UCLA Health

Emerging Treatments for Gambling Disorder: Magnets, Mushrooms and Meds

Timothy Fong MD
UCLA Gambling Studies Program

NCPG Annual Conference
July 18, 2024

CALIFORNIA CalGETS Gambling Education and Treatment Services OFFICE OF PROBLEM GAMBLING

National Conference on Gambling Addiction & Responsible Gambling 2024

Goals and Objectives

- Review emerging treatment for mental health that **may** impact gambling disorder
  - Transcranial Magnetic Stimulation
  - Ketamine
  - Psilocybin
  - Glucagon Receptor Agonists

Current Treatments for Gambling Disorder

Biological

Psychological

Social

Current Treatments Biological

- Medications
  - No FDA-approved meds
  - Naltrexone, Nalmefene, Lithium, N-Acetyl Cysteine,
- Sleep
- Physical Movement
- Nutrition

Current Treatments Psychological

- Individual Therapy
  - Many different treatment modalities
  - Which one works best?
- Family Therapy
- Group Therapy
- Principles of Addiction Care
- Principles of Behavioral Healthcare

Current Treatments Social

- Gambler's Anonymous
- Peer Support and Recovery
- Community activities
- Self-exclusion
- Digital Therapeutics
  - Gambling blockers
  - Recovery Apps

Limitations of Current Treatment Options

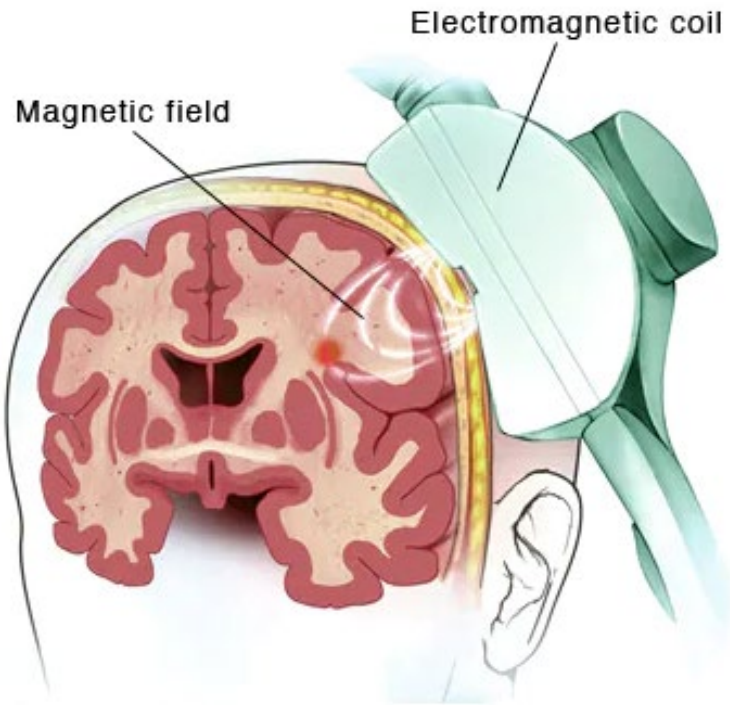
- Slow development and translation from idea to research to clinic
  - Lack of funding, people, participants
- Co-occurring disorders often missed or treatment options are limited
- Demand for treatment fluctuates as most with gambling disorder don't seek or don't know about treatment options

Emerging Treatments

Transcranial Magnetic Stimulation

(Magnets)

TMS



Repetitive transcranial magnetic stimulation (rTMS)

In repetitive transcranial magnetic stimulation (rTMS), an electromagnetic coil placed against the scalp creates a magnetic field that stimulates certain areas of the brain.

Transcranial magnetic stimulation (TMS)

- Applies gentle magnetic pulses (similar to the magnetic field used in an MRI machine) to targeted areas of the brain.
- Stimulating the brain in this way enhances “neuroplasticity,” or the brain’s ability to change itself, and helps restore normal function.
- TMS works differently than medications,
- TMS does not affect other areas of the body, so for most people, it has fewer side effects than medications.

