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Review

Research on Youth and Young Adult Tobacco Use, 2013–2018, From the Food and Drug Administration–National Institutes of Health Tobacco Centers of Regulatory Science

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Abstract

The Tobacco Regulatory Science Program is a collaborative research effort between the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). In 2013, the NIH funded 14 Tobacco Centers of Regulatory Science (TCORS), which serve as partners in establishing research, training, and professional development programs to guide FDA. Each of the fourteen TCORS, and two other NIH-funded research programs, the Center for the Evaluation of Nicotine in Cigarettes (CENIC) and the Consortium on Methods Evaluating Tobacco (COMET), pursued specific research themes relevant to FDA's priorities. A key mandate for FDA is to reduce tobacco use among young people. This article is a review of the peer-reviewed research, including published and in-press manuscripts, from the TCORS, CENIC, and COMET, which provides specific data or other findings on youth (ages 10–18 years) and/or young adults (ages 18–34 years), from 2013 to 2018. Citations of all TCORS, CENIC, and COMET articles from September 2013 to December 2017 were collected by the TCORS coordinating center, the Center for Evaluation and Coordination of Training and Research. Additional citations up to April 30, 2018 were requested from the principal investigators. A scoring rubric was developed and implemented to assess study type, primary theme, and FDA priority area addressed by each article. The major subareas and findings from each priority area are presented. There were 766 articles in total, with 258 (34%) focusing on youth and/or young adults. Findings relevant to FDA from this review concern impact analysis, toxicity, health effects, addiction, marketing influences, communications, and behavior.

Implications: The Tobacco Centers of Regulatory Science, CENIC, and COMET have had a high output of scientific articles since 2013. These Centers are unique in that the FDA supports science specifically to guide future regulatory actions. The 258 articles that have focused on youth and/or young adults are providing data for regulatory actions by the FDA related to the key priority areas

such as the addictiveness of non-cigarette products, the effects of exposure to electronic cigarette marketing on initiation and cessation, and the impact of flavored products on youth and young adult tobacco use. Future regulations to reduce tobacco use will be guided by the cumulative evidence. These Centers are one innovative mechanism to promote important outcomes to advance tobacco regulatory science.

Introduction

There is strong evidence that preventing the onset of tobacco use is the most effective approach to reducing the long-term population-wide prevalence of use. The 1994 and 2012 Surgeon General's Reports both noted that nearly all cigarette smoking (99%) begins by age 25 years. Thus, if youth and young adults can remain non-users, they are not likely to initiate use and become addicted to smoking. These conclusions come from ongoing national epidemiological data.^{1,2} However, the same conclusions were found in the tobacco industry's own documents: "Today's teenager is tomorrow's potential regular customer, and the overwhelming majority of smokers first begin to smoke while in their teens."^{3,4}

A key mandate of the Family Smoking Prevention and Tobacco Control Act (TCA) of 2009 is to reduce youth tobacco use.⁵ The TCA gave the Food and Drug Administration (FDA) the authority to regulate the manufacturing, distribution, and marketing of tobacco products. These products initially included cigarettes, smokeless tobacco products, and roll-your-own tobacco, but the FDA's authority was expanded to all tobacco products, including cigars, hookah/water pipe tobacco, and electronic cigarettes (e-cigarettes), via deeming in 2016.

The Tobacco Regulatory Science Program was established as a collaborative research effort between the National Institutes of Health (NIH) and the FDA. The intent of Tobacco Regulatory Science Program is to foster cutting-edge research through the Institutes and Centers at NIH; this research is intended to be timely and relevant to support the FDA's regulatory authority and mandate over time.⁶ In 2012, the NIH issued a call for proposals for Tobacco Centers of Regulatory Science (TCORS), which would serve as partners in establishing research, training, and professional development programs that would provide important data and trained professionals to help guide FDA. In 2016, the original FDA priorities were subsumed under seven primary priority research areas: impact analysis, toxicity, health effects, addiction, marketing influences, communications, and behavior. In 2013, 14 TCORS were funded via the NIH-FDA collaboration to establish centers primarily focusing on FDA research priorities. These TCORS were funded from 2013 to 2018 (TCORS 1.0).

