Treatment of Adolescent Substance Use Disorders Text

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Disclosures

• Pfizer Inc. Research Support
Learning Objectives

• Treatment and treatment effectiveness - Pharmacotherapies
• Other treatment considerations -
• Reasons for Relapse
• Clinical Summary and Pearls
Treatment: Pharmacotherapies

I. Aversion

II. Craving

III. Reduction—has overlap with other studies discussed during talk—therefore not included in talk

IV. Substitution

V. Detoxification

VI. Treatment of co morbid psychiatric disorders.

• (Simkin and Grenoble, Child and Adol Clinics of North America, 2010)
Two **Windows of opportunity** to prevent opioid dependence:

1. Since opioid addiction seldom occurs in adolescents without previous substance abuse, identification of all risk factors and present use of substances of abuse that can increase the risk of opioid dependence must be addressed during adolescents.

2. Children of Opioid Dependent parents must be identified and proper interventions must be done to decrease the risk of future SUD and co-morbidity in their children.
Treatment

1. Risk factors that are important to address in order to prevent opioid dependence were previously discussed.
   - However, treatment of other substance use dependence disorders and co-morbid conditions were not discussed.
   - Only treatment of marijuana, alcohol, nicotine and opioids will be included here due to the high overlap of use and the reports that alcohol and marijuana use predict opioid use.
Treatment

2. Children of heroin dependent (HD) parents had largely elevated rates of recurrent major depressive disorder.

– Children of HD patients were also at an increased risk for attention deficit hyperactivity disorder and substance use disorders (SUD). There were interactions between SUD in the 2 parents to increase the risk of SUD in offspring.


– So, one cannot treat a parent without treating the family
I. Aversion

• Used to reduce alcohol or drug use through the development of unpleasant responses following the consumption of the abused substance

• A. Alcohol-Disulfiram (Antabuse)
  • FDA approved for adults for alcohol dependence

• An inhibitor of the liver enzyme acetaldehyde dehydrogenase, resulting in an accumulation of acetaldehyde (a toxic by-product with adverse effects) when consumed with alcohol.
Aversion

• Adverse effects may last up to 2 weeks with alcohol consumption after disulfiram is discontinued

• Rare but serious adverse reactions have been reported, including arrhythmias, respiratory depression, toxic hepatitis, seizures, and death

• Two known studies have been published to date on disulfiram treatment in adolescents.
Aversion-Disulfiram

1. Double-blind, randomized, controlled trial compared disulfiram (200 mg daily) to placebo in 49 alcohol-dependent adolescents (aged 16–19 years).
   - Compliance not reported, diarrhea most common side effect
   - At 90 days the proportion of subjects who remained abstinent was statistically higher in the disulfiram group ($P= 5 \times 0.0063$).
   - The most common reason for study withdrawal was relapse
   - Diarrhea=only adverse effect reported more in the disulfiram group

2. A case report was published studying disulfiram (200 mg daily) in two alcohol-dependent adolescents.
   - One subject had comorbid dysthymic disorder and remained abstinent for 4 months
   - The other subject had comorbid major depressive disorder and oppositional defiant disorder and was never compliant with treatment.
   - (Myers WC, et al, JAACP, 1994)

• Summary—mixed results with disulfiram
II. Craving

The goal of this class of agents is to assist in craving and withdrawal reduction, and therefore help prevent relapse.

A. **Alcohol** - When drug-associated drug cues are recognized, there is a profound activation of the PFC and glutamatergic drive to the core of nucleus accumbens (NAc). Drug craving occurs in this scenario.

1. **Acamprosate (Campral)** - Only FDA approved in adults. In vivo studies suggest that it restores the central balance between glutamate and the γ-aminobutyric acid (GABA) that are disrupted by prolonged alcohol exposure.
a) One study in Adolescents

- Double-blind, randomized, controlled trial compared acamprosate (1332 mg daily divided 3 X/d) to placebo.
- In 26 alcohol-dependent adolescents (aged 16–19 years).
- Time to first occurrence of relapse = #1 outcome measure.
- Cumulative abstinence duration = #2 outcome measure.
- At 90 days the # of subjects who remained abstinent was statistically higher in the acamprosate group compared with the placebo group (7 of 13 vs 2 of 13; P = .0076).
- Mean cumulative abstinence duration was statistically greater in the acamprosate group versus placebo (79.8 [SD 37.5] vs 32.8 [SD 19.0] days; P = .012).

