Breaking the Habit

An Evaluation of Ibogaine as a Viable Treatment for Opioid Dependence and Withdrawal

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Abstract

It is the aim of this review to analyse what is known of ibogaines mechanism of action, risk and toxicology and to evaluate its role in combating drug addiction. Ibogaine is a naturally occurring psychoactive indole alkaloid, which has long been used to treat substance-related disorders in a global medical subculture. Following anecdotal reports from the subculture, research in recent years has been focused on the elucidation of ibogaine's mechanism of action. Support for its efficacy in combating opioid withdrawal and dependence has been derived from a variety of studies on animal models for addiction. The mechanism of ibogaines action as an anti-addictive agent is still largely unknown; however its pharmacological profile is seen to involve interactions with a large host of neurotransmitter systems implicated in addiction. Because of this it is hypothesized that ibogaines actions may be related to second messenger system functioning thus allowing it longer action than the duration of its receptor occupancy. Ibogaine provides a plethora of exciting research avenues to be explored that differ vastly from current replacement and monoamine reuptake therapies used to combat of opioid addiction.

[Ibogaine, Opioid Dependence, Opioid Withdrawal, Addiction, Psychedelic-Pharmacotherapy]

Table of Contents

Introduction

A pharmacological sacrament consumed by the followers of the Bwiti and Mbiri religions of West Africa, ibogaine is just one of the many alkaloids found in the root of the shrub *Tabernanthe iboga*(Fernandez & Fernandez, 2001). A practice thought to have been learnt from the pygmies before them, the ritual consumption of ibogaine is done through the ingestion of root bark scrapings. Considered as both a medication and rite of passage, ibogaine has been an integral part of Bwiti and Mbiri traditions for centuries(Fernandez & Fernandez, 2001). As a rite of passage, its use is that of a binding agent, through shared communal experience and facilitation of ancestral connection. In terms of being used as a form of treatment, ibogaine was thought to be most effective in the treatment of somatic conditions, such as venereal disease and even infertility (Kenneth R Alper, Lotsof, & Kaplan, 2008; Fernandez & Fernandez, 2001).

As a psychoactive substance, ibogaine is classified as a tryptamine and idole alkaloid. It is an entheogen that possesses both psychedelic as well as dissociative properties(K R Alper, 2001; Glick, Maisonneuve, & Szumlinski, 2001; H. Lotsof & Wachtel, 2002). The first indication of its ability to attenuate symptoms of dependence and withdrawal arose as anecdotal observations from a group of 'drug experimenters' that would consume hallucinogens in a systematic fashion and note down the resultant physical and psychological effects(K R Alper, Beal, & Kaplan, 2001; Kenneth R Alper et al., 2008; H. S. Lotsof & Alexander, 2001). As ibogaines use as an anti-addictive agent, especially in the case of opioids, began to spread the US Food and Drug Administration (FDA) and National Institute on Drug Abuse (NIDA) took interests (K R Alper et al., 2001).

In non-medical settings ibogaine began to be administered by lay 'providers' in doses between 6-25mg/kg in humans in an attempt to treat symptoms of drug dependency. It was observed that it had the ability to attenuate dependence and withdrawal of psycho-stimulants, opiates, nicotine, and alcohol(K R Alper et al., 2001; Kenneth R Alper et al., 2008). Preclinical trials in rodents confirmed initial observations, showing reduced self-administration of cocaine, morphine and alcohol as well as a reduction in signs of morphine withdrawal(Glick et al., 1994; Glick, Rossman, Rao, Maisonneuve, & Carlson, 1992; Sershen, Hashim, & Lajtha, 2001). However ibogaines classification as a hallucinogen and stimulant saw it labelled as a schedule 1 drug. This subsequently lead to it being banned from research in some countries and created a stigma against it in others. Furthermore, the risk profile of ibogaine posed some problems for its acceptance as a viable treatment of opioid withdrawal due to its acute nonspecific side effects, such as cardiovascular risks, tremors, hallucinations, and cerebellar neurotoxicity(Arias, Feuerbach, Targowska-Duda, & Jozwiak, 2011; Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004;

Szumlinski, Maisonneuve, & Glick, 2000a)Despite this stigma and the hindrance it caused to clinical research, a subculture of medical professions and laymen that used ibogaine as a treatment for dependency boomed(K R Alper et al., 2001; Kenneth R Alper et al., 2008)

In recent years psychedelic research has been on the rise, and with this comes renewed interested in ibogaine as a treatment for substance dependence. Besides its effects on the physical aspects of addiction, Ibogaine appears to be able to provide a moral reset(Harrison, Mojeiko, & Jerome, 2009; H. Lotsof & Wachtel, 2002). When coupled with therapy, the efficacy of Ibogaine treatment was seen to rise with longer lasting effect(Harrison et al., 2009; H. Lotsof & Wachtel, 2002). Testimonies from patients, as well as those from self-treated individuals, claim that the use of Ibogaine causes a shift in the perception of drug use. Creating a more negative way in which drug cues and the drug itself are perceived(Harrison et al., 2009; H. Lotsof & Wachtel, 2002).

With psychedelic research once again stepping forward into the limelight, comes an opportunity to re-evaluate the role that ibogaine could play in the treatment of substance disorders and its place as a therapeutic tool. It will be the aim of this review to do so through examining mechanism of action, toxicology, and the possible use of analogues.

Opioid Addiction

With a long history of use in human societies, opioids can be considered as one of the oldest known drugs with a history of use dating back to prehistoric times(Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010). Opioids consist of both endogenous and exogenous compounds that are seen to bind to opioid receptors within the central and periphery nervous systems. The class opioids encompasses opiates such as opium and its derivatives (such as morphine and codeine,) semi-synthetics (heroin, oxycodone, etc), synthetics (methadone), and endogenous ligands for opioid receptors ((endorphins and enkephalins)(Butelman, Yuferov, & Kreek, 2012; Contet, Kieffer, & Befort, 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo, Martin-García, Berrendero, Robledo, & Maldonado, 2010). The term opioid is often used synonymously with opiates however traditional etymology classifies opiates specifically as naturally occurring alkaloids found in the resin of the opium poppy. Opioids are psychoactive substances that are seen to have analgesic action due to increased pain tolerance as well as decreased pain perception and decreased reaction to pain(Tahsili-Fahadan & Aston-Jones, 2010). Furthermore, Opioids are seen to elicit a strong euphoric response as well as sedation and depression of respiratory activity(Tahsili-Fahadan & Aston-Jones, 2010).

Due to their long history of use and the potency of their effects on pain relief opioids are, to this day, still the most commonly prescribed analgesic (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). However, despite their clinical uses there is a large potential for abuse. Opioids are highly addictive substances and their misuse presents a serious problem for the individual and society (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). Misuse and abuse is seen to lead to increase rates of crime and societal costs as well as a decrease in health and life expectancy of users (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). Use of illicit opioids, such as heroin, is often administered intravenously. This route of administration is coupled with increased risk of HIV, hepatitis and other infections (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). The abuse of opioids is not limited to the illicit, with recent years seeing a dramatic increase in the abuse of those prescribed for pain management(Tahsili-Fahadan & Aston-Jones, 2010; Walwyn, Miotto, & Evans, 2010). In the United States of America it is thought that 24% of patients prescribed opioids for chronic back pain as misusing (Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). The problem arises in distinguishing pain relief from addiction, when does it move from treatment to habitual use?

Misuse and abuse can range from the occasionally problematic to severe, and in some user may escalate to the use of intravenous heroin. Furthermore, the increase in non-medical use is seen to parallel an increase in prescriptions, with pill sharing between family and friends thought to be the leading cause(Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Walwyn et al., 2010). *Fig.1.a* below shows sales of prescription opioids have exploded between 1997 and 2006, a phenomenon that goes above and beyond the increase in prescriptions made in the same time period(Walwyn et al., 2010). The prescription opioid Vicodine is amongst those most abused and 2007 surveys indicated that 9.6% of American 12 grades had been using without prescription (Walwyn et al., 2010). *Fig.1.b* indicates that use of prescription opioids have overtaken marijuana use (Walwyn et al., 2010).

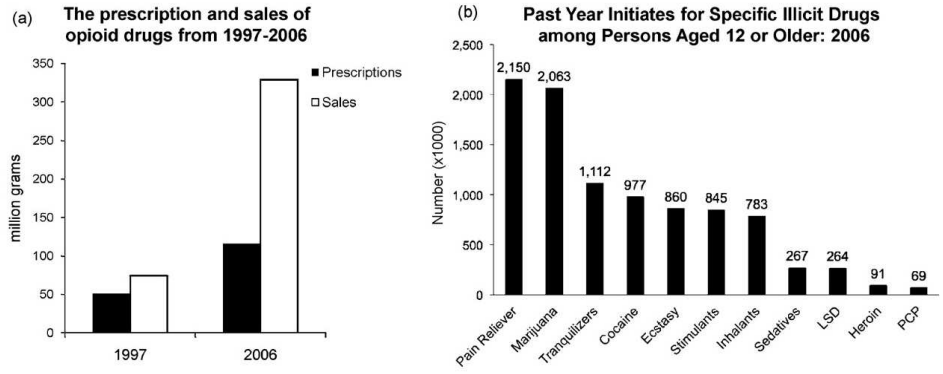


Fig. 1. Indicators of increased opioid use between 1997 and 2006. (a) Prescription and sales of opioid drugs from 1997 to 2006. Data from the Drug Enforcement Administration (DEA, 2007)show an increase in prescription number as well as a dramatic increase in the amount of opiate prescribed between 1997 and 2006. (b) Past Year Initiates. Results from Substance Abuse and Mental Health Services Administration (SAMHSA) of the 2006 National Survey on Drug Use and Health indicates past year initiation of non-medical opioid pain reliever use has been significantly higher than that of marijuana (SAMHSA, 2008)

[Figure obtained from: W.M. Walwyn et al. Drug and Alcohol Dependence *108 (2010) 156–165]*

Prevalence of life time opioid use was as high as 18.7% for non-medical use of prescription opioids and 1.7% for heroin between 19 and 30 years of age in the US (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Veilleux, Colvin, Anderson, York, & Heinz, 2010). Heroin is the most commonly abused opioid worldwide with annual prevalence of 0.4% and even though this is less than that for stimulants, percentage of individuals addicted to heroin out of those who have ever used is much higher (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Veilleux et al., 2010). Heroin is also 3 times more potent than morphine and costs of use (to individual and society) are dramatically higher when compared to other opioids. It is estimated that there are between 800 000 and 1 million heroin addicts residing in the US (Trigo et al., 2010). The abuse of heroin is more common in areas of low socioeconomic background, however due to it wide availability on the black-market with increase in quality and drop in prices its use is spreading. Resent years have also seen a doubling of heroin use in US high schoolers (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Veilleux et al., 2010).

While it is true that only a small portion of opioid users progress to addiction, this is seen to be much higher in the case of illicit users indicating that pharmacology plays a key role. With opioid-associated mortality much higher than that of other drugs of abuse, illicit or otherwise, opioid abuse is a large problem for society (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Veilleux et al., 2010). Like most forms of addiction, opioid dependence is thought to arise from interplay of internal (genetics - metabolism) and external (environmental – drug availability) factors. It is estimated that 3-16% of the population is at greater risk of becoming addicts after long term use due to possessing a greater biogenetic risk to addiction (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Veilleux et al., 2010). Polymorphisms for catechol-o-methyl transferase, cytochrome P450 super-family, dopamine and serotonin transporters, as well as dopamine and opioid receptors found in some opioid addicts(Tahsili-Fahadan & Aston-Jones, 2010). Furthermore, the genetic background of opioid addicts correlates with increased impulsivity, risk-taking and novelty seeking, and a maladaptive response to stress (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Veilleux et al., 2010). Like most forms of addiction, opioid addiction is seen to be comorbid with disorders such as schizophrenia, mood disorders, and ADHD(Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010).

