Current Trends and Solutions in Addiction Recovery from a Medical and Pharmaceutical perspective, including the Use of Psychedelics

Dr Fergus Law
Consultant Psychiatrist in Substance Misuse, PsychInsight

DrFergus.Law@PsychInsight.co.uk
British Doctors & Dentists Group annual convention on 11 Oct 2024

Declaration of Interests

- No ownership or part ownership or personal retainer from a company
- Research grant with Schering-Plough Ltd & Reckitt-Benckiser Healthcare
- Acted as a consultant, sat on focus groups, market research and been on advisory board for Indivior, Schering-Plough, Reckitt-Benckiser, Britannia/Genus, Lundbeck
- Received honoraria for speaking or chairing meetings at industry supported symposia from Britannia/Genus, Indivior, Reckitt-Benckiser, Schering-Plough, Dupont, Bristol-Myers-Squibb, Servier
- Hospitality at meetings from Britannia/Genus, Reckitt-Benckiser, Schering-Plough, Servier, Lundbeck, Lilly
- Written documents for Alpharma, Britannia/Genus, Indivior, Reckitt-Benckiser Healthcare, Lundbeck

Newly Emerging Issues in Addiction

1. Submarines
2. rTMS (repetitive transcranial magnetic stimulation)
3. Electrostimulation
4. Buprenorphine depot
5. Naltrexone implant
6. Psychedelics

Use of Submarines to Transport Drugs Between Countries

Traffickers have been using submarines to reach Africa and Europe for more than 20 years. USA intercepted submarine in international waters in 2019. Two seized by Spanish police in 2019 and 2023.

A trophy in the car park of the Spanish police academy in Ávila. It is 20 metres (65 ft) long, built out of fibreglass and plywood

> 2000kg Tons of Cocaine with a Street Value Worth of > £121m in Submarine

Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive Transcranial Magnetic Stimulation (rTMS)

- Figure of 8 coil penetrates 2-3cm into cortex of brain, with propagation into deeper areas
- Delivers short powerful bursts of magnetic field (1.5-2 Tesla) to induce neuronal firing:
  - High frequency has excitatory effects, e.g. 10Hz
  - Low frequency has inhibitory effects, e.g. 1Hz
- Each session takes 30 minutes
- Typically have 15-30 sessions over 3-6 weeks
- May have > 1 session daily (not recommended for addiction or bipolar depression)

Figure of 8 coil for rTMS

AIM Neuromodulation https://www.broadwaylodge.org.uk/recovery/rtms-therapy/

Side-Effects of rTMS

- Transient effects during sessions:
  - Headaches - Scalp discomfort
  - Fatigue or drowsiness - Facial twitching
  - Temporary hearing changes - Local erythema
  - Fainting or dizziness (rarely)
- More serious side-effects:
  - Seizures 1 in 50,000
- Can drive to and from sessions, and return to work immediately

Contraindications to rTMS

- Absolute contraindications:
  - Ferromagnetic metals in the head (iron, nickel, cobalt, their alloys and alloys of rare-earth metals) e.g. cochlear implants
- Relative contraindications:
  - Epilepsy
  - Severe heart disease
  - Acute alcohol withdrawal
  - Certain electrical implants
  - Certain neurological conditions

rTMS Potential Mechanism of Action

- rTMS is applied to the dorsolateral prefrontal cortex (DLPFC) which is involved in reward, motivation and decision-making circuits
- Craving and compulsive drug-seeking related to loss of inhibitory control in the PFC
- High frequency rTMS (excitatory) to left DLPFC
  - Improves inhibitory control
  - Induces dopamine release in striatum in humans, and reduces craving

rTMS for Addiction Etc.

- **Cocaine:** Reduced craving, use, impulsivity, positive urine drug screen, and increased time to next use (91 days vs 51 days)
- **Alcohol:** Reduced craving and use at 3 months follow-up, enhancing cognitive control
- **Nicotine:** Reduced craving, increased quit rate
- **Others:** Methamphetamine, gambling
- **Mental health:** Depression, bipolar depression, anxiety including OCD and GAD, ADHD
- **Others:** Fibromyalgia, Migraine

Numbers of rTMS Sessions

- Initial treatment:
  - 15 sessions for addiction and ADHD (Mon-Fri for 3 weeks)
  - 30 for depression & OCD (Mon-Fri for 3-6 weeks)
- Maintenance treatment (to prevent relapse):
  - Maintenance rTMS (2 sessions per month) and/or addiction counselling, but minimal research
- Treatment of relapse:
  - As initial treatment

Availability of rTMS

- Limited NHS availability (but increasing), but the NHS have been funding private rTMS for treatment resistant depression (? and/or anxiety)
- Approved in the UK in 2015 by the National Institute for Health and Care Excellence (NICE) for depression (and by the FDA in the USA in 2008)
- rTMS is covered for depression only by most health insurers

Private Providers and Cost of rTMS in UK

- Biggest provider is Smart TMS (8 locations) www.smarttms.co.uk
  - Addiction cost £4,125 (£4,500 London) (15 sessions) age 16+
  - Depression cost £6,000 (£7,500 London) (30 sessions) age 14+
  - OCD cost £8,250 (£9,000 London) (30 sessions) age 16+
- Smaller providers, e.g. AIM Neuromodulation, (based at Broadway Lodge) https://www.aimneuromodulation.com/rTMS
  - £200 Consultation + £3000 (15 sessions)
  - £1000 per 5 additional sessions

Response Rates in Major Depression ECT vs TMS vs Sham

(Systematic Review Mutz et al 2019)

- Bi-temporal ECT: OR 8.9 (95% CI 2.6-30.9) Sig
- Bilateral rTMS: OR 4.9 (95% CI 2.9-8.3) Sig

  [Priming TMS: OR 7.2 (95% CI 2.2-16.4) Sig]
- tDCS: OR 2.65 (95% CI 1.6-4.6) Sig
- [SSRI antidepressants: OR 1.5-1.8 Cipriani et al 2018 sig]

Electrostimulation

Development of Electrostimulation

- Acupuncture – needles in the body which are twiddled to produce a sensation called deqi
- Auricular acupuncture – multiple needles in the ear, used especially in addiction
- Electroacupuncture – electrical stimulation of needles in the body – more sustained stimulation which spreads more in the tissues
- Electrostimulation – electrical stimulation via electrodes (no needles) to the ear or body

Modern Transcranial Electrostimulation

- Electrosleep first used in France:
  - Christian Krazenstein 1745
  - Then Leduc 1902 and Robinovitch 1914
  - Then the Russians, Gilyarovski 1958, Anan'ev et al 1960
- Auricular acupuncture first used in France:
  - Sarlandiere 1825, developed by Paul Nogier 1957
- Electrostimulation for addiction:
  - Wen and Cheung 1973, Meg Patterson 1975 (Hong Kong neurosurgeon), called it NET (neuroelectric treatment), treating celebrities including Boy George, Eric Clapton and Keith Richards

SPERA device with electrodes which are worn on the pinna of the ear

Image kindly provided by Dr Graham Giles, SPERA

Advantages of Electrostimulation in Addiction

- No need for medication (most cases)
- Withdrawal symptoms recover faster
- Better inner wellbeing
- Feel more energetic
- Better mental and emotional clarity
- Minimal protracted withdrawal symptoms (so struggle less post-detox)

Disadvantages of Electrostimulation

- Limited evidence supporting it
- Many different techniques and devices used, so results not always comparable
- Potential side-effects, e.g. headache, nausea, dizziness, fainting, sore electrode site
- Still need to treat psychological issues related to addiction
- May not be used as intended by the client

Potential Cautions or Contraindications for Electrostimulation

- Broken or inflamed skin on electrode site
- History of epilepsy (Use only 10 & 2.5 Hz)
- Pregnancy: Do not use in pregnant women
- Heart problems: Avoid if in-dwelling cardiac pacemaker or recent history of heart problems
- Deep Vein Thrombosis (DVT): Do not apply electrodes to the legs if recently had a DVT
- Metal pins/plates in the skull – may cause pain
- Complex medical esp. neurological problems

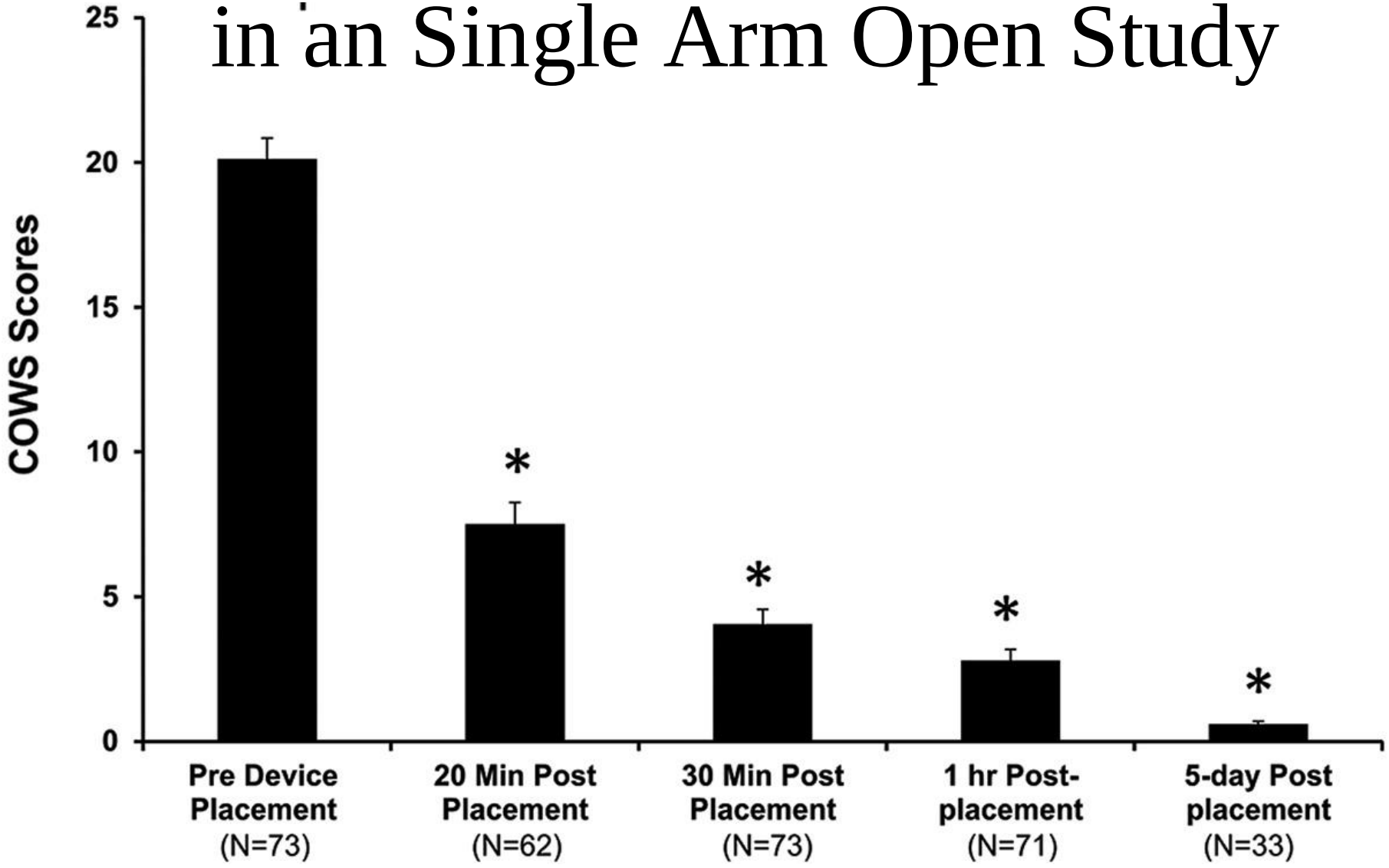
Approval of Electrostimulation in the USA and UK

