# IBOGAINE (*IBOGA TABERNANTHE*) AS A POTENTIAL ANTI-ADDICTIVE TREATMENT IN THE PIPELINE : A REVIEW

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## Abstract

Opioid addiction is still an emerging problem worlwide. In this South East Asia region, particularly Malaysia, opioid is identified as the main substance of dependency. Due to its nestled relationship between Intravascular opiod usage and the seroprevalence of Human Immunodeficiency Virus (HIV) in the population, the Malaysian government has adopted methadone maintenance therapy (MMT) as one of the harm reduction approaches in curbing the problem. Despite evidents of succes, methadone therapy has shown variabilities in terms of results and clinical outcomes which is very much dose and adherence dependence. This has no doubt suggesting for further research and development of anti-addiction treatment. Ibogaine on the other hand is far left behind from the streamline treatment of substance addiction though studies keep on showing auspicious results on the clinical use. Ibogaine or the name Iboga tabernanthe is one of the African shrubs which is used in ritual of African Bwiti Community. Due to its pharmacological properties, it is classified as psychedelic and has been used in various countries (Canada, New Zealand, Australia and Africa) to treat drug addiction. Pharmacologically, Ibogaine was found to exert its effects at various neurological systems including dopaminergic, glutamatergic, serotonergic, nicotinic and colinergic pathway as well as receptors including opioid, sigma and neurotransmitters such as gamma amino butyric acid (GABA). The mechanism of action is through its active metabolites of noribogaine which may act as addiction interrupter. With long half life, it will sustain in the blood concentration and prolong the pharmacological effects. In the case of opioid addiction, ibogaine exhibits the ability to reduce extracellular level of dopamine in the nucleus accumbens and further, its effects on dopaminergic function are largely regulated by its interaction with serotonin receptors. Physical side effects include QT prolongation, ataxia, dystonia, nausea, vomiting and light sensitivity. Various clinical and animal studies have been conducted worlwide with promising results. This paper will review the feasibility evidence of clinical application.

*Keywords : Ibogaine, anti addictive, addiction interrupter.*

## 1. Introduction

Opioid addiction is still an emerging problem worldwide. Before 1960's, drug mainly opioid addiction was regarded solely as social or personal affliction. In the year 1990's, Dr Alan Leshner, a former director of National Institute for Drug Abuse (NIDA) has once described opioid addiction is the illness of the brain with behavioral manifestation [Kreek, 1993]. This was which later found out that it is far beyond the behavioral or attitude connotation which made it classifies now as medical problem that needs medical intervention [Kreek, 1993; Tasman, 2008 and Kuehn, 2005]. In Malaysia, due to its proximity with the Golden Triangle, drug addiction became very prominent and initiated especially during the

era of the hippies in 1960's. The number of opioid addicts are eventually expanding with time and in the year 1985, Malaysian Government has announced 'War against Drug Use' to create awareness and prevention among the public and high risk individual. Three acts- the Drugs Dependants (Treatment and Rehabilitation) Act 1983; The Dangerous Drugs (Special Preventive Measures) Act 1985; and Dangerous Drugs (Forfeiture of Property) Act 1988 were legislated in order to curb the spread [Kamaruddin, 2002].

The negative consequences of such behavior are likely the major concern if not only. Many studies have found the association between opioid addiction with uprising of socioeconomic burden such as criminal cases and loss of productivity [Gossop *et al.,* 2005 and Tami *et al.,* 2001]. The population is also expected to experience a poor health condition with frequent hospitalization, shorter life expectancy [Marlott *et al.,* 1988 and Stanton *et al.,* 1997] and having infected with various contagious diseases such as hepatitis, endocarditis and AIDS [D'Aquila & Williams, 1987; Mascola *et al.,* 1989; Schrager *et al.,* 1991; Des Jarlais *et al.,* 2003; Aceijas *et al.,* 2004; Scorzelli, 1988; Chawarski *et al.,* 2006 and Mazlan *et al.,* 2006].

As noticed, those untoward consequences do not only affecting the said population but also their family members and community as a whole [Scorzelli, 1992; Rusdi, 2008 and UNODC, 2011]. With these justifications, it is important to establish and further develop the appropriate treatment approaches specifically meant for the illness.

## 2. Current treatments available

Many drugs have actually been introduced in the market for such purpo;se namely buprenorphine (partial agonist of opioid receptors), naltrexone (opioid receptor antagonist) and methadone (full opioid receptor agonist). Methadone as maintenance therapy is categorized as one of the harm reduction approaches, whereas buprenorphine and naltrexone are aiming for total abstinence. In Malaysia, methadone maintenance therapy (MMT) was adopted since 2005 by the Ministry of Health, Malaysia with its main intention to avoid risky behavior such as the sharing of syringe, needle and other injecting apparatus [Gossop, 2001]. The service is eventually expanding with time, not only among the government run healthcare facilities, but also in the private clinics. As it requires life-long commitment from the patients and the practitioners, a specific guideline was developed in hand warranting proper clinical use and monitoring procedures [MOH Malaysia Methadone Guideline, 2005]. Buprenorphine is not widely used mainly due to its high cost and high tendency of abuse [Barrett *et al.,* 2001; AT Forum and Donaher & Welsh, 2006]. Naltrexone is the opioid antagonist but the usage is not that popular and poor compliance is common [Gerra *et al.,* 2000].