Substance addiction is classified as a chronic relapsing disorder that is characterized by a loss of control, due to a difficulty in restricting use, and continuation of use despite negative consequences and adverse effects (Goodman, 2008; Trigo et al., 2010). The hallmarks of substance abuse, as defined by DSM IV, are patterned drug use in the face of significant harm /suffering

(Goodman, 2008; Trigo et al., 2010). Drug use is often, but not always, associated with developed tolerance leading to increased consumption as well as periods of withdrawal in abstinence of use (Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). Over the years many theories have arisen to explain the workings of addiction and the continued relapsing behaviour, many of these theories overlap and are not found to be mutually exclusive.

The opponent-process theory of addiction suggests that chronic use of addictive substances may lead to alteration of 'hedonic set-points' due to disequilibrium within the brains reward systems. This in turn leads to compulsive drug use and increased vulnerability to relapse(Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). The incentive sensitization theory of addiction proposed that alterations in brain circuitry responsible for incentive motivation for reward arise following chronic drug exposure creating a hypersensitivity for the drug and associated drug-cues causing a shift from 'liking' to 'wanting' (Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). Liking and wanting are considered to be distinct concepts, involving different brain areas, with tolerance for liking and sensitization for wanting. The learning based theory of addiction puts forward the notion that repeated drug taking becomes associated with strong memories mediated by changes, due to exposure to the drug, in the reward pathways in the brain. Drug taking, according to this theory, can be seen as a learned response to conditioned stimuli (Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010).

A common thread among all theories of addiction is that alteration to the brains circuitry responsible for reward processing and motivation, which result due to chronic exposure to the drug, leads to the formation of maladaptive behavioural strategies that promote continued drug use (Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). It appears that these new strategies encompass a shift of salience for drug and drug related cues, at the cost of natural rewards such as food, sex, and social interaction(Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). The following section of this review will attempted to elaborate on the systems and receptors involved in opioid addiction, the changes that take place, the role of tolerance and withdrawal, and aims and challenges of current methods of pharmacotherapy.

Systems and receptors involved

As stated previously, opioids exert their effects through binding to, and activation opioid receptors that are found widely dispersed throughout the central and periphery nervous systems. Opioid receptors are membrane bound proteins that are coupled to G-proteins(Butelman et al., 2012; Contet et al., 2004; Trigo et al., 2010). Through their binding to G-protein coupled complexes

they in turn modulate the activity of adenylyl cyclase, voltage-gated calcium channels, and G-protein inwardly rectifying potassium currents (Butelman et al., 2012; Contet et al., 2004; Trigo et al., 2010). Furthermore, opioid binding has been also found to exert effects over second messenger systems such as MAP kinases and phospholipid C. There exist three main subtypes of opioid receptors, Mu, Kappa and Delta, each with their own unique anatomical distribution throughout the body (as shown in *Table.1)* (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). The majority of opioids used for clinical purposes are those that have action on the mu-opioid receptor subtype (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010). Clinically used

Table 1 Physiological actions of opioid receptors

Receptor subtype	*Location in CNS*	*Major Actions*	*Agonists*	*Antagonists*
μ	Amygdala, caudate, cortex, nucleus accumbens (NAcc), periaqueductal gray (PAG), spinal cord, thalamus	analgesia, ↓ cough, euphoria, ↑ feeding, ↓ gastrointestinal motility, ↑ prolactin and GH release, ↓ immune function, miosis, physical dependence, respiratory depression, sedation	DAMGO Morphine Methadone Endomorphin Met-enkephalin β-endorphin Levrophanol	CTOP CTAP Naloxonazine Naloxone naltrexone
κ	Claustrum, cortex, hypothalamus, NAcc, PAG, spinal cord	analgesia, ↓ antidiuretic hormone release, ↑ feeding, ↓ gastrointestinal motility, miosis, muscle rigidity, sedation	Dynorphin U50,488 Fentanyl Butorphanol	Nor-BNI Naloxone Naltrexone
δ	amygdala, caudate, cortex, NAcc, olfactory bulb, Pontine nucleus	Analgesia, ↑ feeding	DPDPE Deltrophin Leu-enkephalin Etorphine	Naltrindole Naloxone naltrexone

[Table obtained from: Tahsili-Fahadan, P., & Aston-Jones, G. (2010). Neurobiology of Opioid Addiction. *Encyclopedia of Behavioral Neuroscience*, 393–403]

opioids are used for their relative selectiveness as painkillers that have limited effect over the other sensory modalities. Additionally, clinical opioids are seen to be more effective in their modulation of nociception than neuropathic pain (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010).

Endogenous opioid system has action over a large number of processes such as homeostatic function, movement control, and the modulation of noxious sensory input (see *Table.1*). Exogenous opioids mimic as well as enhance the actions of the neurotransmitters in the endogenous system(Fine & Portenoy, 2004; Tahsili-Fahadan & Aston-Jones, 2010). Endogenous opioid peptides can be divided into three distinct families; the endorphins, the enkephalins, and the dynorphins(Fine & Portenoy, 2004; Tahsili-Fahadan & Aston-Jones, 2010).

In general, opioids repress the coughing reflex and have an overall depressing effect over the respiratory system through action on brain stem centre responsible for both respectively

(Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). Indeed, death from overdose is almost always caused as a result of respiratory arrest (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010). Besides effects on respiratory systems, opioids suppress the immune system in general. Agonists for the mu and kappa receptor subtypes illicit miosis, an effect that is seen to be resistant to the build up of tolerance (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). A side effect of opioid use is that of nausea and vomiting in some cases, this is thought to occur through activation of chemoreceptors in the medulla (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010). Overall, the action of opioids is seen to affect the set temperature of the body through hypothalamic action, the inhibition of release of pituitary trophic hormones, increase the levels of prolatin while decreasing plasma level of testosterone and cortisol (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). All of which is seen to be attenuated through the application of mu-opioid antagonists and naloxene (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010).

Besides being readily self-administered, it has been found that agonists for opioid receptors induce condition place preference in animal models for addiction (Butelman et al., 2012; Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). In terms of their action as addictive agents, it is thought that the acute rewarding properties are, in part, mediated through the actions of the mesocorticolimbic dopaminergic system, in two distinct by parallel pathways(Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010). The first is the mesolimbic pathway, thought to be involved in contextual and conditioned learning, memory formation and the reinforcing properties of drugs and natural rewards; with projections originating in the ventral tegmented area (VTA) and extending to limbic structure such as the NAcc, amygdala hippocampus and ventral palladium (Di Chiara & Imperato, 1988; Goodman, 2008; Trigo et al., 2010). The second is the mesocortical pathway, with projections from the VTA to cortical areas (PFC, orbitofrontal cortext, and anterior cingulate cortex). There is increasing evidence for this pathway's involvement in mediation of cognitive aspects of drug taking such as altered executive functions, craving, loss of control, and compulsive drug use (Goodman, 2008; Guo, Wang, Xiang, & Zhao, 2009; Tahsili-Fahadan & Aston-Jones, 2010). However, the role of dopaminergic transmission, in comparison to mu-opioid receptors and the endogenous opioid system in general, is thought to play a more modest role in reward anticipation and associative learning(Tahsili-Fahadan & Aston-Jones, 2010).

Plasticity

Neural plasticity has long been thought to be the basis for learning and memory, the development of psychiatric diseases and addiction. Through chronic exposure to drugs of abuse,

long term adaptations in reward related areas are seen as the basis for the shift from social use to compulsive drug abuse and relapse (Kalivas & O'Brien, 2008). By means of hyper polarization of inhibitory GABA-ergic synapses onto dopaminergic cells in the VTA, acute opioid exposure is thought to increase firing rates of these DA neurons leading to the phosphorylation of CREB, and subsequent increased turnover of the GluR1 subunit of AMPA glutamatergic receptors(Berettimi, 2005; Kalivas & O'Brien, 2008; Tahsili-Fahadan & Aston-Jones, 2010).

Chronic exposure to morphine is seen to decrease the size of VTA DA neurons, indeed some studies indicate that even a single injection of morphine is capable of inducing long term potentiation (LTP) like enhancement of VTA glutamatergic responses in DA neurons(Guo et al., 2009; Scavone, Asan, & Van Bockstaele, 2011; Tahsili-Fahadan & Aston-Jones, 2010). Furthermore, both contingent and non contingent administration of opioids reduces arborisation of dendrites as well as spine densities of medium spiny neurons in the NAcc in rodents (Tahsili-Fahadan & Aston-Jones, 2010). In terms of medial prefrontal cortex (mPFC) and the hippocampus, chronic opioid use appears to decrease the number and complexity of dendritic spines, in addition to diminished neurogenesis of the hippocampus(Goodman, 2008; Kalivas & O'Brien, 2008; Tahsili-Fahadan & Aston-Jones, 2010).

Other notable brain changes are that fos induction in the basal lateral amygdala (BLA), the NAcc, and lateral hypothalamus (LH) appear to mirror the changes in preference in post dependant animals (Kalivas & O'Brien, 2008; Tahsili-Fahadan & Aston-Jones, 2010). That is to say that there is an increase in fos induction for increased morphine preference and a decrease observed alongside decreased food preference. Moreover, the NAcc shell is thought to play a role as well, due to observed fosb expression 5 weeks after withdrawal that correlates with increased drug preference (Kalivas & O'Brien, 2008; Tahsili-Fahadan & Aston-Jones, 2010). Opioid addicts also exhibit hypofrontality of the PFC, the decreased blood flow and metabolism is thought to play a role in vulnerability to relapse (Kalivas & O'Brien, 2008; Tahsili-Fahadan & Aston-Jones, 2010). In addition to the myriad of other changes within the addicted brain, brain derived neurotrophic factor expression is increased suggesting that neurotropic factors may also play their role.

Tolerance, Withdrawal, Relapse

Tolerance

Tolerance is defined as a reduced response to a drug, for a desired effected, following repeated use (Goodman, 2008; Tahsili-Fahadan & Aston-Jones, 2010). In the majority of opioid addicts this diminished effectiveness leads to an increase in frequency and dose required to achieve the desired effects(Cao & Bhargava, 1997; Trigo et al., 2010). For opioids, tolerance is seen to

develop for some effects, but not all. In terms of analgesia and reward, tolerances builds up fast and could lead to a dramatic increase, in some cases in excess of hundred fold the original required dose. Although tolerance to opioids in general is quite fast in onset, it does vary based on initial dose and pattern of drug administration (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Walwyn et al., 2010). Furthermore, studies have shown that it can be affected by conditioned cue to the point that administration of 'usual dose' could lead to an overdose if taken in a different context (Veilleux et al., 2010).

Tolerance to opioids could occur for a wide variety of reasons, which can essentially be broken down into two different types; innate and acquired. Innate tolerance can be seen as genetic sensitivity, while acquired tolerance is slightly more complicated (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). Acquired tolerance builds up over time, and can occur on top of innate tolerance (Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010). There are three routes toward acquired tolerance that are pharmacokinetic changes (increased drug metabolism), pharmacodynamic (adaptive changes within target system that reduces sensitivity) and learned (situational tolerance may occur as a results of drug taking consistently paired with a distinct given context)(Tahsili-Fahadan & Aston-Jones, 2010). In addition, adaptive/acquired tolerance may develop at any level from cellular, to receptor, to system (Tahsili-Fahadan & Aston-Jones, 2010). An example of receptor tolerance would be the internalization of receptors through increased binding affinity of receptors for arrestin proteins induced by chronic activation and subsequent phosphorylation of the receptors (Tahsili-Fahadan & Aston-Jones, 2010).

