Pharmacotherapy for Adolescents with Substance Use Disorders: A Review of Current Literature and Where We Go From Here

Natalie Do, D.O., Pharm.D
natalieTdo@gmail.com
No financial disclosures
The Scope of Adolescence Substance Abuse Problem

• regular abuse of substances during the teenage years increases the likelihood of developing a substance use disorder in adulthood, especially if use begins before the age 15 [1]

• By twelfth grade, about 50% of adolescents have abused an illicit drug at least once
  – alcohol > marijuana and tobacco [2]

• adverse consequences
  – increased medical and mental health problems
  – absenteeism
  – legal problems
  – unintentional injury
  – death
The Adolescent Brain Changes Overview

• Brain structures involved in emotional processing and evaluating risk/controlling impulsiveness [3-5]:
  – Hippocampus
  – Amygdala
  – Nucleus accumbens
  – Prefrontal cortex

• Different brain regions develop at different rates
  – One of the last aspects of behavior regulation to develop is inhibitory control (controlled by prefrontal cortex)
  – Role of environment

• Dopamine peaks in activity
• Grey matter peaks and then declines
• White matter increases
• Cortical thinning
• As person matures, brain activations more focalized and less diffuse
Hippocampus

• Functions:
  – memory, spatial navigation, negative feedback of hypothalamic-pituitary adrenal stress response, emotional processing
  – helps encode emotional memories via its connections with the amygdala
Amygdala

- Amygdala for emotional processing and assessing risk
Nucleus Accumbens

• Housed by the ventral striatum
• “reward center” active during reward seeking
• Peak volume reached during adolescence
• Regulates addiction behaviors [6]
• Adolescents showed increased ventral striatal activity relative to adults using reward paradigms, but reward processing doesn’t always manifest as increase in activation
  – Geier: decreased ventral striatal activation [7]
• Puberty influences left nucleus accumbens volume in a sex dependent manner
Prefrontal Cortex

- Frontal and parietal cortex have overall decrease in grey matter volume
- The dorsolateral prefrontal cortex is one of the last regions to peak in grey matter volume
  - Important in cognition and regulation of complex behaviors and emotions
- Brainstem and amygdala continue to increase in grey matter volume until 31 y.o. [8]
Grey Matter

• Made of neurons whose alignments in circuits are crucial for neural communication
• Increases in volume during childhood, and then begins to decline in early adolescence [9-12]
• Changes are not uniform
• Greatest impact of age on development:
  – Frontal and parietal cortex
  – Brainstem
  – Amygdala
White Matter

• Associated with myelination of neuronal axons
• Myelination continues through childhood, adolescence, and into adulthood but number of cell bodies in white matter does not increase appreciably beyond 3 years of age
• Frontal and temporal cortices have especially large increase in white matter
• Prefrontal cortex
  – Decline in white matter volumes in late adolescence (especially in females)
  – Parts appear to mature very late in development
  – Most anterior part of prefrontal cortex used to hold a goal in mind while working on secondary tasks or goals [13]
  – Right temporo-parietal junction regulates empathetic behavior [14]
Corpus Callosum

- Large white fiber tract that relays information between 2 hemispheres
- Increases in volume from early adolescence until mid-20s [15]
- Helps with improved capacity for connections throughout the brain
Cortical Thinning

- Neuron and synapse pruning
- Grey matter reductions and cortical thinning during adolescence to “fine tune” adolescent brain in response to environment
Dopamine

- Functions: Reward, regulation of sleep and wakefulness, stress response
  - Risk taking and sensation seeking behavior
- Made mostly in ventral tegmental area and substantia nigra
- Distributed by mesocorticcolimbic tract and mesostriatal tract
  - In adolescence, mesocortical starts to predominate [16]
- Cortical dopamine has overall inhibitory effect in prefrontal areas
  - Less mature mesocortical drive manifests as less behavioral inhibition
Sex Differences in Brain Maturation in Adolescents

