# Ibogaine: A Novel Anti-Addictive Compound
# A Comprehensive Literature Review

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**Introduction and History:**

Ibogaine is a naturally occurring indole alkaloid, found in a variety of African shrubs of the Tabernathe genus (Obach, Pablo, and Mash, 1998). The root of the Tabernathe iboga plant (also known as eboga) is the most frequently cited source of ibogaine, and this plant contains 11 other known psychoactive constituents (Popik, and Skolnick, 1999). Chemically, ibogaine is classified as a tryptamine, being a rigid analogue of melatonin, and is structurally similar to harmaline, another natural alkaloid and psychedelic (Xu et al, 2000). Ibogaine was first extracted from the Tabernathe iboga root in 1901 by Dybowsky and Landrin (Goutarel, Gollnhofer, and Sillans, 1993). It can also be synthesised from nicotinamide by way of a 13 or 14 step process, although extraction from the iboga root is a simpler method for obtaining the compound (Shulgin and Shulgin, 1977).

At low doses, ibogaine exerts primarily a stimulant effect, increasing alertness and reducing fatigue, hunger, and thirst (Rezavani, Overstreet, and Lee, 1995), though not in the manner of stereotypical CNS stimulants, such as amphetamine or cocaine (Da Costa, Sulklaper, and Naquet, 1908). At higher doses (typically above 3 mg/kg), ibogaine's primary psychological effects include the retrieval of repressed memories, closed eye visual imagery (CEVs), and a state characterised as "waking dreaming" (Popik and Glick, 1996). From anecdotal reports, it appears that memories are relived in a sense, primarily in a visual modality, but without the emotional weight they carried when the events occurred, allowing the individual to view them with greater insight (Naranjo, 1974; Alper et al, 1999). Subjectively, these effects have been described as fantasies, "as a movie run at high speed, or a slide show" (Lotsof, 1994). These fantasies are easy to manipulate by both the subjects and the clinician, and therefore this phenomenon has been sighted as a potentially valuable tool in psychotherapy (Naranjo, 1967, 1974). The imagery experienced under the effects of ibogaine is often largely Jungian in content, involving archetypes seemingly common across cultures; frequently animals, birth and rebirth sequences, and/or the subject with or without individuals (Popik and Glick, 1996).

While ibogaine does share features common with many compounds labelled as hallucinogenic, it does not cause thought disturbances, alterations in reality testing, nor is it psychomimetic (Luciano, 1998; Goutarel, Gollnhofer, and Sillans 1993; Popik and Glick, 1996). Rather than classify ibogaine as an hallucinogen, it is suggested that the compound be termed oneirogenic, due to the "waking dream" state it induces, from the Greek, meaning "dream creator" (Naranjo, 1974; Goutarel, Gollnhofer, and Sillans, 1993). Goutarel et al define an oneirogen as a compound "which disconnects the 'I' from Exoreality to reconnect it within Endoreality." Other oneirogenic compounds, as cited by Goutarel et al, include ketamine (an anaesthetic) and salvinorin (the primary psychoactive compound in Salvia

divinorum, an herb used in healing and religious ceremonies of indigenous Mexican peoples).

In addition to ibogaine's psychological effects, it elicits a number of physical effects, which include tremor, light sensitivity, nausea and vomiting, ataxia, and dystonia (Lotsof, 1994; Glick, Maisonneuve, and Szumlinski, 2000). All of these effects, psychological and physical, manifest in a dose-dependent fashion (Schechter and Gordon, 1993). In light of these properties, and that the sum effects of ibogaine can last up to 24 – 36 hours, ibogaine is not considered to have a high potential for abuse (Popik and Glick, 1996). Indeed, those who have experienced ibogaine, typically characterise its effects as a "rough trip;" one that is not suitable for recreational use (Shulgin and Shulgin, 1977).

Accordingly, when ibogaine was introduced to the United States' black market in the 1960's, it showed little popularity, and subsequently has infrequently been seen sold illicitly (Goutarel, Gollnhofer, and Sillans, 1993). The U. S. Drug Enforcement Agency reports having encountered only a few illicit samples in their interdiction efforts (Cooper, 1988). According to Dharir (1971), ibogaine first appeared on the illegal drug market in 1967, and was reported in a handful of cases by the police of Suffolk County, NY and San Francisco, CA. Shortly thereafter, however, ibogaine suddenly disappeared from the black market, perhaps due to a lack of profit motive for drug dealers, resulting from ibogaine's putative anti-addictive effects (which will be discussed later in this paper) (Goutarel, Gollnhofer, and Sillans, 1993).

Various preparations of plants containing ibogaine have been used for centuries in traditional African medicine, as first reported by French and Belgian explorers in the 19$^{th}$ century (Popik and Skolnick, 1999). The iboga root may be eaten whole, or crushed and ground and mixed with other ingredients, sometimes including other psychoactive compounds (Fernandez, 1982). These preparations, in varying quantities, have been used as a stimulant to battle hunger, thirst, and fatigue during hunting, as an aphrodisiac, and as a catalyst for spiritual discovery involved in the initiation rites of the Bouti (Stafford, 1983). The Bouti (also Bwiti) is a religious society of the Gabon, Metsogo, and Kameroon tribes of western Africa, and initiation into this society, involving the use of ibogaine containing substances, is central to their cultures (Fernandez, 1982; Goutarel, Gollnhofer, and Sillans, 1993).

