

# Brazilian guideline for the treatment of patients with opioids dependence syndrome

## Diretrizes para o tratamento de pacientes com síndrome de dependência de opióides no Brasil

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### Abstract

There is a relatively low prevalence of opioid use in Brazil, particularly involving the non-medical use of codeine and opiate-containing syrups. However, opioid dependence syndrome shows a significant total impact on mortality and morbidity. Over the past 20 years, scientific progress has changed our understanding of the nature of opioid addiction and its various possible treatments. Addiction 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 addiction will be part of long-term, medical, psychological, and social perspectives.

This guideline aims at providing guidance to psychiatrists and other mental health professionals who care for 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. Also, the essential historical, epidemiological and neurobiological aspects of Opioid Dependence are reviewed.

**Keywords:** Narcotics; Opioid-related disorders/therapy; Substance-related disorders/therapy; Practice guidelines.

### Resumo

Existe uma prevalência relativamente baixa do uso de opióides no Brasil, em particular envolvendo o uso não médico da codeína e de xaropes que contêm opióides. No entanto, a síndrome de dependência apresenta um significativo impacto total na mortalidade e morbidade. Nos últimos 20 anos, o avanço científico tem modificado nosso entendimento sobre a natureza da adição aos opióides e os variados tratamentos possíveis. A adição é uma doença crônica tratável se o tratamento for realizado e adaptado tendo em vista as necessidades do paciente específico. Há, de um fato, um conjunto de tratamentos que podem efetivamente reduzir o uso da droga, ajudar a gerenciar a fissura pela droga, prevenir recaídas e recuperar as pessoas para o funcionamento social produtivo. O tratamento da dependência de drogas será parte de perspectivas de longo prazo do ponto de vista médico, psicológico e social. Esta diretriz almeja fornecer um guia para os psiquiatras e outros profissionais de saúde que tratam de pacientes com Síndrome de Dependência de Opióides. Ela tece comentários sobre o tratamento somático e psicossocial que é utilizado nesses pacientes e revisa as evidências científicas e seu poder. Da mesma forma, os aspectos históricos, epidemiológicos e neurobiológicos da dependência de opióides são revisados.

**Descritores:** Entorpecentes; Transtornos relacionados ao uso de opióides/terapia; Transtornos relacionados ao uso de substâncias/terapia; Diretrizes para a prática clínica.

## Introduction

### 1. Creation of guidelines

This guideline was developed by psychiatrists who are in active clinical practice and was elaborated during the Brazilian Psychiatric Congress – 2003.

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 Classification of Mental and Behavioral Disorders.<sup>1</sup>

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.

### 2. Definitions of terms

1) 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 (Table 2).

2) 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, although

**Table 1 – Opioid classification**

|                        |   |
|------------------------|---|
| Natural Opioids        | Opium, morphine, codeine, tebaine   |
| Semi-synthetic Opioids | Heroin, oxycodone, hydrocodone, Oxymorphone<br>hidromorphone                                  |
| Synthetic Opioids      | Methadone, meperidine, fentanyl, L-alfa-acetyl<br>metadol or Levometadil (LAAM), propoxyphene |
| Mixed Antagonists      | Buprenorphine, nalbuphine, pentazocine, nalbuphine  |
| Antagonists            | Naltrexone, naloxone  |

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.

3) 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.

4) Relapse – The recurrence on discontinuation of an effective medical treatment of the original condition from which the patient suffered.

5) Withdrawal – The psychological and physiological reactions to abrupt cessation or reduction of the drug dose.<sup>2</sup>

## Epidemiology

### 1. 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).<sup>3</sup>

The 1999 National Household Survey on Drug Abuse (NHSDA) reports the use of illicit drugs by people aged 12 and over. Lifetime prevalence (at least one use in a person's lifetime) of heroin use for people aged 12 and over was 1.4%. By age group, 0.4% were in the 12-17 range; 1.8% were in the 18-25 range; and 1.4% were users aged 26 and over.<sup>4</sup>

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.<sup>5</sup> 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.<sup>6-7</sup>

### 2. Use of illicit opioids in Brazil

Surveys on drug use among students included students from of 1<sup>st</sup> and 2<sup>nd</sup> grade in public schools in 10 Brazilian capitals from all regions of the country, and were carried out in 1987, 1989, 1994 and 1997. The data presented in the IV survey suggest a relatively low prevalence of opioid use in Brazil, particularly involving the non-medical use of codeine and opiate-containing syrups. Lifetime use rates were 1% for syrups (ranging from 0.6% in São Paulo to 1.5% in Salvador) and 0.7% for opioids (ranging from 0.2% in Rio de Janeiro to 1.4% in Porto Alegre). A statistically significant increase in lifetime use of opioids was noticed only in Salvador. Only 12 students (in a sample of more than 15,000) reported having already used injectable heroin: three in Porto Alegre, two in Belo-Horizonte, Brasilia and Curitiba and one in Fortaleza, Salvador and São Paulo. There was also a report of use of injectable pethidine in Recife and one of injectable morphine in Porto Alegre. However, the most recent version of this survey, which assesses drug use among street children and adolescents, does not mention opioid drugs.

