

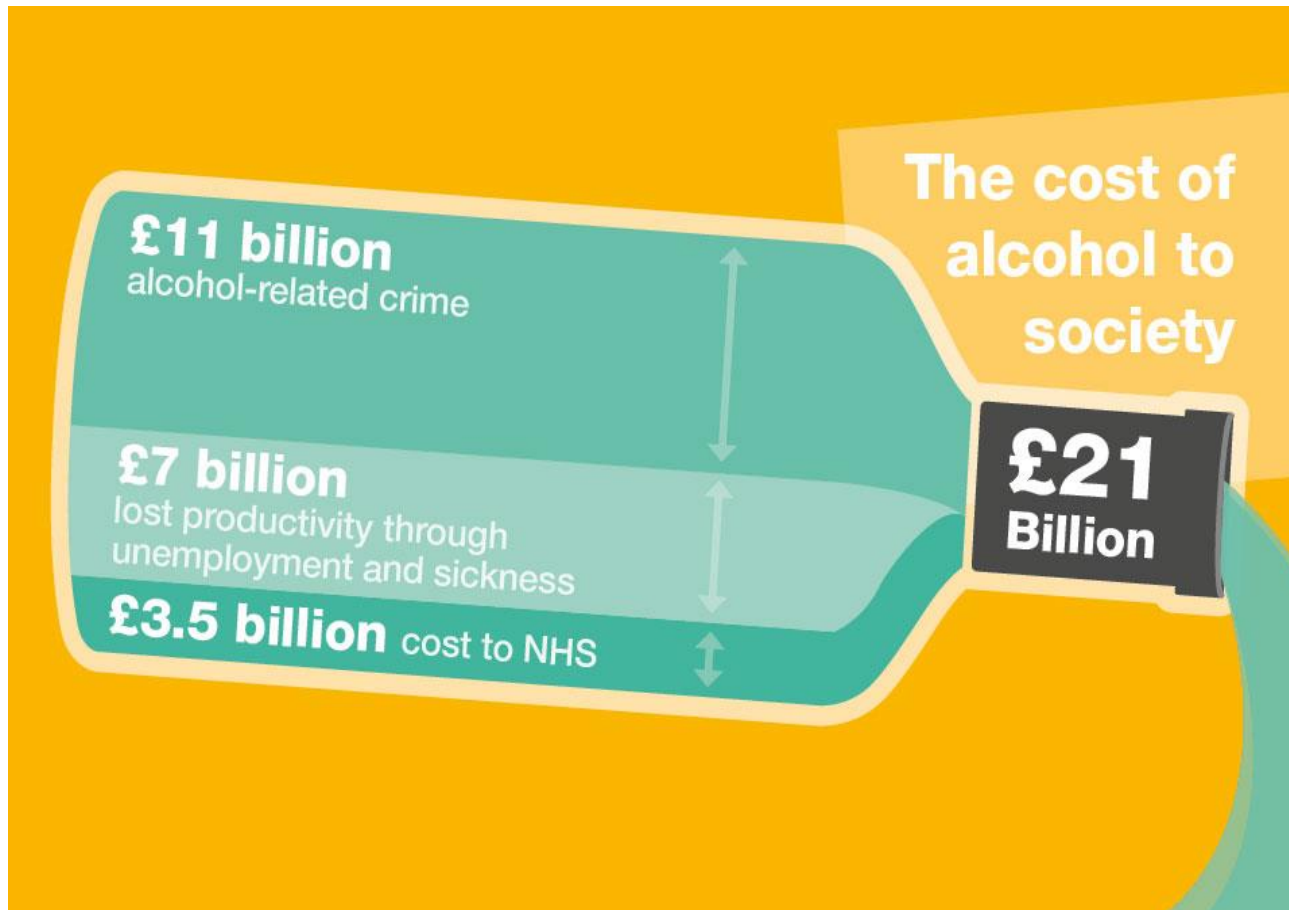
Ketamine: a new treatment for alcohol use disorder?