Literally, Bouti means "those of the chapel". The primary purpose of these initiation rites, as described by the initiates, is to travel through the land of the tribal ancestors, and emerge in the "pristine uterine condition" (Fernandez, 1982). This ritual is referred to by its participants as "cracking the skull" (Sheppard, 1994). The initiate, in the ibogaine-induced state, makes contact with the ancestral spirits, under the guidance of those already initiated. After the ceremony, the initiate is reborn as an adult in the tribe, having previous transgressions and illnesses removed in the initiation process (Fernandez, 1982).

Ibogaine was first introduced to Western medicine in the form of Lamberene, an extract of the Tabernathe manii plant (Popik and Skolnick, 1999). Advertised as a mental and physical stimulant, it contained about 8 mg of ibogaine and was "…indicated in cases of depression, asthenia, in convalescence, infectious disease, [and] greater than normal physical or mental efforts by healthy individuals" (Goutarel, Gollnhofer, and Sillans, 1993). The drug enjoyed some popularity among post World War II athletes, but was eventually removed from the market, when the sale of ibogaine-containing products was prohibited in 1966.

Dr. Claudio Naranjo, a Chilean psychiatrist, was the first to study ibogaine's potential psychotherapeutic effects. In the early 1960's, Naranjo conducted a series of case studies

(approximately 40 studies, with 30 patients) using doses of 4 – 5 mg/kg, in which he found that ibogaine had the ability to facilitate closure of unresolved emotional conflicts (Popik and Glick, 1996). This closure was mediated by ibogaine's aforementioned ability to enhance retrieval of repressed memories. Naranjo found that ibogaine allowed his patients to view their past experiences in an objective manner, which enabled them to confront personal issues that were previously unapproachable (Naranjo 1974).

Around the same time that Dr. Naranjo was conducting his case studies, ibogaine's anti-addictive effects were serendipitously discovered. In 1962, Howard Lotsof, addicted to heroin at the time, took a dose of ibogaine (estimated to be about 500 mg) that a chemist friend had given him, tantalised by the promise of a 32 hour trip (Goutarel, Gollnhofer, and Sillans, 1993, De Rienzo, Beal, et al, 1997). He woke up the next morning with the startling revelation that he no longer desired heroin; in fact he remained free of the drug for years to follow (Lotsof, 1990). Though Lotsof was not a doctor, nor a scientist, his personal experience with ibogaine led him to investigate the drug further.

Over the course of the next year, Lotsof led a series of non-clinical focus groups under the auspices of S & L Laboratories, which he set up "to procure drugs and administer them to interested persons" (Lotsof, Della Sera, and Kaplan, 1995, Alper, Beal, and Kaplan, 2001). At that time, psychedelics were not scheduled drugs, and were effectively available to anyone who started their own chemical "company", needing little more than an official looking letterhead (De Rienzo, Beal, et al, 1997). Between 1962 and 1963, Lotsof administered ibogaine to 20 individuals at a variety of doses, up to 19 mg/kg (Alper, Beal, and Kaplan, 2001). Of these 20 subjects, 7 were heroin dependent, and noted the alleviation of withdrawal symptoms and drug craving after ingesting ibogaine. Additionally, 5 of these 7 individuals were able to maintain abstinence from heroin for 6 months or longer.

Shortly thereafter in 1963, the Food and Drug Administration (FDA) noticed the large amount of psychedelics Lotsof was ordering, and tracked a shipment of 100 g of mescaline to the laboratory he had set up (De Rienzo, Beal, et al, 1997). Though psychedelics were not illegal at that time, unauthorised use of mescaline on humans was punishable by a six month sentence. The FDA's search of his premises discovered no mescaline, but did find 2 g of ibogaine, which the FDA agents forced Lotsof to sell to them. Subsequently, the FDA cut off his access to controlled substances, despite the fact that they found nothing with which they could charge him.

However, in 1966, LSD, mescaline, and psilocybin were categorised by the U.S. federal government as Schedule I narcotics; drugs with no medicinal value and a high potential for abuse. Shortly thereafter, Assistant U.S. Attorney Robert Morenthau had Lotsof arrested on drug conspiracy charges. When Lotsof spoke about ibogaine's anti-addictive effects in court, the judge had his testimony stricken from the record. Lotsof was found guilty on 4 misdemeanours, and sentenced to 14 months in prison. Upon release in 1968, Lotsof was "shattered". He travelled to Nepal, where, for the first time in five years, he ate opium, and became re-addicted. In 1969, he tried to locate some ibogaine with the hopes of breaking his addiction again, but discovered that it had been added to the list of Schedule I drugs, and was unable to find any.

Upon returning to New York, Lotsof entered a methadone maintenance program, which he considered a "prison without walls". Fortunately, he was able to remember what it was like to be drug-free, and endeavoured to slowly wean himself off the "orange handcuffs". In December of 1973, just as he was coming off of methadone, Lotsof met Dana Beal, the then new leader of the Yippie movement. Beal and Lotsof "hit it off from the start",

and over the next six years, collaborated on a variety of projects, including three films, a series of Rock Against Racism concerts, and further investigation of ibogaine.

In 1981, a Yippie subcommittee named Citizens Against Heroin began to fund Lotsof's ibogaine research. He used the bulk of this funding to execute an exhaustive literature search in the New York University library (where he had previously been a film student). By late 1983, Lotsof believed he had enough information to back his claims of ibogaine's anti-addictive effects, and initiated a series of patents for Endabuse (NIH 10567), an oral preparation of ibogaine hydrochloride in capsule form. These patents indicated Endabuse for the "rapid interruption" of opiate dependence disorders (U.S. Patent 4,99,096, 1985), cocaine dependence disorders (U.S. Patent 4,587,243, 1986), nicotine dependence disorders (U.S. Patent 5,026,697, 1991) and poly-substance abuse disorders (U.S. Patent 5,152,994 1992) (Lotsof, Della Sera, and Kaplan, 1995).