With regards to alternative medicine like herbal medicine, *mitragynine sp,* one of the herbs available in Malaysia which has been extensively studied for the last 10 years. However, the evidence for clinical use is not that promising [Assangkornchai *et al.,* 2007 and Ulbritch *et al.,* 2013]. Ibogaine on the other hand has far left behind from the main stream treatment of opioid addiction though preliminary studies keep on showing promising results [Bastiaans, 2004; Alper *et al.,* 2008; Donelly, 2011]. This article will briefly review the addiction interrupter properties of ibogaine and evidence on how it can be used clinically with its studied safety profile.

### 2. 1 About Ibogaine : History and Pharmacological Studies

Ibogaine or the name *Iboga tabernanthe* is one of the naturally found African shrubs which was originally used in the ritual ceremony of African Bwiti Community [Donelly,

2011]. Based on its pharmacological properties, it is classified as psychedelics and has been used in many countries (Canada, New Zealand, Australia and Africa) to treat drug addiction [Alper *et al.,* 2008].

Currently, Ibogaine is widely known as anti-addiction drug with addiction interrupter properties. It helps in decreasing the self-administration of multiple drugs abuse. For an example, Ibogaine was found to interrupt the cravings for alcohol, cocaine and opiates, thus reduces the addiction of those substances. Not only that, Ibogaine was also found to exert the anti-nicotine properties [Popik *et al.,* 1995]. Pharmacologically, Ibogaine was found to exert its effects at various neurological systems including dopaminergic, glutamatergic, serotonergic, nicotinic and colinergic pathway as well as receptors including opioid, sigma and neurotransmitters such as gamma amino butyric acid (GABA).

The main mechanism of action is through its active metabolites of noribogaine which may sustained the blood concentration and prolong the effects of ibogaine [Brown, 2013]. In the case of opioid addiction, it shows that ibogaine does have an inhibitory effect on opioid withdrawal symptoms and suggests that the complex process resulting in morphine withdrawal includes an ibogaine-sensitive functional and transitory alteration of NMDA receptor (non-competitive NMDA antagonist). Ibogaine was also found to exhibits the ability to reduce extracellular level of dopamine in the nucleus accumbens and further, its effects on dopaminergic function are largely regulated by its interaction with serotonin receptors [Popik *et al.,* 1995].

Moreover, there is a detailed account on serotonin and dopamine involvement in the mechanism of action by ibogaine that has been done. Ibogaine has been shown to inhibit serotonin transporter (SERT) noncompetitively, in contrast to all other known inhibitors, which are competitive with substrates only. Ibogaine binding to SERT increases accessibility in the permeation pathway connecting the substrate-binding site with the cytoplasm. Since there are some structural similarity between ibogaine and serotonin, it had been suggested that ibogaine binds to the substrate site of SERT. The results show that ibogaine binds to a distinct site, accessible from the cell exterior only, to inhibit both serotonin transport and serotonin-induced ionic currents, including the homologous dopamine transporter (DAT). Thus, there is an increase in accessibility of the DAT cytoplasmic permeation pathway too. Plus, ibogaine does not inhibit the receptors by forming a long-lived complex with SERT, but rather binds directly to the transporter in an inward-open conformation (Brown, 2013; Bulling & Schicker, 2012).

In animal study, the toxicity level of ibogaine and noribogaine has been determined. The median lethal dose (LD50) of ibogaine and noribogaine equals to 263 mg and 630 mg/kg of mouse body mass, respectively. The toxicity of ibogaine is 2.4 times higher than that of noribogaine. Low doses of ibogaine and noribogaine had no impact on the mouse behavior. External effects including convulsions, nervous behaviour, limb paralysis were observed only when substances were administrated at higher doses [Xu *et al.,* 2000].

Anecdotal and small scale study has been conducted previously with promising results. Clinically, the recommended dose is 15-20mg/kg where the most effective dose was found to be between 17-19mg/kg and only two doses at most are needed. Physical side effects include ataxia, dystonia, nausea, vomiting and light sensitivity [Donelly, 2013]. Controlled clinical trial to date has never carried out because of serious side effects and fatalities reported. Concern about the human safety and lack of solid data from human study has hampered the progress of development for clinical use [Alper *et al.,* 2008].

There was a study conducted involving 33 patients performed in non-medical settings under open label conditions with average daily intravenous use of heroin was 0.64±0.5grams. Single dose of ibogaine administered has resulted in the resolution of the signs of opioid withdrawal without further drug seeking behavior within 24 hours in 25 patients. The effect

was eventually sustained for another 72 hours post treatment observation. However, the study suggested for further clinical investigations in clinical research setting [Alper *et al.,* 1999]

### 2.2 Safety issues of ibogaine

There were quite a number of reported cases of death or life-threatening complications especially the QT prolongation effects [Koenig *et al.,* 2013]. However, the approach towards those reported cases should always case-by case basis in order to rationally weight between the risks and benefits of ibogaine in clinical setting. One reported case suggestive for interaction between methadone and ibogaine progressing patient to QT prolongation and end of life. Others reported death in patient who took ibogaine with underlying medical problem of liver cirrhosis. This is especially true in patients with chronic alcohol ingestion. Overdose of opioids, alcohol and even ibogaine itself may also contribute to the incidence of cardiotoxicity [Vlandeeren *et al.,* 2014; Asua, 2013 and Papadodima *et al.,* 2013].

## 3. Summary

To summarize, though it is understood that ibogaine may produce toxicity, this must not disguise its potential and hinder further clinical investigations. The reported cases of toxicity is the evident of:- 1) Close monitoring is a must during the treatment; 2) Health screening and underlying disease especially related to heart and liver must be ruled out prior to treatment; 3) Concomitant drug use must be avoided pre and post treatment and 4) The main concern is to legalize the drug under supervised environment.

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