Psychopharmacological Treatment of Substance Use Disorder(s)

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OBJECTIVES

- SBIRT
- Review of the reward pathway
- Pharmacologic Management of Alcohol Substance Use Disorder
- Pharmacologic Management of Cocaine Substance Use Disorder
- Pharmacologic Management of Nicotine Substance Use Disorder
- Pharmacologic Management of Opiate Substance Use Disorder
SBIRT

- Screening; Brief Intervention; Referral to Treatment

- Comprehensive, integrated, public health approach to the delivery of early intervention and treatment services
CRAFFT is a mnemonic acronym of first letters of key words in the 6 screening questions. The questions should be asked exactly as written.

- Have you ever ridden in a CAR driven by someone (including yourself) who was “high” or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?
- Do you ever use alcohol or drugs while you are by yourself, or ALONE?
- Do you ever FORGET things you did while using alcohol or drugs?
- Do your family or FRIENDS ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into TROUBLE while you were using alcohol or drugs?

Score of 2 or more is positive
Mesocorticolimbic Pathway in Addiction

- In the brain, dopamine helps regulate reward and body movement.
- As part of the reward pathway, dopamine is produced by neurons in the ventral tegmental area (VTA) and released in the Nucleus accumbens and the prefrontal cortex, leading to the feeling of pleasure.
Reward Pathway

Dopamine Pathways
- Frontal cortex
- Nucleus accumbens
- VTA
- Striatum
- Substantia nigra

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Serotonin Pathways
- Striatum
- Substantia nigra
- Hippocampus
- Raphe nuclei

Functions
- Mood
- Memory processing
- Sleep
- Cognition
Treatment of Alcohol Substance Use Disorder

Action of Alcohol: binds to GABA-A receptors, which is ionotropic receptor and ligand-gated chloride ion channel.

Treatment for Alcohol dependence involves agonizing and or antagonizing GABA-A and sometimes GABA-B receptors.

Pharmacologic treatment options include:
- Naltrexone
- Disulfuram
- Acamprosate
- Gabapentin
- Baclofen
- SSRI’s
- Nalmefene (hot off the press new studied medication, April 2013)
FDA-approved Pharmacological Treatments for Alcohol Dependence

- **Disulfiram**
  - 1951

- **Naltrexone**
  - 1994

- **Acamprosate**
  - 2004
  - 2006

- **Naltrexone for extended-release injectable suspension**

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Treatment of Alcohol Substance Use Disorder

NALTREXONE: Opioid receptor antagonist

- FDA approved in 1994 for treatment of Alcohol Dependence, approval was inspired by two 1992 randomized controlled trials that demonstrated its efficacy in reducing frequency and severity of relapse to drinking.

- Mechanism of action: Naltrexone and its active metabolite 6-β-naltrexol are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptors.

- Plasma half-life of naltrexone is about 4 h and for 6-β-naltrexol 13 h.

- Mechanism of action in alcohol dependence: not well understood, but postulated to involve modulation of the dopaminergic mesolimbic pathway.

- Oral formulation is Revia and Depade.

- Once-monthly extended-release injectable formulation is Vivitrol.

- Common SE’s: Gastrointestinal, diarrhea and abdominal cramping. When given at high doses (beyond 50 mg, there is increased risk for liver damage).

- Multi-center COMBINE study showed the usefulness of naltrexone in a primary care setting, without adjunct psychotherapy.

- Standard dosing is 50 mg per day.
Treatment of Alcohol Substance Use Disorder

**DISULFIRAM (Antabuse): inhibitor of acetaldehyde dehydrogenase**

- Normal metabolism of alcohol: broken down in the liver by the enzyme alcohol dehydrogenase TO acetaldehyde. Acetaldehyde is then converted to less innocuous acetic acid BY *acetaldehyde dehydrogenase*. Disulfiram blocks this metabolic process.
- Initial dose is 500 mg a day for one to two weeks, followed by a maintenance dose of 250 mg (range 125 mg–500 mg) per day
- Total daily dosage should not exceed 500 mg
- Severe reaction within 10 minutes of alcohol intake. Symptoms are reminiscent of a severe hangover to include: Flushing of the skin, accelerated heart rate, shortness of breath, nausea, vomiting, throbbing headache, visual disturbance, mental confusion, postural syncope, and circulatory collapse