Lotsof first made contact with the conventional scientific community in 1986, when he contracted with a professor at McGill University in Montreal to study ibogaine's effects on alcohol dependence. However, the professor turned the project over to a graduate student and never published the results. (Fortunately, the contract for the experiment specified that Lotsof owned the data, and in 1988 he discovered that the results showed a significant reduction in alcohol intake by rats after administration of ibogaine.) Also in 1986, Lotsof founded a New York based organisation, NDA International, Inc., with the dual mission of furthering the humanitarian applications of ibogaine and marketing the proprietary preparation, Endabuse (Goutarel, Gollnhofer, and Sillans, 1993).

After that, Lotsof sent a sample of ibogaine to researchers in the Pharmacology Department at Erasmus University in Rotterdam, where the investigators published the first paper indicating the effectiveness of ibogaine in the reduction of opiate self-administration in an animal model University (Alper, Beal, and Kaplan, 2001). The team at Erasmus also developed a method of injecting it into the ventricles of rat brains. This reduced the amount of ibogaine needed to produce the effects of regular intravenous or intraperitoneal administration (De Rienzo, Beal, et al, 1997).

In 1989, Lotsof contracted with Dr. Stanley Glick, head of the Department of Pharmacology and Toxicology at Albany College of Medicine. This was perhaps the most pivotal of Lotsof's contacts with the scientific community. After examining ibogaine's long lasting effects on morphine self administration in rats, Dr. Glick became keenly interested in furthering ibogaine research. Although Lotsof had run out of funding at the time, having to break his contract with Glick, Glick continued with his own research, and over the years produced a significant body of work on ibogaine and related compounds (De Rienzo, Beal, et al, 1997).

Lotsof and colleagues developed a specific procedure (aptly named the Lotsof Procedure™) for the use of Endabuse, which involves comprehensive short and long term medical, psychological, and social care of the patient. Lotsof describes the procedure a single administration modality (SAM), and summarises the primary obligations of the treatment team as:

> "four-fold: 1) to earn the trust of the patient, 2) to maintain the comfort of the patient, 3) to assist the patient in interrupting their chemical dependency, and 4) to supply the psychosocial support network needed by the majority of patients to enable them to develop a sense of personal accomplishment and the ability to function as productive members of society" (Lotsof, 1994).

One of the differences between the Lotsof Procedure and conventional addiction treatment that it stressed most is the level and nature of the rapport between the clinicians and the patient. As Lotsof describes (1994), "… the sense of conflict seen in most treatment modalities between the doctor and patient over the immediate ceasing of drug use does not exist". Treatment is approached with a "pro-choice attitude" by the caregivers, where abstinence is not demanded (Frenken, 1998). Rather, the patient is allowed to continue using drugs until a certain time before the procedure, based on the amount of time needed for the given drug to clear the body. The position of the treatment team is "that ibogaine will either work to interrupt chemical dependence or it will not" (Lotsof, 1994).

Another noteworthy difference of the Lotsof Procedure is the rapidity with which psychosocial support needs to be provided to the patient. "Ibogaine presents a symptom-free window of opportunity which the patient and therapist must take advantage of" (Lotsof, 1994). Because ibogaine (putatively) allows for an immediate interruption in the patient's addiction, the patient is generally found to me in a receptive psychological state earlier in the course of therapy. Therefore "they will require faster intervention to learn societal skills and to overcome and objectively understand various traumas experienced during their lives" (Lotsof, 1994). Additionally, Lotsof asserts that many of the accepted boundaries between the therapist and patient can hinder ibogaine treatment, that patients will require a closer and more intensive guidance.

As word of Lotsof's discovery gradually spread across the world, an unofficial global network of ibogaine therapy providers developed (Alper et al, 1999). This network was largely supported by the efforts of the New York based International Coalition for Addict Self-Help (ICASH), founded by Robert Sisko. ICASH is described "as having a self-help orientation in the tradition of European user self-help organizations, such as the Junkiebond in the Netherlands" (Alper, Beal, and Kaplan, 2001). This is not surprising, as ICASH often acted in partnership with the Dutch Addict Self Help group (DASH, now known as International Addict Self-Help, or INTASH). Together, these groups are estimated to have treated 40 to 45 individuals between 1989 and 1993. Though not officially sanctioned, the results of these treatments were reported in publications from Erasmus University. Self-help groups for the use of ibogaine also developed in the U. K., Slovenia, Italy, the Czech Republic, and France.

Professionals from various disciplines also became interested in examining ibogaine's potential. Deborah Mash, professor of neurology at the University of Miami, became interested in ibogaine research after hearing a presentation on it at a conference in 1991 (Alper, Beal, and Kaplan, 2001). In 1992, NDA International and the University of Miami collaborated to organise a clinical trial of ibogaine. The following year, Mash received approval for an Investigational New Drug Application from the FDA. The study was not completed, however, due to lack of funds, and NDA International and the University of Miami commenced litigation of intellectual property rights. Since 1996, Mash has operated an ibogaine treatment centre on the Caribbean island of St. Kitts.

