IBOGAINE

A solution or a false promise?

Addiction

FOR DEBATE

doi:10.1111/j.1360-0443.2009.02673.x

The 10 most important things known about addiction

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9. EPIPHANIES ARE HARD TO MANUFACTURE

“Recovery from addiction involves a re-orientation from self-deception to the pursuit of higher ideals [5]. New meaning and hope in life is required, a spiritual experience, which for some is best described as ‘finding God’. Research into ways of assisting people more effectively and predictably re-orientate their lives is needed urgently to fill a gaping hole between current treatment methods and people’s world-views and personal sense of purpose and meaning.”

10. CHANGE TAKES TIME

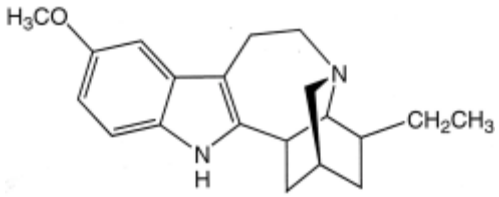
“Having an epiphany, which re-orientates a person’s view of themselves and their place in the universe, is one thing; consolidating these new insights into ongoing real-life behaviour is another.”

The story of Howard S. Lotsof

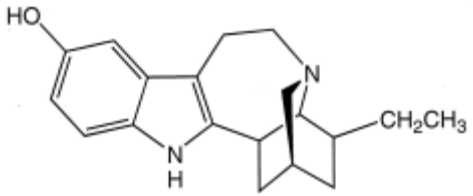
(1943-2010)

“Thirty three hours later I only thought to myself I am exhausted, I am going to sleep for a week and I am never going to take this drug again. I got dressed, walked out of the house and that is when I realised I was not in narcotic withdrawal. And I looked at this large tree in front of me then I looked at the clouds in the sky and I realised that for the first time in my life I was not frightened. I perceived that in my entire life I had been full of fear.”

The Bwiti tradition

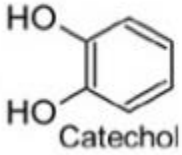


Ibogaine

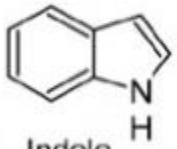


12-Hydroxyibogamine,
(Noribogaine)

