On May 15, 2019, the U.S. Food and Drug Administration (FDA) 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 (CDER) – 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.

The Institute for Advanced Clinical Trials (I-ACT) for Children and the Duke Clinical Research Institute (DCRI) 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 e-cigarette use among youth has led to increase in the use of combustible cigarettes in this population.

- The adverse effects of tobacco are well known; the health effects of e-cigarettes are less well known, although they can deliver much higher levels of nicotine than combustible cigarettes.

- A key barrier to e-cigarette cessation among youth is that they do not perceive e-cigarettes as a health risk, and many do not realize that e-cigarettes contain nicotine.
There are only limited data on the effects of pharmacologic treatments for tobacco 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 (e.g. social influence-oriented, cognitive-behavioral and motivation enhancement) for tobacco cessation have shown benefits, but these strategies have only begun to be applied to address e-cigarette addiction.

Alarmingly, youth are progressing from first trial of e-cigarettes to daily use within just a few months. 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

Addressing the rise in e-cigarette use is an imperative for the FDA, according to Dr. Woodcock. Data from the 2018 Tobacco Use Survey showing a recent rise in tobacco use among youth are deeply troubling, and e-cigarettes are the most popular form of tobacco use among youth. E-cigarette use among youth also increases the risk that they will use combustible cigarettes, according to Dr. Woodcock.

This meeting is part of FDA’s ongoing efforts to reverse the rise of the e-cigarette epidemic among youth, and follows a public hearing on Jan 18, 2019, where stakeholders provided an array of perspectives on the issue. “Science is our best way forward, but we need to advance the science and understand the roots of this phenomenon -- and understand what interventions may be successful in this population,” Dr. Woodcock said. Then “we must do our best to apply those very quickly.”

During his remarks, Dr. Sharpless warned “these products are exposing a whole new generation of kids to nicotine and the possibility of addiction. We cannot afford to have an entire generation of kids addicted to nicotine.”

Dr. Sharpless noted that FDA efforts to stop the epidemic of youth e-cigarette use must start with prevention, but also must help those who are already addicted. The FDA has proposed the restriction of sales of flavors other than menthol to help tackle this problem, and has continued enforcement of laws that prohibit sales of e-cigarettes to minors.

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

Brian King, PhD, MPH, Deputy Director for Research Translation, Office on Smoking and Health at the U.S. Centers for Disease Control and Prevention (CDC), discussed 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, Dr. King said. 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.

“We know marketing strategies that lead to youth smoking include youth-appealing flavors, youth-resonating themes and low prices, so we need a population-based intervention,” Dr. King said. “Price increases, smoke-free policies, cessation 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.”

Kathleen Crosby, MPH, Director of the Office of Health Communication and Education at the FDA’s Center for Tobacco Products, described the agency’s current campaign, “The Real Cost,” launched in September 2018 and aimed at educating youth about the dangers of e-cigarette use. According to Crosby, as many as 80% of youth don’t perceive e-cigarettes as harmful, so there is a much larger target audience for prevention and cessation messages than the audience for similar messages for traditional cigarettes. Young people who use e-cigarettes also are popular and social, aspirational, athletic, and academically driven – in contrast to youth who have historically taken up use of combustible cigarettes – creating a need for different prevention and cessation strategies, messages and channels, Crosby said.

“The Real Cost” 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 are planned for airing throughout the summer. The campaign also mailed posters to 37,000 U.S. high schools, partnered with school-based programs to engage school peer leaders and collaborated with Scholastic to bring 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 to date.

THE SCIENCE OF ADDICTION IN ADOLESCENTS

Teen brains are different from those of both children and adults. Sharon Levy, MD, Director of the Adolescent Substance Use and Addiction Program at Boston Children’s Hospital, explained that 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, Dr. Levy explained. 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.