Craving—Oral naltrexone

B. Alcohol

1. Oral naltrexone
   - FDA approved for the treatment of alcohol dependence in adults.
   - A pure mu-opioid antagonist
   - Chronic alcohol use = increase in endogenous opioids which influences the Ventral Tegmentum (VTA) and Nucleus Accumbens (NaC)
   - It is thought to restore central balance of the endogenous opioid system that is disrupted by prolonged alcohol exposure.
   - This restoration is thought to occur by blocking opioid peptides produced by the influence of alcohol on the arcuate nucleus, which influences the VTA and the NaC.
Craving- Oral Naltrexone

3 cases reported on adolescents:

a) 6-week, open-label trial was conducted with oral naltrexone (50 mg daily) in five alcohol-dependent adolescents (aged 16.8 years ± 3.11);
   – including two subjects with comorbid conduct disorder and three subjects with comorbid oppositional defiant disorder.
   – At the end of 6 weeks, the average drinks per day decreased from 8.94 to 1.33 (P < .0049) with a statistically significant reduction in craving also reported.
   – Adverse effects were minimal, although two subjects reported nausea.
Craving-oral naltrexone

b) A case report
   - included a 17-year-old adolescent with a 6-year history of daily drinking treated with oral naltrexone (50 mg daily)-remained abstinent during the 30-day treatment phase. (Wold M, Kaminer Y., JAACAP, 1997)

c) A case report included two alcohol-dependent adolescents
   - (aged 16 and 18 years) treated with oral naltrexone (50 mg daily) for 12 weeks.
   - One subject remained abstinent for 26 weeks
   - Other subject reported a marked decrease in the number of drinking days and amount of alcohol consumed. (Lifrak PD, et al. Amer J Psych, 1997)

Both subjects reported a decrease in alcohol craving. No adverse effects from naltrexone were observed.
2. A case report - FDA approved for adults for alcoholism
   - Injection given once every 4 weeks
   - Mitigates problems with compliance
   a) One unpublished case report (Simkin, 2010)
      • Remain abstinent for more than 12 months while receiving once-monthly naltrexone injections.
      • A self report from the subject of decreased craving was the reason the adolescent felt she no longer sought the use of alcohol.
      • Four years later, the adolescent is still alcohol free
      • Lost to F/U (Simkin, unpub)
      • **Summary-oral or IM naltrexone decreases or stops ETOH use**
3) Odansetron- One study in Adolescents
   - An 8-week, prospective, open-label study of ondansetron
   - (4 mcg/kg BID) in 12 alcohol-dependent adolescents (aged 14–20 years) with CBT.
   - No subjects discontinued because of adverse effects.
   - At end of treatment total scores as measured by the Adolescent Obsessive Compulsive Scale (A-OCDS) “irresistibility”:
     - Decreased significantly by the end of treatment and
     - Correlated significantly with decreased drinks/d and % days abstinent
     - (Dawes, MA, et al, Addist behav, 2005)
Craving—Ondansetron (Zofran)

- **Ondansetron**— Ondansetron is a highly specific and selective serotonin 5-HT3 receptor antagonist, and has low affinity for dopamine receptors.
- Used in chemotherapy to decrease nausea and vomiting.
- The exact mechanism is not completely understood but blockade of serotonin-3 receptors may decrease dopamine release and subsequent alcohol consumption and craving.
Craving

B. Marijuana

– No FDA approved meds—but exciting work on targeting new receptors
– Endocannabinoid system (ECS) has been implicated in the development of tolerance to alcohol
– Activation of CB(1) receptor increases alcohol craving
– CB (1) is activated by:
  • Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and
  • Endogenous arachidonyl ethanolamide (AEA) and 2-arachidonylglycerol (2-AG) which is increased with chronic alcohol use.
Craving

