Pharmacotherapy of Substance Use Disorders in Children and Adolescents: Special Considerations

Dr. Ajeet Sidana
Department of Psychiatry
Government Medical College & Hospital
Chandigarh

Scope of Presentation

1. Introduction
2. Brief Overview of Substance Use Disorders in children and adolescents and co-morbid psychiatric disorders
3. Pharmacological options for SUDs including RCTs
4. Pharmacological options for co-morbid disorders including RCTs.
5. Conclusion

Introduction:

- Epidemiologic studies have shown that substance use disorders(SUDs) are among the most common mental health disorders in adolescents and young adults (Merikangas KR et al,2010).
- Most adults with SUD began using substance during adolescence, a developmental stage characterized by heightened risk for substance initiation and adverse consequences of use (Casey & Jones,2010).
- Despite this, the large majority of research and clinical efforts to address SUD have focused on adults only.

- To date, a small number of clinical trials have evaluated pharmacotherapies for Tobacco Use Disorder, cannabis use disorder (CUD), Alcohol Use Disorder(AUD), and Opioid Use Disorder (OUD) in youth.
- Additionally, important trials have been undertaken to examine the potential role of pharmacotherapy in youth with co-occurring substance use and psychiatric disorders.

Co-morbidity:

- Comorbidity is the rule rather than the exception among adolescents in treatment for SUDs (Aarons et al., 2001) and over 70% of adolescents with a substance use disorder have one or more psychiatric disorder (Kaminer & Bukstein,2008).

- Comorbid/co-occurring psychiatric disorders may temporally precede, follow, or be concurrent with chronic substance use and comorbidity is associated with increased addiction severity, increased risk for relapse, and poorer treatment outcomes, especially among adolescents (Bukstein & Horner,2010).

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- Virtually any psychiatric disorder may occur in association with SUD.

  Attention-Deficit/Hyperactivity Disorder
  Oppositional Defiant Disorder , Conduct Disorder , Depression, Anxiety Disorders , Post-Traumatic Stress Disorder , Specific Developmental Disorders (e.g., learning disabilities), Bipolar Disorder , Psychotic Disorder

- The presence of ADHD, especially when accompanied by ODD or CD is associated with early onset of substance abuse.

Pharmacotherapy for SUDs:

- Few medication trials have been conducted in adolescents with SUD, several studies conducted in the past decade suggest that a handful of medications are relatively safe, well-tolerated, and may be helpful in the treatment of adolescents with SUD based on the results of at least one randomized controlled trial.

- Nicotine replacement therapy (NRT) and bupropion (alone or in combination) have been shown to increase quit attempts and smoking abstinence in nicotine-dependent adolescents (Gray KM et al, 2011).

- N-acetylcysteine (NAC) has been shown to reduce marijuana craving and use in cannabis-dependent adolescents (Gray KM et al, 2012).

- Opioid-dependent adolescents and young adults who were treated with buprenorphine-naloxone for 6 months had greater treatment compliance and retention (Woody GE et 2011).

Tobacco Use Disorder

- Only eight controlled trials of pharmacotherapy for adolescent smoking cessation have been published. While a number of open-label, non-controlled studies have been conducted.
- Nicotine replacement therapy (NRT), has been evaluated in a number of adolescent studies, most of which have focused on nicotine patch. In the first, 100 adolescent smokers were randomized to receive a 10-week course of nicotine patch or placebo, each added to cognitive-behavioral therapy (CBT) and contingency management (CM) (Hanson et al, 2003).

- End of treatment abstinence, confirmed by carbon monoxide breathalyzer, was achieved by 28% of those in the nicotine patch group and 24% of those in the placebo group, a difference that was not statistically significant.

- Another study of 12-week course of nicotine patch, nicotine gum, or placebo treatment, added to group-based CBT, in 120 adolescent smokers (Moolchan et al,2005). Abstinence was achieved by 21% of those in the nicotine patch group, compared to 9% of nicotine gum participants and 5% of placebo participants. Compliance with nicotine gum was noted to be poor in this study. The end of treatment abstinence difference between the nicotine patch and placebo groups was statistically significant.

- A small (N=40) 10-week study evaluated the effects of nicotine nasal spray, added to weekly counseling, compared to a counseling-only group (no spray) on smoking cessation in adolescents, yielding discouraging results (Rubinstein et al,2008).

- Compliance with the nicotine nasal spray was poor in the active treatment group, and no participants in that group, compared with 12% of those in the counseling-only group, achieved end of treatment abstinence.

