TREATING HEROIN ADDICTION: IMMUNOTHERAPY, BLOOD-BRAIN BARRIER DISRUPTION, IBOGAINE, AND MEDITATION THERAPIES FOR LONG-TERM ABSTINENCE

"Empowering Lives, Embracing Sobriety"

By: William Glickman

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A 5-Step Plan

HEROIN'S BACKGROUND

Discovery

Derived from the opioid poppy plant (Papaver somniferum) and discovered in western societies in 1894 by English chemist Charles Romley Alder Wright while looking for non-addictive substitute for opiate morphine.

Composition

Chemically known as diacetylmorphine, doubly-acetylated morphine, or by its chemical composition C21H23NO5.

PREVALENCE

80%

Users first misused a prescribed opioid

NIDA, 2022

12.5%

Drug-overdose deaths annually

CDC, 2023

United Nations Office of Drugs and Crime (UNODC)

115 TONS OF HEROIN

Seized globally in 2020

31 tons seized out of Iran alone. A 19% increase from the previous year.

UNODC, 2020

DRUG EFFECTS

Positive Reinforcements

- Euphoria
- Sedation
- Analgesia
- Well-Being

Negative Reinforcements

- Insomnia
- Restlessness
- Muscle and Bone Pain
- Diarrhea
- Nausea/Vomiting
- Cold Flashes with Goosebumps
- Involuntary Leg Movements

Backer & Chartoff, 2019

MECHANISMS OF ACTION

How Hijacking Occurs

The Addiction Cycle

Most commonly intravenous (IV) injections into the system

This is the fastest non-clinical route of administration into the brain.

Transportation to Liver

Diacetyl morphine deacetylase (esterase) hydrolysis

The first acetyl group on heroin is removed, producing 6-monoacetylmorphine (6-MAM)

Transportation to Brain and Through Blood-Brain Barrier

Morphine deacetylase hydrolysis, allowing Mu receptor binding

Second acetyl group is removed, producing metabolite morphine, which, as a competitive opioid agonist, binds to Mu receptor in place of natural endorphins

GABA inhibition suppressed, dopamine released into reward pathway

Surge of dopamine levels in ventral tegmental area & nucleus accumbens, causing feelings of sedation, well-being, analgesia, and euphoria

Tolerance and physical dependence build

Basal ganglia forms powerful cue-associated memories and trigger withdrawals & cravings, reduced prefrontal cortex activity induces poor self-control

NIDA, 2014
NIDA, 2022
Chaves et al., 2017
Becker & Chartoff, 2019
Seifert et al., 2015
Trinko et al., 2007
Bossert et al., 2004

WHAT CURRENT TREATMENTS ARE THERE FOR HEROIN ABUSE?

- METHADONE
- BUPRENORPHINE
- NALTREXONE
- COGNITIVE-BEHAVIORAL THERAPY (CBT)
- MOTIVATIONAL INTERVIEWING (MI)

METHADONE

01

What it Does

- Replacement therapy introduced in the 1960s
- Long-lasting opioid agonist, binds to same receptor sites

02

Shown Effectiveness

- Effectively alleviates withdrawal symptoms and reduces cravings
- Study by Buster and Van Brussel in 1996 confirmed its alleviation properties

03

Why it is Ineffective Long-Term

- Buster and Van Brussel study found that nearly 70% of individuals continued to use heroin
- Methadone itself is an opioid and can lead to physical dependence
- While withdrawals and cravings are effectively limited, long-term abstinence is not likely

Hoffman, 2000
Gerra et al., 2003
Buster & Van Brussel, 1996

BUPRENORPHINE

What it is

- Emerged in the late-1990s as a partial opioid agonist
- Prescribed shortly after new millennia began
- Binds to same Mu opioid receptors as heroin

Effectiveness

- Alleviates withdrawal symptoms without a pronounced "high"
- The Prescription Opioid Addiction Treatment Study (POATS) in 2011 highlighted its effectiveness in reducing opioid use and promoting short-term abstinence
- Extended treatment duration improves outcomes