- FDA in the USA has approved various devices based on evidence for:
  - Addiction
  - Pain
  - Insomnia
  - Anxiety
  - Depression
- MHRA in the UK has approved no devices, except TENS for pain
- NICE recommends acupuncture for chronic pain, but nothing else

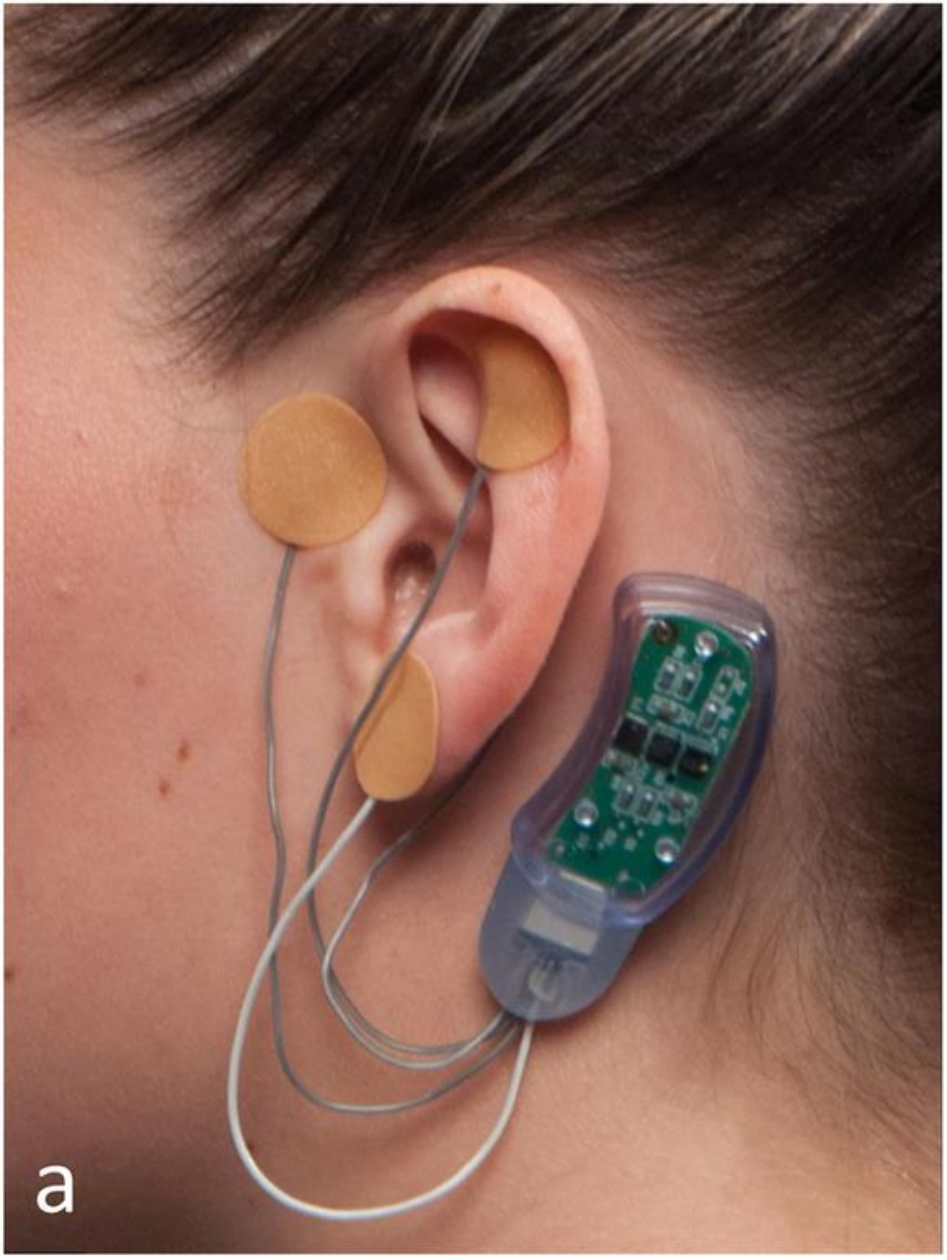
FDA Market Clearance for Devices Reducing Opioid Withdrawal Symptoms

1. NSS-2 Bridge (Nov 2017) by Innovative Health Solutions, Inc. Previously approved by FDA in 2014 for acupuncturists (Electro Acupuncture Device)
2. Drug Relief stimulator (Jun 2018) by DyAnsys, Inc (also Primary Relief and Fast Relief devices for pain)
3. Sparrow Ascent (Jun 2023, previously Sparrow and Roo Therapy System Jan 2021 by Spark Biomedical, Inc.
4. NET Device (May 2024) by NET Recovery Corp

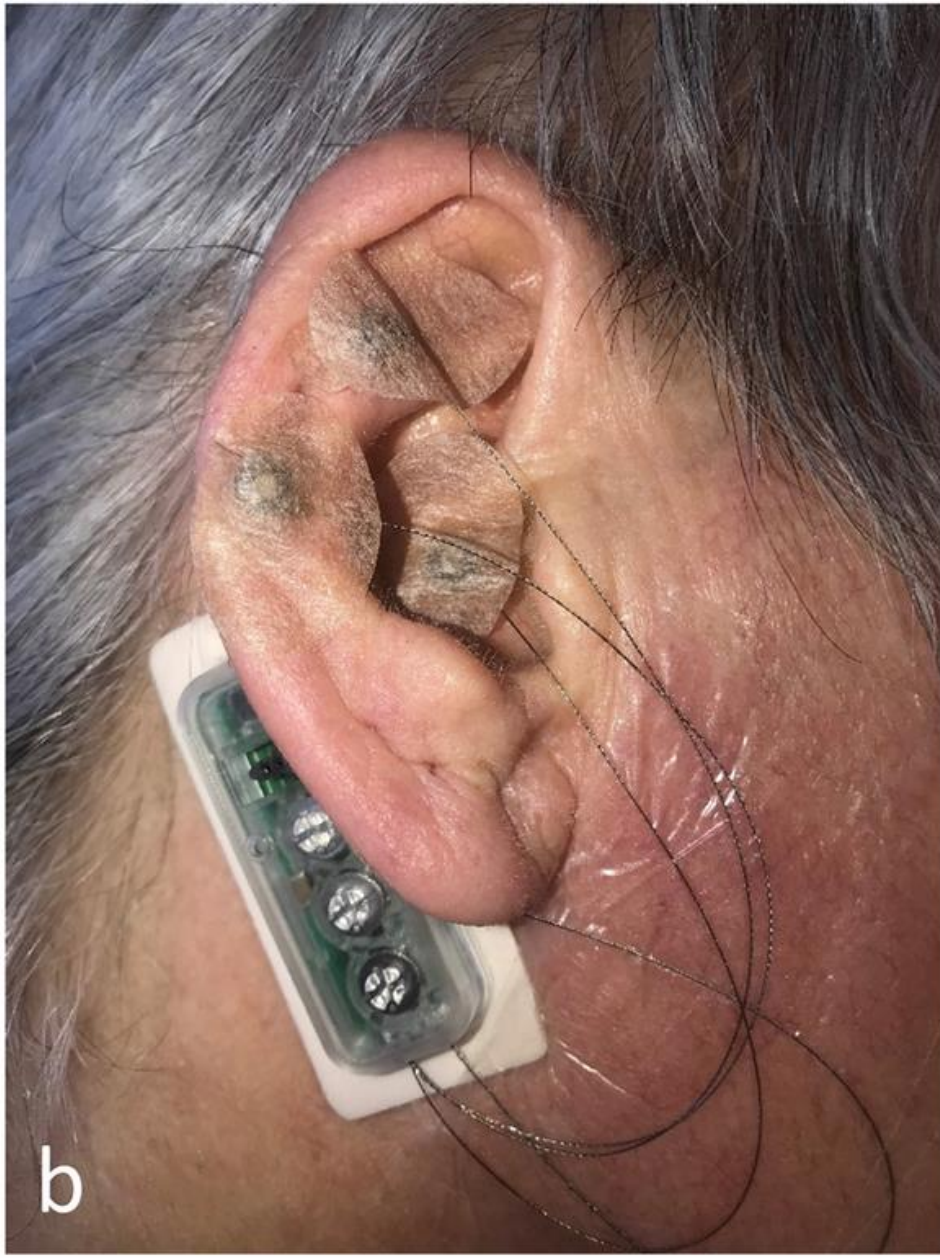
COWS Scores after NSS-2 Bridge in an Single Arm Open Study



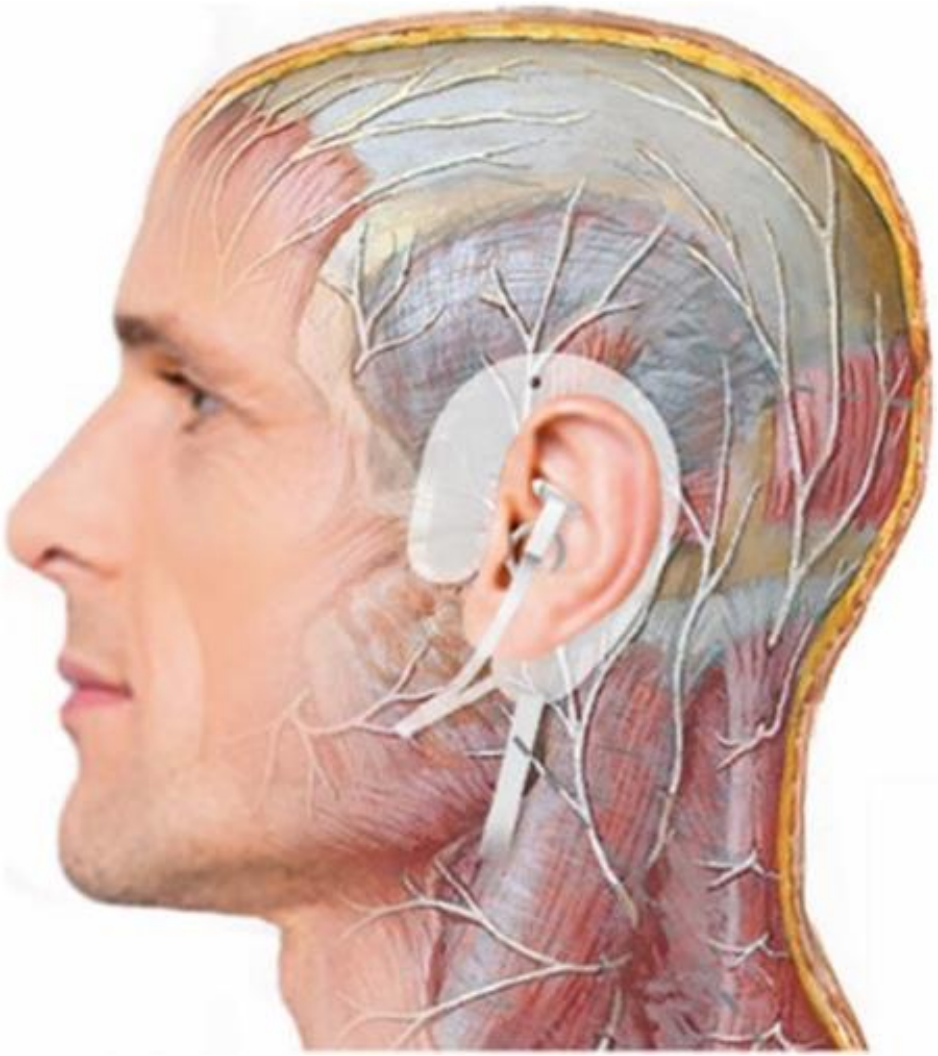
Tirado et al. Bioelectronic Medicine. 2022 Aug 18;8(1):12