Withdrawal

While not life threatening, the effects of opioid withdrawal are an extremely unpleasant experience and can set in quite fast. Indeed the acute effects become noticeable 3 hours after the administration of the drug(K R Alper, Lotsof, Frenken, Luciano, & Bastiaans, 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Usually occurring after the development of dependence following chronic use, the signs and symptoms of withdrawal consist of the opposite effects produce by the drug (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). This can entail, but is not limited to, Yawning, lacrimation (tearing), mydriasis, rhinorrhea, perspiration, gooseflesh, muscle spasm, hot and cold flushes, tremors, anorexia, nauseam emesis, diarrhoea restlessness, insomnia, weight loss, dehydration, hyperglycemia, hyperpyrexia, hypertention and dysphoria (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). The degree of symptoms depend on size of last dose, type of opioid, and route of administration, with long lasting agents seen to produce more gradual withdrawal that is less intense and more

prolonged (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Although avoidance of withdrawal is thought to be a more acute motivation in drug taking, it seems that the rewarding effects of opioid consumption constitute a more major factor in continued consumption (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). There is an increasing body of evidence that the locus cerulus, a noradrenergic (NA) nucleus may be involved in opioid withdrawal (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Administration of opioids is seen to inhibit AC subtypes I and VII as well as cAMP production within the LC. This inhibit causes a drop of firing rates of the LC. However in the chronic consumption of opioids, homeostatic compensation occurs leading to the correction of this decrease (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Following abstinence from use, and during withdrawal, this overcorrection is seen to lead to firing rates several times higher than the norm (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). This over compensation is thought to be the product of enhances excitatory inputs with intrinsic unregulated excitability leading to a hyperactive state LC neurons (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010).

Nevertheless, much still remains to be determined in the causal relationship between this observed hyperactivity and the behavioural signs and symptoms of withdrawal. For example surgical lesions of the LC and a decrease in the turnover of the transcription factor CREB with this structure appear to attenuate withdrawal, while the pharmacological removal of noradrenergic LC function does not (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Furthermore, dysphoria associated with withdrawal from opioids can be dissociated from the physical symptoms indicating its complex and multifaceted nature (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Through blockade of β-NA receptors in the ventrolateral bed nucleus of the stria terminalis (vBNST), or through lesion of the ventral NA bundle in the caudal medullary, attenuation of aversion associated with morphine withdrawal may be achieved while this has little effect over the physical signs of withdrawal (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Thus it may be assumed that different mechanisms, and circuits, may be responsible for the somatic and affective responses. Contrary to above, some studies indicate that caudal NA cell groups, and not LC neurons, are important in mediating the affective response (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010).

During withdrawal it has been observed by some that the opioid peptide dynorphin is released, causing the inhibition of VTA dopaminergic actions as well as diminishing DA release in the

NAcc though binding to κ-opioid receptors in the VTA (K R Alper et al., 1999; Butelman et al., 2012; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Further studies implicated CREB's role in opioid withdrawal, as a NAcc target for dynorphin (Butelman et al., 2012; Tahsili-Fahadan & Aston-Jones, 2010). With increase expression of CREB is seen to attenuate the rewarding effects of morphine. Additionally, mutation of CREB genes has been found to diminish morphine withdrawal symptoms by some (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010).

During protracted abstinence, neuronal adaptations appear to be persistent long after the acute symptoms of withdrawals. There is limited knowledge about brain changes that are brought about during protracted abstinence, however a variety of animal studies suggest that changes within the extended amygdala bring forth elevated levels of anxiety, altered hedonic process, and decreased salience for natural rewards (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010). Increase levels of anxiety and altered hedonic process are thought to increase vulnerability to drug-seeking and relapse (K R Alper et al., 1999; Tahsili-Fahadan & Aston-Jones, 2010; Walwyn et al., 2010).

Craving and Relapse

A major problem in opioid dependency is vulnerability to drug-seeking and relapse, even years after detoxification (Tahsili-Fahadan & Aston-Jones, 2010; Veilleux et al., 2010). The average rate of relapse for heroin, after the first year, is 75-85% and after 15 years is still as high as 25% (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Veilleux et al., 2010). Drug craving and relapse may be induced after re-exposure to drug, drug-related cues, or stressors (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Veilleux et al., 2010). Long-term exposure to chronic drug use appears to disrupt natural rewards salience and thus increase likely hood of relapse (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Veilleux et al., 2010). Many pathways, and neurotransmitters have been implicated in drug and cue primed reinstatement (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Veilleux et al., 2010). Indeed rodent studies have shown that the systemic injection of mu-opioid receptor agonists, D2 agonists and indirect dopaminergic agonists lead to heroin-primed reinstatement of CPP as well as reinstate heroin self-administration (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Veilleux et al., 2010). Furthermore, recent studies have implicated a role of the endocanabinoid system, with CB1 receptor agonists triggering reinstatement of heroin self-administration (Contet et al., 2004; Tahsili-Fahadan & Aston-Jones, 2010; Veilleux et al., 2010).

Glutamatergic inputs into the NAcc core, originating in the PFC or amygdala have been suggested to play a role in the reinstatement of heroin seeking(Guo et al., 2009; Tahsili-Fahadan & Aston-Jones, 2010). Recent studies show an increase in glutamate in the NAcc as a result of drug and cue induced reinstatement. Inhibition of amygdala and PFC afferents appear to attenuate drug-induced reinstatement with an indirect role for the dopaminergic systems suggested in stress-reinstatement (Guo et al., 2009; Tahsili-Fahadan & Aston-Jones, 2010). In rodent models, the chronic administration of non-selective DA receptor antagonists attenuates reinstatement; however selective antagonists for receptor subtypes D1 and D2 do not (Guo et al., 2009; Tahsili-Fahadan & Aston-Jones, 2010). CRF receptor antagonists and α2-adrenergic agonists seen to attenuate foot-shock induced reinstatement of heroin seeking in rodents (Guo et al., 2009; Tahsili-Fahadan & Aston-Jones, 2010).

Aims and Challenges for Pharmacotherapy

When designing a therapy for beating the habit of opioid addiction, there are two main barriers that need to be overcome. The first is that of withdrawal and craving, while the second is the maintenance of abstinence (Kreek, 1997). The majority of therapies that exist today focus on these two aspects separately from each other, often with pharmacological intervention as a means of attenuating withdrawal and craving and extensive therapy and skills training to aid in maintained abstinence (Kreek, 1997). For a treatment to be effective, three conditions have to be met; 1) the reduction or removal of 'drug hunger' 2) prevention of withdrawal symptoms and 3) the normalization of any physiological disruptions caused through chronic drug abuse. In order to increase efficacy of treatment, the life style and drug administration pattern of the use has to be examined (Kreek, 1997). Research and self-reports indicate that heroin users 'get high'3 to 6 times a days, initially the drug is taken to achieve desired effects(K R Alper et al., 1999; Trigo et al., 2010). However, after effects begin to wane and drug is administered to prevent the acute effects of withdrawal kicking in. If heroin is withheld from a tolerant and physically dependant individual, withdrawal symptoms begin to manifest after 3 – 6 hours following last dose (K R Alper et al., 1999; Trigo et al., 2010).

Due to the short acting pharmacokinetic profile of opioids, addicts experience 'withdrawal sickness' many times a day. Because of the profound negative effects of withdrawal, it has been the primary action of current pharmacotherapy is to first deal with this aspect of opioid addiction (Kreek, 1997). Opioid replacement therapy is one such model in the treatment of addiction. Methadone is the most used treatment for heroin/opioid dependence (Veilleux et al., 2010). Methadone is a synthetic opioid widely used in methadone maintenance therapy. The goal of this therapy is to

replace illicit drug use (heroin) with methadone use (Veilleux et al., 2010). This serves to attenuate craving and block euphoric effects of opioids and is meant to be used alongside therapy or within a rehab program (Veilleux et al., 2010). Depending on severity of addiction methadone could be used for months or years. Long term use of methadone has been associated with mood swings, depression, borderline suicidal thoughts and the feeling of being a 'legal addict' (Veilleux et al., 2010). As with other opioids, methadone use is subject to build up of tolerance and can lead to dependence with withdrawal symptoms similar to that of heroin (Veilleux et al., 2010).

Ibogaine

History of Use

Traditional Use

The Bwiti spiritual discipline of West and Central Africa is one that is practiced by the forest-dwelling peoples of Babongo and Mitsogo in Gabon and the Fang people of Cameroon (K R Alper, 2001; Fernandez & Fernandez, 2001). Worshipers of the Bwiti religion incorporate aspects of animism, ancestor worship and Christianity. The use of ibogaine, through the consumption of root bark either as a tea or raw scrapings, is a wide spread practice. (K R Alper, 2001; Fernandez & Fernandez, 2001) It is used for a variety of reasons from spiritual growth to the stabilization of community and family structure and as universal treatment for somatic and metal disease (K R Alper, 2001; Fernandez & Fernandez, 2001). While the use of iboga bark scrapings predates colonial times, its use definitely become more prominent during this time period, mainly due to the sense of loss of cultural and religious identity of native peoples as a result of colonial influence(Fernandez & Fernandez, 2001). During this time period it was also seen that there was a dramatic increase of infectious diseases due to poor working conditions and increasing sexual promiscuity as men were taken from their families to work in different areas(Kenneth R Alper et al., 2008; Fernandez & Fernandez, 2001). It was noted that besides its effects on mind and spirituality, iboga consumption appeared to possess antimicrobial actions making it a somewhat suitable treatment for physical complaints as well (Kenneth R Alper et al., 2008; Fernandez & Fernandez, 2001).

Becoming deeply entangled in the practice of Bwiti, iboga consumption was used as a sacramental rite of passage for initiates and well as being used at lowered doses, $1/10^{th}$ of that use for initiates, as a mild stimulant (K R Alper et al., 1999; Fernandez & Fernandez, 2001; H. Lotsof & Wachtel, 2002). Known as the Path of Life and Death, when consumed at high doses, iboga users where thought to transcend space and time journeying to their beginning and their end (Kenneth R Alper et al., 2008; Fernandez & Fernandez, 2001). Furthermore consumption was thought to

promote ancestral contact allowing to the user to indentify “the work of the ancestors” thus providing direction and purpose, both practically and religiously, to those thought to be “lost” (Fernandez & Fernandez, 2001).

Although the practise of Bwiti is seen to contain a large degree of variability, there are some common features amongst all practitioners, aside from the use of iboga which is the founding principle (Fernandez & Fernandez, 2001). Initiates are often withheld from the consumption of iboga until the initiation ceremony, as its consumption is mainly reserved for practitioners. Furthermore these initiation ceremonies are seen to last for days where it is not uncommon for all full members to partake (Fernandez & Fernandez, 2001). During the ceremony, initiates are accompanied by their Iboga Mother and Iboga Father who are non-family members that are responsible for the guidance and care of the initiate throughout the experience(Fernandez & Fernandez, 2001). This practice of Iboga Mothers and Fathers is seen as a means of social binding amongst practitioners. Aside from initiation ceremonies it is not uncommon for different groups to come together to taking part in weekly binding ceremonies that last all night and include a meal of communion afterwards (Fernandez & Fernandez, 2001). In all practices that involved the consumption of iboga, dosages are carefully controlled by religious leaders (Fernandez & Fernandez, 2001). *Table.2* below displays dosage levels used by the Bwiti compared to those commonly used in the treatment of addiction (Fernandez & Fernandez, 2001).