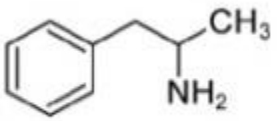
Benzene



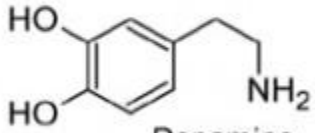
Catechol



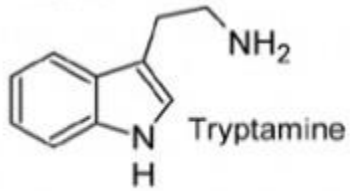
Indole



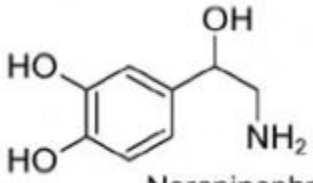
Amphetamine



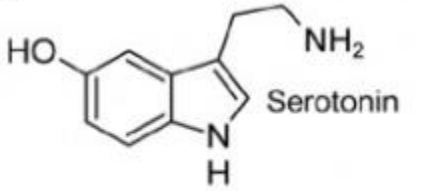
Dopamine



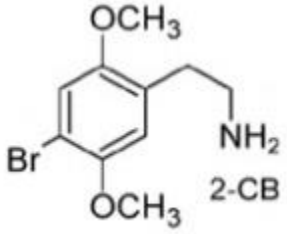
Tryptamine



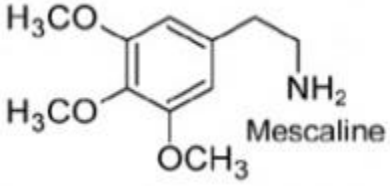
Norepinephrine



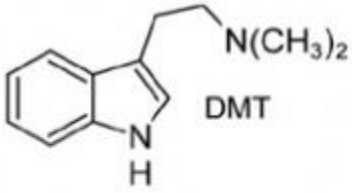
Serotonin



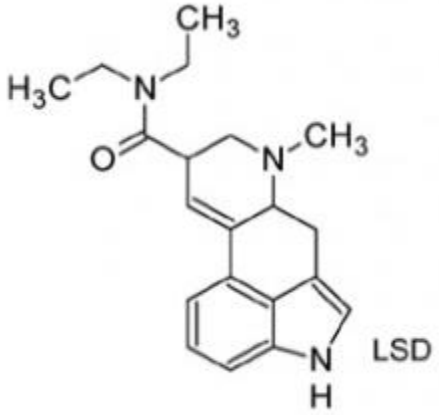
2-CB



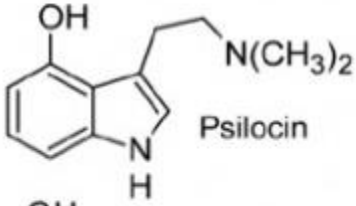
Mescaline



DMT



LSD



Psilocin

Psilocybin

- **Ibogaine has diverse affinities at a relatively large number of receptors and other binding sites, typical of many alkaloids.**

- **Note receptor binding affinities are distinct from functional effects/actions.**

Table 1. Reported receptor/channel affinities and actions of ibogaine, noribogaine, and 18-MC

Receptor/Site/Channel	Action	Ibogaine	Noribogaine	18-MC
ACh (muscarinic, M1)	agonist?	+	+	+
ACh (muscarinic, M2)	agonist ?	+	+	0
ACh (nicotinic, α3β4)	antagonist	+++	NR	+++
ACh (nicotinic, α4β2)	antagonist	++	NR	0
μ-opioid	Ibogaine,18-MC weak antagonists; noribogaine-agonist;	++	+++	++
κ-opioid	Ibog-mixed antagnist/ agonist	++	+++	++
δ-opioid	agonist?	+	++	++
5-HT2A	agonist	+	0	+
5-HT terminal	release	+++	+/ 0	0
5-HT transporter	reuptake inhibition	++	+++	0
D1	NR	0	0	0
D2	NR	0	0	+
DA transporter	reuptake inhibition	+	NR	NR
σ1	agonist	++	+	0
σ2	agonist	+++	+	+
GABA B	NA	0	0	0
NMDA	antagonist	++	+	0
Voltage-gated K+	Not antagonist	NR	NR	NR
Voltage-gated Na+	NR	++	+	+
Voltage-gated Ca2+	NR	+	NR	NR

Physiological effects:

In animal models, ibogaine has demonstrated action at various neurotransmitter sites, including the glutamate, opioid, dopamine, serotonin, and acetylcholine systems (Popik 1999)

US National Institute on Drug Abuse (NIDA) ibogaine project

- **1991-1996**; NIDA supported preclinical contract work, including toxicology and pharmacokinetics which enabled a phase 1 study of single dosages of ibogaine for cocaine dependence.

- The study was approved by the FDA in 1993. It was privately funded. Subjects had received dosages of 1 and 2mg/kg and no adverse events had been reported at the time the study ended in contractual and intellectual property disputes.

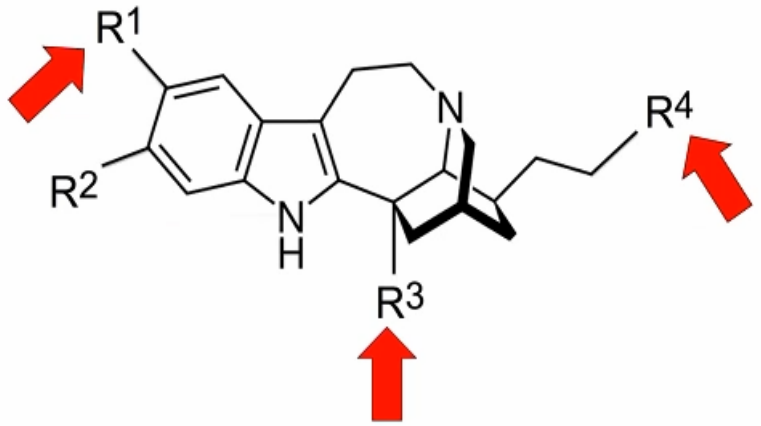
- No subsequent clinical research with ibogaine has been conducted in the US. NIDA subsequently terminated its ibogaine research program in 1996.

The NIDA 18-MC project

- **2013- present:** NIDA has supported preclinical toxicology, pharmacokinetics and chemical manufacturing and control (CMC) work on 18-MC enabling a phase I/II study.