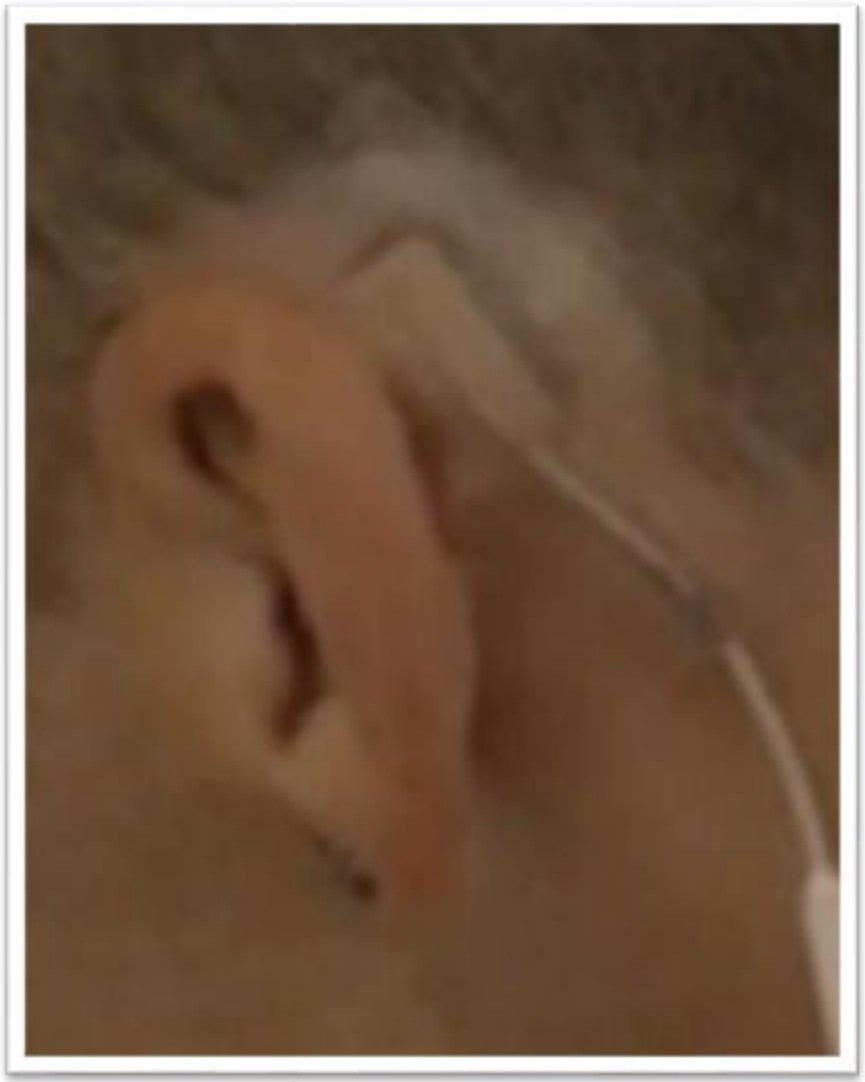
The NSS-2 Bridge device using 2mm titanium needles



The DyAnsys Drug Relief stimulator using needles



The Sparrow Therapy System
without needles



The NET Device
without needles

Possible Mechanism of Action in Auricular Stimulation

- Opiate withdrawal related to high sympathetic nervous system activity
- Pinna innervated by vagus nerve etc
- Electrostimulation may restore the balance of the autonomic nervous system by stimulation of the vagal parasympathetic nervous system (associated with reductions in HR and increases in RR interval)
- May increase endogenous opioid release (endorphins, encephalins, dynorphin) by stimulating the periaqueductal gray (which both the vagal & trigeminal afferent nerves connect to)

Mechanism of Action of Electrostimulation (cont.)

- Neurotransmitters involved:
  - Electrostimulation effects partially blocked by naloxone:
    - low dose blocks mu receptor for met-encephalin (2Hz)
    - high dose blocks kappa receptor for dynorphin (100Hz)
  - Serotonin system
- Reduces inflammatory responses:
  - Reduced pro-inflammatory cytokinins, e.g. tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1)
  - Increased anti-inflammatory cytokinins, e.g. IL-6

Long-Acting Formulations of Buprenorphine

Long Acting Formulations of Buprenorphine

- Buvidal depot (weekly and monthly): Drug cost £239.70 per month (annual £2876.40 + on-costs)
  - UK since Feb 2019. 4 dose levels
- Sublocade depot (monthly): Not available in UK
- Sixmo implant (6 monthly): Drug cost £1438.20 or £239.70 per month (annual £2876.40 + on-costs)
  - Only suitable for low dose buprenorphine users (≤ 8mg)
  - Minor surgery to implant 4 rods in upper arm (and later remove)
  - Only 12 months treatment licenced in Europe (24 months elsewhere)

Changes on CGI in Wales Using Buvidal for 6 Months (N=20)

Very Much Worse

Much Worse

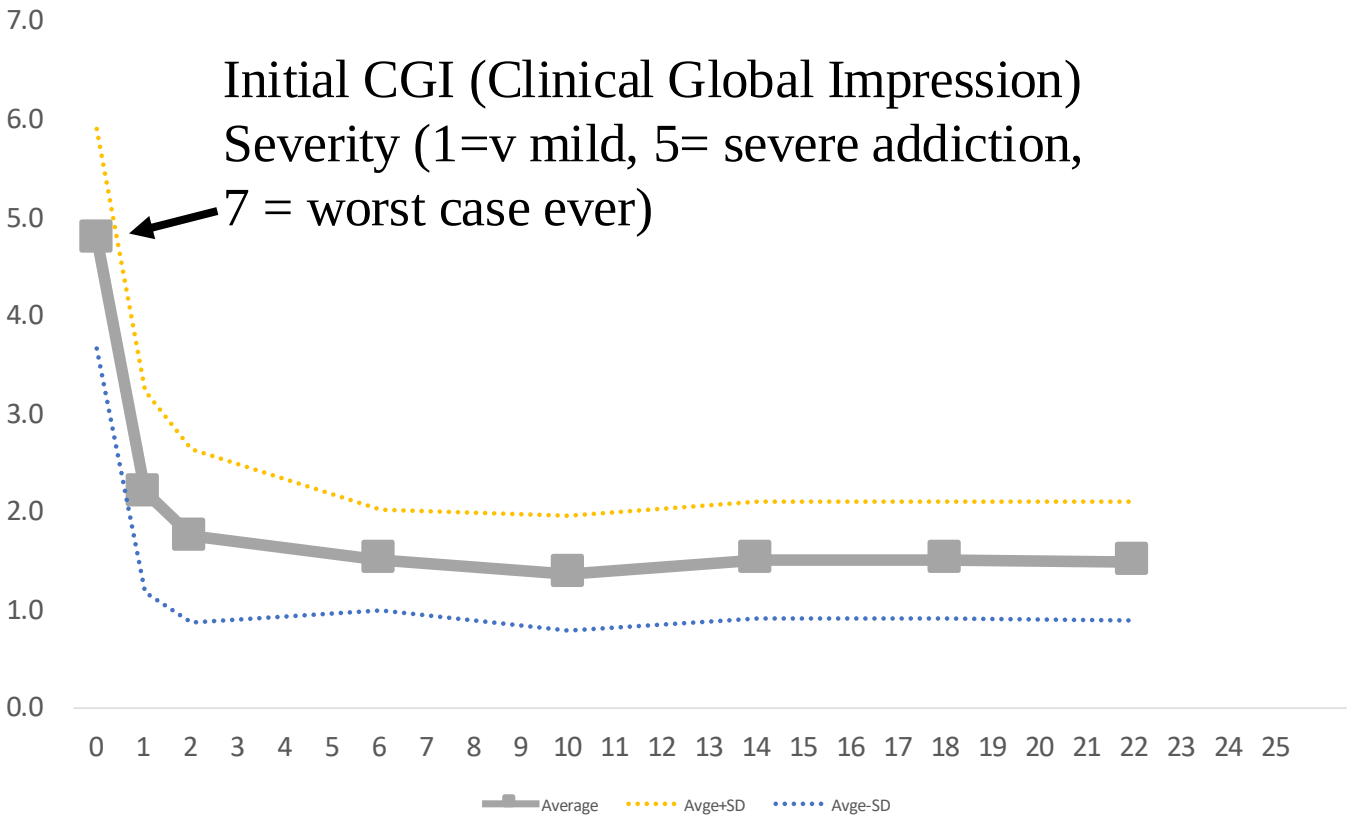
Worse

No Change

Better

Much Better

Very Much Better



Slide kindly provided by Prof Jan Melichar, University of South Wales

What Client’s Say About Buvidal

- I think it is the best one I've been on, even though it’s only been a week. Just think it is a great thing, better than methadone or tablets. I feel like Tony the Tiger GREAT. It means I can just get on with my life
- Love it | It’s a good experience | Never felt better | It’s amazing | It’s brilliant | Brilliant Stuff | Wonder drug | It should be given to everyone | Just got my life back. Feel good
- I’m back to my old self. Heard from a friend how it turned his life around | Everything is positive with this new drug!
- I feel like I'm clean. I think it's a wonder drug for addicts. I think it is the future of drugs for people addicted to opiates

Reducing and Detoxing Off Buvidal

- Stopping it abruptly leads to few opiate withdrawals, based on clinical experience
- As clients feel ‘normal’ they start thinking about coming off
- Clients need to have developed recovery capital first to sustain abstinence once detoxed
  - Personal recovery capital – skills and attributes of client
  - Social recovery capital – social supports and engagement in society
- It is not licenced for detox

Changes in Drug Use on Buvidal

- In an NHS commissioned service keen on detox
- Given if clients not making progress in oral OST (av. 14 months) – using on top or stuck, incl. homeless
- 50% reduced drug use from av. 6 to 2 days/month
- 27% detoxed off Buvidal after av. 8 months, including 7% who used it for a detox (after 2-3 months)
  - 50% considered to have limited potential to change, 50% had potential to change
  - 63% reduced other drug use, 7% increased it
- 10% increased drug use (3% already using other drugs, 7% started other drug use)
- 13% dropped out or went back to oral OST

Adverse Effects in West Dorset Study of Buvidal (N=30)

- Similar to oral buprenorphine
- Stings for 40 seconds after injection, then itches
- May develop palpable lumps at injection site
- Clear headed leading to intrusive thoughts, feelings and memories:
  - 47% said had intrusions (29% a little, 12% quite a bit, 6% a great deal)
  - 35% no intrusions
  - 17% no data
- Clear headed leading to distress:
  - 25% a little
  - 6% quite a bit
  - 6% a great deal
- Preference for Buvidal (over methadone or buprenorphine):
  - 76% preferred Buvidal a lot from after the first dose
  - 6% preferred Buvidal a little throughout
  - 12% no data

Conclusions to Buvidal

- Buvidal is a very promising medication (for opiate maintenance and possibly detox)
- Clients like it – a lot:
  - Feel ‘normal’ on it, because they feel clearheaded and have energy on it
  - Don’t have to visit the pharmacy with its associated impacts daily
- This is despite it:
  - Being a painful injection
  - Being associated with intrusive thoughts, feelings and memories
- Other long acting formulations likely to have similar effects
- Awaiting research results on cost-effectiveness

Long-Acting Formulations of Naltrexone

Four Types of Naltrexone

Tablets (last 1-3 days) Taken daily, but can be taken 3 times weekly (M,W,F) Generic, Nalorex, Adepend, Opizone (licenced in UK 1992, and USA 1984)	**Injectable Depot** (last 3-4 weeks) Intramuscular injection into gluteal muscles Vivitrol (Vivitrex) (Not licenced in UK, but licenced in USA for opiates 2006 and alcohol 2010)
Shorter Acting Implants (last 8-12 weeks) Inserted by surgical procedure under local anaesthesia iGEN, Prodetoxone (NalPlant, Addex and Sherman no longer available) (Not licenced in UK, but prodetoxone licenced in USA and Russia)	**Longer Acting Implants** (last 6-9 months) Inserted by surgical procedure under local anaesthesia GoMedical OLANI, Civil Life (Not licenced in UK – use on named patient basis only)