**SE’s:** Drowsiness (Tryptophol formation); headaches; garlic taste in mouth; rare cases of EPS; interaction with acetaminophen, caffeine and theophylline (occurred in 20-40% and was mild); liver problems

- Aversion therapy
- Doesn’t reduce cravings, so compliance is an issue
ACAMPROSATE: Theorized to work by antagonizing N-methyl-D-aspartate receptors (NMDA) and agonizing gamma-aminobutyric acid (GABA) type A receptors

- Effective when combined with CBT based treatment
- Oral dosing: 666 mg (two 333 mg tabs)
- SE’s: diarrhea, allergic reactions, irregular heartbeats, and low or high blood pressure
- Acamprosate is poorly absorbed after oral administration
- Average bioavailability of only 11%
- Time to reach steady state occurs within 5 days of dosing
- Steady-state peak plasma concentrations are reached within 3–8 hours following dosing
- Acamprosate does not undergo metabolism
- primarily excreted unchanged through the kidneys; avoid in persons with kidney disease
- No significant drug-drug interactions

I. No significant difference between Naltrexone and Acamprosate in terms of average days of abstinence and days until first breach of abstinence
Treatment of Alcohol Substance Use Disorder

GABAPENTIN: GABA analog

- SE’s: dizziness, fatigue, weight gain, drowsiness, and peripheral edema
- Associated with high risk of suicide and violent deaths
- Excreted primarily unchanged from the kidney, avoid in persons with kidney disease
- Limited drug-drug interactions
- Not FDA approved, but recent study published in JAMA shows Gabapentin as a promising treatment option

Barbara J. Mason, PhD et al. *Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial. JAMA Intern Med.* Published online November 04, 2013

- 12-week randomized, double-blind, placebo-controlled study of 150 subjects with alcohol dependence
- Oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling
- Results: Gabapentin (particularly the 1800-mg dosage) was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria, and craving, with a favorable safety profile
Treatment of Alcohol Substance Use Disorder

Baclofen is a GABA-B agonist

- Not FDA approved
- May 2011, a Scottish team from Glasgow presented Baclofen as a drug for use in controlling the craving and consequences of drinking in alcoholics, at the "Royal College of Psychiatrist's Faculty of Addictions" annual meeting
- Used doses between 15 and 360 mg of baclofen per day
Treatment of Alcohol Substance Use Disorder

**NALMEFENE**: opioid receptor modulator with increased relative potency for kappa opiate receptors compared to its potency at mu opiate receptors

Study Design:
- Recruited 604 alcohol-dependent patients
- Half of whom were randomized to receive Nalmefene
- Other half received visually-identical placebo pills
- Neither patients nor their doctors knew which treatment they were receiving
- Patients were instructed to take one tablet on each day they perceived a risk of drinking alcohol
- Each participant was followed by the study investigators for 24 weeks

Results: Promising.
- Nalmefene was significantly better than placebo in reducing alcohol consumption and it improved patients' clinical status and liver enzymes
- Generally well-tolerated
- Most side effects characterized as mild or moderate and quickly resolved

Treatment of Alcohol Substance Use Disorder

SSRI’s

- Shown to reduce cravings
- Mostly helpful in treatment of co-morbid depression and anxiety disorders
Treatment of Cocaine Substance Use Disorders

Cocaine in the brain: In the normal communication process, dopamine is released by a neuron into the synapse, where it can bind to dopamine receptors on neighboring neurons. Normally, dopamine is then recycled back into the transmitting neuron by a specialized protein called the dopamine transporter. If cocaine is present, it attaches to the dopamine transporter and blocks the normal recycling process, resulting in a buildup of dopamine in the synapse, which contributes to the pleasurable effects of cocaine.

