Medication Assisted Treatment: What we’ve learned from the Treatment of Substance Use Disorders

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Conflicts of Interest

• Dr. Moberg has nothing to disclose.
Objectives

• Review the history of medication assisted treatment for substance use disorders.
• Discuss medications being used currently to treat substance use disorders.
• Introduce medications that are being used to treat process addictions.
First, a little bit of history

- 1601 East India Company established
- Britain—desired silk, porcelain and tea from China
- India—grew opium in Bengal (contributed to famine of 1770) and auctioned it in Calcutta with understanding it would be smuggled into China
- China—desired English silver but nothing else; 1838 seizure of British opium shipment; led to first opium war

1601

1773

1839-1842: First Opium War
1856-1860: Second Opium War
More history

• Friedrich Sertturner isolated morphine—thought to cure opium addiction
• Cocaine and heroin promoted to cure morphine addiction
The law of (2) unintended consequences

Intent: synthesize codeine from morphine.
Consequences: heroin synthesized; heroin metabolized to morphine
Did you know Graham crackers were health foods?

Sylvester Graham, 1829
Presbyterian minister
Temperance movement
How about Corn Flakes?

John Harvey Kellogg, 1878
Physician
Seventh Day Adventist
Three scourges of mankind
Freidrich Erlenmeyer (1887)

- Alcohol
- Opium
- Cocaine
The 3 scourges

Morphine
Created by Charlotte Winslow
Marketed by Jeremiah Curtis (son-in-law) and Curtis Brown –1849

Cocaine (6-7.2%) + alcohol

Fans:
Queen Victoria
Pope Leo XIII*
Pope St. Pius X
Thomas Edison
Ulysses S. Grant

Vin Mariani (1863)
Cocaine removed in 1903

Condemned by AMA in 1911
“Baby killer”
The third scourge

John Pemberton’s French wine coca off the market (1885)

Coca Cola (1885)

1903 cocaine removed by using cocaine free leaf extract—Stepan plant in Maywood, NJ
Regulatory history

- 1890—opium and morphine taxed
- 1906—Pure Food and Drug Act—banned foreign and interstate traffic in adulterated or mislabeled food and drug products; required active ingredients be labeled on drugs and set standards for purity (not for food). Alcohol, morphine, opium and cannabis deemed dangerous and had to be on a label.
- 1909—Smoking opium exclusion Act—Banned importation and use of “smoking opium.” Did not regulate opium based medications.
- 1909—US v. Forty Barrels and Twenty Kegs of Coca-Cola; charge was excessive caffeine. Supreme Court agreed but a compromise was reached—caffeine added to the list of habit forming and deleterious substances.
- 1914—The Harrison Act—required all parties involved in importing, exporting, manufacturing and distributing opium or cocaine to register with the Federal Government and be taxed. Physicians exempt.
- 1917—Interpretation changed; physicians cannot prescribe to “maintain addiction.”
Regulatory history

- **1919**—US v Doremus—Harrison Act constitutional
- **1919**—Webb et al. v US. Maintenance was not a legitimate province of medicine.
- **1920**—Moy v US in 1920. Physicians may not prescribe a narcotic to addicted patients.
- **1922**—Narcotic Drug Import and Export Act (Jones-Miller Act)—Assured proper control of importation, sale, possession, production and consumption of narcotics.
- **1924**—Heroin Act—Heroin illegal
- **1925**—Linder v US—Linder was arrested and convicted for prescribing opioids for opioid maintenance but Supreme Court overturned this by stating federal government had no authority to regulate practice of medicine.
- **1927**—Bureau of Prohibition—tracked bootleggers and organized crime leaders
- **1932**—Uniform State Narcotic Act—Encouraged states to pass laws that matched federal laws. Suggested prohibiting cannabis at state level.
- **1938**—Food, Drug and Cosmetic Act—Cosmetics and medical devices under control; drugs must be labeled with instructions; manufacturers had to prove to FDA that drug was safe.
Regulatory history

- 1951—Boggs Act—Imposed criminal penalties and prison sentences for violations of import/export violations
- 1956—Increased Boggs Act penalties
- 1964—Dole and Nyswander begin research study with heroin addicts in New York
- 1965—Drug Abuse Control Amendment—enacted to address problems with abuse of antidepressants, stimulants, hallucinogens. Restricted research into psychoactive like LSD by requiring FDA approval.
- 1970—Controlled Substance Act/Controlled Substances Import and Export Act—laws that regulate the manufacture and distribution of a multitude of drugs that have abuse potential. Scheduling of drugs.
- 1973—DEA formed
Primary conclusion