- Further work is yet to be supported for the study that is, from a regulatory standpoint, enabled.

18-Methoxycoronaridine (18-MC): a putatively safer ibogaine congener



	R^1	R^2	R^3	R^4
Ibogaine	OCH_3	H	H	H
18-Methoxycoronaridine	H	H	CO_2CH_3	OCH_3

- Developed by a process of rational synthesis
- Differs from ibogaine at three positions; both compounds share the same ibogamine parent skeletal structure
- Equally efficacious as and less toxic than ibogaine in animal models of opioid withdrawal and drug and alcohol self-

Clinical Pharmacokinetics:

- plasma saturation peaks at 2 hours after administration
- half-life of up to 7 hours in human plasma (Koenig 2015)
- metabolized into **noribogaine** in the liver by Cytochrome P4502D6 (CYP2D6) enzymes
- noribogaine is stored in fat tissue and released over the course of the following weeks or months.
- Noribogaine possesses some of the same effects as ibogaine, which may account for the prolonged reported benefits.

Physiological effects:

- ataxia
- tremor, (not seizures)
- nausea, vomiting, diarrhoea
- slowed breathing
- heightened sensitivity to sensory stimuli
- bradycardia
- hypotension
- QT interval prolongation
- T-wave morphology changes are rare (flattening of the T-wave, biphasic t-waves, and initial decrease in the anterior slope of the T-wave)
- Insomnia (can last many days in people previously using benzodiazepines or other sedatives)

Ibogaine effects on opioids

- IBG mitigates opioid withdrawal symptoms
- Potentiates opioid effects when co-administered by enhancing opioid signalling (not by direct effect)
- Decreases accumulated tolerance to opioids by re-setting opioid sensitivity of the CNS (Parker 2001).
- This effect is permanent after IBG treatment, clients become opioid naïve
- Patients on long-acting opioids need to be switched to short acting ones (morphine sulphate) before IBG treatment

Other drugs and interactions

Benzodiazepines (BZDs):

- IBG has no effect on GABAergic system(Popik, 1998)
- IBG does not reduce benzo withdrawal symptoms
- BZDs may dull IBG's therapeutic effects
- Ideally client is detoxed from BZDs before IBG treatment
- If not detoxed BZDs must be continued switched onto long acting BZD like diazepam
- If the patient is BZD naïve BZDs can be used for agitation or insomnia

Other drugs and interactions

Alcohol

- Clients with alcohol dependence must be detoxed from alcohol before starting on IBG treatment

- Physical/cardiovascular/nutritional status must be carefully assessed and corrected

- All patients should refrain from drinking ETOH for at least 3 days before and 7 days after IBG treatment

- IBG is used successfully in selected patients to assist abstinence maintenance from alcohol

Other drugs and interactions

Psychostimulants and caffeine

- Beware of QT prolongation and proarrhythmic effects
- Cardiovascular compromise
- IBG potentiates the effect of stimulants
- All patients should refrain from using stimulants including prescription ones and caffeine for 5 days before treatment
- IBG is used successfully in stimulant SUDs

Other drugs and interactions

Antidepressants

- SSRIs and SNRIs increase the risk of serotonin syndrome with IBG.

  Ideally they should be tapered and

  stopped before IBG treatment
- MAOIs must be stopped at least 7 days before, as they can cause unpredictable increase of IBG effects

Other drugs and interactions

- **Corticosteroids** prolong QT interval, need to be temporarily stopped
- **Anabolic steroids** cause liver impairment, pro-thrombotic, can cause high BP and anxiety
- **Thyroxin** should be continued
- **Beta-blockers** must be tapered and stopped while switching to other anti-hypertensives
- **Anti-psychotics** must be tapered and stopped if the patient is otherwise suitable for treatment

Anti-psychotic medications interrupt the effects of psychedelic medicines and they have been known to cause prolonged negative reactions in patients who have taken ibogaine

Psychological effects:

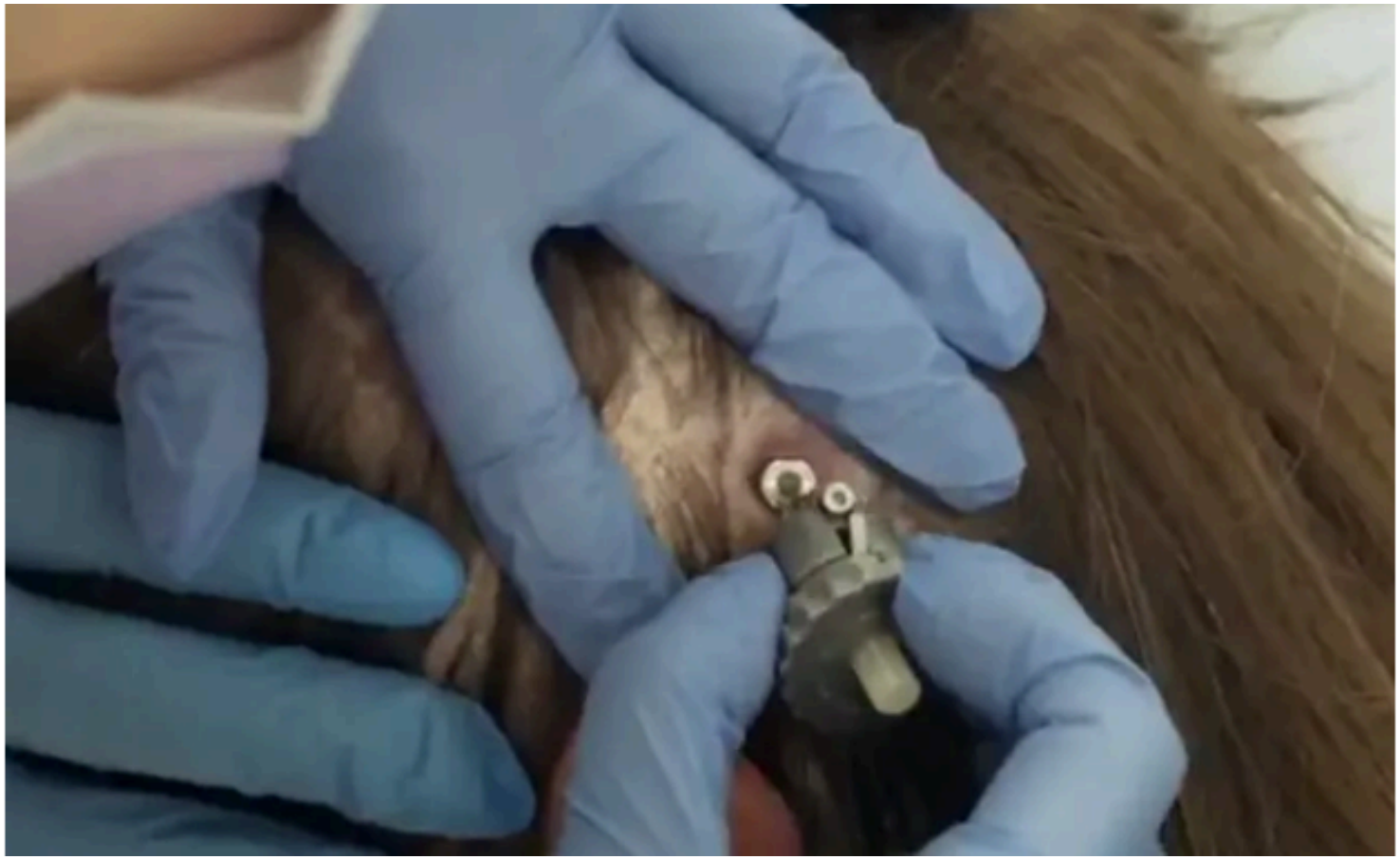
"For its psychological effects, ibogaine is best classified as an oneirogen, a substance that produces waking dreams (Naranjo 1974).
For many but not all ibogaine patients these effects are visual, and this visionary content is deeply subjective and personal, unfolding much the same way as dreams.
The experience has also been likened to watching a film projected on an inner screen – often with a level of emotional detachment, even when the content is very emotional or graphic.
This overall effect can evoke a state of profound contemplation and self-reflection."