- Another 6- to 9-week adolescent trial (smoking more than 20 cigarettes per day) of nicotine patch versus placebo patch, without psychosocial intervention aside from an initial informational meeting, yielded mixed results (Scherphof et al, 2014a, 2015b).

- At end of treatment 14.8% of active and 13.1% of placebo patch participants achieved self-reported abstinence, though rates in the subset of highly patch-compliant participants were 22.4% and 14.5%, respectively, a **statistically significant difference**. Post-treatment follow-up at weeks 26 and 52 revealed abstinence rates of 8.1% versus 5.7% and 4.4% versus 6.6%, respectively. These differences were not statistically significant.

In sum, trials of NRT in adolescent smokers suggest that nicotine patch may be efficacious in the short-term, but relapse after treatment remains a significant concern.

- A large (n=312) 6-week trial compared the efficacy of bupropion SR 300 mg, bupropion SR 150 mg, versus placebo, each added to brief weekly individual counseling (Muramoto et al,2007). Urine cotinine confirmed end of treatment abstinence was achieved by 14% of 300 mg participants, compared to 11% of 150 mg participants and 6% of placebo participants.
- **The 300 mg group's abstinence rates were statistically superior to those of the placebo group at the end of treatment and superior to those of the 150 mg group at post-treatment follow-up**.

- To date, only one trial of varenicline for adolescent smoking cessation has been published (Gray et al, 2012). In this study, 29 adolescents were randomized to receive an 8-week course of varenicline (goal dose 1 mg twice daily) or extended-release bupropion (bupropion XL, goal dose 300 mg), each added to brief weekly individual counseling and medication management. Both groups demonstrated reductions in cigarettes per day, and carbon monoxide confirmed end of treatment abstinence was achieved by **26.7% of varenicline participants and 14.3% of bupropion XL participants.**

- Results of the few controlled trials of smoking cessation pharmacotherapies in adolescents suggest at least short-term benefits from nicotine patch and from bupropion SR (at the 300 mg dose), particularly when combined with psychosocial/behavioral treatment. However, long-term abstinence remains a significant challenge.
- In sum, pharmacotherapy may play a complementary or even synergistic role with smoking cessation psychosocial interventions, but more research is needed on treatments that may yield improved long-term abstinence rates.

Cannabis Use Disorder (CUD):

- While cannabis is the most common substance prompting adolescent admission to SUD treatment (SAMHSA, 2013), existing psychosocial treatment strategies are only modestly efficacious.
- No medications are approved by FDA for CUD treatment in any age group, and investigation of potential pharmacotherapies even in adults is a relatively new pursuit.
- A recent randomized placebo-controlled trial of the glutamate modulating agent N-acetylcysteine (NAC) evaluated its efficacy in adolescents with a DSM-IV-TR diagnosis of cannabis dependence (N=116) (Gray et al., 2012)

- Participants were randomized to receive an 8-week course NAC 1200 mg or placebo twice daily (total daily NAC dose 2400 mg), each added to brief weekly cessation counseling and a contingency management (CM) intervention. Those in the NAC group achieved superior abstinence outcomes, compared with those in the placebo group. **Negative urine cannabinoid tests were achieved at 41% of visits in the NAC group, compared to 27% of visits in the placebo group. End of treatment abstinence was achieved by 36% of NAC participants and 21% of placebo participants.**

Alcohol Use Disorder (AUD):

- No systemic studies on pharmacological interventions for alcohol withdrawal syndrome in adolescent samples are available.
- Treatment approaches for adolescents experiencing alcohol withdrawal syndrome are extrapolated from the adult literature and anecdotal evidence (Clark, 2012). While alcohol withdrawal syndrome is uncommon among adolescents with AUD (with 5-10% experiencing withdrawal symptoms), severe alcohol withdrawal remains a life-threatening emergency due to the risk for withdrawal-related seizures and delirium (Martin et al., 1995; Chung et al., 2002).
- Benzodiazepines are the first line pharmacotherapy for treatment of AWS in adults and may be used in adolescents with severe AUD who experience severe alcohol withdrawal symptoms in supervised inpatient settings (Mayo-Smith et al., 1997; Clark, 2012).