“We have been comparing e-cigarettes to [combustible] cigarettes because both deliver nicotine, but they are actually very different,” Dr. Levy said. The biggest problem is the amount of nicotine being used in e-cigarettes and the impact those levels of nicotine can have on the brain, she added, saying that “we are seeing signs of nicotine toxicity, including stomach pain, dizziness, headaches and decreased concentration.” The long-term consequences of this type of nicotine toxicity are unknown, according to Dr. Levy.

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 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 good movement in increasing national and state-based surveillance of youth tobacco use,” said Allison Hoffman, PhD, Associate Director of Health Science in the Office of the Commissioner at FDA. “There has been medium progress on increasing our understanding of youth tobacco experimentation, youth addiction and cessation.” She added that there are limited data from young adults to inform science-based tobacco use cessation, although 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

Steven Sussman, PhD, Professor of Preventive Medicine and Psychology at the University of Southern California’s Keck School of Medicine, provided an overview 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 faster than we can study,” Dr. Sussman said. 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, he said, 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,” Dr. Sussman said. “Information needs to be accurate and we need to be careful what we say, as teens will look up statistics and instantly disengage if they find the information to be false.”

Rachel Grana Mayne, PhD, MPH, Program Director in the Tobacco Control and Research Branch within the Behavioral Research Program of the Division of Cancer Control and Population Sciences at the National Cancer Institute, described several “lessons learned” from youth tobacco-cessation literature 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 potential efficacy of behavioral interventions to get youth to quit.
- The promise for mobile technology delivery modes (text messaging, apps, etc.) for cessation interventions.

Dr. Grana Mayne also noted 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.

“When considering interventions for youth e-cigarette use, we must consider the challenges posed by the product class,” Dr. Grana Mayne said. “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, skins [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, Dr. Grana Mayne said. 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.

Thomas McRae, MD, Global Clinical Lead at Pfizer, shared results from a randomized, double blind, placebo-controlled trial of varenicline (marketed under the brand name Chantix) in adolescents who smoked combustible cigarettes. 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, Dr. McRae reported. The study also showed a low incidence of serious adverse events. Dr. McRae noted that 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, Dr. McRae said.

While it is not known why varenicline would show no benefit in this population when it has shown efficacy in adults, Dr. McRae did note several factors that could have contributed to his results, including strict efficacy criteria (acknowledging smoking “even a puff” disqualified someone as being a treatment responder).

Susanne Tanski, MD, Associate Professor of Pediatrics at Dartmouth Geisel School of Medicine, represented the American Academy of Pediatrics (AAP) at the meeting. She cited key findings from the AAP’s Adolescent Smoking Cessation in Pediatric Primary Care study, a national randomized controlled trial of 11,000 adolescents that 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 urges FDA to use its authority to increase the study of pharmacologic cessation therapies in adolescents, Dr. Tanski said, including under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The AAP also encourages 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. Dr. Tanski also cited the 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, according to Carlos Peña, PhD, MS, Director, of the FDA's Office of Neurological and Physical Medicine Devices. Dr. Peña reminded attendees of his division’s interest in increasing patient access to medical devices – including mobile applications – that could be effective in addressing e-cigarette addiction. “The best way to begin an engagement with us is pre-submission,” Dr. Peña said, adding that this helps 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?**

CDC’s Dr. Brian King moderated the afternoon panel discussion, which 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.

Dr. Wilson Compton, MD, MPE, Deputy Director of the National Institute on Drug Abuse (NIDA) shared that NIDA’s role has been to support a broad portfolio of research related to nicotine and tobacco, especially related to the multiplicity of what youth are using. He noted that a NIDA survey first showed signs of e-cigarette use among youth in 2014. The National Institutes of Health, FDA and CDC also 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,” Dr. Compton said, noting that “the risk of transitioning from e-cigarettes to combustible tobacco may be particularly acute” among youth who otherwise would be at low risk for using combustible cigarettes.