Cocaine blocks reuptake of DA, NE and 5HT.
Treatment of Cocaine Substance Use Disorder

No FDA approved treatments at this time

Studies implicate the use of

- **Topiramate** - a glutamate receptor antagonist and GABA agonist
- **Disulfuram** - inhibits dopamine beta-hydroxylase resulting in an excess of dopamine and decreased synthesis of norepinephrine
- **Modafinil** - elevates hypothalamic histamine levels
- **Naltrexone** – reduces cravings by acting on mesocorticolimbic pathway

![Chemical Pathway Diagram]

**Phenylalanine**

- Phenylalanine Hydroxylase
- Tyrosine
- Tyrosine Hydroxylase
- DOPA
- DOPA Decarboxylase
- Dopamine
- Dopamine Beta-Hydroxylase
- Norepinephrine
Topiramate (Topomax)
DESIGN Double-blind, randomized placebo-controlled, 12 week trial of 142 Cocaine-dependent adults in clinical research facilities at the University of Virginia between November 2005-July 2011

INTERVENTIONS Topiramate (n = 71) or placebo (n = 71) in escalating doses from 50 mg/d to the target maintenance dose of 300 mg/d in weeks 6 to 12, combined with weekly cognitive-behavioral

OUTCOMES the primary outcome was the weekly difference from baseline in the proportion of cocaine nonuse days; the secondary outcome was urinary cocaine-free weeks, and exploratory outcomes included craving and self- and observer-rated global functioning on the Clinical Global Impression scales

CONCLUSION Topiramate > Placebo in reducing use and cocaine cravings

Johnson, BA et al. Topiramate for the Treatment of Cocaine Addiction: A Randomized Clinical Trial. JAMA Psychiatry. 2013 October 16
Disulfiram

- Seven studies, 492 participants, met the inclusion criteria for Disulfiram versus placebo: no statistically significant results for dropouts but a trend favouring disulfiram, two studies, 87 participants, RR 0.82 (95% CI 0.66 to 1.03)

- One more study, 107 participants, favoring disulfiram, was excluded from meta-analysis due high heterogeneity, RR 0.34 (95% CI 0.20 to 0.58)

- For cocaine use, it was not possible to pool together primary studies, results from single studies showed that 1 of 4 comparisons, was in favor of disulfiram (number of weeks abstinence, 20 participants, WMD 4.50 (95% CI 2.93 to 6.07)

- Disulfiram versus naltrexone: no statistically significant results for dropouts but a trend favoring disulfiram

Treatment of Cocaine Substance Use Disorder

Modafinil

- Double-blind placebo-controlled study
- 12 weeks of treatment and a 4-week follow-up
- Six outpatient substance abuse treatment clinics participated in the study
- 210 treatment-seekers randomized, having a diagnosis of cocaine dependence
- 72 participants were randomized to placebo
- 69 to modafinil 200 mg, and 69 to modafinil 400 mg, taken once daily on awakening
- Participants came to the clinic three times per week for assessments and urine drug screens, and had one hour of individual psychotherapy weekly
- The primary outcome measure was the weekly percentage of cocaine non-use days

Treatment of Nicotine Substance Use Disorder

FDA Approved Pharmacotherapeutic agents – treat cravings

- Verinicline (Chantix)
- Bupropion (Wellbutrin)

FDA Approved Nicotine Replacement Therapy (mainly to treat w/d sx’s and should be distinguished from Verinicline and Bupropion that treat cravings)

- Nicotine Patch: Approved for 3-5 months of use, possible SE’s include skin irritation, dizziness, racing heartbeat, sleep problems, headache, nausea, muscle aches and stiffness
- Nicotine Lozenges: Lozenge makers recommend using them as part of a 12-week program. Recommended dose is 1 lozenge every 1 to 2 hours for 6 weeks, then 1 lozenge every 2 to 4 hours for weeks 7 to 9, and finally, 1 lozenge. SE’s include trouble sleeping, nausea, hiccups, coughing, heartburn, headache, flatulence
- Nicotine Gum: Recommended for 6-12 weeks of use with the maximum being 6 months. SE’s include nausea, bad taste, throat irritation, mouth sores, hiccups, jaw discomfort, racing heartbeat
- Nasal Spray: FDA recommends 3 month rx periods and no use longer than 6 months total. SE’s include nasal irritation, runny nose, watery eyes, sneezing, throat irritation and coughing
- Inhalers: FDA recommends 3 month rx periods an no use longer than 6 months total. SE’s include coughing, throat irritation and upset stomach
Treatment of Nicotine Substance Use Disorder

**HOW VARENCLINE WORKS**

- Nucleus accumbens
- Ventral tegmental area

**NICOTINE—AGONIST ACTION**

1. **SMOKING**
   - Nicotine receptors
   - Cell body of dopamine neuron
   - Nicotine
   - Dopamine release from nucleus accumbens

