Introduction

Americans annually consume significant amounts of alcohol, tobacco, prescription opioids, and illegal drugs. The National Survey of Drug Use and Health (NSDUH) estimated that in 2014, 52.4% of U.S. citizens 12 years of age or older were currently using alcohol, 25.4% were using tobacco, 8.0% were using marijuana, 3.3% were using some other type of illicit drug, and in the past year, 4.1% had taken prescription opioids for nonmedical purposes. This level of substance use has resulted in substantial economic and social consequences and represents a significant public health challenge for the nation [1]. The excessive use of alcohol alone cost the US $249 billion in 2010 [2], with tobacco costing $289 billion in 2014 [3], illicit drugs $193 billion in 2007 [4], and prescription drugs $53.4 billion in 2006 [5]. Assuming spending rates remained stable, these expenditures represent a combined total of approximately $876.6 billion in 2017 dollars. These estimates do not begin to represent the significant personal costs resulting from the consequences of substance use such as addiction, loss of employment, familial disruption, health problems, and criminal justice involvement [1]. Loss of life is the most serious outcome related to substance use; 44,827 U.S. deaths in 2015 were tied to alcohol or drug use [6], and an additional 480,000 deaths were attributable to tobacco use [3].

With the exception of tobacco, which is used at significantly higher rates in Indiana, the use of alcohol, prescription pain relievers, and illicit drugs parallels the consumption levels noted for the rest of the country [1]. While the overall economic cost of Hoosiers’ substance use to Indi-
ana is not currently known, the state is estimated to spend over $6.1 billion annually to address the health and social consequences that stem from the use of alcohol and tobacco [2, 7] and more than $650 million per year on healthcare costs for prescription opioid misuse [8].

In order for policy makers to reduce the impact drug use has on the state, it is important for them to understand what factors may put Hoosiers at increased risk for escalating use and ultimately addiction. Brain development is one such factor. Although ingestion of substances of abuse at any age can adversely affect the brain, there are critical periods when use can have substantially greater impact. One of these critical periods is adolescence. The use of substances of abuse during this phase of development has been tied to many negative, long-term consequences. The purpose of this brief report is to (a) highlight how brain changes during adolescence elevate the risk for substance abuse and (b) describe the impact of alcohol and drugs on the adolescent brain and discuss the consequences associated with these changes. We believe this report will be particularly valuable to state- and local-level legislators, persons who work in social services agencies, prevention and treatment professionals, and those who are interested in designing approaches that can more effectively address substance use in Indiana.

**Basics of Adolescent Brain Development**

From the perinatal period through childhood, the brain grows in size and complexity as brain cells (neurons) multiply, coalesce into individual structures, and subsequently become linked together through tens of thousands of neural connections [9]. During adolescence, which begins at approximately age 12 and lasts till somewhere between the ages of 18 and 20, the brain changes rather dramatically. The most significant changes involve two processes: synaptic pruning and myelination. Synaptic pruning is a process that allows the brain to become more streamlined and efficient. During pruning, connections between neurons, or specific types of brain cells, that are used regularly are strengthened while those which are used infrequently disappear. Structurally, the pruning process is reflected in a decrease in the overall volume of cell bodies (gray matter) present in the brain. At the same time that pruning is occurring, the long, finger-like projections that grow off of neurons (axons) and allow for intercellular communication are being coated in a fatty substance (myelin) in a process called myelination. Myelination allows neurons to communicate with each other at dramatically increased speeds. From a structural standpoint, myelination results in steadily increasing white matter (myelin covered axons) throughout the brain [9-12].

Pruning and myelination proceed in a very specific manner. Phylogenetically older parts of the brain go through these processes sooner than newer ones. The limbic system and the prefrontal cortex are two areas of the brain that are of particular importance during adolescence. The limbic system is a group of brain structures that are biologically older and are tied to movement, emotion, reward, novelty seeking, memory, and impulsivity.
This part of the brain matures relatively early in adolescence. In contrast, the prefrontal cortex is biologically newer. It is responsible for executive functions including planning, decision making, and impulse control; it finishes maturing significantly later than the limbic system. Due to this pattern of older-to-newer development, adolescent behavior is driven somewhat more by impulses and desires to have new experiences and sensations, and somewhat less by critical and logical considerations of outcomes, especially in situations that are emotionally charged. Behaviorally, the maturation process of the adolescent brain is reflected in the greater propensity of adolescents to take part in risky activities such as unprotected sexual activity, reckless driving, and substance use, than at any other point in their lives [10-14].

Another important change noted in the adolescent brain is an increase in the activity of numerous neurochemical systems, particularly the dopamine system. Dopamine is a chemical messenger (neurotransmitter) that regulates feelings of pleasure and aids the brain in creating associations between behaviors that lead to positive outcomes and the environments in which these behaviors occurred. Heightened dopamine activity during adolescence means that adolescents are more sensitive to rewards and more likely to engage in actions that result in pleasure or positive outcomes.