It is important that messaging to encourage tobacco cessation among youth address peer groups, ethnic/racial minorities, and a younger age range, said Paula Riggs, MD, Professor and Director of the Division of Substance Dependence in the Department of Psychiatry at the University of Colorado School of Medicine. She discussed 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; this is particularly a problem in Colorado,” Dr. Riggs said. She added that quitlines
should be more developmentally informed for adolescents and young adults. Dr. Riggs also stressed that “we need more research [in youth] on [the] evidence-based interventions we already have, such as cognitive-behavioral therapy,” as well as NRT and other medications for smoking cessation.

Suchitra Krishnan-Sarin, PhD, Professor of Psychiatry at Yale University, said the main thing to understand is that much remains unknown about successful interventions in younger populations. “We need to better understand e-cigarette use behaviors and dependence among youth and how to educate and motivate youth to quit,” Dr. Krishnan-Sarin said. She discussed the need to develop and test interventions adapted from tobacco-cessation literature and noted that behavioral interventions are a good first-step approach. Dr. Krishnan-Sarin added that 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. Amanda Graham, PhD, Senior Vice President of Innovations at the Truth Initiative, said that 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, Dr. Graham said. 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. “Our next steps include how we 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,” Dr. Graham said.

John Alexander, MD, MPH, Deputy Director of FDA’s Division of Pediatric and Maternal Health in the Center for Drug Evaluation and Research, discussed the need to carefully examine how pharmacologic therapies for cessation in youth should be studied. “Drug treatment for youth tobacco cessation looks pretty dismal based on information shared from the Chantix study, and we don’t want to jump into pharmacologic intervention if we are uncertain it will be effective,” Dr. Alexander said. He added that although adult data can be extrapolated in some cases if the expectation is that a medication will act similarly in a pediatric population, it is unclear whether this would be possible in the case of e-cigarette cessation studies.

Celia Winchell, MD, Medical Team Leader for Addiction Products, Division of Anesthesia, Analgesia and Addiction Products at the FDA’s Center for Drug Evaluation and Research, added that it may be difficult to extrapolate data from adult studies when it comes to cessation therapies, noting the significant difference between varenicline’s positive effects in adults and its lack of effects in youth. “We need to be considerate of giving kids pharmacologic interventions if they don't need it,” Dr. Winchell said.

Cathy Backinger, PhD, MPH, Senior Science Advisor for the Office of Science at FDA’s Center for Tobacco Products, said that key success factors for clinical trials of pharmacotherapies are recruitment and retention. “If kids want to quit, get them in the study instead of using strict
inclusion criteria,” Dr. Backinger said. Parental consent also is important, she said, although she added that it may be possible to secure a waiver for consent and instead require only patient assent.

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 apply those interventions to e-cigarette cessation.
- Seek involvement of schools, student advocacy groups, and other organizations as partners in 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 should 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 research include the need for frequent blood 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 attraction to e-cigarettes. But flavors also can be useful in helping smokers quit by offering options to those 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 policies also could be effective policy interventions.

**MEETING SUMMARY AND NEXT STEPS**

The meeting ended with summaries from Iilun C. Murphy, MD, Director of the Division of Individual Health Science, Office of Science, at FDA’s Center for Tobacco Products; Susan McCune, MD, MPH, Director of the Office 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.

“Youth vaping has become an epidemic,” Dr. Murphy said, citing reports of seizures caused by e-cigarette use as well as nicotine toxicity in youth. FDA’s current system for identifying these
adverse events relies on voluntary reporting, Dr. Murphy said, adding that “a rapid surveillance system may have assisted us in destroying the epidemic.” She also suggested that education through public campaigns, such as FDA’s The Real Cost campaign, are having an impact.

Dr. McCune noted the 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 are really different,” Dr. McCune said. “They don’t identify as addicts or have increased motivation to quit, so messaging to reach them must be tailored to those factors.” Dr. McCune added that 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.

Dr. Michele said that science is the best way forward and to get to a good scientific result, we must ask the right questions. “We stand on the strength of our basic science in clinical trials. We really need to know what the harms are and what the safety is with e-cigarette products,” Dr. Michele said, explaining that 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.