TABLE 2
COMPARISON OF IBOGAINE DOSAGES REPORTED BY FRENKEN AND ALPER ET AL., WITH THOSE OF BWITI AS REPORTED BY FERNANDEZ, MEDIATED BY CALCULATIONS BY LOTSOF

Frenken, INTASH (*4*)	
Ibogaine low dose for spiritual impact:	nd
Ibogaine full dose for addiction interruption session, in capsule form:	nd
Alper et al. (*5*)	
Ibogaine dose to facilitate personal growth and change:	10 mg/kg
Ibogaine single dose in self-help network for addiction interruption:	20 mg/kg
Animal studies for neurotoxicity; alternate ibogaine doses over 60 days [no toxicity]:	10 mg/kg
Ibogaine dose associated with no evidence of toxicity [but decrease in drug self administration]	40 mg/kg
Ibogaine dose associated with cerebellar damage:	100 mg/kg
Lotsof (*personally communicated in preparation for ibogaine conference*)	
Ibogaine dosage causing modest psychoactivity with euphoria, altered perception of time:	90-120 mg
Amount of ibogaine ingested by an adept that would allow remaining centered enough to assist in initiation ritual:	200 to 300 mg
Ratio of fresh root scrapings to dry root bark:	15/1
Proportion of *iboga* alkaloids in dry root bark:	2 to 3% (50% ibogaine)
Rounded teaspoon of dry root bark:	3 to 4 g
Amount of *iboga* alkaloid yielded by rounded teaspoon of dry root bark, according to above range of approximations:	60 to 120 mg
Fernandez (*1,2*)	
Pick-up dose, *iboga* alkaloid content of 1 rounded teaspoon of dry root bark:	60 to 120 mg
Large dose for initiation into Bwiti, gradual intake of fresh root scrapings, maximal dose observed:	1000 g [one kilo]
Dose recalculated as dry scrapings [1000/15]:	67 g
Content of *iboga* alkaloids of the above quantity of root scrapings,assuming an average 2.5% *iboga* alkaloid content:	1.675 g
Total maximal Bwiti *iboga* alkaloid dose in mg:	1,675 mg
Maximal Bwiti *iboga* alkaloid dose calculated per kilo of body weight in a small initiate weighing 50 kilos [hence a high estimate]:	33.5 mg/kg

[Table obtained from Fernandez, J. W., & Fernandez, R. L. (2001). *The Alkaloids. Chemistry and biology*, *56*, 235–47.]

Clinical History

While Ibogaine had been known to the west long before the 1960s as a dietary supplement in low doses, it was not until the sixties that a clinical use for it first was proposed (K R Alper et al., 2001; K R Alper, 2001; Kenneth R Alper et al., 2008). The initial observation of its effectiveness in attenuation of drug dependence and withdrawal was noted by accident by Howard Lotsof who observed the effects on his own heroin dependence in 1962 (K R Alper et al., 2001; K R Alper, 2001; Kenneth R Alper et al., 2008). Following this realization, Lotsof subsequently administered ibogaine to 20 individuals that were part of his network of lay drug experiments that would systematically administer hallucinogens and note their effects (K R Alper et al., 2001; Kenneth R Alper et al., 2008; H. S. Lotsof & Alexander, 2001). It should be noted that the group were not out to look for a cure to heroin addiction, but were purely interested in psychoactive substances as a whole. After the administration of ibogaine at varying doses up to and including 19mg/kg, it was noted that for the subset of the group (7 out of the 20) who were addicted to heroin, that there was an alleviation of the symptoms of dependence such as withdrawal and craving (K R Alper et al., 2001; Kenneth R Alper et al., 2008; H. S. Lotsof & Alexander, 2001). Of the 7 addicts, 5 were seen to abstain from heroin use for 6 months or longer while the other 2 returned to use claiming that this was not because of persistent withdrawal symptoms but more out of identification as addicts (K R Alper et al., 2001; H. S. Lotsof & Alexander, 2001). In 1963 the activity of the group was ground to a halt due to increasing restrictions by FDA and law enforcement agencies that made procuring hallucinogens more difficult or illegal addicts (K R Alper et al., 2001; H. S. Lotsof & Alexander, 2001). Although questions were raised about the clinical validity of these observations, due to the unconventional setting and lack of control group, the systematic approach of the group regarding them and dosage could not be ignored and the path was paved towards (pre)clinical research(K R Alper et al., 2001; H. S. Lotsof & Alexander, 2001).

During the late 60s (1996-1970) as the war on drugs continued to gain ground, ibogaine became classified as a hallucinogen and stimulant and as a substance that is likely to cause dependence or endanger human health (K R Alper et al., 2001; Kenneth R Alper et al., 2008). This was followed closely by the FDA classification of ibogaine as a schedule I drug and its subsequent ban by the International Olympic Committee as a potential doping agent (K R Alper et al., 2001; Kenneth R Alper et al., 2008). It was in 1969 that psychiatrist Dr. Claudio Naranjo received the French patent for the psychotherapeutic use of ibogaine at doses of 4-5 mg/kg, a feat later achieved in 1985 by H Lotsof for the US patent (K R Alper et al., 2001). Between 1988 and 1994 US and Dutch research began to publish initial findings of ibogaines efficacy in animal models of addiction where it was found that it had the potential to diminish opioid self administration and signs of withdrawal as

well as cocaine self administration in rodents (K R Alper et al., 2001). From 1989 until 1993 ibogaine treatment was conducted outside of the conventional clinical/medical setting in the Netherlands with the help of International Coalition of Addict Self Help, Dutch Addicts Self Help, NDA international (K R Alper et al., 2001). 1991 saw the initiation of The Ibogaine Project by NIDA Medication Development Division based off of evidence found in the preclinical trials and the case studies (K R Alper et al., 2001). The focus of this project was on preclinical toxicological evaluations and the development of a protocol for use in humans. In 1993 the FDA advisory panel gave its approval for human trails to be conducted at doses of 1, 2, and 5 mg/k in phase I dose escalation trial, however these trials were suspended by the end of the year due cessation of funding(K R Alper et al., 2001).

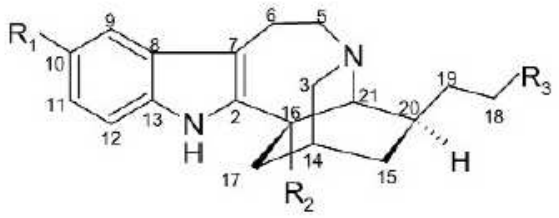
Around the same time, in 1994, NIDA conducted a series of developmental meetings for phase I and II clinical trials, creating a protocol that called for single administration of a fixed dosage of either 150 mg/kg or 300mg/kg ibogaine compared to placebo for the treatment of cocaine addiction (K R Alper et al., 2001). The following year at the NIDA review meeting, human funding is once again considered but dropped due to criticisms put forth by pharmaceutical industry representatives, but support was granted for preclinical trials (K R Alper et al., 2001).

As of yet there have been no randomised controlled clinical trials have been conducted. From the mid 1990s onwards, ibogaine's popularity in alternative settings, that followed the conventional treatment model, began to rise (Kenneth R Alper et al., 2008). Partly due to word of mouth and partly due to the boom of the internet with increased access to information and the Ibogaine Mailing List, informal settings for treatment began to spring up all over the world from the Netherlands, Great Britain, Slovenia, Czech Republic and the US (Kenneth R Alper et al., 2008).

Structure and Properties of Ibogaine

Ibogaine, also known as 10-methoxyibogamine, as shown in *fig.2* below and confirmed by x-ray crystallography is the most abundant alkaloids found in the African shrub *Tabernanthe iboga* (K R Alper, 2001; Popik & Skolnick, 1998). It has the molecular formula C20H26N20 and a molecular weight of 310.44 (K R Alper, 2001). The common method of ingestion is the consumption of the dried root bark of the shrub where its concentration is found to be highest (5-6%)(K R Alper et al., 2001; Popik & Skolnick, 1998). Ibogaine is a chiral compound that is optically active, rotating polarized light in a counter clockwise fashion ([α]D -53˚ in 95% ethanol) and thus is levorotary (K R Alper et al., 2001; Popik & Skolnick, 1998). Found to be soluble in ethanol, acetone, ether, chloroform, and benzene but barely so in water. With a melting point of 153˚ and a pKa of 8.1 in 80%

methylcellosolve decomposition occurs by exposure to heat and light. Furthermore, ibogaine crystallizes into prismatic needles from ethanol (K R Alper et al., 2001; Popik & Skolnick, 1998). In hydrochloride form, it has been found to be soluble in water, ethanol and methanol. Also in this state Ibogaine is levorotary ([α]D -63˚ in 95% ethanol and [α]D -49˚ in water) and decomposition happens at 299˚ (K R Alper et al., 2001; Popik & Skolnick, 1998). As a hydrochloride, ibogaine is barely soluble in acetone and chloroform and not at all in ether. Its principal metabolite, noribogaine, is produced through demethylation (K R Alper et al., 2001; Pearl, Herrick-Davis, Teitler, & Glick, 1995; Popik & Skolnick, 1998). A congener of ibogaine, 18-methoxycoronarine (18-MC) has been reported to be similar in terms of efficacy in animal models of drug dependence (K R Alper et al., 2001; Pearl et al., 1995; Popik & Skolnick, 1998) and will be discussed later in this review. The chemical structures of both the metabolite and congener can also be found in *fig.2*.



Alkaloid	R_1	R_2	R_3
Ibogaine	OCH_3	H	H
Noribogaine	OH	H	H
(+)-18-Methoxycoronaridine	H	CO_2CH_3	OCH_3

FIGURE.2 CHEMICAL STRUCTURES OF IBOGAINE, NORIBOGAINE, AND 18-METHOXYCORONARIDINE. The ibogamine skeleton above is numbered using the LeMen and Taylor system in which ibogaine is designated as 10-methoxyibogamine and noribogaine as 10-hydroxyibogamine. Alternatively, according to the Chemical Abstracts numbering system for the ibogamine skeleton which is frequently encountered in the biological and medical literature, ibogaine and noribogaine have respectively been referred to as 12-methoxyibogamine and 12-hydroxyibogamine.

[Figure obtained from Alper, K. R. (2001). Ibogaine: a review. The Alkaloids. Chemistry and biology, 56, 1–38.]