Therapist Eric Taub also relocated from Florida to the Caribbean in order to establish an ibogaine therapy program. Since 1992, Taub has treated approximately 310 patients, 130 of which sought treatment for chemical dependency (Alper, Beal, and Kaplan, 2001). Through ibogaine therapy, Taub aides the patient in changing patterns of "reactive" or subconsciously determined behaviour, including, but not limited to substance addiction. Ibogaine's role in this psychotherapy is to facilitate a reduction of "pathologically acquired or learned" associations of cues or internal representations with corresponding motivational

states and behaviour. In accord with Lotsof's methods, Taub stresses the rapidity and intensity with which support must be provided following the administration of ibogaine for successful treatment.

Dr. Jan Bastiaans was the president of the Psychoanalytic Institute in Amsterdam from 1954 to 1961, professor of psychiatry at the State University of Leiden from 1963 to 1985, and a major figure in the history of the psychotherapeutic use of psychedelics (Grof, 2001). Bastiaans work with psychedelics was sparked by his interest in the use of pharmacological methods in the treatment of war related trauma in the wake of World War II. In particular, his work focused on the treatment of concentration camp survivors, often using LSD or psilocybin to facilitate therapy (Snelders, 1998). Over time, Bastiaans began to develop the methods he used in therapy with war survivors to treat survivors of other traumas. In 1992, Bastiaans collaborated with NDA international, adapting his methods to treat those with substance addictions (Alper, Beal, and Kaplan, 2001). However in 1993, one of the few known ibogaine related fatalities occurred under his supervision. Although the official Dutch inquiry found no evidence to suggest wrongdoing on the part of Bastiaans, he was forced to give up his practice by the Medische Tuchtraad, the Dutch medical supervisory board. In his last years, Bastiaans became bitter over the lack of recognition for his contributions to psychotherapy and died in 1997.

**Pharmacology:**

The principle method of ibogaine metabolism is O-demethylation by the liver, which yields O-desmethylibogaine (also known as 12-hydroxyibogaimine or, most commonly, noribogaine) and perhaps other, as of yet undetected, metabolites (Popik and Skolnik, 1999; Mash et al, 2000). Obach et al (1998) found that, of ibogaine consumed, 75 – 80 % was accounted for as noribogaine. Hough et al (1996) reported that ibogaine, when administered intraperitoneally in rats, is subject to a significant "first pass" effect; that is its pharmacological actions begin before it is metabolised. They also found that ibogaine has a high propensity to be deposited in adipose tissue, showing high levels in fat for at least 12 hours after administration. It is hypothesised that this quality may enable a single dose of ibogaine to provide a long acting "depot-like time course of action" (Popik and Glick, 1996).

Additionally, noribogaine has a longer half-life than ibogaine, and is also psychoactive; therefore it is possible that this metabolite may play a role in ibogaine's long-term effects (Mash et al, 2000). Pearl et al. (1997) detected presence of noribogaine in rodent brains up to 19 hours after an intraperitoneal administration of 40 mg/kg of ibogaine, while the half-life of ibogaine has been established to be 60 minutes (Dhahir, 1971; Zetler, Singbarth, and Schlosser, 1972). Oral administration of ibogaine in rabbits (10 mg/kg) yielded peak urine concentrations at a maximum of 4 – 5 hours, rapidly decreasing thereafter, until complete absence at 6 hours (Dhahir, 1971; Cartoni and Giarusso, 1972). In addition to urine, both ibogaine and noribogaine are detectable in many other bodily materials, including blood, liver, and brain (Cartoni and Giarusso, 1972; Bertol, Mari, and Froldi, 1976).

The O-demethylation of ibogaine in the liver is catalysed by the P4502d6 cytochrome, which has important clinical implications (Obach, Pablo, and Mash, 1998). Approximately 5 – 10 % of Caucasians lack the gene needed to produce this enzyme, and are therefore more prone to adverse reactions from drugs metabolised by it (Gonzalez and Meyer, 1991). In addition, this cytochrome is involved in the metabolism of a number of pharmacological compounds, including neuroleptics, beta-blockers, tricyclic antidepressants, and opioids, raising possible issues of adverse interactions with ibogaine (Eichelbaum and Gross, 1990;

Fromm, Kroemer, and Eichelbaum, 1997). Furthermore, individuals lacking this gene are less likely to benefit from the therapeutic effects of drugs metabolised by P4502d6 (Obach, Pablo, and Mash, 1998).

Like many tryptamines (e.g. serotonin, melatonin, d-lysergic acid diethylamide or LSD, psilocybin, N,N-dimethyltryptamine or DMT), the pharmacodynamics of ibogaine are particularly complex, involving multiple sites of action. Ibogaine affects, both directly and indirectly, dopaminergic, glutamatergic, serotonergic, opioid, nicotinic, sigma, gamma-aminobutrylic acidergic (GABA), nicotinic, cholingeric, and muscarinic pathways, as well as calcium regulation and voltage-dependent sodium channels (Popik and Glick, 1996; Glick and Maisonneuve, 1998; Alper et al, 1999; Popik and Skolnik, 1999). It is therefore thought that ibogaine's effects are a product of a combination of its interactions with these systems. However, there have been a number of discrepancies reported with regard to the specific manners in which ibogaine exerts its pharmacological actions (Popik and Skolnick, 1999). Additionally, noribogaine affects many of the same neural components as ibogaine, which further complicates the study of its pharmacological profile (Mash et al, 2000).

