

## MEETING SUMMARY

### YOUTH TOBACCO CESSATION: SCIENCE AND TREATMENT STRATEGIES

MAY 15, 2019

FDA WHITE OAK CAMPUS, BUILDING 31, SILVER SPRING, MD 20993

On May 15, 2019, the U.S. Food and Drug Administration hosted a meeting that addressed three key questions:

1. How does addiction operate in the adolescent brain – specifically with regard to nicotine – and how does that differ from addiction in adults?
2. What evidence do we have regarding the efficacy of behavioral and pharmacological cessation strategies for tobacco and/or e-cigarette addiction in adolescents – and where are the gaps in that evidence?
3. Where can FDA focus resources to help fill those evidence gaps as it works to address the e-cigarette epidemic among the nation's youth?

The significance of the meeting was underscored by the attendance of Acting FDA Commissioner Ned Sharpless, MD, and Janet Woodcock, MD, Director of FDA's Center for Drug Evaluation and Research – both of whom gave remarks that set the stage for the importance of preventing e-cigarette use among youth and finding successful strategies to treat those who are already addicted.

I-ACT for Children and the Duke Clinical Research Institute organized the meeting.

#### KEY TAKEAWAYS

- E-cigarette use among middle and high school students has increased significantly in the past several years. Between 2017 and 2018 alone, use among high school students increased 78%, from 11.7 to 20.8%— one in five students in this age group.
- There is evidence that teens who vape are more likely to start smoking cigarettes.
- There are many studies demonstrating the adverse effects of traditional tobacco products; the health effects of e-cigarettes are much less known, although they can deliver much higher levels of nicotine than combustible cigarettes.
- Many youth do not perceive a health risk associated with regular use of e-cigarettes, and teens who vape may not realize how much nicotine the brain is exposed to in a single session.
- There are limited studies on the effects of pharmacologic treatments for smoking cessation among youth populations – and those data have shown little to no benefit. No studies among youth are known to have been conducted in the U.S. to determine the efficacy of pharmacologic therapies in treating e-cigarette addiction.
- Some behavioral strategies for tobacco cessation have shown benefits, but these strategies have only begun to be applied to address e-cigarette addiction and may not be easily implemented.
- Alarmingly, youth are progressing from first trial of e-cigarettes to daily use within just a few months. For teens, there may be an increased risk of addiction with use of some vapes. Vapes can contain high levels of nicotine and may be used more

frequently because they are easier to hide. There is a need to explore the natural history of e-cigarette addiction in this age group to determine the best points in time to intervene.

- Adolescents are sensitive to stigma, which has contributed to the historical decline of combustible-cigarette smoking among youth. Because e-cigarettes are viewed positively by many youth (even seen as “cool,”) new approaches will be needed to both prevent e-cigarette use in this age group and convince current users to quit.
- Given the significant and continued rise in e-cigarette use among youth, it is critical to identify cessation therapies that will be effective against this new type of addiction.

## INTRODUCTION

According to the FDA, addressing the rise in e-cigarette use is an imperative. Data from the [2018 National Youth Tobacco Survey](#) showing a recent rise in tobacco use among youth are deeply troubling. E-cigarettes are the most commonly used tobacco product among youth. E-cigarette use among youth increases the risk that they will use combustible cigarettes.

This meeting is part of FDA’s ongoing efforts to stop the e-cigarette epidemic among youth, and follows a [public hearing](#) on January 18, 2019, where stakeholders provided an array of perspectives on the issue. It was noted that science is the best way forward. There is a need to advance the science and understand the roots of the phenomenon and what interventions may be successful in this population. In addition, we must do our best to apply those interventions quickly.

FDA noted that e-cigarettes are exposing a whole new generation of kids to nicotine and the possibility of addiction and that we cannot afford to have an entire generation of kids addicted to nicotine. FDA believes that efforts to stop the epidemic of youth e-cigarette use must start with prevention, but also must help those who are already addicted. FDA plans to finalize a compliance policy that would prioritize enforcement of the premarket authorization requirements for non-tobacco-flavored e-cigarette products, and has continued enforcement of laws that prohibit sales of e-cigarettes to minors.