Professor Celia Morgan
University of Exeter, UK



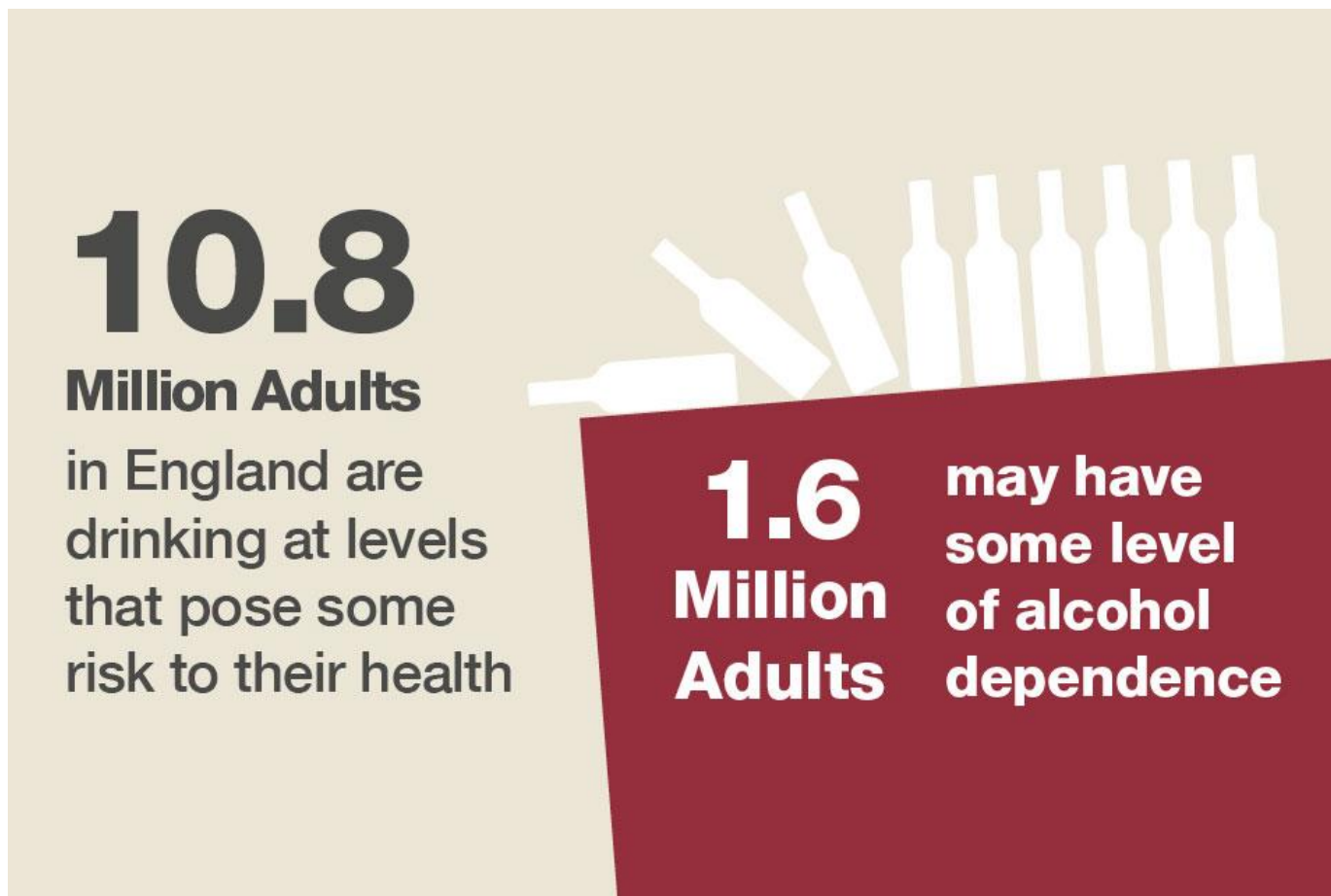


Alcohol use in the UK





Alcohol use in the UK





Alcohol treatments

Alcohol is associated with a wide range of health and social harms

Investment in alcohol interventions, including specialist alcohol treatment can produce a high return

For every 100 alcohol-dependent people treated, at a cost of £40,000:

Save:

£60,000

Prevent:

18 A&E visits

22 Hospital admissions



Treatments

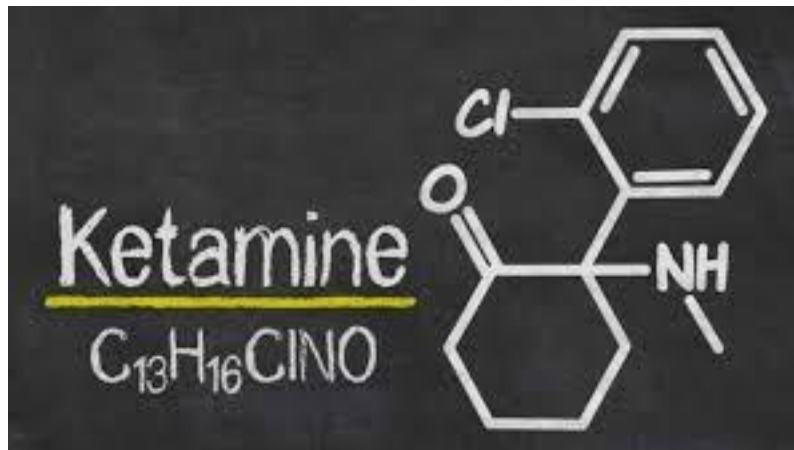
- Current therapies have relapse rates of around 50% at 3 months and 70% at 12 months
- So there is a clear need for more effective treatments...





What is ketamine?

- Synthesised as anaesthetic





What is ketamine?

