comorbid conditions. Nicotine dependence and its related morbidity/mortality and treatment options need to be addressed with the patient.

Treatment settings

1. Treatment for substance related disorders can take place in a number of different settings depending on the clinical presentation of the patient and the specifics of his/her situation. The following six dimensions could be assessed:
   a) Acute Intoxication and/or Withdrawal Potential;
   b) Biomedical Conditions and Complications;
   c) Emotional/Behavioral Conditions and Complications;
   d) Treatment Acceptance/Resistance;
   e) Relapse/Continued Use Potential;
   f) Recovery Environment.
2. Multidimensional patient placement criteria such as these play an important role in:
   a) defining assessment dimensions to profile severity and level of functioning,
   b) providing a common language, definition and description of a continuum of levels of service,
   c) profiling a variety of patient severities and functioning that guide placement for the site of individualized services, matched to assessed needs, and
   d) promoting the infrastructure needed to generate outcomes data that can be compared across systems and patient populations.

3. The six dimensions are assessed initially and intermittently thereafter as patients move within and between levels of service. The criteria provide a framework for approaching the patient in a holistic, integrated fashion, taking account of both clinical and social needs. Individualized treatment that addresses these specific needs can then be defined and implemented.

PRACTICE GUIDELINES FOR OPIOID USE DISORDERS

Treatment goals for patients with opioid use disorders are generally the same as for patients with any type of substance related disorder. These goals include:

1. Abstinence or reduction in the use and effects of addictive substances. The preferred outcome for opioid-dependent patients is total cessation of psychoactive substance use. Although some opioid-dependent patients are able to achieve abstinence from all opioid drugs, many require and do benefit from opiate agonist maintenance (e.g. with methadone or LAAM)

2. Reduction in the frequency and severity of relapse. Reduction in the frequency and severity of relapse is a critical goal of treatment for substance related disorders. Working with opioid dependent patients may begin with the goal of lengthening the period of time between relapses. Later, the patients may become more motivated towards a goal of total abstinence.

3. Improvement in psychological and social/adaptive functioning. Opioid dependent patients have problems in psychological development and social adjustment, alienation from friends and family, impaired school or work performance, financial and legal problems, and deterioration in general health. Ongoing substance abuse counseling and other psychosocial therapies enhance program retention and positive outcomes.

CHOICE OF TREATMENT SETTING.

A. Patients with opioid abuse or dependency problems can be successfully treated in a variety of settings. Patients should be treated in the least restrictive setting that is likely to be safe and effective and this decision needs to be taken by the clinicians depending on specific situations.

Commonly available treatment settings for opioid dependence include:

1. Outpatient. Treatment of opioid dependence on an outpatient (low intensity) basis is appropriate for those whose clinical condition or environmental circumstances do not require a more intensive level of care. High rates of attrition are a problem in outpatient services, particularly in the early phase. Specific efforts should be directed toward motivating patients to stay in treatment. Treatment should encouraged be integrated with patients participation in self-help programs where appropriate. Such efforts to motivate may also include the use of legal, family, or employer pressure when available and appropriate.
2. **Partial Hospitalization.** Partial hospital care is an intensive and structured experience for patients who require more services than are typically available in outpatient settings. Opioid patients can use this setting for methadone detoxification and/or maintenance services or as a step-down service from residential care. There is some evidence that patients who would have been treated in hospital or residential care do just as well in partial hospital care.

3. **Residential Centers.** Residential programs can include halfway homes, social setting non-hospital medical detox centers, and the more traditional “therapeutic communities”. These programs vary in staffing, intensity of services available, length of stay, and requirements placed on patients in residence. Patients with opioid histories who have had multiple treatment failures, have profound personality problems, and are in need of a highly structured non-hospital medical detox setting are typically good candidates for this level of care.

4. **Hospitals.** Detoxification is a primary concern with opioid dependent patients and generally takes place in the hospital. Heroin intoxication does not warrant admission into the hospital unless significant medical stress related to physiological tolerance and withdrawal is noted with the patient. Available data do not support the notion that hospitalization, per se, has specific benefits over other treatment settings beyond the ability to address treatment objectives that require a medically monitored environment.