**Addiction and the Brain**

Alcohol, tobacco, and other drugs are used for a variety of reasons, including for their pleasurable and mind-altering effects, for their ability to enhance performance, and to help reduce unpleasant psychological symptoms [15, 16]. Most drugs of abuse induce a sense of pleasure or a positive emotional state by directly or indirectly increasing dopamine levels within specific structures of the limbic system [15-17]. With continued use, drugs alter not only dopamine but in many cases other neurotransmitter systems, such as the serotonin system which helps to regulate mood. These neurochemical alterations are associated with shifts in how brain structures communicate with one another, in the shape and function of neurons, and in the physical composition of various areas of the brain; these shifts ultimately result in addiction, a condition characterized by intense cravings to use a particular drug and by compulsive drug seeking and drug taking even in the face of serious adverse health and/or social consequences [15-17]. As mentioned above, the brain areas and neurotransmitter systems implicated in addiction are precisely those that are still maturing, making them particularly vulnerable to drug exposure.

**Impact of Selected Drugs on the Adolescent Brain**

Most peoples’ first exposure to alcohol, tobacco, and other drugs typically occurs at some point during adolescence. Data from several sources indicate that the rate of substance use begins to increase at about the time children enter the 8th grade and peaks when they reach their late teens or early twenties. Similar to adolescents nationally, Hoosier adolescents most commonly experiment with alcohol, tobacco (primarily in the form of cigarettes and e-cigarettes1), and marijuana,

1 E-Cigarettes are electronic devices that allow users to inhale vaporized nicotine.
with use of these substances increasing from junior high through high school [1, 18, 19]. The following section focuses on the most frequently abused substances among youth.

**Alcohol**

Alcohol is the most widely used substance by adolescents across Indiana and the nation. In 2016, nearly 35% of Indiana’s 12th grade students said they were current users of alcohol (U.S.: 33.2%) [18, 19], and approximately 18% reported binge drinking in the past 14 days (U.S.: 15.5%). Binge drinking is a pattern of alcohol consumption that can result in more serious outcomes.

The impact of alcohol on the adult brain is well known. Adults who engage in chronic and heavy alcohol use show distinct changes in brain structure, and these changes can result in conditions such as alcohol-induced amnestic disorder, a form of dementia.

The impact alcohol has on the adolescent brain appears to be more subtle than that seen in long-term adult users; however, because of the dynamic physiological changes taking place in the brain during adolescence and the high rate of use within this population, alcohol exposure is still a significant concern [12]. In studies using non-invasive imaging technology, the brains of young people who were abusing alcohol or who had an alcohol use disorder were found to have structural differences compared to their non-using peers. Alcohol-using youth were most often reported to have smaller prefrontal cortices and smaller hippocampi. Among its many activities, the prefrontal cortex is responsible for planning of complex, goal-directed behavior; decision making; and impulse control. The hippocampus aids in the creation of long-term and spatial memories [20-23]. Small reductions were also noted in the temporal cortex, which is associated with memory formation, and the cingulate cortex, which plays a role in reward anticipation, decision-making, and impulse control [22]. Alcohol-using youth also typically had poorer white matter development in several brain areas, the most significant of which being the corpus callosum, the large group of axons that communicate information from one side of the brain to the other [22, 24]. Many of these structural changes were more pronounced among youth with longer histories of excessive use and of binge drinking [22].

In general, the brain changes noted among adolescents with higher levels of alcohol use appear to result in impairments that are cognitive in nature, including difficulties with attention, memory, and response inhibition—all of which could negatively affect academic performance [20]. Additionally, brain structure alterations among adolescent drinkers may be partly responsible for findings that the earlier adolescents begin to use alcohol, the more likely they are to develop an alcohol use disorder during young adulthood or at some point within 10 years of their first drink [25-27].

**Nicotine**

Nicotine, mainly in the form of cigarettes and e-cigarettes, is used more frequently throughout Indiana than it is in the rest of the nation. In 2016, nearly 15% of high school seniors indicated that they currently used cigarettes with almost 22%

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2 Binge drinking is defined as consuming five or more drinks in a row in the past two weeks.
reporting use of e-cigarettes [18]. Unlike in many other states, Indiana’s adolescents appear to start their substance use experimentation with cigarettes, turning to alcohol and then potentially to other drugs at slightly older ages [18].

