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Editor's Note

Dear Colleagues,

During the Coronavirus pandemic, like the other inequities and disparities in our healthcare system, the crisis of mental health disease and substance abuse have reached a breaking point.

According to the Kaiser Family Foundation, 41% of adults reported anxiety and/or depression in January 2021 compared to 11% in January to June 2019. And 11% of the adults reported that they had suicidal thoughts in the past one month.

Similar to other disparities and inequities, communities of color have been disproportionately impacted by mental health incidences during the pandemic.

Young adults have fared much worse than adults in the pandemic when it comes to mental health issues as well.

Children and adolescents faced increased issues of emotional health now versus before the pandemic. Parents' mental health continues to worsen. With school closures, children have lost not only their social support and network but also some of the mental health services available at the schools. Their routines have been disrupted. The overall impact of the pandemic has also resulted in a decrease in reports of child abuse but increased seriousness of injuries in children due to child abuse. The overall visits of children to emergency departments increased from 24% to 31% (https://www.cdc.gov/mmwr/volumes/69/wr/mm6945a3.htm?s_cid=mm6945a3_w).

I can attest to the huge increase in mental health disease from our own experience in my community. One non-scientific but a suitable surrogate is the huge number of admissions of children with mental health illness to Wolfson Children's Hospital in Jacksonville. This negatively impacted the mental health services for children to the degree that some of the mental health providers closed their ambulatory availability to deal with the inpatient crisis of mental health.

This special supplement issue of *The Florida Pediatrician* is very timely. My thanks to Editorial Board member Dr. James Burns on taking the lead for this issue and serving as the Guest Editor.

This issue has seven terrific articles on some of the most pressing mental health issues facing adolescents and children. I want to thank all of the authors for an exceptional issue. In addition to this issue, of the *Journal* your Florida Chapter of the AAP also offers several useful resources for parents that can be found on the Florida Chapter website (https://fcaap.org/parents/covid-19/).

The American Academy of Pediatrics offers many resources for pediatricians and parents to deal with mental health diseases in children, especially those related to the pandemic:

https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-on-supporting-the-emotional-and-behavioral-health-needs-of-children-adolescents-and-families-during-the-covid-19-pandemic/

We will need to support the "children of pandemic" for years and decades to come as a result of their adverse childhood experience. We must be prepared to have a system of care for mental health for children and adults, which is equitable and free. We may need an effort in line with the Ryan White program for the HIV epidemic. We know that even after we conquer the Coronavirus pandemic, the mental health issues will remain with us for years. We must have mental health services in schools, workplaces, and in the wider community. If we fail to respond to this crisis in a timely and effective manner, we risk losing a generation of citizens. It would be catastrophic for our nation. We have a window of opportunity, and we must respond quickly before it closes.

As pediatricians, we can lead this effort and advocate for our children and families as generations of pediatricians have done before.

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Editorial Board

Editorial Board

Foreword to the Mental Health Supplement for the Florida Pediatrician

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General pediatric health care providers are required to address high volumes of routine physical health problems in their day-to-day practice. In addition to this fast-paced practice focused on physical health, pediatricians are now increasingly the first point of contact for the parents of children and adolescents presenting with mental health conditions. These may include concerns of substance abuse, problems with depression with potential suicide risk and anxiety disorders. Many times, these problems are related to the trauma of adverse childhood events including physical, sexual and verbal abuse, bullying, parental mental illness, domestic violence or parental absence due to illness, substance abuse, divorce, or imprisonment. It is now a common expectation for pediatric care providers to evaluate school performance problems which may be related to attention deficit hyperactivity disorder, intellectual disability, or specific learning disabilities. Autism is all too common today, but is not always apparent, requiring vigilance to diagnose early in order to intervene in a timely manner.

Therefore, mental health problems are emerging as a major clinical domain for those who provide primary care to children and adolescents; yet most children and adolescents with mental health problems do not receive treatment. Finding efficient evidenced-based screening, diagnostic, and treatment modalities that can be applied to the environment of outpatient pediatric practice efficiently and effectively is an emerging unmet need. It is also vital to collaborate with mental health professionals and streamline the navigation process for patients.

More recently, with the consequences of the Covid-19 pandemic, including disruption of school, sports, extracurricular activities, community and religious activities, our parents/caregivers are struggling to maintain their employment and serve the developmental needs of their sons and daughters. These are certainly unprecedented times that require new paradigms of care.

In this supplement on Mental Health for *The Florida Pediatrician*, we have assembled an outstanding group of ten authors from the fields of General Pediatrics, Internal Medicine, Developmental Pediatrics, Adolescent Medicine, and Psychiatry to provide seven practical reviews on common mental health problems for the primary care provider. The goal is to optimize delivery of mental health services to children and adolescents. The article titles include:

Screening the Adolescent for Mental Health Disorders: In this review, the classic global HEEADSSS assessment; Screening, Brief Intervention and Referral to Treatment (SBIRT); and CRAFFT tools for substance abuse screening and the PHQ-9 for depression are introduced.

Adolescent Substance Use provides the latest information on the clinical aspects of alcohol, tobacco, and marijuana. This review describes in detail the SBIRT process which entails categorization of drug use, reinforcement of abstinence from substances, early detection, motivational interviewing, and referral for treatment when needed.

Pandemic Blues: Identifying and Treating Adolescent Depression in Light of the COVID-19 Pandemic presents a practical, evidenced-based review proposing a three-step process of evaluation and pointers on management including cognitive behavioral therapy and medications. I find this reference especially helpful in that it provides a clinical tool that can be directly applied in the clinical setting.

Anxiety Disorders in Primary Care Pediatrics is a comprehensive review of the clinical subtypes of anxiety disorders with a discussion on differential diagnosis, tools to assess, and a multimodal approach to management including cognitive behavioral therapy and medications. The authors finish up with an impressive list of resources for patients and clinicians.

ADHD: An Overview for Pediatric Primary Care is an excellent resource providing a comprehensive, yet practical review, containing management algorithms and tables that can be directly used in care of patients.

Navigating Learning Problems in Children: A Closer look at Intellectual Disability (ID) and Specific Learning Disorder (SLD) describes the effects of ID and SLD on academic performance. The authors emphasize the need to approach problems with school achievement with a broad differential diagnosis of medical and mental health conditions in addition to the article's main focus on ID and SLD. Excellent information on assessment and management of these two important conditions is concisely presented.

Autism Spectrum Disorder - A Clinical Perspective contains key information on the diagnosis and management of autism spectrum disorder. Practical algorithms and tables on screening, diagnostic testing, and multidisciplinary interventions guide clinicians with information that can significantly improve quality practice for these patients.

On behalf of the authors of this collaboration, we wish you the best as you meet the challenge of providing mental health care to your patients.

REVIEW ARTICLE

Screening the Adolescent for Mental Health Disorders

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ABSTRACT

Leading causes of mortality have underlying mental health etiologies, including depression leading to suicides and substance use disorder leading to violent behaviors and fatal motor vehicle accidents. Primary care providers are in an excellent position to screen and deliver timely intervention. This is because they often have developed a longitudinal relationship with the adolescent, can coordinate care, and facilitate excellent access to services. Early detection of mental health disorders can prevent progression to severe and more intractable conditions. The use of tools such as the HEEADSSS assessment, Brief Intervention, and Referral to Treatment (SBIRT), and the Patient Health Questionnaire can efficiently detect and define these mental health problems that may not be apparent during outpatient encounters. Motivational interviewing techniques that effect change can be accomplished in the primary care office. Medications can be implemented by primary care providers for common conditions such as anxiety, depression, and attention deficit disorder as long as there are no 'red flag' symptoms such as acute suicidality, manic symptoms, psychosis, or severe substance abuse disorder. In those cases, it is ideal to have a psychiatrist available for collaborative care.

BACKGROUND

In 1974, Past President of the AAP, Robert Haggerty, coined the term "new morbidity" to describe the priority to address mental health in children and adolescents.[1] In the United States, by age eighteen, 51% of the population will have been diagnosed with a mental disorder[2], and suicide is the second most common cause of death.[3] In a survey of 512 pediatricians, 65% stated they lacked training in the treatment of mental problems in children and adolescents, 40% lacked confidence they could recognize these problems, and 50% said they lacked confidence in treating them.[4] In a survey of program directors, 23% thought their graduates would be comfortable treating depression or anxiety with medications, 39% felt their graduates could use tools such as motivational interviewing, and only 54% felt their graduating residents were somewhat comfortable managing behavior problems.[5]

Many adolescents present to clinics with mental health issues that are not visible. Examples include a thirteen-year-old teen with headaches who is severely depressed over being abused; an eighteen-year-old who had had a significant workup for vomiting but who is bulimic; or a fifteen-year-old who presents to the Emergency Department with vomiting and dehydration who is sent home with the diagnosis of gastroenteritis but who on follow-up is found to have taken a massive overdose of acetaminophen with severe liver dysfunction developing. Seriously disturbed teens may not always reveal their problems unless someone asks them.

Over 70% of adolescents are seen in primary care each year.[6] In many cases, primary care providers (PCPs) may have to assume care for mental health problems. The reason for this may be because of delays in getting to a psychiatrist. With the

PCP, there are many advantages, including a longitudinal relationship that has been built up over time, and a prevention-oriented practice where early detection can be beneficial. The primary care practitioner frequently has knowledge of the family, including the social context, provides a child and teen-friendly place, has honed abilities to coordinate care, has greater access, and less stigma. Sometimes mental health issues in parents lead to a lack of effective parenting, domestic violence, or child abuse. A primary care practitioner may impact a child's mental health by reporting abuse, addressing bullying, and early detection of depression and substance use. PCPs who plan to provide mental health services should schedule more visit time and receive training.[7] The REACH Institute mini-fellowship is an excellent source of training.[8]

HEEADSSS

Implementing the HEEADSSS tool is an invaluable way to connect with a teen and their sometimes hidden lives.[9,10] General advice about conducting teen visits include first, gaining rapport with the teen, starting out with light conversation to make the teen feel comfortable. Sometimes teens have "medical office aphasia"; you may find yourself in periods of silence and should expect this! Confidentiality is a crucial component of getting an accurate history. It is essential to get the parents to step out of the exam room so that a one-on-one interview with the teen can be obtained. Sometimes, if the parent is hesitant, it is best to accompany the parent out of the room, ask them if they have concerns about their teen, and ask permission to then speak to their teen confidentially. This one-on-one interview of the teen has many advantages in that it enables the teen to be truthful about key health issues which they might not be comfortable talking about with a parent in the room. On the other hand, we should take every opportunity to encourage the teen to communicate with parents when appropriate, with the exception being if there is ongoing abuse. There are exceptions to maintaining confidentiality, including situations where a serious threat to life exists, such as suicidality, the threat of homicide, abuse, or serious substance abuse disorder. During the screening, it is essential to encourage the teen and praise when some positive information such as good grades or avoidance of risk behaviors is discussed. This technique is referred to as therapeutic history taking. It is crucial to show you care by being empathetic as the answers to your screening questions unfold and avoid being too clerical in your approach to asking questions. The clinician should make good eye contact with the teen and not be buried in the computer. It is important to be genuine in that teens have a very keen sense of when you are insincere or superficial.

HEEADSSS questions should be asked in a particular manner, including the least threatening questions first, such as talk about their school and hobbies. Questions should be open-ended, and the practitioner should look for positive qualities and resiliency factors as well as risks. One should try to get to know the teen as an individual and respect their autonomy.

The HEEADSSS assessment includes discussion about **H**ome, **E**ducation/Employment, **E**ating, **A**ctivities with Peers, Use of **D**rugs, **S**exuality, **S**uicidality, Depression, and **S**afety.

With regards to *home*, ask about living arrangements, relationships with key family members, divorce history, history of domestic violence or abuse, and whether they feel safe. Try to determine the parenting style and how much time the parents spend with the teen; teens spell love T-I-M-E.

Questions about *education* should be directed at school performance, including grades, any history of suspension, missed school days, being retained in grade, or problems with bullying. As per the Youth Risk Behavior Survey (YRBS), 15.2% of teens are victims of electronic bullying, 17.4% were bullied in school, 23.6% were in a physical fight, and 10.6% did not attend school because they felt unsafe at school.[11] When bullying is present, it is important to determine if interventions such as discussion with school officials are needed; also, referring the patient to www.**stopbullyingnow.hrsa.gov/** can be helpful. If grades are low, consider screening for problems with a learning disability, reading, or Attention Deficit Hyperactivity Disorder with the administration of the Vanderbilt forms to be completed by parents and teachers. Attention Deficit Disorder occurs in 9% of 13-18-year-old teens.[12] Additionally, other psychological problems associated with poor school performance include substance use disorder, depression, and anxiety. It is often useful to show interest in the teen's future career plans during the assessment.

Screening for problems with *eating*, including obesity, or eating disorders, including anorexia nervosa or bulimia, is essential. Eating disorders occur in 3% of 13-18-year-old teens.[13]

Discussion about the teen's *activities* can give a snapshot of their lifestyle. For example, is the teen involved in church groups, hobbies, scouts, sports, volunteering, music, or are they hanging out with gangs or doing video games all the time. A good question is, what is their favorite thing to do?

Next, screening for *drug* problems is vital in that much morbidity and mortality can be prevented before serious use sets in. Substance abuse statistics also measured by the YRBS, show 13% report binge drinking 4-5 drinks in a row at least once in

the past month, 18.5% have used marijuana in the past month, 3.4% have ever used cocaine, 6.9% ever used spice (synthetic marijuana), 2.5% ever used methamphetamine, 4.0% used ecstasy, 6.6% used hallucinogens, 1.7% ever used heroin, and 10.6% took prescription pain medication without doctor's approval.[11]

The American Medical Association (AMA), the American Society of Addiction Medicine (ASAM), the Center for Substance Abuse Treatment (CSAT), the AAP, and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) support substance abuse screening for adolescents. In 2016, the AAP Committee on Substance Use and Prevention published SBIRT Guidance.[14] In this report, the risk of even one-time use of substances can have significant consequences, including risky sexual activity resulting in pregnancy or sexually transmitted infections, fighting, or injuries from motor vehicle accidents. Younger age of onset is correlated with a higher incidence of developing a substance use disorder. Children and adolescents have a higher risk of developing addictions neurodevelopmentally when compared to adults. Substance use is often associated with psychiatric co-morbidity, including mood disorders, anxiety disorders, and post-traumatic stress- disorder (PTSD). There is a tremendous opportunity for PCPs to address substance abuse.

The SBIRT screening consists of simple frequency questions which place use over the past year into four categories: 'never used', 'once or twice', 'monthly', and 'weekly'. This screening can be administered through a questionnaire completed by the patient or by the clinician as part of the private face-to-face interview.

The first stage of questions pertains to tobacco, alcohol, and marijuana with advancement to other substances only if one of these shows positive responses greater than 'never used'. The other substance questions include prescription drugs, illegal drugs such as cocaine or ecstasy, inhalants, and synthetic drugs such as bath salts, K2, or spice.

The four categories have been found to correlate with the DSM-V (Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition) Substance Use Disorder (SUD) Criteria. 'Never used' corresponds to being abstinent, 'once or twice' in the past year use corresponds to use without a disorder, 'monthly use' corresponds to mild to moderate SUD, and 'weekly use' corresponds to severe SUD.

For any positive responses, the guideline recommends using the CRAFFT assessment tool to determine the extent of substance use. CRAFFT is a six yes or no question screening tool where the clinician asks about specific features of a teen's substance use including use while driving or in a **C**ar, to **R**elax, when **A**lone, despite **F**riends/family urging the teen to quit, resulting in **F**orgetting what happened and use resulting in getting into **T**rouble. Any score greater than or equal to 2 indicates a need for further assessment.[15]

Interventions for each of the four categories from the SBIRT questions include positive praise for 'never used', advise to stop for 'once or twice', motivational interviewing counseling with consideration for referral to change use for 'monthly use', and more focused counseling, referral, involving parents and motivational interviewing to get patient into higher level of services for 'weekly use'.

Motivation interviewing is a non-directive, non-authoritative patient-centered collaborative method of counseling designed to bring about change in a teen's substance use resulting in abstinence. This technique involves using open-ended questions, asking permission to discuss topics, affirming statements directed at the patient, empathy, acceptance of the patient, reflective listening, paraphrasing the patient's words without being judgmental, and summarizing the patient's situation and feelings expressed. This technique avoids direct confrontation and argument, but rather the clinician explores the pros and cons of substance use and 'rolls with resistance', adjusting the conversation when encountering the patient's unwillingness to change initially. It involves understanding the patient's readiness for change, engaging in change talk, gaining trust, and respecting the patient for being autonomous and responsible for their life. In motivational interviewing, the clinician explores the patient's desire, ability, reason, need, and commitment to change. It evaluates actions the patient has taken to change and the intention to change. The clinician does not impose interventions but rather through a series of directed questions that develop a discrepancy between the patient's goals or values and their current behavior, elicits within the patient, a motivation to change. This technique can be applied in the outpatient setting and is recommended for moderate and severe SUD.[16,17]

The referral process involves knowing what is available in the community, including individual counseling, group therapy, family therapy, intensive outpatient, or partial hospitalization. Consideration for inpatient detoxification may be needed for chronic use of alcohol or benzodiazepine and may help those on opioids and cocaine. Inpatient options include residential treatment programs and therapeutic boarding schools. Finding programs close to home can facilitate family involvement when appropriate. Keeping track of the financial costs of the referral center treatment is also very important. Regardless of which referral option is taken, it is important that the PCP continues to be available to monitor progress, offer support, and provide follow-up.

Screening for *sexual risk behaviors* is necessary to provide timely interventions to prevent sexually transmitted infections and teen pregnancy. Ask open-ended, non-judgmental questions about their sexual involvement, including their preferred pronouns, whether they identify as being attracted to male, female, or both, if they ever had sexual activity, the number of partners, and whether they use protection with condoms and birth control. Also, it is important to determine if there is a history of sexually transmitted infection or teen pregnancy, which can have devastating effects on a teen's mental health and life trajectory. It is important to give positive reinforcement to the teen who chooses abstinence; they should not be given the impression that everyone at their age is sexually active.

The next topic is *depression* screening. As per the most recent YRBS, in Florida over the past 12 months, 38.1% (57.8% LGBT) felt sad or hopeless. In the past 12 months, 18.1% (39.5% LGBT), report serious suicidal ideation, 14.1% (31.6% LGBT) made plan about how they would attempt suicide, 8.9% (22.5% LGBT) attempted suicide and, 2.4% (6.8% LGBT) attempted suicide requiring medical care.[11] A major depressive disorder is found in 8% of adolescents with a lifetime prevalence by age 20 years of 20%. Risk factors include female sex, older age, family history of depression, a previous bout of depression, other psychiatric diagnoses, chronic medical illness, overweight, obesity, Hispanic ethnicity. Also, a history of abuse, neglect, exposure to trauma, relationship breakup, family discord, LGBT status, poverty, and poor grades in school can play a role. Depression in adolescents is a leading cause of poor grades, poor interactions with family, suicidal ideation, attempts, and completion.

The US Preventive Task Force and the AAP Guidelines for Adolescent Depression in Primary Care (GLAD-PC) recommend screening for major depressive disorder age 12-18 years.[18,19] Contingent on this recommendation is that the provider should ensure accurate diagnosis, effective treatment, and appropriate follow-up.

The Patient Health Questionnaire-9 for Adolescents is a recommended screening test.[20] The PHQ-9-A had the best sensitivity of 73% and specificity of 94% for major depressive disorder.

When screening for depression, it is vital to determine if there are red flag symptoms, including evidence for manic symptoms with significantly elevated mood and diminished need for sleep, psychosis or suicidal ideation, intent, plan, or attempt (see article on Depression in this issue by *Elise M. Fallucco, MD, and Michaela L. Denison, MD*). Reviewing the DSM-V symptoms of major depressive disorder is reasonable including SIGECAPS with five or more over the past two weeks being consistent with a diagnosis of Major Depressive Disorder: **Depressed Mood**, **S**leep disturbance, Loss of **Interest** (boredom), **G**uilt, Low-**E**nergy, problems with **C**oncentration, increased or decreased **A**ppetite, **P**sychomotor Agitation or Slowing, **S**uicidality. Note at least **depressed mood** or **loss of interest** must be identified.

Using the PHQ-9-A score, the number of DSM-V symptoms, the overall functioning level, level of distress, and the presence of red flag symptoms determine the need for interventions. Evidence-based interventions include Cognitive Behavioral Therapy, and Serotonin Specific Reuptake Inhibitors (SSRI). The three medications recommended include Fluoxetine, Sertraline, and Escitalopram. The clinician should determine whether referral to a psychiatrist is indicated. During the assessment, where there is concern about suicidality, the clinician should devise a safety plan including locking up lethal methods of injury such as guns, sharps and medications and providing a go-to person when suicidal thoughts become a problem outside of the clinical setting. The clinician should exercise good judgment on whether to admit the patient to inpatient services on an emergency basis.