5. **Community Camps:** In places where deaddiction services are not available or acceptable, deaddiction programmes can be initiated by organizing community camps of various durations. Results have been found to be encouraging in Indian studies done so far. So far no structural approach to set up a deaddiction camp is available and psychiatrists use their own experience in organizing such camps. More deliberations are needed in order to adopt a uniform approach which is practical and acceptable in the Indian setting.

**OVERVIEW OF PHARMACOLOGICAL MANAGEMENT**

Non-medical clinical care by counseling staff requires a working knowledge of the pharmacotherapies employed by physicians working with addiction patients. The counselors are in frequent contact with the patients and are often able to report patient concerns, requests, and compliance to the physician's orders between scheduled medication checks. Pharmacological agents used in the treatment of opioid dependence are of two basic types: (1) **Agonistic drugs** used to maintain the physiological dependence at a stable dosage level (e.g., Methadone); and (2) **Antagonistic drugs** used to block the subjective effects of narcotics, discouraging drug use, and facilitating extinction of classically conditioned drug craving.

It is imperative that counseling staff have a close working relationship with the medical staff that is based on a sound knowledge base of medicines used in the treatment of addictive disorders. An integrative approach to treatment that recognizes the importance of varied treatments and the collaboration among professionals from different disciplines will greatly increase the potential for successful outcomes with the difficult to treat opioid patient.

**PSYCHOSOCIAL TREATMENTS**

A key component of any treatment plan specifies the psychosocial interventions and strategies that facilitate; a) abstinence from opioids, with or without an opioid antagonist or, b) includes the use of an opiate agonist.
A. **Cognitive Behavioral Therapies.** There have been several large studies where methadone patients were assigned to one of three groups: a) drug counseling, b) drug counseling & supportive-expressive therapy, or c) drug counseling with cognitive behavioral therapy. For patients with moderate to high degrees of depressive or other psychiatric symptoms, cognitive behavioral therapies were much more effective than drug counseling alone when outcomes were measured at 7 and 12 months.

B. **Behavioral Therapies.** Numerous studies have documented the efficacy of behavioral therapies using a variety of techniques. Cue exposure, urine testing with rewards and sanctions, and adding contingencies (i.e., medical care, psychiatric care, employment services, family therapy) to general drug counseling have all shown favorable results. Methadone alone without other psychosocial treatments was effective for only a very small percentage of patients in any of these studies.

C. **Psychodynamic Psychotherapies.** Studies show mixed results. The potential benefit of this treatment approach is unclear.

D. **Group and Family Therapy.** Some studies have examined the use of psychodynamically oriented group therapy for substance abusing patients and found it to be effective when combined with behavioral monitoring and individual supportive psychotherapy. A positive effect on reducing opioid use, unemployment, and criminal activities in recently detoxified patients was observed when a relapse prevention group using a conditioning model was combined with self-help groups. Controlled studies have shown family therapy to be effective for opioid patients when focused on the nuclear family, multifamily groups, spouses, and siblings.

E. **Self-Help Groups.** Peer support to continue in treatment, avoiding drug-using peers, confronting denial, and early interventions into patterns of thinking that could lead to relapse are all cited as reasons for patients to attend self help groups like Narcotics Anonymous. While there is little empirical data to support the efficacy of self-help groups, clinical experience suggests that participation can be an important adjunct to treatment for many patients. Self-help groups are helpful to many but not all patients and refusal on the part of the patients to attend is not synonymous with resistance to treatment in general. Patients need a system for orientation and, ideally, a person to attend the first few meetings with that they can safely ask questions about the norms and functions of the group.

**CLINICAL FEATURES INFLUENCING TREATMENT**

A. **Management of Intoxication.** Mild or moderate intoxication usually does not require treatment, but severe opioid overdose with signs of respiratory depression, stupor, or coma needs ventilatory assistance.

B. **Management of Withdrawal.** There are currently four pharmacological strategies in general use to address opioid withdrawal and to facilitate the entry of the patient into recovery and/or rehabilitation programs.

1. Methadone substitution, with gradual methadone tapering.
2. Clonidine-assisted detoxification.
Additional methods discussed in the research is a controversial approach that would use sedative-hypnotics or anxiolytics to treat insomnia, anxiety, and muscle cramps associated with opioid withdrawal. Acupuncture is also referenced but with mixed reviews on efficacy and reliability of the data.