Mechanism of Action

Pharmacokinetics

Absorption of Ibogaine has been found to be subject to a wide degree of variation, *Jeffcoat, Cook, Hill, Coleman, & Pollack (1994)* observed gender differences in the bioavailability of single oral doses of both 5 mg/kg and 50mg/kg in rats. In females, a bioavailability of 16% and 71% were recorded for the 5 and 50mg/kg doses respectively, while in male rats it was recorded as being 7% and 43% (Jeffcoat et al., 1994). *Hough, Pearl, & Glick* (1996) conducted a study in which rats were

administered 40mg/kg ibogaine intraperitoneal, and checked for whole brain levels of ibogaine and its metabolite, noribogaine, at intervals of 1, 5, and 19 hours post admin. Gender differences were also found, with male rats show lower levels of both ibogaine and noribogaine at all time points (K R Alper, 2001; Hough et al., 1996). Female levels were seen to be 10, 1, 0.7µM and males 6, 0.9, 0.2µM respectively for ibogaine at each time point(K R Alper, 2001; Hough et al., 1996). Levels for noribogaine were recorded at 13, 7, 0.1 µM in males and 20, 10, 0.8 µM in females, respectively for each time point(K R Alper, 2001; Hough et al., 1996). The dose dependent nature of bioavailability that has been observed for ibogaine has lead to the hypothesis that its absorption and first pass elimination is nonlinear

Ibogaine has a wide bodily distribution and can be indentified in a variety of organs and biological materials post administration. Evaluations of distribution in plasma, brain, kidney, liver, and fat have found that at 1 hour after administrations ibogaine presence in fat is 100 times higher than that of plasma, while brain levels are seen to be 30 times higher than plasma levels(Chèze, Lenoan, Deveaux, & Pépin, 2008; Hough et al., 1996; Pearl, Hough, Boyd, & Glick, 1997). Due to the lipophilic nature of ibogaine and noribogaine it is thought that adipose tissue might act as a reservoir thus enabling release and metabolism over an extended period of time(K R Alper, 2001; Hough et al., 1996; Popik & Skolnick, 1998). This could provide an explanation for the long lasting effects observed. Furthermore it is hypothesised that, because of its greater polarity the presence of noribogaine is responsible for this prolonged effect. Studies have also shown that following subcutaneous administration of ibogaine levels are high, suggestive of a large first pass effect after IP dosing, though hepatic extraction (Hough et al., 1996).

As previously mentioned, noribogaine is ibogaines major metabolite, and is produced by demethylation. Detectable in brain tissue 15 minutes after oral administration of 50mg/kg ibogaine, metabolism is thought to occur through the actions of cytochrome P-450 2D6 isoform (CYP-450 2D6)(K R Alper, 2001; Obach, Pablo, & Mash, 1998; Popik & Skolnick, 1998). Noribogaine is pharmacologically active itself, producing many of the same effects as ibogaine(K R Alper, 2001; Baumann, Pablo, Ali, Rothman, & Mash, 2001; Kontrimaviciūte, Larroque, Briedis, Margout, & Bressolle, 2005; Obach et al., 1998; Pearl et al., 1995; Popik & Skolnick, 1998; Rabin & Winter, 1996). It has been identified that there are two distinct ibogaine O-demethylase activities, one with a high and one with a low michaelis constant(K R Alper, 2001; Obach et al., 1998; Popik & Skolnick, 1998). It is thought that the low one constitutes CYP-4502D6 activity, which is responsible for more than 95% of total intrinsic clearance(K R Alper, 2001; Obach et al., 1998; Popik & Skolnick, 1998). Additionally, three types of metabolizers have been identified, rapid, intermediate, and poor; this is consistent

with observed pharmacogenetic polymorphisms for CYP-4502D6 (K R Alper, 2001; Obach et al., 1998; Popik & Skolnick, 1998).

The estimated half-life of ibogaine in rodents is around 1 hour and it is thought to be are 7.5 hours for humans. Extraction of ibogaine and its metabolites occurs though excretion though renal and gastrointestinal tracts with 70% of elimination occurring within 24 hours after administration (K R Alper, 2001; Obach et al., 1998; Popik & Skolnick, 1998). Between 1 and 12 hours post administration plasma and tissue levels decrease 10-20 fold (K R Alper, 2001; Hough et al., 1996; Obach et al., 1998; Popik & Skolnick, 1998). Based off of pharmacokinetic data obtained in rodents, concerns were raised over the effectiveness of ibogaine as a treatment. With low bioavailability due to presystemic clearance, saturable first pass clearance, and interpatient variability called into question. However, interspecies differences had not been taken into account when these concerns were raised. It has since been discovered that in humans, 90% of 20mg/kg oral ibogaine is eliminated in 24 hours while elimination of noribogaine is significantly slower and is still persistently high in comparison (K R Alper, 2001; Popik & Skolnick, 1998).

Pharmacodynamics

Found to have low micromolar affinities for kappa- and mu-opioid receptors, NMDA subtype of glutamate receptors, 5-HT_3 receptors, sigma2 sites, sodium channels, and serotonin and dopamine transporters, a key question surrounding ibogaines efficacy as an anti-addictive agent is whether or not a single or multiple receptor system actions are at the core of these effects (K R Alper, 2001; Cao & Bhargava, 1997; Glick et al., 2001; Popik & Skolnick, 1998; Sershen et al., 2001; Szumlinski, Maisonneuve, & Glick, 2000b; Wei, Maisonneuve, Kuehne, & Glick, 1998).

An antagonistic relationship with glutamate receptor subtype NMDA, though to be a key receptor in long-term potentiation (LTP) and thus learning and memory formation, is thought by some to be putative to ibogaine's effects on drug dependence (K R Alper, 2001; Levant & Pazdernik, 2004; Pace et al., 2004; Paskulin, Jamnik, Zivin, Raspor, & Strukelj, 2006; Popik & Skolnick, 1998; Skolnick, 2001). Proposed to be a non-competitive antagonists based off of evidence that ibogaine competitively inhibit MK801, a NMDA no-competitive antagonist, and that the administration of glycine, a NMDA co-agonist, attenuates some of its effects on drug dependence (K R Alper, 2001; Levant & Pazdernik, 2004; Pace et al., 2004; Paskulin et al., 2006; Popik & Skolnick, 1998; Skolnick, 2001).

Further action of ibogaine is found at the opioid receptors, where its role is not as clear cut (Ali, Newport, Slikker, Rothman, & Baumann, 1996; K R Alper, 2001; Glick et al., 2001; Popik & Skolnick, 1998; Rabin & Winter, 1996; Sershen et al., 2001). In terms of the μ-opioid receptor, there

is thought to be an agonistic action at play however, unlike other MOR agonists ibogaine did not appear to have antinociceptive effects (K R Alper, 2001; Popik & Skolnick, 1998; Sershen et al., 2001). This has lead to the suspicion that there may be more of a second messenger role to explain the enhanced functionality (K R Alper, 2001; Popik & Skolnick, 1998; Sershen et al., 2001). There still remains much debate as to whether ibogaine has an antagonists or agonist effect on K-opioid receptors. While it has been observed that KOR antagonists diminish the effects of ibogaine in morphine treated rats and that some KOR agonists may imitate some of its effects the offset of KOR agonist decreases in DA efflux through the addition of ibogaine remains puzzling (K R Alper, 2001; Popik & Skolnick, 1998; Sershen et al., 2001).

Containing an indole ring itself, ibogaine has been observed to bind to serotonin transports and thereby increasing serotonin levels in the NAcc (Ali et al., 1996; K R Alper, 2001; Baumann et al., 2001; Popik & Skolnick, 1998; Sershen, Hashim, & Lajtha, 1997; Wei et al., 1998). Furthermore it has been seen to block reuptake of serotonin and consequently ibogaines effects on extracellular serotonin levels may be partially mediated by uptake inhibition and well as release. Ibogaine has also been reported by some studies to bind to $5HT_{2A}$ receptor (though to be the psychedelic receptor) and to $5\text{-}HT_3$ (Ali et al., 1996; K R Alper, 2001; Baumann et al., 2001; Popik & Skolnick, 1998; Sershen et al., 1997; Wei et al., 1998).

For dopamine function, ibogaine is a competitive blocker of reuptake at DA-transporters (K R Alper, 2001; Popik & Skolnick, 1998; Sershen et al., 2001; Szumlinski et al., 2000a, 2000b). However reported affinities for serotonin transports are 10-50 times stronger. Ibogaine has also been found not to effect norepinephrine reuptake transporters (K R Alper, 2001; Popik & Skolnick, 1998; Sershen et al., 2001; Szumlinski et al., 2000a, 2000b). Additionally following intravenous application of ibogaine, and not after IP administration, an increased firing rate is observed for VTA dopamine neurons. Lower concentrations of DA, along with increased levels of its metabolites have been reported following ibogaine treatment in rodent models (K R Alper, 2001; Popik & Skolnick, 1998; Sershen et al., 2001; Szumlinski et al., 2000a, 2000b). It is hypothesised that the blockade of transporters prevents translocation of DA into vesicles as well as its redistribution to cytoplasmic pools, leading to increased dopamine metabolism by monoamine oxidase (K R Alper, 2001; Popik & Skolnick, 1998; Sershen et al., 2001; Szumlinski et al., 2000a, 2000b).

Ibogaines general pharmacological actions have been test in a battery of animal models to determine its effects on drug dependence based on attenuation of withdrawal, its effects on the self administration of other drugs, fear and anxiety, as well as learning and memory (K R Alper, 2001; Popik & Skolnick, 1998). Animal studies have shown that ibogaine appears to invoke anxiogenic

effects in quite a few species (K R Alper, 2001; Popik & Skolnick, 1998). Behavioural studies conducted in cats show that intravenous ibogaine doses of 2-10mg/kg produce fear –like responses within 1-2 hours after injection followed by a display of atypical arousal (K R Alper, 2001; Popik & Skolnick, 1998). In dogs, ibogaine produces and alert and tensed disposition thought to be the result of a loss of recognition of their environment and regular handler (K R Alper, 2001; Popik & Skolnick, 1998). Rodent studies have been the most compelling in this regard, with both rats and mice showing a reduction in open arm entries in the elevated plus maze, an observation that can be attenuated with the application of an anxiolytic agent (K R Alper, 2001; Popik & Skolnick, 1998).

Ibogaine, along with some of the other iboga alkaloids has been observed to reduce self administration of cocaine, opioids such as heroin and morphine, alcohol as well as reduce nicotine preference, and effect that has been reported to be persistent by some labs (K R Alper, 2001; Glick et al., 1994; I M Maisonneuve et al., 1997; Popik & Skolnick, 1998; a H. Rezvani, Overstreet, & Lee, 1995). *Glick et al.* (1992)conducting studies on ibogaines effects on cocaine and morphine self administration demonstrated a dose-depend relation for the attenuation of both, for doses between 2.5 and 80mg/kg ibogaine. They further reported that the effect was subject to individual variation amongst the rodents with some showing reduce self administration for days afterwards while others required repeated treatment with ibogaine to achieve this. *Dworkin, Gleeson, Meloni, Koves, & Martin* (1995) observed similar effects on ibogaine for heroin self administration. Rodents were treated with 40 and 80mg/kg ibogaine and showed reduced heroin intake, it was also observed that there was a 97% reduction in the response for a food reinforcement schedule (Dworkin et al., 1995). Additional studies have shown that ibogaine attenuates alcohol intake in alcohol preferring rats but has no observable effect on water or food intake (a H. Rezvani et al., 1995; A. H. Rezvani, Overstreet, Perfumi, & Massi, 2003). Overall it has been observed that there is a reduction in food, water and drug intake on the day of ibogaine administration. However many labs have reported that in terms of food and water there is no further reduction on subsequent days, even in the cases when drug self administration appears to be persistently attenuated (K R Alper, 2001; Glick et al., 1994; I M Maisonneuve et al., 1997; Popik & Skolnick, 1998; a H. Rezvani et al., 1995).