Another question to ask as part of the HEEADSSS assessment is whether anxiety is interfering with the teen's life. Consider administering a validated screening test such as Screen for Child Anxiety Related Disorders (SCARED) to delineate further the type of anxiety such as panic disorder, generalized, social, separation, or school avoidance-related anxiety. The National Institute of Mental Health reports that anxiety occurs in 32% of 13 to 18-year-old teens.[21]

Finally, questions on *safety* include a history of domestic violence, physical, emotional, or sexual abuse. As per the YRBS, 8.7% were forced into sexual intercourse.[11] The teen should be asked if they feel safe at home and at school. Asking about the use of weapons among peers is appropriate to explore. An excellent screening tool for post-traumatic stress syndrome is the Trauma in Primary Care PTSD screen adapted for adolescents (PC-PTSD-A). Another screening tool is the Adverse Childhood Events (ACE's) questionnaire, which provides background on the teen's exposure to trauma such as abuse and parental substance abuse, imprisonment, or mental health problems.

A useful resource is the University of South Florida's Florida Pediatric Psychiatry Hotline which provides PCPs with a number to call a psychiatrist for advice on managing mental health problems. More information can be found on their website http://www.medicaidmentalhealth.org/fppHotline.cfm. Also, there is an extensive list of Florida Medicaid guidelines for medication use in various mental health problems, including autism, anxiety, depression, ADHD, and tic disorders.

In conclusion, teens should be screened for mental health disorders. The HEEADSSS assessment, the SBIRT program for

substance abuse, and GLAD-PC for depression provide a framework where timely detection of problems can make a big difference in a teen's life. There are many positive interventions that the PCP can implement once a problem is uncovered. Finally, the PCP may be the only resource a troubled teen has in facing their mental problems.

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REVIEW ARTICLE

Adolescent Substance Use

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INTRODUCTION

"It is the worst of plagues. It knows no season and no boundaries. No mosquito will be identified, no microbe isolated, no vaccine invented to end its reign. It is a pestilence with all the classic trappings of social disruption, suffering, and death--and one terrible, defining difference: We invite it to kill and maim and diminish us. We know how it enters us, and we open the doors to it, lured by the short-term pleasure it offers, lulled by the years or decades it incubates before erupting into host-killing maturity. And because its vector is pleasure and its mask is time, we have not even recognized its horror fully enough to grant it a name worthy of its grisly power. How inadequate it is to call this peerless filler of graves and plunderer of nations by so pallid a name as "substance abuse."[1]

With these haunting words the Robert Wood Johnson Foundation succinctly stated, in 1992, one of the major problems we face in our battle against substance use disorder in both adolescents and young adults. So many of us welcome, at least initially.

Our biology, sadly, works against our young in regard to substance use disorders. Science has shown that the brain matures in a rostral to caudal direction.[2] Thus, an adolescent's pleasure centers, located in the nucleus accumbens and striate areas of the brain, mature before the pre-frontal "executive (or control) centers." Adolescents, therefore, are pleasure seekers. If they become involved with substance use, their risk of addiction is higher than adults, who, presumably, have more input from their prefrontal cortices. Moreover, the younger a child is when he/she begins using substances the more likely he/she is to develop a chronic substance use disorder.[3,4] As an example, The National Longitudinal Alcohol Epidemiologic Study has reported that the rates of alcohol dependence in adults varied by age of first use:[5-7]

Age at First Use	% With Alcohol Dependence
≤ 12 years	40.6%
18 years	16.6%
21 years	10.6%

The same increased risk of chronic addiction by age of initiation is true with other substances of abuse, as well.[2]

EPIDEMIOLOGY

In 1975 Lloyd Johnston and his group at the University of Michigan published the first of an annual survey of high school students called the *Monitoring the Future* Study, with data obtained from in-school anonymous surveys of approximately 40,000 high school students from around the United States. In the original survey almost 80% of high school seniors had used alcohol (in a capacity other than religious), and almost 40% had binge drunk in the previous 30 days (Figure 1). Almost 40% had used tobacco and marijuana in the previous month (Figures 2 and 3). Over the past 45 years the *Monitoring the Future* studies have given professionals annual snapshots of use of substances in adolescents. In that time the "big three" are still by far the most common—alcohol, tobacco/nicotine, and marijuana—with other substances being used at a much lower frequency by high school students. This paper will discuss these three drugs primarily, since they are so commonly used in the USA. For information on some of the newer drugs of abuse the reader is referred to *Newer Drugs of Abuse in Adolescents* in the Summer 2017 issue of *The Florida Pediatrician*.[8]

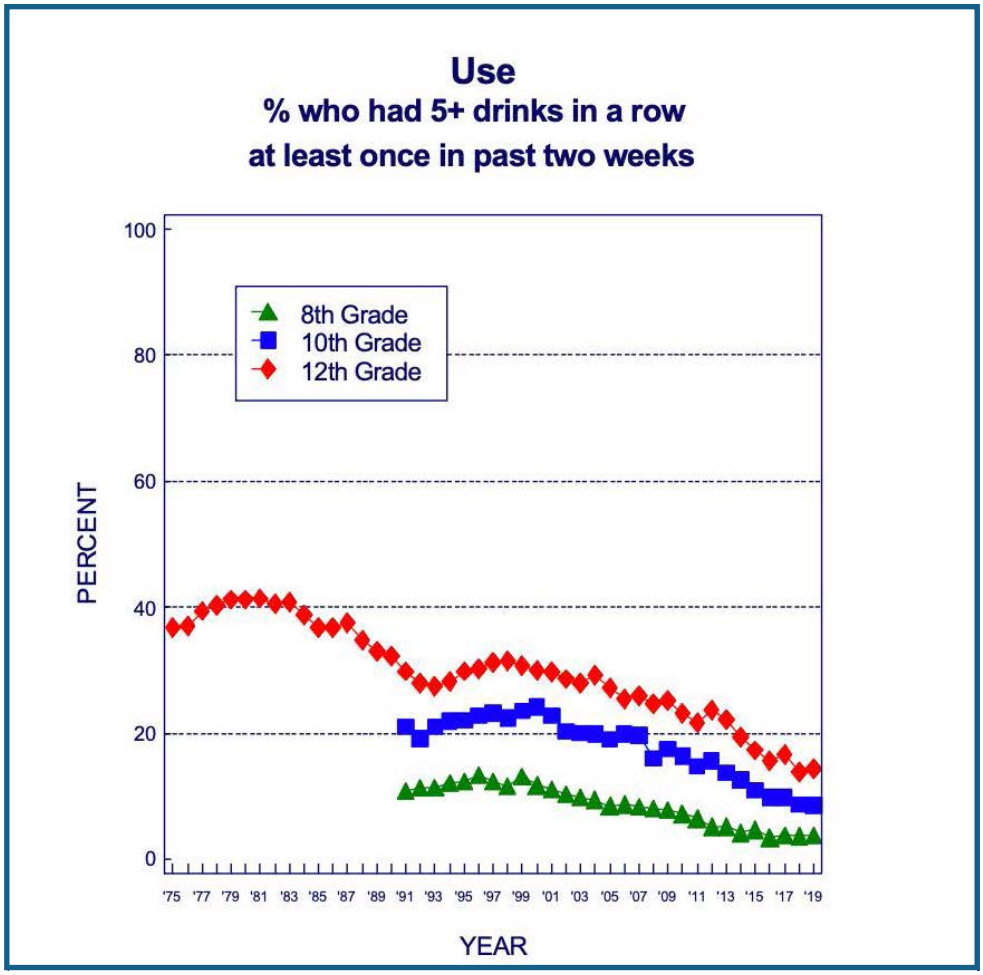


Figure 1: Alcohol Use
Source: The Monitoring the Future study, The University of Michigan[9]

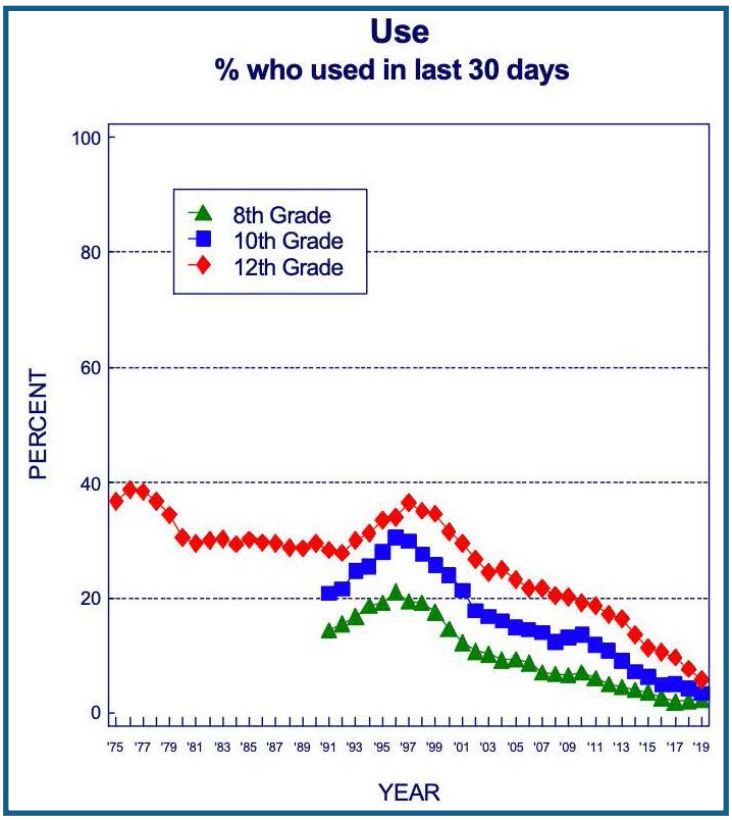


Figure 2: Tobacco Use
Source: The Monitoring the Future study, The University of Michigan[9]

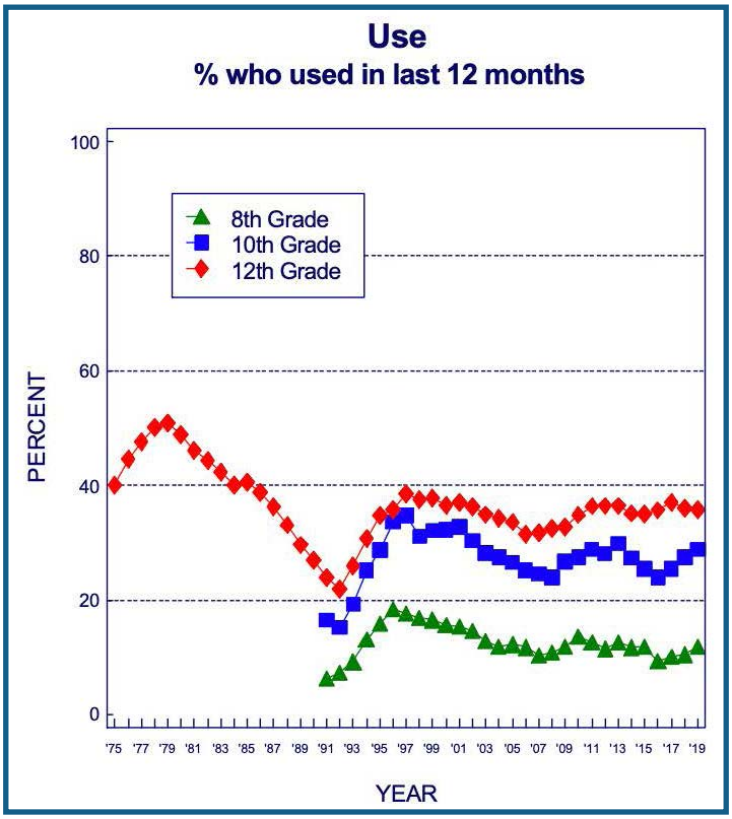


Figure 3: Marijuana Use
Source: The Monitoring the Future study, The University of Michigan[9]

The percent of students using alcohol and tobacco has declined sharply over the past 45 years (Figures 1 and 2), and the use of marijuana has remained relatively stable over the past 25 years (Figure 3) according to the *Monitoring the Future* studies.[9] It should be noted that, since these are in-school surveys they are, at best, valid minimum estimates of use, as approximately 10% of students are absent from school on any given day, and a large percent of these children likely have issues with alcohol or substance use.

A recent study of Canadian youth during the COVID-19 pandemic[10] found that use of most substances declined, although use of alcohol and cannabis increased significantly. Solitary use was reported by 49.3% of respondents. 31.6% reported use with peers via technology, and 23.6% used in face-to-face settings.

ALCOHOL

As noted in Figure 1, alcohol use by youth has been steadily declining over recent years. Nevertheless, it is an important cause of morbidity and mortality in adolescents. Approximately 20% of fatal motor vehicle accidents in youth are alcohol related, down from approximately 50% in the 1970's. Most states have done a very good job decreasing the youth-involved moving vehicle accident (MVA) death rate by instituting graduated licensing and zero tolerance blood alcohol levels in youth less than age 21.[7, 11, 12] The use of designated drivers has become much more accepted than in the 1970's and 1980's. In addition, repealing the failed 1970's era laws allowing youth to drink at age 18 in several states has also helped decrease youth deaths.

When youth drink they tend to binge drink, defined as five or more drinks in a two hour period in males and four or more drinks in a two hour period for females,[13] rather than drinking more slowly over a longer period of time. Drinking episodes are usually more episodic than in adults, and adolescents tend to drink in social groups with friends. Early alcohol use has been shown to affect cognitive and brain development in adolescents.[2, 14] Alcohol is significantly related to violent and other anti-social behaviors in adolescents and adults, including sexual assaults, physical assaults, robbery, and even violence with guns or other weapons. Approximately 50% of all trauma seen in emergency rooms is alcohol related.

Alcohol use is believed to start, generally, in peer or family groups. However, genetic influences and age at first use (noted above) have been shown to increase one's risk of developing addiction. Young people with 2 alleles of the Cholinergic M2 receptor gene appear to have a much higher risk of developing an alcohol-use problem quickly once they begin drinking.[15]

TOBACCO AND NICOTINE

As is the case with alcohol, nicotine use often starts with friends or family. The earlier a child uses nicotine products the more likely he/she is to become addicted.[16] 66% of smokers who begin in junior high vs. 46% of those who begin in their junior year of high school. Even smoking as little as once monthly increases the risk of eventual dependence by ten-fold![17] After very little exposure adolescents find themselves drawn to the feeling nicotine gives them. Soon, craving begins, and, finally, they have to smoke to avoid abstinence symptoms.

Pharmacologically nicotine is a potent parasympathetic alkaloid which stimulates nicotinic acetyl-choline receptors (nAChR) in the central and peripheral nervous systems. Speaking simplistically, these appear to become quickly desensitized to the chemical, leading to the production of more nAChR and tolerance, habituation, and withdrawal. Nicotine also appears to stimulate multiple neurotransmitters in the brain, the most important of which may be dopamine, which boosts attention, reward-seeking behaviors, and, perhaps, addiction. After being dosed with nicotine most people report lower anxiety rates, increased concentration/memory, and a mild euphoria. However, despite these positive subjective responses, studies have shown that nicotine negatively affects cortisol levels, sleep-wake cycles, rapid eye movement (REM) sleep, and, of course, the cardiovascular system. Low levels of nicotine actually stimulate catecholamine production in the adrenal gland. Nicotine also leads to the release of free fatty acids and proliferation of vascular smooth muscle cells, with the expected long-term response of heart disease. Infants exposed to tobacco *in utero* show decreased cognitive functioning, lower birth weights, smaller head circumferences, and an increased risk of developing substance use disorders through adolescence and young adulthood. An excellent and thorough review of the pharmacology and chemical actions of nicotine, as well as an explanation of its differing effects on different sexes and ethnicities, can be found in the AAP Technical Report *Nicotine and Tobacco as Substances of Abuse in Children and Adolescents.*[18]

Thankfully, as with alcohol, tobacco use in adolescents has declined over the past 45 years (Figure 2). However, over the past several years, as tobacco use has declined, the use of electronic nicotine delivery systems (ENDS) has exploded, leading the MTF researchers to add that particular type of substance use to their survey in its 2017 publication. As an example, in 2019, 25% of high school seniors report using an ENDS within the previous 30 days, up from 11.9% in 2017.[9] These products have been aggressively marketed to the public as aids for smoking-cessation, though they have not even been shown to be

effective, in that goal, for adults. In teens they likely increase the rate of taking up cigarette smoking over time.[19, 20] They have been marketed to teens through the use of flavors and fancy electronic delivery devices such as Juul®, vape pens, and pod systems, to name a few. The Food and Drug Administration (FDA) was caught "asleep at the switch" through too much of the last decade, allowing the spread of these devices and the flavors (bubble gum, mint, that attract adolescents, until they finally outlawed flavors in January 2020.

MARIJUANA

Marijuana is used by adolescents more than any substance except alcohol. In America, MTF surveys show that youth feel marijuana is not a dangerous drug.[9] Given the fact that, at the time of this writing, 14 states, in addition to the District of Columbia, have fully legalized marijuana and only 6 states—Alabama, South Carolina, Tennessee, Kansas, Idaho, and Wyoming—still have laws completely prohibiting its use, the above fact should not be surprising. Neither, of course, should the fact that marijuana use in adolescents has been stable in recent years, despite the fall in rates of alcohol and tobacco use [see figure]. The main active ingredient of marijuana, Delta-9-tetrahydrocannabinol (THC), is derived from the plant *Cannabis sativa*. This fat-soluble compound works on the body's central and peripheral cannabis receptors, CB-1 and CB-2 as a partial agonist. Usually smoked, it can also be ingested. In the first decade of the 21st century synthetic marijuana (K-2, Kronic, or Spice) emerged. These substances also stimulate the cannabis receptors, but as full, not partial agonists. Unfortunately, given this fact, overdose and even death are more likely with synthetic than real marijuana, the level of which plateaus even with higher dosage because of the fact that it is a partial CB1 and CB2 agonist. In recent years the vaping epidemic has also expanded to include the vaping of marijuana with occasional episodes of severe lung damage, perhaps because of Vitamin E in the vape mixture.

Because THC is fat soluble, it easily and quickly crosses the blood-brain barrier. In pregnant women it also easily crosses the placenta. Its lipophilic quality also causes it to be stored in fat, from which its elimination half-life can be prolonged, several days in light users and up to a month in chronic heavy users.

The physiologic effects of inhaled marijuana peak approximately 30 minutes after it is smoked. Ingested marijuana can take as long as 6 hours to take effect, though usually more like 1-2 hours. Both forms last approximately 2-4 hours. The physiologic effects include improved sociability, increased perception, a feeling of slowing of time, euphoria, and relaxation. People also tend to experience less pain. Some also experience decreased attention, paranoia, increased appetite, and poor balance and judgement.[21] Because most studies involving adolescents and marijuana have been observational in nature, researchers do not yet know the safe "dose" in adolescents.[21] However, heavy use has been associated with psychosis and schizophrenia as well as anxiety, though not depression. Heavy use has also been shown to affect cognition and attention, thus negatively affecting school performance and employment outcomes. In adults, heavy marijuana use affects testosterone levels which can lead to erectile dysfunction. Inhaled marijuana is associated, of course, with increased mucus production, wheezing, and cough. Because a large number of people who smoke marijuana also smoke tobacco, scientists have not yet been able to work out if there is an association between marijuana use and later lung cancer or chronic obstructive lung disease. Reviews by Dharmapuri[22] and Hadland[21] are very informative reviews of marijuana's pharmacologic and physiologic effects on humans.

ARE ALCOHOL, TOBACCO, AND MARIJUANA GATEWAY DRUGS?

Over the last 40 years, experts have been arguing the question of whether use of alcohol and tobacco leads to the use of illicit drugs. Does the pharmacologic actions of alcohol and tobacco lead to heavier and more illicit use, or is it, as Benjamin Franklin said in *Poor Richard's Almanack*, that "he that lieth down with dogs shall arise with fleas?"[23] Current research seems to support both theories as operative. Certainly, adolescents who use substances tend to hang with friends who use, and those friends can push them, directly or by example, to try new drugs and other problem behaviors. But it is starting to appear that the substances themselves may also be operative in this matter. For example, alcohol appears to increase the response of nAchR. Even small amounts of alcohol seem to increase nicotine effects, leading to increased smoking behaviors. In mice, nicotine seems to activate a gene that increases the rate of cocaine abuse.[1] In like manner, rats exposed to THC appear to have a greater response when exposed to opioid substances.[24]

SCREENING AND BRIEF INTERVENTION

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[25] lists criteria for substance use disorders, including the development of tolerance, withdrawal, more use than expected or planned, and life revolving around the use of the substance of addiction (to name a few of the criteria). It should be noted, however, that the research used in developing these criteria was primarily performed on adults. As an example, adolescents rarely develop withdrawal symptoms from

alcohol, particularly when they are young. However, many adolescents may be using alcohol, or other substances, in a very risky manner despite the fact that DSM-5 criteria for substance use disorder are not met. For this reason, there are several substance use screening tools for adolescents (see below), which may be more useful than the DSM-5 in this age group. Pediatricians should not be expected to make a definitive diagnosis of substance use disorder nor, in general, treat the condition. We should, however, universally screen our tweens and adolescent patients for substance use, and, when necessary, perform a brief intervention and/or referral to treatment (SBIRT).[26, 27] A detailed description of this process is outside the scope of this paper, but adequate screening involves several important steps:

A. Discuss with patients the importance of confidentiality. It is important for us to remember that we cannot give blanket confidentiality for everything they might tell us, but we can make it clear that confidentiality is important. I tell my patients that everything they tell me will be confidential unless…..(1) they are being abused in any way, (2) they are considering harming themselves or someone else, or (3) they are in a situation that could truly become life-threatening. While the third situation above is not required, it allows me to step in if an adolescent is involved in behaviors that could truly threaten their lives (for example drinking and driving). It goes without saying that we will not get a true picture of any problem behaviors in which our patients may be involved if we do not first discuss confidentiality. If a provider must break confidentiality the patient should be the first to know. It destroys patient trust if a provider takes a history, gets details of what the patient might be involved in, then divulges the behavior to the patient's parents behind his/her back.