FDA is accepting research proposals for pharmacologic therapies to support cessation of combustible cigarette use and e-cigarette use in youth. FDA believes that no child should be using any tobacco or nicotine-containing product and that there is a need for a broad coalition of dedicated researchers, doctors and other partners to find scientifically sound treatments to help kids overcome their addiction to nicotine.

There was further discussion of how the unique nature of e-cigarettes poses new challenges that require new prevention and cessation strategies. Current e-cigarette products allow users to customize the level of nicotine and flavor – and use nicotine salts, which lower the acidity and make the product less harsh to the throat. This allows higher levels of nicotine to be delivered more efficiently. Current e-cigarette products also are smaller than earlier versions (some look like flash drives), and do not emit the smell of combustible cigarettes, making their use easier to conceal.

Concern was expressed as marketing strategies that lead to youth smoking include youth-appealing flavors, youth-resonating themes and low prices, so there is a need for population-based intervention. Price increases, smoke-free policies, cessation treatment access and hard-hitting media campaigns are effective strategies for cessation and prevention. Everyone who plays a role with youth – from teachers to health professionals to parents -- can help.

The agency’s “The Real Cost” Youth E-Cigarette Prevention Campaign was launched in September 2018 to reach the 10.7 million youth aged 12-17 who have ever used e-cigarettes or are open to trying them. It was noted that a significant number of youth do not perceive great risk of harm in regularly using e-cigarettes, highlighting a critical need for prevention and cessation messages designed to educate youth about the harms of using e-cigarettes in adolescence. Further, the e-cigarette prevention campaign’s target audience includes youth that are popular and social, aspirational, athletic, and academically driven. This contrasts with the youth who have traditionally been at risk for using combustible cigarettes, thus there is a need for different prevention and cessation strategies, messages and channels to reach youth e-cigarette users.

“The Real Cost” E-cigarette Prevention Campaign targets youth through online advertisements, social media, and other relevant channels. The campaign achieved nearly 700 million impressions in the first 8 months, and new television ads launched in July 2019. The campaign also mailed posters to U.S. high schools, partnered with school-based programs to engage school peer leaders and collaborated with Scholastic to bring educational resources including lesson plans, infographics and scientific facts, to more than 700,000 students. Social media engagement has been positive, with nearly 400,000 likes, 41,000 shares and 23,000 comments as of May 2019.

## THE SCIENCE OF ADDICTION IN ADOLESCENTS

Teen brains are different from those of both children and adults. As children grow into adolescents, there is increased activity in the nucleus accumbens, which is important for motivation and helping to distinguish between important and unimportant rewards. The teen years lead to more activity in the pre-frontal cortex, which supports decision making. Teens are vulnerable to both drug use and addiction because they have an imbalance between the nucleus accumbens and pre-frontal cortex, which leads to sensation-seeking behaviors.

Youth are more susceptible to addictive substances because of how they respond to rewards. While young children respond equally to small and large rewards, small rewards lead to a decrease in brain activity (meaning low response to the reward) in adolescents, while the adolescent brain’s response to large rewards is high. Adolescents are particularly susceptible to addictive drugs because the drugs activate the reward pathway.

In comparing e-cigarettes to combustible cigarettes, although both deliver nicotine, they are actually very different. The amount of nicotine being used in e-cigarettes and the impact those levels of nicotine can have on the brain are problematic. Signs of nicotine toxicity, including stomach pain, dizziness, headaches and decreased concentration, are being seen. The long-term consequences of this type of nicotine toxicity are unknown.

## WHAT CAN WE LEARN FROM THE BLUEPRINT FOR ACTION?

The [National Tobacco Blueprint for Action](#) was published in 2000 by the Youth Tobacco Cessation Collaboration (YTCC) and was based on outcomes of a youth tobacco cessation conference sponsored by the CDC 20 years ago. The YTCC was active from 1998-2011 and was made up of several private and government organizations and institutes related to health.

The Blueprint for Action addressed five target audiences: the research community, policy decision makers, community practitioners and gatekeepers, the general public, and youth as a heterogeneous population. It focused on three areas: research, implementation, and support and demand.