Ineffective Medication Assisted Treatment
Secondary conclusions

Movement to regulate certain substances

Addiction is not a sufficient reason to prescribe opioids

Dispensing vs. Prescribing

The Controlled Substances Act (1970)
Narcotic Addict Treatment Act (1974)

Second, where the rubber meets the road
or I think I’ll go eat worms
Timeline

- Berlin chemist M. Grodzki synthesized a chemical in 1881
- Introduced into the rubber industry (accelerates vulcanization) in early twentieth century
- Workers discovered an adverse reaction with ingestion of alcohol
- E.E. Williams (plant physician) wrote a description of the phenomenon and thought it may be a cure for alcoholism in 1937.
- No follow-up
- Scabies and intestinal worms (England, 1942)
- In Denmark, in the 1940’s Erik Jacobsen and Jens Hald confirmed its efficacy against scabies and Dr. Jacobsen administered the drug to himself to test the worm hypothesis

Kragh, 2008
A lot of publicity

December 6, 1948
What happened?

• Time magazine, December 6, 1948

Copenhagen’s Dr. Erik Jacobsen, 45, likes to try out new drugs on himself before giving them to his patients. One night before going to a dinner party he swallowed a couple of pills made of tetraethyl-thiuram-disulfide; they were supposed to be good for intestinal worms. To his surprise, Dr. Jacobsen found that any form of alcohol revolted him. When he sipped even a small glass of beer, his face got red, his heart started to pound, and he had trouble getting his breath.
Antabus

- Anti-abuse
- Professional community—The Lancet 1948
- Lay community—Time 1948
- American Psychological Association Meeting 1949—3 physicians presented patients (emphasized that success was that the drug paves the way for psychotherapeutic procedures)
- Approved by FDA in 1951
Tetraethylthiuram disulfide
Disulfiram

• Alcohol sensitizing agent
• Binds to nicotinamide adenine dinucleotide coenzyme
• Irreversible block of aldehyde dehydrogenase
• Genetic evidence ALDH2*2 allele deficiency increases reaction
Disulfiram (alcohol)

Ethyl alcohol $\rightarrow$ Acetaldehyde $\rightarrow$ Acetate
Mechanism of Action

Alcohol dehydrogenase

Ethyl alcohol → Acetaldehyde

Aldehyde dehydrogenase

Acetaldehyde → Acetate

Disulfiram
Disulfiram ethanol reaction

- rapid heart rate
- low blood pressure
- flushing
- sweating
- chest pain
- fainting
- nausea
- vomiting
- weakness
- confusion
- headache
- vertigo
- blurred vision
- hyperventilation
- shortness of breath
Disulfiram side effects

- Hepatotoxicity
- Optic neuritis
- Peripheral neuropathy
- Skin eruptions
An Explosion
Medication Assisted Treatment

• FDA approved
  – Disulfiram—alcohol
  – Naltrexone (IM and oral)—alcohol and opioids
  – Acamprosate—alcohol
  – Methadone—opioids
  – Buprenorphine—opioids
  – Buprenorphine/Naloxone—opioids
  – Nicotine—nicotine
  – Bupropion—nicotine
  – Varenicline—nicotine
Medication Assisted Treatment

• “Off label”
  – Gabapentin—alcohol and cannabis
  – Topiramate—alcohol and stimulants
  – Baclofen—alcohol
  – Disulfiram—cocaine
  – Ondansetron—alcohol
  – Modafinil—cocaine
  – Nortriptyline—nicotine
  – Clonidine—nicotine
  – Valproate—alcohol
  – Carbamazepine—alcohol
...but does it work?

• Difficult to say
• Best trial to date, Fuller et al. (1986). JAMA 256:1449-55.
• 600 veterans in VA system
• 3 groups
  – Disulfiram 250 mg/day
  – Disulfiram 1 mg/day
  – Placebo
• No difference in relapse rates between groups
• Those who relapsed the 250 mg/day group had fewer drinking days
• Compliance rates
  – 20% compliant—43% remained abstinent
  – 80% non-compliant—8% abstinent
Evidence

  – 12 week study—70 patients (placebo controlled)
  – Relapse rates: 23% vs. 54.3% (defined below)
    • 5/7 days per week
    • A heavy drinking day (5 or more drinks)
    • Reporting to follow up appt. with a BAC of 0.100
  – Cravings decreased
  – Slips and relapses (95% placebo vs. 50% naltrexone)
Another trial

- Six months
- Disulfiram vs. Vitamin C under supervision (patient and supervisor of patient’s choice not blinded)
- Increased abstinent days
So...