B. Part of a reasonable screening strategy for adolescents is using the HEADDSSS examination. Using this well-known screening tool providers can assess a child's Home situation, Educational achievements or problems, Activities (and work), Diet, Drug use, Safety, Sexuality, and Suicidality. By going through the history using open-ended questions a provider can develop rapport with a patient before addressing some of the more sensitive questions in the HEADDSSS mnemonic.

C. If a child admits to the use of alcohol, tobacco, ENDS, marijuana, spice, or other substances of abuse there are several instruments that can be used to help a provider decide if the use is problematic (Figures 4-6). The Screening to Brief Intervention (S2BI) (Figure 4) screen has a 0.90 sensitivity and a 0.94 specificity in any non-tobacco substance use problem. In this questionnaire, a score of "used once or twice" does not correlate with a diagnosis of substance use disorder, "monthly" correlates with mild or moderate substance use, and "weekly" correlates with severe substance use disorder.[28] The CRAFFT, written by John Knight at Harvard[29] (Figure 5) has a Sensitivity of 0.76 and specificity of 0.94 for any substance use behavior and a sensitivity/specificity of 0.80/0.86 for any substance use disorder.[30] In this screening instrument a score of 2 or greater in the bottom section of the questionnaire (Figure 5) is significant.

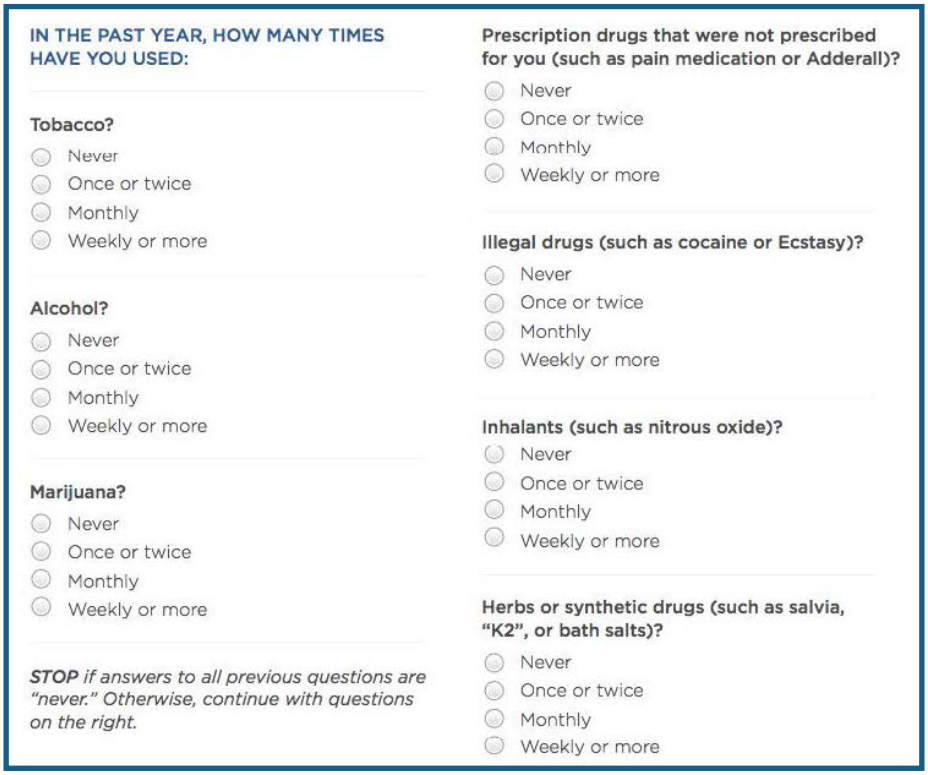
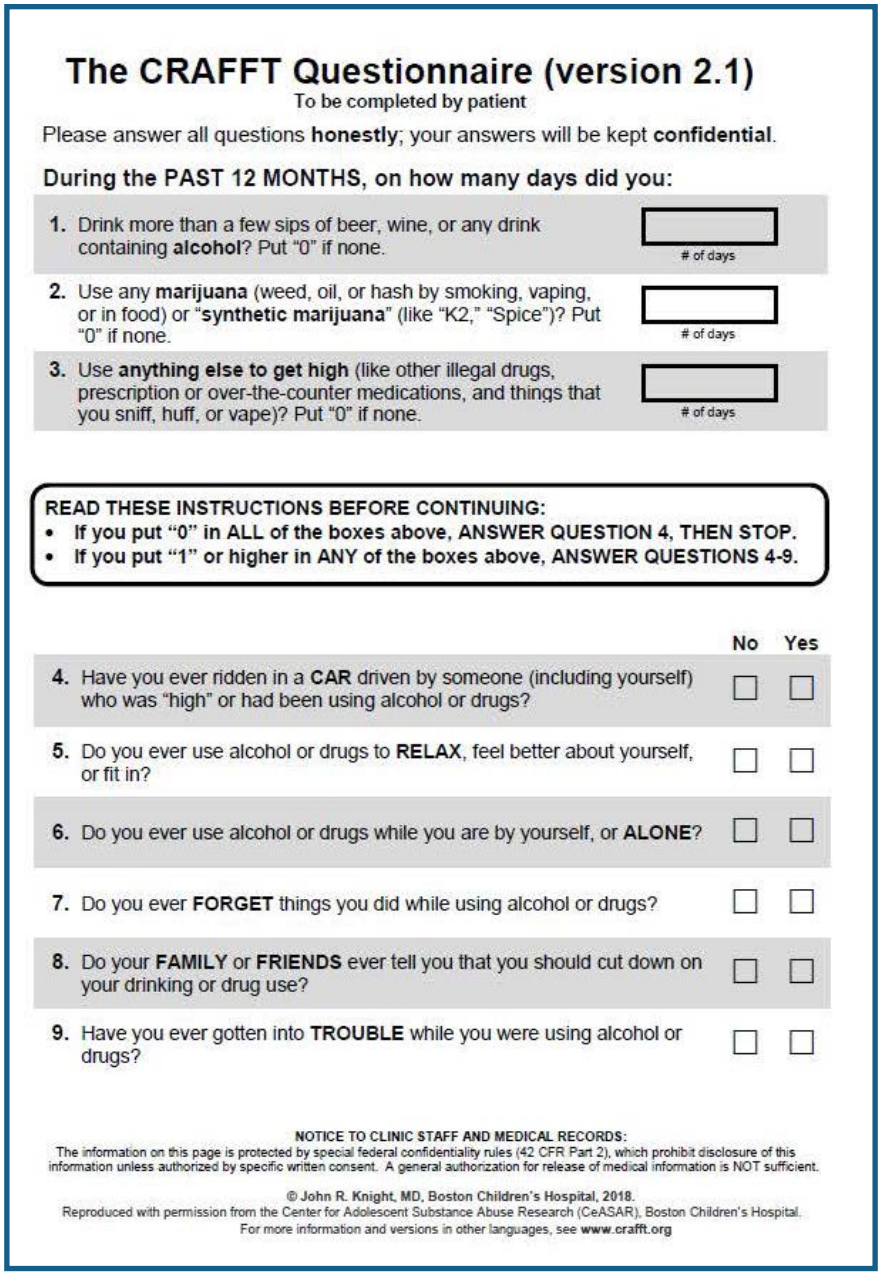


Figure 4: Screening to Brief Intervention (S2BI)



The CRAFFT Questionnaire (version 2.1)

To be completed by patient

Please answer all questions **honestly**; your answers will be kept **confidential**.

During the PAST 12 MONTHS, on how many days did you:

1. Drink more than a few sips of beer, wine, or any drink containing **alcohol**? Put "0" if none. ☐ # of days
2. Use any **marijuana** (weed, oil, or hash by smoking, vaping, or in food) or "**synthetic marijuana**" (like "K2," "Spice")? Put "0" if none. ☐ # of days
3. Use **anything else to get high** (like other illegal drugs, prescription or over-the-counter medications, and things that you sniff, huff, or vape)? Put "0" if none. ☐ # of days

READ THESE INSTRUCTIONS BEFORE CONTINUING:
- **If you put "0" in ALL of the boxes above, ANSWER QUESTION 4, THEN STOP.**
- **If you put "1" or higher in ANY of the boxes above, ANSWER QUESTIONS 4-9.**

	No	Yes
4. Have you ever ridden in a **CAR** driven by someone (including yourself) who was "high" or had been using alcohol or drugs?	☐	☐
5. Do you ever use alcohol or drugs to **RELAX**, feel better about yourself, or fit in?	☐	☐
6. Do you ever use alcohol or drugs while you are by yourself, or **ALONE**?	☐	☐
7. Do you ever **FORGET** things you did while using alcohol or drugs?	☐	☐
8. Do your **FAMILY** or **FRIENDS** ever tell you that you should cut down on your drinking or drug use?	☐	☐
9. Have you ever gotten into **TROUBLE** while you were using alcohol or drugs?	☐	☐

NOTICE TO CLINIC STAFF AND MEDICAL RECORDS:
The information on this page is protected by special federal confidentiality rules (42 CFR Part 2), which prohibit disclosure of this information unless authorized by specific written consent. A general authorization for release of medical information is NOT sufficient.

Figure 5

The CAGE for adolescents is one that many pediatricians learned in residency. It is easy to use because it only has four questions. Originally formulated for adults, it was adapted to adolescents by changing "eye opener" to "early" use before school:

- Have you tried to cut back?
- Have you become angry when people attempt to discuss your use?
- Have you felt guilt about anything that happened while you were drunk or high?
- Have you used early, before school?

In this screening instrument 2 positives are significant. Sensitivity/Specificity is 0.67/0.82[30], admittedly not quite as good as the CRAFFT or S2BI.

D. Brief intervention can run the gamut of positive reinforcement for patients who are not using substances to explaining risks to those who are using but not heavily, along with a recommendation they stop the use. These should be done after asking for permission to teach. For those using this method, heavily motivational interviewing will need to be used,[31] and, sometimes, referral to treatment will need to be made even against an adolescent's will. When this situation occurs,

it is important for the provider to emphasize the disease nature of the teen's condition in a non-judgmental tone and the need for treatment, in the same manner as the teen may need treatment for another condition. While the teen will undoubtedly be very angry, they will understand as they progress through treatment.

CONCLUSION

With the exception of the current explosion in the use of electronic nicotine delivery systems, substance use in adolescents has declined (most substances) or remained steady (marijuana) over the past 40 years. However, substance use is still a major issue that can destroy people's aspirations and even lives. All providers who care for children need to be comfortable in screening and brief intervention to help these patients. All efforts to delay the onset of use should be employed because of the known detrimental effect early substance use has on brain development.

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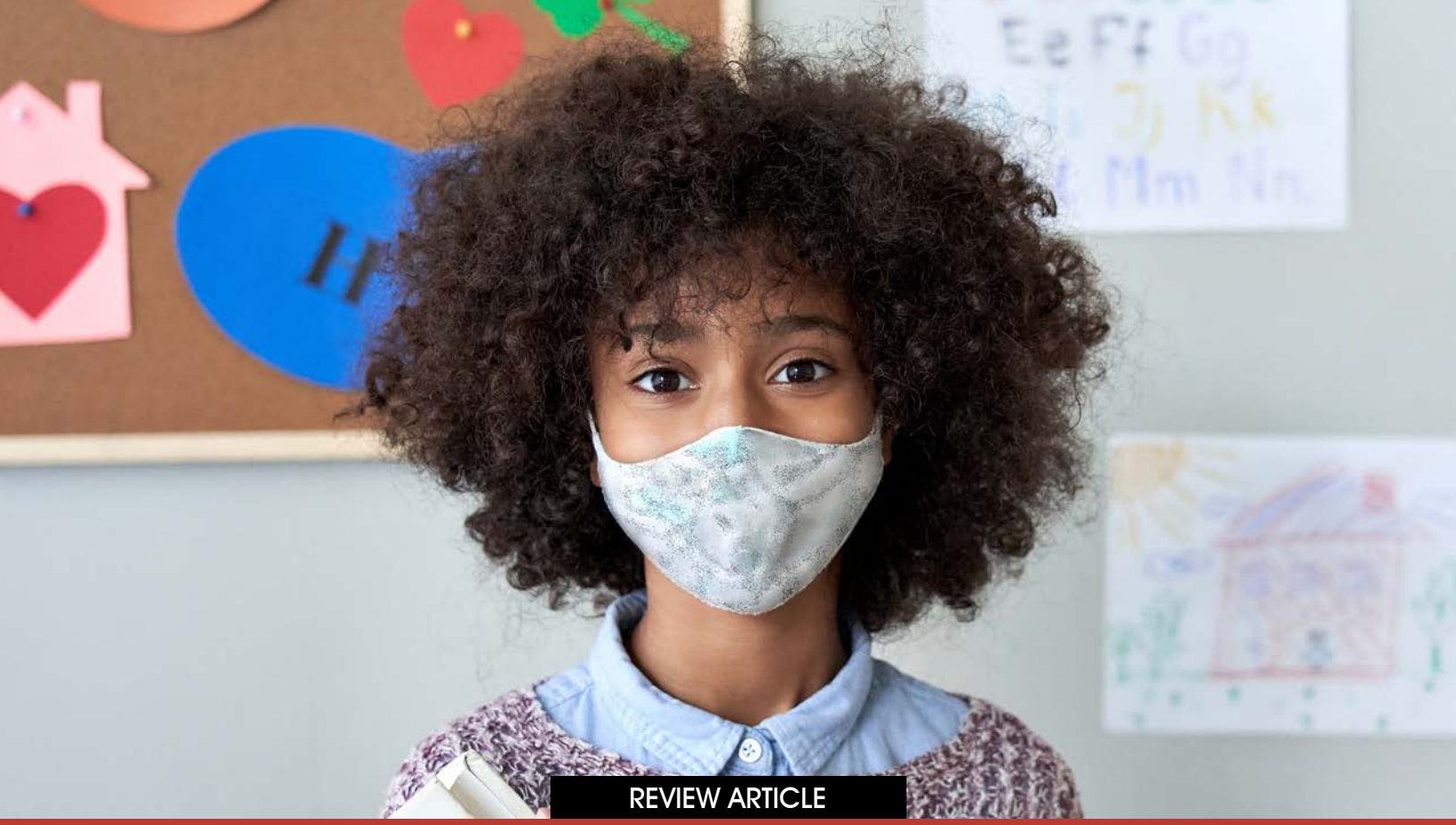

REVIEW ARTICLE

Pandemic Blues: Identifying and Treating Adolescent Depression in Light of the COVID-19 Pandemic

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The COVID-19 pandemic has disrupted the lives of families across the globe, while social distancing measures have prevented parents and children from participating in activities that would typically reduce their stress. This has resulted in significant mental health consequences including elevated rates of depression, anxiety, and sleep problems among adults[1,2,3] as well as adolescents.[4,5] Even prior to the pandemic, adolescent depression had been a major public health problem, affecting 11.3% of US adolescents.[6] Now that youth are at higher risk for psychiatric illness during the pandemic, it is especially important for pediatric clinicians to screen for signs of depression.

SCREENING ADOLESCENTS FOR DEPRESSION

The American Academy of Pediatrics has identified various depression screening tools that can be used in primary care,[7] one of which is the Patient Health Questionnaire-9 Item modified for adolescents (PHQ9A).[8] The PHQ9A is a brief, well validated screening tool that adolescents can complete privately at the start of their well visit. Adolescents rate how often they have experienced the nine key symptoms of depression over the previous two weeks, ranging on a scale from "not at all" (scored as zero points) to "nearly every day" (3 points). Total scores of 11 or higher have a high sensitivity (89.5%) and specificity (77.5%) for detecting moderate severity depression.[8] Pediatric clinicians must pay close attention to the response on item number 9 which asks about suicidal thoughts, even if the total depression score is normal.

THE 3-STEP ASSESSMENT OF ADOLESCENTS WITH POSITIVE DEPRESSION SCREENS

It can be helpful to use a **3-step approach** to further evaluate patients with positive depression screens.

Step One: Context, Duration, Severity of Symptoms

The first step is to determine the context, duration, and severity of the patient's depressive symptoms. Make sure to ask the following questions.

- Are any major stressors at home, at school, or with friends that could be affecting how the patient is feeling?
- How long has the patient felt this way?
- How has it affected the patient's life at home, school, and with friends?

To distinguish depression from developmentally typical mood fluctuations which may or may not be related to the pandemic, adolescents would have to experience depressive symptoms nearly every day for at least two weeks which have affected their functioning at home, school, and/or with their friends.

CASE EXAMPLE 1

Qayla is a 15-year-old cisgender female who is new to your practice and presenting for a well-visit. She completes the PHQ-9 before coming into the exam room. The total score is 16 and question number 9 is positive indicating that she has some suicidal thoughts. Qayla's mom is concerned that her grades dropped and she is spending a lot of time in her room.

Clinician: Thank you so much, Qayla, for filling out this questionnaire [referring to the PHQ9A]. I noticed that you mentioned that you've been feeling irritable or upset lately. Can you tell me more about that?

Qayla reports that she been really "stressed and annoyed" with virtual school… and worried about upcoming standardized tests. She has had trouble falling asleep and has felt tired with low energy for the past 6 months. She doesn't enjoy spending time with friends, and has been getting into more arguments with her mom.

To summarize, it sounds like Qayla has felt stressed and annoyed (note that irritability is a key feature of adolescent depression) for six months in the context of increasing academic pressure and distance learning. These symptoms have progressed to the point that they are interfering with her grades, relationships and basic needs like sleep. The severity and duration of the symptoms suggest that they are serious, and unlikely to be explained by typical teenage mood fluctuations.

Step Two: Differential Diagnosis, Comorbidities

In step two, it is important to consider a broad differential diagnosis to rule in or rule out other problems that could be explaining these symptoms. While depression is more common than many other medical illnesses that present with depressive symptoms, it is important to conduct a thorough review of symptoms and physical exam to evaluate the patients for other medical conditions that can present with depressive symptoms.

- Rule out possible **medical illness** that manifest with depressive symptoms (i.e. hypothyroidism, anemia, mononucleosis, and diabetes). While bloodwork is not required in the evaluation of depression, it may be helpful to check a CBC, CMP, and TSH with reflex T4, and Vitamin D to rule out underlying medical problems manifesting as depression.
- Evaluate the patient for frequent or **heavy alcohol/drug use** (i.e using at least 2-3 times a week) that could present as depressive symptoms.
- Review the patient's list of **medications** for anything that could contribute to symptoms. In pediatric clinical practice, oral contraceptives are the class of medications that would be most likely to cause depressive symptoms. Make a note of whether the timing of depressive symptoms correlates with the initiation of any of these potentially depressogenic medications.

A thorough differential diagnosis would also include psychiatric diagnoses such as bipolar depression or psychotic depression which are treated differently than unipolar depression.

To rule out **bipolar depression**, make sure to ask about decreased need for sleep which is a cardinal feature for bipolar, "Have you ever had a couple nights where you didn't need to sleep and still had plenty of energy the next day without napping?" A history of about five days or more in a row with decreased need for sleep without using caffeine or other stimulants together with a history of episodic euphoric or irritable mood would be concerning for a possible diagnosis of bipolar.

To evaluate the patient for **psychotic depression**, ask the patient, "Have you ever had any unusual experiences where you hear voices and you turn around and no one is there?"

After assessing the patient potential medical and psychiatric diagnoses, remember to think about comorbidities. With depression, comorbidity is the rule rather than the exception. Depression commonly occurs with anxiety, trauma, and disruptive behavioral

disorders like ADHD. Two free screening tools that can be used in pediatric primary care to rule out anxiety or trauma include the Screen for Child Anxiety Related Disorders (SCARED)[9] and the Primary Care PTSD screen- adapted for adolescents (PC-PTSD-a). Copies of these tools are available for free online at the Center for Collaborative Care website: http://partnershipforchildhealth.org/center-for-collaborative-care/.