Nicotine affects the brain by binding to receptor sites along cells in various areas of the brain called nicotinic receptors. A large percentage of nicotinic receptors are located in the limbic system. When stimulated by naturally occurring neurotransmitters, these receptors control the release of dopamine and serotonin. In the presence of nicotine, nicotinic receptors send messages for the brain to overproduce dopamine and reduce serotonin production while also causing certain limbic structures to produce more nicotinic receptors [28, 29]. Not only can increased dopamine in the limbic system allow this region of the brain to exert greater control over behavior than the more logical prefrontal cortex, it can also lead to long-term changes in the organization of cells in brain structures responsible for processing information regarding rewards [30]. In fact, these reward-processing areas show higher levels of activation in adolescent smokers when they are exposed to smoking-related advertisements compared to non-smokers [31].

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Unlike in adults, the nicotine-induced increase in nicotinic receptors appears to make adolescents more sensitive to nicotine, and make it more likely they will continue to use products which contain it [28]. In fact, in one imaging study, a nicotinic-rich area of the brain believed to be involved in addiction, the insula, was found to be thinner in young smokers compared to nonsmokers; greater thinness was associated with a smoker’s self-rated level of nicotine dependence and urge to smoke. The nicotinic receptor system is also believed to play a role in the development of neurons and in myelination. Young smokers have greater amounts of white matter in areas of the corpus callosum as well as other main communication tracts in the brain compared to non-smokers. These findings may imply compromised development along these tracts, although the clinical implications of these changes are not clear [28].

Regardless of what specific areas of the brain nicotine affects, it is clear that adolescents who begin using cigarettes place themselves at very high risk for continued use; approximately 90% of adult smokers begin smoking before the age of 18 [3], and those starting very early in adolescence report the greatest difficulty quitting [32, 33]. There is also a strong link between adolescent smoking and depression, which may be partially explained by the decrease in serotonin caused by cigarette use. Although the relationship between cigarette use and depression is not entirely clear, there is
evidence that adolescents who suffer from depression or mood disorders and smoke, generally began smoking well before the onset of significant psychological symptoms [34-36]. Early use of cigarettes among adolescents is also tied to use of illicit substances particularly marijuana, cocaine, and heroin later in life [37, 38].

**Marijuana**

Marijuana is the most widely used illicit drug in the U.S. In 2016, 6.6% of Indiana’s 8th graders, 13.7% of 10th graders, and 20.3% of 12th graders were reported to be current users of marijuana, with similar percentages doing so nationally (5.4%, 6th; 14.0%, 8th; 22.5%, 12th) [18, 19]. Within the brain, there exists a neural receptor system known as the endocannabinoid system. A significant portion of the endocannabinoid system is located within the limbic system and the prefrontal cortex [39]. By interacting with various neurotransmitters, endocannabinoid receptors help control it stands to reason that as the brain is undergoing significant maturation during adolescence, the introduction of substances of abuse during this process can lead to disruptions in its pattern of normal development.

Imaging studies of adolescents suffering from cannabis use disorders reveal that these adolescents have poor gray matter development in their prefrontal cortex, hippocampus, and other brain structures associated with memory storage. White matter development is also affected with regular cannabis users showing greater amounts of white matter compared to non-users. Additionally, when engaging in cognitive tasks, functional imagining studies show that adolescent users of marijuana demonstrate poorer connections between parts of the limbic system and prefrontal cortex, whereas non-using adolescents demonstrated the reverse pattern [42]. Taken together, these findings support the view that marijuana use in adolescence may result in premature or altered tissue development within the brain [22, 41, 43-45].

The impact of these brain alterations is threefold. First, adolescents who use marijuana have difficulties with impulse control, attention, memory, learning, and problem solving—activities that are controlled by the brain areas found to be affected by marijuana [44-46]. These and other cognitive deficits have been linked to poorer educational and social outcomes among adolescent users compared to their peers [47-49]. Second, marijuana use during adolescence, and especially early adolescence, appears to be linked to an increased risk for future substance use problems and for developing a substance use disorder later in life [47-50]. Third, correlational and longitudinal studies show a clear link between adolescent marijuana use and development of mood disorders later in life and an even stronger link between adolescent use and the development of either psychotic symptoms or some form of a psychotic disorder in young adult-
hood. In both cases, use of marijuana before the age of 15 was found to result in the highest level of risk for future mental health difficulties [51-55].