Each of the fourteen TCORS, and two other NIH-funded research programs, the Center for the Evaluation of Nicotine in Cigarettes (CENIC) and the Consortium on Methods Evaluating Tobacco (COMET), pursued specific research themes relevant to the FDA. Despite differences in overall themes of each Center, all produced some research important to the understanding of youth and young adult tobacco use and the seven key priority areas noted earlier. This article is a review of that research, including published and in-press manuscripts, which provides specific data or other findings on youth (ages 10–18 years) and/or young adults (ages 18–34 years), from 2013 to 2018. This review provides substantive insights into the current research originating from the TCORS program, CENIC, and COMET, relevant to these age groups that should be of importance to the FDA's regulation of tobacco products that may affect young people.

Methods

Citations of all TCORS, CENIC, and COMET (referred to as "Centers") peer-reviewed (accepted or in-press) articles from September 1, 2013 to December 31, 2017 were collected by the TCORS coordinating center, the Center for Evaluation and Coordination of Training and Research. These articles were organized on a spreadsheet by Center. However, some articles included authors from two or more Centers, so these overlapping articles were counted as one article in the review. We then wrote to the principal investigators of each of the 16 Centers in May 2018 to obtain any additional articles from their Center that were published or in press up to April 30, 2018. We asked for articles relevant to youth and/or young adult tobacco use for these additional articles. We allowed the principal investigators until July 2018 to respond to this request and received responses from the Centers. A total of 766 articles were collected after duplicates were removed. Abstracts and copies of all articles were obtained for review and were made available to the writing team.

A scoring rubric was developed to determine eligibility and study attributes for the current review article, and each coauthor coded articles from at least two of the sixteen Centers. The rubric considered whether each article was peer-reviewed, focused on youth and/or young adults, data source, type of study, primary theme, and FDA priority area addressed. Note that the articles in this review needed to focus on data specifically relevant to youth (10–18 years) or young adults (18–34 years). If a larger age range, such as adulthood, was considered, then data had to be presented separately for one/both of these age groups. In addition, if the article focused on young adults, the age range had to include those <25, as our preference was to consider the younger side of the young adult spectrum.

The rubric that was developed included providing yes/no answers to each of the following questions for each article. The first four questions determined eligibility for our review. Eligible articles were required to be peer-reviewed and focus on, or be relevant to, youth and/or young adult tobacco use. The other questions provided information on study attributes.

1. Is the article peer-reviewed?
2. Does the article focus on/or separately analyze data on youth (eg, ages 10–18)?
3. Does the article focus on and/or separately analyze data on young adults (eg, ages 18–34)?
4. Is the article specifically relevant to youth or young adult tobacco use (eg, marketing and communication)?
5. Is the data source partially attributed to a Center generated study (eg, main study and pilot study)?
6. Is the data source from a national data set (eg, on-going youth surveillance, such as Monitoring the Future)?
7. Is the study type (yes/no for each): (1) qualitative, (2) cross-sectional, (3) longitudinal, (4) experimental, (5) observational, (6) systematic review or meta-analyses, (7) other?
8. Does the primary theme include (yes/no for each): (1) prevalence of use, (2) trajectories of use, (3) transitions in use, (4) specific

tobacco product use, (5) dual/poly use, (6) psychosocial risk factors, (7) marketing-related factors, (8) social media factors, (9) communication or communicating risks, (10) sociodemographic factors, (11) toxicity, (12) health effects, (13) addiction, (14) other?

9. Is FDA priority research area addressed directly (yes/no for each): (1) impact analysis, (2) toxicity, (3) health effects, (4) addiction, (5) marketing influences, (6) communications, (7) behavior?

After initial coding, the articles were recoded by another investigator or graduate student to ensure reliable coding. There were 258 youth and young adult peer-reviewed articles (after removing duplicates). Of all 258 articles, 141 primarily focused on youth, 128 primarily focused on young adults, and 156 additional articles were relevant to youth or young adult tobacco use. Articles within each priority research area were further reviewed for subareas (as discussed next within each area), as this division of the articles by priority areas was considered by the group to be most important for the FDA's current regulatory needs. Each member of the writing team reviewed the articles from one of the seven research priority areas. The primary foci and outcomes of these articles by priority research area are summarized next. Articles for each priority area are not mutually exclusive—some articles could be in more than one priority area. Group review of each priority area, subareas, and potential overlap of priority areas was done via group conference calls and e-mail.