There has been increased data collection through national and state-based surveillance of youth tobacco use, as well as improved understanding of youth tobacco experimentation, youth addiction and cessation. Although there are limited data from young adults to inform science-based tobacco use cessation, the increase in e-cigarette use in youth has prompted a renewed push to gather these data.

Progress made since the Blueprint was published include development and funding of grants and programs, multiple surveillance projects and surveys, special issues of journals addressing youth cessation, conferences, environmental scans and a Youth Cessation guide. Lessons learned since the Blueprint include the benefit of coordination and collaboration among agencies and partners and the need to focus on pressure points.

## EXPERIENCE WITH CESSATION THERAPIES IN ADOLESCENTS

### BEHAVIORAL STRATEGIES

An overview was provided of 64 studies of behavioral cessation strategies in adolescents. While the overall findings were “optimistic” (with a program advantage of about 4%), the landscape is changing fast. The review found that interventions needed at least five “contacts” (such as a counseling or other type of session) to be effective.

Text messaging has shown some effect, but has high relapse rates; interactive personal contact seems to be important, while policy strategies such as limiting retail access for teens have a weak effect and are hard to enforce. Successful program content is most likely to include motivation enhancement plus cognitive behavioral strategies, provided in a format engaging to teens. The most important factor is the need to establish trust. Information needs to be accurate. For example, attention should be given to what is said, as teens will look up statistics and instantly disengage if they find the information to be false.

Several “lessons learned” from youth tobacco-cessation literature were presented that could be applied to efforts to treat e-cigarette addiction:

- The need to increase motivation to quit.
- The need to identify windows of opportunity for quitting.
- The need to ensure that the unique cognitive and emotional needs of adolescents are considered.
- The importance of addressing interpersonal context (e.g., parents are still important as messengers).
- The opportunity in evidence to support the efficacy of some behavioral interventions.
- The promise for mobile technology delivery modes (text messaging, apps, etc.) for cessation interventions.

It was noted that there are special recruitment and retention challenges with respect to cessation-treatment research in a youth population, including the need for parent consent and logistical challenges (such as transportation to the research site). Several speakers at the meeting echoed the parental consent issue as a key hurdle, because not only do many youth keep their e-cigarette use secret from their parents, they also have increased ability to do so with e-cigarettes, given that these products do not emit an odor and are easily hidden in clothing sleeves and pockets.

Therefore, when considering interventions for youth e-cigarette use, we must consider the challenges posed by the product class. The most commonly cited reasons for e-cigarette use among youth are curiosity, good taste and low perceived harm. There are fewer perceived negative effects of e-cigarettes compared with combustible cigarettes, and the devices offer a unique appeal to teens because of the flavors, decorative packaging, and social media posts that encourage youth to do ‘tricks’ using the e-cigarettes.

In addition, the episodic nature of e-cigarette consumption affects enrollment eligibility, so adequate sample size in cessation research can be hard to obtain. Thus, researchers often need multi-site studies to reach enrollment goals.

### PHARMACOLOGIC AND OTHER THERAPIES

Few studies have been conducted among adolescents and teens to determine the efficacy of pharmacologic tobacco-cessation therapies – and none are known to have been conducted among youth to combat e-cigarette addiction.

Results from a randomized, double blind, placebo-controlled trial of varenicline (marketed under the brand name Chantix) in adolescents who smoked combustible cigarettes were shared. The study included two doses, adjusted by weight, for 12 weeks of treatment and 40 weeks of follow-up. The study included healthy adolescents ages 12-19 who were smoking an average of five cigarettes/day for the past 30 days, who exhibited evidence of nicotine addiction and motivation to stop smoking, and at least one prior quit attempt.

Unfortunately, study results showed no significant differences between youth taking the higher dose of varenicline, the lower dose, or a placebo. The study also showed a low incidence of serious adverse events. In addition, study recruitment was challenging; it took 6 years to enroll enough patients and required expansion to trial sites outside of the United States. The original plan to recruit through schools was not workable, and study participation proved demanding for both participants and their parents.

While it is not known why varenicline would show no benefit in this population when it has shown significant efficacy in adults, several factors were noted that could have contributed, including strict efficacy criteria (acknowledging smoking “even a puff” disqualified someone as being a treatment responder), even though these were the same efficacy criteria used in other trials.