C. Comorbid Psychiatric Disorders
1. The high prevalence of co-occurring psychiatric disorders among opioid dependent patients has been established. The most common diagnoses are mood disorders, alcoholism, antisocial personality, and anxiety disorders.
2. There is some evidence that methadone patients with preexisting psychiatric disorders may experience considerable distress when dosages are reduced. The reduction may precipitate the reemergence of previously controlled psychiatric symptoms, which may in turn increase the risk of relapse to substance use.
3. Dependence on other psychoactive substances is often a problem for the opioid patients. Cocaine, alcohol, and benzodiazepines have all been identified in studies as co-occurring dependencies in methadone patients. Comorbid substance-related disorders require special attention in that reduction of one drug from the user’s system may be complicated by the presence of another. In such cases, elimination of the drugs one at a time may be indicated.

D. Comorbid General Medical Disorders
1. Injection of opioids can result in a variety of medical problems such as tetanus infection, sclerosing of the veins, cellulitis, abscesses, bacterial endocarditis, hepatitis C (HCV) and HIV.
2. HIV risk is estimated as high as 60% in some areas of the U.S. and counseling on this area of IV drug use should always be a routine part of treatment. Tuberculosis is a particularly serious problem among IV opioid users, especially those dependent on heroin and explicit guidelines have been developed regarding patients with a positive skin test for TB.

E. Pregnancy
1. Opioid use disorders may have adverse effects on the health of the pregnant woman, the course of the pregnancy, fetal development, early child development, and parenting behaviors.
   a) In pregnant women opioid effects include:
      • Poor nourishment with accompanying vitamin deficiencies or iron and folic acid anemias
      • General medical complications from frequent use of contaminated needles
      • Sexually transmitted diseases (gonorrhea, chlamydia, syphilis, and herpes)
   b) Effects on the pregnancy may include:
      • Toxemia
      • Miscarriage
      • Premature rupture of membranes
      • Infections
   c) Possible short- and long-term effects on the baby would include:
      • Low birth weight
      • Prematurity
      • Stillbirth
2. The goals of treatment for the pregnant opioid-using patient include:
   a) Ensuring physiologic stabilization and avoidance of opioid withdrawal
   b) Preventing further abuse of illicit drugs or alcohol
   c) Improving maternal nutrition
   d) Encouraging participation in prenatal care and rehabilitation
   e) Reducing the risk of obstetrical complications (e.g., low birth weight, neonatal withdrawal)
   f) Arranging for appropriate postnatal care when necessary

PHARMACOLOGIC TREATMENTS FOR PATIENTS WITH OPIOID-RELATED DISORDERS.

The opiates, which include heroin, morphine, hydromorphone (Dilaudid), codeine, and methadone, all produce similar withdrawal signs and symptoms. The timing and duration vary, however, between the individual agents. The symptoms may be divided into four categories: (1) gastrointestinal distress, (2) pain, typically arthralgia, myalgia, or abdominal cramping, (3) anxiety, and (4) insomnia. The severity of the withdrawal syndrome depends on the particular drug used, the total daily dose, the interval between doses, the duration of use, and the health and personality of the addict.

A. Medication Treatment for Opiate Intoxication and Withdrawal

1. Management of Intoxication: Acute intoxications of mild to moderate degree generally do not require specific treatment. Severe overdose, marked by respiratory depression, may be fatal and requires treatment in a hospital emergency room or inpatient setting. Uncomplicated overdose with an opioid that has a relatively short half-life (heroin e.g.) may be treated in an ER, with release after a few hours. Overdose with methadone or LAAM requires close observation for 24-48 hours. Overdose as part of a suicide attempt requires thorough psychiatric evaluation. Patients with signs of respiratory depression, stupor, or coma need ventilatory assistance. Special attention must be paid to maintaining an airway and preventing aspiration. Gastric lavage should be performed on patients who have ingested drugs within the past 6 hours. Hypoglycemia and pulmonary edema need to be considered.