Results

Of the 258 articles relevant to youth and/or young adults, 132 articles came from Center-generated data and 45 from national datasets; additional articles included reviews or analyses of data from other datasets. As seen in [Table 1](#), the majority of articles were cross-sectional ($n = 146$) or observational ($n = 141$). Further, most articles examined prevalence of tobacco use ($n = 144$) or specific tobacco product use ($n = 177$). There were at least 18 articles addressing each of the FDA priority areas: impact analysis ($n = 18$),⁷⁻²⁴ toxicity ($n = 22$),^{17,25-45} health effects ($n = 33$),^{25-27,32-40,43,45-64} addiction ($n = 45$),^{10,15,22,25,27,32-34,36-39,41,45,48,50,54-56,58,60,64-87} marketing influences ($n = 53$),^{8,9,15,17,20,21,25,29,36,39,45,48,53,55,63,64,71-73,86,88-120} communications ($n = 62$),^{7-9,14,18,19,25,29-34,36-38,49-51,54,55,64,69,71-73,92,95,97,99,102-107,115,116,120-143} and behavior ($n = 206$).^{7-12,14-22,24,25,27-40,43,45,48-51,53-65,68-81,85,87,91,93-99,101-108,110,111,113,114,117-121,123,124,127,130,131,133-135,138-140,143-171,173-243} These are further discussed next. Each section describes articles within predominant subareas, with two or more articles supporting that subarea, within each priority area. The major findings from each priority area are shown in [Table 2](#).

Impact Analysis

Eighteen articles focused on impact analyses.⁷⁻²⁴ Several studies examined the impacts of anti-smoking campaigns, including the FDA's "The Real Cost" campaign, on smoking-related beliefs and how to improve campaign effectiveness. For adolescents aged 13–17 years, one article demonstrated that those who recalled specific ads in the campaign subsequently endorsed the beliefs presented in those specific ads. The beliefs included smoking's impact on teeth, wrinkles, and loss of control, suggesting how the "The Real Cost" campaign was effective.¹⁴ Another study tested the ability of health messages to reduce the social acceptability of peer smoking on YouTube and shows that exposure to such videos with a message about the mortality risk to those smokers increased beliefs about

Table 1. Primary Classification of Youth and Young Adult Studies From TCORS 1.0, CENIC and COMET (September 2013–April 2018), by Study Type, Primary Theme, and FDA Priority^a

Classification	No. of studies ($n = 258$)
Study type	
Systematic Review or Meta-Analysis	15
Longitudinal	46
Experimental	46
Qualitative	79
Observational	141
Primary themes included	
Social media	18
Toxicity	22
Health effects	34
Other	34
Addiction	39
Transitions in use	42
Marketing	59
Trajectories of use	60
Dual/poly use	63
Communications	73
Psychosocial risk factors	89
Sociodemographic factors	124
Prevalence of tobacco use	144
Specific tobacco product use	177
FDA priorities directly addressed	
Impact analysis	18
Toxicity	22
Health effects	33
Addiction	45
Marketing influences	53
Communications	62
Behavior	206

CENIC = Center for the Evaluation of Nicotine in Cigarettes; COMET = Consortium on Methods Evaluating Tobacco; FDA = Food and Drug Administration; TCORS = Tobacco Centers of Regulatory Science.

^aClassifications of articles in each category are not mutually exclusive.

smoking's adverse health outcomes and negative attitudes toward smoking by adolescents.¹⁸

Six studies analyzed the effects of existing and potential regulations on youth tobacco use.^{12,13,16,19-21} For example, one study¹² examined the consequences of the 2009 flavored cigarette ban among youth, showing reductions in smoking prevalence and cigarette consumption among youth. However, the ban was also positively associated with increased use of menthol cigarettes, cigars, and pipes among adolescents. Two additional studies^{20,21} assessed the associations between point-of-sale ad bans and youth smoking and found that those bans were associated with lower odds of ever smoking, smoking prevalence, and daily smoking among youth.