Case Example 1 Continued

Qayla has no medical problems and is not taking any medications. She smokes marijuana once a month, but denies using other drugs or alcohol. She denies decreased need for sleep or psychosis. She reports some anxiety and worries about her mom but has no history of trauma.

Step Three: Safety

Step three involves conducting a safety and suicide risk assessment which will guide the clinician in determining the appropriate level of care.

- The first part of a suicide risk assessment involves asking about whether the patient has thought about wanting to die. Given that more than one out of six high school students report having serious suicidal thoughts each year[10], and that suicidal thoughts are a core symptom of depression, many patients with depression will report serious suicidal thoughts. Simply having suicidal thoughts alone is not enough to require emergent evaluation.
- To follow-up, you want to determine if the patient has any "red flags" or serious suicidal thoughts or behavior that would warrant a referral for emergency psychiatry evaluation. Red flags include having a suicidal plan, serious suicidal intent or desire to act on their thoughts of suicide, or recent suicidal attempts. Suicide attempts that have occurred within the past few days or weeks are particularly concerning. However, any history of suicide attempt increases risk for suicide.
- When a patient discloses suicidal ideation it is imperative that the provider discuss safety proofing the environment with the family to prevent suicide attempts. As the number one way that people die by suicide is by gunshot wounds, it is critical to counsel families to limit access to lethal means. If the patient has access to guns, make sure to counsel the family to keep them in a locked safe with ammunition stored separately. Make sure that any pills are also secured at home for safety.

Case Example 1 Continued

Clinician: Qayla, a lot of times when people are feeling the way that you described, they may want to fall asleep and never wake up, have you ever felt that way? Or have you thought about wanting to end your life?"

Qayla shares that she has had suicidal thoughts without intent, plan, or recent attempt. Her family owns a gun which is locked in a password-protected safe.

DEVELOPING A TREATMENT PLAN FOR DEPRESSION

One way to think about different treatment plans is to use the stoplight example where red means stop and go to the emergency room, yellow means proceed with caution, and green means that the case is safe for treatment in a pediatric outpatient setting. Patients who presents with possible mania or psychosis or with any of the red flags (i.e. suicidal intent, plan, or attempt) should be referred to the emergency room. It is advisable to refer or consult with a psychiatrist for patients with depression who have a history of trauma or a first degree relative with bipolar or psychosis. It is also important to refer these patients for psychotherapy. The patients who are best-suited treatment in a pediatric outpatient setting are those who have depression with or without anxiety, without any of the red flags.

Once you've determined the appropriate level of care, you can shift to discussing treatment options with families. It is a good idea to talk to the teen first and simply thank the teen for sharing their feelings and thoughts; because teens often feel embarrassed or ashamed for having depression. Then, meet with both the teen and the parent(s), recap your findings, including the PHQ-9A score, and offer hope by shifting focus to ways to helping the teen feel better.

Non-pharmacological depression treatment

The mainstay of depression treatment involves cognitive behavioral therapy (CBT). Ideally, a good therapist is like a coach who can give patients exercises and tips to manage stress that patients can use for the rest of your life. Some adolescents may also be interested in free apps based upon the principles of CBT to help manage symptoms of depression. Some popular, helpful apps include: What's Up?; Stop, Breathe, and Think; and Headspace.

It is important to encourage healthy behaviors that promote mental wellness. There is evidence to suggest that moderate exercise,[11] proper sleep,[12] and limiting social media time to fewer than 2 hours a day[13] are all associated with a reduction in depressive symptoms and anxiety.

Medication Treatment for Depression

When is medication helpful for depression? There is convincing evidence from a large-scale multi-site randomized control trial for adolescent depression that helps to answer this question.[14] In this clinical trial, teens with moderate severity depression were randomized to one of four treatment arms: placebo, cognitive behavioral therapy, fluoxetine, or combination of CBT and fluoxetine. At 12 weeks, the greatest response rate was for combination treatment with fluoxetine + CBT (71%). This response rate was slightly better than response rate of fluoxetine treatment alone (61%). There was no significant difference between the response rate for treatment with CBT alone (41%) and placebo (35%). Over a longer term of up to a year, CBT is associated with similar response rates to combination treatment and to medication alone. The bottom line is that existing evidence suggests that the greatest chance to get a fast response is with combination treatment.

There are three things to consider when choosing medication treatment. Treatment efficacy is the first and most important factor. All of the selective serotonin reuptake inhibitors (SSRIs) have excellent evidence for the treatment of adolescent depression. The second thing to consider is family history of treatment. Is there a medication that the patient's parent responded well to? If so, the teen may do well on it also. The third aspect to consider is the side effect profile. SSRIs as a class tend to be very well tolerated. Some people develop self-limited side effects like a mild headache or abdominal pain in the first couple of days of treatment as they are adjusting to the medication. Around 2% of adolescents can experience severe activation on SSRIs which presents as disinhibition, worsening irritability, and hyperactivity. These symptoms resolve when the dose is decreased or the medication is stopped.

It is ideal to choose a medication with limited side effects and/or with side effects that may help the patient's symptoms of depression. As an example, fluoxetine (Prozac®) is very activating, so it is really good for children and adolescents who are feeling sluggish and having trouble getting motivated. Both fluoxetine and its active metabolite, norfluoxetine, have long half-lives of about 2 weeks. This factor makes it ideal for people who cannot remember to take their medication every day. Fluoxetine has FDA approval for treatment of depression in youth 8 years of age and older. Sertraline (Zoloft®) is in some ways is the opposite of Fluoxetine. It tends to be more sedating, so you can dose it nightly as opposed to in the morning. It has excellent evidence for treatment of anxiety. The downside for Fluoxetine and Sertraline is that they each can have drug-drug interactions through the cytochrome P450 system. While not contraindicated in patients on other medications, these medications must be used with care for kids on other medications that can be affected by or affect the metabolism of these medications. One benefit of Citalopram (Celexa®) and Escitalopram (Lexapro®) is that they each have few drug-drug interactions. In addition, Escitalopram has the FDA approval for the treatment of depression in children 12 years and older.

Starting Antidepressant Medication

When starting SSRI medication, please refer to the SSRI dosing table which lists dosing recommendations. It is standard practice to maintain the starting dose for four to six weeks because it takes that time to see the maximum effect. Just like other medications for the pediatric population, the dose of the medication is based on the patient's weight. A very small 12-year-old may need to start at a dose that is half of the dose listed. Likewise, an adult-sized 17-year-old may need their starting dose to be slightly higher than the dose listed. After the patient is on their starting dose for the necessary four to six weeks, they can be re-evaluated to determine if they have responded to treatment and if they would benefit from a higher dose. Throughout treatment, clinicians can use the PHQ-9A to monitor response to treatment in addition to taking a history and checking compliance with medications. If the patient has tolerated the medicine well, but still has residual symptoms, it is reasonable to increase the dose by 50%. Target dosing ranges are listed for both treatment of depression and anxiety. Typically, depression tends to respond to lower doses than anxiety.

Stopping Antidepressant Medication

Once patients have had a full response to treatment with reduced PHQ-9A scores and improvement in symptoms, it is advisable to maintain patients on the same dose for 9-12 months before deciding whether or not to taper off the medication. Tapers should be done gradually, by decreasing the dose in half every four weeks and evaluating the patient's response.

Black Box Warning

Perhaps the most controversial issue surrounding treatment with SSRIs is the black box warning stating that there is an increased risk of suicidal thoughts or behavior during treatment. Large systematic reviews and meta-analyses have demonstrated an increased risk of aggression and suicidality in children and adolescents who take SSRIs.[15,16] Clinical practice suggests that there is a small population of youth that can feel worse on SSRI medication. Both the teen and the parent can easily recognize when this is happening, and the symptoms resolve when the medication is stopped. While there is a risk of treatment with SSRI medication, the vast majority of depressed patients feel better on medication. Large studies have shown that teens are eleven times more likely to benefit from treatment with antidepressants than to experience any harm.[15]

Depression and Anxiety Medication: Pediatric Dosing (mg)					
	Starting dose*	Effective dose ψ		Max dose	Notes
		Depression	Anxiety		
FLUOXETINE (Prozac®)	5-10	10-20	30-40	60	activating FDA approved: 8+ depression
SERTRALINE (Zoloft®)	25	25-50	100-150	200	sedating (qhs) Best evidence for anxiety
CITALOPRAM (Celexa®)	10	10-20	30-40	40	few med interactions
ESCITALOPRAM (Lexapro®)	5	5-10	15-20	20	few med interactions FDA approved: 12+ depression
* Wait 4 weeks before increasing by this dose increment. Children <10: Consider starting at ½ starting dose. ψ Once at an effective dose, maintain x 9-12 months. Can then decrease by ½ every 4 weeks. All of the SSRIs listed above are available in liquid.					
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PRACTICE CASES

CASE EXAMPLE 2

Trey is a 17-year-old cisgender male with a PHQ9-A of 19. He presents with a six-month history of depressive symptoms and anxiety. He has trouble falling asleep, and endorses suicidal thoughts but no suicidal intent, plan, or previous attempt.

Question: Is he appropriate for management in the outpatient setting? If so, which medication could you start for his depression and anxiety?

Answer: As Trey has initial insomnia, you could choose a sedating medication like Sertraline. As he is an adult-sized young man, you could start at 25mg Sertraline nightly for 1 week, and then increase to 50mg nightly for 4-6 weeks. You would also refer him for CBT and share free apps that he could use to help with his anxiety and depression.

At Trey's 4-6 week follow up visit, he is sleeping better, but still feels like his mood is sometimes low. He denies suicidal thoughts recently. No side effects. He has started CBT. His PHQ9-A has come down to a 16.

Question: Would you keep him at Sertraline 50mg or increase the dose?

Answer: Remission is the goal for treatment of depression. In this case, Trey continues to report symptoms of low mood and his PHQ-9 score is still high. Ideally, the PHQ9-A score should be less than 10 points. To achieve this, you could titrate the Sertraline from 50mg to 100mg and continue CBT.

One month later, Trey returns for a second follow-up appointment with a PHQ-9 of 10. He is feeling so much better on 100mg of Sertraline. He has no side effects. CBT is going really well.

Question: For how long should you continue the medication?

Answer: It is recommended to continue treatment for 9-12 months once his symptoms improve. After this time, the pediatric clinician and the family can discuss whether it makes sense to taper off of the medication. To taper, divide the dose in half and follow up every 4 weeks. If the patient tolerates the decreased dose without emergent symptoms of depression, continue to divide the dose in half until the patient reaches the starting dose. If the patient continues to tolerate the starting dose for an additional 4 weeks, then it is reasonable to stop the medication with a plan to follow-up in 3-6 months to make sure the patient is still feeling well.

CASE EXAMPLE 3

Zoie is a 16-year-old cisgender female with a PHQ-9 of 24. She has an 8–9-month history of depressive symptoms with low energy. She has some anxiety with suicidal thoughts but no intent or plan.

Question: Is she appropriate for management in the outpatient setting? If so, which medication could you start for her depression and anxiety?

Answer: Since Zoie has depression with low energy, it may make sense to start an activating medication like Fluoxetine. You could start Fluoxetine 10mg every day in the morning for one week, then increase to 20mg daily for 4-6 weeks, refer her to CBT, and have her follow up in 4-6 weeks.

At her first follow up, Zoie says she has more energy and is starting to feel a little better but her PHQ-9 is 17 so you will increase the Fluoxetine from 20mg to 30mg and continue CBT. At her second follow up, (8 weeks) her mood is a little better, PHQ-9 is at 15. You increase her Fluoxetine from 30 to 40mg to get maximum benefit from medication.

After 2-3 weeks of starting 40mg of Fluoxetine, Zoie's mom calls to say she has been feeling more anxious, irritated, and agitated ever since the dose increase. There has been no other stressor or major change in her life since the dose increase.

Question: What could explain Zoie's feelings of worsening irritability, anxiety, and agitation?

Answer: Zoie is likely experiencing severe activation that can occur with activating medications like Fluoxetine. The treatment is to decrease the dose and see if the symptoms resolve. If the symptoms do not resolve with a dose decrease, then the treatment will be to stop the medication. Since Fluoxetine and its active metabolite each have a long half-life, it may take a few weeks to clear her system. After that time, you may want to decide whether it makes sense to start another trial of a less activating SSRI medication.

CONCLUSION

In summary, depression is common and can be identified through routine screening. Adolescents with at least moderate severity depression respond well to combination therapy involving antidepressant medication together with cognitive behavioral therapy. Pediatric clinicians play a vital role in early intervention to prevent the morbidity and mortality associated with untreated depression including suicide.

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REVIEW ARTICLE

Anxiety Disorders in Primary Care Pediatrics

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Anxiety disorders are identified when worries and fears occur outside normal developmental responses and cause significant distress or impairment in functioning in school, home or social settings.[1] These disorders are among the earliest psychiatric conditions to occur, with a median age of onset of 11 years old.[2] They can present as early as preschool years, but often do not cause significant impairment until school age.[1] Primary care practitioners (PCPs) are in an ideal position to identify and begin treatment for pediatric anxiety disorders. The demand for pediatric clinicians to care for children and adolescents with any mental health condition will only continue to increase over time; therefore, these PCPs should act as a primary resource for patients and their families who have concerns about their emotional health.[3] Patients with anxiety tend to present to their PCP first, often times with physical or behavioral complaints as the presenting symptom.[1] If untreated, anxiety disorders can have a chronic and unrelenting course.[2]

Anxiety disorders are quite prevalent in the pediatric population. Approximately 2% of children have a diagnosable anxiety disorder and this increases to 8% in adolescents.[4] During adolescence, girls are twice as likely to develop an anxiety disorder than boys; however, during childhood, they are equally affected. Not only can anxiety disorders lead to psychiatric disorders later in life, such as other anxiety disorders, substance use disorders and depression; they are also associated with poor long-term functioning, decreased general health, and suicidality, as well as interpersonal, financial and educational difficulties.[5]

Fears are a normal part of development and change throughout the lifetime. In an infant or toddler, age-appropriate fears include loud noises, darkness, strangers and separation. In preschool age, common fears include separation, darkness, imaginary creatures and storms. In school age children, typical worries include bodily injury, death, school performance and natural disasters. Lastly, in adolescents, public speaking, social situations, health and school performance are common fears.[1]

When evaluating a patient, it is important to distinguish developmentally appropriate worries and fears from those that cause significant impairment. Questions to consider include: is the reaction out of proportion to the trigger?; is it preventing the child from doing everyday activities or experiencing personal distress?; and how much are parents going out of their way to reassure/support their child to prevent any anxiety triggers from being present?[6]

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) classifies anxiety into 7 types: generalized anxiety disorder, social anxiety disorder, separation anxiety disorder, specific phobia, panic disorder with or without agoraphobia, agoraphobia without a history of panic disorder, and selective mutism. In the DSM-4 acute stress disorder, posttraumatic stress disorder and obsessive-compulsive disorder were classified as anxiety disorders, but were moved to separate diagnostic categories in DSM-5.[7] In order to meet criteria for an anxiety disorder, the symptoms must be persistent and cause significant impairment or distress to the child or adolescent.

Generalized anxiety disorder is characterized by disproportionate worry and uncertainty. These children and adolescents often are restless, irritable, easily fatigued, have difficulty concentrating, and difficulty falling asleep. They are unable to control their worries. Social anxiety is characterized by excessive shyness and fear of humiliation in a social setting. These children are anxious to be around other people, soft spoken, self-conscious, think others will judge them, avoid places with people, sweat around other people and feel "sick to their stomach" when around other people. Separation anxiety disorder is characterized by excessive difficulty separating from parents or caregivers. It is often associated with school refusal, fear of being left alone and difficulty falling asleep.[8] Specific phobia is a fear of an object or situation that is out of proportion to the actual danger, not developmentally appropriate and manifests as an anxiety reaction that is extreme. Panic disorder consists of children or adolescents having panic attacks without clear warning. This unpredictability leads to extreme anxiety about having another panic attack. Individuals with panic disorder often avoid any situation they associate with having a panic attack.[1] Agoraphobia is characterized by extreme anxiety about using public transportation, being in open or enclosed spaces, being outside of the home alone or being in a crowd. Selective mutism is a fear of speaking in certain situations in which there is an expectation for speaking despite their ability to speak normally in other scenarios.[7]

A positive family history should alert the pediatric clinician to have a high index of suspicion for the possibility of an anxiety disorder, especially in school age children. While taking the history, the clinician may elicit concerns regarding persistent worries, problems separating from caretakers, performance problems, inability to tolerate uncertainty and excessive shyness. Physical symptoms may include headaches, dizziness, chest pain, abdominal pain, tingling in perioral region or fingertips, shortness of breath or bowel/bladder urgency. Children will often try to avoid triggers that make them nervous such as avoiding school, tasks or certain people. They may over achieve or under achieve in school, have eating and sleep concerns, oppositional behaviors and anger. Children with anxiety frequently ask "Is everything okay?" Many parents will try to do whatever it takes to help their child avoid triggers for anxiety and provide constant reassurance; however, this will actually make anxiety worse.[8]

Medical conditions to consider in the differential diagnosis for anxiety include hyperthyroidism, migraine, asthma, seizure disorders, caffeinism, lead intoxication, pediatric acute-onset neuropsychiatric syndrome (PANS) and less commonly, hypoglycemia, pheochromocytoma, CNS disorders and cardiac arrythmias. Other psychiatric disorders to consider that may mimic anxiety symptoms include ADHD, psychotic disorders, autism spectrum disorder, learning disabilities, bipolar disorder and depression. Other diagnoses to consider include substance use, adjustment disorder, abuse, bullying, pregnancy, threatening environment and medication side effects.[4]

When an anxiety disorder is suspected, further screening and assessment should be done with both the child and parent to assess for the presence and severity of symptoms. There are several screening tools that may be used to assess the presence, type and severity of anxiety symptoms. These tools are not diagnostic in and of themselves, but are useful tools to screen and monitor symptoms over time. The SCARED (Screen for Child Anxiety Related Emotional Disorder) is a free self-report for parents and children ≥8 years old. It is a validated tool to screen for anxiety and helps differentiate between the subtypes.[7] The SCAS (Spence Children's Anxiety Scale) is a free parent and child rating scale developed for children 2.5-6.5 years old.[9] The PARS (Pediatric Anxiety Rating Scale) is a clinician-rated instrument, that includes 50 questions, and is used to assess generalized anxiety disorder, separation anxiety disorder and social anxiety disorder.[7]

Treatment for anxiety disorders should include a multimodal approach. The different aspects of treatment include: educating the parents and child about anxiety disorders, consulting with school personnel and other providers, referring to a mental health specialist to begin cognitive behavioral therapy, and pharmacotherapy.[4] With patient education, pediatric clinicians should discuss the function of anxiety as well as how avoidance results in increased symptoms with each exposure while dealing with anxiety results in lower level of symptoms with each exposure[1]. Furthermore, the treatment plan should also include coaching parents to reduce accommodations of a child's attempt to avoid situations that make them anxious as well as assisting the child or adolescent to develop coping skills. Lastly, during office visits, pediatric clinicians can demonstrate how to use coping strategies such as deep breathing.[10] If therapy and medication are not helping, refer to a specialist for a reevaluation.[4]

Cognitive behavioral therapy (CBT) is the first line treatment for children and adolescents with anxiety. If a child or adolescent has moderate to severe anxiety, use a combination of medication with a selective serotonin reuptake inhibitor (SSRI) and CBT.[4] Consider using an SSRI when impairment from anxiety makes participation in psychotherapy difficult and/or there is only a partial response to therapy.