Key findings from the AAP’s Adolescent Smoking Cessation in Pediatric Primary Care study were presented. This national randomized controlled trial of 11,000 adolescents assessed the primary care provider’s role in youth tobacco cessation. The study intervention was primary-care provider training on the Five Major Steps to Intervention, known as the “5As,” (Ask, Advise, Assess, Assist and Arrange) with a control arm of social media training. The study found that a teen’s level of addiction was the only significant driver of cessation in this population; more highly addicted teens were less likely to have quit smoking at 12-month follow-up.

The AAP urged FDA to use its authority to increase the study of pharmacologic cessation therapies in adolescents, including under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The AAP also encouraged the FDA to urgently fund studies that evaluate behavioral, pharmacologic and combination interventions for adolescent e-cigarette users, based on evidence from combustible cigarette cessation that can be implemented and tested in real time. Finally, the AAP noted that there is a need for FDA to fund studies into outstanding questions around adolescent e-cigarette dependence, including the specific adverse effects of nicotine dependence.

When considering the need to explore cessation strategies for e-cigarette use in youth, the use of medical devices should also be considered. There is an interest in increasing patient access to medical devices – including mobile applications – that could be effective in addressing e-cigarette addiction. The FDA encouraged early engagement with the Center for Devices and Radiological Health, as early as pre-submission to ensure that the expectations of both FDA and the device sponsor are aligned before a study begins.

## ADDRESSING THE GAPS: WHERE SHOULD CESSATION EFFORTS BE FOCUSED?

The afternoon panel discussion brought together experts in youth addiction and youth tobacco cessation to discuss how to fill the gaps in knowledge highlighted during the morning presentations. The panel included researchers who have conducted studies with adolescents as well as representatives from government agencies and advocacy groups who also have worked in areas related to youth tobacco cessation.

The role of the National Institute on Drug Abuse (NIDA) at the NIH has been to support a broad portfolio of research related to nicotine and tobacco, especially related to the variety of products that youth are using. A NIDA survey first showed signs of e-cigarette use among youth in 2014. NIDA and FDA are conducting the Population Assessment of Tobacco and Health (PATH) Study, a large-scale longitudinal study of tobacco use and health among US adults and youth (ages 12-17). The PATH Study is a major source of information, and can be used to examine myriad topics, including the risk of transitioning from e-cigarettes to combustible tobacco among youth who otherwise would be at low risk for using combustible cigarettes.

The importance of addressing peer groups, ethnic/racial minorities, and a younger age range in messaging to encourage tobacco cessation among youth was discussed, as was the importance of school-based interventions and the need to include support groups, as well as more scalable and cost-effective interventions.

Kids who are vaping and smoking cigarettes are at elevated risk for developing cannabis use disorders. The need for quitlines to be more developmentally informed for adolescents and young adults was identified.

More research in youth is needed on evidence-based interventions we already have, such as cognitive-behavioral therapy, as well as NRT and other medications for smoking cessation. Much remains unknown about successful interventions in younger populations. There is a need to better understand e-cigarette use behaviors and dependence among youth and how to educate and motivate youth to quit. The need to develop and test interventions adapted from tobacco-cessation literature was discussed. Behavioral interventions were thought to be a good first-step approach. However, a better understanding is needed of why tobacco-cessation medications seem to be similarly ineffective in youth.

The Truth Initiative recently launched a campaign aimed at e-cigarette cessation among youth. The campaign, called "[This is Quitting](#)," focuses on the use of text messaging to provide real-time support for youth and young adults. More than 16,000 teens and young adults have enrolled in This is Quitting, with 100 to 150 additional people enrolling each day. Results to date show that 73% of those enrolled have set a quit date, with 46% reporting a reduction in frequency of e-cigarette use after two weeks, and 12% to 13% reporting complete abstinence after 2 months.

Social media has been a key driver of enrollment. For example, a segment about the program on Mashable's Snapchat channel led to 17,000 youth enrolling. Program users receive an average of one text message a day – and program leaders are seeing a demand for even more support. Next steps include how to identify pressing questions about youth vaping that the program can help answer going forward, and how to identify an appropriate (rigorous and ethical) comparison condition to consider in a randomized clinical trial for the intervention.