Once Daily Oral Naltrexone Tablet

- One tablet daily started after opiate, alcohol, stimulant detox, and for opiates when the urine is clear of opiates
- Reduces reinforcement from alcohol and stimulants (used in The Sinclair Method for alcohol)
- Blocks reinforcement from opiates, preventing impulsive relapse for the next 3 days
- Not a cure for addiction: Allows time during the most vulnerable period following detox for essential psychosocial work to be done
- Never use naltrexone on its own – Always combine with psychosocial support & motivational counselling
- Compliance poor unless highly motivated (on average take tablet for 6 weeks)
- Best outcome when naltrexone is given under supervision by a relative or friend & in highly motivated clients

How Naltrexone Works

- An opioid antagonist that blocks opioid receptors:
  - Reduces unwanted cravings by ~50%
  - Blocks reinforcement from taking opioids (also reduces reinforcement from taking alcohol or major stimulants, but higher blood levels needed)
  - Increases sense of self-control over drug and alcohol use – both first use and subsequent use

Naltrexone for opiates acts like a helmet, shield & body armour: It deflects temptations & any wayward impulses

Advantages of Long Acting Naltrexone

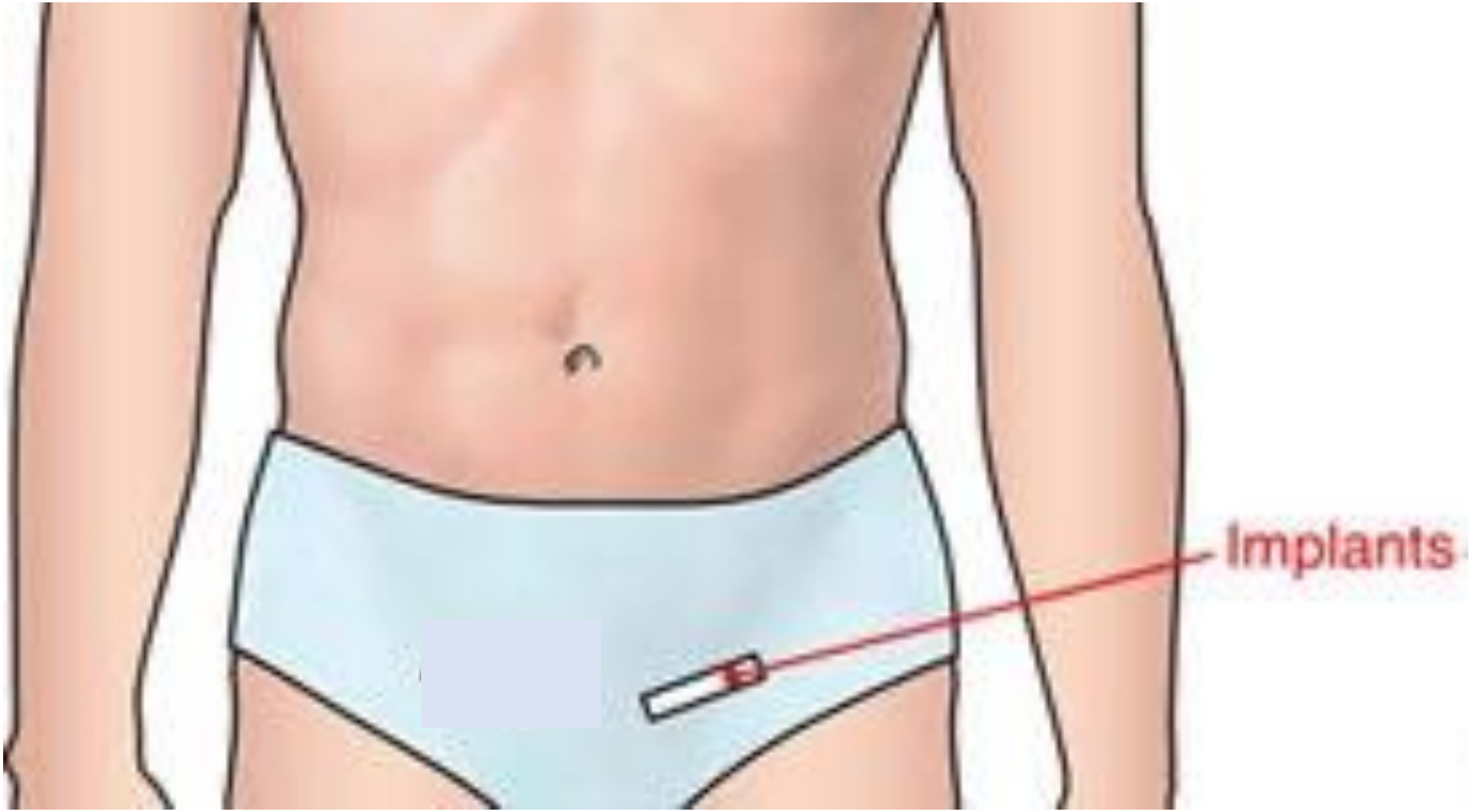
- Enhanced compliance – no need to make a decision every daily about whether to take it or not
- Works with all motivated clients, not just highly motivated ones
- The more longer acting the formulation, the better the compliance:

  9 mthly implant > 3 mthly implant > mthly depot > tablet
- On average clients may need 3 years of naltrexone to sustain abstinence (some fine after one dose)
- Reduced opioid overdose risk on active treatment

Procedure for Naltrexone Implant

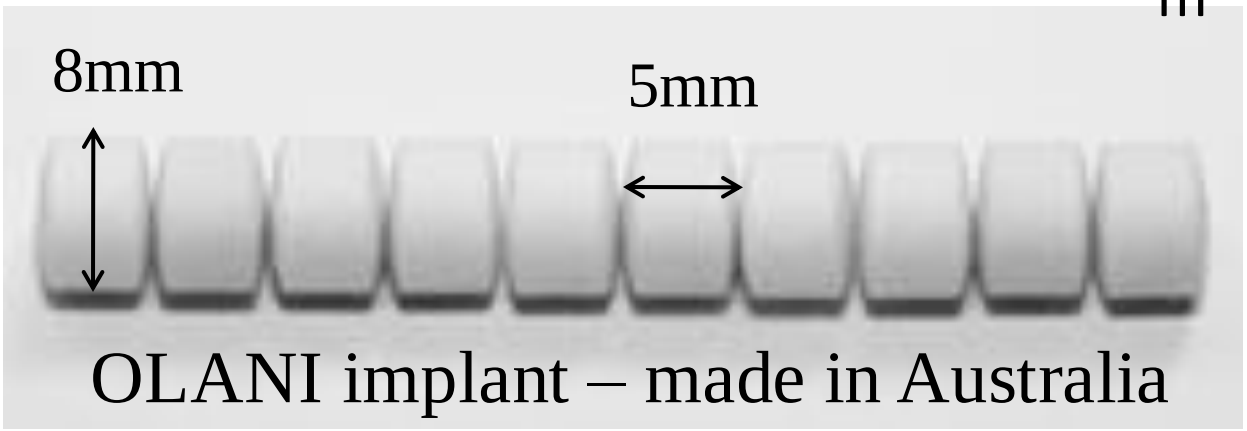
- Confirm wishes to remain abstinent
- Consent and urine screen
- 20-30 min procedure under local anaesthesia
- Insertion in subcutaneous tissue below belt or bikini line
- Antibiotics as prophylaxis
- Incision stitched or glued
- Sterile dressing
- Followed up

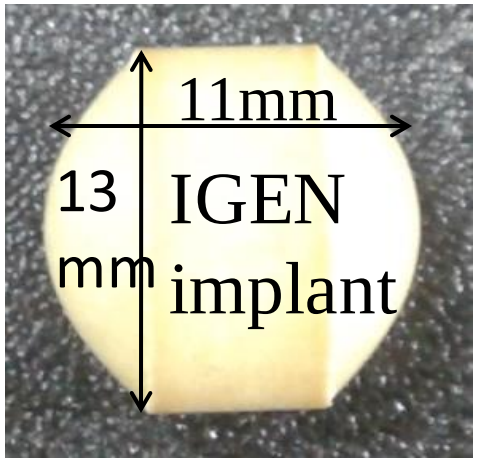
Insertion Site for Naltrexone Implants
(below the belt line in subcutaneous tissue)



Picture kindly supplied by Dr George O'Neil of GoMedical Industries, Perth, Australia

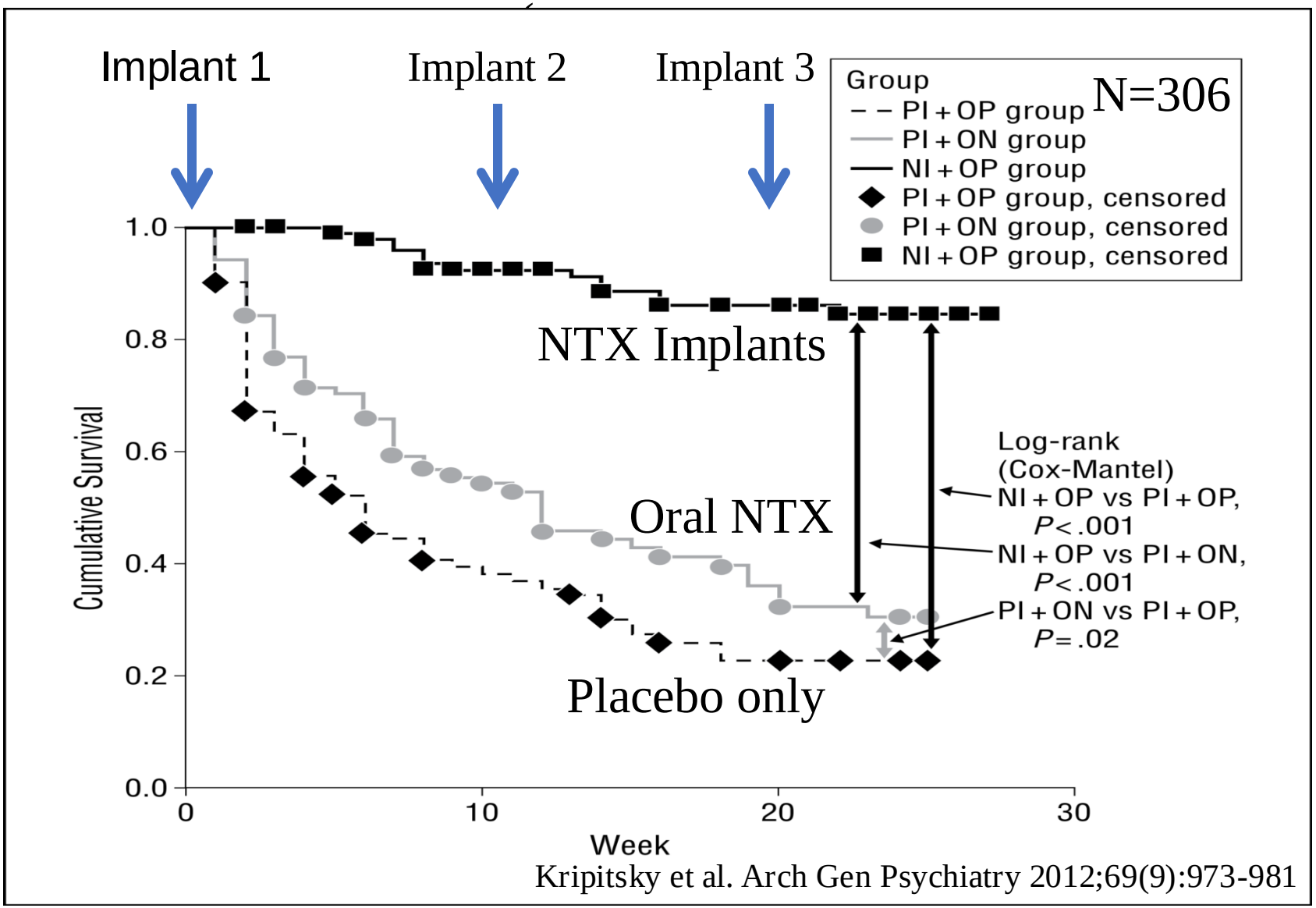
What Naltrexone implants look like (with a typical applicator)