National Youth Tobacco Survey¹³ analyses found that e-cigarette minimum legal sale age laws were associated with lowered cigarette smoking among adolescents, but this association became nonsignificant after adjusting for covariates. In addition, state e-cigarette minimum legal sale age laws did not affect youth cigarette smoking. With regard to school policies, students attending schools that had an e-cigarette policy, compared to those who attended schools that did not, have lower odds of ever e-cigarette use, susceptibility to use e-cigarettes, and perceived peer use of e-cigarettes.¹⁶ A discrete choice experiment¹⁹ examined the effects of e-cigarette attributes, including warning messages on youth preference on

Table 2. Main Findings on Youth and Young Adults from TCORS 1.0, CENIC, and COMET (September 2013–April 2018) by FDA Priority Area

Impact analysis

- Anti-smoking campaigns are associated with the endorsement of campaign-targeted beliefs, reduced social acceptability of peer smoking, and negative attitudes toward smoking.
- Bans on flavored cigarettes (other than menthol) and point-of-sale cigarette advertising are associated with decreased cigarette smoking.
- Electronic cigarette (e-cigarette) policies regulating characterizing flavors, warning messages, minimum age sales laws, and school-level e-cigarette policies are associated with decreased e-cigarette use.

Toxicity

- Common user behaviors can alter toxicant exposures (eg, product modification and using in groups).
- Youth and young adults are often uncertain or hold misperceptions regarding tobacco product constituents—a knowledge gap communication campaigns should address.
- Most tobacco constituents are perceived unfavorably; communication about specific toxicants could discourage tobacco use.

Health effects

- Long-term health effects of new and emerging products are relatively unknown for adolescent and young adult users.
- Mental health disorders and chronic bronchitis symptoms were more prevalent among e-cigarette users.
- Adolescents desire to understand what the constituents are in products and the health effects of individual constituents; yet most adolescents believe tobacco products, including e-cigarettes, to be harmful.

Addiction

- Product characteristics play an important role in initiation of, and addiction to, combustible and non-combustible tobacco products.
- Flavored tobacco products increase appeal and decrease perceptions of harm and addictiveness.
- Use of non-cigarette tobacco products is associated with nicotine dependence.

Marketing influences

- Adolescents' recall of e-cigarette and cigar ads, at the point of sale or online, is associated with increased risk of subsequent tobacco product use.
- Young adults who recall e-cigarette marketing displays at the point-of-sale report lower odds of cigarette smoking cessation six months later.
- Youth/young adults who view e-cigarette ads have positive beliefs about e-cigarettes, and lower perceived risk of combustible cigarettes.

Communication

- Tobacco product warnings that are graphic (vs. text), elicit greater negative emotion, and are a larger size, are more likely to be effective with youth. These findings can be used to revise mandated cigarette warnings and strengthen warnings for non-cigarette tobacco products.
- Promising themes for health communications directed at youth and young adults include those focused on expression of independence, acute and cosmetic health effects, social stigma, industry practices, and constituent-based messages.

Behavior

- E-cigarette use leads to future cigarette use.
- Youth and young adults disproportionately use flavored products and find flavors appealing; these data support a ban on all characterizing flavors in tobacco products.
- Online and retail environments are key points of access for new and emerging products for youth; these studies support the Food and Drug Administration's Youth Prevention Plan to target retailers illegally selling products to minors.

e-cigarettes and found that warning messages reduce the probability of choosing e-cigarettes among youth never users of e-cigarettes.

Further, although these articles, published by the Centers, evaluate the associations of existing or potential regulatory policies with youth tobacco use behaviors, none of the articles address the cost-benefit analysis or the regulatory impact analysis requested by the executive orders.²⁴⁴ In summary, the literature on the policy impacts on tobacco use behaviors among youth and young adults is sparse and how tobacco use behaviors among this population should be factored into the regulatory impact analysis needs further investigation.

Tobacco Product Toxicity

Of the 22 identified articles,^{17,25–45} 17 specifically discussed toxicity concerns regarding rising youth and young adult use of new and emerging tobacco products, including e-cigarettes⁴⁵ and hookah/water pipe.⁴³ The primary subareas that are summarized for this review were exposure to harmful substances ($n = 3$),^{41,42,44} cross-sectional surveys on toxicity perceptions ($n = 3$),^{29–31} and focus groups on tobacco constituents ($n = 2$).^{32,38}

Few studies ($n = 3$) assessed biomarkers of exposure to harmful or potentially harmful constituents in samples restricted to young adults, although two studies connected the manner of use to toxicant exposures. Blank *et al.*⁴¹ assessed the impact of “hying” a Black &