The latest and also more comprehensive Brazilian survey is the I home survey of psychotropic drug use in Brazil, which includes the 107 largest cities in the country (towns with a population of more than 200,000 people). The sample included 8,589 persons between 12 and 65 years of age who were interviewed. Lifetime use of any other substance except alcohol and tobacco was reported by 19.4% of those assessed. Non-medical use of opioids can be deemed relatively infrequent, lifetime use of codeine-containing syrups was reported by 2.0% of those interviewed, opioid use by 1.4% and heroin by 0.4%. Lifetime use of codeine-containing syrups is higher among interviewees aged 35 and over (2.3%) and use of opioids is higher among those aged 25 to 34. There was a trend towards higher lifetime use among women (codeine: 2.4%; opiates: 1.6%) than among men (codeine: 1.5%; heroin: 1.1%). The data for heroin are rather limited.<sup>8</sup>

There have been considerable studies performed in Brazil on the use of alcohol and drugs among medical students, but none among doctors.

## Opioids – General aspects

Most opioids are important medications employed for specific medical purposes. Their high dependence-inducing potential, however, demands care during the administration of these psychoactive substances.

### 1. History

There are historical reports on the use of opioids 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*.<sup>9</sup>

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 Serturmer. 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. By the twentieth century, opiate addiction was a widespread problem in the United States.<sup>10</sup>

In Brazil cases of opioid dependence were reported with remarkable frequency until the mid-1930s, as shown by the sanatorial statistics in the largest cities, particularly Rio de Janeiro and São Paulo. In the state of Rio de Janeiro, for instance, 'fuméries d'opium' could be found in small broken-down buildings by the docks. These so-called 'blacksmith's alleys' were places where people of different social classes gathered together to consume the substance.<sup>11-12</sup>

The post-modern world can be characterized by 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.<sup>13</sup>

## 2. Opioids – Classification

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.<sup>12</sup>

Opioids can be classified as natural, semi-synthetic and synthetic, as is shown in Table 2.

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 cineritious, i.e.:

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

Kappa ( $\kappa$ ) – mediates analgesia, sedation, miosis, dysphoria and psychotomimetic symptoms as depersonalisation and derealization;

Delta ( $\sigma$ ) – mediates analgesia and may be associated with mood changes;

Epsilon ( $\epsilon$ ) – may be associated with sedation.<sup>14</sup>

## 3. 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.<sup>15</sup>

The opioid receptors are coupled to G<sup>o</sup> and G<sup>i</sup> 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<sup>+</sup> channel and inhibition of an inward Na<sup>+</sup> flow. Chronically, LC neurons develop tolerance to these acute inhibitory actions 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.<sup>16</sup>

Located in the dorsolateral pontine tegment 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.<sup>17</sup>

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 an important role in mediating the reinforcing actions of opiates on brain function.<sup>18</sup>

Based on the heterogeneous distribution of opioid receptors in the brain, many neurons and pathways are affected by different opioid agonists.<sup>19</sup>

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 ( $\mu$ ) receptors in cortical regions of rats induces the inhibition of norepinephrine release, while the stimulation of Kappa type ( $\kappa$ ) receptors inhibits striate dopamine release and the activation of Delta ( $\sigma$ ) receptors inhibits acetylcholine release.<sup>20-21</sup>

## 4. Opioids – Clinical aspects

Opioids are centrally activating at low dosages and sedating at higher dosages. They are important and valuable drugs used in medicine.<sup>22</sup> However, a review of the use of opioid medications for other medical conditions besides addiction, such as pain, is outside the scope of the present review.

### 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.

#### 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 orgasm-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 (Table 1). This clinical picture may be treated in clinical emergency services.<sup>23</sup>

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).<sup>24</sup>

#### 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:
  - 1) A need for markedly increased amounts of the substance to achieve intoxication or desired effect;
  - 2) Markedly diminished effect with continued use of the same amount of the substance.
- ii) Withdrawal syndrome;
  - i) The substance is often taken in larger amounts or over a longer period than was intended;
  - iv) There is a persistent desire or unsuccessful efforts 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).<sup>24</sup>
- d) Opioid withdrawal