- Veterinary anaesthesia
- Chronic pain
- Paediatrics
- Field medicine, developing countries
- Excellent safety profile e.g. does not affect cardiac or respiratory function





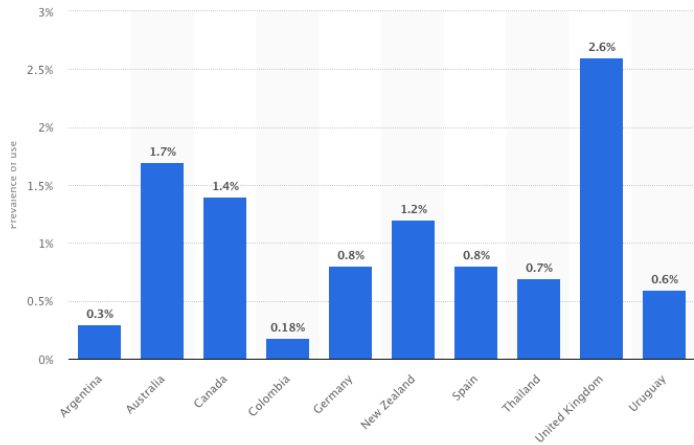
Ketamine is still an important medicine

- World Health Organisation (WHO) Essential Medicines List since 1985
- ‘for sedation of both children and adults ... perhaps the most widely used agent in the world’ (WHO, 2014).



Non-medical ketamine use

Life-time prevalence of ketamine use in selected countries as of 2015



UK :

- 2001 ketamine use 25% up to 70% 2010 (nightclub goers)
- Class C substance in 2006
- After which use went up and quality down (Muetzelfedt et al. 2008)...





What do you like about taking ketamine?

- “I love the ego dissolution, my consciousness becomes intertwined with divine entities and all semblance of the physical realm disappears.”



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- “The numbness and detachment and the enhancement of music. Combined with E it is warm and glowy”
- “It is cheap and it gets me really off my head”



Subjective experiences

DOSE

- Stimulant
- Distorted perceptions e.g. feeling "as big as the universe" or "as small as an electron"
- Sense of melting into people or things
- Visions and hallucinations
- Spiritual and out of body experiences
- K-hole – experiencing intense hallucinations, completely dissociated from reality





How is ketamine a potentially useful treatment in addiction?



Earliest reported work using ketamine

Salvador Roquet
Mexico 1967-1974

“Psicosintesis”

Engineered bad trips to
produce intense experiences

Imprisoned – charges
eventually dropped.





Previous work in addiction

Ketamine Psychedelic Therapy (KPT): A Review of the Results of Ten Years of Research

E.M. Krupitsky, M.D., Ph.D.* & A.Y. Grinenko, M.D., Ph.D.*

Abstract—Ketamine is a prescription drug used for general anesthesia. In subanesthetic doses, it induces profound psychedelic experiences and hallucinations. The subanesthetic effect of ketamine was the hypothesized therapeutic mechanism in the authors' use of ketamine-assisted psychotherapy for alcoholism. The results of a controlled clinical trial demonstrated a considerable increase in efficacy of the authors' standard alcoholism treatment when supplemented by ketamine psychedelic therapy (KPT). Total abstinence for more than one year was observed in 73 out of 111 (65.8%) alcoholic patients in the KPT group, compared to 24% (24 out of 100 patients) of the conventional treatment control group ($p < 0.01$). The authors' studies of the underlying psychological mechanisms of KPT have indicated that ketamine-assisted psychedelic therapy of alcoholic patients induces a harmonization of the Minnesota Multiphasic Personality Inventory (MMPI) personality profile, positive transformation of nonverbalized (mostly unconscious) self-concept and emotional attitudes to various aspects of self and other people, positive changes in life values and purposes, important insights into the meaning of life and an increase in the level of spiritual development. Most importantly, these psychological changes were shown to favor a sober lifestyle. The data from biochemical investigations showed that the pharmacological action of KPT affects both monoaminergic and opioidergic neurotransmitter metabolism, i.e., those neurochemical systems which are involved in the pathogenesis of alcohol dependence. The data from EEG computer-assisted analysis demonstrated that ketamine increases theta activity in cerebrocortical regions of alcoholic patients. This is evidence of the reinforcement of limbic cortex interaction during the KPT session.

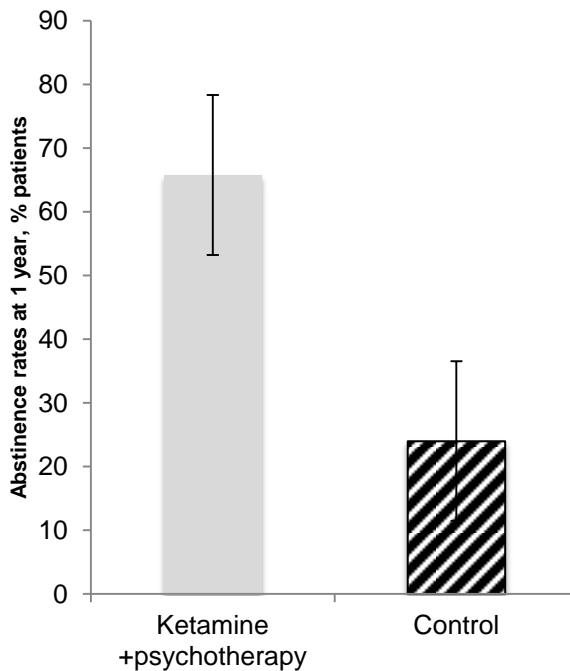
Keywords—alcoholism, hallucinogen, ketamine, psychedelics, psychotherapy, Russia





Previous work in addiction

- Studied in Russia in the 80s and 90s.