TMS: How it works

- A treatment coil is applied to the head above the targeted area of the brain, called the prefrontal cortex.
- This part of the brain is involved with mood regulation.
- TMS magnetic fields do not directly affect the whole brain; they only reach about 2-3 centimeters into the brain directly beneath the treatment coil.

TMS: Logistics

- Patients remain awake and alert during treatment
- Treatment sessions are usually scheduled five days per week (Monday-Friday) for six weeks, followed by a three-week taper phase.
- Sessions last between 10-45 minutes depending on the treatment protocol

TMS: Clinical Conditions

- TMS was FDA approved for the treatment of Major Depressive Disorder in 2008 and is also FDA approved for Obsessive-Compulsive Disorder (OCD).
- Studies suggest that TMS is also helpful for anxiety disorders, Post-Traumatic Stress Disorder (PTSD), chronic pain, tinnitus, and other conditions.
- Approved for SMOKING CESSATION

TMS and Substance Use Disorders

- Could we treat other conditions?
- NIDA-sponsored trials (ongoing)
  - Nicotine use disorder
  - Cocaine use disorder
  - Opioid use disorder

TMS and Smoking

- targeting the lateral prefrontal cortex and insula bilaterally, has demonstrated a **reduction** in cigarette consumption with an abstinence rate of 44% at the end of treatment,
- decreased cue craving, reduced cigarette consumption, and increased smoking quit rate
- 2020 FDA Approval

TMS Review Paper

brain sciences

MDPI

Systematic Review

Betting on Non-Invasive Brain Stimulation to Treat Gambling Disorder: A Systematic Review and Meta-Analysis

Lilia Del Mauro [1,2,†], Alessandra Vergallito [3,*,†], Gaia Gattavara [1], Lucrezia Juris [2], Alessia Gallucci [4], Anna Vedani [1], Laura Cappelletti [2], Pietro Maria Farneti [2] and Leonor J. Romero Lauro [3]

How TMS might treat Gambling Disorder

- Treat co-occurring mood or anxiety disorder
- Similar brain region as substance use disorder that are responsible for
  - Craving
  - Control of gambling (starting /stopping)
  - Impulsivity

TMS Results

- Very limited number of studies
  - Case reports
  - No controlled studies, with comparison groups
- More and more clinics opening and offering services
- Protocols need to be refined
  - Induce cravings or at rest

TMS Roadmap

- Develop more specific protocols
  - Frequency, location, settings, # of sessions
- How long do treatment effects last?
- Which specific symptoms are impacted?
  - DSM-5 criteria (11 potential targets)
  - Recovery activities
  - Gambling behaviors

Medications

Ketamine

- Ketamine is an approved as an injectable, short-acting **anesthetic** and as esketamine (Spravato®) as a nasal spray for treatment resistant depression.

  – Ketamine (IV) is only FDA-approved as an anesthetic, and is still widely used for anesthesia and acute pain in surgical, operative, and emergency trauma settings.

  – Esketamine was brought to market around 2019 for the management of treatment-refractory depression [depression not responsive to standard treatment].


Spravato
(esketamine) C
nasal spray

Ketamine

- FDA is aware that compounded ketamine products have been marketed for a wide variety of psychiatric disorders (e.g., depression, anxiety, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder); however, FDA has not determined that ketamine is safe and effective for such uses.