- Differences between sexes but also differences within groups
- Female peak grey matter volumes before males, although not in all brain regions [17]
- Males have larger total brain volume relative to females and a larger white matter to whole brain ratio
- Amygdala volumes increased in both boys and girls but hippocampus volumes decreased in girls only as puberty progressed [18]
- Amygdala and hippocampus volumes increased in boys but decreased in girls with advanced pubertal status [19]
- Puberty influences left nucleus accumbens volume in a sex dependent manner
  - females have smaller but males have larger left nuclei as puberty progresses
  - Decrease in both left and right, as well as caudate and putamen (right side only in females) [20]
Adolescent Brain on Drugs

• Alterations in dopaminergic system -> increase in reward seeking behaviors [21]
• Drug seeking behavior may be due to two phenomena:
  – 1. Augmented incentive/motivational qualities of the drug and associated stimuli (due to limbic/amygdalar dysfunction)
  – 2. Impaired inhibitory control (due to frontal cortical dysfunction) [22]
2016 National Survey on Drug Use and Health

• 1 in 13 people >=12 y.o. needed substance use treatment
  – 1.4% of people >=12 y.o. received any substance use treatment in the past year
  – 0.8% received substance use treatment at a specialty facility
  – 1 in 10 >=12 y.o. who needed substance use tx got tx at a specialty facility in the past year
Psychosocial Treatment Modalities

• Screening, brief intervention and referral to treatment (SBIRT)
• Motivational interviewing
• Functional family therapy (FFT)
  – Engagement
  – Motivation
  – Relational assessment
  – Behavior change
  – Generalization
Opioid and Heroin

• death from heroin overdose in all age groups doubled from 2010 to 2012 [23]

• Treatment adults vs adolescents
  – chronic opioid agonist vs. detox and counseling
  – Approx. 50% relapse rate

• Pharmacologic options:
  – Methadone
  – Naltrexone
  – Buprenorphine
Methadone

- synthetic analgesic drug similar to morphine effects but longer acting
- full mu-opioid receptor agonist
- Elimination half life: 24-36 hours
- clinical studies in adolescent humans have used an average maintenance dose of approximately 50mg methadone, with recommendations generally ranging from 20 to 100mg daily [24]
- Therapeutic methadone plasma levels range between 100 and 1000ng/mL
  - plasma levels over 200 ng/mL are usually necessary for clinical response
  - A plasma range of 400-500 ng/mL is recommended for optimal therapeutic efficacy [25]
- Primary safety concern: potential increase in QT interval -> arrhythmias
  - Obtain baseline EKG
Methadone

• Barwatta study:
  – higher potential risks with repeated exposure to morphine during adolescence in mice, specifically to the D2/D3 dopamine receptors signaling [26]
  – adolescent mice were administered 0.1-0.4mg/kg buprenorphine, 25-100mg/kg methadone, or saline once daily for 6 days
  – methadone exposure disturbs the D2 like receptor’s response by causing a supersensitivity to dopamine, thereby reinforcing the rewarding properties of opioids
Methadone vs. Buprenorphine vs. Non-Opioid Medication

• Retrospective review
  – 61 adolescents heroin users ages 14-17 years old at the time of starting drug treatment
  – compared retention and re-entry to treatment of those teens treated with methadone, buprenorphine, or non-opioid medication only [24]
    • Methadone tx:
      – significantly longer retention in first treatment episode than those treated with buprenorphine.
      – Time to re-entry into treatment due to relapse was significantly longer with methadone treatment as well

• methadone maintenance may be more effective than buprenorphine at preventing premature drop out from treatment in adolescent heroin users
Limitations to Use of Opioid Agonists in Adolescents

- FDA approved only in adults and typically administered through daily visits to specialized treatment programs.
- Concerns about starting a youth on a treatment that is usually long-term and with unknown long-term consequences.
- Reluctance to have young patients come into daily contact with older persons with extensive histories of addiction and antisocial behavior.
- Given the sparsity of research into the safety and efficacy of methadone use in adolescents it would not be recommended to consider this as a first line treatment option in youths at this time.
Naltrexone