Ineffectiveness

- POATS emphasized the high relapse rates following taper phase (preliminary 4 weeks)
- Extended treatment requirements likely mirror dependence on the drug
- Reliant on adherence to prescription regimen - improper use can render medication ineffective

NIDA, 2021
Weiss et al., 2011
Carroll & Weiss, 2016
Cascade et al., 2007
Gerstein & Harwood, 1990

NALTREXONE

What it is

- FDA-approved in 1984 for office-based settings
- Opioid antagonist that is a longer-lasting version of naloxone, which was introduced in the 1960s
- Binds to the same Mu opioid receptors as heroin

Effectiveness

- Diminishes the rewarding and reinforcing properties associated with heroin use
- Study done by Edward Nunes et al. in 2018 showed that extended-release injection naltrexone treatments were effective in limiting relapse rates for a short period of time (1 month)

Ineffectiveness

- Prior to treatment commencement, individuals must be abstinent for an extended period, otherwise withdrawals get severely worsened
- Withdrawals are exacerbated and a strict regimen must be followed
- Study showed that after 6 months, relapse rates were high, emphasizing the drug's long-term inefficacy

NIDA, 2021
Srivastava & Gold, 2018
Gerstein & Harwood, 1990
Nunes et al., 2018

COGNITIVE-BEHAVIORAL THERAPY (CBT)

What it is

- A valuable tool that helps address underlying psychological and behavioral aspects of addiction
- It is a non-pharmacological intervention aimed at assisting individuals in recovery from drug abuse

Effectiveness

- Study by Magill and Ray showed that CBT alone had a small but statistically significant treatment effect, but that it diminished over time (short-term success)
- Study also showed a positive association between the female participants and the treatment effect size

Ineffectiveness

- Effectiveness hinges upon active engagement, motivation, and commitment from individuals
- The significant treatment effects diminish as time goes on, as shown in the Magill and Ray study (long-term not viable)

Gerstein & Harwood, 1990
Magill & Ray, 2009

MOTIVATIONAL INTERVIEWING (MI)

What it is

- Similar to CBT, it is a psychological therapy that aims to understand an individual's personal struggle with addiction, and motivate them to pursue their goals
- Helps patients acquire coping strategies beyond the therapy sessions and remain consistent with their treatment and personal goals

Effectiveness

- A meta-analysis study conducted by Geir Smedslund et al. in 2011 found that, compared to no treatment, MI had a significant effect on reducing substance use, particularly at post-intervention (effects significant only short-term)

Ineffectiveness

- Similar to CBT, the study showed that MI was insignificant at limiting substance use after a certain period of time, and was only effective in short-term treatments (long-term ineffectiveness)
- Limited treatment accessibility, financial constraints, and social support deficiencies can impede the treatment's efficacy, especially long-term

Gerstein & Harwood, 1990
Magill & Ray, 2009
Smedslund et al.,2011

THE PROPOSED TREATMENT PACKAGE

Immunotherapy (Antibody Generation)

Ultrasound & Microbubble-Mediated Blood-Brain Barrier Disruption

Ibogaine Therapy

Meditation Therapy

IMMUNOTHERAPY

How it Works

- Also known as antibody generation; developing and administrating monoclonal antibodies (mAbs), which bind with high affinity and specificity to the targeted drug, disallowing it to interact with the proper receptors or cause the intended effects.
- Can be used to target heroin to prevent blood-brain barrier entry.

Treatment Effectiveness

- The antibodies bind to drug molecules in the bloodstream, preventing their entry into the blood-brain barrier, thereby blocking the rewarding and reinforcing effects (reducing/eliminating psychoactive effects).
- A study conducted by Thomas Kosten et al. in 2014 aimed to evaluate the efficacy of a vaccine TA-CD at targeting and binding to cocaine, limiting its access to the brain.
    - Findings suggested that individuals with higher amounts of antibodies stayed abstinent longer and continued treatment.
    - Limitations also arose, as patients seemingly were able to take more cocaine to produce intended effects.
    - Demonstrates long-term abstinence potentiality.