- Two pilot studies have examined the safety, tolerability, and efficacy of naltrexone in AUD. **Deas & Colleagues (2005)** completed a six-week open label clinical trial of naltrexone in five treatment-seeking adolescents meeting DSM-IV criteria for Alcohol Dependence. They found a **significant reduction in number of drinks per day (reduction of 7.5 drinks per day) and a reduction in alcohol-related thoughts/obsessions. Naltrexone was well tolerated with few side effects reported and no adverse events.**
- Another study examined 28 adolescent non-treatment seeking heavy drinkers with no prior treatment for AUDs using a double-blind, placebo-controlled crossover design with randomization into a naltrexone condition and a placebo condition for 8-10 days with washout period in between conditions. Naltrexone blunted alcohol cravings in both natural and laboratory settings and was associated with decreased likelihood of drinking on a study day and drinking heavily.

- Ondansetron, a selective 5-HT3 (serotonin) receptor antagonist, has demonstrated promise for treating early-onset adult AUD and a series of small studies have shown positive results in young adults with AUDs starting before the age of 25 (Johnson et al., 2000; Kranzler et al., 2003; Sellers et al. 1994).
- The safety, tolerability, and efficacy of disulfiram have also been studied in adolescents with AUD in a 90-day double-blind placebo-controlled trial (Niederhofer & Staffen 2003).
- 26 Study participants were randomized to receive disulfiram (200 mg/day) versus placebo, and alcohol use outcomes were assessed by self-report and psychiatric interview. Disulfiram was well tolerated with no adverse events reported and no significant differences reported between active medication and placebo groups on frequency and severity of side effects. With regard to efficacy, the proportion of **patients who remained abstinent through 90 days was higher and the mean cumulative abstinence duration was significantly greater in the disulfiram group compared to the placebo group.**

- **In summary, Preliminary pharmacotherapy trials are encouraging. Initial pilot studies of naltrexone, ondansetron, and disulfiram suggest that these medications are safe and tolerable in adolescents with problematic alcohol use and that they may reduce subjective response to alcohol**

Opioid Use Disorder (OUD):

- Options for adolescents with OUD remain limited and few controlled studies have been performed in this population. Despite efficacy in adults with OUD, agonist-based harm reduction approaches are controversial in adolescents and young adults.

- A few small studies completed in the 1970s examined methadone and 1-alpha-acetyl-methadol (LAAM) maintenance in youth meeting DSM-III diagnostic criteria for heroin dependence, suggesting clinical benefit (Hopfer et al., 2003; Rosenberg & Patch, 1972; Lehmann, 1976).

- Buprenorphine, a schedule III, mu-opioid partial agonist, which is FDA-approved for treatment of individuals aged 16 years and older, may present a better detoxification and maintenance medication option in adolescents.
- 12 weeks of buprenorphine-naloxone maintenance therapy has been shown to increase treatment retention and decrease opioid positive urines compared to 2 weeks of buprenorphine detoxification in a multi-site trial of adolescents and young adults (Woody GE et al, 2011).

- Discontinuation of buprenorphine/naloxone maintenance was associated with relapse to opioid use at follow up for 48% of those treated.
- Marsch and colleagues (2005) completed a double-blind, randomized controlled trial comparing the efficacy of two pharmacotherapies, buprenorphine and clonidine, for opioid detoxification in 36 adolescents meeting DSM-IV diagnostic criteria for opioid dependence in an outpatient clinic setting.
- Both groups received behavioral counseling three times weekly and contingency incentives for opioid negative urines.

- At the end of the 28-day detoxification, 72% of participants randomized to receive buprenorphine remained in treatment compared to 39% of those randomized to receive clonidine. The buprenorphine and behavioral intervention group had a significantly higher percentage of opioid negative urine tests, were significantly more likely to transition to extended medication assisted therapy with naltrexone, and had less opioid-related HIV risk behaviors during the study period compared to the clonidine and behavioral intervention group. ***These results, though preliminary, suggest that buprenorphine in combination with behavioral interventions may be the opioid detoxification treatment of choice for adolescents with OUDs.***

- A recent NIDA CTN multisite randomized clinical study examined short-term buprenorphine-naloxone detoxification for two weeks versus twelve weeks of buprenorphine-naloxone extended medication assisted therapy for the treatment of OUD in adolescents (Woody et al., 2008).
- 152 adolescents, aged 15-21 , opioid dependence were recruited across six sites and randomized to buprenorphine-naloxone 2-week outpatient detoxification or buprenorphine-naloxone 12-week maintenance/extended medication assisted treatment. Both groups received behavioral counseling.