- oral, long acting, opioid antagonist with a high affinity to mu-opioid receptors
- A daily dose of 50mg of naltrexone will block the pharmacologic effects of 25mg IV heroin for as long as 24 hours, and increasing the dose to 100mg or 150mg extends the duration of action to 48 hour and 72 hours respectively [27]
- No tolerance or dependence
- Most serious SE: hepatotoxicity
Naltrexone

• Fishman study:
  – sample of 16 serial adolescent and young adults (mean age of 18.5 years) who were treated with extended-release naltrexone
  – Of the 16 cases, 10 out of 16 (63%) were retained in treatment for at least 4 months
    • Of those, 9 out of 16 (56%) had a ‘good’ outcome which was defined as having substantially decreased opioid use [28]
  – extended release naltrexone in adolescents is well tolerated over a period of 4 months and is associated with good outcomes
Buprenorphine

- partial mu-opioid agonist and a potent kappa antagonist with a slow onset and a long duration of action
- Concern for QT prolongation
- FDA indicated for opioid dependence in adolescents >=16 years old
- Possible antidepressant effects [29]
Buprenorphine

• A Cochrane review of buprenorphine found two randomized controlled trials investigating pharmacological interventions with or without psychosocial interventions for detoxification in adolescents [30]
• The first study looked at opiate detoxification and compared buprenorphine to clonidine in opiate dependent adolescents
  – It showed that buprenorphine was helpful in reducing the drop out rate (although not statistically significant), and there was no difference between detoxification treatment duration and severity of withdrawal symptoms.
• The second study compared buprenorphine maintenance to buprenorphine for detoxification only
  – At one year follow up, self reported opioid use was less in the maintenance group and more adolescents were enrolled in other addiction programs
• Difficult to make definitive conclusions as to whether buprenorphine is superior to other options for opiate detoxification such as clonidine and methadone
  – safety and tolerability is often the guiding factor
Alcohol

• Alcohol use onset is a reliable predictor of later problematic use and dependence on alcohol and other drugs [31,32].
• Impact on the developing brain: especially the prefrontal cortex -> leading to cognitive dysfunction and problems with attention [33], visuospatial ability [34], and executive control [35]
• In 2013, approximately 23% of youth ages 12 years or older in the United States reported binge alcohol drinking in the past month [36]
• Intermittent binge-like alcohol use in adolescence can induce long term aberrant synaptic remodeling and cause anxiogenic effects
• Pharmacotherapies:
  – Naltrexone
  – Disulfiram
  – Acamprosate
Naltrexone

• MOA: antagonize mu-opioid receptors decreases dopamine release in the nucleus accumbens, thus decreasing the reinforcing and rewarding effects of alcohol [37]
• FDA approved for use in the treatment of alcohol use disorders in adults
• Naltrexone has demonstrated efficacy and safety in the general adult population [38], but implications of these findings for adolescents is unclear due to youths having substantial neuronal remodeling in brain regions during the period of adolescence [39]
• Promising for adults because it has been shown to reduce the frequency of heavy drinking [40] and can be used on an “as needed” basis because it appears to help by reducing the cravings for alcohol [41,42]
Naltrexone

• Deas study [43]:
  – n=5
  – safe and well tolerated in adolescents and lead to a significant decrease in alcohol use
  – significant decrease from baseline alcohol use to the end of week 6, with an average reduction of 7.61 standard drinks per day
  – Primary side effect: nausea
  – No reported elevation in liver enzymes
  – Suggests that naltrexone is safe, well tolerated and may lead to a significant reduction in alcohol consumption and cravings in adolescents with alcohol use disorder
Disulfiram

• Approved in 1951, disulfiram was the first drug approved in adults for treatment of alcohol dependence [44]
• aversive agent for alcohol cessation
• synthetic compound that acts as an aldehyde dehydrogenase inhibitor that interferes with the breakdown of serum acetaldehyde, one of the metabolites of alcohol
• High levels of acetaldehyde causes uncomfortable symptoms such as flushing, nausea, thirst, palpitations, chest pain, vertigo, and hypotension
Acamprosate