   Naloxone, a pure narcotic antagonist, is used to reverse the respiratory depression of opioid overdose. The usual dose is 0.4 mg (1 ml) i.v. and a positive response should be seen within 2 minutes. In case of no response, the same or a higher dose (0.8 mg) can be given twice more at 5 minute intervals. Nonresponse suggests a different etiology for the problem. Naloxone may precipitate signs and symptoms of withdrawal in patients who are physically dependent on opioids. Caution should be exercised with Naloxone administration because the patient may become combative upon awakening.


   The treatment of opioid withdrawal is directed at ameliorating acute symptoms and facilitating entry into a long-term treatment program for opioid use disorders.

   a) Goals. Some opioid-dependent patients will be able to achieve abstinence. Others require long-term maintenance with opioid agonists (methadone or LAAM). The goals of
pharmacologic treatment are to achieve a stable maintenance dose and to facilitate engagement in a rehabilitation program. Maintenance on methadone or LAAM may be appropriate for patients with a history of dependence that exceeds 1 year. Maintenance on Naltrexone is an alternative treatment strategy. Its utility is limited, however, by lack of patient compliance and low treatment retention.

b) Strategies

- Methadone or LAAM substitution with gradual tapering (highest level recommendation, APA)
- Abrupt discontinuation of opioids, with the use of clonidine to suppress withdrawal symptoms
- Clonidine-Naltrexone detoxification
- Buprenorphine substitution followed by discontinuation (abrupt or gradual) of buprenorphine

(1) Methadone Substitution (Subject to availability)

- Used for withdrawal from heroin, fentanyl, or any other opiate.
- Treatment of choice for many populations, including those with many treatment failures.
- Opiate-dependent inpatients being treated for an acute medical illness may be administered methadone if opiate withdrawal would complicate treatment of their medical condition.

(a) SETTING.

(i) Inpatient drug treatment program licensed for methadone detoxification.
- Starting dose of 30-40 mg q day, taken orally
- 10 mg administered 4 times daily, with observation for 2 hours following each dose. If patient is sleepy, decrease to 5 mg. If patient shows objective signs of withdrawal, increase dose to 15 mg.
- After 24 hours, withdraw methadone 5 mg per day. (Most patients are withdrawn over 8 days.)

(ii) Outpatient methadone detoxification clinic.
- 20 mg, given orally twice daily is usual starting point.
- After the second day, tapered by 2.5 mg per day.

(b) SHORT-TERM DETOXIFICATION.

- Patients may not take their methadone home.
- Counselor to monitor progress toward the goal of short-term detoxification and to provide a drug treatment referral.
- Patient must wait at least 7 days between conclusion of one such treatment episode before starting another.

(c) LONG-TERM DETOXIFICATION.

- Longer than 30 days, but not in excess of 180 days.
- Conditions:
• Patient must be under observation while ingesting the methadone for at least 6 days a week.
• Physician must document in record that short-term detox is not of sufficiently long enough duration to provide for rehabilitation.
• Initial drug screen required. Additional random urine screens monthly.
• Initial treatment plan and monthly treatment plan evaluation.
• Patient must wait at least 7 days after concluding a long-term treatment episode before beginning another. Physician must again document that patient is physiologically dependent.

(2) Clonidine-assisted detoxification.

Clonidine is a non-opioid antihypertensive drug that reduces symptoms of opioid withdrawal (nausea, vomiting, diarrhea, cramps, sweating) by reducing noradrenergic hyperactivity. It does not alleviate myalgia, insomnia, or drug craving. Some patients experience profound hypotension even at low doses.

(a) PROCEDURE.
• 0.1 to 0.3 mg clonidine in 3 divided doses on day 1
• Dose adjusted until withdrawal symptoms are reduced
• Monitoring for hypotension and sedation necessary. If BP falls below 90/60 mm Hg, next dose should be withheld.