The need to carefully examine how pharmacologic therapies for cessation in youth should be studied was discussed, especially in light of the information shared from the Chantix study. In some drug development programs, adult data can be used to extrapolate efficacy to the pediatric population if the expectation is that the disease is sufficiently similar and the medication will act similarly in the pediatric population. It is unclear whether this would be possible in the case of e-cigarette cessation drug development programs. It may be difficult to extrapolate efficacy data from adult studies when it comes to cessation therapies, as evidenced by the significant difference between varenicline's positive effects in adults and its lack of effects in youth. The use of pharmacologic interventions in youth should be reserved for products where the data support their safety and efficacy.

Key success factors for clinical trials of pharmacotherapies are recruitment and retention. The need for studies' inclusion criteria to allow for participation of youth who want to quit was discussed. Parental consent also is important, although it may be possible to secure a waiver for consent and instead require only patient assent. However, this should be considered on a case by case basis.

The panel's discussion of interventions focused on three types: Practice, Research, and Policy. Key points from the discussion were:

#### PRACTICE INTERVENTIONS

- Case studies from the research community are needed to determine what treatments have worked best for cessation of combustible cigarettes – then consider how to apply those interventions to e-cigarette cessation.
- Seek involvement of schools, student advocacy groups, and other organizations as partners in overcoming the new landscape of e-cigarette addiction. Foster programs and youth Medicaid centers also could play an important role. Given that many e-cigarette users are student athletes, youth coaches, the NCAA and other athletic groups also could be involved in intervention efforts.

#### RESEARCH INTERVENTIONS

- There is a constant need for real-time data on e-cigarette use, given how quickly the landscape and marketplace are changing.
- There is a need to understand how youth think about quitting e-cigarette use – but also what messages might convince them not to start.
- Issues unique to teen e-cigarette clinical research include the need for frequent biospecimen samples (which can be a logistical barrier for both teens and parents) and the need for parental consent (many youths may not want their parents to know about their e-cigarette use).

## POLICY INTERVENTIONS

- The restriction of e-cigarette flavors is being used as a policy tool to limit the youth attraction to e-cigarettes. But flavors also may be useful in helping adult smokers quit by offering options to adults who are using e-cigarettes as a step-down tool, so both sides of the equation must be considered with regard to policy interventions.
- Reducing nicotine levels in e-cigarettes could protect against nicotine's effects on adolescent/teen brains, but also could appeal to teens who do not like the irritating effects of nicotine.
- Price increases and clean indoor air policies also could be effective policy interventions.

## MEETING SUMMARY AND NEXT STEPS

The meeting ended with summaries from Lilun C. Murphy, MD, Director of the Division of Individual Health Science, Office of Science, at FDA's Center for Tobacco Products; Susan McCune, MD, Director of Pediatric Therapeutics, Office of the Commissioner at FDA; and Theresa Michele, MD, Director of the Division of Nonprescription Drug Products, Office of New Drugs, at FDA's Center for Drug Evaluation and Research.

It was noted that youth vaping has become an epidemic and there are concerns for potential serious adverse health impacts in youth using e-cigarettes, such as reports of seizures associated with e-cigarette use as well as other nicotine toxicity. FDA's current system for identifying these adverse events relies on voluntary reporting. However, a rapid surveillance system may have assisted in better detecting the epidemic. Education through public campaigns, such as FDA's "The Real Cost" campaign, are having an impact.

There is a critical need to understand the unique nature of e-cigarette addiction -- and how that is tied to the unique nature of the youth who are addicted. Youth smokers don't identify as addicts or have increased motivation to quit, so messaging to reach them must be tailored to those factors. In addition, there is a need to understand the interpersonal context when considering how best to address e-cigarette addiction, including the cognitive and emotional needs of adolescents.

Science is the best way forward and to get to a good scientific result, the right questions must be addressed. It is key to know what the harms are and what the safety is with e-cigarette products, as it is difficult to reach youth who are addicted to e-cigarettes with effective messages if the full extent of the harm is not yet known.