Cognitive behavioral therapy is a specific type of psychotherapy that explores the relationships between a person's feelings, thoughts and behaviors. It is goal-oriented (patients will complete homework assignments) as well as time-limited (average number of sessions is 12-16 sessions). It includes somatic management skills training, psychoeducation, cognitive restructuring and relapse prevention plans.[4]

SSRI's are the first line pharmacotherapy treatment for children and adolescents with anxiety. When starting a SSRI medication, start at the lowest dose and increase the dose slowly. Initially, follow the patient weekly to assess for side effects and monitor for progress, then every other week, and then monthly once on a stable dose. You can expect some improvement by 4 weeks, but full effect can take 8-12 weeks. If treatment is effective, taper the medication after 6-12 months. SSRI medications include fluoxetine, sertraline, and escitalporam[4]. Common side effects include nausea, gastrointestinal (GI) upset, dry mouth, somnolence, tremor, insomnia, and sexual dysfunction. While counseling a patient and their family on the side effects of SSRI medication, it is imperative to discuss the bolded warning. The warning indicates that SSRI use has been associated with increased suicidal thoughts and behaviors when used to treat depression in children, adolescents and young adults; however, there have been no actual reported cases of completed suicide in the studies that led to the warning and no increase when treating anxiety. The serotonin-norepinephrine reuptake inhibitor (SNRI), duloxetine, is also approved for the treatment of anxiety. Benzodiazepines and buspirone have not been shown to be efficacious in the treatment of anxiety in children and adolescents.[4]

In a large, multi-site, randomized control trial, the Child/Adolescent Anxiety Multimodal Study (CAMS) assigned 488 children and adolescents (ages 7-17) with a primary diagnosis of separation anxiety disorder, generalized anxiety disorder or social phobia to 4 treatment groups (sertraline monotherapy, CBT monotherapy, combination of sertraline and CBT or placebo). All treatment groups were superior to placebo and combination therapy of sertraline and CBT had a superior response rate than either treatment alone.[11]

Primary care providers may be hesitant to discuss anxiety with the parents of a patient due to a variety of reasons including time constraints, lack of experience with diagnosing and managing anxiety disorders, parent refusal of this type of conversation or fears that the child will be stigmatized.[2] In 2019, researchers in Colorado conducted a study to assess pediatric primary care providers' knowledge, perceived barriers, and needs related to pediatric anxiety in their practice. One hundred and fifteen PCPs, including medical doctors, nurses and nurse practitioners, completed an online knowledge and needs assessment survey. The majority (70%) regularly ask their patients about anxiety symptoms, but 43% reported feeling uncertain about diagnosing their patients. Further results of the study showed that 77% of PCPs surveyed were unaware of evidence-based practice parameters and recommendations; 18% used evidence-based anxiety screeners for assessment; 37% of those with prescription privileges felt uncomfortable prescribing anxiety medication; 13% of prescribers use medications that are not recommended or contraindicated for use in pediatric patients; and only 19% were aware of best practices with nonmedication interventions. Only 17% of PCPs in this study received any mental health training and 7% received specialty anxiety training. The authors concluded that there is a marked need for PCP training in learning how to assess, treat and refer patients with anxiety.[12]

There are several useful resources for primary care providers and patients, such as the child and youth mental health toolkits (http://shared-care.ca/toolkits-anxiety).[4] "What to Do When You Worry Too Much" by Dawn Huebner is a helpful book for children and their parents that guides them through cognitive behavioral techniques used to treat anxiety.[13] The MindMasters2 is a resource that helps children to master emotional regulation (https://www.ottawapublichealth.ca/en/

professionals-and-partners/iecmh.aspx#Guidebook). The Mindshift app is a free app for smart phones that uses CBT strategies (https://www.anxietycanada.com/resources/mindshift-cbt/). The American Academy of Child and Adolescent Psychiatry along with the American Psychiatric Association created a website with information for parents, patients and clinicians (http://www.parentsmedguide.org/). Another great website, https://www.anxietycanada.com/, is a useful tool to help parents and clinicians have resources to help children with anxiety. Lastly, the Anxiety and Depression Association of America (ADAA) has useful information about anxiety and related disorders (https://adaa.org/understanding-anxiety/generalized-anxiety-disorder-gad).[4] See corresponding websites for additional information.

In summary, given that anxiety disorders are the most common psychiatric disorder in children and adolescents, pediatric clinicians should be responsible for preventing and addressing their patients' mental health concerns, including symptoms of anxiety. PCPs see their patients longitudinally, giving them the unique opportunity to establish rapport with patients and their families; to promote healthy social-emotional development with every contact; to address mental health concerns through education and guidance; and to resolve issues when risks or symptoms arise.[14] All pediatric clinicians, whether in primary care or pediatric subspecialties, must have a basic understanding of mental health concerns, diagnosis and treatment as children and adolescents will often present for evaluation of somatic complaints. Recognition of anxiety symptoms can prevent costly workups and facilitate referral to mental health services. Lastly, children and adolescents have a better prognosis with early recognition and treatment of anxiety disorders.

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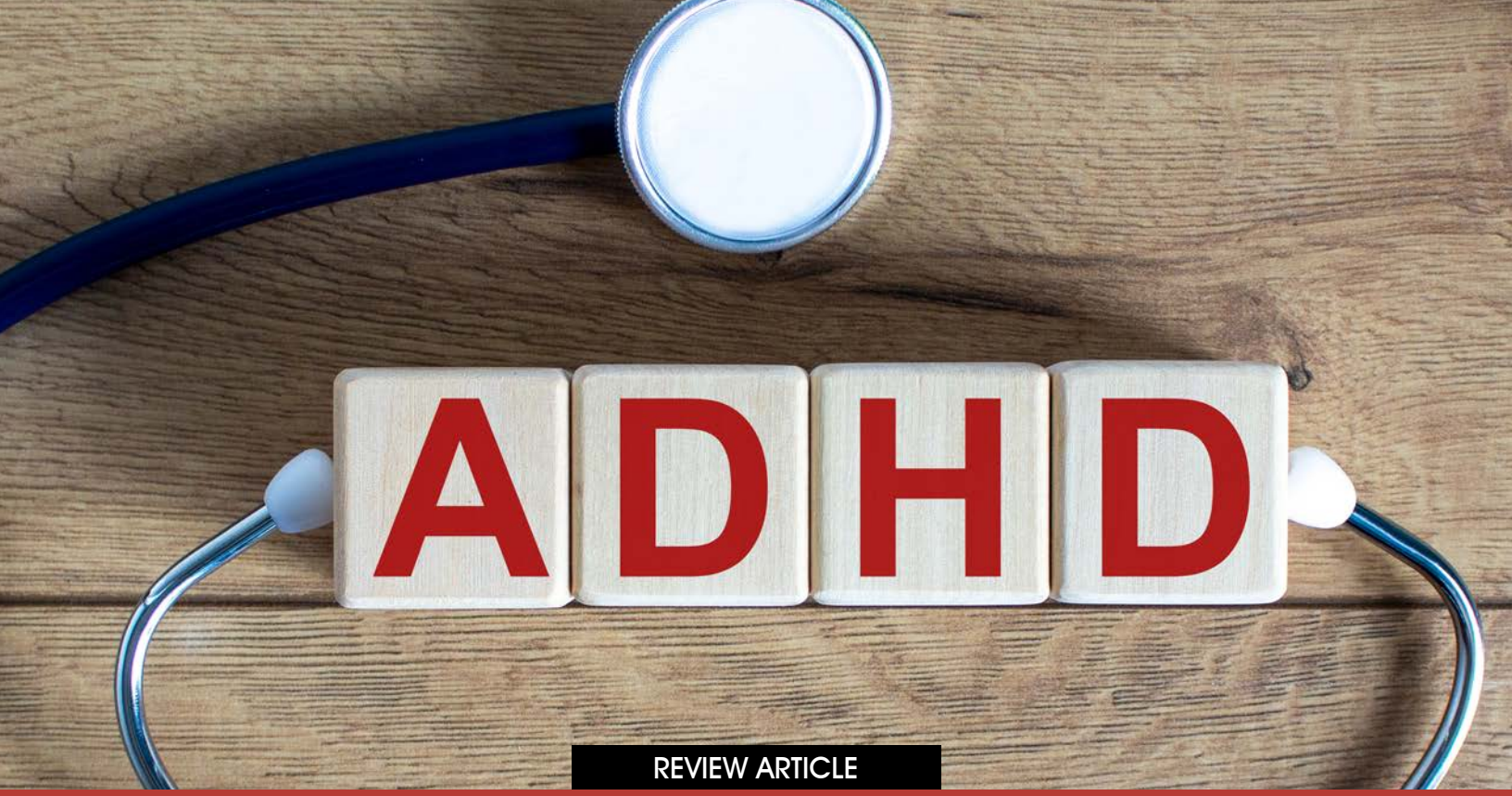

REVIEW ARTICLE

ADHD: An Overview for Pediatric Primary Care

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On March 4, 6, and 11, 1902, Sir George F. Still, Britain's first professor of pediatrics, delivered three, visionary Goulstonian Lectures to the Royal College of Physicians in London, calling "urgently for scientific investigation" of "the occurrence of defective moral control as a morbid condition in children" which he thought may "persist into adult life."[1] Over the ensuing century the "morbid condition" that Dr. Still eloquently described in three Lancet papers has been alternatively identified as minimal brain damage, hyperkinetic disease of infancy, minimal brain dysfunction, hyperkinetic reaction of childhood, attention deficit disorder, and ultimately attention-deficit/hyperactivity disorder. Dr. Still wrote that by "defective moral control" he meant impaired "cognitive relation to environment" as well as impaired "consciousness of the relation of every volitional activity on the part of the individual to the good of all."

Today, ADHD is conceptualized as a neurodevelopmental syndrome that emerges in early childhood, runs in families, occurs more commonly in males, and presents with persistent and pervasive inattention, distractibility, impulsivity, hyperactivity, and disruption of reward and motivation. As defined in the 2013 Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th Edition, its diagnosis *requires* that the *magnitude* of the specified ADHD symptoms, occasionally experienced by everyone, *must greatly exceed developmentally appropriate levels, must persist (unabated) for 6 months,* and *must cause social, academic, or occupational impairment in functioning.*[2] Global epidemiological studies adhering rigidly to DSM diagnostic criteria put the prevalence of pediatric ADHD at 3-5.3%.[3]

WHY SHOULD PEDIATRICIANS BE CONCERNED ABOUT ADHD?

There are compelling reasons for pediatricians, healthcare "first responders" for our nation's children, to recognize, begin treatment of, and continue to manage ADHD. Academic difficulties, failure, or grade retention due to ADHD are not only clear to teachers and parents in the U. S., but also widely reported in other countries.[4] ADHD is associated with increased risk of accidental injuries, the leading cause of pediatric morbidity and mortality in the U. S., and treatment reduces that risk.[5] Untreated childhood ADHD increases the risk of smoking at an early age, more than doubles the risk of adolescent illicit substance abuse and nicotine dependence, and appears to be associated with excessive use of electronic cigarettes (vaping).[6,7] Teenage drivers with untreated ADHD are at greater risk for speeding tickets, revoked or suspended licenses, and motor vehicle crashes.[8]

Severity of conduct disorder is linked to ADHD. A prospective study of young adults conducted 16 years after their participation as children in the NIMH Multimodal Treatment Study of Children with ADHD (MTA 1992-1997), a groundbreaking trial to understand long term, best practice management of ADHD, found that compared to a normative, non-ADHD, age and gender matched group of adults, the MTA participants had lower educational attainment, a higher likelihood of needing public assistance, greater impulsivity and emotional lability, a higher likelihood of police contact, increased cannabis and other illicit substance abuse, and earlier sexual activity, as well as a greater number of offspring.[9]

MIGHT ADHD SOME DAY BE FORMULATED AS A SPECTRUM?

The DSM-5 diagnostic criteria for ADHD are replicated word for word in the first 18 items of both Teacher and Parent NICHQ Vanderbilt Assessment Scale Informant forms. The first 9 symptoms rate the severity of inattention and distractibility along a Likert scale from 0 to 3, while symptoms 10-18 rate the severity of hyperactivity and impulsivity. To interpret for a parent (or teacher) the meaning of *Occasionally*, weighted as 1, *Often*, weighted as 2, and *Very Often*, weighted as 3, think "mild," "moderate," or "severe," respectively.

DSM-5 provides five "buckets" of ADHD into which patient symptoms can be dropped:

- *Combined Presentation (F90.2)*, when at least 6 of the first 9 inattentive and at least 6 of the following 9 hyperactive-impulsive symptoms are endorsed at the moderate and/or severe level (only 5 inattentive and hyperactive-impulsive symptoms are required if age 17 or greater)
- *Predominantly Inattentive Presentation (F90.0)*, when 6 inattentive, but less than 6 hyperactive-impulsive symptoms are endorsed at the moderate and/or severe level (again, 5 inattentive symptoms is the threshold for age 17 or greater)
- *Predominantly Hyperactive-Impulsive Presentation (F90.1)*, when less than 6 inattentive symptoms, but 6 or more hyperactive-impulsive symptoms are endorsed at the moderate and/or severe level (again, 5 symptoms is the threshold for age 17 or greater)
- *Other Specified ADHD (F90.8)* when neither inattentive nor hyperactive-impulsive symptom cutoffs are reached to meet the diagnostic threshold, but social, academic, or occupational functioning is impaired for understandable reasons
- *Unspecified ADHD (F90.9)* when neither inattentive nor hyperactive-impulsive symptom cutoffs are reached to meet the diagnostic threshold, but social, academic, or occupational functioning is impaired without enough information to make a specific diagnosis

Parsing ADHD into the current five buckets is an artifact of the history and evolution of field research findings compiled by the professional committees that contributed to the DSM. The late C. Keith Conners, PhD, (of Conners ADHD rating scales) observed in a 2013 New York Times interview, "*I now believe that ADHD is part of a normal continuum going from very mild restlessness and inattention to a severe form that requires treatment and skilled diagnostic assessment by well-trained clinicians.*"

WHAT'S NOT IN DSM-5?

The DSM-5 criteria do not address other important signs of moderate to severe ADHD, including difficulty with transitions, emotional dysregulation (loosely called "mood swings"), social disability, disorganization, inability to remember or perform multistep commands, expressions of "boredom," and risk-taking behaviors. Children with ADHD have low frustration tolerance, sometimes mistakenly called "aggression" by caretakers, who, if asked for clarification, often self-correct, recognizing frustration as the trigger of problematic behaviors. **Table 1** illustrates the changing presentation of ADHD as a function of developmental stage.

AGE GROUP	ADHD BEHAVIORS
Preschoolers, Ages 3-5	Motor restlessness (always "on the go"), destructive play, multiple accidents, tantrums, defiance, argumentativeness
School Age, Ages 6-12	Distractibility, "off task", disorganization, incomplete work, intrusiveness, low frustration tolerance, "class clown", "immature", classroom disruption, difficult transitions
Adolescents	Boredom, inner restlessness, interpersonal conflicts, trouble with authority, risk taking behaviors, substance abuse including vaping

Table 1: ADHD Presents Differently Across Developmental Stages

A threshold of salience seems to modulate attention in ADHD, which means that tasks or commands must be sufficiently novel, sensory activating, or inherently interesting to capture attention. The primary cognitive deficit in ADHD is impaired working memory, measured empirically by a comprehensive psychological evaluation that only a licensed psychologist is qualified to conduct. ADHD disrupts the brain's reward system and motivation so that delayed rewards are not effective in ADHD (reward value decays rapidly with time), while immediately delivered rewards improve task performance and motivation.[10] Disrupted reward and motivation, as well as a salience threshold explain why parents notice that their ADHD child can remain intently engaged in a video game for hours but cannot stay focused on math homework for more than a few minutes.

CLINICAL RISK FACTORS

Twenty twin studies in the United States, Australia, Scandinavia, and the European Union have shown that ADHD runs in families with heritability estimates averaging 76%.[11] Excessive exposure *in utero* to nicotine, alcohol, illicit substances, and valproate increase the risk of ADHD, as well as pre-eclampsia, prematurity (birth weights less than 1500 grams), and perinatal hypoxia. Other injuries to the developing brain, such as encephalitis, neurotoxin exposures (especially lead), severe head trauma, and severe malnutrition are implicated in ADHD. Congenital heart disease, autism, and many genetic disorders with neurodevelopmental impact are associated with high rates of ADHD. Care should be taken to sort out conditions manifesting behaviors that only mimic ADHD, such as hearing loss, vision problems, sleep deprivation and/or apnea, or chronic headaches.

AT WHAT AGE CAN ADHD BE CONFIDENTLY DIAGNOSED?

The American Academy of Pediatrics clinical practice guidelines for the diagnosis and treatment of ADHD in children and adolescents advise clinicians that "there is insufficient evidence to recommend diagnosis and treatment for children younger than 4 years."[12] That statement should be tempered by the child psychology and psychiatry literature replete with studies of ADHD symptoms recognized as early as age 2. The largest NIMH-sponsored, multisite, randomized study in the U.S. to test the efficacy and safety of methylphenidate in 3.0 to 5.5-year-olds (Preschoolers with ADHD Treatment Study/ PATS 2001-2006) found that the Conners Rating Scales (especially the DSM hyperactive-impulsive criteria), part of the PATS highly structured diagnostic protocol, correctly identified ADHD in preschoolers with more than 85% accuracy.[13] The PATS data showed that hyperactive-impulsive symptoms predominate in preschoolers until inattention becomes more apparent in school age children.[14]

CONFOUNDING COMORBIDITIES

Decades of international studies have shown that other mental health problems are commonly comorbid with ADHD. Pediatricians should diligently screen for the following conditions in preschoolers and children with ADHD: oppositional defiant disorder (Vanderbilt Parent Informant only symptoms 19-26), conduct disorder (Vanderbilt Parent Informant only symptoms 27-40), anxiety disorders (which predict greater severity of ADHD), mood disorders (depression, both persistent and single episodes), learning disorders and intellectual disability (requiring referral to a school district or other licensed psychologist for diagnosis), autism spectrum disorder, fragile X, substance use disorders, Tourette syndrome, and sleep problems.[15]

ADHD and epilepsy are extraordinarily and bidirectionally comorbid. The prevalence of ADHD in the epileptic population is as high as 40% where male preponderance disappears.[16] Referral to subspecialists, such as a developmental and behavioral pediatrician, child and adolescent psychiatrist, pediatric neurologist, pediatric psychologist, or psychotherapist is highly advisable when comorbidities complicate care.

ADHD TREATMENT: A BIOPSYCHOSOCIAL MODEL

Expert consensus recommends that treatment of preschoolers with ADHD should begin with psychosocial intervention, commonly called parent training. Two leading behavioral treatments, Parent Management Training (PMT) where parents are taught social learning strategies to change their child's behavior, and Parent-Child Interaction Therapy (PCIT) where parents receive step-by-step, behind the one way mirror bug-in-the-ear coaching while working with their children to strengthen their relationship and improve the child's pro-social behaviors. Both have a strong evidence base for efficacy in preschooler ADHD. PCIT is limited to use in the early years from toddlers up to age 7 years, while PMT can be used up to and including adolescence. For PMT or PCIT resistant preschoolers, the PATS study demonstrated the safety and efficacy of conservative, low dose, immediate release (IR) methylphenidate. Interestingly, IR dextroamphetamine products have a labeled indication for ADHD in 3-year-olds.

The NIMH MTA study mentioned above randomized 579 children ages 7-9 years with expertly diagnosed ADHD into four treatment arms: intensive medication management (IR methylphenidate) alone, state of the art behavioral therapy and parent training alone, their combination, and routine community care (the control group) over a period of 14 months.[17] Ultimately,

both teachers and parents rated the two arms that included methylphenidate as significantly more effective than high quality behavioral treatment alone or routine community care, giving the edge in effectiveness to medication combined with parent training. These findings argue for both the power of well-managed stimulant medication and the value of behavioral therapy plus parent training in the comprehensive care of children with ADHD. Children in the study who did poorly tended to have severe ADHD, below average IQ, or depressed parents.

SCHOOL ACCOMMODATIONS

School accommodations, medication management, and parent training comprise the optimal treatment triad for pediatric ADHD. ADHD is considered a disability under the Americans with Disabilities Act (1990), the Individuals with Disabilities Education Act (1975), and Section 504 of the Rehabilitation Act (1973). Under the IDEA the disability category for ADHD, known as Other Health Impaired, may entitle a child to a free evaluation of academic performance to ensure appropriate support. By law, a 504 plan, which is a list of classroom accommodations (without goals or objectives), must be provided to every student with ADHD in schools that receive federal funding. Parents should be encouraged to make an appointment with their child's school guidance counselor or principal to discuss accommodations available for ADHD.

PHARMACOTHERAPY

Recent fascinating and complex investigations hypothesize that ADHD results from diminished connectivity among neural hubs responsible for sustained attention and working memory (dorsolateral prefrontal cortex), selective attention, what teachers call "focusing", motivation, and novelty assessment (anterior cingulate), attention allocation (parietal cortex), impulse control and behavioral inhibition (orbitofrontal cortex), reward processing (striatum), and motor control, planning, and spatial processing (cerebellum), as well as the problem of scattered neural noise.[18] Advanced imaging techniques have found structural and functional differences in all these regions in severe ADHD.[19]

The neurotransmitter pathways connecting these hubs relevant to ADHD are principally the norepinephrine pathway that works as a signal amplifier ensuring good connectivity and two of five dopamine pathways (mesolimbic or "reward center" and mesocortical or cognitive tract) that improve signal over noise. The mechanism of action of all FDA approved medications for ADHD improve functioning of one or both of these neurotransmitter pipelines. The two psychostimulants, methylphenidate and amphetamine, both act as presynaptic norepinephrine and dopamine reuptake inhibitors (NDRIs), ideal for improving connectivity and signal over noise. At higher doses amphetamine causes release of norepinephrine and dopamine from presynaptic storage vesicles, forces the reuptake transporter into reverse, and inhibits monoamine oxidase.