Made in Portugal

DB RCT Placebo vs Oral Naltrexone (NTX) vs 3 Two Month Implants for 6 months (Prodetoxone)



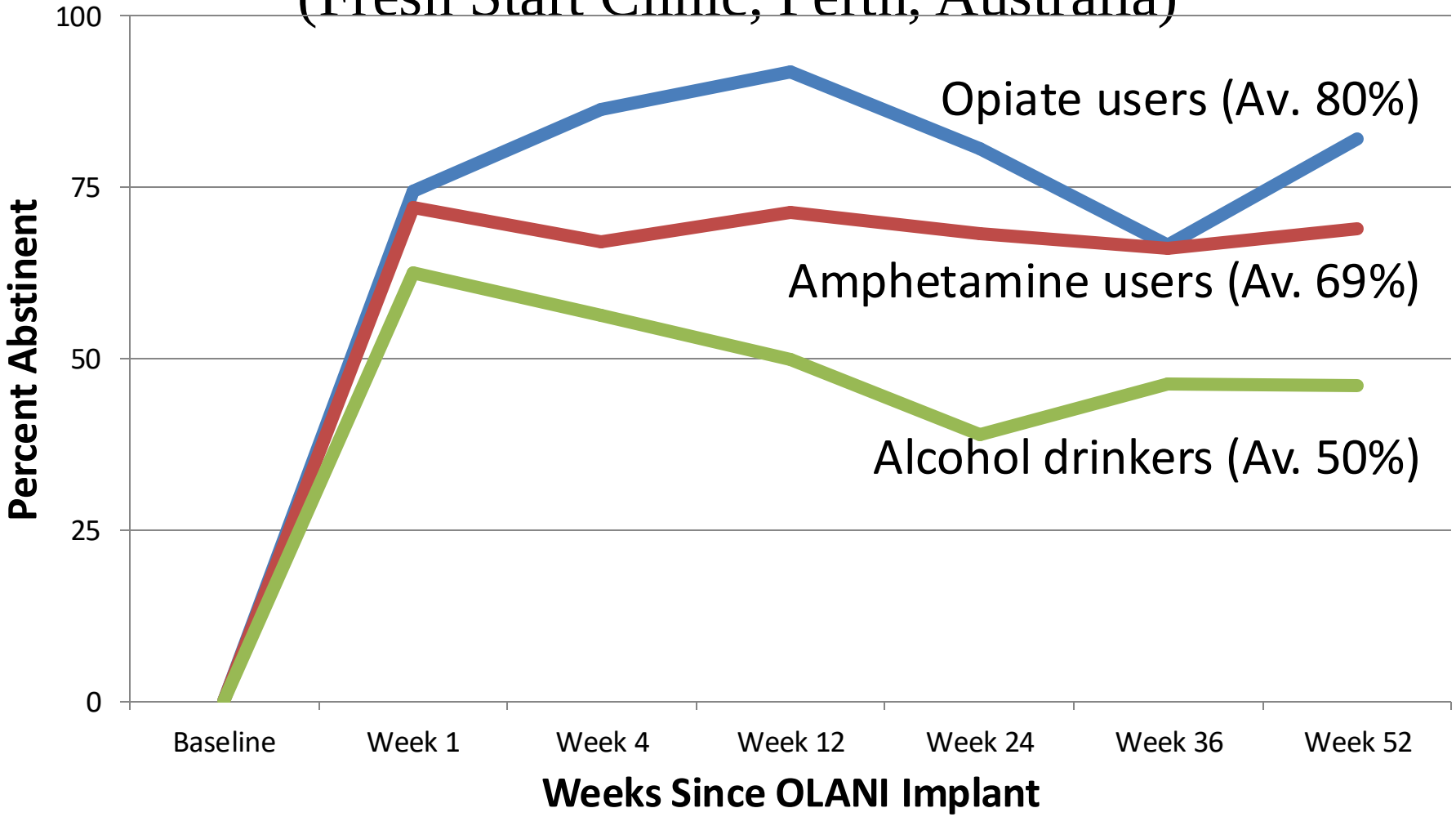
Kripitsky et al. Arch Gen Psychiatry 2012;69(9):973-981

Types of Significant Adverse Events

- Most adverse effects similar to oral naltrexone e.g. nausea, abdo pain, headaches, fatigue
- Self-testing of opioid blockade is normal
- Increased local adverse effects near or at implant insertion site
- Sterile effusions around implant with swelling and itching (treat with oral or injectable steroids)
- Opiate overdose (O/D) risk reduced, but
  - Increased risk of sedative O/D in polydrug users early on in implant treatment
  - Increased risk of opioid O/D as naltrexone wears off

Audit Results of 1 Year Abstinence Rates Following a Single OLANI Implant

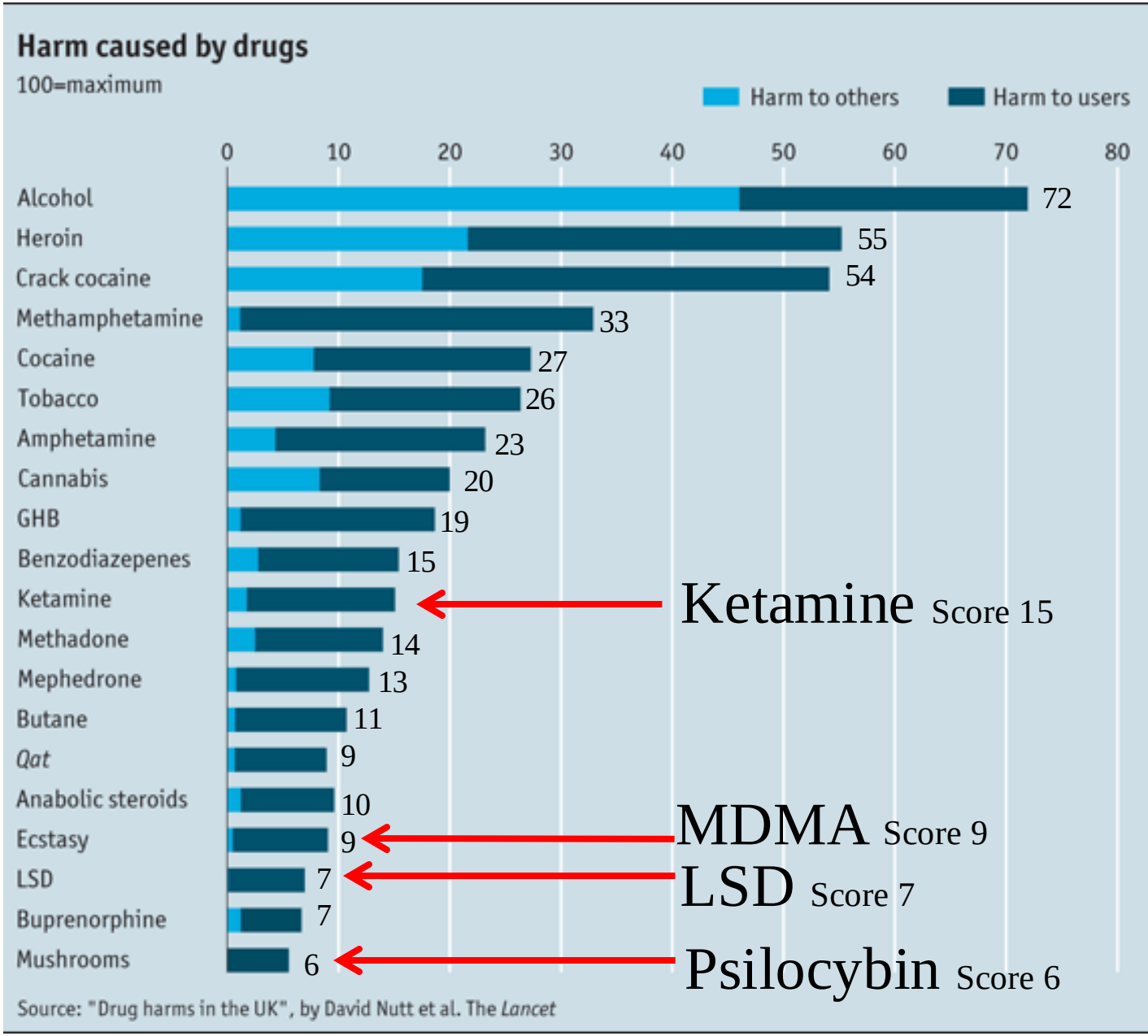
(Fresh Start Clinic, Perth, Australia)



Psychedelics

Thanks to Professor David Nutt for providing some figures and pictures

How harmful are psychedelics compared to alcohol & other drugs in the UK?

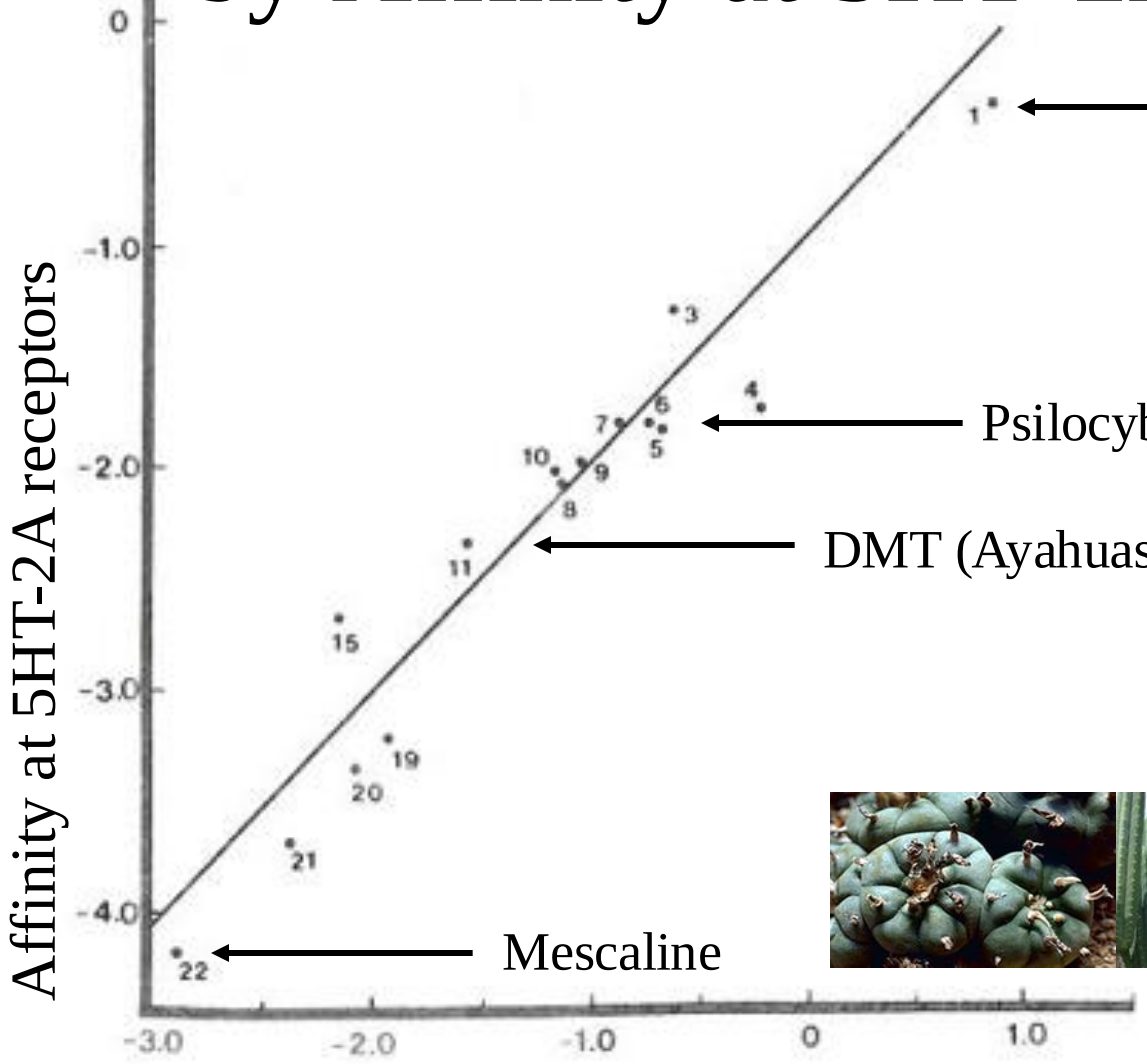


Drug Harms in the UK: A Multicriteria Decision Analysis. Nutt, King and Phillips. Lancet 2010;376(9752):1558-65