How it is supplied

- Esketamine (Spravato)
  - Nasal Spray
  - 28 mg / 0.2 ml
- Ketamine IV
  - 0.5mg /kg for mood disorder
  - 1.5 mg and up for anesthesia
- Ketamine IM
- Ketamine Powder (Capsules)

frontiers in Psychiatry

MINI REVIEW
published: 24 July 2018
doi: 10.3389/fpsyt.2018.00277

Efficacy of Ketamine in the Treatment of Substance Use Disorders: A Systematic Review

Jennifer L. Jones[1]*, *Camilo F. Mateus*[1], *Robert J. Malcolm*[1], *Kathleen T. Brady*[1,2] and *Sudie E. Back*[1,2]

[1] *Medical University of South Carolina, Charleston, SC, United States,* [2] *Ralph H. Johnson VA Medical Center, Charleston, SC, United States*

Ketamine and Addictive Disorders

- Systematic reviews and meta-analyses provide support for robust, rapid and transient antidepressant and anti-suicidal effects of ketamine.
- Evidence for other indications is less robust, but suggests similarly positive and short-lived effects
- Ketamine may act as a modulator of the reward system

Ketamine and Addictive Disorders

- Improvement in cravings, motivation to quit, and self-administration have been shown in cocaine use disorder
- Significant long-term improvements in complete abstinence from alcohol and heroin
- ketamine reduced physiological response during opioid withdrawal

Ketamine and Gambling

The Primary Care Companion
FOR CNS DISORDERS

CASE REPORT

Response of Refractory Gambling Disorder to Intravenous Ketamine

Jon E. Grant, JD, MD, MPH, and Samuel R. Chamberlain, MB/BChir, PhD, MRCPsych

Published: January 16, 2020

Jon E. Grant, JD, MD, MPH[a,*], and Samuel R. Chamberlain, MB/BChir, PhD, MRCPsych[b,c]

Case Report (Grant)

- Mr. A underwent a total of 4 sessions of intravenous ketamine over 2 weeks. The dose of ketamine hydrochloride was 0.5 mg/kg, and it was delivered intravenously over 45 minutes twice weekly for 2 weeks.
- His overall gambling disorder symptoms improved from a pretreatment PG-YBOCS score of 31 to a score of 7 after the second infusion.
- This improvement has continued for the subsequent 6 months (i.e., to date) with no gambling behavior and only fleeting thoughts of gambling. Mr. A reported no side effects related to treatment.

Glucagon-Like Peptide 1 Agonists

GLP-1 Agonist Drugs Comparison

	DOSAGE	DOSAGE FORM	APPROVED FOR	WHO CAN TAKE IT?	OTHER BENEFITS
Ozempic (SEMAGLUTIDE)	1 WEEKLY		TYPE 2 DIABETES	ADULTS	HEART, KIDNEYS, WEIGHT LOSS
Rybelsus (SEMAGLUTIDE)	1 DAILY		TYPE 2 DIABETES	ADULTS	WEIGHT LOSS
Wegovy (SEMAGLUTIDE)	1 WEEKLY		WEIGHT LOSS	12+ KIDS + ADULTS	N/A
Trulicity (DULAGLUTIDE)	1 WEEKLY		TYPE 2 DIABETES	10+ KIDS + ADULTS	HEART, KIDNEYS, WEIGHT LOSS
Victoza (LIRAGLUTIDE)	1 DAILY		TYPE 2 DIABETES	10+ KIDS + ADULTS	HEART, KIDNEYS, WEIGHT LOSS
Saxenda (LIRAGLUTIDE)	1 DAILY		WEIGHT LOSS	12+ KIDS + ADULTS	N/A
Byetta (EXENATIDE)	2 DAILY		TYPE 2 DIABETES	ADULTS	WEIGHT LOSS
Bydureon BCise (EXENATIDE)	1 WEEKLY		TYPE 2 DIABETES	10+ KIDS + ADULTS	WEIGHT LOSS
Mounjaro (TIRZEPATIDE)	1 WEEKLY		TYPE 2 DIABETES	ADULTS	WEIGHT LOSS

GoodRx Health

GLP-1 Receptor Agonists

- The two most common agents include subcutaneous semaglutide (Ozempic, approved for type 2 diabetes, and Wegovy, approved for weight loss)
- liraglutide (Saxenda, approved for weight loss, and Victoza, approved for type 2 diabetes),
- oral formulation of semaglutide is available (Rybelsus)

How do they work?