- 3 infusions: 2.5 mg/kg IM and psychotherapy (n=111) compared to control (n=100).
- 73 out of 111 (65.8%) alcoholic patients in the KPT group, compared to 24% (24 out of 100 patients) abstinent at 12 months
- Not randomised, placebo controlled or blind.



Ketamine and severe alcohol use disorder

- Aimed to replicate Krupitsky's work but not research study
- Case reports
- High dose 2.0 mg/kg IM



Ketamine and severe alcohol use disorder

First, my mind was pulled out of my body and was thrown into a void. Then, my mind started dissolving into the void and soon nothing was left except my soul. I continued alone, existing in an infinite but empty black space. I realized I had died and immediately my entire alcoholic life started flashing before me. I relived all the dismay of my life as a drunkard and remorsefully witnessed waking up in my own puke, suffering from repeated hangovers, continually hurting my body, stupidly destroying my precious mind. ...



Ketamine and severe alcohol use disorder

My body dissolved and I became a tiny bubble of living energy floating away into the darkness of the land of the dead... I collided with another bubble that was very gloomy and recognized my dead step-father.... I became conscious how tormented his soul was and, for the first time, I was able to forgive him abusing me.... Instantaneously, I moved from the darkness into the luminous white light and became one with God. I felt profound peace and became filled with unconditional love. This experience seemed to last an eternity and, for the first time in many years, I became joyful and hopeful again.



Ketamine and severe alcohol use disorder

- Kolp reported good effects in his case studies but uncontrolled research



Ketamine treatment for severe alcohol use disorder

Mechanisms?



Ketamine treatment for severe alcohol use disorder

Mechanisms?

- Reduction in depressive symptoms
- Boosting neurogenesis & synaptogenesis
- Enhancing psychological therapies
- Mystical experiences



Ketamine treatment for severe alcohol use disorder

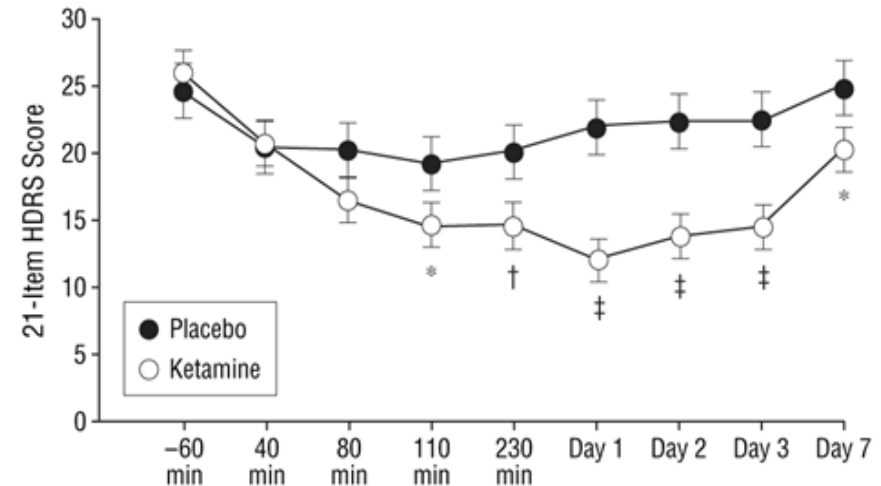
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Ketamine and depression

- 17 treatment-resistant patients with MDD
- 71% greater than 50% reduction in depressive symptoms within 24 hours of ketamine administration
- 30% sustained for a week
- Meta-analyses (e.g. McGirr et al., 2014)