**Table 2 – Signs and Symptoms of opioid intoxication and withdrawal**

| Intoxication  | Withdrawal   |
|---|--|
| Activation or “rush” (with low dosages) and sedation/apathy (with high dosages) | Depressed mood and anxiety. Dysphoria  |
| Euphoria or dysphoria   | Cravin   |
| Feelings of warmth, facial flushing, or itching                                 | Piloerection, lacrimation or rhinorrhea  |
| Impaired judgement, attention or memory   | Frequently, “high” attention   |
| Analgesia   | Hyperalgesia, joint and muscle pain  |
| Constipation  | Diarrhea and gastrointestinal cramping, nausea, or vomiting  |
| Pupillary constriction  | Pupillary dilatation and photophobia   |
| Drowsiness  | Insomnia   |
| Respiratory depression, areflexia, hypotension, tachycardia                     | Autonomic hyperactivity (e. g., hyperreflexia, tachycardia, hypertension, tachypnea, sweating, hyperthermia) |
| Apnéia, sedação, coma   | Yawning  |

SOURCE: Martin e Hubbard, 2000<sup>23</sup>

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 (Table 1).<sup>23</sup>

## 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.<sup>25</sup>

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.

Table 3 shows a few opioids, with their corresponding administration routes and elimination half-lives.

## Approaches to the treatment of opioid dependence

The main forms of treatment for substance use disorders are: psychotherapies, mutual self-help groups (Narcotics Anonymous), inpatient treatment, outpatient treatment and psychopharmacological treatment.

Pharmacological treatment is usually restricted to the management of intoxication, withdrawal syndromes, drug-induced aggression or behavioral changes, medical complications and, in some cases, there is a need to use agonist compounds that bind competitively to the same receptors that mediate the effects of the abused drugs, preventing or even hindering their effects.<sup>26</sup>

Unlike other substance addictions, the pharmacological management of opiate dependence seems to play a crucial role, whereas other methods of approach display questionable effectiveness.<sup>27-28</sup>

### 1. Management of Opioid Intoxication (including opioid overdose)

The opioid intoxication itself does not lead individuals to seek medical treatment, except in cases of overdose.

Opiate overdoses usually take place in persons with low tolerance or who are relatively inexperienced in opioid use, in addicts that mix opioid use with other CNS depressant drugs (such as benzodiazepines, ethanol, or barbiturates) and in persons who err in the dosage.

The management of cases of opioid overdose, which should occur in medical emergency units, includes:

- Establishment of an adequate ventilatory support;
- Correction of hypotension;
- Management of pulmonary edema. Remember that the pulmonary edema is related to leakage in pulmonary capillaries rather than to fluid overload. Diuretic drugs are therefore contraindicated;
- Coma and respiratory depression are common findings in these cases. The use of naloxone is proposed for all cases in which there is suspicion of opioid overdose. The following schedule is suggested:
  - Administrate 0.8 mg of naloxone IV, waiting for the patient to wake up. If there is no response in 15 minutes, 1.6 mg of naloxone IV can be given. If even then there is no response, 3.2 mg of naloxone IV are given and one waits 15 minutes more. If there is no response, such as mydriasis, agitation, improvement in the level of consciousness and of the respiratory pattern, it is imperative to review at once the diagnosis of opiate intoxication;
  - Assessment of body temperature. If feverish, check for infections, including aspiration pneumonia, endocarditis, cellulites, meningitis, HIV and hepatitis;
  - Seizures induced by meperidine are reversed by the use of naloxone<sup>29</sup>.

### 2. Pharmacological treatment of the Opioid Dependence Syndrome

Physical dependence to opioids develops rapidly. Preclinical studies, and similar work in humans, suggest that adaptational changes occur with ingestion of the first dose of an opioid (called ‘acute physical dependence’). Mild or moderate opioid withdrawal symptoms may be seen after a regular use of an opioid for only a few days.

There are two pharmacological approaches for the treatment of Opioid Dependence:

- Supervised withdrawal (also known as detoxification) – This can vary by both the length of the treatment (for example, relatively

**Table 3 – Opioids: Aspects of pharmacokinetics and dosing via**

| Drug                 | Dosing route  | Pharmacokinetic aspects   |
|----------------------|---|---|
| <b>Morphine</b>      | Oral (including the slow-release form), intravenous, intramuscular, intrathecal | Half-life 3-4 hours<br>Converted to active metabolite (morphine-6-glicurone)                          |
| <b>Heroin</b>        | Intravenous, intramuscular, smoked, oral  | Half-life < 1 hour<br>Partly metabolized to morphine  |
| <b>Methadone</b>     | Oral, intravenous, intramuscular  | Half-life > 24 hours<br>No active metabolite  |
| <b>Pethidine</b>     | Oral, intramuscular   | Half-life 2-4 hours<br>Active metabolite (norpethidine)   |
| <b>Buprenorphine</b> | Sublingual, intrathecal, subcutaneous, intravenous, intramuscular               | Half-life de 12 hours<br>Slow onset of action<br>Inactivated by the oral via due to first-pass effect |
| <b>Fentanyl</b>      | Intravenous, epidural, transdermal patch  | Half-life de 1-2 hours  |
| <b>Codeine</b>       | Oral  | Acts as pro-drug<br>Metabolized to morphine and other active opioids                                  |

SOURCE: Rang et al 2000<sup>19</sup>

brief withdrawals that last up to 30 days or protracted withdrawals that last for more than 30 days), and by the type of medications used (substitution therapies versus symptomatic treatments).

b) Maintenance – In general, this form of treatment involves continuous medication administration without dose tapering (or withdrawal), and can last for years<sup>30</sup>.