- Compliance is a big factor
- Taking it under supervision may be the best context
- Side effect profile significant
Naltrexone (alcohol and opioids)

- Opioid antagonist
- Reduces relapse rate
- FDA: opioids 1985
- FDA: alcohol 1994
Alcohol mechanism

• Blockade of alcohol induced dopamine release via the opioid neurotransmitter system in VTA
• Reduces drinking days
• Slips and relapses
• Reduces cravings
Prefrontal cortex, Anterior cingulate gyrus: executive functions, error detection
Orbital frontal cortex, subcallosal cortex: modulate response behaviors to rewarding drugs; disinhibition and perseveration when damaged
Nucleus accumbens, ventral pallidum (globus pallidus): reward circuitry
Amygdala, Hippocampus: emotional memory, factual memory
Mechanism
Opioid mechanism

- **Heroin**: Full agonist
- **Buprenorphine**: Partial agonist
- **Naloxone**: Antagonist

Activity zone

Affinity zone
Evidence: alcohol

  – 12 week study—70 patients (placebo controlled)
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    • 5/7 days per week
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    • Reporting to follow up appt. with a BAC of 0.100
  – Cravings decreased
  – Slips and relapses (95% placebo vs. 50% naltrexone)
Evidence: alcohol

  - 12 week study—97 patients (placebo controlled)
  - Added psychosocial intervention (CBT/supportive therapy)
  - Results
    - 61% CBT + naltrexone abstinent
    - 28% support + naltrexone abstinent
    - 21% CBT + placebo
    - 19% support + placebo
  - Slips less likely to turn into relapses
  - Naltrexone patients had fewer drinking days (4.3% vs. 9.9%)
  - Less craving as well
Evidence summary

• 50 randomized controlled trials
• 7793 patients
• Alcohol dependence
• Reduction of heavy drinking days by 83%
• Reduction of number of drinking days by 4%
Evidence: opioids

• Cochrane review: 1973-2010
  – 1158 patients
  – No statistically significant difference from placebo in preventing relapse
Naltrexone (practical points)

- 50 mg/day (start with 25 mg/day)
- Liver disease
- Alcohol: start when detox is complete
- Opioids: start 7-10 days after last opioid use
- Potential side effects
  - Nausea
  - Fatigue
  - Mood
  - Hepatotoxicity
- Guaranteed side effect
  - Opioid analgesic blockade
IM naltrexone (alcohol and opioids)

- FDA
  - Alcohol 2006
  - Opioids 2010
- Lower cumulative dose (380 mg per month vs. 1500 mg per month)
- Compliance
- Side effects milder
...but there are unique side effects

- Eosinophilic pneumonia—rare
- Sterile abscess at injection site
- Swimming pools and hot tubs
Evidence: alcohol

- Six month trial (380 mg/190 mg/placebo)
- Psychosocial intervention
- Decreased heavy drinking days by 25%/17% compared to placebo
- Discontinuation 14.1%/6.7%/6.7%
Evidence: opioids

• Krupitsky et al., 2011. The Lancet vol. 977: 1506-1513
  – 250 patients randomized to the following for 6 months
    • 380 mg IM naltrexone plus counseling
    • Placebo plus counseling
  – Median patient in study group had 90% drug free urines
Another way to skin the cat or the pendulum starts swinging back

• Methadone
  – Developed by Farbenindustrie in 1937
  – Bockmuhl and Ehrart applied for a patent in 1941
  – After WWII patents transferred to the U.S. and Eli Lilly began synthesizing methadone
  – FDA approval occurred in 1947
  – Dole and Nyswander studies in the 1960s
Dole and Nyswander
Methadone Clinic opened 1964
Rockefeller Institute (now Rockefeller University)

Vincent Dole, MD (1913-2006)
Marie Nyswander, MD (1919-1986)
The Real Message

Heroin Addiction – A Metabolic Disease
Vincent P. Dole, MD and Marie E. Nyswander, MD, New York
Arch Intern Med–Vol 120, July 1967
Opioid maintenance

- Methadone (two enantiomers $\alpha$ and $\beta$)
  - $\alpha$ – NMDA antagonist
  - $\beta$ – opioid full agonist
- long plasma half life—13-47 hours
- useful for detoxification and maintenance
Benefits/Harm Reduction

• Decreased mortality (1/3)
• Pregnant women generally experience uneventful pregnancies
• Decrease in HIV sero-conversion rate (50%-2.5%)
• Reduced criminal activity
• Increased retention in treatment
• Improved psychosocial adjustment
Buprenorphine: a partial agonist for opioid replacement therapy
Pharmacology of partial agonists
Calcium acetylhomotaurinate  
Acamprosate

- Structural analog of GABA and taurine
- Post acute withdrawal syndrome
  - Low concentrations: increases low receptor activity
  - High concentrations: decreases high receptor activity
Mechanism

NMDA receptor complex

Illustrates four types of reaction inhibition

Glutamate and glycine are co-agonists

Polyamine = acamprosate site?