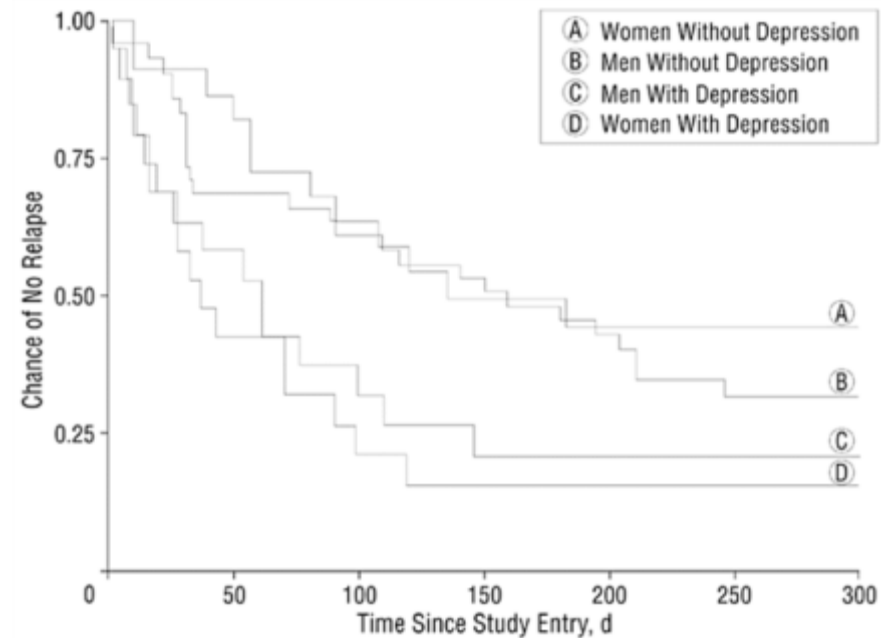


Zarate et al (2006) :
JAMA Psych



Ketamine and depression

- Depressive symptoms predictive of relapse in alcohol use disorder
- Targeting symptoms in risky window following detox?



Greenfield et al., 1998



Ketamine treatment for severe alcohol use disorder

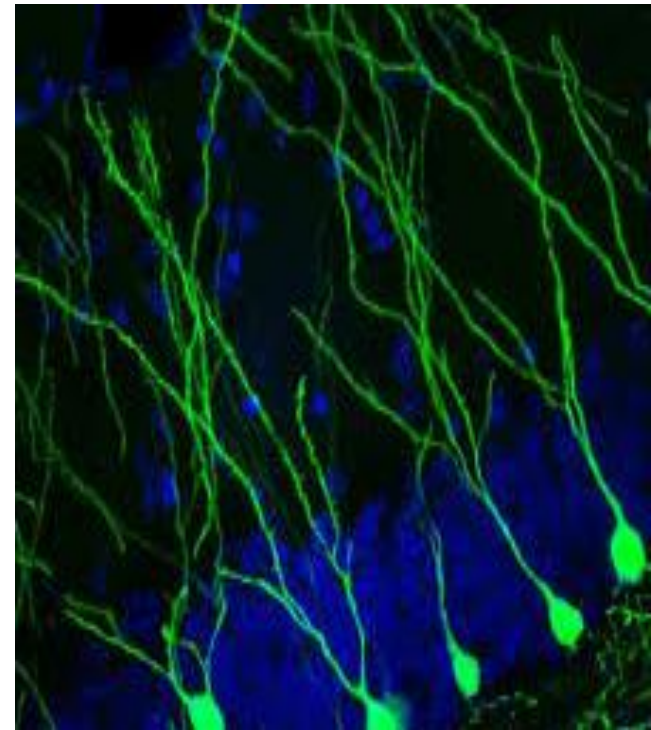
Mechanisms?

- Reduction in depressive symptoms
- Boosting neurogenesis & synaptogenesis
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Ketamine and neurogenesis

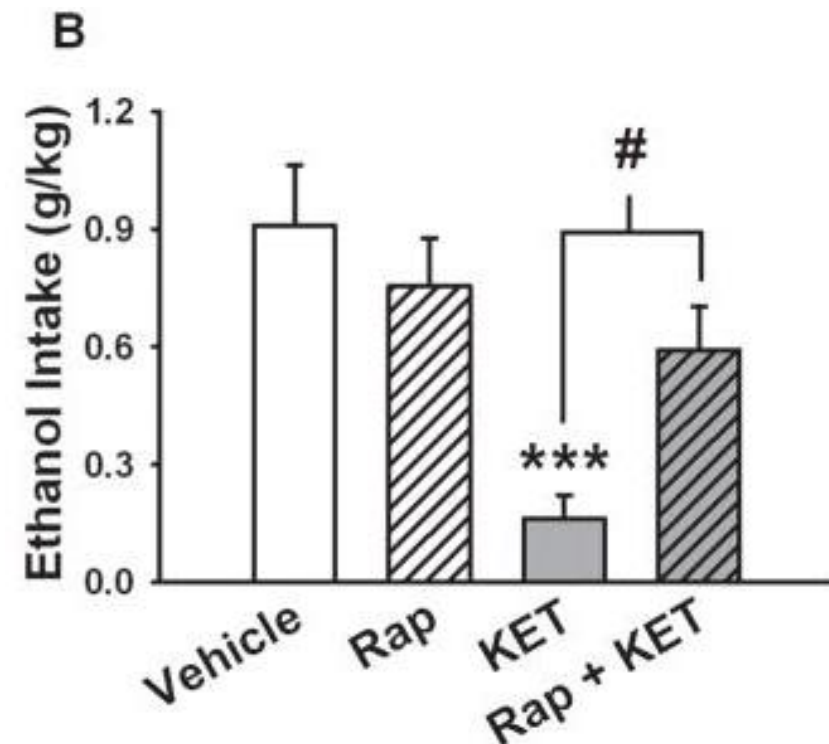
- Birth of new neurons in hippocampus
- Ketamine stimulates neurogenesis (rats) and release of BDNF (humans)
- Neurogenesis crucial for antidepressant effect (Duman & Monteggia 2013)
- Neurogenesis impaired in with prolonged alcohol use (eg Chambers, 2013; Koob & Mandyam, 2013) recovers following detox (Sonmez et al., 2016)