B. Marijuana (cont)

– CB1 receptor antagonist SR141716A (rimonabant) has been shown to block voluntary ETOH intake in rodents

– May play role in not only blocking the direct reinforcing effect of cannabis, opioids, nicotine and ethanol but also may prevent the relapse to various drugs of abuse, including opioids, cocaine, nicotine, alcohol, and amphetamine

– (Basavarajappa BS, Hungund BL., Alcohol Alcohol, 2005; Parolaro D, Rubino T., Drug News Perspective, 2008)
Craving

B. Marijuana

1. One study in adolescents using valproic acid.
   - A 5-week, open-label trial was conducted with divalproex
   - (1000 mg daily) in eight adolescents with marijuana abuse and dependence who also reported frequent mood irritability and temper outbursts.
   - At the end of the 5-week trial, all subjects showed a significant improvement in marijuana use (P<.007) by self report
   - Whether this effect was caused by anti-craving effects or improving mood lability is unclear.

2. One study with N-Acetylcysteine
   - (Gray, et al. CDPP, 2011)
   - Number of (+) marijuana drug screens lower that with placebo
3. Opioids

- Buprenorphine-Mu Opiate Partial Agonist/Antagonist
  - (low dose=agonist but high dose =antag)
- Not FDA approved in adolescents
- Has been recommended in adolescents when they fail 2 rehab attempts and >16 yo (Wood, et al., 2008)
- Advantage:
  - Less respiratory depression, less risk overdose, less dependency risk and, thus, more safe than full agonist
a) 152 patients aged 15 to 21 years who were randomized to 12 weeks of buprenorphine-naloxone or a 14-day taper (detox).

- Patients in the 12-week buprenorphine-naloxone group (B-N grp) were prescribed up to 24 mg per day for 9 weeks and then tapered to week 12;
- Patients in the detox group were prescribed up to 14 mg per day and then tapered to day 14. All were offered weekly individual and group counseling.
- B-N grp at 8 weeks had less use but high levels of opioid use occurred in both groups at follow-up.

(Woody GE, et al. JAMA, 2008)
Craving

4) Nicotine:
• Increases DA release in CNS=stim reward system
• Increases glutamate, GABA and beta endorphins=
• reduces anxiety, increases concentration, decreases appetite & increases reward circuitry
• FDA approved varenicline (Chantix) and Bupropion in adults
  – Chantix is an alpha 4 beta 2 partial agonist that gradually increases dopamine in the Nac and prevents binding of nicotine
  – Both medications have warning that the use of these medications has been associated with serious mental health events, including changes in behavior, hostility, agitation, depressed mood, suicidality, and attempted suicide.

Use with caution in adolescents
a. 14 d dosing study for varenicline in adolescents
   - Steady state exposure similar to adults observed:
     >55 kg =1 mg BID and 0.5 mg BID;
     <55 kg=0.5 mg BID and 0.5 mg once daily

b. Randomized, Double blind study varenicline vs buproprion (15-20 yo)
   - varenicline reduced from 14.1 ± 6.3 (mean ± SD) to 0.9 ± 2.1 cigarettes/day (CPD, 4 achieved abstinence)
   - bupropion XL reduced from 15.8 ± 4.4 to 3.1 ± 4.0 CPD (2 achieved abstinence).
   - 2 D/C’d buproprion due to side effects
   - Cotinine-confirmed 7-day point prevalence abstinence
   - (Gray, KM, Nicotine Tob Res, 2012)

c. Randomized, double blind placebo controlled study
   - Buproprion SR 150 mg BID for wt > 90 kg with contingency management best effect short term smoking cessation-high relapse rate if stopped
d) **Double-blind, placebo-controlled, RCT of nicotine patch**

- No differences nicotine patch and placebo at 7 and 30 day.
- But compared with placebo patch group, active nicotine patch group experienced a significantly lower:
  - craving score and
  - overall withdrawal symptom score abstinence analysis. (Hanson, K. et al. 2003)

e) **RCT open label trial of nicotine patch and nicotine gum w/ placebo control**

- At 6 months, with regard to the percentage of participants who achieved a 50% reduction of baseline smoking, there were no significant differences among treatment groups. (Hanson, K, et al. 2008)
- Note: reduction rather than abstinence may be a starting goal but not an end goal
Craving-nicotine patch/gum

f) A randomized, open-label trial was conducted using nicotine patch, nicotine gum, and an added placebo control.