Other than its effects on drug self administration ibogaine has been reported to diminish signs of withdrawal in animal models as well as humans (K R Alper et al., 1999; Glick, Gallagher, Hough, Rossman, & Maisonneuve, 1992; Glick, Rossman, & Steindorf, 1991). For morphine-dependent rats, given naloxene to promote withdrawal syndrome, ibogaine dose dependently reduces signs of withdrawal such as increased rearing, digging, and jumping (K R Alper, 2001; Glick, Rossman, et al., 1992; Glick et al., 1994; Popik & Skolnick, 1998). This effect is observable after

administration either intracerebroventricularly (4-16µg) or IP (40 and 80mg/kg) ibogaine (K R Alper, 2001; Cappendijk, Fekkes, & Dzoljic, 1994; Popik & Skolnick, 1998). Further studies have shown that morphine dependent monkeys when given a subcutaneous dose of 2 or 8 mg/kg ibogaine, there is a partial suppression of some signs of opioid withdrawal (K R Alper, 2001; Glick, Rossman, et al., 1992; Popik & Skolnick, 1998). Additional evidence is found in mice, where ibogaine treatment dose dependently causes a resolution of morphine withdrawal as well (K R Alper, 2001; Popik & Skolnick, 1998).

Events involved in learning and memory are significantly affected by the action of ibogaine as well, particularly those involved with the learning and encoding of drug salience (K R Alper, 2001; Luxton, Parker, & Siegel, 1996; Popik & Skolnick, 1998; Popik, 1996). Ibogaine's antagonist effect on NMDA receptors are thought to be responsible for its effects on learning and memory(K R Alper, 2001; Sershen et al., 2001). Initial evidence for ibogaine potential effect on memory came from anecdotal evidence from patients and individuals who had take the substance, where reports of a panoramic readout of past memory are common place (K R Alper, 2001; H. Lotsof & Wachtel, 2002; Popik, 1996). In some instances it has been observed that ibogaine attenuates the acquisition of spacial memory, thought to be brought about by reduced locomotor activity and diminished detection of sensory information. At lower doses, were ibogaine is also seen to have more of a stimulant effect. It is found to even facilitate spacial memory retrieval (K R Alper, 2001; Popik & Skolnick, 1998; Popik, 1996). *Helsley, Fiorella, Rabin, & Winter* (1997) in their experiments to further determine ibogaine's effects on spacial memory, found that at a dose of 50mg/kg spaced out over 8 hours decreases response but not acquisition rates in a memory task. In addition to this they also observed that 46mg/kg ibogaine administered 20 minutes prior to a learning trail had no effect on task acquisition (Helsley, Fiorella, et al., 1997). Furthermore they found that if administered after the trail, ibogaine facilitated consolidation of the memory trace (Helsley, Fiorella, et al., 1997).

Evidence for efficacy in humans

Testament for ibogaines effects on attenuation of acute opiate withdrawal in humans comes largely from anecdotal reports from the addicts themselves, as well as the demand created for ibogaine treatment over the years (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; Mash et al., 2001; Popik & Skolnick, 1998; Sheppard, 1994). As information about ibogaine has been spread by word of mouth, over the internet, and in recent times through documentaries, an increasing number of an informal network of treatment facilities have sprung up all over the world (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; Mash et al., 2001; Popik & Skolnick, 1998; Sheppard, 1994). Opioid dependence is seen to be the most common motive for seeking out ibogaine treatment. Addicts who have undergone the treatment claim that there is a reduction in craving and attenuations of signs of

withdrawal already within the first two hours post administration, and that there is a complete resolution of opioid withdrawal syndrome by the end of the experience/treatment (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; Mash et al., 2001; Popik & Skolnick, 1998; Sheppard, 1994). These effects have been consistently reported over the years and confirm what is seen in animal models (K R Alper, 2001; Popik & Skolnick, 1998).

Initially it was thought that these observations might be hindered by methalogical limitations of the non medical setting and that the results could easily be subjectively skewed (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; Mash et al., 2001; Popik & Skolnick, 1998; Sheppard, 1994). However in their summary of 33 cases of independent treatment outside of the medical, K R Alper et al. (1999) found that the signs of acute opioid withdrawal are a highly robust clinical phenomenon and thus could offset the potential limitations of this setting due to clinical obviousness and un-ambiguity of their presences or absence (K R Alper et al., 1999). For the patients treated in these studies the average daily dose of heroin consumed was that of 0.64g (± 0.50) and the primary route of administration was done intravenously (K R Alper et al., 1999). For their treatment and oral dose of ibogaine was given that ranged from 6 to 29mg/kg (averaging 19.3± 6.9mg/kg) across treatments (K R Alper et al., 1999). Of the 33 patients 25 showed resolution of signs of opioid withdrawal without further heroin seeking. Other outcomes observed were; drug seeking without withdrawal (4), drug abstinence with attenuated withdrawal (2), drug seeking with continued withdrawal (1) and fatality (1) (K R Alper et al., 1999). However this fatality was not conclusively linked to ibogaine administrations and might have cause in heroin use subsequent to treatment (K R Alper et al., 1999). In a study conducted in 150 patients with substance dependence, a subset of these patients (32) was treated with a fixed dose of 800mg/kg ibogaine for the treatment of opioid dependence (K R Alper, 2001; Popik & Skolnick, 1998). Similar to the independent treatments, signs and symptoms of withdrawal were seen to be attenuated 24 hours after ibogaine treatments and 36 hours after last use of opioids (K R Alper, 2001; Popik & Skolnick, 1998). Furthermore it was noted that resolution of symptoms remained on week after the treatments with diminished depression and craving still reported one month after administration of ibogaine (K R Alper, 2001; Popik & Skolnick, 1998). Ibogaines effectiveness was not limited to heroin use, and was found to be effective in treating a range of opioids including methadone (K R Alper, 2001; Popik & Skolnick, 1998).

Long Term Outcomes

There exists very little data with regards to the long term outcomes of ibogaine assisted therapy for the treatment of opioid addiction as currently the long-term effectiveness studies are still ongoing. There does however exist a large body of anecdotal observations, in 1995 the first

formal attempt to systematically sort through these observations was made by H Lotsof and presented at the Ibogaine Review Meeting (K R Alper et al., 2001; K R Alper, 2001). The report consisted of data from 41 individuals, gathered as retrospective self reports, which had been treated with ibogaine for substance dependence between 1962 and 1993. Of the 41 patients 9 had to be treated twice and 1 individual underwent 3 treatments, make the total treatments undergone 52 (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; Popik & Skolnick, 1998; Sheppard, 1994). Based on these self-reports it was seen that 29% of the treatments resulted in cessation of drug use for up to 2 months, another 29% was reported to be effective for 2 – 6 months, 13% for between 6 months – 1 year, 19% had a reported effectiveness for more than a year, and for 10% of the treatments data could not be obtained (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; Popik & Skolnick, 1998; Sheppard, 1994). It should be noted that 38 out of the 41 individuals reported 'some' opioid use at some point after the treatment, and that 10 of that 38 claimed to have used other drugs (alcohol and/or cocaine) post treatment (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; Popik & Skolnick, 1998; Sheppard, 1994)..

Risk and toxicology

In terms of neurotoxic effect, there exists a growing body of evidence to suggest that ibogaine maybe have a degenerative effect on cerebellar purkinje cells in rats (K R Alper, 2001). However, this appears to be at levels higher than those that affects opioid withdrawal and self-administration as *Molinari et al* (1996) found no evidence of purkinje cell degeneration at 40mg/kg IP administration of a single dose. When evaluating biomarkers of cerebellar toxicity, *Xu et al.* (2000) found that the administration of Single dose 25 mg/kg IP had no observable adverse effects. A similar result was found by *Helsley et al* (1997), who observed no evidence of neurotoxicity after treating rats with 10mg/kg every day for 60 days.

Studies conducted by O'Callaghan, Rogers, Rodman, & Page (1996) examined the expression of glial fibrillary acidic protein (GFAP) in rats. GFAP expression is a general response of astrocytes to CNS damage; elevations in expression are thought to be relatively sensitive to neuronal damage but are not necessarily specific to it. In these studies rats were subject to either an acute regime of ibogaine administration intraperitoneal at doses of 50, 100, 150 mg/kg daily for 3 consecutive days. Or they were placed on chronic ibogaine administration of oral doses of 25, 75, 150 mg/kg for 14 consecutive day(O'Callaghan et al., 1996). The results showed that following the acute regime, elevations in GFAP were found in both males and females and was not restricted to the cerebellum. At 50mg/kg increased expression levels in the hippocampus and cerebellum were found, while at the 100mg/kg dose cortex, hippocampus, olfactory bulb, brainstem and striatum all showed

elevation of GFAP expression (O'Callaghan et al., 1996). However, it is worth noting that the effects of the acute regime ere no longer present after 14 days in males and was restricted to the cerebellum in females dosed with 100mg/kg ibogaine (O'Callaghan et al., 1996). 17 days post chronic regime no elevations in GFAP were found in males, at any dose or region, but were found in females at 25mg/kg (restricted to hippocampus) and at 150mg/kg (present in hippocampus, olfactory bulb, striatum, and brainstem) (O'Callaghan et al., 1996).

Through use of silver degeneration selective strain as a histological marker, Binienda, Scallet, Schmued, & Ali (2001) treated both mice and rats with a single administration of ibogaine at a dose of 100mg/kg IP and found that only rats showed evidence of degeneration and that it appeared to be confined to the cerebellum. Based on these observations it appears that sensitivity to ibogaine neurotoxicity varies significantly between species, additionally monkeys treated with repeated doses of ibogaine between 5 and 25mg/kg showed no signs of neurotoxicity following 5 consecutive days of treatment (K R Alper, 2001). 1000mg/kg subcutaneous administration produced the same results (K R Alper, 2001)..

It appears that the cerebellum is the most vulnerable to the neurotoxic effects of ibogaine; it is hypothesised that this could be related to excitatory effects, mediated though glutamatergic excitatory inputs of sigma2 receptors in olivocerebellar projections to purkinje cells (K R Alper, 2001; Helsley, Dlugos, et al., 1997; O'Hearn & Molliver, 1993). The synaptic redundancy of purkinje cells is thought to increase their susceptibility to excitotoxicity while sigma2 agonists have been seen to induce apoptosis (K R Alper, 2001; Helsley, Dlugos, et al., 1997; O'Hearn & Molliver, 1993). Indeed, In vitro studies have shown that ibogaine activation of sigma2 receptors leads to the initiation of apoptosis (K R Alper, 2001; Helsley, Dlugos, et al., 1997; O'Hearn & Molliver, 1993).

Thus the neurotoxic effects of ibogaine may result from a combination of direct neurotoxicity through the initiation of apoptosis as well as excitotoxicity due to enhanced glutamatergic activity(K R Alper, 2001; Helsley, Dlugos, et al., 1997; O'Hearn & Molliver, 1993). However it appears that this neurotoxic effect can be separated from actions on drug withdrawal and dependence as sigma2 receptors do not appear to be involved in suppression of drug administration or signs of withdrawal (Szumlinski et al., 2000a).