Ketamine and synaptogenesis

- Growth of new synapses
- Ketamine reduces ethanol consumption in alcohol preferring rats
- Blocking synaptogenesis inhibits the antidepressant and anti-alcohol effects of ketamine (Li et al., 2011; Sabino et al., 2013)





Ketamine treatment for severe alcohol use disorder

Mechanisms?

- Reduction in depressive symptoms
- Boosting neurogenesis & synaptogenesis
- **Enhancing psychological therapies**
- Mystical experiences



Ketamine enhances psychological therapy

- Neurogenesis and synaptogenesis mean more plasticity in brain, easier to learn, make new connections (literally)
- Allows to take a different perspective on your own life





Ketamine treatment for severe alcohol use disorder

Mechanisms?

- Reduction in depressive symptoms
- Boosting neurogenesis & synaptogenesis
- Enhancing psychological therapies
- **Mystical experiences**



Mystical experiences

- Krupitsky: related to insight and impact from KPT -negative
- Mystical experiences, not dissociative effects, mediate ketamine's increase motivation to quit 24 h after the infusion in cocaine addicts (Dakwar et al. 2014).
- BUT metabolites exert effects without the psychotomimetic effects (Zanos et al. 2016)





Ketamine and severe alcohol use disorder

- Emerging evidence from anecdotal, case reports and preliminary research of effectiveness in alcohol use disorder
- Mechanism of action, through reduction of depressive symptoms and enhancing uptake of psych therapies.
- Need for high quality controlled research studies





Ketamine for reduction of Alcoholic RELapse



- Examine whether ketamine is effective (with and/or without therapy) in promoting and prolonging abstinence in patients with alcohol use disorder following detox.
- Multi-site: Exeter and London.
- 96 patients



Ketamine plus
relapse
prevention
based CBT

Ketamine plus
education

Placebo plus
relapse
prevention
based CBT

Placebo plus
education



- Examine whether ketamine is effective (with and/or without therapy) in promoting and prolonging abstinence in patients with alcohol use disorder following detox.
- Multi-site: Exeter and London.
- 96 patients **currently 31**



Ketamine plus
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Exclusion criteria

- Currently taking relapse prevention medication
- Currently taking antidepressants
- History of psychosis or in a 1st degree family member
- Comorbid DSM psychiatric disorder (excluding depression)
- Previous or current diagnosis of other substance use disorder
- Liver function >3 x normal
- Hypertension
- BMI outside healthy limits
- Currently taking medications contraindicated with ketamine
- Suicidal ideation
- >10 detoxifications from alcohol
- Pregnant or breastfeeding
- Willing to wear SCRAM-X bracelet



The SCRAM-X bracelet

- Measures alcohol content in sweat.
- Takes a reading every 30 mins
- Wear for ~ 8 weeks





What the patient does

Speak on the phone	Visit 1 (screening)	Visit 2 (baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 (3 month follow up)	Visit 10 (6 month follow up)
...	Day -14 to Day 0	Day 0	Day 1	Day 7	Day 8	Day 14	Day 15	Day 21	Week 12	Week 24
Eligibility questions	Consent, eligibility, bracelet	T/E + K/P	T/E	T/E + K/P	T/E	T/E + K/P	T/E	T/E		

T/E = therapy/education; K/P = ketamine/placebo

Doing questionnaires and cognitive tasks throughout.