Koch et al., 2023
Maoz et al., 2013
Normal & Ball Jr., 2013
Peterson & Owens, 2009
Kosten & Owens, 2005
Kosten et al., 2014

ULTRASOUND/MICROBUBBLE-MEDIATED BLOOD-BRAIN BARRIER (BBB) DISRUPTION

How it Works

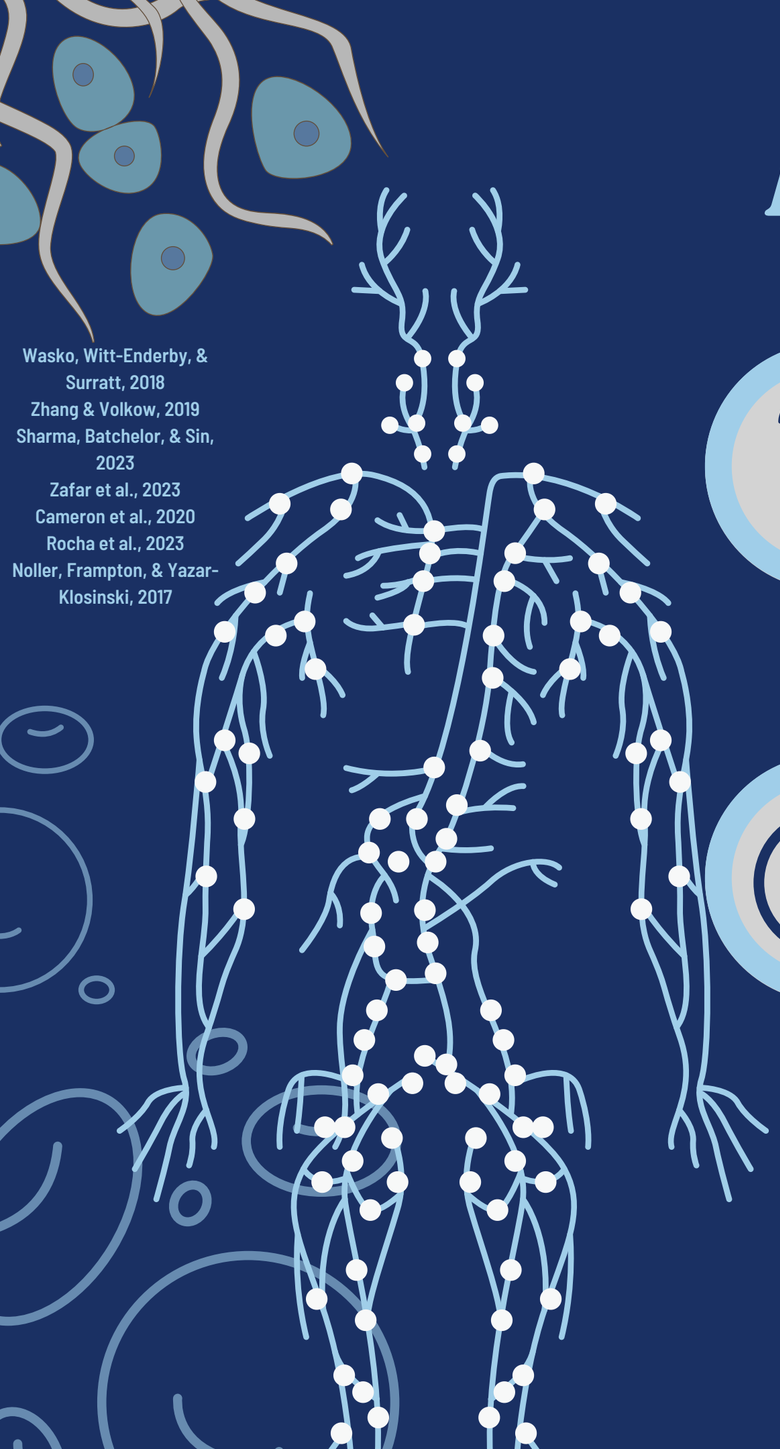
- Involves temporarily disrupting the blood-brain barrier using ultrasound waves in conjunction with microbubbles, enabling targeted deliveries of therapeutic agents to the brain.
    - These agents can be the antibodies generated from immunotherapy.