When talking to parents, it is fair to say that stimulants "don't stimulate anything in the brain," but they instead manage communication links between brain circuits necessary for best attention and behavioral control. Long before knowing why, Charles Bradley, MD, was first to publish in 1937 observations that the psychostimulant Benzedrine® (a 50/50 racemic mixture of dextro- and levo-amphetamine sulfate now marketed as Evekeo®) given to hospitalized, behaviorally dysregulated children provided "spectacular change in behavior [and] improved school performance."[20] Of historical note, during WWII Benzedrine® was handed out to Royal Air Force and U.S. Army Air Forces aviators to ensure alertness.

In 2002 the FDA approved and Eli Lilly introduced the next modern agent for ADHD, atomoxetine (Strattera®, a failed antidepressant). It was marketed as a "non-stimulant," only half correctly. It has minimal to no dopaminergic activity but is (almost) exclusively a norepinephrine reuptake inhibitor (NRI) and an NMDA receptor antagonist. In 2009 and 2010, respectively, the FDA approved extended release guanfacine (Intuniv®) and extended release clonidine (Kapvay®) for ADHD. Both act as postsynaptic $\mathbf{a}_{2A}$ receptor agonists, increasing norepinephrine-driven signal strength in the prefrontal cortex. Neither alpha agonist has any effect on dopamine neurotransmission and their combined use with stimulants is FDA approved.

Ample published evidence exists for other agents efficacious in ADHD but without FDA approval. They include the tricyclic antidepressants imipramine, desipramine, and nortriptyline, all norepinephrine and serotonin reuptake inhibitors (and histaminic and cholinergic antagonists), the antidepressant bupropion (Wellbutrin®), a norepinephrine and dopamine reuptake inhibitor (exactly like stimulants), modafinil (Provigil® and others), a dopamine reuptake inhibitor (DRI), and two antiparkinsonian drugs, amantadine (Symmetrel®), a dopamine reuptake inhibitor, and selegiline (Eldepryl®), a selective MAO-B inhibitor. All these agents have problematic, if not dangerous, adverse effects and probably should be considered beyond the scope of practice in pediatric primary care of children with ADHD. Perhaps surprisingly, two first generation antipsychotics, haloperidol (Haldol®) and chlorpromazine (Thorazine®), were FDA approved for ADHD decades ago, intended only to target excessive motor activity and conduct disorder, especially aggression, in children. Their mechanism of action,

predominantly dopamine$_2$ receptor antagonism throughout the brain, blunts cognition and reward.

CHOOSING AMONG THE MARKETED COMPETITORS

Best practices research has informed the sequencing of approved agents to treat ADHD. The sequence (see **Figure 1**) follows the order of decreasing effect size. After thorough assessment, start with a titration trial of stimulant, either methylphenidate or amphetamine. The PATS, MTA study, and newer research suggest that methylphenidate may be the preferred first choice. If the first titration trial of one stimulant is not tolerated or ineffective, then the next step is a titration trial of the alternate stimulant. Failing both stimulants suggests a trial of atomoxetine, followed, if unsuccessful, by a trial of an alpha$_{2A}$ agonist.

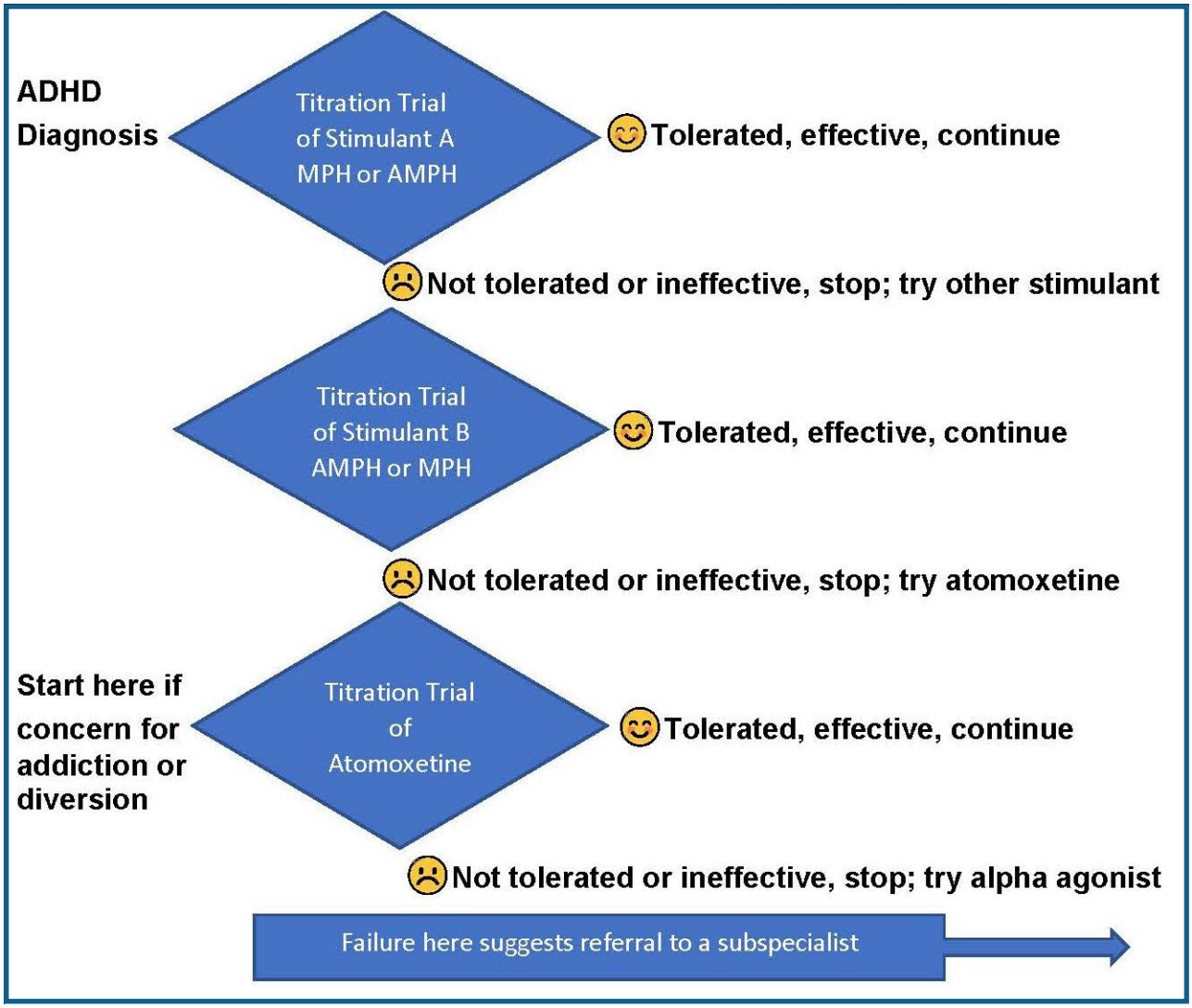

Figure 1: Sequencing FDA Approved Agent: Expert Consensus

The only significant differences among all the marketed stimulant products are potency and the delivery vehicle, whether tablet, liquid, sprinkle, patch, disintegrating particles, or other technology intended to optimize convenience, compliance, or timing (see **Table 2**). All amphetamine stimulants and the lone dextromethylphenidate stimulant (Focalin®) are roughly twice as potent as all other methylphenidate products. Stimulants are generally quite safe regarding drug-drug interactions. Methylphenidate is hydrolyzed in the liver to inactive ritalinic acid, while amphetamine is only partly metabolized by liver CYP2D6 enzymes. Genetic differences in CYP2D6 metabolism seems to have little effect in the overall clearance of amphetamine, so pharmacogenetic testing to choose a stimulant is a waste of both time and money. Stimulants have such a short elimination half-life that any stimulant product can be discontinued abruptly with no concern for withdrawal. It is perfectly permissible to skip weekends and expect a stimulant to return to full efficacy Monday morning.

DELIVERY SYSTEM	METHYLPHENIDATE PRODUCTS	AMPHETAMINE PRODUCTS
Immediate release tablets	Methylphenidate, Ritalin®, Focalin®	Mixed d-,l-amphetamine salts, Adderall®, dextroamphetamine sulfate, Zenzedi®, Evekeo®, Desoxyn® (methamphetamine)
Chewable tablets	Methylphenidate® chewable	Vyvanse® chewable
Osmotic pump	Concerta®	Not available
Double pulse (biphasic) bead sprinkles	Ritalin® LA, Focalin® XR, Metadate® CD, Aptensio® XR	Adderall ® XR, Dexedrine® Spansule
Triple pulse bead sprinkles	Not available	Mydayis®
Multilayer bead sprinkles	Adhansia® XR, Jornay® PM	Not available
Disintegrating microparticles	Contempla® XR-ODT	Adzenys® ODT, Evekeo® ODT
Transdermal (patch)	Daytrana®	Not available
Suspended ion exchange particles	Quillivant® XR	Dyanavel® XR, Adeznys® XR
Liquid	Methylin® oral solution	ProCentra® oral solution
Chewable ion exchange particles	Quillichew® ER	Not available
Soluble amide-linked prodrug	Not available	Vyvanse®

Table 2: Marketed FDA Approved Stimulants for ADHD

Titration of any stimulant product should begin with the lowest manufactured dose, increasing stepwise in two or three week intervals. Stimulant response occurs immediately, but in practical terms it may take a week or two for a teacher to be convinced of a consistent, measurable difference in a busy classroom between titration steps. Response is best measured with Vanderbilt Assessment Follow-up scales (short form) given to both parents and teachers. Immediate release stimulant tablets, both methylphenidate and amphetamine, take effect within 30 or 40 minutes after ingestion, with a duration of action in the 3 to 4-hour range, methylphenidate perhaps a little shorter, amphetamine perhaps a little longer. Sustained release products usually take effect about an hour after ingestion (the lone transdermal release system may take double that). Oral sustained release products are engineered in theory to provide treatment across a school day, but do not always in practice. When parents and teachers complain that extended release stimulants lose effectiveness by midday, it is often due to taking the medicine far too early in the morning (e.g., when school bus pickup or drop off at before school care is well ahead of the start of the school day) or by faster than average metabolism.

The beaded sprinkle (biphasic) delivery systems replicate IR BID dosing by packaging immediate release beads (first pulse) and delayed release, coated beads (second pulse) in the same capsule. They differ only in the fraction of total dose in each pulse; e.g., Ritalin® LA, Focalin® XR, Adderall® XR, and Dexedrine® Spansule each deliver half the total dose per pulse, whereas Metadate® CD back loads delivery by releasing 30% of the total dose in the first pulse and 70% in the second pulse. Similarly, Aptensio® XR splits total release into 37% and 63% in the first and second pulses, while Adhansia® XR uses multilayer beads, releasing 20% of the dose from an outer layer immediately and delaying 80% of the dose in the core. The plasma concentration curve of these products resembles a camel's back, where concentration dips between pulses, but remains high enough to prevent loss of effectiveness. **Table 3** below is a cross comparison of selected extended release stimulants showing bioequivalence horizontally to assist in substituting one product for another for problems.

All extended release stimulant products are recommended for children 6 years of age or older except for the triple pulse (triphasic) amphetamine bead system (Mydayis®) for use at age 13 or older. Virtually any of the few immediate release tablet stimulants can be used in the 4 to 6-year-old range. The PATS study made clear that preschoolers may not tolerate stimulants as well as school age children and that dosing should begin no higher than 2.5 mg before school, roughly half the starting dose suggested for 6-year-olds. The recommended FDA maximum total daily dose for methylphenidate products is 100 mg and 70 mg for amphetamine products.

Unlike stimulants, atomoxetine, approved for ages 6 and older, is dosed by weight where the common target for optimal effectiveness is between 1.2 and 1.5 mg/kg of body weight. The maximum daily dose, regardless of body weight, should not exceed 100 mg daily. Titration begins with a dose equal to half the body weight in kilograms before school for a week,

SELECTED METHYLPHENIDATE EXTENDED RELEASE PRODUCTS EQUIVALENT TO IR BID DOSING						IR TID DOSING EQUIVALENTS**	
Biphasic Release				Suspended Microparticles	Disintegrating Microparticles	Osmotic Pump Design	Transdermal Patch
50/50 *	50/50 *	30/70*	40/60*				
	Focalin XR 40						
	Focalin XR 35						
Ritalin LA 60	Focalin XR 30	Metadate CD 60	Aptensio XR 60				
n/a	Focalin XR 25	Metadate CD 50	Aptensio XR 50				
Ritalin LA 40	Focalin XR 20	Metadate CD 40	Aptensio XR 40	Quillivant XR 8 ml		Concerta 72	
Ritalin LA 30	Focalin XR 15	Metadate CD 30	Aptensio XR 30	Quillivant XR 6 ml	Contempla XR ODT 25.9	Concerta 54	Daytrana 30
Ritalin LA 20	Focalin XR 10	Metadate CD 20	Aptensio XR 20	Quillivant XR 4 ml	Contempla XR ODT 17.3	Concerta 36	Daytrana 20
Ritalin LA 10	Focalin XR 5	Metadate CD 10	Aptensio XR 10	Quillivant XR 2 ml	Contempla XR ODT 8.6	Concerta 18	Daytrana 10

SELECTED AMPHETAMINE EXTENDED RELEASE PRODUCTS EQUIVALENT TO IR BID DOSING						
Amide-link Prodrug	Biphasic Release		Disintegrating Microparticles	Suspended Microparticles		Chewable Amide-link Prodrug
	50/50*	50/50*				
Vyvanse 70	Adderall XR 30		Adzenys XR ODT 18.8	Adzenys ER 15 ml		
Vyvanse 60	Adderall XR 25		Adzenys XR ODT 15.7	Adzenys ER 12.5 ml	Dyanavel XR 7.5 ml	Vyvanse Chewable 60
Vyvanse 50	Adderall XR 20		Adzenys XR ODT 12.5	Adzenys ER 10 ml		Vyvanse Chewable 50
Vyvanse 40	Adderall XR 15	Dexedrine Spansule 15	Adzenys XR ODT 9.4	Adzenys ER 7.5 ml	Dyanavel XR 5 ml	Vyvanse Chewable 40
Vyvanse 30	Adderall XR 10	Dexedrine Spansule 10	Adzenys XR ODT 6.3	Adzenys ER 5 ml		Vyvanse Chewable 30
Vyvanse 20	Adderall XR 5	Dexedrine Spansule 5	Adzenys XR ODT 3.1	Adzenys ER 2.5 ml	Dyanavel XR 2.5 ml	Vyvanse Chewable 20
Vyvanse 10	No equivalent	No equivalent	No equivalent			Vyvanse Chewable 10

Table 3
§All products listed are registered trademark®
****Percentage split of total dose delivered in first and second pulses of biphasic release products***
*****N.B.: Concerta® was engineered to replicate TID dosing of IR methylphenidate***

increased to BID (morning and evening) for a week, then consolidated to before school only. Further titration to the target range depends on response. Occasionally reverting to splitting the most effective total dose into morning and evening halves maintains adequate response while improving tolerability. Because atomoxetine has no effect on dopamine neurotransmission, its effect size for ADHD is lower than that of stimulants. Its metabolism is by CYP450 2D6, which causes a highly variable elimination half-life from 5 to 22 hours depending upon normal or slow 2D6 metabolism and adds the risk of drug/drug interactions (especially with SSRIs). Package insert warnings for rare hepatotoxicity and very rare treatment emergent suicidal thoughts were added in 2004 and 2005, respectively.

The alpha$_{2A}$ agonists guanfacine ER (Intuniv®) and clonidine ER (Kapvay®), approved for ADHD in children 6 and older, do not improve attention as well as stimulants, but do improve working memory, frustration tolerance, and behavioral inhibition. These agents provide a general calming effect, may be helpful for defiance, and are certainly helpful for tics. They reduce brainstem sympathetic outflow that can lead to bradycardia and hypotension. They have an effect size smaller than that of atomoxetine for

ADHD and to a lesser extent for ODD.[21] It takes several hours for both to reach maximum peak plasma concentration and both are partially cleared unchanged by urinary excretion and partially by CYP450 enzymes. Clonidine XR is cleared faster when used with methylphenidate and significantly slower when used with amphetamine. The maximum recommended dose of guanfacine ER is 4 mg/day in children and 7 mg/day in adolescents. The maximum recommended dose of clonidine ER is 0.4 mg/day.

ADVERSE EFFECTS OF PHARMACOTHERAPY

The formidable list of adverse effects of the approved ADHD medicines is summarized in **Table 4** below. Fortunately, the most commonly reported adverse events caused by stimulants are few and completely reversible, but must be discussed at each and every visit. They include appetite suppression, sleep onset delay, nausea and abdominal distress, headaches, fadeout irritability, and tics. Seizures do not appear in the list because there is no clear evidence that methylphenidate and atomoxetine reduce seizure threshold. Parents often express the fear that stimulants "will turn my child into a zombie." This adverse effect, known as personality constriction, is dose dependent. Careful titration and monitoring will prevent it from happening in the first place. Except for tics, many of the adverse effects of stimulants are also reported with atomoxetine. Parents complain most frequently about somnolence and significant irritability due to the alpha agonists, and these two common problems must be reviewed at every visit.

Papers describing growth deceleration on stimulants and growth rebound after stimulant discontinuation date back to the early 1970s. Stimulants have no effect on growth hormone. The culprits in growth deceleration associated with stimulants and atomoxetine are reduced caloric intake and suboptimal nutrition. A new paper detailing height and weight data of the MTA participants as well as 289 age and gender matched classmates (called the local normative comparison group) collected at 2, 3, 6, 8, 10, 12, 14, and 16 years after the end of the study concluded that cumulative exposure to methylphenidate (i.e., associated appetite suppression), especially during the time of rapid growth, is most likely the factor causing growth deceleration.[22] Discontinuation of stimulant over the summer and during long holidays may help mitigate growth deceleration.

Parents and caretakers often ask if stimulants are addictive, given their designation by the US DOJ DEA as Schedule IIN drugs, often leading to the misconception that stimulants are "narcotics," certainly not the case. The best explanation is that a "high" is a function of the speed at which a drug enters the brain. Snorting or smoking are the fastest routes for explosive delivery of a psychoactive substance into the brain, which can lead to addiction. Oral ingestion of stimulants, properly dosed and carefully monitored, markedly slows delivery to the brain, especially after first past liver metabolism, reducing the risk of addiction to a negligible level.

Stimulants are designated Schedule IIN because of the potential for diversion and abuse. Studies show that appropriate stimulant treatment of ADHD in childhood actually reduces the risk of later drug and alcohol abuse.[23]

If substance abuse comorbid with ADHD is suspected and treatment for ADHD is desired, then initial treatment with atomoxetine is the better starting point. Alternatively, lisdexamfetamine (Vyvanse®), a prodrug compound of dextroamphetamine bonded to lysine, was designed to have low risk of abuse because the compound is not thought to cross the blood-brain barrier, but after ingestion and absorption in the gut, dextroamphetamine is released by hydrolysis in the circulation.

WHAT CAN BE DONE ABOUT COMMON ADVERSE EFFECTS?

Every follow-up visit for ADHD management must include documentation of height, weight, heart rate, and blood pressure. Slowing, loss, or reversal of weight gain demands that children eat breakfast before the morning dose of medicine (which may also prevent headaches and stomachaches), preparing lunches with favorite treats, and adding high calorie snacks in between meals. Pediatricians should consider reducing the stimulant (or atomoxetine) dose, trying an alternate stimulant or delivery system, or enhancing appetite with cyproheptadine. The first step in assessing delay in sleep onset is to determine if it were present prior to stimulant treatment. Good sleep principles, including avoiding naps, enforcing a routine wake/sleep schedule, rigidly limiting screen time, and establishing soothing bedtime rituals, are the initial interventions in any case. Caffeinated beverages, nicotine, and alcohol must be avoided near bedtime. Adjusting the timing of stimulants or changing delivery systems to avoid fadeout too close to bedtime often helps to avoid insomnia. Melatonin, especially in the sustained release form, may be very helpful when given around the time of sunset. Low dose IR clonidine or guanfacine helps with bedtime hyperarousal and sleep onset (but will not help with sleep maintenance). Irritability, if occurring when starting, titrating, or fadeout of medication calls for dose reduction or switching to another medication. On the other hand, assessment for a potential psychosocial cause or comorbid mood disorder is highly encouraged. Finally, tics, new onset skin picking, or nail biting, should be addressed by dose reduction, a trial of an alternate medication, or addition of an alpha agonist.

WHAT ABOUT CARDIAC PRECAUTIONS?