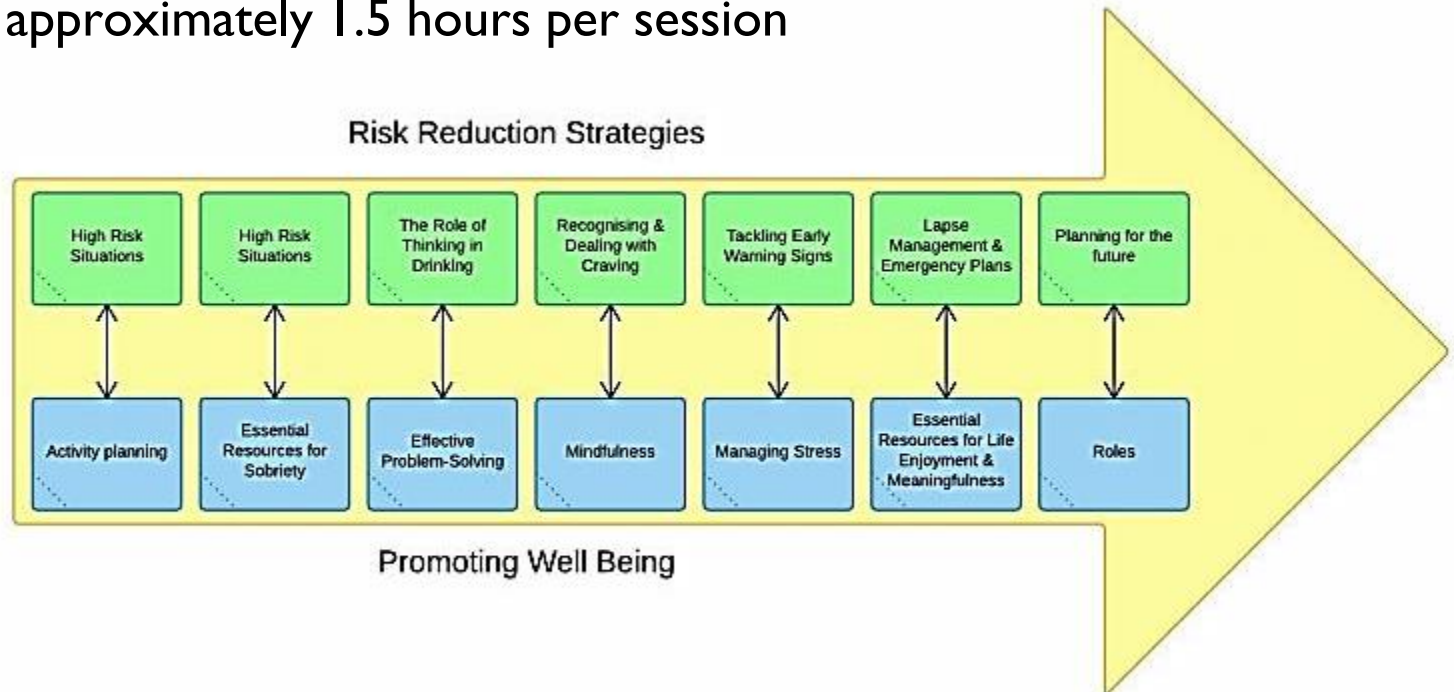
KARE trial – drug dose

- 0.8 mg/kg IV over 40min
 - Smaller dose than Krupitsky work, minimise adverse effects, use anti-depressant properties
 - Higher than anti-depressant dose, evidence of cross-tolerance ket and alcohol (Petrakis et al., 2009)



Relapse prevention therapy

- Relapse prevention model:
 - Risk reduction strategies (e.g. identify high risk situations, coping with cravings, restructuring unhelpful thinking).
 - Promoting wellbeing (e.g. planning weeks, problem-solving, relaxation and mindfulness).
- 7 sessions approximately 1.5 hours per session





Outcomes

Primary

- Relapse rates at 6 months (TLFB)
- Percentage Days Abstinent at 3 and 6 months (TLFB / SCRAM-X)

Secondary

- Depression (Beck Depression Inventory; Hamilton Depression Scale)
- Anxiety (Speilberger Trait Anxiety Inventory)
- Quality of Life (SF-12)
- Working Memory (N-back; Prose Recall)
- Hippocampal Functioning (Pattern Recognition Test)
- BDNF, mTOR
- Response Inhibition (Stop Signal) and Delay Discounting
- Craving



KARE trial

- 31 patients
- 1 lost to follow up
- 1 discontinued through treatment non-tolerability
- Double blind





KARE trial

- Findings Dec 2019





A cautionary tale: Use of repeated ketamine in depression

- Initial findings of small studies
- Explosion in off-label prescribing
- > 100 private clinics offering ketamine for depression in US
- Absence of Phase III trials



Ethical considerations – relevant use of ketamine (and psychedelics) in addiction treatment

Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight



Ilina Singh, Celia Morgan, Valerie Curran, David Nutt, Anne Schlag, Rupert McShane

We present a review and analysis of the ethical considerations in off-label ketamine use for severe, treatment-resistant depression. The analysis of ethical considerations is contextualised in an overview of the evidence for ketamine use in depression, and a review of the drug's safety profile. We find that, based on current evidence, ketamine use for severe, treatment-resistant depression does not violate ethical principles; however, clinicians and professional bodies must take steps to ensure that guidelines for good practice are enacted, that all experimental and trial data are made available through national registries, and that the risk potential of ketamine treatment continues to be monitored and modelled. We conclude with a set of key recommendations for oversight bodies that would support safe, effective, and ethical use of ketamine in depression.