Types of Psychedelics

- Classic or serotonergic (5HT-2A) psychedelics:
  - LSD (lysergic acid diethyamide) – synthetised 1938
  - Psilocybin (magic mushrooms)
  - DMT (dimethyltryptamine) or Ayahuasca (plants)
  - 5-MeO or 5-MeO DMT (5-methoxy DMT) or Toad
  - Mescaline (3,4,5 trimethyoxyphenethylamine)
- Psychedelics which act by different mechanisms:
  - Ketamine (dissociative anaesthetic) synthesised 1960's
  - MDMA (ecstasy) – synthesised 1880's, empathogen
  - Ibogaine – acts as a kappa opioid receptor agonist etc

Dose of Classic Hallucinogens Predicted by Affinity at 5HT-2A Receptors



Graph from Glennon et al. 1984. Human dose data from Shulgin 1978. Slide kindly provided by Professor David Nutt

Side-Effects of Short-Term Use of Psychedelics

- Disappointment – if don't have a (life changing) trip
- Bad trip: Fear, anxiety, paranoia, esp if in a bad initial mental state (mental 'set') or environment ('setting')
- Accidental death, e.g. thinking can fly, Matthew Perry
- Suicide: Linked to unsafe setting or pre-existing conditions, but rare as generally it reduces suicidality
- Cardiovascular risks: Raised pulse and BP (MDMA)
- Psychiatric: Fear of worsening psychotic experiences or precipitating it (if a high risk) or a manic episode

The Risks of Psychedelic Therapy

- Addiction risk low, but fear it will result in continued use, but primarily anti-addictive:
  - Classic hallucinogens are anti-addictive, but mild withdrawal effects from DMT, ketamine, MDMA
  - MDMA has low addiction potential
  - Ketamine higher risk, but given only a few times and dose is relatively low
- Ibogaine: Can affect heart rhythm and liver, but lower doses and ibogaine derivatives may be safer
- MDMA: CVA risks (↑ HR/BP, hyperthermia, dehydration, hyponatraemia, serotonin syndrome, autoimmune reaction

Exclusions to Use of Psychedelics

- Pregnancy or breastfeeding, or in next 3 months
- Diagnosed with psychosis, or first degree relative (parent or sibling) of someone who has had psychosis/schizophrenia
- Bipolar disorder – risk of mania
- Heart condition – as increased HR & BP (MDMA)
- Medications that block 5HT-2A receptors (mirtazapine, amitriptyline, risperidone, olanzapine) with serotonergic psychedelics. SSRI's reduces effects, but fine with ketamine

Approved Use of Ketamine and Esketamine nasal spray (Spravato)

- Esketamine nasal spray (Spravato) in combination with a SSRI or SNRI, for treatment resistant major depression. One spray in each nostril, then 2-3 doses twice weekly for weeks 1-4, then weekly for weeks 5-8, then every 1-2 weeks from week 9 for at least 6 months after depressive symptoms improve (marketed by Janssen-Cilag Ltd). Approved by European Union & EEA and USA in 2019, Australia in 2021). Cost £326 for 2 sprays (1 dose). 6 months = £18-27,000.
- Ketamine infusions/lozenges are legal in UK, for use off label for mental health by private clinics as ketamine assisted therapy or ‘guided journeying’

Psychedelics Approved for Medical Use by Specifically Licenced Practitioners

- **Most drugs:** Canada (not ibogaine), Switzerland
- **Ibogaine:** Australia, New Zealand, South Africa, Bahamas, **Not** Canada or USA except Oregon. Mainly for treatment resistant depression
- **MDMA:** Australia, Canada, Israel, **Not** USA. Mainly for treatment resistant PTSD
- **Psilocybin:** Colorado in 2024 (USA)
- **LSD:** Switzerland, Canada
- **DMT** (ayahuasca): Canada
- **Mescaline** (Peyote): Alberta (Canada)

Psychedelics Unregulated or Legal for Personal Use - So Clinics Legal

- **Most drugs:** Portugal, Spain, Czech Republic, Costa Rica, Switzerland, Nepal, British Columbia (Canada), Colorado (USA), **Not** Europe, **Not** The Netherlands
- **Ibogaine** (iboga root): The Netherlands, Germany, Australia, Bahamas, South Africa, Panama, Gabon, Brazil, Costa Rica, Mexico
- **Psilocybin:** The Netherlands (truffles only), Bahamas, Jamacia, Nepal, British Virgin Islands, Nepal, some USA cities (e.g. Washington, DC)
- **DMT** (Ayahuasca): Brazil, Peru, Bahamas
- **5 MeO DMT:** Canada, Bahamas

How Psychedelics are Used Medically

- In a safe and controlled environment
- Combined with therapy, typically with two ‘guides’:
  - To help the subject get the most out of the experience
  - To reduce the possibility of harm, i.e ‘bad trips’
- Guides act as a safe anchor, who actively listen and facilitate the experience:
  - Not there to stop person going into difficult emotional places but to facilitate them to move in and through them
- Letting the subject follow their own insights and self-discovery, rather than intervening

Why Use Therapy with Psychedelics?

- Ketamine with psychotherapy better outcome than ketamine alone (KARE study 2022)
- Guides actively listen and facilitate experience:
  - Actively listen and encourage talking if it important or discourage if they are avoiding tricky areas (as trips can be very intense and frightening)
  - Assist if subjects get stuck in a painful or dark place (which can be frightening if you are alone)
- Counselling (integration) sessions are used to maximise the benefit from the period of brain plasticity (2 days ketamine, 2 weeks MDMA & psilocybin, 3 weeks LSD, 4 weeks ibogaine)

The Stages of Psychedelic Therapy

- Preparation:
  - Develop sense of trust and rapport with the two guides, who are to provide a safe anchor for the client
  - Visualise the experience, like going on a pearl dive, to find the deepest layers of themselves
  - Play soothing, relaxing music (as on the day)
- Trip day and integration sessions:
  - Lie on bed wearing eye shades and headphones
  - Guides sit on either side and actively listen
  - After drug wears off (2½ hrs ketamine, 5-6 hrs ibogaine), talk with therapist through anything that has come up, any pearls they have gathered, and how to take it into life
- Follow-up: Talk several times over the next few weeks

Psychedelics and Bill Wilson

"Suddenly the room lit up with a great white light. I was caught up in an ecstasy which there are no words to describe. It seemed to me in my mind's eye, that I was on a mountain and that a wind not of air but of spirit was blowing. And then it burst upon me that I was a free man..." (Bill W 1934)

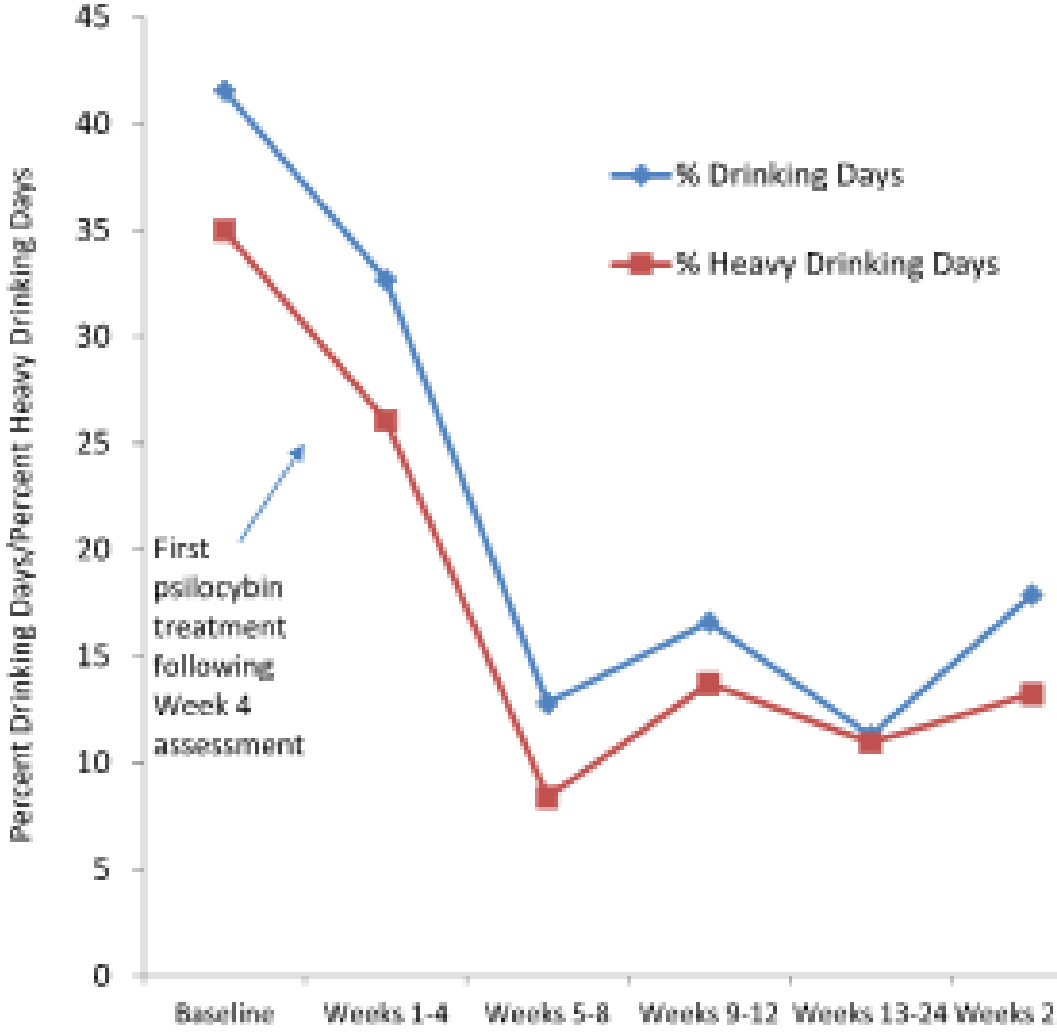
In Bill W's 4th detox, he had Belladonna treatment & never drunk again (it contained the psychedelic scopolamine)

Bill W and LSD (1950's)

- When LSD was legal in 1956, Bill W first took it at the Veteran's Administration Hospital in Los Angeles and later formed an experimental group for LSD sessions (possibly with Aldous Huxley)
- Bill W came to believe that LSD used in a carefully structured controlled way, could help alcoholics recover by connecting them with a higher power (step 2)
- US Govt funded 6 clinical trials of LSD for alcohol, showing high abstinence rates (2012 reanalysis showed 2-3x higher abstinence rate than any other treatment)
- US Govt made LSD illegal in 1967 because of fears it was fuelling anti-war sentiment during Vietnam war

Psilocybin for Alcohol (Open Study)

(N=10 at baseline, N=9 at all other points)