In healthy children and adolescents without cardiac risk factors, neither a pretreatment ECG nor routine ECG monitoring is necessary. Large studies have never shown evidence of PR, QRS, or QTc interval changes due to stimulants. If the patient's

STIMULANT ADVERSE EFFECTS (ALL RESOLVE SOON AFTER DISCONTINUATION)	
• agitation • anxiety • appetite suppression • chest pain • diaphoresis • diplopia, blurry vision • dizziness • dry mouth • emesis • emotional lability, dysphoria • eye pain • formication • growth deceleration • hallucinations • headaches • hypertension • irritability, especially at fadeout	• jitteriness • lethargy • manic behavior • nail biting • nausea • palpitations • paranoia • personality constriction • priapism • Raynaud's phenomenon • skin discoloration (MPH patch) • skin picking • sleep onset delay • tachycardia • tics (movement disorder) • tremor • weight loss
ATOMOXETINE ADVERSE EFFECTS	
Most stimulant adverse effects, including hypertension and tachycardia, PLUS • constipation • cough • hepatotoxicity (rare) • suicidality (very rare) MINUS • tics	
ALPHA2 AGONIST ADVERSE EFFECTS	
Few stimulant adverse effects, PLUS • appetite increase • aggression • bradycardia • constipation • enuresis • hypotension • lethargy • irritability • rebound hypertension, tachycardia • somnolence • syncope • weakness MINUS • tics (these medicines are effective in treating tic disorders)	

Table 4: Dose Dependent Adverse Effects Of FDA Approved Medicines for ADHD

medical history includes syncope, cardiac anatomical abnormalities, or sudden cardiac death in a first-degree relative, then a pretreatment referral to pediatric cardiology is highly recommended. If the uncommon adverse effects of persistent hypertension or tachycardia develop during treatment or chest pain and persistent palpitations occur, then evaluation by a pediatric cardiologist is recommended. Aortic stenosis, Wolf-Parkinson-White syndrome, and arrhythmogenic right ventricular dysplasia generally preclude stimulant treatment.[24]

WHAT ABOUT CAM TREATMENTS?

When parents or caregivers decline evidence-based medicines for ADHD and suggest complementary or alternative medicine (CAM) therapies, it is best to respond in a non-pejorative and instructive fashion explaining there is little science to support CAM

treatment of ADHD. Neither provocation restriction diets (e.g., eliminating cow's milk, eggs, gluten, etc.) nor additive elimination diets (e.g., avoiding food coloring, chocolate, etc.) have evidence for improving core ADHD symptoms.[25] Nutritional supplements, including trials of L-carnitine, iron, zinc, and magnesium (potentially fatal in overdose) have done no better than placebo in treating ADHD. *Gingko biloba* trials in ADHD have not only failed, but also increased bleeding risk. St. John's Wort was found to be no better than placebo in a randomized controlled trial for ADHD. The only weak evidence for CAM benefit in ADHD with very low effect size is for heavy supplementation at 1 gram or more daily with omega-3 fatty acids, specifically, eicosapentaenoic acid.[26] Finally, when parents ask about CBD oil, the best response is that large scale, high quality, randomized, controlled U. S. studies reviewed by the FDA specifically for treating core symptoms of ADHD in children and adolescents do not exist. Unless and until such studies are published, the safety and efficacy of cannabidiol for ADHD cannot be endorsed by pediatricians (there are adult studies in Europe showing no benefit).

Neurofeedback and cognitive training have been proposed and marketed to treat ADHD. However, a newly published double blind, randomized controlled U. S. trial of 7- to 10-year-olds with moderate to severe ADHD given neurofeedback versus a sham treatment revealed no difference on parent or teacher ratings between treated and sham-controlled children out to 13 months.[27] There is essentially no database of randomized controlled trials of acupuncture for ADHD that provides any thoughtful guidance to parents about this option.[28] The sparse evidence that chiropractic intervention has any benefit for core ADHD symptoms is of poor quality.[29] A small, four week, blinded trial (n=30 treated, n=26 sham) of trigeminal nerve stimulation in 8- to 12-year-olds with ADHD (low current pulses to the forehead during 8 hours of sleep) yielded a gradual reduction in ADHD symptoms (separating from sham after one week) as measured by parent ADHD rating scales.[30] Interestingly, the FDA granted marketing authorization in April 2019 of a proprietary trigeminal nerve stimulator, available by prescription only, for use in children between 7 and 12 years of age for ADHD. In June 2020 the FDA, using the same regulatory pathway, authorized marketing of a digital, interactive game by prescription to improve only attention in children 8 to 12 years age. Neither device has a published, convincing effect size or meta-analytic evidence for use in replacing pharmacotherapy, parent management, and school accommodations to treat ADHD.

ADHD AND THE COVID-19 PANDEMIC

Constriction of the US economy, school closures, and widespread remote learning during the Covid-19 pandemic have undoubtedly challenged normal child, adolescent, and family functioning. Pandemic related anxiety, loss of classroom structure, children unnaturally separated from peers, changes in parenting roles, parental job loss or a shift to working from home, and disrupted mealtimes and sleep patterns conspire to make treatment of ADHD even more difficult. Parents may be tempted to call their pediatricians to ask for increased doses of current medications or perhaps a trial of more potent agents such as antipsychotics. The European ADHD Guidelines Group suggests that pediatricians exercise great care and thoughtful consideration before making any changes in pharmacotherapy during the pandemic, while providing guidance on improved behavioral structure and sleep hygiene principles.[31]

The exponential increase in telemedicine visits during the pandemic may signal improved access to clinicians, perhaps a silver lining in the dark cloud of Covid-19, but reliable telemedicine is dependent on quality broadband availability, uneven at best across this country. If initial ADHD evaluation was performed by telemedicine, the European ADHD Guidelines Group cautions against starting a stimulant when history taking elicits syncope, congenital heart anomalies, prior cardiac surgery, or sudden death in a first-degree relative.[32] Blood pressure, heart rate, weight, and height monitoring are still advisable during telemedicine visits and easily done using home devices.

Finally, a recent, large study conducted by a leading healthcare agency in Israel found that the rate of Covid-19 positivity was higher among untreated ADHD subjects compared to treated ADHD subjects[33], implying that inattention, distractibility, impulsivity, and hyperactivity reduce the likelihood of wearing a mask, remaining socially distant, and remembering to wash one's hands effectively. If treating ADHD actually does reduce the risk of Covid-19 infection, then, recalling the prescient words of George Still, MD, it may be due to *improving* the "*consciousness* of the relation *of every volitional activity* on the part of the individual *to the good of all*."

RESOURCES

For parents and caregivers who wish to read more about ADHD, parenting the ADHD child, and navigating educational and social challenges, suggest "Taking Charge of ADHD: The Complete Authoritative Guide for Parents" by Russell A. Barkley, PhD, the newly revised 4th edition, 2020, available in paperback.

The Florida Department of Education provides a multitude of online resources for parents interested in accommodations for their children with ADHD, for example "A Parent and Teacher Guide to Section 504: Frequently Asked Questions" available at http://www.fldoe.org/core/fileparse.php/7690/urlt/0070055-504bro.pdf.

The nonprofit organization Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) maintains a helpful website covering a wide range of topics, available at https://chadd.org.

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REVIEW ARTICLE

Navigating Learning Problems in Children: A Closer look at Intellectual Disability (ID) and Specific Learning Disorder (SLD)

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The parents' concern about their child's academic problems is frequently brought up during visits, both with specialists and with primary care providers. Academic problems may be due to various reasons, including chronic medical conditions, leading to missed school days due to treatments/doctor visits, inattention problems, mental health problems, intellectual disability (ID), Specific Learning Disorder (SLD)/Learning Disabilities, and low literacy in parents, to name a few. It can be challenging for parents to figure out how to navigate the system to obtain resources for their child, leading to parental stress and stress on the child with potential missed opportunities for early intervention. In addition, persistent academic failure might be a risk factor for bullying, being bullied, or for development of anxiety/depression. Poverty is known to be a risk factor for mild ID and SLD.[1] Children from low-socioeconomic backgrounds are more likely to have problems with grade retention, academic failure, and to be diagnosed later with learning disabilities.[2] Adults with deficits in reading skills might experience missed educational and employment opportunities, leading to a vicious cycle of poverty and poor health literacy.[3] Therefore, pediatricians play a profound role in helping identify academic deficits and providing resources to help patients succeed to the best of their ability. This article will focus on ID and SLD and will highlight some resources available through the Florida Public School System.

The patient history provides great insight into the potential etiologies for learning difficulties. Determining when symptoms first started presenting can be useful. Children with ID or SLD will start presenting with early onset learning problems, such as pre-academic difficulties with language deficits, learning nursery rhymes, and deficits in recognizing sounds of letters (phonological awareness), etc. They continue to perform below grade expectations. Letter and number recognition might be problematic even as grade level progresses. Children with ID will also have delays in several domains of development that show slow progress with interventions. Children with inattention or hyperactivity problems, such as with Attention Deficit and Hyperactivity Disorder (ADHD), might have problems with academic achievement, however, academic performance is not generally significantly below grade expectation with ADHD alone. Children with acute stressors, such as trauma,

anxiety, depression, or acute illness, might show regression in academic performance or might not be performing at grade level. Therefore, spending some time obtaining pertinent history with a timeline is of great value. Table 1 outlines some examples of helpful screening measures and testing available. After gathering relevant information, if ID or SLD is suspected, appropriate testing and treatments will help provide needed interventions.

	AGE FOR EVALUATION/ DIAGNOSIS	SCREENING TOOL	TESTING
ADHD	4 and above	-Vanderbilt Rating Scales -Conners-3rd Ed	Clinical
ID	-Evaluation: Any age -Diagnosis: 6 and above	School based grade level measures (e.g. iReady in Florida)	Done by Psychology • WISC-V • Woodcock Johnson-IV
SLD	-Evaluation: Any age -Diagnosis: 6 and above	School based grade level measures (e.g. iReady in Florida)	Done by Psychology • WISC-V • Woodcock Johnson-IV
Anxiety	Any age	-SCARED Child Report -SCARED Parent Report -GAD-7: age 12 and over	Clinical
Depression	Any age	PHQ-9: Modified for Teens	Clinical

Table 1

INTELLECTUAL DISABILITY

Definition and Severity Levels:

Intellectual Disability, previously referred to as "mental retardation", as defined by Diagnostic and Statistical Manual-5th Edition (DSM-5), is a neurodevelopmental disorder characterized by intellectual difficulties as well as difficulties with social, practical, and conceptual domains of development.[4] As opposed to the DSM-4, DSM-5 does not rely on specific IQ scores as diagnostic criterion but continues to consider the idea of IQ scores being 2 or more standard deviations below the general population with more emphasis given to deficits in adaptive functioning. Severity level is based on levels of functioning. People with mild ID can live independently with minimal need for support. In those with moderate ID, independent living might be possible with moderate support, such as through group homes. Severe ID might require daily support to help with self-care and safety and profound ID requires 24-hour care.[1]

Diagnostic evaluations:

Children with severe-to-profound deficits, are usually identified early in childhood due to significant impairment as opposed to children with mild-to-moderate symptoms, who are usually identified in early elementary school. If a child is suspected to have ID due to academic impairment and impairment in day-to-day activities, pediatricians can write a letter to the school recommending consideration for psychoeducational testing, evaluating cognitive abilities, as well as academic functioning, if not already done so by the school. Children who are identified early on by the school will undergo such testing by at least 6 years of age, when diagnostic tools are more accurate and valid.[5] A widely used IQ measure for children in the United States is the Wechsler Intelligence Scale for Children (WISC-V). The WISC-V provides an overall Intelligence Quotient (IQ) score as well as five other scores for verbal comprehension, visual spatial skills, fluid reasoning, working memory, and processing speed. In addition to the IQ measure, an adaptive measure is also used to determine functional domains of living. The Vineland Adaptive Behavior Scale is a widely used measure of adaptive abilities,[1] typically completed by parents and teachers.

In terms of genetic testing, the chromosome microarray is considered the first line in evaluation for underlying genetic abnormalities in all children with ID of unknown etiology. Additionally, Fragile X testing is also warranted, especially given that studies of incidence and prevalence show a 40% excess of boys over girls. 2% to 3% of boys and 1% to 2% of girls with ID of unknown etiology will have Fragile X syndrome.[5]

Treatment:

Treatment and interventions are targeted at providing appropriate academic support, via Individual Education Plans (IEP) and special class resources at school, including skills training, continued support in adulthood, and treating any mental health comorbidities. Mental health disorders are commonly seen in individuals with ID, however, diagnosis can be challenging due

to verbal and cognitive impairments, making treatment even more difficult.[1] Close follow-up with mental health providers will be important. Functional impairment of ID can be lifelong, however, with appropriate support, most individuals with ID will be able to function adequately in society.

SPECIFIC LEARNING DISABILITY/SPECIFIC LEARNING DISORDER

Definition:

SLD is defined in both medical and educational contexts. The educational system uses the term Specific Learning Disability (as opposed to disorder) and defines it according to the Individuals with Disabilities Act (IDEA) as "a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, which disorder may manifest itself in the imperfect ability to listen, think, speak, read, write, spell, or do mathematical calculations".[6] Medical diagnosis uses the term Specific Learning Disorder (as opposed to disability) and is based on the following DSM-V criteria:

1. Difficulties in reading, reading comprehension, writing, arithmetic, or mathematical reasoning present for at least 6 months despite intensive interventions
2. Academic skills are significantly below expected for the child's age and are impairing
3. Learning difficulties begin during the school-age years.
4. Difficulties are not better explained by other conditions, such as ID, sensory deficits (such as vision or hearing problems), neurological deficits, socioeconomic disadvantage, or lack of understanding of the language.[4]

Diagnostic Evaluation:

Children at risk for academic problems or showing below-grade performance are usually identified by their teachers and recommended for the school system's MTSS (Multi-Tiered System of Supports). Children who are not yet identified by schools may be identified by pediatricians and a letter of recommendation for MTSS may be provided. MTSS is an "evidence-based model of schooling that uses data-based problem-solving to integrate academic and behavioral instruction and intervention."[7] Children at risk are then started on tiered interventions, with the child progressing through 3 tiers, each with more intensive interventions than the previous one if improvement, in a given tier, is not noted.[7] If persistent deficits are noted, testing is undertaken to determine if the child has a Specific Learning Disability (SLD). The diagnosis of SLD can only be made if attempts to improve a child's academic performance have not been successful with intensive interventions. Widely used and validated measures are the Weschler Intelligence Scale for Children (WISC-V) and the Woodcock–Johnson IV.[1] Language evaluations are also typically undertaken to evaluate for underlying language/speech deficits that might contribute to academic deficits.

Treatment/Interventions:

Once the diagnosis of Specific Learning Disability has been established, the child may qualify for an IEP, under the SLD exceptionality, and have goals established to maximize academic progress, with interventions continuing through the school years. Additionally, the child may also receive speech/language therapy to help optimize communication as well as language-based academic performance if language evaluation shows deficits. Various comorbidities are noted with SLD, including ADHD, disruptive behavior disorders, and communication disorders, therefore, a comprehensive look at all impairments and treatments needed will be beneficial in optimizing the child's overall functioning. SLD is a lifelong condition, however, individuals learn to compensate over time.[1] One-third of children with SLD have had grade retention at least once. Approximately 68 percent of children with SLD graduate with a regular diploma, with 19 percent dropping out. Adults with SLD are less likely to enroll in higher education and are less likely to be employed as opposed to adults without SLD.[9] Therefore, it is imperative that children with SLD are identified early on and receive the appropriate interventions in order to have an overall enriching life.

The relationship and communication between pediatricians/clinicians, parents, and school personnel is essential to the success of identifying the children in need and achieving appropriate interventions and resources. For children with academic concerns, it is important to request school records, via a current IEP and any report of psychoeducational testing done through the school. The parent may request this information and pass it along to the clinician for review. This will help provide accurate information of school accommodations and diagnosis, will prevent duplication of services, and will also help parents better understand the resources that they child might already have in place. There is strength in partnership and together we can move towards a promising future.

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REVIEW ARTICLE

Autism Spectrum Disorder - A Clinical Perspective

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Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with significant behavioral manifestations. It affects 1 in 54 children.[1] This means, as clinicians, each of us will encounter individuals with ASD in our practice. Thoughtful diagnosis of children with autism, as well as assessment of comorbidities and referrals to ancillary service providers are increasingly becoming essential parts of general pediatric practice.

HISTORICAL PERSPECTIVE

The word autism originates from the Greek word "autos" which means self. It was first used in 1911 by German psychiatrist Eugen Bleuler who described some schizophrenic patients who were especially "self-absorbed" and "withdrawn". In 1943, an American child psychiatrist Leo Kanner, MD, described 11 children who were highly intelligent but preferred "aloneness" and "insisted on sameness". In 1944, Hans Asperger, MD, who was the Chair of Pediatrics at the University of Vienna after WWII, described boys who were highly intelligent but had trouble with social interactions. In 1988, the movie *Rain Man* raised public awareness of this disorder. It was not until 1991 when public schools began identifying children with autism and offering them special educational services.

WHAT IS ASD?

Autism literally means "alone". ASD involves two core issues: deficits in social communication and interaction and restricted and repetitive patterns of behavior, interests, or activities. Children with ASD may avoid interactions, have difficulty understanding "other people's" perspective, have difficulty reading emotions, and often will have rigid behaviors, which are also repetitive. A clinical study by Pierce et al in 2010[2], compared responses to social and geometric pattern stimuli in children less than 4 years of age and found that if a child looked more than 70% of the time at a non-facial stimulus, probability of autism was 100%. This study had limitations, but showed that children with autism do not have a preference for human faces or emotion, but are more interested in geometrical patterns, like the moving blades of a fan or the spinning wheels of a car. While a typical child will regard the eyes of his caregiver, children with ASD will regard the motor area. While most

children will look at the big picture, children with ASD focus more on the minute details. While children with ASD have deficits in social communication, some will also demonstrate superior ability in other areas.

HOW COMMON IS IT?

The prevalence of ASD is approaching 1.7%[3] and seems to be increasing with a preponderance of males that is yet unexplained. Recent prevalence data reveals increasing rates of ASD in Hispanic and African American children.[3] The reason for the dramatic increase in prevalence is somewhat controversial but is certainly a function of improved screening tools and expanded diagnostic criteria. It is a chronic medical condition with lifetime management costs of a child with ASD ranging from $1.4 to $2.4 million[5] or more.

WHEN DO WE AS PEDIATRICIANS START LOOKING FOR ASD?

Symptoms of ASD typically start manifesting in the first year of life and become more apparent by the age of two years. However, the average age of diagnosis currently stands at 4-5 years and lags further behind in children from low-income and minority backgrounds. In children with minimal functional impairment and good verbal and cognitive skills, ASD might not get diagnosed until early adolescence or even early adulthood.

HOW DO WE LOOK/SCREEN FOR ASD?

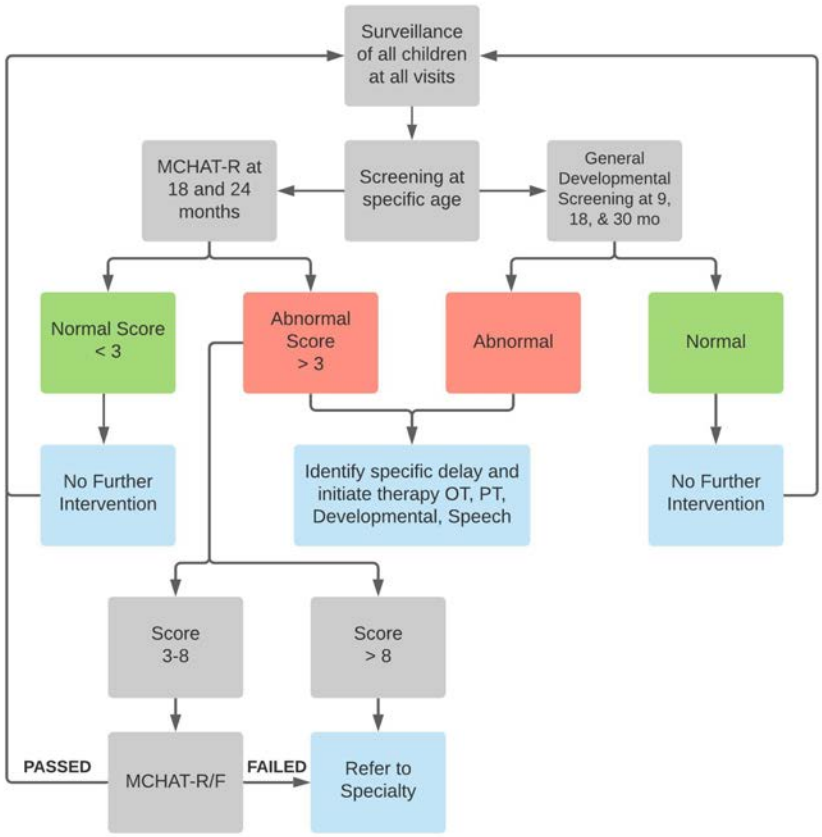

Figure 1

The American Academy of Pediatrics recommends developmental surveillance for all children at all visits. General developmental screening is recommended at 9, 18, and 30 months of age, with additional autism specific screening at 18-month and 24-months visits:

12-18 months - In high-risk children including siblings of children with ASD, language delay can be identified by using the infant and toddler checklist parent questionnaire.

18-24 months - Universal screening for autism is recommended at 18 and 24 months of age by using a standardized autism specific screening tool like the modified checklist for autism in toddlers, M-CHAT. M-CHAT–R/F is the newer version of the M-CHAT with better specificity. It is a two-stage screening tool.