Mild cigarillo (removing the inner tobacco binder) among 20 predominantly male, non-Hispanic black young adults. The authors reported no difference in nicotine intake, topography, or subjective effects but found lower CO exposure under the hying condition.⁴¹ Ramôa *et al.*⁴² observed young adults under assigned sessions of hookah/water pipe smoking alone or in pairs, finding that as a dyad, individuals took more puffs but had lower expired CO concentrations, whereas the smoke produced contained higher concentrations of butyraldehyde, anthracene, tar, and other toxicants. Elsewhere, plasma menthol glucuronide showed promise as a biomarker of acute inhaled menthol exposure.⁴⁴

In addition to toxicant exposures, Center investigators measured toxicity-related perceptions, aiming to inform communication about tobacco constituents. In focus groups, adolescents and young adults expressed lack of awareness but desire to know more about constituents in novel tobacco products, as well as health concerns regarding both familiar (eg, arsenic) and less familiar (eg, *N*-nitrosornicotine) chemicals.³⁸ For novel products, such as hookah/water pipe tobacco, perceived lower health risks were related to being “pure” and with fewer additives relative to cigarettes.³² In a national telephone survey of adolescents, nicotine was the most familiar chemical in cigarette smoke, but formaldehyde, ammonia, and lead were the constituents viewed as most likely to discourage smoking.³¹ Nearly as many adolescents believed manufacturers add most constituents in cigarette smoke as correctly believed that most constituents derive from

combustion.³¹ In another national telephone survey, young adults were more likely than older adults to seek information about cigarette or cigarette smoke constituents, although only 37% reported that they had.³⁰ Pooling adolescents and young adults from both surveys, constituents in cigarillo and hookah/water pipe tobacco smoke were found to be more “worrisome” than cosmetic effects (eg, wrinkles), particularly among tobacco users.²⁹

In summary, few publications have focused on tobacco product toxicity specifically among youth or young adults, representing a research gap for future investigations. Youth and young adults generally perceive specific tobacco product and smoke constituents unfavorably, which could serve as a point of emphasis in tobacco prevention communication.

Health Effects

Ten articles directly discussed health effects in the context of youth and young adults.^{32,35,38,40,49,53,55,56,59,60} Given the young age range of participants in the reviewed studies, no studies examined long-term health and disease consequences of tobacco product use. In addition, none of the studies compared health effects between adolescents and young adults. Subsequently, the Centers’ research on health effects of tobacco product use included studies on adolescents and/or young adults, focused on one or more of the following: (1) immediate and short-term physiological and mental health consequences of use ($n = 3$)^{40,59,60}; (2) perceptions and beliefs about health effects of use ($n = 5$)^{32,38,53,55,56}; and/or (3) discussion about implications of study findings for health effects ($n = 2$).^{35,49}

Studies examining physiological or psychological consequences were all in adolescent populations. Mental health problems of depression, panic disorders, and internalizing behavior were more prevalent among e-cigarette users compared to conventional cigarette users.^{59,60} One article revealed that adolescent e-cigarette users had increased rates of chronic bronchitis symptoms, but more investigation is needed to determine long-term effects.⁴⁰ These studies provide important information on potential short-term health effects, particularly focusing on adolescents.

Among the five articles specifically examining perceptions or beliefs about health effects, all included an adolescent sample and three included young adults. The research methods regarding perceptions were not consistent between studies. Three of the articles used qualitative data. Wiseman *et al.*³⁸ focused on perceptions and knowledge of constituents in e-cigarettes among youth and young adults; participants wanted to know more about health effects of individual constituents. Wagoner *et al.*⁵⁵ examined e-cigarette use and perceptions in youth and young adults. E-cigarettes were perceived as having fewer risks than cigarettes, and specifically that vapor is not at all harmful. Not knowing what is in e-cigarettes was concerning to participants. Cornacchione *et al.*³² examined perceptions of cigar products and hookah/water pipe tobacco in youth and young adults. All participants brought up health effects regarding hookah/water pipe tobacco and cigar products. Because these products are used infrequently, long-term health effects were not a big concern for participants. The remaining articles used quantitative data, one in an adolescent sample in California⁵⁶ and one in an adolescent North Carolina sample.⁵³ Barrington-Trimis *et al.*⁵⁶ found that most students believed both cigarettes and e-cigarettes are harmful to one’s health. Among e-cigarette users, nearly 50% believed they were not harmful. In Kowitz *et al.*⁵³ 90% of all students believed breathing someone else’s smoke was harmful and 86% agreed or strongly agreed that all tobacco products were harmful. Greater use by a participant was associated with disagreeing that tobacco products are harmful, including secondhand smoke.