2. **'GOLD TURKEY'**
   - Drug blocks receptors yet still triggers dopamine release

3. **WITH VARENCLINE**
   - Nicotine
   - Dopamine released over time

**CHANTIX—AGONIST AND ANTAGONIST ACTIONS**

- Nicotine is blocked
- Less dopamine is released over time
Treatment of Nicotine Substance Use Disorder

Varenicline (FDA Approved)

- The efficacy of CHANTIX in smoking cessation is believed to be the result of Varenicline's activity at $\alpha_4\beta_2$ sub-type of the nicotinic receptor, where its binding produces agonist activity at a significantly lower level than nicotine while simultaneously preventing nicotine binding to these receptors.

- Varenicline also acts as an agonist at 5-HT3 receptors.

- Due to its competitive binding on these receptors, varenicline blocks the ability of nicotine to bind and stimulate the mesolimbic dopamine system.

- Dosing: ½ tab BID for first week, then increase to 1 mg BID. Recommended use for 3 months intervals, NTE 6 months of use.

- SE’s: increased SI risks, abdominal pain, nausea, vomiting, flatulence, abnormal dreams, increased cardiovascular risks.
Treatment of Nicotine Substance Use Disorder

DESIGN

- Study is double-blind, parallel-arm adaptive treatment trial
- A total of 606 cigarette smokers started open-label nicotine patch treatment 2 weeks before the quit date
- Those whose ad lib smoking did not decrease by >50% after 1 week were randomly assigned to one of three double-blind treatments:
  - Nicotine patch alone (control condition);
  - “Rescue” treatment with bupropion augmentation of the patch
  - Rescue treatment with varenicline alone
- Participants whose pre-cessation smoking decreased >50% but who lapsed after the quit date were also randomly assigned to the two rescue treatments or to nicotine patch alone
- Logistic regression analyses compared each rescue treatment against the control condition in terms of abstinence at the end of treatment (weeks 8–11) and at 6 months

RESULTS

- Abstinence rates were higher with Buproprion + Patch
  - Buproprion + patch (28%) > Verinicline (16.5%) > Patch Alone (6.6%)

Treatment of Nicotine Substance Use Disorder

**Bupropion (Wellbutrin)**

SNRI that increases levels of dopamine and norepinephrine, brain chemicals that are also boosted by nicotine

**DOSING**

- Bupropion usually is started as 150 mg once daily for three days, and then the dose is increased if the patient tolerates the starting dose. Smoking is discontinued two weeks after starting bupropion therapy.
- Wellbutrin SR is given as two daily doses
- Wellbutrin XL is given as one dose daily

SE’s: insomnia, headache, lower seizure threshold, alopecia, anorexia
Treatment Opiate Substance Use Disorder

FDA approved pharmacological interventions for Opiate Substance Abuse Disorder

- Methadone: opioid agonist
- Buprenorphine (subutex): mu agonist, kappa antagonist
- Buprenorphine + Naloxone (suboxone) = oral, film and sublingual (Zubsolv) formulation
- Naltrexone (po form and IM form, Vivitrol): opioid antagonist