- GLP-1 agonists **work by activating the GLP-1 receptor**.
  - slow gastric emptying, inhibit the release of glucagon, and stimulate insulin production, therefore reducing hyperglycemia in people with type 2 diabetes.
  - reduce food intake and therefore body weight, making them an effective treatment for obesity.

How do they work?

- GLP-1 is also produced in the nucleus tractus solitarius (NTS) of the brain stem and is released as a neurotransmitter in several brain regions.
- GLP-1 receptors are expressed in brain regions believed to be involved in reward and addiction (Ventral Tegmental and Nucleus Accumbens)

frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 01 February 2023
DOI 10.3389/fendo.2023.1085799

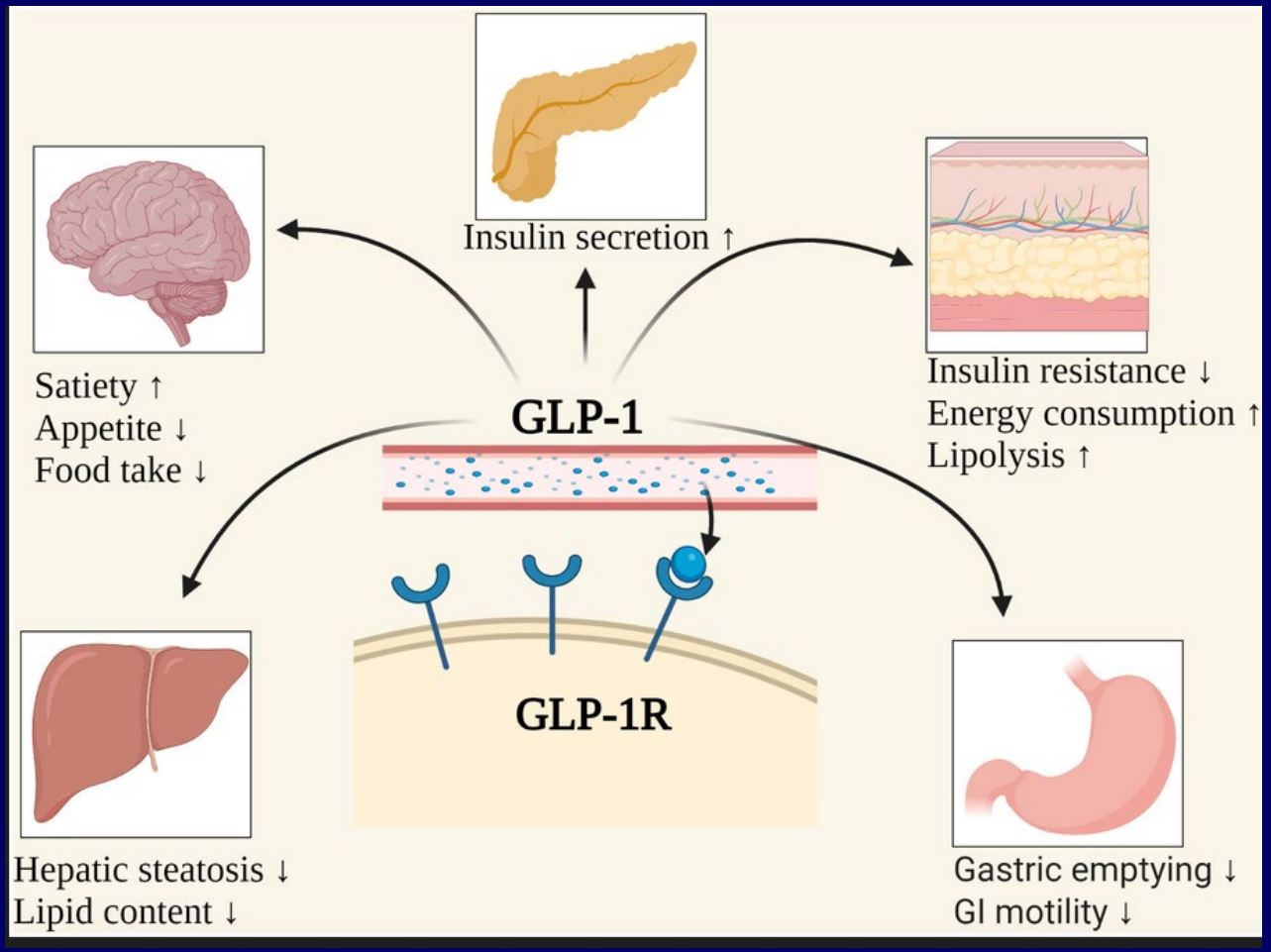
OPEN ACCESS

EDITED BY
Xiaodong Sun,
Affiliated Hospital of Weifang Medical University, China

REVIEWED BY
Kefei Dou,
Chinese Academy of Medical Sciences and Peking Union Medical College, China
Finbarr P. M. O'Harte,

GLP–1 receptor agonists for the treatment of obesity: Role as a promising approach

Jing-Yue Wang[1†], Quan-Wei Wang[1†], Xin-Yu Yang[1], Wei Yang[1], Dong-Rui Li[1], Jing-Yu Jin[1], Hui-Cong Zhang[1] and Xian-Feng Zhang[2*]



GLP-1 Agonists on SUD

Physiology & Behavior 206 (2019) 232–242

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/physbeh

Review

The effect of glucagon-like peptide-1 (GLP-1) receptor agonists on substance use disorder (SUD)-related behavioural effects of drugs and alcohol: A systematic review

Amanda Brunchmann, Morgane Thomsen, Anders Fink-Jensen*