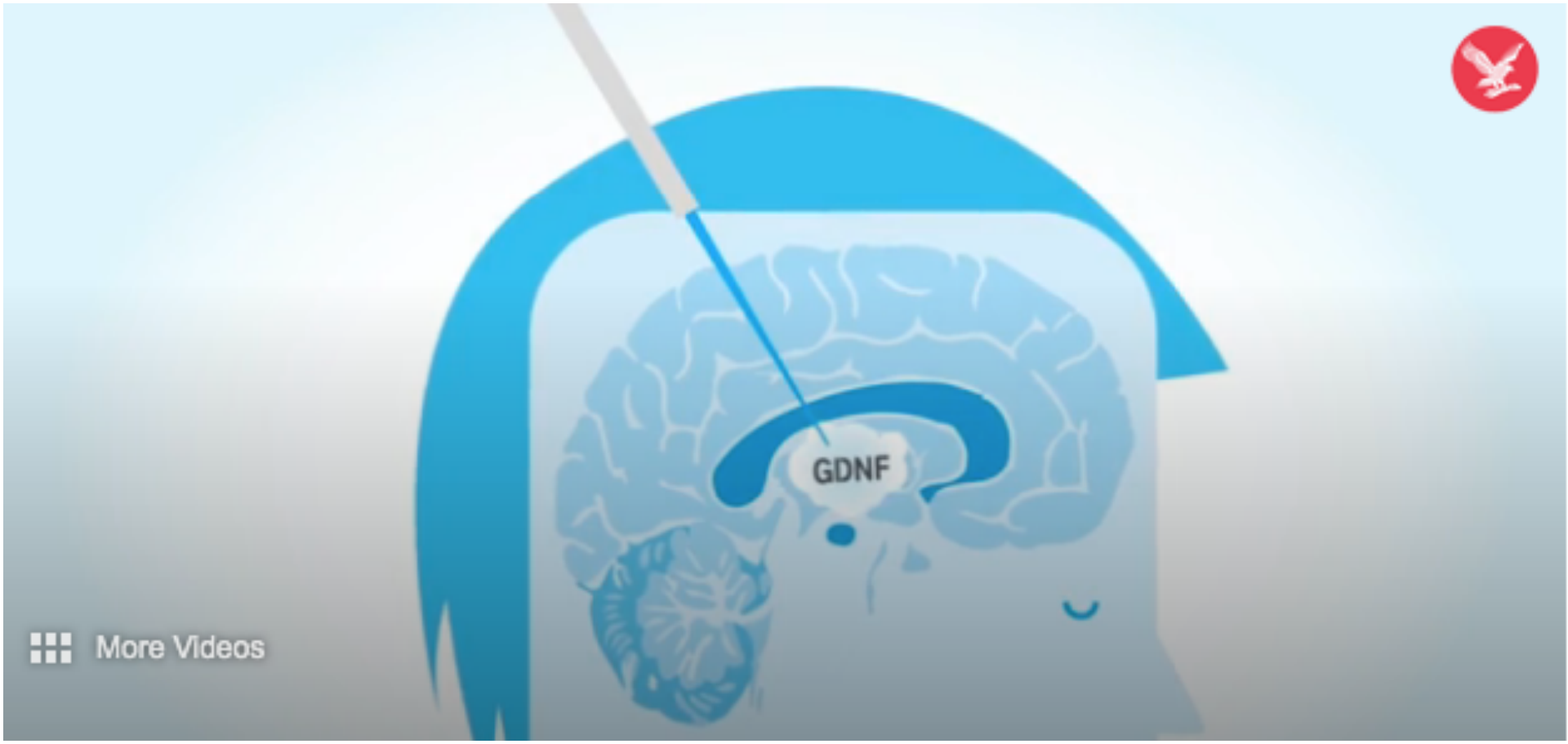
"These effects are distinct from classic psychedelic compounds, both subjectively and also because of the complex nature of the physiological effects that accompany them."

Parkinson's and cancer hope from implant drilled into skull to deliver drugs with pinpoint precision

'It sounds as if she's furiously sharpening a pencil inside my head'

Alex Matthews-King Health Correspondent |
Wednesday 27 February 2019 01:02 |




GDNF
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ORIGINAL RESEARCH ARTICLE

Front. Pharmacol., 05 March 2019 | https://doi.org/10.3389/fphar.2019.00193

Ibogaine Administration Modifies GDNF and BDNF Expression in Brain Regions Involved in Mesocorticolimbic and Nigral Dopaminergic Circuits