1. Mild activation in setting of low concentrations and low activation (alcohol ingestion)

2. Inhibition in setting of high concentrations and high activation (alcohol withdrawal and post alcohol withdrawal)

Zinc = allosteric inhibitor

PCP and other dissociatives block channel

Mg blocks channel
A. Glutamate and glycine must be bound for activation to occur—co-agonism

B. Competitive antagonism: glutamate site blocked

C. Noncompetitive antagonism: allosteric site of blocked (zinc)

C. Glycine antagonism: glycine site blocked

E. Uncompetitive antagonism: site blocked on enzyme substrate complex (PCP, ketamine, nitrous oxide)
Acamprosate
practical matters

• Dose 666 mg tid for up to one year.
• Eliminated via kidneys
• Non-addictive
• Does not interact with any other medication
• Side effects: diarrhea, bloating, mood changes
Evidence

- For relapsers
  - Less quantity
  - Less frequency
  - Less risk of heavy drinking (five or more per day)
Tobacco

- Varenicline
- Bupropion
- Nicotine replacement
- Bupropion + nicotine replacement
Varenicline

- Partial agonist at the nicotinic receptor
- Prevents binding by nicotine
- Results in a low level of dopamine in the nucleus accumbens to reduce craving and ameliorate withdrawal
- Trials so far show superiority to placebo and bupropion (treatment periods 12 weeks with additional 40 week follow-up)
Finally buprenorphine

• 1986—Anti-Drug Abuse Act of 1986—Strengthened federal efforts at enforcement, improved foreign cooperation, reimposed mandatory sentencing laws
• 1988—Anti-Drug Abuse Act of 1988—Established office of National Drug Control Policy in Executive Office of the President; focused on school based prevention efforts and treatment for injecting users with AIDS
• 2000—The Drug Addiction Treatment Act of 2000—Allows physicians to prescribe schedule III and IV drugs that are FDA approved for the purpose of treating addiction
• 2002—FDA approves buprenorphine
Let’s shift the discussion

Chemical Addictions

Process Addictions

With a special focus on gambling
First, what are they?

- Gambling
- Sex
- Shopping/spending
- Internet gaming
- Binge eating
- Hoarding
- Trichotillomania
- Kleptomania
- Internet
What do we know?

• We know less about process addictions than substance use disorders.
• We know more about gambling disorder than the other process addictions.
• Dopamine, a chemical that plays a role in chemical addictions, also plays a role in gambling disorder. There is evidence for involvement of other neurotransmitters as well.
• The mesolimbic and mesocortical systems are involved in both chemical and gambling disorders.
• Parkinson’s disease patients provide an interesting model to study some process addictions.
Gambling disorder or “ludomania”
Some definitions

• Reward
• Vulnerability
• Neuroplasticity
Some definitions

• Reward (reinforcement)
• Vulnerability (risk factors)
• Neuroplasticity (learning)
THE REWARD SYSTEM: THE CORE
MESOCORTICAL AND MESOLIMBIC
Relevant areas of the brain

• Reward and reinforcement
  – Ventral tegmental nucleus
  – Ventral pallidum [receives DA input from VTA; projects to thalamus (memory)]
  – Nucleus accumbens
• Memory
  – Hippocampus
  – Amygdala
• Executive function
  – Pre-frontal cortex
• Coordination of movement and behavior
  – Dorsal striatum
  – Substantia nigra
• Reward anticipation, decision making, impulse control, error detection
  – Anterior cingulate cortex
Pre-frontal cortex = the “brake”

- Processes reward
- Decision making
- Controls whether a behavior is performed and to what intensity
Implicated neurotransmitters

- Norepinephrine—arousal and excitement
- Serotonin—impulse control
- Dopamine—rewarding and reinforcing aspects
- Opioids—pleasures and urges
- Cortisol—stress responsiveness
- Glutamate—cognitive functioning and flexibility

Potenza, 2013
Functionally…

Dopamine D2 Receptors are Decreased by Addiction
Normal                          Obese

Cocaine                         Alcohol

BRAIN REWARD CENTER
What do the colors mean?