- N-methyl-D-aspartate (NMDA) glutamate antagonist thought to decrease craving through
  - Mesolimbic dopaminergic effects [45]
  - Increasing the release of taurine in the nucleus accumbens [46]
- Adults: improves abstinence with alcohol use disorder with efficacy similar to naltrexone [47]
- Adolescents: significantly higher abstinence rate compared to placebo [58]
- Renal excretion
Nicotine

• ~90% adult smokers started smoking before 18 years old [49]
• Consequences of nicotine use:
  – Early pregnancy
  – Dropping out of high school
  – Stealing and other illegal behaviors
• 25% of adolescents who smoke show signs of addiction within 1 month [50]
• >4.5 million adolescents initiate tobacco use but form of nicotine is changing:
  – Cigarette use: 70.4% in 1997 to 41.1% in 2014 [51]
  – Cigar use: 11.6% to 8.2% [52]
  – E-cigarettes: 1.5% in 2011 to 4.2% in 2013, and then between 2013 and 2014 to 13.4% [53]
  – Hookah: 4.1% to 9.4%
  – Smokeless tobacco: stable at 5.5% [52]
• Smoking cessation pharmacotherapies:
  – Nicotine replacement therapies
  – Bupropion
  – Varenicline
Nicotine Replacement Therapies

- Nicotine gum, nasal spray, and transdermal patch
- Patch:
  - U of Michigan study: no significant difference in 30 day point prevalence rates between active and placebo nicotine patches for smoking abstinence at the end of treatment [54]
  - Scherphof study: abstinence at 2 weeks of treatment but not at the end of treatment, with no differences observed at 6 and 12 month follow ups [55]
Bupropion

• nicotinic acetylcholine-receptor antagonist with dopamine and norepinephrine reuptake inhibition
• reduce craving for smoking, irritability, and depressive symptoms [56]
• available in 3 dosage forms:
  – immediate release, sustained release (SR), and extended release.
• Bupropion SR for smoking cessation in adol:
  – Muramoto study: Quit rates for bupropion SR 150mg/day group did not differ statistically from the placebo group at any time point, however the bupropion SR 300mg/day group had significantly higher 7-day abstinence rates compared to the placebo group at week 6. No statistically significant difference in abstinence rates appeared among groups after treatment was ended. [57]
  – Niederhofer study: reduction in the number of cigarettes smoked per day occurred in 5.4% of patients receiving bupropion compared with 5.9% on placebo [58]
• May help prevent relapse once patients have already stopped use and in some adolescents who continue to use, it may help with decreasing the amount of cigarette use
Varenicline

- partial agonist at the nicotinic receptors that binds to these receptors and may reduce withdrawal effects and cravings
- Faessel [59]:
  - 12-16 years old with >=3 cigs/day
  - Classified according to body wt (high: >55kg, low: <55kg)
  - Placebo vs. Varenicline
    - High body wt: 1mg po BID or 0.5mg po BID x14 days
    - Low body wt: 0.5mg po BID or 0.5mg po daily x14 days
  - Result:
    - High body weight group, higher doses of varenicline were associated with greater reductions in smoking at 16 day follow up
    - Low body weight group, reductions in smoking were similar across standard dose, low dose, and placebo group
Cannabis

• close to 20 million people age 12 years or older reporting use within the past month [60]
• after alcohol, is the most common drug that causes adolescents and adults to seek treatment [61]
• Consequences:
  – increased risk of psychotic disorders [62]
  – cognitive impairment [63]
  – higher unemployment [64]
  – lower educational attainment and life satisfaction
  – poor mental health outcomes [65]
• Effect of legalization
  – Among 12 to 17 year old adolescents: perception that smoking marijuana 1 or 2 times per week poses a “great risk” decreased from 54.6% in 2007 to 39.5% in 2013 [60]
Cannabis