- At the end of the treatment study, 49.4% of the participants (n = 41/83) had reduced smoking by at least 50%, but there were no significant differences among treatment groups. (Hanson, K, et al. Drug Alcoh Depend, 2008)

- Note: Best tx. For adults when using NRT is extended (40 week) CBT (Hall, SM, et al. Addic, 2009)
Substitution

- Agents of substitution are usually used to replace addictive substances with another substance that prevents withdrawal.
- However, continued use should occur under supervision to prevent functional impairment or misuse of the drug or use of other illicit drugs.
Substitution

A. Alcohol
   - long-term use of benzodiazepines poses an obvious risk for cross addiction and is generally not recommended for alcohol substitution in either adults or adolescents.

B. Marijuana-DSM V withdrawal
   - Three (or more) of the following develop typically within a week after Criterion A:
     1. irritability, anger, or aggression
     2. nervousness or anxiety
     3. sleep difficulty (e.g., insomnia, disturbing dreams)
     4. decreased appetite or weight loss
     5. restlessness
     6. depressed mood
     7. at least one of the following physical symptoms causing significant discomfort: stomach pain, shakiness/tremors, sweating, fever, chills, or headache

   • Resolve in a few weeks
Substitution

C. Opioids

– 5 FDA-approved medications for opioid dependence in adults.

1. Oral methadone-
   – full mu-opioid agonist
   – binds to the glutamatergic NMDA (N-methyl-D-aspartate) receptor (acts as a receptor antagonist against glutamate transmission)
   – this mechanism may decreases craving for opioids

2. Oral naltrexone-long acting mu antagonist (Revia)

3. Oral levo-a- acetylmethadol (LAAM)- (LAAM) is similar to methadone, but has a longer duration of action and therefore may be administered three times per week versus once daily for opioid substitution treatment.
Substitution

4. Sublingual buprenorphine – partial mu agonist (Subutex)- less risk for death due to overdose than methadone

5. Sublingual combination buprenorphine-naloxone (short acting mu antagonist) =(Suboxone) 4:1 comb

6. Long-acting injectable naltrexone (Vivitrol)-FDA-approved for alcohol dependence only
   – more acceptable than methadone or buprenorphine-naloxone to adolescents and/or their families because it has no abuse liability, does not interact with benzodiazepines or other drugs to produce a ‘high,’ and needs to be administered only once per month.
Opioids

- According to the Treatment Episode Data Set (TEDS), which records admissions to publically funded inpatient and outpatient drug and alcohol treatment in the USA, of the 251,930 admissions of patients aged 12–20 years for treatment of opioid use disorders in 2010, only 4,575 (2 %) were associated with a treatment plan using buprenorphine or methadone.
Substitution

• No effective standard of care exists for the population of opioid--dependent youth and thus there is a demand for novel & effective interventions.

• Psychosocial treatment and high rates of psychiatric comorbidity should be addressed

• Buprenorphine and buprenorphine/naloxone recommended by FDA age 16 or older

• Methadone maintenance and not detox is recommended for pregnant adolescent
Substitution - Opioids

1. Comparison therapeutic detox, methadone maintenance, therapeutic community (Residential Treatment Center) and outpatient. Abstinence:
   - 4-6 years later methadone maintenance had lowest opioid use but not lower use of other substances, employment or productive activities.
   - Youth in therapeutic communities did superior compared to methadone maintenance in all opioid use, other substance use, employment

(Sells, SB et al, 1979)
2. Retrospective cohort study of 100 consecutive heroin-dependent adolescents who sought these treatments over an 8-year recruitment period.

