



# Reviewing Emerging Treatments: TMS / Psilocybin / Ozempic / AI

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UCLA Gambling Studies Program

Focus on The Future Conference

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# Goals and Objectives

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

# 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)

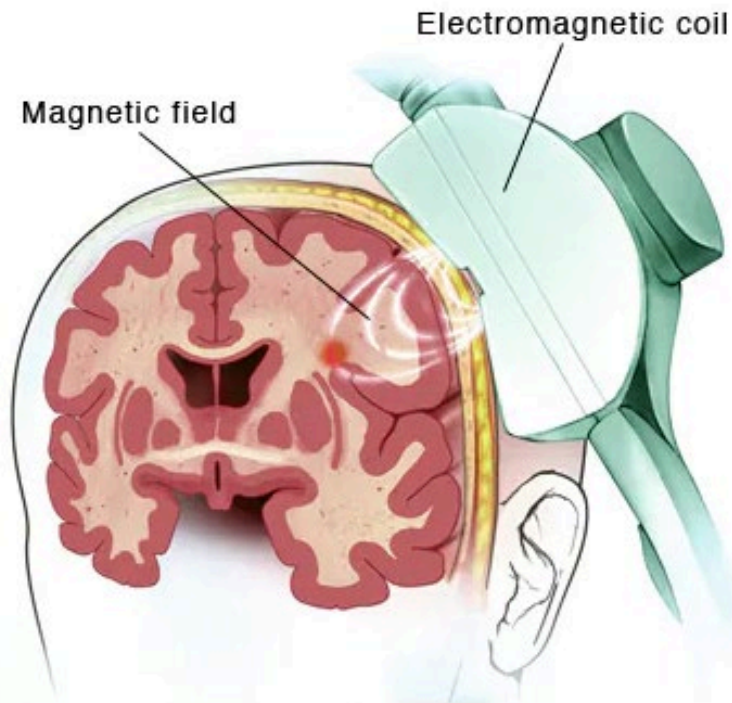
# TMS



# 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.

- 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.



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## **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.

# TMS

- 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.
- TMS sessions generally 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.

# TMS: FDA-Approval

- Currently, rTMS is cleared by multiple regulatory agencies for the treatment of TRD, depression with comorbid anxiety disorders, obsessive compulsive disorder, and substance use disorders, such as smoking cessation.

# TMS and Substance Use Disorders

- What is we MOVED the magnet?
  - Could we treat other conditions?
- NIDA-sponsored trials (ongoing)
  - Nicotine use disorder
  - Cocaine use disorder
  - Opioid use disorder

# TMS and Smoking

- Among substance use disorders, high frequency dTMS, 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, leading to FDA clearance for smoking cessation

# TMS and smoking


- Previous studies have reported that rTMS decreased cue craving, reduced cigarette consumption, and increased smoking quit rate in tobacco use disorders(TUDs).
- However, the treatment parameters and exact mechanism for rTMS increasing smoking quit rate need further refinement

# TMS Review Paper



*Systematic Review*

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

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

# 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 medical product as an injectable, short-acting anesthetic for use in humans and animals and as esketamine (Spravato®; the active form of the drug) as a nasal spray for treatment resistant depression.
- Ketamine 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].



# 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)



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

*Jennifer L. Jones*<sup>1\*</sup>, *Camilo F. Mateus*<sup>1</sup>, *Robert J. Malcolm*<sup>1</sup>, *Kathleen T. Brady*<sup>1,2</sup> and *Sudie E. Back*<sup>1,2</sup>

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# 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 simply 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 ([23](#)).