1) Supervised withdrawal (or detoxification)

a) Brief versus Protracted withdrawal

In general, evidence suggest that outpatients have a greater likelihood of success in achieving and maintaining abstinence from opioid use when supervised withdrawal is conducted over longer rather than shorter periods. Specifically, clinical experience suggests that outpatient withdrawals of 4 weeks or less are more likely to produce relapse to opioid use compared to withdrawals that last 26 weeks. When withdrawal is conducted on an inpatient basis, briefer withdrawals are possibly and often successful given the supervision and support of the inpatient environment.

2) Medications used for supervised withdrawal

a) Substitution therapies

Substitution medications are pharmacotherapies from the same class of the abused substance. They can be either the same substance which was abused, or a similar substance. There are currently two primary substitution medications used for withdrawal of opioids: methadone and buprenorphine.<sup>27</sup>

i) Methadone

Methadone is the most commonly used medication for the treatment of opioid withdrawal.

When dosed orally, onset of effects is gradual and peak plasma levels occur at 4 hours; 90% of methadone is protein bound.<sup>31</sup>

Methadone has good oral bioavailability, a long half-life that allows once daily dosing, and at sufficient doses produces both suppression of opioid withdrawal symptoms and blockade (or cross-

tolerance) to the effects of other opioids. In addition, it produces minimal side effects. Methadone is the most widely used pharmacotherapy for opioid dependence, and should be considered a first choice in the treatment of opioid withdrawal.<sup>32</sup>

The treatment of the opioid withdrawal syndrome in the Interdisciplinary Study Group on Alcohol and Drugs of the Psychiatric Institute of the Clinical Hospital of the Medical School of the University of São Paulo (GREA-IPq-HCFMUSP) involves a short-term medically supervised withdrawal that occurs at an inpatient setting and utilizes methadone as the primary pharmacological intervention.

The protocol used is based upon the definition of Withdrawal Syndrome defined by the following four criteria:

- Mydriasis;
- 10 mm Hg rise in systolic blood pressure;
- 10 beats/minute rise in heart rate;
- the whole set: sweating, chills, sighs, body pain, diarrhea, rhinorrhea, lacrimation.

If the patient has two or more criteria, he will receive methadone –10 mg. The patient is checked every 4 hours throughout the first day in the hospital and a 10 mg dose of methadone is given in case he presents two of the above criteria. The total methadone dose in the first 24 hours, which rarely is greater than 50 mg, is defined as the stabilization dose. In the second day this same dose is split into two dosages. The total daily methadone dose is then reduced in increments of 5 mg/day until the completion of discontinuance. Following the last dose of methadone, clonidine is given in a dosage of 0.3-1.2 mg, aiming to prevent or relieve the noradrenergic symptoms due to the Withdrawal Syndrome.<sup>12</sup>

Our protocol does not begin clonidine until methadone treatment has been completed. However, some researchers have suggested that clonidine should be started before the complete discontinuance of methadone and proposed an introduction

schedule for clonidine by the time methadone dose reaches 30 mg/day, during the discontinuance phase.<sup>33</sup>

Methadone may be also used on an outpatient basis for opioid withdrawal. When used in this manner, doses are typically reduced on a less than daily basis (often weekly, or at even greater time intervals), and reductions may occur in progressively smaller increments as daily doses reach 30 mg or less. Such methadone withdrawals are usually conducted in methadone treatment clinics, which are described in more detail later in this document. In general, patients have better long-term outcomes with methadone maintenance rather than methadone withdrawal, even when such withdrawals occur over several months.

The outpatient use of methadone is carried out in many countries where there is a strict system for the distribution of the medication. Opioid dependent patients in methadone treatment often come daily to the treatment centers and obtain the medication directly from the person in charge of its distribution.<sup>34</sup>

#### ii) Other substitution medications

Other substances can be used in the management of the Opioid Dependence Syndrome. Other opioids, with longer half-life than that of the drug abused, are often used for the replacement and progressive tapering of the substance.<sup>35</sup> In these cases it is useful to have available a table correlating the doses of the different opioids, so as to provide an effective treatment, as shown by Table 4.