The remaining two articles included adult participants.^{35,49} Mendel *et al.*³⁵ examined if adults switch brands to reduce health risks. Older adults were more likely to have switched brands to reduce health risks than young adults. Participants reported switching after learning about specific constituents in one brand. Francis *et al.*⁴⁹ used an experimental design to determine believability of messages in new diseases linked to cigarette smoking in the 2014 Surgeon General’s Report. Approximately 56% of young adults found messages about new diseases associated with smoking to be very believable. There were no differences between older and young adults in believability of messages.

Addiction

The Centers’ research on addiction included 45 articles, with specific foci including perceptions and correlates of nicotine addiction/dependence, and the potential to become addicted as a theme in tobacco prevention. Other related topics are also discussed next.

Four qualitative studies^{11,32,38,55} and two quantitative studies^{77,79} examined perceptions of nicotine addiction in cigarettes, e-cigarettes, hookah/water pipe tobacco, and little cigars/cigarillos. Study findings suggested that tobacco users and nonusers were aware that nicotine was addictive.^{11,32,38} Nonusers, relative to users, were more likely to report addiction as a negative attribute.^{32,38,55,77,79} Youth also perceived that non-cigarette tobacco products were less addictive than cigarettes.^{10,32,79} Studies that specifically focused on perceptions of addiction in e-cigarettes found that (1) perceptions of low nicotine addiction were positively associated with e-cigarette initiation and current use⁷⁷; (2) different e-cigarette devices were associated with different perceived levels of nicotine dependence⁵⁵; and (3) perceptions of low addiction of flavored e-cigarettes were associated with e-cigarette use.⁷⁷

Five quantitative studies,^{76,80,81,245,246} one ecological momentary assessment study,⁷⁵ and one qualitative study⁸⁴ examined correlates of nicotine dependence. Nicotine dependence was measured for cigarettes, e-cigarettes, and hookah/water pipe using modified versions or select items of various nicotine dependence measures (eg, Hooked on Nicotine Checklist).²⁴⁷ The findings showed that greater nicotine dependence was associated with greater tobacco use,¹⁴⁴ difficulties in quitting,⁷⁶ multiple tobacco products use^{76,80} including use of marijuana,²⁴⁶ and greater likelihood of belittling health warning labels.⁵⁴

Two studies using telephone surveys examined reactions to addiction themes used in tobacco prevention. One study found that adolescents were more likely to recall ads in “The Real Cost” campaigns that emphasized themes of physical appearance than loss of control because of addiction.⁷² Another study that examined believability of various themes used in cigarette health warning showed that adolescents believed that cigarettes were addictive and that nicotine was an addictive chemical.³⁴ However, adolescents did not find believable the warnings that menthol cigarettes were more addictive than non-menthol cigarettes.

Three additional themes related to addiction included (1) nicotine dependence being a reason for tobacco use,¹⁵ (2) young adults having reduced smoking satisfaction and psychological reward from low-nicotine-content cigarettes,⁶⁵ and (3) activation of neural cue reactivity in response to sweet/fruit-flavored e-cigarette advertisements.⁸⁶ One study on cessation observed that e-cigarette use was associated with poor smoking cessation outcomes.¹⁷³

Marketing Influences

The Centers’ research publications on tobacco product marketing included 53 articles that primarily focused on: (1) descriptions of

marketing techniques that attract youth and young adults, (2) associations between tobacco marketing exposure and tobacco use, and (3) associations between tobacco marketing bans and tobacco use.