Koch et al., 2023
Song, Harvey, & Borden, 2018
Chaves et al., 2017
Gandhi et al., 2022
McMahon, Poon, & Hynynen, 2019
Aryal et al., 2014
Epelbaum et al., 2022

Treatment Effectiveness

- A pilot study conducted by Stéphane Epelbaum et al. in 2022 investigated the effectiveness of this disruption intervention in patients with mild Alzheimer's disease.
    - Findings highlighted the success of the treatment, suggesting that it is well-tolerable with no significant adverse effects observed long-term.
- Targeted delivery through the BBB would allow for a second line of defense against the drug molecules that made it past the antibodies in the bloodstream.
    - Addresses the limitation of immunotherapy.

IBOGAINE THERAPY



Wasko, Witt-Enderby, & Surratt, 2018
Zhang & Volkow, 2019
Sharma, Batchelor, & Sin, 2023
Zafar et al., 2023
Cameron et al., 2020
Rocha et al., 2023
Noller, Frampton, & Yazar-Klosinski, 2017

How it Works

- Derived from the iboga plant, the psychedelic ibogaine possesses unique abilities to promote neuroplasticity and rewire the brain by modulating the default mode network (DMN).
    - DMN - Involved in self-referential thoughts, addictive behaviors, and rumination.

Treatment Effectiveness

- Stands out among psychedelics due to its non-abusable nature; shows great promise in reducing cravings and withdrawal symptoms (physiological) long-term.
    - Safer option for therapeutic use because of its low propensity for abuse.
- Study conducted by Geoffrey Noller et al. in 2017 demonstrated the significant reduction in drug use, depression, and withdrawal symptoms after a 12-month trial.
    - Importantly, this was merely a single ibogaine treatment.