A great deal of attention has been paid to ibogaine's effects on the dopaminergic system, as dopamine is theorised to play a primary role in the sensitisation, reinforcing, and motivational properties of drugs of abuse (Fibiger and Phillips, 1986; Berrige and Robinson, 1998). Robinson and Berrige (1993) proposed that the incentive salience of drug-taking behaviours is related to neurotransmission in mesotelencephalic dopamine pathways, in which the repeated administration of addictive drugs sensitises the incentive salience of drug related cues. Compared to drug-naïve individuals, drug addicts have increased sensitivity to both the positive (Grant et al 1996; Ligouri, Hughes, Goldberg, and Callas, 1997) and negative (Ellinwood 1968; Angrist, 1983) reinforcing effects of drugs of abuse. These reinforcements are apparently mediated through enhanced brain activity in brain regions innervated by the mesolimbic dopamine system, including the frontal cortex (Alper et al, 1999) and the amygdala (Childress et al, 1999). According to this theory, if activity in sensitised dopamine pathways is decreased, it should alleviate addictive drug craving (Blackburn and Szumlinski, 1997).

Though ibogaine does not appear to affect binding at dopamine receptors or transporters (Broderick, Phelan, and Berger, 1992), it has been found to reduce extracellular levels of dopamine in the nucleus accumbens (Glick and Maisonneuve, 1998; Glick et al, 1999). Ibogaine effects on dopamine metabolites appear to be inconsistent. When measurements are taken shortly after administration (within 2 hours), or when high concentrations are used (greater than 100 μM), increases in dihydroxyphenyl-acetic acid (DOPAC) and homovanilic acid (HVA) are seen (Maisonneuve, Keller, and Glick, 1991; Maisonneuve, Rossman, Keller and Glick, 1992; Sershen, Hashim, Harsing, and Lajtha, 1992). However, when lower concentrations are used (e.g. 10 μM) or measurements are taken after a longer period of time (up to a week), dopamine brain concentrations remain unchanged, and metabolite concentrations decrease (Maisonneuve, Keller, and Glick, 1991; Shershen, Hashim, Harsing, and Lajtha, 1992).

Sershen et al (1994) reported that ibogaine's effects on dopaminergic function are largely regulated by its interactions with serotonin receptors. This was inferred from their finding that ibogaine inhibited the ability of the 5-$HT_{1b}$ agonist CGS-12066A to increase stimulation induced dopamine release in rat and mouse striatal slices. It has also been demonstrated that ibogaine increased the ability of the 5-$HT_3$ agonist phenylbiguanide to produce stimulation evoked dopamine release in mouse striatal slices (Sershen, Hashim, and

Lajtha, 1995). Taken together, these findings support the notion that ibogaine's effects on serotonin have a role in determining its dopaminergic effects, but the specific nature of this role has yet to be determined.

Ibogaine has been found to increase 5-HT concentrations in both the nucleus accumbens and striatum of the rat (Broderick, Phelan, Eng, and Wechsler, 1994; Ali et al, 1996). However, Benwell et al (1996) found that ibogaine reduced serotonin levels in the medial prefrontal cortex. Furthermore, studies of ibogaine's specific actions at serotonin receptors have been inconclusive. Deecher et al (1992) found that ibogaine did not displace ligands acting at 5-$HT_{1a}$, 5-$HT_{1b}$, 5-$HT_{1c}$, 5-$HT_{1d}$, 5-$HT_2$, or 5-$HT_3$ receptors, while Repke et al (1994) found that it did inhibit binding of 5-$HT_{1a}$, 5-$HT_{2a,}$ and 5-$HT_3$ ligands with low affinity (>100, 12.5, and >100 μM). Additionally, Sweetnam et al showed that ibogaine inhibits radioligand binding to both 5-$HT_2$ and 5-$HT_3$ receptors, with considerably higher affinity (approximately 4 μM), while Helsley et al (1998) found that ibogaine bound to 5-$HT_2$ receptors with low affinity in vitro ( > 40 μM), but occupied this receptor in vivo following systemic administration.

It is postulated that ibogaine may act as a reversible inhibitor of serotonin transporters, as concluded from the observation that it inhibited transporters in the isolated kidney cells of pigs (Popik and Skolnick, 1999). Sershen et al (1994) found that, at doses of 40-50 mg/kg, ibogaine decreased levels of 5-hydroxyindoleacetic acid [5-HIAA] in the frontal cortex, hippocampus and olfactory tubercle of the mouse. Ibogaine was also found to decrease 5-HIAA levels in the nucleus accumbens and striatum of the rat, but to increase 5-HIAA levels in the medial prefrontal cortex (Benwell, Holtom, Moran, and Balfour, 1996; Ali et al, 1996). The differing effects of ibogaine on serotonergic function in different areas of the brain have yet to be explained. Indeed, this is the case with most psychedelic compounds, making a strong case for the further scientific study of these substances.

Like dopamine systems, the glutamatergic pathway has often been implicated in drug abuse and addiction, specifically N-methyl D-aspartate (NDMA) channel receptors. Preclinical data have consistently indicated that NMDA antagonists interfere with sensitisation, tolerance, and dependence related to stimulant, alcohol, benzodiazepine, barbiturate, and opiate use (Trujillo and Akil, 1991; Wolf and Khansa, 1991; Khanna, Kalant, Shah, and Chau, 1993; File and Fernandez, 1994; Popik and Skolnik, 1996). Furthermore, blockers of NDMA receptors have been show to reduce nalaxone-induced jumping in morphine-dependent mice (Layer et al, 1996; Popik and Skolnick, 1996). NMDA antagonists act by occupying a binding site within a calcium channel, which is normally gated by glutamate, the brain's principle excitatory neurotransmitter (Helsley, Rabin, and Winter, 2001).