Ibogaine has been seen to produce tremors in both humans and animals(Blackburn & Szumlinski, 1997; Glick, Rossman, et al., 1992; Glick et al., 1994; Zubaran, Shoaib, Stolerman, Pablo, & Mash, 1999). In rodent models and IP dose of 10mg/kg produces tremors in rats while a subcutaneous dose of 12mg/kg elicits the same in mice (Blackburn & Szumlinski, 1997; Glick,

Rossman, et al., 1992). Much like the effects on cerebellar neurotoxicity, it has been observed that the mechanisms behind tremor production appear to be independent from those responsible for ibogaines effects on drug self administration (Blackburn & Szumlinski, 1997; Glick, Rossman, et al., 1992; Glick et al., 1994; Zubaran et al., 1999). Through examination of a variety of iboga alkaloids it has been observed that the methoxy group at position 10 or 11 appears to enhance the tendency to produce tremors while the addition of a carbomethoxy group at position 16 diminished tremor production (K R Alper, 2001; Glick, Rossman, et al., 1992; Glick et al., 1994). Noribogaine and the ibogaine congener 18-MC were seen to not produce tremors, both of which are missing the methoxy group at position 10 and 18-MC is in possession of an extra carbomethoxy group at position 16 (K R Alper, 2001; Glick, Rossman, et al., 1992; Glick et al., 1994).. Observations into lasting effects of ibogaine tremors in humans found no evidence of abnormalities on clinical neurological exams 7 days after the administration of varying doses of 10-30mg/kg (K R Alper, 2001; Glick, Rossman, et al., 1992; Glick et al., 1994). Furthermore, FDA safety trials showed that 6 hours after receiving a 1-2 mg/kg dose of ibogaine body sway was not effected significantly (K R Alper, 2001; Glick, Rossman, et al., 1992; Glick et al., 1994).

Studies done into ibogaines potential cardiac risks have produced some conflicting data. Studies done in rodents by *Glick et al* (2001) found no changes in heart rat or blood pressure after the administration of 40mg/kg ibogaine, they did report that higher doses (100 and 200mg/kg) caused a decrease in heart rate with no effect on blood pressure by (Isabelle M. Maisonneuve & Glick, 2003; Szumlinski, Haskew, Balogun, Maisonneuve, & Glick, 2001). In the same study 18-MC was found to have no effect on heart rate or blood pressure at any of these doses by (Isabelle M. Maisonneuve & Glick, 2003; Szumlinski et al., 2001). *Z. Binienda et al.* (1998) in their studied observed a significant decline in heart rate at 50mg/kg in rats. Cardio-monitoring studies conducted in 39 cocaine and/or heroin dependent human subjects administering fixed doses of 500, 600, 800, 1000mg/kg ibogaine reported a significant drop in resting pulse rate in 6 subjects and only 1 with a significant drop in blood pressure (K R Alper, 2001). Furthermore, no EKG abnormalities were found and the authors concluded that a single dose appeared to be well tolerated (K R Alper, 2001). Additional studies show that ibogaine potentially blocks cardiac ion channels, even at therapeutic doses, and there is potential for proarrhythmic effect, however the same study found that ibogaine also shows antiarrhythmic properties (Koenig et al., 2012). In their article on 3 case reports involving ibogaine related fatalities *Paling, Andrews, Valk, & Blom (2009)* suggest that there exists a causal relationship between ibogaine and the development of serious respiratory and cardiac problems based on the 3 case reports presented. The authors show that a lengthening of QT is observed and offer explicit negative advice against the use of ibogaine (Paling et al., 2009)

With regards to abuse potential, there is no evidence that points to ibogaine becoming a possible liability (K R Alper, 2001; Popik & Skolnick, 1998). Animal studies show that it is neither adverse nor rewarding in the conditioned place preference paradigm and that regardless of acute or chronic administrations animals do not exhibit signs of withdrawal upon cessation (K R Alper, 2001; Popik & Skolnick, 1998). Furthermore none of the consultants to NIDA, at the Ibogaine Review Meeting, identified the potential for abuse of ibogaine or that there was any safety concern (K R Alper, 2001; Popik & Skolnick, 1998).

Between 1989 and 2000 around 19 ibogaine related fatalities have been recorded worldwide (K R Alper, 2001; Kenneth R Alper, Stajić, & Gill, 2012; Maas & Strubelt, 2006). However currently there is no evidence, post-mortem or clinical, that suggest a characteristic syndrome of neurotoxicity (K R Alper, 2001; Kenneth R Alper et al., 2012; Maas & Strubelt, 2006). In fact only 14 of the 19 reported deaths had adequate post-mortem data, of which 12 showed highly developed, and pre-existing, medical comorbidities (K R Alper, 2001; Kenneth R Alper et al., 2012; H. S. Lotsof & Alexander, 2001; Maas & Strubelt, 2006). First recorded death as a result of treatment with ibogaine came from France in 1989 where a 40 year old woman was treated with 8mg/kg ibogaine for use in assisted psychotherapy. After the autopsy it was found that there was a significant blockage of the main arteries leading to the heart and that she had a history or cardiac disease (K R Alper, 2001; Kenneth R Alper et al., 2012; H. S. Lotsof & Alexander, 2001; Maas & Strubelt, 2006). Another case was that of a young woman in her mid 20ies that died in the Netherlands. She was administered 29mg/kg ibogaine in a split does of 23mg/kg at first and 3 hours later 6mg/kg was given. 16 hours following the administration of ibogaine the girl died, although the autopsy could not determine the cause of death conclusively it should be noted that the possible synergic effect ibogaine has on enhancing opioid toxicity might have been at work here (K R Alper, 2001; Kenneth R Alper et al., 2012; H. S. Lotsof & Alexander, 2001).

Due to the risk profile of ibogaine, as well as to other policy-based reasons, no clinical trials have been conducted to date. However, ibogaine treatment continues to be conducted around the world at an increasing rate. While the risk profile presented here does show some points for concern with regards to ibogaines use, it is far from conclusive due to conflicting results found between studies and in some cases even within studies. Furthermore, the risk-benefit ratio of ibogaine use needs to be taken into account. Does the potential risk of ibogaine consumption outweigh the risks associated with a sustained addictive lifestyle or other treatments?

Ibogaine treatment

Protocol for use

Currently there are a wide variety of protocols in use from ibogaine treatment for opioid addiction. The reason for this variation comes about as a result of the informal, non medical, setting that most ibogaine therapy is practised in (H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). Despite this fact, the majority of these protocols are based on, and even closely adhere to, the protocol drafted by NIDA at the 1994 Ibogaine Review Meeting in (H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). In Appendix A of this review is included some aspects of this protocol (made available with the Freedom of Information Act and obtained from Manual for Ibogaine Therapy by H Lotsof and B Wachtel)(H. Lotsof & Wachtel, 2002; NIDA, 1995). There is however a point of disagreement from some researchers over the exclusion criteria, as they feel it does not allow for realist treatment of addicts (often comorbid with depression or other psychiatric disorders)(H. Lotsof & Wachtel, 2002).

By and large, most protocols call for a screening process that must take place prior to administration of ibogaine. The main goal is to determine medical history and test for any cardiovascular abnormalities with an EKG, as the cardio-risks associated with ibogaine are not fully understood (Harrison et al., 2009; H. Lotsof & Wachtel, 2002; NIDA, 1995). Furthermore, it is of the utmost importance that patients undergo a short detoxification process before treatment as it has been observed that ibogaine has a synergistic effect with some drugs of abuse, such as heroin and cocaine, increasing toxicological risks (Harrison et al., 2009; H. Lotsof & Wachtel, 2002; NIDA, 1995). It is therefore recommended that drug use is abstained from for at least a 24hour period preceding treatment.

Another recommended point across protocols is that patients need to be constantly observed and cared for during the initial stages after administration (Harrison et al., 2009; H. Lotsof & Wachtel, 2002; NIDA, 1995). Heart rate and blood pressure should be taken at regular intervals to ensure safety, however this needs to be done in as non invasive way as possible and patients should feel comfortable enough to report any discomfort that they might experience (Harrison et al., 2009; H. Lotsof & Wachtel, 2002; NIDA, 1995). It is also not uncommon for patients to confuse the working of ibogaine with signs of withdrawal which could culminate in the patient requiring an explanation of the effects of ibogaine to calm them down (Harrison et al., 2009; H. Lotsof & Wachtel, 2002; NIDA, 1995). Ideally the patient would have been asked about any past experience with withdrawal and would get a clear explanation of proceedings so as not to become anxious.

In terms of post treatment therapy there is no single consensus on what is the most beneficial, however there is an agreement that post-treatment therapy is indeed needed (H. Lotsof & Wachtel, 2002). Patients are encouraged to seek out support systems to aid them in staying off opioids that is more tailored to their needs. Following treatment with ibogaine, patients tend to be more open to change and therefore should make use of this opportunity through psychoanalysis, psychotherapy both individual and group or even groups like narcotics anonymous(H. Lotsof & Wachtel, 2002).

Common agreed upon dosage for the treatment of opioid addiction range between 15 and 20mg/kg ibogaine (Harrison et al., 2009; H. Lotsof & Wachtel, 2002; NIDA, 1995). There is exists some evidence that lower doses may be effective however this is currently a disputed topic. In some studies dosage increases are used throughout treatment, but there is some dispute on the necessity of this (Harrison et al., 2009; H. Lotsof & Wachtel, 2002; NIDA, 1995).

Subjective Effects

Common elements are often reported amongst those who have taken ibogaine either recreationally or as a treatment. Vomiting and nausea are frequently reported to occur suddenly within the first several hours post administration, and as such, patients tend to want to lie still in a darkroom (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). At the end of a session it is not unheard of for patients to complain of muscle soreness that could result from reduced movement, stretching or movement will help alleviate this relatively quickly (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002).

As for the psychological effects of ibogaine this can be divided into three stages. The first is the acute stage. This begins 1-3 hours after administration and lasts from 4 to 8 hours (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). A commonly reported sensation is that of having a panoramic readout of long term memory(K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). A large role for the visual modality is expected with visions and waking dreams usually of archetypical experiences, such as meeting a transcendent being/s. Descriptions appear to be more consistent with dreams than with hallucinations, with the feeling of being placed in a different reality or experience rather than the invasion of audio and visual hallucinations (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). Visual experiences are more strongly associated with eye closure or with the suppression of opening them. Furthermore not all subjects experienced visual phenomena; this is thought to be in relation to the dose and bioavailability as well as general variation (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002).

The second phase is the evaluative phase, which occurring around 4-8 hours after hours after onset and has a duration of 8-20 hours (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). This phase is hallmarked with the volume of material recalled slowing and an overall neutral and reflected tone often reported. Attention appears to be focused on inner subjective experience (as with the acute phase) and is directed at evaluating the experiences had during the acute phase (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). Patients are easily distracted during these two phases and often get annoyed by ambient stimuli as it breaks focus on the inner experience (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002).

The third and final phase is the residual stimulation phase. Its onset takes place 12-24H after administration and lasts 24-74 hours (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). A return to normal allocation of attention to external environment as psychoactive experience lessens (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002). Additionally mild arousal/vigilance, to varying degrees, and a reduced need for sleep are often reported to last several days-weeks post treatment (K R Alper, 2001; H. S. Lotsof & Alexander, 2001; H. Lotsof & Wachtel, 2002).

Discussion

In summary, because of their effectiveness in pain relief, opioids are still the most commonly prescribed analgesics to date. However there exists a large potential for abuse of both the legal prescribed opioids as well as those such as heroin (Mash et al., 2001; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Walwyn et al., 2010). Indeed recent years have seen a sharp increase in the abuse if prescription opioids, particularly in teenagers and highschoolers (In the US)(Walwyn et al., 2010).