- The participants' average age was 16.6 years, and 54 were female.
- Half of the patient group remained in treatment for over 1 year.
- Among those still in treatment at 12 months, 39% demonstrated abstinence from heroin.
- The final route of departure from the treatment program was via planned detox for 22%, dropout for 32%, and imprisonment for 8%.
3. The remaining 39% were transferred elsewhere for ongoing opiate substitution treatment after a median period of 23 months of treatment.

- Males were more likely to exit via imprisonment (p < .05), but other outcomes were not predicted by gender.
- There were no deaths during treatment among these 100 patients who had a cumulative period of 129 person years at risk.
- Findings suggest that this treatment delivers reductions in heroin use and that one fifth of patients will exit treatment following detox completion within a 1- to 2-year time frame.

4. Smyth et al. conducted a retrospective study of 100 heroin-dependent adolescents who were maintained on an agonist medication at a specialized youth clinic in Ireland over an 8-year period.

- Methadone was the only available there until buprenorphine became available in 2005.
- Methadone or buprenorphine (Subutex, Suboxone) were the main treatments, but individual and group counseling and family therapy were available; 81 patients received methadone, and 19 received buprenorphine.
5. Methadone was initiated at 20 mg and titrated to 40–70 mg; buprenorphine was initiated at 2 mg in the morning of the first day, with 2–6 mg in the afternoon, and titrated to 6–12 mg/day.
   – Half of the patients were retained in treatment for 12 months or more, and of those patients, 39% were abstinent from heroin at that time point.
   – Overall, 22% left the program through planned detoxification, 32% dropped out, 8% were incarcerated, and 39% were referred to an adult program after turning 20 years of age. There were no deaths during treatment.
6. Bell and Mutch conducted a retrospective medical records review of 61 heroin-dependent adolescents treated with methadone or buprenorphine in Australia. They found that time in treatment was significantly longer for patients who received methadone, and patients who received buprenorphine re-entered treatment significantly sooner.

They concluded that methadone is more effective than buprenorphine in this population, but these findings need to be tested in a randomized controlled study.

(Bell, J, Mutch, Drug Alcohol Rev, 2012)
Detox-Opioids

1. Combining buprenorphine & behavioral treatment was highly & more efficacious than combining clonidine & behavioral treatments for opioid--dependent adolescents (ages 13--18), including on measures of retention, opioid abstinence, and withdrawal (in a 28 abstinence, 28--day outpatient taper).

   – Buprenorphine treatment was shown to be safe with this group of youth and also produced significant reductions in HIV risk behavior and significant improvements in psychosocial functioning. Also, more entered oral naltrexone post detox

Detox-medications provide relief during withdrawal from opioids

1. Study comparing methadone to LAAM for maintenance age 13-18 for 12 weeks and then detox.
   (Woody, GE, et al JAMA, 2008)

2. Comparison of buprenorphine/naloxone maintenance to 2 week detox buprenorphine/naloxone
   Minozzi S., et al, Coch Data Base, 2009

**Conclusion**: maintenance allows for higher retention rates and lower self reports of opioid use
Other treatment considerations-

• Some Evidence Based Substance Abuse Treatment Modalities:
  • Motivational enhancement therapy (MET)
  • Cognitive behavioral therapy (CBT)
  • Residential treatments, including short term acute and long term TC
  • Strategic family therapies (MST, MDFT, BSFT)
  • Contingency management
  • Community interventions (assertive, school-based, home-based)
  • Mindfulness Based Relapse Therapy (MBRT)-target substance abusers by using cognitive behavioral therapy, mindfulness and relapse prevention techniques.
  • Transcendental Meditation
  • LORETA Neurofeedback
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Meta-analysis of 97 studies

- TM Technique
- Peer Influence
- Relaxation
- DUI Programs
- Preventive Education

Effect Size (Standard Deviations)

Risk Factor 2: Effectiveness in Decreasing Alcohol Abuse
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Risk Factor 3: Effectiveness in Decreasing Drug Abuse—
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Meta-analysis of 70 studies

Mindfulness Based Relapse Therapy

• Treatment as usual (TAU), MBRP and Standard Cognitive Behavioral Relapse Therapy (RP)

• MBRT reported:
  – Significantly lower risk of relapse to substance use and heavy drinking and, among those who used substances,
  – Significantly fewer days of substance use and heavy drinking at the 6-month follow-up.
  – Cognitive-behavioral RP showed an advantage over MBRP in time to first drug use.
  – At the 12-month follow-up, MBRP participants reported significantly fewer days of substance use and significantly decreased heavy drinking compared with RP and TAU.