- Primary outcome measures included opioid urine tests at weeks 4, 8, and 12. Adolescents randomized to receive buprenorphine-naloxone extended treatment were less likely to provide opioid positive urine tests at weeks 4 and 8 but not week 12 compared to those randomized to receive buprenorphine-naloxone detoxification. In both treatment groups the rate of relapse was high. At 6-months and 12-months more than half of adolescents in both groups had relapsed (at 12 months72% and 53% in detoxification and 12-week extended treatment group respectively).
- Secondary analyses of predictors of treatment outcome found that **adolescents with IVDU, more severe OUD, and comorbid psychiatric conditions receiving ancillary treatment were more likely to have lower opioid use at the study endpoint** (Subramaniam et al., 2011). The results of this study do not suggest that short-term opiate agonist treatment is effective for adolescents with OUD.

- Maintenance therapy with agonists may have a role in youths with more advanced illness and/or comorbidity.
- Treatment with the opioid receptor antagonist naltrexone may represent another treatment approach for adolescents with OUD.
- To date, the primary intervention for OUD among youth remains medically-assisted detoxification followed by counseling and behavioral interventions. There may be a role for maintenance pharmacotherapy, especially in youth with advanced disease (i.e. severe OUD, IVDU, psychiatric comorbidities). ***Preliminary studies have demonstrated that buprenorphine is safe and well tolerated, and may be the pharmacotherapy of choice for detoxification in this population.***

Pharmacotherapy of Co-morbid disorders:

- In parallel to clinical psychopharmacology trials targeting SUD among adolescents, there is a paucity of data on pharmacotherapies for combined psychiatric and substance use disorders too.
- The most well studied comorbid psychiatric disorders with substance use disorders include mood disorders and ADHD.
- Six randomized pharmacotherapy clinical trials to date have examined comorbid mood disorders and SUD, five focusing on comorbid Major Depressive Disorder (MDD) and one focusing on comorbid Bipolar Disorder. For specific SUDs, controlled pharmacotherapy studies have examined cannabis use disorders (CUD) and alcohol use disorders (AUD) in relation to mood disorders.

- Cornelius and colleagues (2010) completed a 12-week, double-blind randomized placebo-controlled trial of fluoxetine for treatment of depressive symptoms and cannabis use among seventy youths (ages 14-25) with comorbid DSM-IV diagnoses of current major depressive disorder (MDD) and CUD, with all participants receiving manualized individual cognitive behavioral therapy/motivational enhancement therapy (CBT/MET) . No fluoxetine versus placebo treatment group differences were noted for depression or cannabis use but both groups demonstrated significant improvement in their depressive symptoms and cannabis use severity from baseline to week 12.

- Two double-blind placebo-controlled 12-week trials of antidepressants have assessed the treatment of depressive symptoms and alcohol use in adolescents with comorbid AUD and MDD (Cornelius et al. 2009; Deas et al. 2000b).
- Cornelius and colleagues (2009) recently completed a clinical trial examining the effect of fluoxetine in combination with individual manualized CBT versus placebo with CBT over 12 weeks on depression and alcohol use in fifty adolescents meeting DSM-IV criteria for current MDD and AUD. **They found significant improvements in depressive symptoms and level of drinking in both groups (fluoxetine + CBT and placebo + CBT).**

- Both Cornelius et al. (2009) and Deas et al. (2000b) found that depression treatment response was associated with alcohol use—that is, adolescents whose depression remitted demonstrated reductions in their alcohol use and adolescents whose depressive symptoms remained elevated were more likely to maintain problematic drinking behaviors.

- Another 6-week double-blind placebo-controlled study examined the safety, efficacy and tolerability of pharmacokinetically-dosed lithium for the treatment of 25 adolescents meeting DSM-III diagnostic criteria for comorbid Bipolar Disorder and Substance Dependence Disorders (88 % of which were AUD) (Geller et al. 1998). Lithium was well tolerated, though significant between group differences were noted in side effects for thirst, polyuria, nausea, vomiting, and dizziness. ***Researchers found that adolescents randomized to lithium, compared to those in the placebo group, had significantly fewer positive urine drug tests and had greater clinical improvement.***

- A recent review has suggested that ADHD and SUD are “inextricably intertwined” in adolescents and that pharmacological treatment of ADHD during pre-adolescence may reduce the risk for adolescent-onset SUD (Harstad et al., 2014; Wilens et al., 2003).
- The largest study to date, by Riggs and colleagues (Riggs et al, 2011) a 16-week, double-blind, placebo-controlled multi-site clinical trial through the NIDA CTN examined the safety and efficacy of osmotically-controlled release oral delivery system methylphenidate (OROS-MPH) with a CBT behavioral platform for symptoms of ADHD and non-tobacco substance use.