Drinking Days

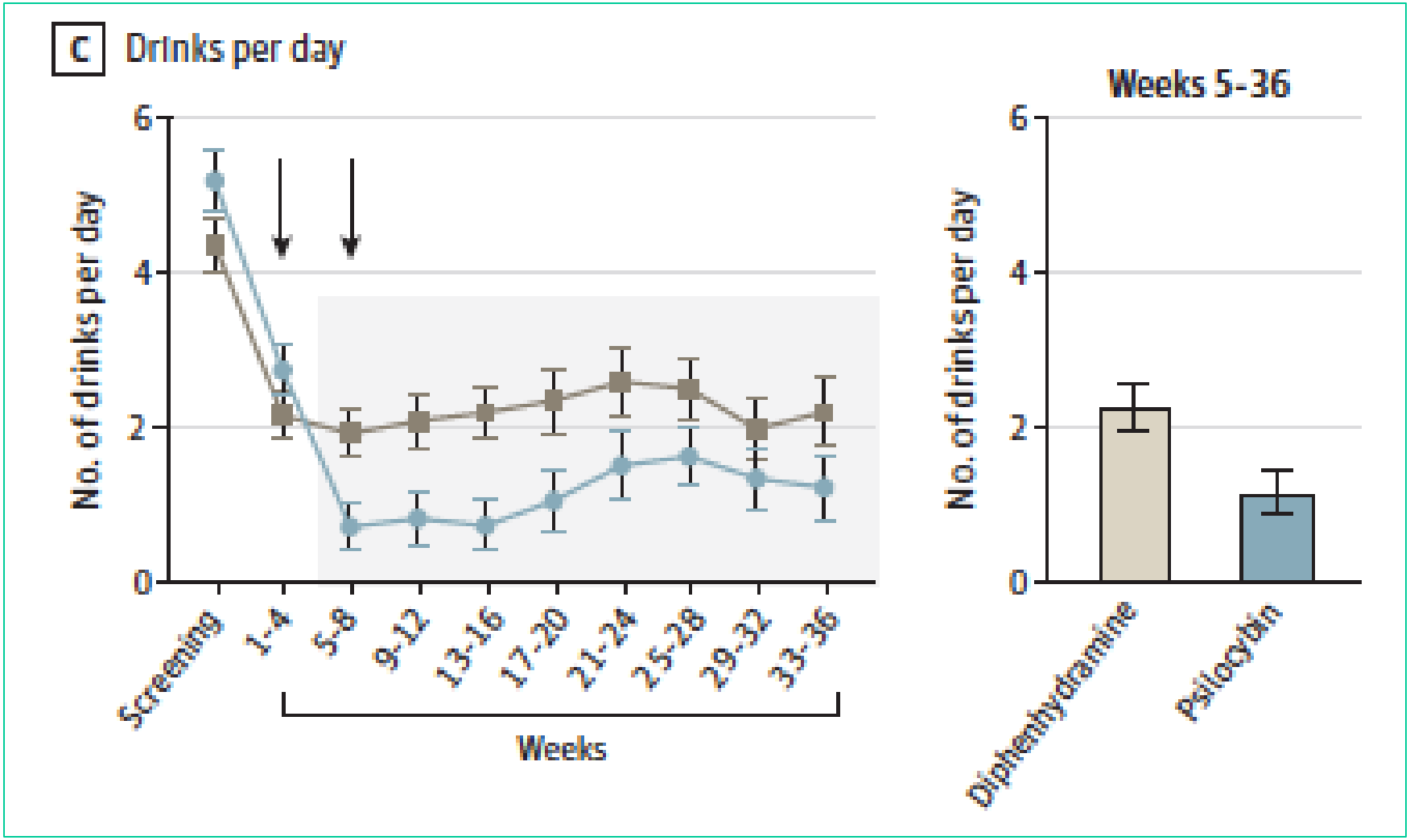
Baseline vs.		
Weeks 1-4	$p = .164$	$d = 0.490$
Weeks 5-8	$p = .009$	$d = 1.194$
Weeks 9-12	$p = .015$	$d = 1.033$
Weeks 13-24	$p = .006$	$d = 1.332$
Weeks 25-36	$p = .007$	$d = 1.187$
Weeks 1-4 vs.		
Weeks 5-8	$p = .016$	$d = 1.109$
Weeks 9-12	$p = .033$	$d = 0.869$
Weeks 13-24	$p = .014$	$d = 1.163$
Weeks 25-36	$p = .013$	$d = 1.036$

Heavy Drinking Days

Baseline vs.		
Weeks 1-4	$p = .158$	$d = 0.492$
Weeks 5-8	$p = .007$	$d = 1.249$
Weeks 9-12	$p = .019$	$d = 0.985$
Weeks 13-24	$p = .010$	$d = 1.161$
Weeks 25-36	$p = .004$	$d = 1.383$
Weeks 1-4 vs.		
Weeks 5-8	$p = .022$	$d = 1.046$
Weeks 9-12	$p = .059$	$d = 0.750$
Weeks 13-24	$p = .038$	$d = 0.876$
Weeks 25-36	$p = .018$	$d = 1.040$

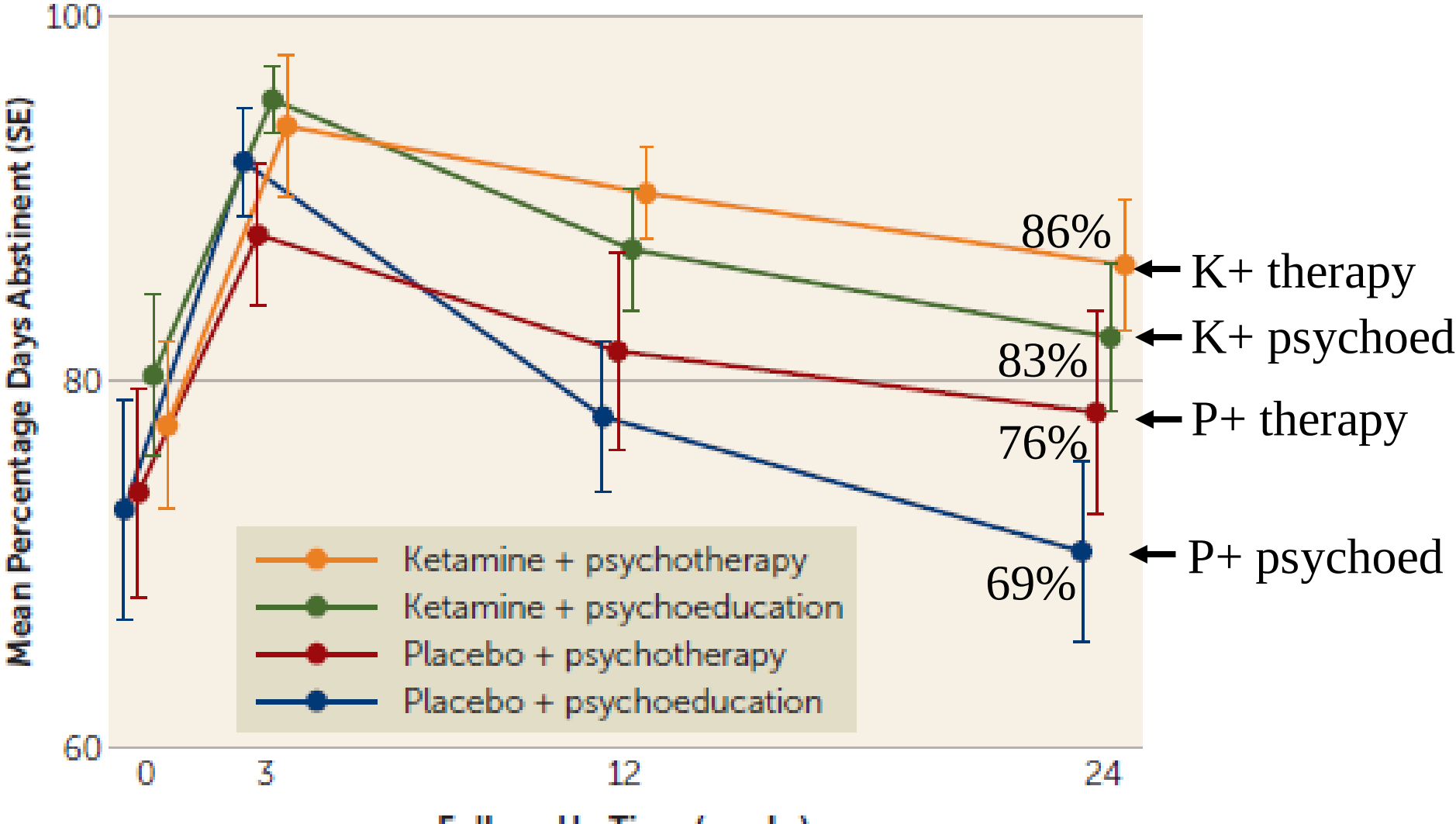
Bogenschutz et al. J of Psychopharmacology 2015 29(3) 289-99

RCT Psilocybin vs Antihistamine for Alcohol (Means ± SE) (N=93)



Bogenschutz et al. JAMA Psychiatry 2022 79(10) 953-62

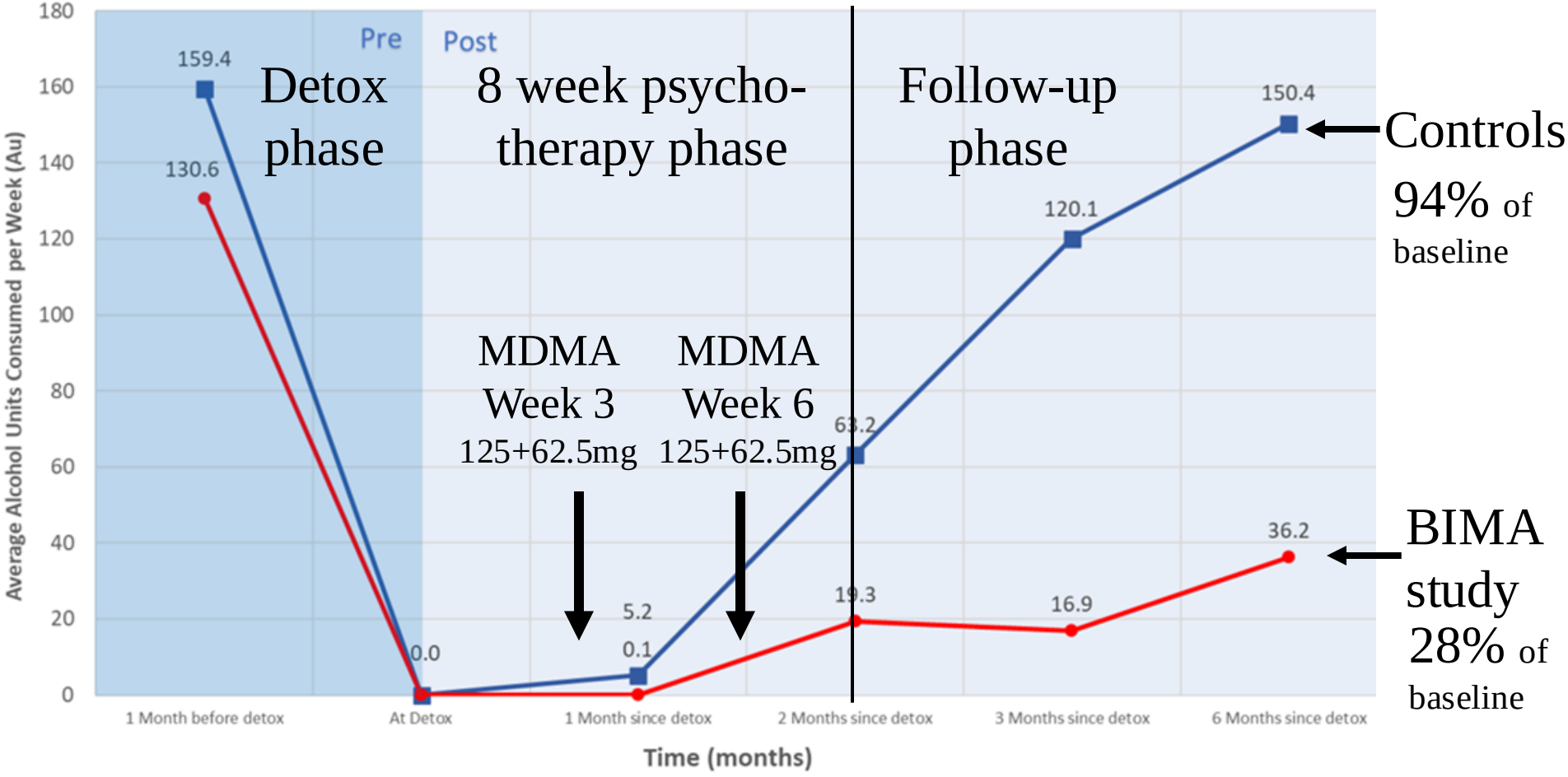
RCT Ketamine for Reduction of Alcohol Relapse (KARE, N=96)