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**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<sup>a,\*</sup>, and Samuel R. Chamberlain, MB/BChir, PhD, MRCPsych<sup>b,c</sup>

# 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
<b>Ozempic</b> (SEMAGLUTIDE)	1 WEEKLY		TYPE 2 DIABETES	 ADULTS	HEART, KIDNEYS, WEIGHT LOSS
<b>Rybelsus</b> (SEMAGLUTIDE)	1 DAILY		TYPE 2 DIABETES	 ADULTS	WEIGHT LOSS
<b>Wegovy</b> (SEMAGLUTIDE)	1 WEEKLY		WEIGHT LOSS	12+ →  KIDS + ADULTS	N/A
<b>Trulicity</b> (DULAGLUTIDE)	1 WEEKLY		TYPE 2 DIABETES	10+ →  KIDS + ADULTS	HEART, KIDNEYS, WEIGHT LOSS
<b>Victoza</b> (LIRAGLUTIDE)	1 DAILY		TYPE 2 DIABETES	10+ →  KIDS + ADULTS	HEART, KIDNEYS, WEIGHT LOSS
<b>Saxenda</b> (LIRAGLUTIDE)	1 DAILY		WEIGHT LOSS	12+ →  KIDS + ADULTS	N/A
<b>Byetta</b> (EXENATIDE)	2 DAILY		TYPE 2 DIABETES	 ADULTS	WEIGHT LOSS
<b>Bydureon BCise</b> (EXENATIDE)	1 WEEKLY		TYPE 2 DIABETES	10+ →  KIDS + ADULTS	WEIGHT LOSS
<b>Mounjaro</b> (TIRZEPATIDE)	1 WEEKLY		TYPE 2 DIABETES	 ADULTS	WEIGHT LOSS

# 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)



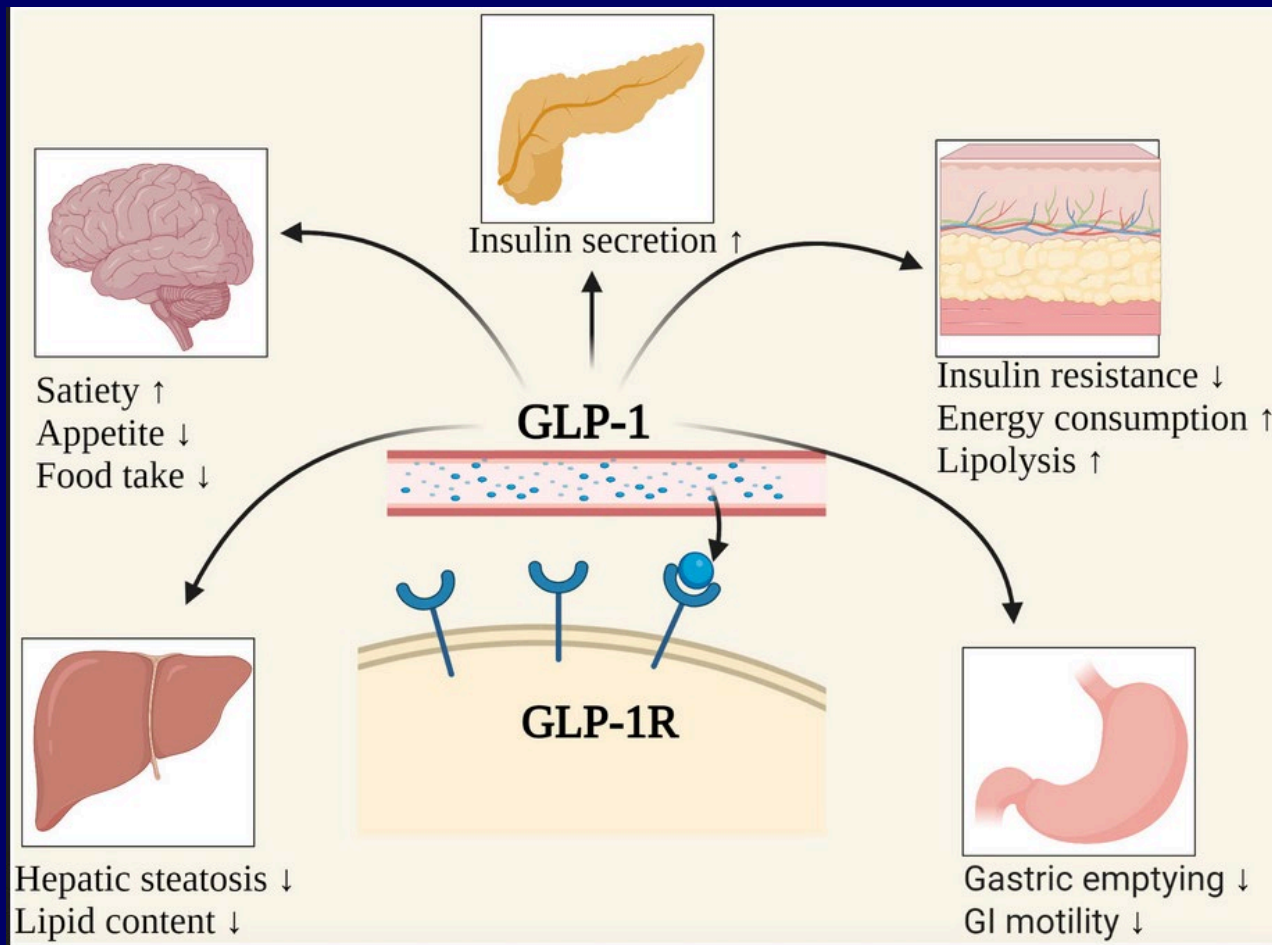
## GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach

### OPEN ACCESS

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# GLP-1 Agonists on SUD

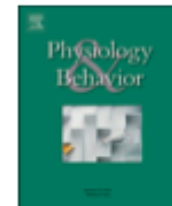
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Review

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



# How people use

- Today, people use the mushrooms in the hopes of having 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  $\mu\text{g}$



# 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

# 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 Roadmap

- Schedule I drug
- States are decriminalizing
- Rise of “big mushroom”
- Essential questions remain
- How would this be different from other treatment approaches?

# Artificial Intelligence

# AI in Addictive Disorders

- Current uses / emerging uses
  - AI to predict who will relapse or leave treatment (based on social media posts)
    - language analysis showed the language most predictive of opioid overdose was not explicitly about drug use, but was about physical and mental pain, boredom, and long work hours
  - AI to showcase areas of emerging concerns
    - Hotspots of use, emerging substance use patterns

# AI in Gambling Disorder

- Predictive models to do interventions
  - Recognize emerging stress and offer solutions before reoccurrence
- AI support tools for therapy and in the moment sessions of support (AI therapist) that are more interactive
- AI to monitor types of wagers / bets that are more or less problematic

# UCLA Gambling Studies Program (UGSP)

- UGSP examines the causes, course and impact of gambling disorder while developing evidence-based treatment strategies
- Funded by NIDA, Office of Problem Gambling, Annenberg Foundation
- Lab Space available for pre and post-docs

# uclagamblingprogram.org

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**The Hot New Form Of Fantasy Sports Is Probably Addictive, Potentially Illegal And Completely Unregulated**

**Dr. Fong discusses the rise of paid fantasy sports**

Sacha Feinman and Josh Isreal interview Dr. Timothy Fong for an article on fantasy sports betting for Think Progress

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### Freedom from Problem Gambling

The UCLA Gambling Studies Program (UGSP) is a non-profit organization within the Department of Psychiatry and Biobehavioral Sciences at the University of California, Los Angeles. Our mission is to reduce the individual, familial, and societal harm caused by pathological gambling. Since 2005, we have been engaged in conducting research, providing cost-effective prevention and treatment services, and offering education and training opportunities to healthcare providers and the community at large.

#### Research

UGSP is committed to the advancement of research. We use a wide range of research methods to continually investigate the biological, psychological, and

#### Treatment

UGSP has a number of outpatient treatment options available for problem gamblers and their families. Our team of experts understand and treat problematic

#### Education

UGSP provides educational and training opportunities for mental health providers across Southern California. We also welcome local and international volunteers,

# Acknowledgements

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California Dept of Public Health

Office of Problem Gambling

LifeWorks

Beit T'Shuvah

Health Right 360

UPAC

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Friday Night Live

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Cases, Questions,  
Discussions, Ideas?