Soledad Marton[1†], Bruno González[2†], Sebastián Rodríguez-Bottero[1], Ernesto Miquel[1], Laura Martínez-Palma[1], Mariana Pazos[2], José Pedro Prieto[3], Paola Rodríguez[2], Dalibor Sames[4], Gustavo Seoane[2], Cecilia Scorza[3*], Patricia Cassina[1*] and Ignacio Carrera[2*]

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[2]Laboratorio de Síntesis Orgánica, Departamento de Química Orgánica, Facultad de Química, Universidad de la República, Montevideo, Uruguay

[3]Departamento de Neurofarmacología Experimental, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay

[4]Department of Chemistry, Columbia University, New York, NY, United States

"(In rats) the I 40 (ibogaine 40mg/kg) dose selectively increased GDNF mRNA content in the midbrain regions: VTA (12-fold increase compared to the control group) and SN (6-fold increase vs. the control group) with no appreciable effects in the PFC and NAcc."

Int Rev Neurobiol. Author manuscript; available in PMC 2016 Mar 23.
Published in final edited form as:
Int Rev Neurobiol. 2014; 118: 1–12.
doi: 10.1016/B978-0-12-801284-0.00001-4

PMCID: PMC4804710
NIHMSID: NIHMS766227
PMID: 25175859

Neuroimmune Mechanisms of Alcohol and Drug Addiction

Changhai Cui,[*,1] David Shurtleff,[†] and R. Adron Harris[‡]

"Alcohol and other drugs of abuse have significant impacts on the neuroimmune system. Studies have demonstrated that drugs of abuse interact with the neuroimmune system and alter neuroimmune gene expression and signaling, which in turn contribute to various aspects of addiction."

The four essential steps of psychedelic assisted therapies:

1. Patient selection

2. Patient preparation

3. Medicine session (set, setting and dose)

4. Integration

Problems occur when providers skip over some of the steps

Patient selection

Inclusion criteria

- *Personal commitment* and willingness to undergo the ibogaine treatment process, including preparation before and integration after treatment
- Demonstrated understanding of what it involves, the difficulties and potential adverse effects based on *informed consent*
- Understanding that Ibogaine is *not a 'magic bullet'* and it is not likely to achieve lasting results without going through the whole treatment process.
- It only provides an opportunity to start life on a different path

Patient selection

Exclusion criteria:

- Schizophrenia, psychosis (not episodes of drug induced psychosis)
- Acute states of confusion
- Acute intoxication
- Bipolar disorder for which patient has been hospitalized or medicated
- Depersonalization and/or Derealization Disorder
- Cerebellar dysfunction
- Epilepsy
- Organic brain disease
- Dementia

Patient selection

Exclusion criteria:

- Prolonged QTc Interval
  - The FDA considers prolonged QTc to be: > 450 milliseconds for males and > 470 milliseconds for females
- Heart failure, enlarged or hypertrophic heart
- Severe hypertension or hypotension
- Active blood clots
  - Pulmonary embolism
  - Deep vein thrombosis
- Emphysema
- Chronic Obstructive Pulmonary Disorder
- Cystic Fibrosis
- Some drug interactions,
- Alcohol, benzodiazepine withdrawal

Patient selection

Exclusion criteria:

- Abnormal blood test results:
  - Particularly K+ or Mg++ are outside normal ranges they must be corrected.
- Impaired Kidney or Liver function
  - Any patient with liver enzymes greater than 2.5 times normal levels, on dialysis for kidney failure, or with abnormal Blood Urea Nitrogen (BUN) or creatinine levels may not be able to metabolize or clear ibogaine effectively
- Active infection or abscess
- Within 6 months of major surgeries
- Bleeding GI ulcers
- Pregnancy

Patient selection

Exclusion criteria:

- The risk of experiencing cardiac complications while undergoing ibogaine treatment is significantly increased when
- **Drugs that block or compete with Cytochrome P4502D6 (CYP2D6) enzymes and/or**
- **Drugs that prolong QT intervals are used**

- Other considerations should be guided by the American Society of Anaesthesiologists risk stratification

ASA Classes >2 generally not suitable for ibogaine treatment

Patient preparation

Psychological:

- Therapeutic alliance and trust in therapists need to be established before IBG treatment.
- Ideally IBG session is preceded by a number of information and initial psychotherapy sessions
- The patient is fully informed about the process, the difficulties, the potential risks and adverse effects
- Informed Consent is discussed, checked and signed

Patient preparation

Physical:

It is essential to review investigation results and exclude acute conditions plus