Lancet Psychiatry

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Department of Psychiatry
Oxford Health Care



Ethical considerations – relevant use of ketamine (and psychedelics) in addiction treatment

Panel 1: Six principles of responsible research in novel neurotechnologies³⁶

- Clearly identified need
- Securing safety and efficacy
- Generating robust evidence
- Continuous reflexive evaluation
- Coordinated interdisciplinary action
- Effective and proportionate oversight

UK Nuffield Council on Bioethics
Novel Neurotechnologies Report
(2016)



Recommendations for researchers and clinicians

Panel 2: Three virtues of importance in the context of novel neurotechnologies³⁶

- Inventiveness: expressed through technological innovation and by identifying ways to provide widened access to therapies
- Humility: acknowledging the limits of current knowledge and ability to use technologies to alleviate the harms of brain disorders
- Responsibility: shown by robust research and clinical practices, and by avoiding hype in communication about their potential uses

UK Nuffield Council on Bioethics
Novel Neurotechnologies Report
(2016)



Recommendations for professional bodies

- Development and maintenance of national registries to share trial information, safety and efficacy data; link up of national registries through an international network
- Publication of guidelines on use and recommendations about any governance procedures
- Support for research to investigate the therapeutic and misuse potential, and to model the effects of diverse risk management, pathways for patient need, medical use, and societal harms



Summary

- Preliminary evidence of efficacy of ketamine in alcohol use disorder
- Phase II trial underway currently to investigate
- Climate has changed for ketamine and changing for psychedelic drugs
- Use ethical principles to guide how we present these chemicals to patients and wider public
- Develop professional guidelines and oversight of practice



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Ilina Singh, Rupert McShane





Thank you!



Ketamine and severe alcohol use disorder

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Alcohol treatments

150,640

Number of people in England receiving specialist treatment for alcohol dependence in 2014-15



Average waiting time for service users seeking help for alcohol dependence



60%

for problematic drinking only



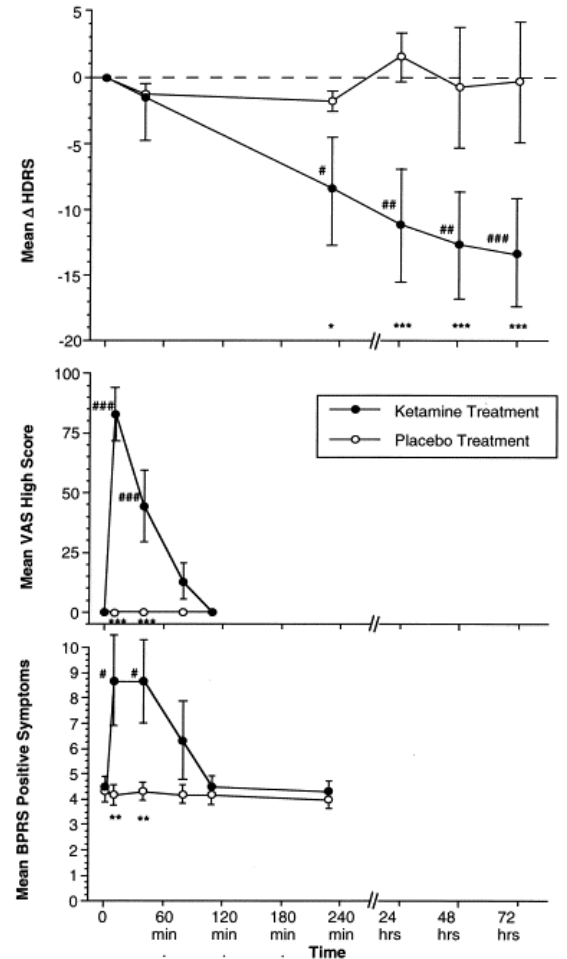
40%

for alcohol alongside other substances



Ketamine and depression

- Berman et. al. (2000)
- Reduction in 7 subjects with depressive symptoms within 72 hours after ketamine (0.5mg/kg) but not placebo infusion



Berman et. al. (2000), Biological Psychiatry



Relevance for psychedelic research?

Key interests

We identified five key interests that must be considered in relation to novel neurotechnologies:

- Protection of safety, taking into account risks alongside expected benefits.
- Promotion of autonomy (both in the sense of supporting people's capacity to make their own decisions and in the sense of protecting their sense of who they are).
- Protection of people's privacy, bearing in mind that some devices may collect sensitive personal data.
- Promotion of equity both in terms of access to innovative products, and in addressing social stigma and discrimination.
- Promoting public understanding of and trust in novel neurotechnologies.

UK Nuffield Council on Bioethics
Novel Neurotechnologies Report
(2016)



Virtues

In describing the kinds of behaviours and approaches that are needed to protect and promote these interests, we highlight three virtues that are especially relevant in guiding the activities of all parties across a wide range of settings and applications of novel neurotechnologies. These virtues are:

- Inventiveness – expressed through technological innovation and by identifying ways of providing wider access to therapies.
- Humility – acknowledging the limits of current knowledge and of our ability to use technologies to alleviate the harms of brain disorders.
- Responsibility – shown by robust research and clinical practices and by avoiding hype in communication about their potential uses.

These virtues should be exemplified in the professional practices of all those involved in the development, funding, use, regulation and promotion of novel neurotechnologies, and supported by the structures and rules of the institutions within which they work.