**Table 4 – Equivalence of doses among the opioids**

1 mg de methadone corresponds to:

1-2 mg of heroin;

3-4 mg of morphine;

30 mg of codeine;

20 mg of meperidine;

0.5 mg of dilaudid;

7-8 ml of paregoric;

3 ml of laudanum

*SOURCE: Kleber, 1994<sup>26</sup>*

In Germany, for example, codeine is the opioid more commonly used in the management of the Opioid Dependence Syndrome.<sup>35</sup>

#### iii) Buprenorphine

Buprenorphine, a partial agonist of mu ( $\mu$ ) type opioid receptors, has shown promising results in the management of the Opioid Withdrawal Syndrome.<sup>36</sup> Buprenorphine is more potent than meperidine, can be given by sublingual or parenteral routes, has a long half-life, and has a relatively low abuse potential (although it has been misused by injectable route). When used for maintenance treatment (described in more detail below), the recommended dosage is 8-16 mg/day. Buprenorphine is equally effective when given thrice a week, for it has a slow dissociation from opioid receptors.

Several studies have examined the use of injectable buprenorphine for relatively rapid opioid withdrawal (i.e., withdrawals in less than 2 weeks). In general, injectable buprenorphine is effective – it suppresses symptoms of withdrawal, and is well tolerated and safe. When compared to clonidine, buprenorphine appears to produce greater early withdrawal symptom relief and less adverse effects such as lowered blood pressure.<sup>37</sup>

In France, buprenorphine was associated with some deaths, whether due to overdose or to association with other CNS depressants.<sup>38</sup>

One disadvantage for buprenorphine is that it may not produce sufficient opioid agonist effects to compensate patients with higher levels of physical dependence. Studies with buprenorphine have primarily focused upon its use as a substitution maintenance

medication rather than for withdrawal, and most countries have focused upon the former indication.

#### b) Non-substitution therapies: clonidine, symptomatic treatments

Clonidine, an alpha-2 agonist, is effective in the reduction of opioid withdrawal signs and symptoms such as sweating, piloerection, tingling, nausea and vomiting. It has minimal or no effect, however, in reducing opioid craving. The results from treatment of the Withdrawal Syndrome with clonidine in the literature are controversial. The reported effectiveness ranges from 0%-30% for outpatient treatments and 80% -90% for inpatient treatments.<sup>9,36</sup>

When used for the treatment of opioid withdrawal, clonidine doses range from 0.6-1.2 mg/day. The two primary side effects associated with clonidine use for opioid withdrawal are hypotension and sedation. Clonidine is not recommended for patients with a recent history of stroke, pregnant women and heart disease patients.

Other symptomatic medications can also be used for treatment of opioid withdrawal. These can include non-steroidal anti-inflammatory drugs (NSAIDs) for muscle and joint pain, antiemetics for nausea and vomiting, and sedatives for sleep disturbance.

#### 2) Maintenance

The maintenance treatment of opioid dependent patients is one of the most extensively evaluated treatments in the field of addictions. In general, it is characterized by a period of more than 180 days of medication use. Several medications are available for this modality of treatment, such as methadone, buprenorphine, clonidine, LAAM, other opioids (codeine, tramadol) and at least 15 days after the withdrawal of any opioid, naltrexone.

It must be pointed out that throughout the treatment, these patients should be engaged in another therapeutic approach, such as mutual help groups, psychotherapies or psychosocial support.

Two drugs are prescribed for opioid dependence in France: methadone and high dosages of buprenorphine. There are no specific guidelines for choosing between the two products.

#### a) Methadone

The reasons for choosing methadone are: possibility of oral administration, long half-life, lesser likelihood of variations in plasmatic concentration what would imply in prevention of withdrawal symptoms, greater compliance by the patients engaged in methadone programs, significant decrease in non-prescription opioid intake and legal problems, reduction of 'overdose' episodes and reduction of risk behavior for infectious and transmissible diseases.<sup>32</sup>

Maintenance treatment with methadone is carried out in many centers in the USA and Europe.<sup>30</sup> Those centers employ criteria such as:

i) Patients must be at least 18 years old; if minors, the legal guardian must authorize and follow up the treatment;

ii) A urinalysis has to confirm opioid use;

iii) Presence of needle marks (in case of injectable drugs);

iv) Presence of withdrawal symptoms. This criterion is not needed in three circumstances: pregnant women, patients who are inmates of correctional facilities and patients known to have previously taken part in such a treatment.<sup>27,30</sup>

This approach is one of the main models of pharmacological management used and studied.<sup>40-41</sup>

Methadone maintenance treatment, however, has several positive aspects, for it is a safe and effective therapy, it seems to improve the patients' nutritional state, reduces antisocial behavior, enhances professional life, promotes social reinsertion, reduces risk behavior (intravenous drug use, syringe and needle sharing) and increases the patient's compliance with treatment.<sup>42-43</sup>