Ages 30 months-5 years - There is no validated screen currently available for universal screening above 30 months age. Social communication questionnaire (SCQ) has been studied but it is non-specific, as it can identify symptoms of other conditions, like attention deficit hyperactivity disorder (ADHD).

School age - Ongoing surveillance is recommended as children with minor symptoms can be missed and diagnosis delayed especially in girls who have lesser intensity of symptoms and fewer behavioral issues. For at risk children, cognitive and language testing should be initiated through the school.

M-CHAT-R scoring – All items except 2, 5, and 12 should have the response "YES".

- **Children with scores 0-2** – are considered low risk and should be screened again after second birthday if the screen was performed at younger than 24 months of age.
- **Children with scores 3-7** - should have the follow-up interview with MCHAT-R/F. This is the second stage and is limited to only the failed items. Follow the flowchart format, asking questions until a pass or fail is scored. The interview is considered to be a positive screen if the child fails any two items on the follow-up.
- **Children who score more than 8** - are at high risk for ASD or other developmental delays and should be referred immediately for further diagnostic assessment by a specialist in this field. At the same time, interventional services for all identified delays should be started immediately without waiting for further evaluation.

Despite recommendation of M-CHAT-R screening by AAP, recent studies including a retrospective study done by Carbone et al,[6] show that it is likely to result in type II errors or false negatives. If the healthcare provider or the parent has concerns about ASD, children should be referred for evaluation regardless of the score on the MCHAT-R or the MCHAT-R/F.

WHAT DOES ASD LOOK LIKE CLINICALLY?

Difficulty in diagnosis arises due to its highly variable clinical presentation. While identifying a three-year-old child who is nonverbal, with no eye contact, no reciprocal interactions, and constant rocking and head-banging is easy, a nine-year-old with good cognitive skills, good verbal skills, but limited social skills can be diagnostically challenging. ASD is associated with intellectual disability in 25 to 50% of the cases and with seizure disorder in about 25% cases.

RED FLAGS

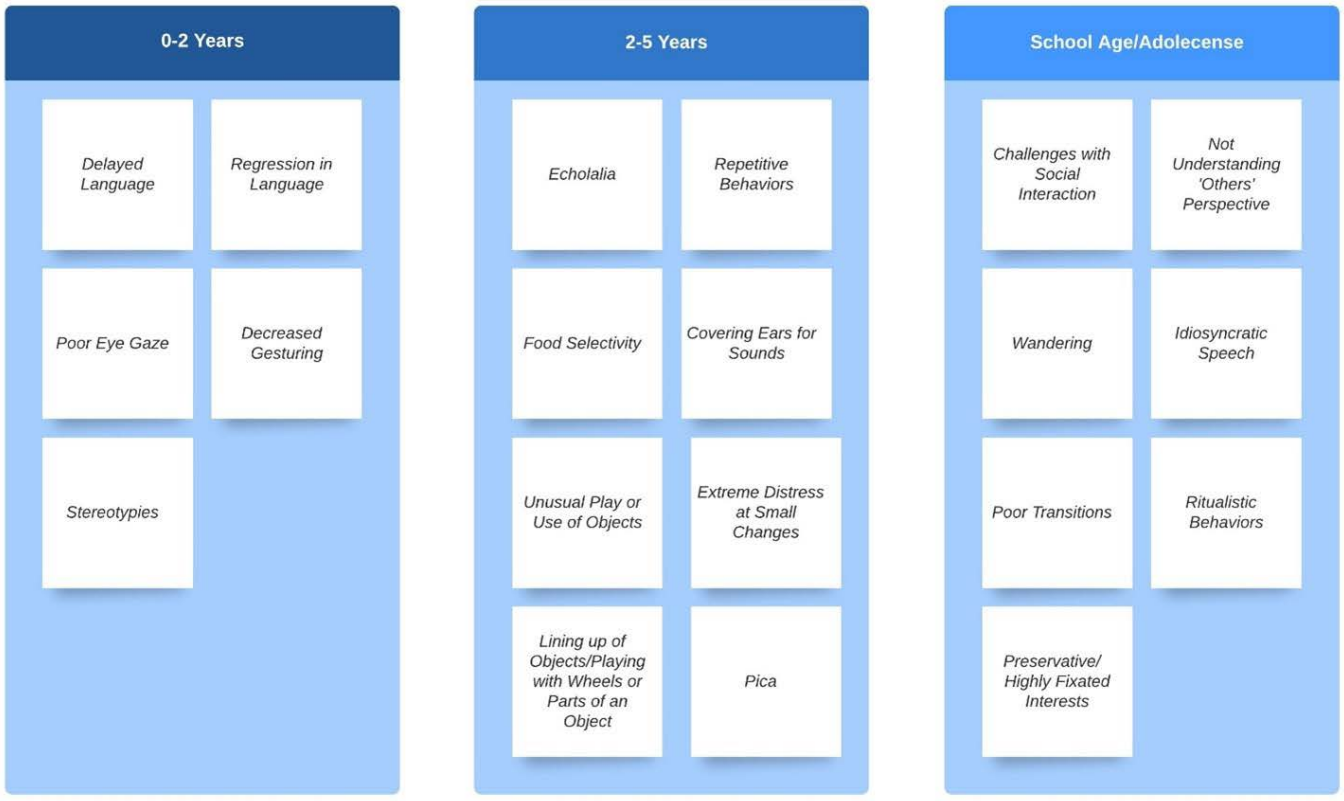

Figure 2

WHAT CAUSES ASD?

The etiology of ASD is considered to be multifactorial with neurological, genetic and environmental components. ASD is associated with abnormal neurodevelopment. Variations in brain structure include increased number of neurons, defective neuronal pruning, smaller corpus callosum, larger amygdala, and loss of brain volume, dysplasia and most commonly an abnormal decrease in number of Purkinje cells in the cerebellum. Variations in the brain function have been observed in functional MRI studies with decreased activity in the posterior cerebral cortex and decreased activity in the areas associated with executive functioning, language, social, and visual processing. Children less than two years of age, presenting with loss of some milestones like speech are secondary to synaptic pruning in response to genetic factors.[7]

ASD is also heritable. There are higher rates of occurrence in siblings compared to the general population and even higher rates in monozygotic twins. Genetic factors in the etiology are variable and include de novo mutations, syndromes involving chromosomes like fragile X, tuberous sclerosis, and non-syndromic single gene mutations or copy number variants (CNV).

Other contributing factors include history of gestational diabetes, preterm birth, and advanced maternal or paternal age, multiple gestations, low birth weight, and exposure to environmental factors including teratogens like certain medications, alcohol, or drugs. It is important to note that autism is not associated with vaccinations.

HOW DO WE DIAGNOSE ASD?

Diagnosis of ASD is currently based on a combination of historical findings and clinically observed characteristics. The clinical diagnostic criteria are found in the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5, 2013).

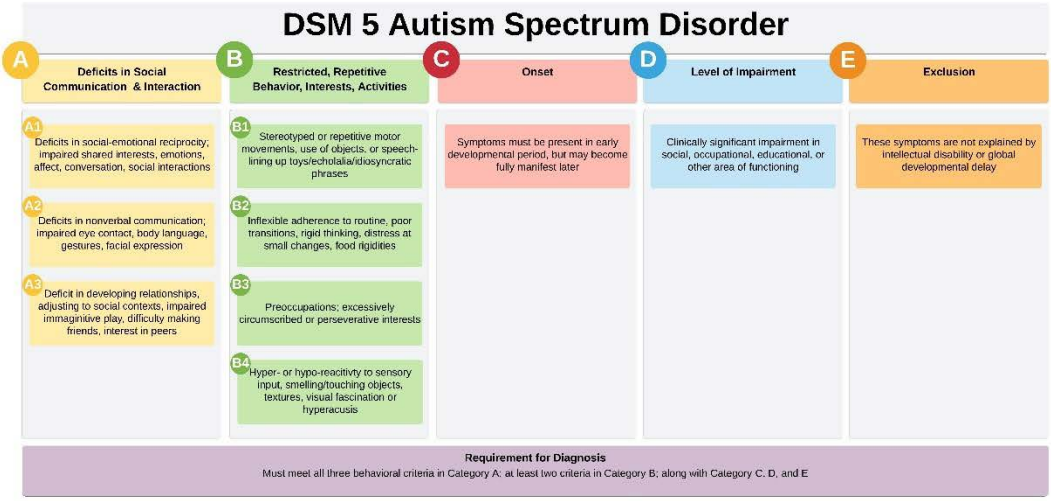

Figure 3

The clinical diagnosis can be further supported by questionnaire tools, e.g. the social communication questionnaire (SCQ), Gilliam Autism Ratings Scale (GARS), or the social responsiveness scale (SRS). These tools are not diagnostic, but only supportive. Other measures used include Behavior assessment System for Children, 3rd Ed., Diagnostic Interview for Social and Communication Disorders (DISCD), Child Behavior Checklist (CBCL) and Autism Diagnostic Inventory (ADI).

In general, the "gold standard" for confirmation of diagnosis is the Autism Diagnostic Observation Schedule (ADOS). The Childhood Autism Rating Scale (CARS) is also used by some specialists. No single observation tool is appropriate for all settings. For diagnostic clarification or further validation and management, referral must be made to providers/facilities with expertise in ASD.

Once a diagnosis of ASD is made, the DSM-5 includes additional specifiers that should be indicated and include: intellectual impairment, language impairment, known medical/genetic condition or environmental factor, association with other mental or behavior disorder or neurodevelopmental conditions, and presence of catatonia. Likewise, every diagnosis should include a child's severity level based on impairment in functioning requiring different levels of support and should be described. It ranges from Level 1 requiring some support to Level 2 requiring substantial support and finally Level 3 requiring very substantial support, often indicating that the parent will need to supervise or have one on one care for this child.

In comparison to previous editions of the DSM, the diagnostic criteria have been broadened in DSM-5. Behavioral criteria

can be met based on historical report alone. Symptoms no longer have to be apparent before age 3 and sensory reactivity is now included as a behavioral symptom. Functional impairment must be present for a diagnosis. There are no longer diagnostic subcategories, such as Asperger's disorder, and PDD- NOS. Rett syndrome, now with a clear genetic etiology, and Childhood Disintegrative Disorder (CDD) are no longer included in the DSM. For children with significant deficits in social communication who do not have restricted or repetitive behaviors, the DSM-5 has a new diagnosis outside of ASD, social pragmatic communication disorder.

HOW DO WE MANAGE ASD?

Children with ASD require myriad services. Management strategies are variable but should include:

1) Hearing - Children with language delay or inattention to language should have a hearing evaluation.

2) Vision - visual impairments may affect interactive gaze or cause stereotypical behaviors. Children should have vision examined.

3) Early intervention - Children less than 3 years of age with developmental delays should be referred to Early Steps Early Intervention. Speech therapy, Occupational therapy, Physical therapy, and Developmental intervention should be initiated immediately, if needed.

4) Educational Intervention - Children older than 3 years should be referred to the Florida Diagnostic and Learning Resources (FDLRS) for placement in early education programs along with behavioral and educational interventions in place. School aged children (5 years and older) should have cognitive and language assessment done for their educational needs.

5) Behavioral Intervention - Children with functional impairments, maladaptive behaviors or aggression will benefit from Behavioral interventions including Applied Behavioral Analysis (ABA) and Parent mediated therapy (PMT).

6) Medical management of co-occurring medical conditions is essential. Common comorbidities include disorders of sleep, gastrointestinal tract symptoms like constipation, restrictive eating habits, obesity, seizures, mental health issues, food refusal, dental health, pica, and developmental coordination disorder. 70 to 90% of children and youth with ASD have psychiatric issues including intellectual disability, ADHD, anxiety disorders, learning disabilities, speech and language disorders, obsessive compulsive disorder (OCD), aggression and self-injury. Depressive disorders are common. Cognitive behavioral therapy (CBT) and medication management should be considered.

In children with sudden behavioral worsening or new symptoms, physical /medical causes of the behavior change should be excluded prior to considering behavioral interventions.

7) Referral to specialist care like Developmental Pediatrics, Child Psychiatry, comprehensive autism diagnostic centers is essential. Referral to Neurology, endocrinology, genetics, cardiology and Gastroenterology should be made as needed.

8) Legal interventions - In case of Intellectual disability or significant medical issues, the family should consider full guardianship. Limited Guardianship should be considered when individuals with ASD can participate in decision-making. Conservatorship is recommended in cases where only oversight is needed for financial decisions.

9) Young adults who cannot support themselves independently, can be eligible for supplemental Security income (SSI).

10) Parents should be involved in advocacy throughout and should work closely with the school system to improve social skill training and to provide vocational training for the workforce.

TO DO OR NOT TO DO?

Genetic testing - The American College of Medical Genetics guideline recommends chromosomal microarray (CMA) for all patients with ASD and Fragile X testing in boys. The American Academy of Pediatrics 2019 ASD clinical guidelines agreed with genetic testing for all children with ASD. Most patients with pathogenic findings on CMA need further evaluation and subspecialty support. Interestingly, Ho et al[8] demonstrated a higher rate of pathogenic mutations in female patients with complex ASD.

Pediatricians need to be aware, however, that insurance coverage for genetic testing in individuals with ASD varies. Most public insurances cover testing, but private insurance reimbursement is variable and can result in unintended out-of-pocket expenses for the families.

Neuroimaging is typically not indicated as there are no ASD specific imaging findings while incidental findings are more common. The rare need for MRI should be directed by history and physical exam.[9]

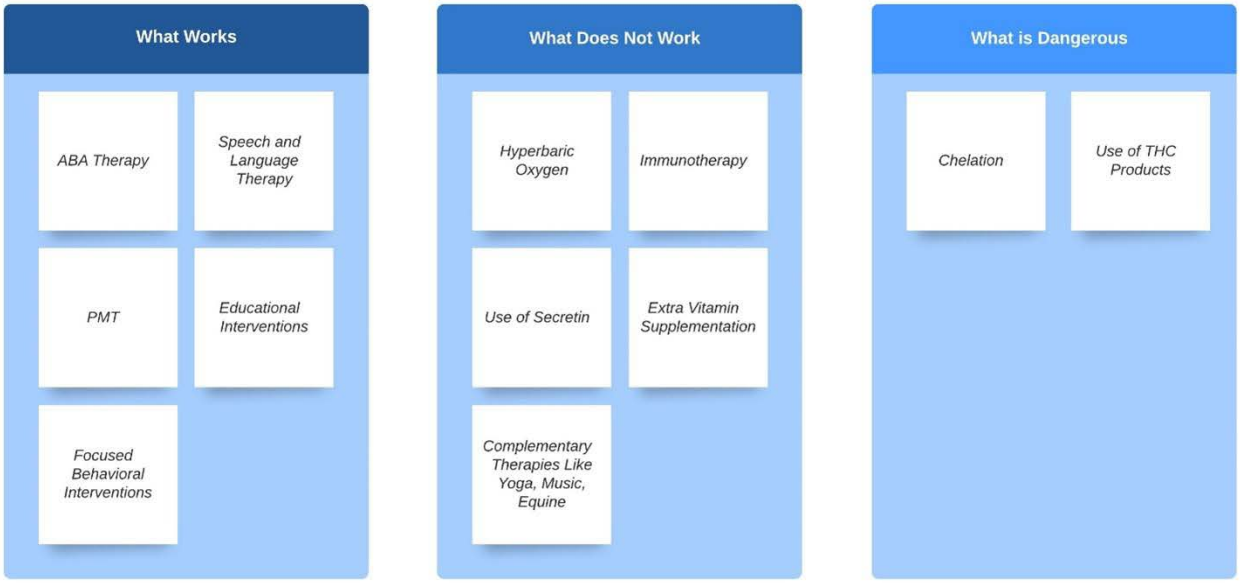

Figure 4

Metabolic testing yield is low and is not recommended.[10,11]

EEG - Children with ASD are at increased risk for seizures and have EEG abnormalities, however EEG is not recommended as a routine evaluation without any symptoms.[12]

Alternative interventions- In 1999, TV and print media widely reported a journal article purporting that three autistic children were symptom free after IV secretin was administered during endoscopy. More than 700 children with autism participated in seven randomized controlled trials of secretin and none ever improved. While many families pursue complementary interventions, there is clear and substantial evidence that secretin[13] use is of no benefit. Similarly, trials of baclofen targeting social withdrawal, acetylcysteine for irritability, oxytocin to promote social bonding, and memantine for core symptoms have all been failures. Chelation[14] therapy has clear evidence of potential harm. In a meta-analysis, of 27 RCTs of dietary interventions in more than a thousand children with autism, Fraguas et al[15] found no effect of nonspecific dietary interventions on core symptoms of autism, but some evidence with low effect size for supplementation with omega-3 and some vitamins.

PROGNOSIS

ASD with its variable etiologies, clinical presentations, and co-occurring medical conditions, will also have variable prognosis. Children with intellectual disability, significant language impairment and poor executive functions have the worst prognosis.

WHAT INTERVENTIONS ARE THERE?

Behavioral - These interventions are meant to improve functional skills, minimize problematic behavior and improve core deficits. These interventions can be provided in different settings including home, daycare, school, clinic, or therapy centers and serve as the core interventions for most children with ASD. Wong at al has described two categories of interventions - comprehensive treatment models (CTM) and focused interventions. Comprehensive approaches include ABA, early start Denver model for promoting skills or the classroom-based LEAP or TEACCH approaches for preschoolers.

Most evidence-based treatments are based on **ABA (Applied Behavioral Analysis)**. It is the most frequently used intensive behavioral intervention in early childhood. ABA can be prescribed by a physician or licensed psychologist.

Focused interventions are useful in improving a specific behavior or learning a skill over a short period of time. Evidence-based approaches include **Parent Management training** which includes parent support and parent mediated interventions in which the parents are trained to deliver interventions. These have been found to be one of the most effective interventions and should be included in the management plan for the child.

Educational interventions - Not all children with the diagnosis of ASD will qualify for educational interventions. Most schools are also limited in the range of interventions offered. They can provide interventions that can range from ABA based classrooms to developmental supports only. Children with average or above average cognitive ability and no significant

comorbidity can be educated in mainstream classrooms with little or no support. Others will need 504 accommodations plan for some support. Children with intellectual disability, limited verbal skills or significant comorbidities will need individualized educational programs (IEP).

RESOURCES FOR ASD?

Florida resources for individuals with autism spectrum disorder include:

APD - Agency for persons with disabilities

The Arc of Florida - it is the largest national community-based organization advocating for and serving people with intellectual and developmental disabilities and their families.

CARD - The Center for Autism and Related Disabilities

These are 7 state-funded, university-based outreach and support centers in Florida dedicated to optimizing the potential of people with ASD, sensory impairment and other disabling conditions and related disabilities. Some of their services include individual and family support, family and professional training, public education and community outreach, and technical assistance.

Children's Medical Services Florida's Early Steps program - Early Steps is Florida's early intervention system that offers services to eligible infants and toddlers with significant delays.

Florida Diagnostic and Learning Resource system - FDLRS provides diagnostic, instructional and technology support services to district exceptional education programs and families of students with disabilities.

Gardiner Scholarship provides eligible students scholarships in order to design a customized education program. It is administered through the AAA Scholarship Foundation and the Step Up For Students.

Florida Department of Education

McKay Scholarship - provide students with special needs the opportunity to either attend a participating private school or offer parents public school choice.

Florida Division of Vocational Rehabilitation - is a federal-state program to help people with disabilities find and maintain employment and enhance their independence.

ASD AND PANDEMICS LIKE COVID-19

The current coronavirus pandemic has made children with autism spectrum disorder even more vulnerable to mental health problems. It is important to help the child understand the new situation and the pandemic using social stories. For children with difficulty transitioning, it is important to create new routines and be consistent. As social isolation increases, caregivers need to spend more time with the children focusing on non-electronic activities. Medical providers need to be aware of potential food scarcity at home, economic strain on families, and should maintain a low index of suspicion for abuse especially in children with comorbid psychiatric diagnosis or intellectual disability.

SO, ARE WE THERE YET?

Autism spectrum disorder is a complex neurodevelopmental disorder characterized by impaired social communication and restricted and repetitive behaviors causing functional impairment. Behaviors can change overtime and so developmental surveillance is important. Approximately 9% of the children diagnosed with ASD in early childhood may not meet the criteria by young adulthood.[16] There are controversies regarding screening and genetic testing. Diagnosing ASD early requires both well informed parents and an astute clinician. No one single intervention is effective for all individuals. Interventions should be individualized, initiated as early as possible, and be evidence-based. Early interventions result in better outcomes. Speech therapy is most commonly used along with comprehensive approaches like ABA therapy and educational interventions. Management should be collaborative considering family preferences. Importantly, while we focus on the deficits, it is equally important to develop the strengths in each individual child. Intense research needs to be done for autism to be better understood and managed. For those of us practicing medicine, the words of Dr. Hans Asperger are illuminating: "For success in science, a dash of autism is essential".

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