Psychiatric Centre Copenhagen, Edel Sauntes Allé 10, Copenhagen 2100, DK, University of Copenhagen, Denmark

GLP-1 Peptide Like Agonists: Ongoing Clinical Trials

2021 – Ongoing human trials examining

- Alcohol use disorder
- Cocaine use disorder
- Nicotine use disorder
- Opioid use disorder

- Where did all of this interest come from?

GLP-1 Receptor Agonist Possible Mechanisms

- Targeting
  - Decrease rewarding / reinforcing aspects of activity (substance, food, gambling?)
  - Decrease Craving / Preoccupation
  - Achieve satiety faster
  - Increase aversion
    - Loss aversion?
  - Break up conditioned responses

GLP-1 Receptor Agonists and Gambling

- Is there a signal?
- Case reports with those taking for diabetes or weight loss
- Could there be replacement addiction (a la gastric bypass surgery)
- What message does this send?
- Partner with PCP, Endocrine, Weight Loss Clinics to screen for gambling disorders

Mushrooms

Psychedelics

- Classical psychedelics, both plant derived and synthetic compounds, include serotonin-2A receptor agonist drugs that have powerful dose-related effects on perception, cognition, and emotion.
- Examples include lysergic acid diethylamide (LSD), psilocybin and ayahuasca.

Psilocybin

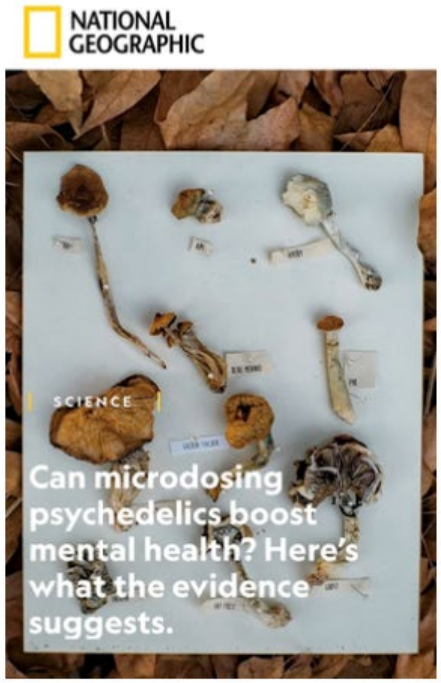
- Psilocybin *(4-phosphoryloxy-N,N-dimethyltryptamine)* comes from certain types of mushrooms
- When a person takes psilocybin, their body converts it to, psilocin.
- Psilocin attaches to and activates the serotonin 5-hydroxytryptamine 2A (5HT2a) receptor