Pregnant women should not go through the opioid detoxification treatment before the 14<sup>th</sup> gestational week, due to the risk of induction of abortion, or after the 32<sup>nd</sup> week, due to the risk of premature labor.<sup>44</sup>

Despite the effectiveness of methadone maintenance treatment, there are critical needs to develop alternatives to methadone for

opioid agonist maintenance treatment. Problems with methadone maintenance include its limited availability, the need for daily dosing, possible diversion of take-home doses, the potential for opioid overdose for patients who use illicit opioids, and difficult withdrawal from methadone. The need for daily dosing and consequent initial requirement for daily clinic attendance may deter many patients from receiving treatment by this modality.<sup>45</sup>

#### b) Buprenorphine

Buprenorphine has a long duration of action, blocks the euphoric effects of opioids and produces only few withdrawal symptoms following abrupt cessation of use.<sup>46</sup> It could be an alternative to methadone maintenance pharmacotherapy and may also have a role in helping patients in their transition from methadone maintenance to treatment with an antagonist such as naltrexone. It has also been used to decrease opiate withdrawal symptoms. The opioid-like euphoric effects of buprenorphine may lead to psychic dependence.<sup>47</sup>

Buprenorphine is a relatively new drug that, compared with methadone, seems to be safer in case of overdose, may have an easier withdrawal phase, and can be used on an alternate day dosing schedule in most patients. A number of randomized clinical trials have reported that buprenorphine is as effective as methadone for the use in maintenance therapy of opioid dependent patients.<sup>48</sup> However, many heroin users are initially reluctant to consider maintenance treatment, but after experiencing the stability produced by buprenorphine during outpatient detoxification, they often choose to remain on the drug for prolonged periods.<sup>49</sup>

Due to its partial agonist properties in  $\mu$  ( $\mu$ ) receptors, with high affinity, low intrinsic activity and slow dissociation from the receptors, this medication implies more therapeutic safety, lesser potential for physical dependence than other opioids and greater flexibility of dosing. It is characterized by low oral bioavailability and high liposolubility.<sup>38</sup>

This partial agonist of opioid receptors is approved by the U.S. Food and Drug Administration (FDA) for treatment of opioid dependence.<sup>37</sup>

The dose of sublingual buprenorphine used in the treatment of opioid dependence varies, and the maximum dosage has been as high as 32 mg/day in some clinical trials. Under certain circumstances, buprenorphine can act as an opioid antagonist precipitating a withdrawal state.

This medication can be given sublingually either daily or thrice a week and it has shown very significant results in the maintenance treatment of opioid dependent patients.<sup>37</sup> Laqueille et al<sup>50</sup> reported that the use of buprenorphine is indicated for patients with less than 10 years' history of opioid use and no depressive symptoms associated.

Johnson and McCagh<sup>51</sup> pointed out the promising possibility of the association of buprenorphine with naloxone in the management of opioid dependent patients. This association was reportedly effective in keeping patients in treatment, reducing the use of other opioids and decreasing opioid craving. However, they stated that the use of this combination may precipitate rather severe withdrawal states.

Pharmacological interactions between any of the consumed products can be dangerous. Some scientific publications have reported deaths related to the association of benzodiazepines with high dosage of buprenorphine.<sup>52</sup>

#### c) Clonidine

In spite of its questionable efficacy, this  $\alpha_2$  agonist is an alternative for the maintenance treatment of opioid dependent patients, aiming to relieve the adrenergic symptoms of the withdrawal syndrome. The recommended dosage is 0.3-1.2 mg/day.<sup>9</sup>

#### d) Levo-alpha-acetylmethadol (LAAM)

LAAM is a synthetic opioid agonist with an action that is qualitatively similar to morphine, a prototype  $\mu$ -agonist that affects the central nervous system and smooth muscles. The main actions of LAAM, to which tolerance develops over time, are analgesia and sedation. An abstinence syndrome, similar to that observed

with other opiates but with slower onset, less intensity, and a more protracted course, occurs on cessation after chronic dosing.

After oral administration, LAAM is well absorbed in the gastrointestinal tract. It is metabolised by sequential N-demethylation to nor-LAAM and dinor-LAAM, with a half-life of approximately 2 hours for the removal of one N-methyl group.<sup>53</sup>

The clinical advantages of LAAM are related primarily to its slow onset and long duration of action. These advantages are both pharmacological and logistic. Pharmacologically, the slow onset of action makes LAAM less subject to abuse because addicts tend to seek an immediate 'pacing out'. The longer duration of action provides a smoother blood level with less fluctuation between doses. Logistically, less frequent dosing means less paperwork, less record keeping, and less dose preparation time, enabling clinics to treat a larger number of patients.