Ibogaine has been found to act as a non-competitive antagonist at NDMA receptor channels (Popik et al, 1995), which is supported by the finding that ibogaine has a high affinity for NDMA site binding (Glick and Maisonneuve, 1998; Helsey, Rabin, and Winter, 2001). Popik et al (1994) showed that ibogaine substituted for MK-801 (dizocilipine, a known NMDA antagonist) at a rate of approximately 70% in drug discrimination studies in mice. In addition, ibogaine has been shown to inhibit binding of both MK-801 (an NDMA antagonist) and PCP at NDMA receptors (Layer et al, 1996; Helsley et al, 1998). Ibogaine, at 80 mg/kg, also blocked NMDA-induced convulsions in mice for up to 72 hours after administration (Leal, de Souza, and Elisabetsky, 2000).

It has been demonstrated that certain sigma ligands may be effective in the treatment of drug abuse, due to their ability to block the behavioural effects of cocaine and

amphetamine in non-human subjects (Helsley et al, 1998). Of all binding sites that have been studied thus far, ibogaine shows the greatest affinity for $\sigma_2$ receptors, with reported $K_1$ values ranging from 90 – 201 nM (Bowen et al, 1995; Mach, Smith, and Childers, 1995). Because of its high affinity for $\sigma_2$ receptors, ibogaine has been proposed to act as a $\sigma_2$ agonist (Bowen, Vilner, Bandarage, and Keuhne, 1996). Studies have also shown that ibogaine also binds to $\sigma_1$ receptors with an affinity of less than 10 μM (Mach, Smith, and Childers, 1995). In support of this finding, ibogaine was shown to inhibit [$^3$H]pentazocine (a $\sigma_1$ receptor ligand) binding to high and low affinity sites in the mouse cerebellum (Popik and Skolnick, 1999).

Bowen et al (1995) hypothesised that ibogaine's interaction with sigma receptors, particularly $\sigma_2$ receptors, may be responsible for its effects on the regulation of calcium release from intracellular stores. They found that ibogaine produced a concentration dependent increase of 13 – 45 % in intracellular calcium levels. Additionally, ibogaine was shown to non-competitively antagonise calcium-induced contraction of the aorta and mesenteric artery in the rat (Hajo-Tello et al, 1985). The practical implications, however, of ibogaine's effects on calcium regulation are not yet clear.

Of particular interest with regards to its putative role in interrupting opiate dependence are ibogaine's effects on the opioid system. Ibogaine does not appear to be a conventional opioid agonist or antagonist (Alper et al, 1999). Bhargava et al (1997) found that ibogaine bound to μ-, δ-, and κ-opioid receptors low affinity, 11.0, > 100, and 3.77 μM, respectively. However, they did find that noribogaine had considerably higher affinities for these receptors; 2.66 μM for μ-, 24.72 μM for δ-, and 0.96 μM for κ-opioid receptors. These findings have been supported by results showing even higher affinities for noribogaine binding, with affinities of up to 160 nM at the μ-opioid receptor (Pablo and Mash, 1998). It is therefore hypothesised that noribogaine may play a significant role in ibogaine's effects on opiate dependency (Bhargava, Cao, Zhao, 1997; Mash et al, 2000).

While ibogaine does not show high affinity for opioid receptor binding, it has been shown to exert some less direct effects on the opioid system. Ibogaine inhibits the binding of [3h]U-69593 to κ-opioid receptors, with a $K_i$ value of 2 – 4 μM (Repke, Artis, Nelson, and Wong, 1994). However this inhibition is reversible, and therefore is not likely to contribute to ibogaine's long-term effects (Popick and Skolnick, 1999). Additionally, it has been shown, through a two-site model, that ibogaine inhibits naloxone binding at μ-opioid receptors in the forebrain of mice with a $K_i$ value of 130 nM (Codd, 1995). This suggests that ibogaine may act as μ-opioid agonist of a novel type (Bhargava, Cao, and Zhao, 1997).

Ibogaine, at concentrations < 10 μM, has been shown to selectively inhibit nicotinic receptor mediated catecholamine release in the mesolimbic system (Mah et al, 1998). This inhibition was reversible at low doses (10 μM), but persisted for at least 19 hours with washout at higher doses. Like NDMA and dopaminergic systems, the mesolimbic catecholamine system is implicated in the addictive process. It is considered to be a part of the reward pathway that mediates positive reinforcement in drug addiction (Di Chiara and Imperato, 1988).

**Toxicology:**

The $LD_{50}$ of ibogaine seems to vary depending on the animal, and the route of administration. When administered intraperitoneally in the guinea pig, the $LD_{50}$ was shown to be 82 mg/kg (Dhahir, 1971). In the rat, the $LD_{50}$ was shown to be 145 mg/kg when administered intraperitoneally, but 327 mg/kg when administered intragastrically (Popick and Skolnik, 1999). Thus, ibogaine does not seem to have a great liability for lethality.

There have been, however, three recorded human deaths related to the intake of ibogaine, reported by Lotsof et al (2002). The first, in 1989, was a 40 year old woman, administered 8 mg/kg for the purpose of psychotherapy. This is the lowest dose known to precipitate an ibogaine related death. Four hours into the session, she suffered cardiac arrest, and an autopsy showed significant blockage of the main arteries to the heart. Thus, should ibogaine prove to be a viable therapy, contraindications for patients with cardiovascular problems would most likely be necessary.

The second fatality (the fatality that led to Dr. Jan Bastiaans dismissal) occurred in 1993, a 24 year old Dutch woman being treated for heroin dependency. She received 29 mg/kg in a split dose of 23 mg/kg followed by an additional dose of 6 mg/kg 3 hours later. The patient died 16 hours later of unknown causes; an autopsy did not reveal any specific pathology. However, a sheet of charred tinfoil was found in her personal affects, indicating the possibility that she had consumed heroin during the course of her ibogaine treatment. (A popular method of heroin administration among Dutch addicts is to heat the heroin on a sheet of tinfoil and inhale the vapours, sometimes known as "chasing the dragon"). It is conceivable then, that a heroin-ibogaine interaction may have been the cause of death, as ibogaine has been shown to increase the effects and toxicity of opiates (Popick and Glick, 1996).