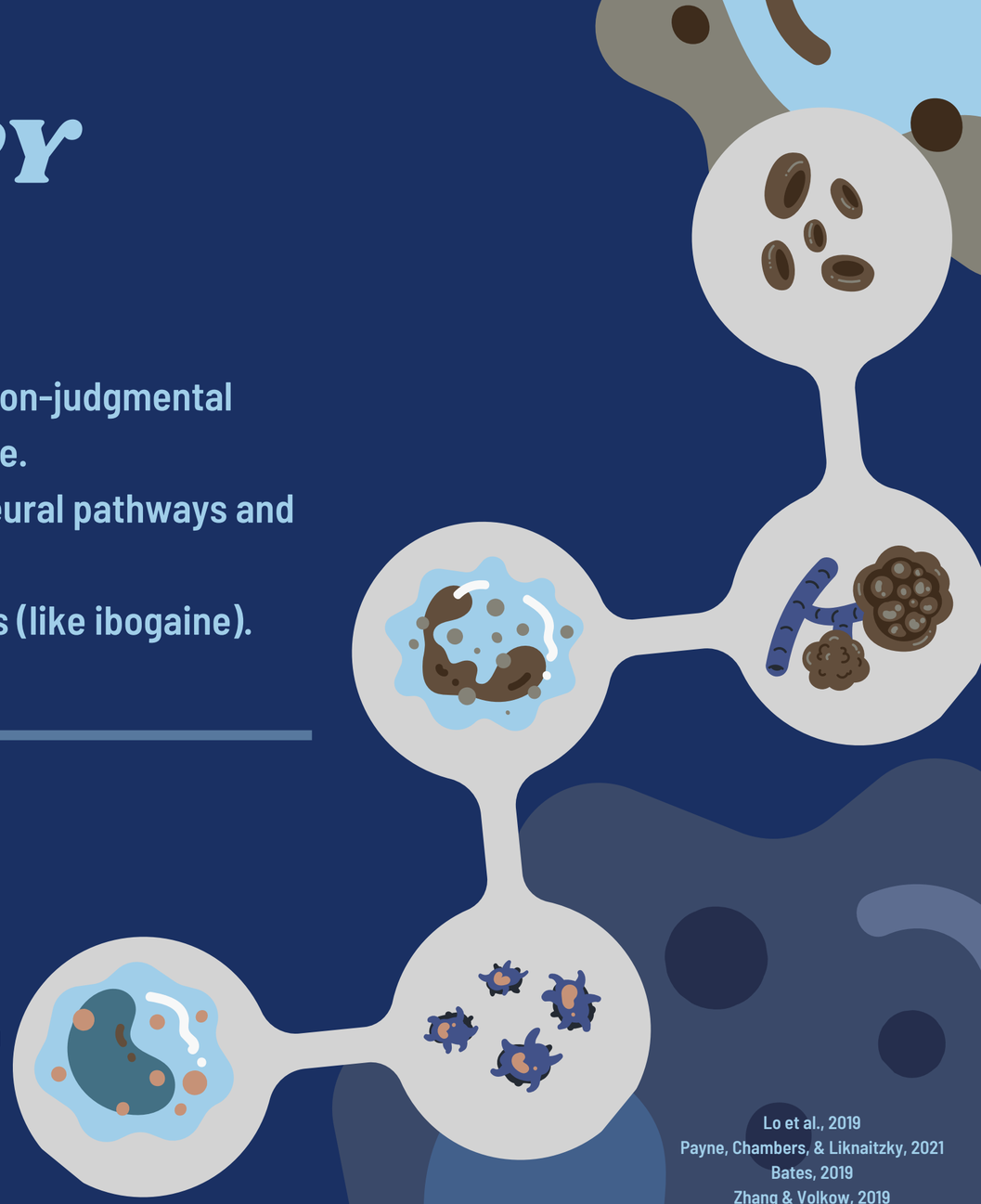
MEDITATION THERAPY

How it Works

- Meditation is a practice that involves cultivating present-moment awareness, non-judgmental observation of thoughts and sensations, and the development of inner resilience.
- Can combine with psychedelic treatments to further enhance the rewiring of neural pathways and promote sustained long-term abstinence.
    - Fosters neuroplasticity and strengthens default mode network connections (like ibogaine).
    - Physiological and psychological intervention.

Treatment Effectiveness

- By engaging in regular practice, individuals can strengthen their ability to navigate the discomfort and cravings associated with withdrawal.
- A study conducted by Sam Himelstein et al. in 2015 revealed significant increases in self-esteem, decision-making skills, and good behavior, and a decrease in emotional withdrawal among the entire studied sample due to meditation therapy treatments.
    - Support role of mindfulness-based interventions in patients with unenriched backgrounds, which is one of the leading causes of addiction.



Lo et al., 2019
Payne, Chambers, & Liknaitzky, 2021
Bates, 2019
Zhang & Volkow, 2019
Zgierska et al., 2009
Eleftheriou & Thomas, 2021
Himelstein, Saul, & Garcia-Romeu, 2015
NIDA, 2021

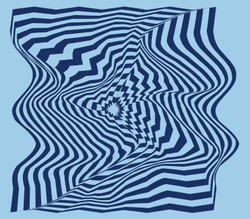
PACKAGE OVERVIEW

A Brief Review

Immunotherapy

Ultrasound/Microbubble-Mediated Blood-Brain Barrier Disruption

Psychoactive Intervention



Ibogaine Therapy

Meditation Therapy

Psychological and Physiological Intervention

CONCLUSION

- Heroin has had a profound impact on western societies since its discovery in 1894.
- Despite initially being marked non-addictive, heroin quickly revealed its true nature as a highly-addictive substance with devastating consequences.
    - Incredulous number of heroin-related overdose deaths annually.
    - High accessibility and prevalence - a grave public concern.
- Powerful effects stem from its high affinity for Mu opioid receptor, quickly initiating dopamine surges in the reward pathway, inducing euphoria, sedation, and analgesia.
    - Physical dependence quickly ensues, causing devastating withdrawal symptoms.
- Current treatments including methadone maintenance, buprenorphine, naltrexone, cognitive-behavioral therapy, and motivational interviewing are all effective short-term, but not in sustaining long-term abstinence.
- The proposed innovative treatment package of immunotherapy, BBB disruption, ibogaine, and meditation therapies target various aspects of addiction.
    - These include psychoactive, psychological, and physiological components.
    - Serves as a steppingstone for future research, urging scientists to explore and validate the potential of these interventions.

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QUESTIONS?

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