• Camchong study: repeated exposure to cannabis during adolescence may have detrimental effects on brain resting functional connectivity, intelligence, and cognitive function [66]

• Approximately 50 percent of heavy cannabis users also smoke tobacco [67,68]
Cannabis

• Psychotherapeutic treatment for cannabis use disorder
  – promising results with a combination of motivational interviewing, cognitive behavioral therapy, and contingency management for abstinence producing the best outcomes for reducing frequency and quantity of use [69].
  – However, most youth do not experience sustained benefit from existing psychosocial treatments.

• At present there are no FDA-approved pharmacotherapies for cannabis use disorder in adults or adolescents
  – Gabapentin
  – Topiramate
  – N-acetylcysteine
Gabapentin

- alkylated analog of gamma butyric acid (GABA) approved for neuropathic pain and epilepsy
- theorized to normalize the corticotropin-releasing factor (CRF)-induced GABA activation in the amygdala [70]
- Mason study: [71]
  - 50 adult patients, 18 completed
  - significantly less cannabis use by both self report and urine toxicology, significantly decreased cannabis withdrawal symptoms, and greater improvement in executive function compared to placebo
Topiramate

- enhances the GABAergic system and antagonizes the glutamatergic system
- Theory: GABA agonists decrease dopamine reward response
- Miranda study [72]:
  - Titrate to 200mg/day over 4 weeks, then cont for another 2 weeks
  - Motivational enhancement therapy + topiramate or placebo
  - Topiramate was superior to placebo for reducing the number of grams smoked per use day, but did not improve abstinence rates
  - Dropout rates higher for the topiramate group (52% vs 23% for placebo) with adverse medication side effects being the most common reason for withdrawal in the topiramate group
N-Acetylcysteine

• Mixed efficacy
• Gray study [88]:
  – 116 adolescents/young adults 15-21 y.o.
  – NAC 2400mg po daily or placebo x8 weeks
  – All weekly therapy and 2x/week contingency management
  – NAC group: odds ratio 2.4 negative UDS
  – 2 wks: 36.2% point prevalence abstinence vs. 20.7%
N-Acetylcysteine

• Gray study [89]:
  – 302 adults 18-50 yo
  – NAC 2400mg po daily or placebo x12 weeks
  – Weekly counseling and 2x/week contingency management
  – Result: same proportion of UDS negative for THC (22.3% vs. 22.4%, odds ratio 1.00)
Stimulants

• wide range of substances: Rx stimulants, cocaine, methamphetamine, and OTC rx

• 1 in 10 American adolescents and young adults (16-25 y.o.) reported misuse of stimulants in their lifetime
  – Rx stimulant misuse more frequent and typically occurring earlier than methamphetamine use [73]

• Methamphetamine most widely available and misused amphetamine-type stimulant worldwide [74].
  – After marijuana, amphetamines/methamphetamines are the illicit drugs most likely to be used by high school students [75].

• ER visits involving Rx stimulants tripled between 2005 and 2010 [60]

• Type of Rx stimulant differs on gender [73]:
  – Males: methylphenidate (78% vs. 56%)
  – Females: diet pills or amphetamines (14% vs. 38%)
Stimulants

• Lisdexamfetamine (pro-drug) potentially less abuse potential
  – lisdexamfetamine, dextroamphetamine/amphetamine extended release, and dextroamphetamine/amphetamine immediate release
  • odds of abuse was 2.3 times higher for dextroamphetamine/amphetamine immediate release compared to lisdexamfetamine and dextroamphetamine/amphetamine extended release combined with the odds of dextroamphetamine/amphetamine extended release abuse 1.9 times higher than lisdexamfetamine [76]
Stimulants

• 26% of 9th grade students reported the misuse of OTC cough medications to get high (greater than marijuana use (25%) for the same reporting period) [77]

• 3.1 million persons 12 years and older have misused OTC medication at least once in their lifetime
  – 3.7% of misuse occurring in adolescents younger than 18 years old [78]