The third recorded fatality occurred in 2000, in the U.K. The patient was a 38 year old male, and suffered from hepatitis C. He was administered a total of approximately 5 grams of a total iboga extract standardised to 15% ibogaine. This was a most peculiar case, as the fatality did not occur until after the effects of ibogaine had subsided, 38 hours after initial administration. It is conceivable that the patient's compromised liver functioning may have contributed to his death, due to the metabolisation of ibogaine by liver enzymes, but there is no direct support for this hypothesis.

Of more importance to the general population than these isolated incidents, are recent reports of ibogaine neurotoxicity. There are, however, some discrepancies among these reports. Dhahir (1971) found no pathological changes in the liver, kidney, heart or brain of the rat following chronic intraperitoneal ibogaine administration (10 mg/kg for 30 days, and 40 mg/kg for 12 days.) Likewise, Sanchez-Ramos and Mash (1994) found no evidence of gross pathology in African green monkeys given ibogaine in oral doses of 5 – 25 mg/kg for four consecutive days.

In higher doses, though, ibogaine has been shown to cause definitive neurotoxic effects. At a single intraperitoneal dose of 100 mg/kg, ibogaine was shown to cause marked degeneration of Purkinje cells and activation of microglia in discrete radial bands of the rat cerebellar cortex (O'Hearn and Molliver, 1997). In support of these findings, Xu et al (2000) found that degeneration of Purkinje cells was visible at intraperitoneal doses beginning at 75 mg/kg, showing increasing damage at 100 mg/kg. This study revealed that the neurotoxicity of ibogaine is dose-dependent, a finding also supported by other investigations (Molinari, Maisonneuve, and Glick, 1996).

O'Hearn and Molliver (1997) propose that ibogaine is not directly toxic to Purkinje cells, but rather causes Purkinje cell degeneration through sustained activation of the olivocerebellar projection. Scallet et al (1996) reported that activation of serotonin receptors in the forebrain is the initial site of ibogaine neurotoxicity. Cortifugal axons could then stimulate the inferior olive and its excitotoxic climbiner-fiber pathway to the cerebellum (Xu et al, 2000). This lends support to O'Hearn and Molliver's theory of trans-synaptic excitoxicity mediated by the olivocerebllar projection.

In light of these findings, a number of researchers have recently been studying the effects of a synthetic congener of ibogaine, 18-methoxycoronaradine, more commonly known as 18-MC. Similar to ibogaine, 18-MC decreases levels of extracellular dopamine in the nucleus accumbens (Szumlinksi, Maisonneuve, and Glick, 2000). Likewise, 18-MC has similar effects to ibogaine on the attenuation of morphine and cocaine self-administration (Glick et al, 1996) and alcohol intake (Rezvani et al, 1997). However, unlike ibogaine, 18-MC is non-tremorigenic, does not induce brachycardia, nor does it cause damage to Purkinje cells, or the brain in general (Glick et al, 1996; Molinari, Maisonneuve, and Glick, 1996; Glick, Maisonneuve, and Szumlinski, 2000). FDA protocol studies of human toxicity are currently underway at the University of Miami, under the direction of neurologist Deborah Mash. Should these studies deem ibogaine too hazardous for clinical use, 18-MC could represent a viable alternative.

**Use as an Anti-Addictive:**

Currently pharmalogical treatments for substance addiction disorders can be broadly defined as falling two categories; replacement therapy and aversion therapy (Barber and O'Brien, 1999). 1) Replacement therapy includes treatments such as methadone maintenance and non-tobacco nicotine drugs. These therapies replace the drug of abuse with a theoretically safer drug, off which the patient is then slowly weaned.
2) Aversion therapy includes drugs such as naltrexone and antabuse, which interact with the drug of abuse, causing unpleasant effects such as physical pain, nausea, and vomited. The hope is that while on these drugs, the patient will avoid use of the drug of abuse, out of desire to avoid the painful side effects.

Ibogaine has distinct advantages over both these models of treatments. Both replacement and aversion therapies are long-term treatments, requiring frequent visits to the clinician over an extended period of time. Contra wise, ibogaine therapy, as described previously, involves more intensive intervention over a shorter time frame (Lotsof, 1994). Unlike the drugs used in replacement therapies, ibogaine itself does not appear to be addictive. Repeated administration of ibogaine, at doses of 10 and 40 mg/kg, did not result in dependence in rats as measured by the Primary Physical Dependence test (Aceto, Bowman, and Harris, 1990). A large concern with methadone treatment is its potential for illicit use; it is not uncommon for patients to sell their supply of methadone on the black market, and revert to heroin use (Barber and O'Brien, 1999). As noted earlier, ibogaine is considered to have a low potential for abuse. Aversion therapies, due to their unpleasant nature, often show high incidences of patient-non-compliance, and subsequent relapse (Barber and O'Brien, 1999). This is generally not an issue with ibogaine therapy, patients treated with ibogaine tend to be more receptive to intervention (Lotsof, 1994).