RED
high dopamine
normal pleasure and
interest

YELLOW
medium dopamine
difficulty feeling joy or
pleasure

GREEN
low dopamine
lack of pleasure
Individual Differences in Response to Drugs: DA Receptors influence drug liking

As a group, subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant

Adapted from Volkow et al., Am. J. Psychiatry, 1999.
Treatment

• Cognitive Behavioral Therapy
• Mindfulness
• Motivational Interviewing
• 12 step
• Financial Planning
• Self restriction from casinos—video gaming, internet gaming
• Medication Assisted Treatment
Medication Assisted Treatment
Gambling

• Opioid antagonists
  – Nalmefene—Grant et al., 2006; Grant et al., 2010
  – Naltrexone—Kim et al., 2001; Grant et al., 2008; Grant et al., 2008
• Selective serotonin reuptake inhibitors
  – Paroxetine—Kim et al., 2002
  – Fluvoxamine—Hollander et al., 2000; Blanco et al., 2002
  – Sertraline—Saiz-Ruiz et al., 2005
  – Escitalopram—Grant & Potenza, 2006; Black et al., 2007
• N-Acetyl Cysteine—Grant et al., 2007 (glutamate)
• Carbamazepine—Black et al., 2008 (GABA)
• Lithium—Hollander et al., 2005
• Amantadine—Pettoruso et al, 2012 (CR); Thomas et al., 2010 (PD patients) (glutamate)
• Topirimate—Dannon et al., 2005 (GABA-A)
• Modafanil—Zack & Poulos, 2009 (dopamine)
• Memantine—Grant et al., 2010 (glutamate)
• Acamprosate—Black et al, 2011 (glutamate)
Medication Assisted Treatment for Process Addictions

• Hypersexuality
  – Opioid antagonists—naltrexone (Bostwick & Bucci, 2008)

• Kleptomania
  – Opioid antagonists—naltrexone (Grant & Kim, 2002)

• Shopping/spending
  – SSRIs—citalopram (Koran et al., 2002)

• Hoarding
  – SSRIs—paroxetine (Saxena et al., 2006)

• Binge eating
  – SSRIs—sertraline (McElroy et al., 2000); citalopram (McElroy et al., 2003)

• Internet gaming
  – SSRIs—escitalopram (Dell’Osso et al., 2008)

• Trichotillomania
  – Opioid antagonists—naltrexone (Carrion, 1995)
Amantadine is a complex medication...or a drug looking for an indication

• Anti-viral (influenza)
• Dopaminergic (Parkinson’s, cocaine withdrawal)
• NMDA receptor antagonist (Alzheimer’s, gambling)

Hubsher et al., 2012
N-Acetyl Cysteine

- 1476.9 +/- 311.3 mg/day
- Over the counter
A suggested algorithm

- If urges or cravings to gamble are present
  - If resistant to prescription medications try NAc
  - Trial of opioid antagonist
  - If co-occurring SUD trial of opioid antagonist
  - If depression/anxiety playing a major role trial of SSRI
  - If mania/hypomania playing a major role trial of Li

- Always consider CBT

Grant and Kim, 2006
Addictions?

• Tanning?
• Sugar?
• Chocolate?
Tanning

• Tanning an addiction
  – Met DSM IV-TR criteria
    • Warthan et al. 2005 Arch. Derm.

• UV light hypothesis
  – UV light vs placebo
    • Wagner and Kaur 2005
  – Brain imaging
    • Adinoff et al. 2011 (SPECT imaging—increased activity striatum)

• Body dysmorphic disorder

• Withdrawal phenomenon
  – Naltrexone (2006) varying doses
  – 50 mg
  – Starting with 5mg and increasing
    • Kaur et al., 2006
Chocolate

- Phenylethylamine
- Endorphins
- Anandamide
- Tryptophan
- Caffeine
- Theobromine
Sugar

• What triggers endorphin and other neurotransmitter release?
  – Sugar
  – Fat
  – Phenylethylamine
But...

- These also result in endorphin release or synthesis
  - Exercise
  - Meditation
  - Healthy diet
Summary and major themes

• There is a long history of medication assisted treatment for substance use disorders...not all of which was helpful.
• There are multiple analogies between substance use disorders and process addictions.
• The similarities in neurobiology have assisted investigators in pursuing medication assisted treatments for process addictions.
Mindfulness

"What day is it?" asked Pooh. "It's today." squeaked Piglet. "My favorite day." said Pooh.

My thanks to Ilene Robeck, MD
Questions

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