Grabski et al. Am J Psych 2022 179(2) 152-62

MDMA after Alcohol Detox, with 6 Month Follow-up (BIMA open study)

(N=14 in study vs N=12 controls)



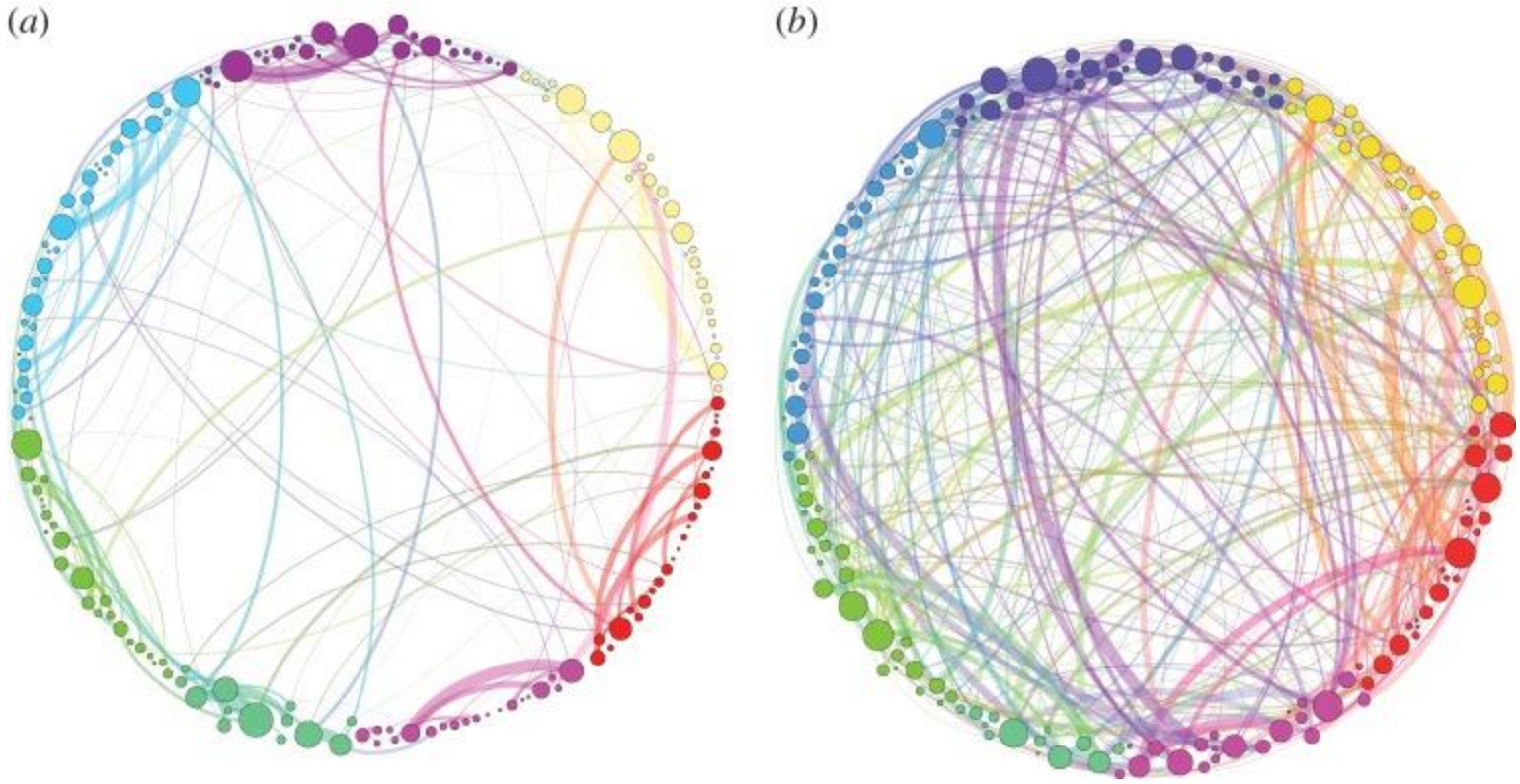
Sessa et al. J of Psychopharmacology 2021 35(4) 375-83

Why do Different Psychedelics Working in Different Ways All Seem to Help?

- Different Effects: Psychedelic trips with classic hallucinogens, dissociative experiences with ketamine, changed state with MDMA
- Helps with ‘internalizing disorders’ where cognitions are self-referential and ruminative - psychedelics increase connections, e.g. addiction, depression, OCD
- More intense experiences resulted in greater gains with classic hallucinogens (psilocybin for alcohol)
- Increased plasticity in brain (neurogenesis), so can lay down new ways of thinking
- Effect enhanced and made longer lasting by therapy

Psychedelics Desynchronise Brain Activity on BOLD fMRI after Psilocybin & Placebo

(functional connectivity between 169 cortical/subcortical regions)



Placebo: 7200 connections mostly around edge – more efficient

Psilocybin: 7200 connections across the network – ‘child’s brain’

Petri G et al. Journal of The Royal Society Interface. 2014 Dec 6;11(101):20140873

Ketamine Assisted Therapy for Addiction Available Privately in UK

- The Ketamine Clinic: IM ketamine for addiction and mental health at Gorleston-on-Sea, Great Yarmouth, Norfolk £4,500 (8 sessions) with therapy for integration https://theketamineclinic.co.uk/
- Silva Wellness: Low cost model with ketamine sublingual lozenges (100-600mg) £3669 (6 sessions) or £2555 (6 group sessions with 4 clients) with 'guided journeying' for integration https://silvawellness.com/
- Awakn clinic (Bristol) & Klearwell clinic (London): Closed £6000 IM Ketamine (4 sessions) closed due to lack of clients. Awakn now focusing on research

Side-Effects of Ketamine

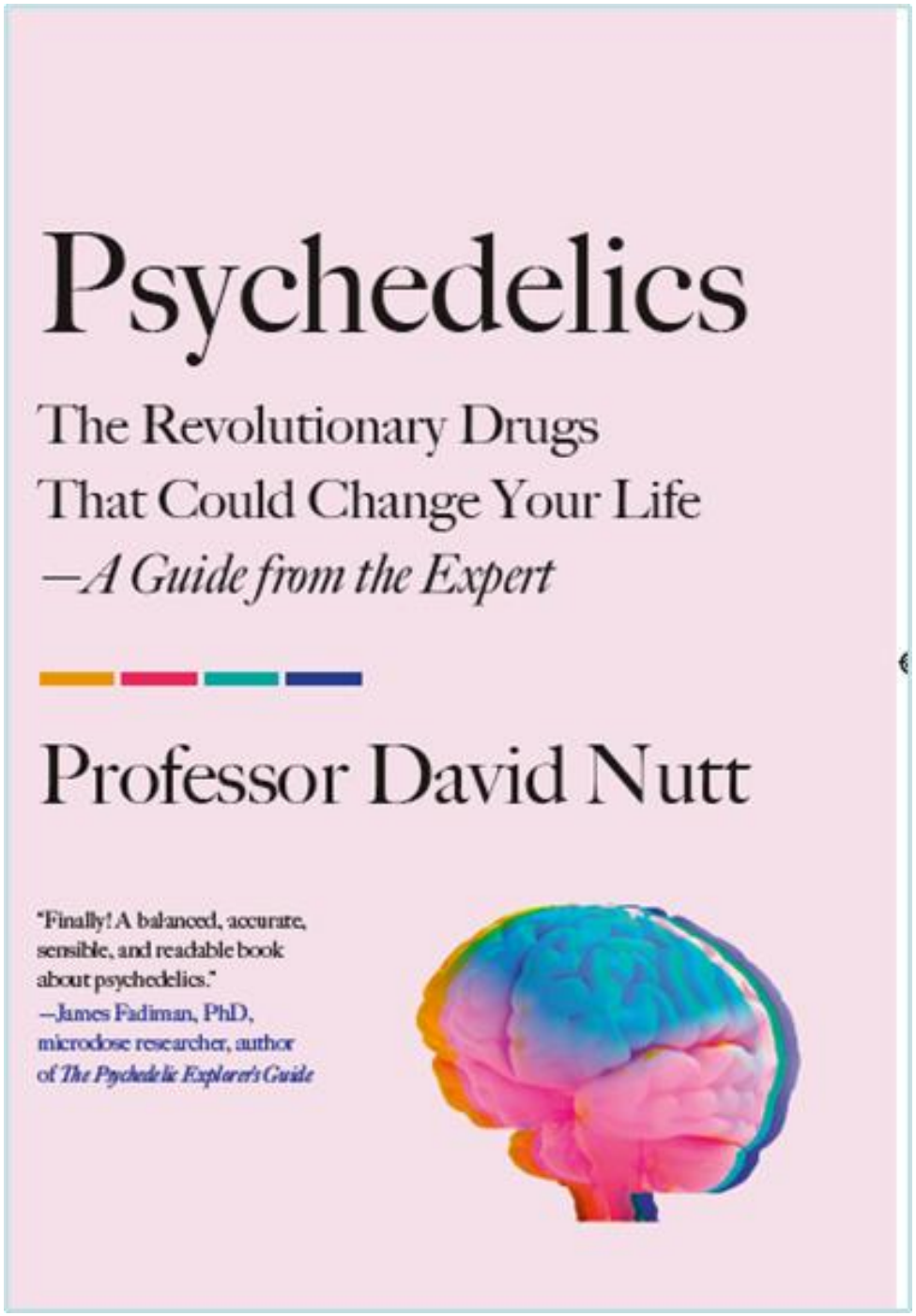
- Bronchodilation with no suppression of gag reflex (swallowing or coughing), so used on battlefields & other trauma situations e.g. major crashes, asthmatics, conscious sedation
- Impaired performance of complex tasks requiring sustained attention & muscle control, so sit in the corner of the room and so are at risk of being robbed or abused
- Withdrawal after longer term use is like coming off stimulants: sleepy, lethargic, low mood for 1-2 weeks

Matthew Perry
1969-2023

- Died aged 54 years
- Death an accident due to the acute effects of ketamine, with drowning, buprenorphine and coronary artery disease

Death of Matthew Perry

- Found unresponsive in his pool at his Los Angeles home on 28 Oct 2023
- Had been receiving ketamine-assisted psychotherapy sessions to treat anxiety
- Long history of addiction and spent $9 million on treatment, 15 stays in rehab, and therapy 2x/week for 30 years, attended ~ 6,000 AA meetings and had 14 stomach surgeries (e.g. for GI perforation from opiates)
- Parents divorced and felt abandoned by both of them
- His personal assistant, two drug dealers and two doctors were charged. He had paid the two doctors $55,000 in cash for ketamine in the last two months



Easy to Read Factual Book by Professor David Nutt with co-author Brigid Moss 2023 (328 pages) £16

Research Studies in Psychedelics that People can Access in the UK

- **MORE-KARE:** Trial of increasing alcohol abstinence with ketamine-assisted psychological therapy in severe alcohol use disorder, with 3 x IV ketamine, 7 psychological sessions, 12 month follow-up https://sites.exeter.ac.uk/morekare/
- **Clerkenwell Health:** No trials currently in addiction, but psilocybin and 5-MeO DMT for treatment resistant depression, methylone (MDMC, similar to MDMA) for PTSD https://www.clerkenwellhealth.com/patients
- **Oxford University:** Ketamine clinic for treatment resistant depression led by Prof Rupert McShane, 4-8 IV doses given by anaesthetist 2-4 weeks apart

Conclusions

- We live in interesting times, with many new techniques showing promise for specific aspects of addiction
- But:

"There is no treatment strategy
- not even a psychedelic –
that is a miracle cure for addiction"