Furthermore opioid addiction is not an easy habit to break, with a high potential to relapse. The average rate of relapse for heroin, after the first year, is 75-85% and after 15 years is still as high as 25% (Mash et al., 2001; Tahsili-Fahadan & Aston-Jones, 2010; Trigo et al., 2010; Walwyn et al., 2010). The majority of therapies in place for the treatment of opioid addiction rely on pharmacological blockade of symptoms of withdrawal through an opioid replacement (Kreek, 1997; Walwyn et al., 2010). Often this replacement is an opioid itself, such as methadone which the most used treatment for heroin/opioid dependence (Kreek, 1997; Walwyn et al., 2010). However being an opioid itself, methadone is seen to cause dependence and mood alterations, it can even be accompanied by withdrawal syndrome is treatment were to be stopped (Kreek, 1997; Walwyn et al.,

2010). In the Netherlands, Germany and Switzerland, heroin itself is used in replacement therapy for treatment resistant addicts (Blanken et al., 2010). Twice a day addicts are presented with pharmaceutical grade heroin of a fixed dose and are supervised by medical professionals during administration (Blanken et al., 2010). Furthermore they are supplied with a single dose of methadone for attenuation of withdrawal during the night (Blanken et al., 2010). While seen to be an effected strategy for harm reduction (Blanken et al., 2010), patients are still bound by their addiction and are highly dependent on the existence of these centres which are still a long way away from being widely approved in the majority of countries.

Since the sixties, ibogaines popularity has been on the rise outside of the professional medical field (K R Alper et al., 2001; Kenneth R Alper et al., 2008). Due to the large demand of ibogaine treatment of opioid dependence informal treatment centres have sprung up all over the world (K R Alper et al., 2001; Kenneth R Alper et al., 2008; Donnelly, 2011). While there is evidence from animals models, and anecdotal evidence from humans treated with ibogaine to its effectiveness there is still a lot that is unknown about its mechanism of action as an anti-addictive agent (K R Alper, 2001; Popik & Skolnick, 1998). Despite its popularity outside of the medical field, research into the workings of ibogaine have been impeded over the years due to social and political stigmas associated with the use of psychoactive substances as pharmacotherapy as well as its risk profile (K R Alper et al., 2001; Kenneth R Alper et al., 2008).

But it seems the tides are changing. Over the last decade a new interests has been taken in psychedelics as a form of therapy. Thanks to the internet increased information dissemination amongst the wider public and new media coverage have shown that there is less of a social stigma to researching these compounds than there was 20 years.

As the ibogaine subculture and number of informal treatment centres continue to grow, it is imperative that research into the mechanisms of ibogaines action continues.

Further Research

While ibogaines effectiveness as an acute attenuator of opioid withdrawal syndrome has received support from a wide variety of animal studies and patient observations, there exists very little data is available on the long-term outcomes of ibogaine treatment. Currently the organisation MAPS (Multidisciplinary Association for Psychedelic Studies) is conducting two long-term outcome studies in Mexico and New Zealand (Harrison et al., 2009).

Another focus of further research is the isolation of ibogaines beneficial properties while minimizing unwanted effects such as neurotoxicity, cardiovascular complications, or other behavioural effects. To this end research is being conducted into the use of a synthetic iboga alkaloid, 18-Methoxycoronaridine.

18-MC: A Novel Congener

Although ibogaine's reported efficacy on attenuating opioid withdrawal and dependence is very promising, the existence of a number of acute nonspecific side effects, such as cardiovascular risks, tremors, hallucinations, and cerebellar neurotoxicity pose a potential problem for its full acceptance as a viable treatment (Arias et al., 2011; Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a). The synthetic iboga alkaloid congener 18-Methoxycoronaridine (18-MC, structure shown earlier in this report) is a novel compound that mimics ibogaine's effects on drug administration and withdrawal without the manifestation of ibogaines more adverse effects (Bowen et al., 1995; Glick, Kuehne, Maisonneuve, Bandarage, & Molinari, 1996; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a).

Several animal models for addiction have shown that 18-MC attenuates the reinforcing properties of morphine, cocaine and alcohol in a conditioned place preference paradigm (Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a). 18-MC has also been shown to decrease morphine and cocaine self administrations in rats without effecting bar pressing for natural rewards such as food or water (Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a). Prolonged abstinence of cocaine and morphine intake have been observed in rodents treated with 40mg/kg 18-MC lasting for days or even weeks post treatment (Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a).

A study investigating the interactions between morphine and 18-MC found 40mg/kg IP dose of the iboga congener found that dopamine responses in the nucleus accumbens to acute morphine exposure were attenuated 19 hours post treatment (Glick et al., 2001; Maisonneuve & Glick, 2003; Maisonneuve, & Glick, 2000). The same study also reported a shift in the dose-response curve, to the left, in sensitized rats as compared to non-sensitized however, following pre-treatment with 18-MC sensitized and non-sensitized rats responded similarly (Glick et al., 2001; Maisonneuve & Glick, 2003; Maisonneuve, & Glick, 2000). From this result it is thought that 18-MC could block sensitization to morphine. An additional study showed that low-dose combination of 18-MC and

other similar acting drugs can attenuate self administration of morphine, methamphetamines, and nicotine in rats, at dose levels that were sub-active if administered alone (Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a). Due to its role in the NAcc, it is thought that this synthetic analogue of ibogaine's potential anti-addictive efficacy may be a result of its ability to restore normal functioning to a hypersensitive mesolimbic dopamine system (Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a). Unlike ibogaine, 18-MC does not produce tremorigenc effects nor has there been any evidence of cerebellar toxicity, even aft high doses (100mg/kg)(K R Alper, 2001). Despite the fact that it appears to be safer than ibogaine in animals models, there are yet to be human trials conducted with this ibogaine like agent (Bowen et al., 1995; Glick et al., 2001; Isabelle M. Maisonneuve & Glick, 2003; Pace et al., 2004; Szumlinski et al., 2000a).

Conclusion

Due to the wide body of support available from both medical and not medical sectors the effectiveness of ibogaine, at least in terms of acute opioid withdrawal can no longer be ignored. With a pharmacological profile that includes interactions with a large host of neurotransmitter systems implicated in addiction, the study of ibogaines action could possible lead to new pharmacological strategies in combating varies drug addictions. While not fully understood, it is thought that ibogaines activity involves a long-lived metabolite and that its interactions with multiple systems may have effect on second messenger systems to produce effects long after duration of receptor occupancy.

Because of the persistent and ever increasing demand for ibogaine therapy, researchers need to be able to work more closely with practitioners from the informal sector to make use of the vast amounts of data that have been collected over years of treatment.

It is this author's opinion that ibogaine provides a plethora of exciting research avenues to be explored in the combat of opioid addiction, and that while there are those that claim our current knowledge of ibogaine does not yet warrant its use in a therapeutic setting the fact of the matter is that it is already being widely used. Thus, with the view of public safety in mind, there needs to be an increase in research into ibogaines mechanisms of action and more close collaboration with centres currently providing ibogaine therapy. Clear, clinical guidelines for ibogaine-treatment for use by lay practitioners that is aimed at harm-reduction should be drafted. Furthermore, the use of the ibogaine congener, 18-MC, appears to circumvent some of the issues raised about ibogaines workings thus potentially making it a more viable treatment of opioid addiction in the near future.

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Appendix A – MDD-NIDA Draft Protocol (1995)

Exclusion Criteria

1. Patients with a history of active neurological or psychiatric disorders (cerebellar dysfunction, psychosis, bipolar illness, major depression) that require treatment or that would make study compliance difficult.

2. Patients who have a Beck Depression Inventory score greater than or equal to twenty-four.

3. Patients requiring concomitant medications that may interfere with a clinical trial or evaluation (e.g., anti-epileptic drugs, sedatives, hypnotics, antidepressants, neuroleptics, methadone, meperidine, etc.)

4. Patients with a history of sensitivity or adverse reactions to the treatment medication.

5. Patients with a history of significant heart disease or a history of myocardial infarction.

6. Patients with blood pressure above 170 mm Hg systolic/105 mm Hg diastolic or below 80 mm Hg systolic/60 mm Hg diastolic or a pulse greater than 120 beats per minute or less than 50 beats per minute.

7. Patients who have a history of hypertension uncontrolled by conventional medical therapy.

8. Patients who have received any investigational drug within 6 months prior to entering the study

9. Patients who have received any drug known to have a well-defined potential for toxicity to a major organ system within the month prior to entering the study.

10. Patients who have clinically significant laboratory values outside the limits thus specified by the investigators laboratories.

11. Patients who have any disease of the gastrointestinal system liver or kidneys, or abnormal condition which compromises a function of these systems and could result in a possibility of altered metabolism or excretion of the study medication will be excluded. As it is not possible to enumerate the many conditions that might impair absorption, metabolism or excretion, the investigator should be guided by evidence such as:

A. History of major gastrointestinal tract surgery (e.g., gastrectomy, gastrostomy, bowel resections., etc.) or a history or diagnosis of an active peptic ulcer or chronic disease of the gastrointestinal tract, (e.g. ulcerative colitis, regional enteritis, Crohn's disease* or gastrointestinal bleeding).

B. Indication of impaired liver function.

C. Indication of impaired renal function.

12. Patients who test positive for HIV virus.

13. Patients with active tuberculosis.

Psychological Assessments

1. Interviews

A. Addiction Severity Index (ASI)
B. Diagnostic Interview Scale (DIS)

2. Questionnaires

A. Visual Analogue Scale cocaine craving (VAS)
B. Beck Depression Inventory (BDI)
C. Minnesota Multiphasic Personality Inventory-2 (MMPI-2)*

Neurological Assessments

1. Electroencephalography (EEG)

2. Neurological Assessment Battery

A. Coordination/tremor
   a. Finger-to-nose
   b. Finger-to-finger
   c. Heel-to-shin

B. Coordination/tremor, repeated rapid alteration tests

   a. Palm/back hand slap knee
   b. Prone/supine forearm

C. Coordination /ataxia

a. Heel-to-toe walking
b. Romberg test (feet together, eyes open/eyes closed)

D. Muscle tone/hypertonia

a. Resistance to stretch

E. Reflexes

a. Acoustical startle
b. Pupilary light reflex
c. Vestibulo-occular reflex

Opioid Withdrawal Assessments

1. Objective Opiate Withdrawal Scale (OOWS)

2. Subjective Opiate Withdrawal Scale (SOWS)

General Physical Condition

1. History and Physical

2. Electrocardiogram (EKG)

3. Laboratory

Blood Work

a. CBC DIFF
b. AST ALT
c. Hepatitis screen
d. Thyroid panel
e. SMA-18 profile
f. CHEM-25

Urine

a. Routine urine analysis
b. Toxicology screen (positive for target drugs)

I. Cocaine
II. Morphine (heroin)
III. Ibogaine

4. Dermal Tuberculin (if positive or previously immunized, then chest x-ray)

5. Breathalyzer

6. Vital signs with weight

7. HIV test and counseling

Support staff and design of environment

Generally, the session room should be pleasant and the social interactions with staff members supportive. Pastel-colored walls, comfortable hospital bed, soothing murals, paintings or pictures, a comfortable chair for the staff member or therapist to constantly observe the subject during the ibogaine experience. Dim lighting and quite setting. Dialogue should be initiated by the patient. Reduce the need for walking by having a patient lavatory nearby.

Within this context, allow the patient to sleep and rest peacefully ad lib. Otherwise, when the patient is in the talkative phase, the staff member should attentively and unobtrusively attend to but not initiate conversation.

Assessments [during treatment]

Cardiovascular - Apply ambulatory pulse and blood pressure apparatus that is programmed to obtain and record digital quantities q 30 min for a 24 h period. Apply device just before dosing.

Neurological - Observe for the onset (that is time from the administration of ibogaine) for drug-related changes in neurological functioning (e.g., the onset of changes in speech patterns, nausea and vomiting)

Psychological - Observe and record what patients spontaneously say, Record the onset and duration of the somnolent phase.