- Cardio-vascular status is stabilised
- Nutritional status corrected
- Venous access assessed

Ibogaine session

Caregivers:

Most important quality: **Empathy**

Client is in an open vulnerable state

During ibogaine session:

Medical staff with experience in acute care/anaesthetics and ACLS trained should be available

- Two therapists, male and female ‘therapist dyad’ is preferable but same gender if single therapist,
- Therapists are familiar working with clients in altered states of consciousness

During the medicine session strong emotional outbursts can occur with projections towards therapists

- It is important not to block the clients emotional process but to provide a safe container allowing ‘anything to happen’ within safe parameters

More directive and/or prescriptive psychotherapeutic approaches in this setting may result in adverse outcomes

Ibogaine session

Dosing:

- wait until in opioid withdrawal, OOWS (Objective Opioid Withdrawal Scale): 3-7
- If in full withdrawal oral dosing is difficult, compromised (nausea, vomiting)

  Consider re-stabilise on short acting opioid

  and re-schedule ibogaine session

IV access and fluid pre-loading is preferable

Monitor pulse, O2 Saturation, ECG

Ibogaine session

Dosing:

- Starting with a small ‘test dose’ or single threshold dose 1-3 hours before the effective dose
    - To monitor for allergic reactions
    - To establish sensitivity to ibogaine
- There is a range of individual sensitivity to ibogaine
- Booster doses may be given at least 24-36 hours after the effective dose if residual withdrawal

Ibogaine session

Onset of effects is generally noticeable within 1-3 hours with marked decrease in physiological withdrawal from opioids as well as the subjective effects

Three distinct phases (Alper 2001):

1. Acute

4 to 8 hours, the most intense and visual part of the experience described as oneirogenic. Physiological effects, especially ataxia, will be most pronounced.

2. Evaluative

can last between 8 to 20 hours, and consists largely of a cognitive and more or less emotionally neutral review of material that was experienced in the acute phase. Patients generally prefer to be left undisturbed, and to lie mostly still and quietly during this early integration phase.

3. Residual Stimulation

lasts for another 24 to 72 hours. some level of exhaustion, and in some cases difficulty sleeping

cognitive and introspective processes begin to relax and attention returns to the outer environment.

Ibogaine session

- Some clients regress and go through developmental stages of the psyche from as early as the birth-process.
- The client may be acting like an infant-toddler-child-adolescent-youth. This could be falsely interpreted as temporary cognitive impairment.
- Suppressed traumatic experiences may emerge, sometimes associated with apparent distress, agitation
- It is essential to gently support clients working through this process, not blocking them, keeping them safe, not trying to pull them out back into “normality”

Ibogaine safety

- 3414 treatment events between 1989 and 2006 events, 11 fatalities coinciding with ibogaine treatment

- This number included mainly non-medically supervised treatments

- Between 1990 and 2008 19 reported fatalities

  14 of them had post-mortem exams

- Majority of them resulted from opioid overdoses, some of seizures from alcohol or benzodiazepine withdrawals and some of cardiac complications with pre-existing cardiac conditions

Ibogaine safety

- Self administration of ibogaine should be strongly discouraged !
- If a person decided to undergo treatment it is only safe with experienced treatment providers and medical supervision
- Ibogaine treatment has proved safe in carefully selected individuals who are ready for real change in their lives

Ibogaine Treatment Centers in Canada

- Sacred Soul Therapy House – Vancouver, Canada
- Toronto Ibogaine Centre – Toronto, Canada
- Liberty Root Ibogaine Therapy – Vancouver, Canada

Ibogaine Treatment Centers in Mexico and Caribbean

- Crossroads Treatment Center – Bahamas, Caribbean
- Clear Skies Recovery – Cancun, Mexico
- Experience Treatment Center – Rosarito, Mexico
- Holistic Hope House – Rosarito, Mexico