• Bowen, et al, 2014
Other treatment considerations-

• Juvenile justice mandate and collaboration
• 12 step programs-Jaffe’s *Adolescent Substance Abuse Intervention Workbook* (2001) utilizes MET
• Community Reinforcement Approach (CRA) is a treatment approach originally developed for adults, in which the individual's life is rearranged so that abstinence is more rewarding than drinking.
• This modality has been adapted for adolescents, manualized and evaluated as part of the Cannabis Youth Treatment Study (Dennis et.al. 2004)-Similar to Entusiastic Recovery by Jaffe.
How do youth in treatment perceive their risk for substance use after treatment and what are factors associated with relapse?

General Themes of Substance Use Relapse Among Youth 12-24 (N=118)

<table>
<thead>
<tr>
<th>Group Response</th>
<th>% overall</th>
</tr>
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<tbody>
<tr>
<td>Emotional Reasons</td>
<td>90%</td>
</tr>
<tr>
<td>Life Stressors</td>
<td>85%</td>
</tr>
<tr>
<td>Cognitive Factors</td>
<td>75%</td>
</tr>
<tr>
<td>Socialization Processes</td>
<td>65%</td>
</tr>
<tr>
<td>Environmental Issues</td>
<td>55%</td>
</tr>
</tbody>
</table>

Reasons for Relapse

- *Emotional*: cope with negative feelings, anger, sadness, loneliness, guilt, fear, pain, and anxiety”...”fears”

- **Stressors**-(12-17), stress was referred to more so because of parents (criticizing, nagging, mistrust, conflict, put-downs, no faith/confidence in us, not being around), school (failing classes, getting in trouble), and peer pressure (fitting in).

- **Cognitive**: poor motivation (coerced, craving/urges, and low confidence)

- **Socialization process**: peer pressure and media influence

- **Environmental Issues**: access/availability and cues/triggers
Clinical Summary and Pearls

• Studies in youth are limited
• Disulfiram use has mixed results in adolescents AUD
• Acamprosate is promising in in reducing use of ETOH
• Oral naltrexone and odansetron may help decrease amounts of ETOH used, more studies on IM Naltrexone and oldansetron are needed for abstinence
• More studies on rimonabant, valproic acid and N-acetylcysteine are needed in regards to marijuana.
• Buprenorphine/naloxone maintenance better in one study for retention for opioid users and decreases risk of HIV
Clinical Summary and Pearls

• Buprenorphine may be preferred over buprenorphine/naloxone by youth because it wards off cravings and withdrawal but this should not be seen as “drug seeking’.

• Buprenorphine may cause a compliance issue since it is taken daily—parents must monitor the adolescent

• Buprenorphine may enhance the adolescent’s self-reinforcing properties such that patients may like it for the way it makes them feel, in advance of later learning to be reinforced by the natural rewards of abstinence—so it may be helpful to start treatment
Clinical Summary and Pearls

- Injectable Naltrexone only requires once per month injections but due to 7 day washout period needed before it is started, inpatient settings are preferred due to lack of access to opioids.
- Buprenorphine may cause a compliance issue since it is taken daily-parents must monitor the adolescent.
- Buprenorphine may enhance the adolescent’s self-reinforcing properties such that patients may like it for the way it makes them feel, in advance of later learning to be reinforced by the natural rewards of abstinence-so it may be helpful to start treatment.
- Treatment for opioid dependence may take years to finally “conquer” this chronic disease.
- For a list of treatment protocols, risks and potential side effects the participant is referred to:
  - (Pecoraro, et al, Pediatric drugs, 2013)
Clinical Pearl-Use Humor

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