- They found no significant OROS-MPH + CBT versus placebo + CBT treatment effects for primary ADHD and substance use outcome measures, but did observe that treatment with OROS-MPH as compared with placebo was associated with significant reductions in secondary outcome measures for both ADHD (ADHD Rating Scale-Parent form) and substance use (number of negative urine drug toxicology screens). Both treatment groups demonstrated significant improvements over time, evidenced by reductions in ADHD symptoms and days of non-tobacco substance use, suggesting that the manualized CBT for SUD may have efficacy for both substance use and ADHD.

- Non-stimulant medications such as atomoxetine, a selective norepinephrine reuptake inhibitor, and buproprion, a norepinephrine and dopamine reuptake inhibitor, have also been examined in adolescents with ADHD and SUD (Thurstone et al., 2010; Riggs et al., 1998; Sohlkhan et al., 2005).
- Thurstone and colleagues examined the safety and efficacy of atomoxetine (100mg/day) in 70 adolescents with ADHD and at least one non-tobacco SUD using a 12-week, double-blind, placebo-controlled study design with manualized CBT behavioral intervention platform (Thurstone et al., 2010).

- Parallel to previous studies, both treatment groups (atomoxetine + CBT and placebo + CBT) experienced significant reductions in ADHD symptomatology and substance use from baseline to week 12, but no significant between-group differences were noted for any ADHD or substance use outcomes.
- Lastly, two open-label pilot studies have shown positive preliminary results for the efficacy of buproprion for treatment of ADHD and SUD in youth, and a randomized controlled trial is currently underway

Summary & Conclusion:

- Epidemiologic studies have shown that substance use disorders(SUDs) are among the most common mental health disorders in adolescents and young adults.
- Till date, a small number of clinical trials have evaluated pharmacotherapies for Tobacco Use Disorder, cannabis use disorder (CUD), Alcohol Use Disorder(AUD), and Opioid Use Disorder (OUD) in youth.
- Over 70% of adolescents with a substance use disorder have one or more co-morbid psychiatric disorder.

- Trials of NRT in adolescent smokers suggest that nicotine patch may be efficacious in the short-term, but relapse after treatment remains a significant concern.

- Although no medication has been approved by US-FDA for Cannabis Use Disorder but N-acetylcysteine (NAC) has shown promising results in RCT with placebo.
- Initial pilot studies of naltrexone, ondansetron, and disulfiram suggest that these medications are safe and tolerable in adolescents with problematic alcohol use and that they may reduce subjective response to alcohol.
- Preliminary studies have demonstrated that buprenorphine is safe and well tolerated, and may be the pharmacotherapy of choice for detoxification in this population.

- Adolescents with SUD and Bipolar disorders, who received Lithium compared to those in the placebo group, had significantly fewer positive urine drug tests and had greater clinical improvement.

- Fluoxetine, for co-occurring major depressive disorder and osmotic-release methylphenidate and atomoxetine for co-occurring ADHD have been shown to be relatively safe, well-tolerated, and promising for treating co-occurring psychiatric disorders in non-abstinent adolescents who are concurrently receiving outpatient substance treatment.

References:

Christopher J H & Gray M. Pharmacotherapy for Substance Use Disorders in Youths. J Child Adolesc Subst Abuse. 2016; 25(4): 292–316.

Katherine A B & Paula R. Treatment of Adolescent Substance Use Disorders. Curr Treat Options Psychiatry. 2014 Jun 1; 1(2): 175–188

Merikangas KR, et al. Lifetime prevalence of mental disorders in US adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A) Journal of the American Academy of Child & Adolescent Psychiatry. 2010;49(10):980–989. [PMC free article] [PubMed]

Gray KM, et al. Bupropion SR and contingency management for adolescent smoking cessation. Journal of Substance Abuse Treatment. 2011;40(1):77–86. [PMC free article] [PubMed]

Gray KM, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. American Journal of Psychiatry. 2012;169(8):805–812. [PMC free article] [PubMed]

Woody GE, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth. JAMA: The Journal of the American Medical Association. 2008;300(17):2003–2011. [PMC free article] [PubMed]


Thank You!