(b) DURATION.
• 4-6 days for short-acting opioids (heroin)
• 0-14 days for longer-acting opioids (methadone)

(c) ADVANTAGES OVER METHADONE.
• Does not produce opioid-like tolerance or physical dependence
• Avoids postmethadone rebound in withdrawal symptoms
• Patients completing a clonidine-assisted withdrawal can be immediately given an opioid antagonist (Naltrexone) if indicated
• May be administered in patch form (subject to availability)

(d) DISADVANTAGES
• Side effects: insomnia, sedation, hypotension
• Will not ameliorate withdrawal symptoms of insomnia and muscle pain
• Low rate of completion for clonidine-treated outpatients, roughly comparable to that with methadone

(e) CONTRAINDICATIONS.
• Acute or chronic cardiac disorders
• Renal or metabolic disease
• Moderate to severe hypotension
• Hypersensitivity to clonidine

(f) SETTING.
• Easier in inpatient setting, but outpatient detoxification with clonidine is a reasonable
approach with experienced staff. Outpatients should not be given more than a 3-day supply of clonidine for unsupervised use.

- The clonidine transdermal patch (subject to availability) comes in 3 sizes and delivers an amount of drug equivalent to twice daily dosing with 0.1, 0.2, or 0.3 mg of oral clonidine (over 24 hours). One patch lasts for up to 7 days. The patch minimizes drug cravings, eliminates disruptions caused by administration of medication, overcomes the problem of missed doses, and prevents the buildup of withdrawal symptoms during the night.

(3) Clonidine-Naltrexone ultrarapid withdrawal.
- Safe and effective for rapidly withdrawing patients from heroin or methadone.
- Naltrexone-precipitated withdrawal avoided by pretreating patient with clonidine.
- Most useful for patients in transition to narcotic antagonist treatment.
- Limitations:
  - Potential severity of Naltrexone-induced withdrawal: need to monitor patients for 8 hours on day 1
  - Need for careful BP monitoring during entire detoxification procedure

(4) Buprenorphine.
- Partial opioid agonist which at low dose (2-4 mg/day sublingually) blocks signs and symptoms of opioid withdrawal.
- Less risk of respiratory depression as with pure agonists (morphine).

PHARMACOLOGIC TREATMENTS FOR DEPENDENCE AND ABUSE.
A. AGONIST SUBSTITUTION THERAPY.
- Methadone is the most widely used and thoroughly studied.
- LAAM is a longer-acting preparation that can be administered less frequently.
- Buprenorphine is a partial opioid agonist with promising results.

1. Methadone Maintenance Therapy (subject to availability in India)
- Research has shown that a majority of opiate-dependent individuals cannot achieve or sustain a drug-free state (NIH, 1997). The goals of treatment with opioid agonists (methadone or LAAM) are to achieve a stable maintenance dose and to facilitate engagement in a comprehensive program of rehabilitation.

2. LAAM (subject to availability in India)
- LAAM itself in not a potent opiate; its opiate effects are produced by its long-acting metabolites. Oral ingestion or IV injection of LAAM does not produce rapid onset of opiate effects as does ingestion of methadone, heroin, morphine.
- LAAM can be used in place of Methadone as it is long acting and offers advantage of less frequent dosings.

DISCONTINUATION FROM LAAM MAINTENANCE
- Gradual discontinuation of LAAM will result in slow decline in plasma levels of its long-acting metabolites and in the emergence of withdrawal symptoms.
- No evidence exists to suggest withdrawal from LAAM differs qualitatively from withdrawal from methadone or any other opioid. Withdrawal will have a delayed onset and protracted, but usually less intense course.
• Options.

The LAAM dose can be reduced gradually depending on patient’s response. Alternately, patients on LAAM can be switched to methadone (at 80% of their LAAM dose) and then withdrawn. Clonidine is another option.

3. Buprenorphine

• A potent analgesic available in an injectable form, buprenorphine is being investigated as a treatment for opiate dependence and detoxification.
• Produces less physical dependence than morphine or heroin and results in less intense withdrawal.
• Safer than methadone or LAAM if an overdose is ingested.

DISCONTINUATION FROM BUPRENORPHINE MAINTENANCE

• Buprenorphine produces physical dependence of the opiate type, thus requiring tapering. Can be discontinued by tapering the dosage to zero over 7 to 21 days.