Information obtained from the American Society of Addiction Medicine

- SUBOXONE PA FOR UP TO SIX MONTHS; PA FOR VIVITROL REQUIRES PATIENT TO HAVE FAILED ALL THREE OTHER MEDICATIONS: ORAL NALTREXONE, SUBOXONE AND METHADONE
- In Oregon, Medicaid will cover methadone, buprenorphine, buprenorphine + suboxone and naltrexone
- Regarding Buprenorpine/Buprenorphine + Naloxone; in Oregon, Medicaid lifetime limit is 99 months, dose is capped at 24 mg. Different in other States. New Jersey Medicaid allows upper limit dosing of 32 mg of buprenorphine.
<table>
<thead>
<tr>
<th>Product</th>
<th>Formulations</th>
<th>Receptor Pharmacology</th>
<th>FDA Approval</th>
<th>DEA Schedule</th>
<th>Treatment Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Oral solution, liquid concentrate, tablet/diskette, and powder</td>
<td>Full mu opioid agonist</td>
<td>Didn’t go through formal approval, <strong>but is approved</strong></td>
<td>II</td>
<td>OTP</td>
</tr>
<tr>
<td>LAAM</td>
<td>Oral solution</td>
<td>Full mu opioid agonist</td>
<td>1993</td>
<td>II</td>
<td>OTP</td>
</tr>
<tr>
<td>Buprenorphine (Subutex®)</td>
<td>Sublingual tablet</td>
<td>Partial mu opioid agonist</td>
<td>2002</td>
<td>III</td>
<td>Physician's office, OTP, or other health care setting</td>
</tr>
<tr>
<td>Buprenorphine-naloxone (Suboxone®)</td>
<td>Sublingual tablet</td>
<td>Partial mu opioid agonist/mu antagonist</td>
<td>2002</td>
<td>III</td>
<td>Physician's office, OTP, or other health care setting</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Oral tablet</td>
<td>Mu opioid antagonist</td>
<td>1984</td>
<td>Not scheduled</td>
<td>Physician's office, OTP, any substance abuse treatment program</td>
</tr>
</tbody>
</table>

**Treatment of Opiate Substance Use Disorder**

**Methadone**
- Opioid agonist
- FDA Schedule II
- Dosing: 80-125 mg
- Rule of thumb: go low and go slow
- Doses should be increased by no more than 5 to 10 mg on any day and the total weekly increase beyond the starting day’s dose should not exceed 20 mg
- Long acting
- Several drug-drug interactions: enzymes CYP3A4, CYP2B6 and CYP2D6
- SE’s: anxiety, sleep problems (insomnia), feeling weak or drowsy, dry mouth, nausea, vomiting, diarrhea, constipation, loss of appetite, decreased sex drive, impotence, or difficulty having an orgasm
- Notable SE’s: QTc prolongation; affects testosterone and thyroid
Buprenorphine and Buprenorphine/ Naloxone Help Patients Quit Opiate Abuse


**Buprenorphine**

- DEA, Schedule III
- Subutex (buprenorphine) = Suboxone (buprenorphine + naloxone) and both are > placebo
- Naloxone = special narcotic drug that reverses the effects of other narcotic medicines (mu antagonist)
- Transdermal & injectable formulation is used primarily for chronic pain
- Sublingual & oral used for treatment of opiate substance use disorder
- Buprenorphine is metabolized by the liver, via CYP3A4; CYP2C8 isozymes of the cytochrome P450
- Half life: 20–73 hours
# Methadone VS. Buprenorphine

<table>
<thead>
<tr>
<th>METHADONE (narcotic blockade achieved)</th>
<th>BUPRENORPHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Full mu agonist</td>
<td>▪ Partial mu agonist</td>
</tr>
<tr>
<td>▪ 24-36 hour half life</td>
<td>▪ 36-48 hour half life</td>
</tr>
<tr>
<td>▪ Daily dose frequency</td>
<td>▪ Daily or alternative dose frequency</td>
</tr>
<tr>
<td>▪ More abuse potential</td>
<td>▪ Less abuse potential</td>
</tr>
<tr>
<td>▪ No protective overdose factors</td>
<td>▪ Ceiling effect limits overdose risk</td>
</tr>
<tr>
<td>▪ More effective for severe dependence</td>
<td>▪ Limited to mild-moderate dependence</td>
</tr>
<tr>
<td>▪ Moderate/severe protracted w/d</td>
<td>▪ Mild w/d symptoms</td>
</tr>
<tr>
<td>▪ Oral liquid = less risk of injection</td>
<td>▪ Tablet preparation = risk of injection</td>
</tr>
<tr>
<td>▪ Tablet preparation is available</td>
<td>▪ Moderately expensive</td>
</tr>
<tr>
<td>▪ Inexpensive</td>
<td></td>
</tr>
</tbody>
</table>

Did you learn anything????

1. Name 2 FDA approved drugs for treatment of Alcohol Substance Use Disorder.
2. Name 2 FDA approved drugs for the treatment of Cocaine Substance Use Disorder.
3. Name 2 FDA approved drugs for the treatment of Nicotine Substance Use Disorder.
4. Name 2 FDA approved drugs for the treatment of Opiate Substance Use Disorder.
5. What is SBIRT?
QUESTIONS???????