The initial dose depends on the patient's degree of dependence. In general, the recommended initial dose for street addicts is between 20 and 40 mg with successive every-other-day dose adjustments of 5-10 mg until a pharmacokinetic and pharmacodynamic steady state is reached, usually within 1 or 2 weeks.

For patients who are already receiving methadone maintenance most can transfer to LAAM at a three-per-week dose that is slightly higher than their daily methadone dose. The recommended dose of LAAM is 1.2 to 1.3 times the patient's daily dose of methadone, not to exceed 120 mg. Subsequent doses, administered at 40 to 72 hour intervals, can be adjusted according to clinical response. The crossover from methadone to LAAM should be accomplished in a single dose; complete transfer to LAAM is simpler and preferable to more complex regimens that involve escalating doses of LAAM and decreasing doses of methadone.

LAAM should never be given daily. Most patients will stabilize on LAAM doses in the range of 60 – 90 mg three times per week. Doses as low as 10 mg and as high as 140 mg have been used successfully in clinical trials.

Adverse reactions to LAAM in opioid-dependent patients are rare. Side effects are nausea, vomiting, constipation, excessive sweating, decreased sexual interest, and delayed ejaculation.

LAAM is an opioid agonist with a long duration of action. It is metabolised into two metabolites with long half-lives, nor-LAAM (half-life 62 hours) and dinor-LAAM (half-life 162 hours), which are both more potent than the parent compound (half-life 47 hours).

These long half-lives allow the medication to be given thrice a week. It must be pointed out that it takes two to three weeks for LAAM to reach an optimal 'steady state' and that a rapid dosage increase carries the risk of overdose, due to cumulative dosing.<sup>54</sup>

Several recent studies have shown that LAAM is effective for the treatment of opioid dependence, as reflected by the reduction of withdrawal symptoms, decrease in the intake of other opioids and negative urinalysis for the detection of opioid metabolites.<sup>55</sup>

One meta-analysis carried out by Farré et al<sup>56</sup> (2002) showed that patients treated with LAAM were less compliant to treatment than those treated with methadone.

LAAM was associated with the development of a rare form of ventricular tachycardia, known as 'torsades de pointes', in which the amplitude of the ventricular complexes varies within a sinusoidal pattern, with small amplitude complexes bridging opposite polarity phases.<sup>57</sup> It has been withdrawn off the U.S. and European markets as of 2004.

#### e) Naltrexone

This opioid antagonist is an effective treatment for addicts with high motivation to recover and with the social supports that eventually encourage total abstinence. Naltrexone is taken orally three times weekly in doses of 50 to 100 mg on weekdays and 100 to 150 mg at weekends. Naltrexone acts as an opiate antagonist by discriminately binding with opiate receptors and, thereby, blocking the effects of heroin, methadone, or exogenous opiates. This medication has been used effectively as an interim

phase in opioid addiction and total abstinence in those patients actively engaged in psychotherapy and Alcoholics Anonymous and Narcotics Anonymous. A period of 10 to 15 days after last opiate should elapse before starting naltrexone.<sup>37,58</sup>

Many opioid-addicted patients have very little motivation to take naltrexone and to remain abstinent. However, patients with better identified motivation, among them groups of recovering professionals (physicians, attorneys) and federal probationers who face loss of license to practice a profession or legal consequences, have significantly better success with naltrexone.<sup>27</sup>

f) Other opioids

The use of opioids with longer half-life than the drug abused, given orally, is an option often used in centers where methadone, buprenorphine or LAAM are not available.

**3. Psychosocial treatments**

Psychosocial interventions are a key component of a treatment plan that includes a strategy to facilitate abstinence from opioids.

The psychotherapeutic approaches to dependence range from traditional psychoanalysis to cognitive-behavioral techniques.<sup>59</sup>

Mello et al<sup>60</sup> separated didactically the psychotherapeutic approaches used for the treatment of substance dependence:

1) Psycho-educational – Though not exactly a therapeutic approach, it has been used in several forms of psychotherapy. Patients and family members should receive the information required for the understanding of the concept of disease, its signs and symptoms, the recovery process and the occurrence of relapses.

2) Cognitive-behavioral – this approach has obtained good results in the management of dependence. It relies on the assumption that dependent patients may take advantage of the development of new methods of establishing relationships, including the identification of stimuli that may provoke relapses and ways to handle the desire to

take alcohol and other drugs. Relapse Prevention is a cognitive-behavioral treatment combining the training of behavioral skills and the techniques of cognitive intervention, aiming to assist patients in the maintenance of the abstinent behaviour.<sup>61</sup>

3) Insight-oriented psychotherapy – although discredited for substance dependent patients, it becomes useful to the patient when included in multimodal approaches.