B. OPIOID ANTAGONIST TREATMENT WITH NALTREXONE.

• Maintenance on the opiate antagonist Naltrexone is an alternative treatment. The goal is to block the effects of opioids, thereby discouraging opioid use and decreasing classically conditioned drug craving.
• Long duration of action (24-72 hrs depending on dose): can be given 3 times per week (100 mg p.o. MONDAY, WEDNESDAY, 150 mg p.o. FRIDAY).
• No abuse potential.
• Administered to patients who have been withdrawn from opioids under medical supervision and have remained opioid free for at least 5-7 days.
• Test dose of naloxone, 0.8 mg i.m. should be used to assess the degree of opioid dependence. (Naloxone Challenge Test)
• Rapid opioid withdrawal, with use of clonidine and Naltrexone has been used to shorten the interval between detox and initiation of Naltrexone maintenance.
• Utility decreased by lack of patient compliance and/or low treatment retention
• Higher rates of success reported for court-mandated treatment and for professionals at risk of losing their professional licenses.

TERMINATING OPIATE MAINTENANCE TREATMENT.

For some patients, eventual withdrawal from methadone maintenance is a realistic goal. Other patients may be discontinued from medication for disciplinary reasons.

Involuntary: Methadone dosage should be tapered until the patient is receiving 30 to 40 mg a day at which time clonidine and other medications may begin.

Voluntary: A decision to withdraw from methadone maintenance is best left to the patient and to the clinical judgment of the physician. Patients should receive supportive treatment during detoxification and aftercare services to aid in maintaining abstinence.

PATIENT CARE AND COMFORT.

A. In particular, patients should be monitored for anxiety, sweating, chills, nutritional intake, diarrhea and gastrointestinal distress, sleep dysfunction, muscle cramps, aches, and bowel function. A complete physical exam should be conducted. The patient should be evaluated for TB, symptoms of AIDS and opportunistic infections, hepatitis A, B, and C, and sexually transmitted diseases.
B. Medications recommended for symptomatic relief of opiate withdrawal.

Table: Medications

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>DRUG</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Loperamide</td>
<td>4 mg followed by 2 mg after each motion maximum 16 mg in 24 hrs for 5 day.</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>Promethazine</td>
<td>25 mg followed by a second one on same evening and 25 mg every night thereafter.</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>Domperidone</td>
<td>10-20 mg every 4-8 hrs.</td>
</tr>
<tr>
<td>General aches and Pains (eg Headache, Muscular pain or high temperature)</td>
<td>Metoclopramide</td>
<td>5-10 mg thrice daily.</td>
</tr>
<tr>
<td>General aches and Pains (eg Headache, Muscular pain or high temperature)</td>
<td>Ibuprofen</td>
<td>400 mg thrice daily Maximum 2.4 gm daily</td>
</tr>
<tr>
<td>General aches and Pains (eg Headache, Muscular pain or high temperature)</td>
<td>Diclofenac</td>
<td>100-150 mg daily in 2-3 divided doses maintenance = 50-100 mg in divided doses.</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Tramadol</td>
<td>Maximum 4 gm</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Clonazepam</td>
<td>Dosage has to be individualized Initially 1.5 mg/day Maintenance dose / day Maximum dose / day</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Chlordiazepoxide</td>
<td>20-40 mg daily Severe cases 50-100 mg daily 0.25 to 0.5 mg 2-3 times daily Maintenance dose 0.5 to 4 mg daily in divided doses.</td>
</tr>
<tr>
<td>Anxiety/Agitation</td>
<td>Diazepam</td>
<td>5-30 mg orally at Bed time.</td>
</tr>
<tr>
<td>Anxiety/Agitation</td>
<td>Lorazepam</td>
<td>1-2 mg at Bed time</td>
</tr>
<tr>
<td>Anxiety/Agitation</td>
<td>Zolpidem</td>
<td>10 mg immediately before bed time</td>
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<tr>
<td>Anxiety/Agitation</td>
<td>Zaleplon</td>
<td>10 mg at bed time</td>
</tr>
<tr>
<td>Anxiety/Agitation</td>
<td>Nitrazepam</td>
<td>50-10 mg at bed time</td>
</tr>
<tr>
<td>Anxiety/Agitation</td>
<td>Propranolol</td>
<td>10-40 mg a day</td>
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</tbody>
</table>

Other symptoms (e.g. Stomach cramps, Muscle cramps, Bone pains, sleepiness and agitation) should be managed symptomatically with the appropriate therapy, as per the choice of the therapist.
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