There is a significant body of evidence supporting ibogaine's efficacy in the treatment of substance addition disorders. Case studies and anecdotal reports of humans have sighted ibogaine's ability to interrupt opiate and cocaine addictions for 6 months or longer (Goutarel, Gollnhofer, and Sillans, 1993; Judd, 1994; Sheppard, 1994; Luciano, 1998; Alper et al, 1999). Clinical trials with non-human subjects have substantiated these results. A single intraperitoneal dose of 40 mg/kg reduced self-administration of cocaine for up to 5 days in cocaine-preferring rats (Cappenijk and Dzoljic, 1994). In support of this finding, intraperitoneal doses of ibogaine at 20 – 40 mg/kg reduced cocaine-induced hypermotility (Sershen, Hashim, Harsing, and Lajtha, 1992; Broderick, Phelan, Eng, and Wechsler, 1994; Maisonneuve et al, 1997). Some studies, however, have shown increased locomotor activity

induced by ibogaine in non-human cocaine and amphetamine dependent subjects (Maisonneuve, Keller, and Glick, 1992; Maisonneuve and Glick, 1992). Maisonneuve et al (1997) propose that these differences are a result of the time interval between the injections of ibogaine and the given stimulant. Furthermore, ibogaine's effects on stimulant-induced locomotion, as well as on reduction of cocaine self-administration, appear to be dose-dependent (Glick et al, 1994).

Ibogaine has also been shown to reduce morphine self-administration in clinical trials using non-human subjects. In rats, ibogaine dose dependently reduced intravenous morphine self-administration both immediately after injection and the next day, at doses of 2.5 – 40 mg/kg (Glick et al, 1991). Dworkin et al (1995) found that intraperitoneal doses of ibogaine at 40 and 80 mg/kg reduced heroin self-administration in rats, but only on the day it was administered. The reason for this discrepancy is not yet clear. In human users of heroin (with a daily average use of 0.64 g), oral ibogaine doses of 6 – 29 mg/kg eliminated heroin seeking behaviour for at least 72 hours in 76% of patients treated (Alper et al, 1999).

In addition to reducing opiate self-administration, ibogaine has been shown to reduce symptoms of opiate withdrawal. In rats, intraperitoneal doses of 40 and 80 mg/kg dose-dependently reduced naloxone-induced withdrawal symptoms; including rearing, head hiding, chewing, teeth chattering, writhing, and penile licking (Glick et al, 1992, Parker et al, 2002). In morphine dependent rhesus monkeys, subcutaneous injections of ibogaine (2 and 8 mg/kg) partially suppressed the total number of withdrawal signs (Aceto, Bowman, and Harris, 1990). Alper et al (1999) found that, out of 33 human patients treated with ibogaine, 25 reported no subjective complaints of withdrawal symptoms at 24 and 48 hours post-treatment.

Ibogaine has also been shown to interfere with both alcohol and nicotine dependency. When administered intraperitoneally or intragastrically, but not subcutaneously, ibogaine dose-dependently reduced alcohol intake in rats, without altering blood alcohol levels or food intake (Rezvani, Overstreet, and Lee, 1995). The difference in effects of route of administration may reflect a role of noribogaine in mediating ibogaine's reduction of alcohol intake. Glick et al (1998) found that intraperitoneal ibogaine pretreatment (19 hours beforehand) of 40 mg/kg significantly decreased oral nicotine self-administration in rats for at least 24 hours. Additionally, this ibogaine pre-treatment significantly attenuated nicotine-induced dopamine release in the nucleus accumbens (Benwell, Holtom, Moran, and Balfour, 1996).

**Conclusion and Commentary:**

Ibogaine could represent a truly novel approach to addiction treatment. Very loosely, ibogaine seems to "reset" the neural pathways and behavioural phenomena that comprise substance addiction, directly addressing the etiology of the disorder. Though the specific pharmacological actions of ibogaine are not yet clear, the evidence thus far seems to suggest such a hypothesis, at least in its broadest sense, and clearly warrants further investigation. This notion is also reflected in the theme of rebirth seen in the religious use of the iboga root by the indigenous peoples of western Africa.

Should further study replicate the results found thus far, and find ibogaine safe for use in clinical practice, this would be a major step forward in addiction treatment. Current methods of therapy, particularly in the United States, are often ineffectual, typically it takes an addict 4 to 7 times through conventional rehabilitation before abstinence is achieved

(Anderson, 1996; Finney, Moos, and Timko, 1999). Ibogaine therapy represents a possibility to significantly reduce the length of time needed to break the addictive cycle

In addition to the amount of effort and time needed, current rehabilitation programs are often degrading to the individual, perpetuating the stigma that addicts are somehow "bad people" (Luciano, 1998). As one patient stated, "ibogaine is a much more humane and dignified approach to detox [sic]" (Judd, 1994). Ibogaine treatment involves a more intimate relationship between the patient and the clinician (or, more appropriately, the team of clinicians), involving a greater level of trust and compassion than is generally seen in typical addiction counselling (Lotsof, 1994). Judd (1994) observed that ibogaine has significant advantages over traditional treatment methods with respect to what she considers the three major obstacles in addiction treatment; fear of detoxification, lack of insight, and the inability of addicts to control their urges to use drugs. The potential benefits of this compound necessitate a greater amount of clinical research. Should further studies suggest that the risks of ibogaine are too great for general use, research on the compound's effects may nevertheless elucidate unknown aspects of the psychophysiological basis of substance addiction.

While it is fortuitous that serious scientific inquiry into ibogaine's potential has begun, it is unfortunate that it took such a length of time from the initial discovery of its therapeutic properties. It is unfortunate that politics continue to impede the progress of science. There is a great need for a return of objectivity to science, as far too often today biases and self-serving interests are the driving forces behind scientific exploration.

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