Ibogaine Treatment Centers in Europe

- Tabula Rasa – Portugal
- Iboga Tree Healing House – Portugal

Legal status of ibogaine

USA: Schedule 1 - illegal

UK: Illegal – but no Hx of prosecution

Canada: On prescription drugs list

New Zealand: Legally available on prescription

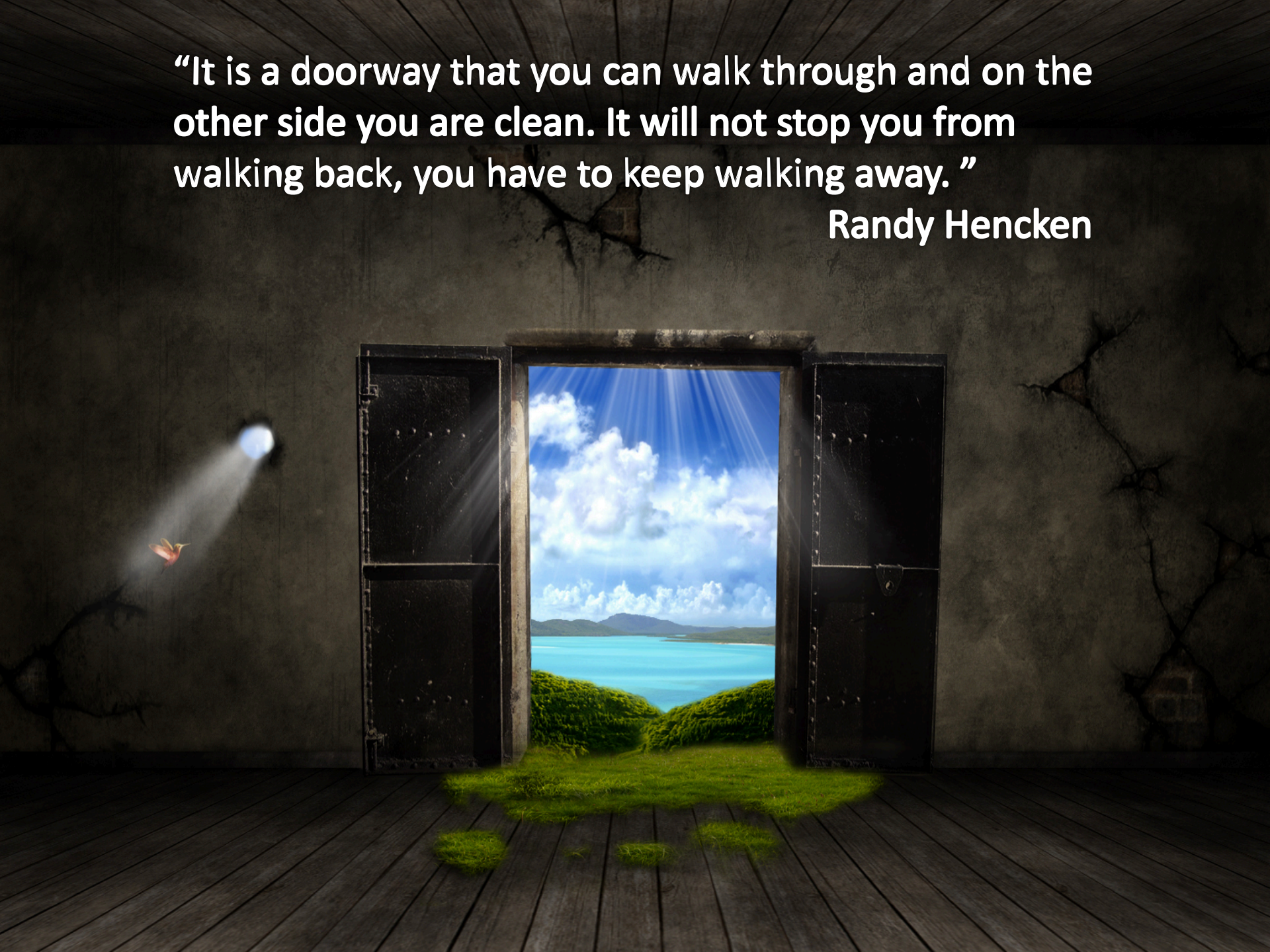
Australia: Schedule 4 – prescription only

"This is the worst censorship of science in the history of the world… since the dark ages. It's worse than the Catholic Church banning the telescope in 1616”

(David Nutt)

What is ibogaine treatment and what it is not ?

- It is an addiction interrupter, not a cure for addiction
- It is an opportunity, not a solution
- It is safe in the right setting, it can be dangerous in the wrong hands or without expert help


“It is a doorway that you can walk through and on the other side you are clean. It will not stop you from walking back, you have to keep walking away. ”
Randy Hencken