• Ethnic/racial differences between two age groups who presented for treatment for prescription and OTC drug problems
  – < 18 years old were predominantly Latino and African American
  – > 18 years old were mostly Caucasian [79]
Stimulants

• Possible pharmacotherapies:
  – N-acetylcysteine
  – Aripiprazole
  – Bupropion
N-Acetylcysteine (NAC)

- stimulates inhibitory metabotropic glutamate receptors, reducing the release of glutamate from the synapse
  - restoring the extracellular glutamate concentration in the nucleus accumbens -> compulsive behaviors can be blocked [80]
- some promise in reducing cocaine use [81] by reducing desire to use and interest in cocaine
- double-blind, placebo controlled study of NAC plus naltrexone:
  - no difference between methamphetamine and placebo [82]
Aripiprazole

- atypical antipsychotic with partial agonist properties at the D2 dopamine receptor
- During initial abstinence from chronic stimulant administration, there is low neurotransmitter tone of dopamine
  - Theory: partial agonist should produce reception stimulation -> function as medication replacement [83]
Aripiprazole

• Lile and Stoops
  – aripiprazole 20mg with d-amphetamine in adults
    • aripiprazole attenuated the abuse-related effects of d-amphetamine [84]
    • However, in that same study, aripiprazole alone significantly impaired performance on digit symbol substitution test (DSST)
      – DSST is a test that is sensitive to the effects of orally administered sedative and stimulant drugs
      – It was hypothesized that the attenuation that was observed may have been functional instead of receptor mediated
Aripiprazole

• Stoops follow up study [85]
  – Can aripiprazole 10mg could acutely attenuate the DSST and physiological effects of d-amphetamine (2.5-15mg)?
    • aripiprazole 10mg did attenuate some abuse-related behavioral effects of d-amphetamine without significant performance impairment, even when aripiprazole was administered alone [109].
  – suggests that aripiprazole 10mg would be a reasonable starting dose for the treatment of stimulant abuse and dependence
Bupropion

- nonselective dopamine and norepinephrine reuptake inhibitor that also has antagonist properties at the nicotinic acetylcholine receptors
- increases dopamine transmission in the nucleus accumbens and in the prefrontal cortex by inhibiting the dopamine transporter
- Theory:
  - by restoring depleted dopamine levels, bupropion may be effective in decreasing withdrawal symptoms in those with methamphetamine dependence -> to a decrease in methamphetamine use
- Current findings:
  - no additional benefit compared to placebo for methamphetamine use and cravings [86, 87]
  - adults with a lower frequency of baseline methamphetamine use, those treated with 300mg/day sustained release bupropion were more likely to provide methamphetamine-free urine drug screens compared to placebo [87]
Conclusion

• evidence for the effectiveness of pharmacotherapy for adolescents with substance use disorders is limited compared to adults with substance use disorders

• AACAP practice parameters recommend psychosocial interventions as primary tx

• When selecting adolescents with substance use disorders for whom pharmacotherapy is likely to be helpful, consider motivation, family support, and presence of any comorbid mood disorders
Conclusion

• Opioid use disorder:
  – buprenorphine and naltrexone appear to have promising evidence for safety and efficacy

• Alcohol use disorder:
  – disulfiram appeared to be the most effective at maintaining abstinence, however its use must be carefully considered given the potentially lethal effect it could have on those that relapse on alcohol

• Nicotine use disorder:
  – nicotine replacement therapy appears to have the most success, with a good safety profile
  – Bupropion also appears to be efficacious and well tolerated

• Cannabis use disorder:
  – Topiramate appears to have some promising benefit of helping increase abstinence rates in adolescents

• Stimulant use disorders:
  – low dose aripiprazole has shown some effectiveness at attenuating the effects of d-amphetamine abuse
References

References


References

References


References


75. Smart RG, Ogborne AC. Drug use and drinking among students in 36 countries. Addict Behav. 2000;25:455-460.