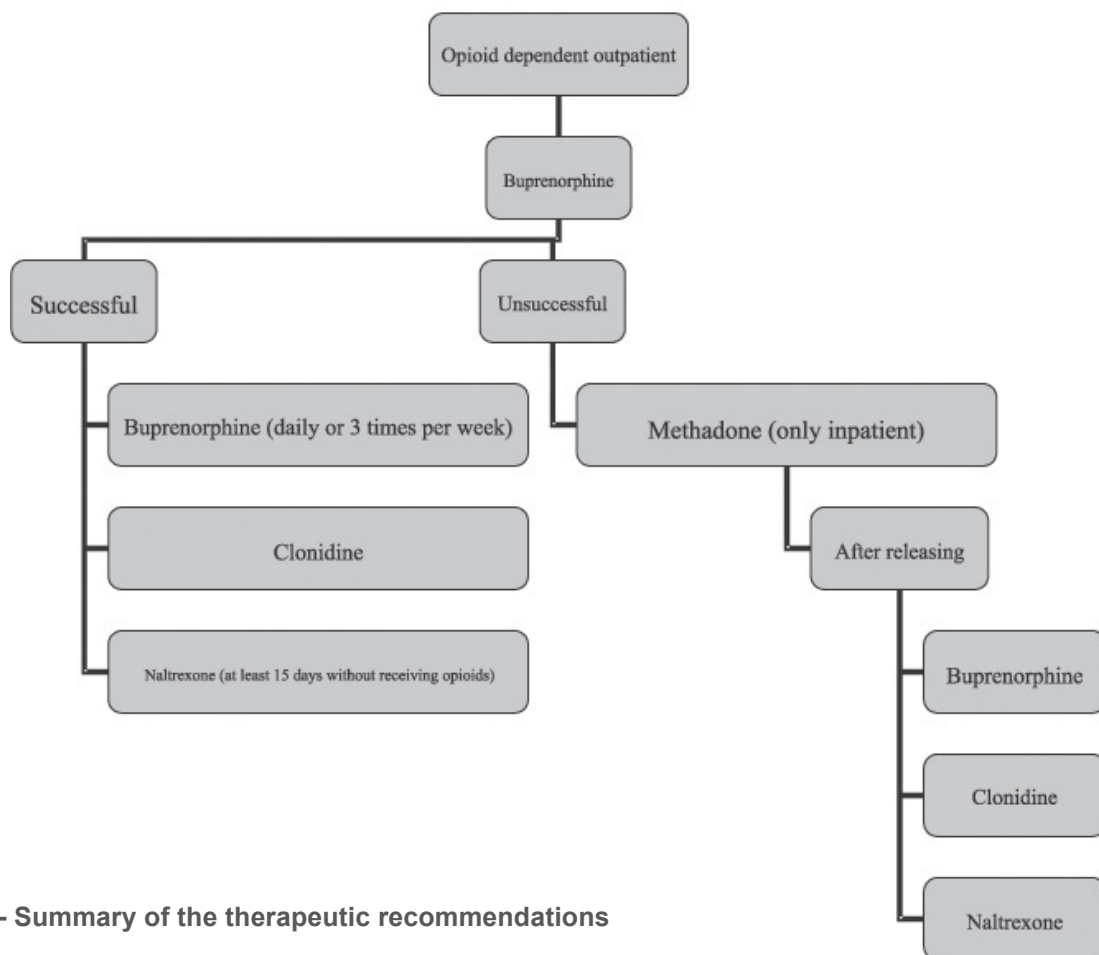
The techniques of Relapse Prevention have been widely used in the management of substance dependence for the last two decades and were proved to be effective for the patients thus treated.<sup>62-63</sup> Irvin et al,<sup>64</sup> in a meta-analysis, concluded that the techniques of Relapse Prevention are effective, particularly when applied to alcohol and polydrug dependents, as well as when combined with pharmacological treatment.

**Aspects of treatment in Brazil**

In Brazil, there are no available specialized clinics for the maintenance treatment with methadone. Methadone use is thus restricted to psychiatric hospital inpatients, patients admitted to clinics for the treatment of substance dependence and general hospitals. In outpatient settings, the pharmacological maintenance treatment of opioid dependent patients is carried out using buprenorphine, naltrexone and clonidine, according to the guidance cited above and based on scientific evidence.

As the use of methadone is the main form of treatment for opioid addicts, the creation of methadone clinics specialized in the treatment of these patients in Brazil is an important initiative and should be strongly encouraged.

Based on these observations we suggest the below sequential model for the opioid dependence syndrome treatment:



**Figure 1 – Summary of the therapeutic recommendations**



Study performed at the Department on Chemical Dependence of the Brazilian Psychiatric Association (ABP).

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