**Thoughts for Policymakers**

It stands to reason that as the brain is undergoing significant maturation during adolescence, the introduction of substances of abuse during this process can lead to disruptions in its pattern of normal development. Alcohol, nicotine, and marijuana, the most commonly used substances by adolescents, have all been tied to such disruptions, particularly in the limbic system and prefrontal cortex, the brain areas experiencing the greatest amount of change [12]. These structural changes are associated with higher rates of cognitive impairments and academic difficulties, higher rates of future substance use and substance use disorders, and higher rates of mood and psychotic disorders [27, 56-58]. In order to help lower the impact substance use has on adolescent brain development and associated consequences, policymakers could consider the following actions:

**Increase prevention efforts that target adolescents and preadolescents.**

One overall finding related to adolescent substance use and the brain is that delaying the onset of substance use to late adolescence or beyond greatly reduces the chances for long-term adverse consequences across a number of life domains. Policymakers could consider directing additional state monies to prevention programming that targets youth prior to reaching adolescence as well as throughout this critical developmental period. Because many prevention programs have little evidence of effectiveness, policymakers will have to carefully review what options are available to ensure that some positive benefit will be gained [21, 59, 60]. In tandem with expanding prevention programming, policymakers and state agency administrators might consider creating funding mechanisms that would encourage development and evaluation of more effective prevention strategies that take adolescent brain development into account; for example, strategies could provide adolescents with new experiences like rock climbing or BMX bicycling, activities that are socially acceptable, healthy, provide a sense of risk, and would allow for development of positive peer relationships.

**Support legislation that limits adolescent access to alcohol, cigarettes, and marijuana.**

A proven method for reducing alcohol and cigarette consumption among adolescents is to enact policies and law enforcement strategies that make these products less accessible. Effective approaches policymakers might consider would be to further raise taxes on alcoholic beverages, cigarettes and e-cigarettes; raise the age for purchasing cigarettes to 21; and raise funding for law enforcement agencies to increase their alcohol and tobacco compliance check efforts. To reduce access to marijuana, policymakers could push for keeping marijuana illegal in Indiana; however, should
marijuana be legalized, policymakers could institute similar tax, age, and carding procedures currently in use for alcohol and nicotine-containing products [15, 61].

Increase adolescent-specific treatment services.
Although preventing use till after individuals pass through adolescence would help ensure healthy brain development, expediting adolescents who are abusing substances into specialized treatment may help mitigate the adverse effects of alcohol, tobacco, and other drugs. Within Indiana 69 substance abuse agencies report offering specialized treatment services for adolescents [62]. Lacking specific guidelines to define what specialized treatment means, agencies reporting such services could be indicating that they offer comprehensive programming exclusively for adolescents or simply that they allow adolescents to be clients of the agency. Policymakers could collaborate with state agencies that oversee substance use treatment to require agencies receiving state dollars to follow a specific set of treatment guidelines that would ensure that adolescent Hoosiers receive services that are effective and appropriate for their unique needs.

Provide training to healthcare and other professionals on how substance use can affect the brain, how to identify signs of substance use, and how to effectively intervene.
Because parents may not always be aware of whether or not their adolescent children are using substances, other professionals who come in contact with these young people need to be prepared to address this issue. Directors of training programs for physicians, nurses, and other healthcare professionals could require that their students receive enhanced training on substance abuse and how it presents in adolescent patients. Licensing boards could consider implementing license renewal guidelines that require healthcare professionals to receive training in the screening, brief intervention, and referral to treatment (SBIRT) approach. Knowledge of SBIRT can help health professionals identify patients who have or are at risk for a substance use disorder and ensure that they are connected to appropriate services in a timely fashion [63].

Increase prevention efforts that target pregnant women, expand services for pregnant women who have substance use problems, and reduce barriers to accessing those services.
Alcohol, nicotine, and marijuana are all considered to be teratogens, or substances that can disrupt the development of a fetus. These and other substances of abuse are known to affect prenatal brain development to differing degrees. The consequences associated with prenatal substance use are variable, ranging from quite severe, such as with fetal alcohol syndrome, to more subtle difficulties associated with learning, attention, and behavioral problems [64-71]. More importantly, structural brain alternations associated with in utero drug exposure may predispose these children to substance use. Adolescents with prenatal exposure are more likely to use substances and develop substance use disorders compared to their unexposed peers [72-75]. These behavioral outcomes may then lead to additional brain alterations that could further exacerbate drug use. Thirty agencies across the state report having specialized services...
for pregnant women [62]; however, as with adolescents, the nature of these services is not known and guidelines are also needed. Many pregnant women may choose not to receive services due to laws categorizing prenatal substance use as a form of child abuse, as Indiana legislates. Indiana law also requires doctors to test a pregnant patient if it is believed she is using substances. Indiana law does not currently protect pregnant women from discrimination in publicly-funded drug treatment, nor does it allow pregnant women priority access to substance use treatment [76]. To increase the likelihood that a pregnant woman receives treatment and to reduce the risks to her unborn child, policymakers could alter the laws around substance use during pregnancy so it is not considered child abuse, increase access to treatment services for substance-using women who discover they are pregnant, and ensure that these women are allowed equal access to care.

References

8. Duwve, J., et al., Report on the toll of opioid use in Indiana and Marion County. 2016, IU Richard M. Fairbanks School of Public Health at Indiana University-Purdue University Indianapolis: Indianapolis, IN.


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