How people use

- Today, people ingest mushrooms in search of a unique, interesting, enlightening, and/or spiritual experience.
- Others take very small amounts of the substance regularly, a practice called microdosing, trying to improve their mental state and productivity.

What is a microdose?

- 5-10% of a typical dose
- Psilocybin mushrooms: 0.1 – 0.4 grams
- LSD: ~10 µg



Notes from users

Microdosing claims

Psilocybin mushrooms: In general, a tiny dose of psilocybin makes me think much more deeply in every aspect of life. Instead of having a monkey mind, creating noise, my mind is still. It is in a mode that it has been in before, but that was a long time ago. Psilocybin makes me feel exactly how I felt when I was a kid in school. It is happiness, because you realize that you have all you need. During my test days, I feel more love for myself, and I can give that to others. I also have this sense of being the pilot of my body. My cravings for sugar, smoke and sodas nearly went away. I wanted to give my body the best fuel, I feel like I attract positive people and happenings in my life. I got a job offer landing on my lap, without working for it. I can't prove that there is some connection, and scientist would deny it, but I feel like there is something bigger going on.

Current thinking from American Psychiatric Association

APA Position:

There is currently inadequate scientific evidence for endorsing the use of psychedelics to treat any psychiatric disorder except within the context of approved investigational studies. APA supports continued research and therapeutic discovery into psychedelic agents with the same scientific integrity and regulatory standards applied to other promising therapies in medicine. Clinical treatments should be determined by scientific evidence in accordance with applicable regulatory standards and not by ballot initiatives or popular opinion.

Psilocybin and Addictive Disorders

- Preliminary research indicates that psilocybin may be helpful in treating substance use disorders, including tobacco use disorder.
- NIDA is funding a large, multi-site study on the effectiveness of psilocybin versus a nicotine patch, in combination with therapy, to help people stop smoking.
- Brain plasticity = teach people new things

Psilocybin and Gambling Disorder

- Romero P, Czakó A, van den Brink W, Demetrovics Z. Psychedelic-assisted therapy for people with gambling disorder? J Behav Addict. 2024 Feb 28;13(1):6-11
- Gibraltar

Psilocybin and Gambling Disorder

- Dr. Romero --
  - Psilocybin-assisted therapy may help people affected by GD by increasing self-awareness, promoting introspection, and facilitating a spiritual experience that can help individuals break free from negative thought patterns.

Psilocybin Situation

- Schedule I drug
- States are decriminalizing
- Rise of “big mushroom”
- How similar to the story of medical cannabis?
- Does this add to the toolbox or distract from the toolbox?

uclagamblingprogram.org

Acknowledgements

UCLA Gambling Studies Program
Richard Rosenthal
Monica Vaughn
Mike Campos
Elizabeth Hall
Rory Reid
Didi Huezo
Vandana Joshi
Fiona Donovan
Leah Abraham
Aaron Nguyen
Tracy Park
Tom Naar

Partners:
California Dept of Public Health
Office of Problem Gambling
Telus
Beit T'Shuvah
Westside Gambling Treatment
UPAC
CalGETS Providers
CalGETS Supervisors
CCPG
NCPG
RSBIHC
Vision y Compromiso
Friday Night Live

Contact Information

Timothy Fong MD
UCLA Gambling
Studies Program
310-488-3916
tfong@mednet.ucla.edu

twitter: @fongster98

Cases, Questions, Discussions, Ideas?