Content analyses of tobacco product marketing messages have identified features that could appeal to youth/young adults. These include cartoons, animation, references to video games, product placement in music videos, and themes of happiness, friendship, sex, and success.^{100,103,248} Youth/young adults have self-reported that they prefer descriptions of flavors, price promotions, branding, and marketing claims such as “natural,” for cigars¹²⁰; attractive packaging, time-limited promotional offers, and social acceptance and entertainment themes for smokeless tobacco products^{88,91}; and sex appeal themes for e-cigarettes.⁸⁸ An experimental *functional magnetic resonance imaging* study⁸⁶ found that sweet/fruit-flavored e-cigarette ads produced more nucleus accumbens activity, a brain biomarker of product preference, among youth/young adults than tobacco-flavored e-cigarette ads.

Center studies examined associations between tobacco marketing exposure and tobacco use among youth/young adults, using cross-sectional, longitudinal, and experimental designs. In cross-sectional analyses of the Population Assessment of Tobacco and Health Wave 1 survey,¹¹³ the 2014 National Youth Tobacco Survey,⁶³ a sample of North Carolina high school students,⁹⁷ and a sample of college students,¹¹⁹ self-reported recall of tobacco marketing exposure was associated with tobacco product use. Longitudinal studies of adolescents^{114,118} found that self-reported recall of e-cigarette and cigar ads at the point of sale or online was associated with increased risk of tobacco product use 6 months later. Young adults who recalled e-cigarette marketing displays at the point of sale reported lower odds of cigarette smoking cessation 6 months later.¹¹¹

To prevent recall bias inherent in retrospective self-reports of tobacco marketing exposure, studies have used ecological momentary assessment methods to measure participants' exposure to tobacco marketing several times per day. An ecological momentary assessment study of young adults¹⁰⁹ found that exposure to e-cigarette or hookah/water pipe marketing messages produced favorable attitudes toward the products and intentions to use the products. Another ecological momentary assessment study⁸⁹ found that participants who used tobacco products more frequently reported more frequent exposure to tobacco ads and reported more positive attitudes toward tobacco ads, relative to less frequent users.

Experimental laboratory studies have examined associations between tobacco product marketing exposure and tobacco-related attitudes and beliefs. Youth/young adults who were randomly assigned to view e-cigarette ads exhibited more positive beliefs about e-cigarettes and tendency to choose e-cigarettes in a product choice task,¹⁷ as well as lower perceived risk of combustible cigarettes,⁹² compared with youth/young adults who viewed control ads.

The Centers' studies have examined associations between tobacco marketing bans and tobacco product use. Analyses of adolescent survey data from 130 countries in the Global Youth Tobacco Survey found that adolescent cigarette smoking was less prevalent in countries with point-of-sale tobacco advertising bans.²⁰ This association was similar among boys and girls and persisted after controlling for numerous individual-level covariates.²¹

Communication

The 62 Center research articles on communication about tobacco products have largely focused on three areas: (1) tobacco product

warnings, (2) campaign evaluation, and (3) promising themes for health communication.

The Centers' researchers published ten studies^{19,33,34,37,54,110,126,132,141,249} on the impact of tobacco product warnings on adolescents and young adults, including eight experiments, one qualitative study, one in-person survey, and one longitudinal study. Results from these studies identified several features that can increase warning effectiveness among adolescents and young adults, including graphic versus text,^{37,126,249} warnings that elicit more negative emotion,^{37,126,249} and larger warning size.^{126,132}

Several studies investigated the impact of warning content for various products. For example, one study of adolescents found that a cigar warning focused on lung cancer and heart disease was more believable than those focused on mouth and throat cancer or cigars not being a safe alternative to cigarettes.³³ Similarly, adolescents found cigarette warnings focused on addiction and nicotine to be more believable than a warning focused on the relative risk of menthol cigarettes (compared to non-menthol cigarettes).³⁴ In neither of these studies, did source of the warning (FDA, Centers for Disease Control and Prevention, Surgeon General) have an impact on believability. A discrete choice experiment found that the inclusion of a text warning decreased the likelihood that a never user would choose an e-cigarette product, suggesting warnings could deter uptake.¹⁹ Finally, a qualitative study of text warnings for hookah/water pipe found that factual warnings about health consequences were preferred over warnings that used sensationalistic wording (“Smoking hookah can kill you.”).¹¹⁰ In a longitudinal study conducted in four countries, disparagement, in the form of mocking, was positively associated with quit attempts and younger adults were more likely to disparage warnings than older adults.⁵⁴

One study also assessed other features of tobacco product warnings, including format. Mays *et al.*¹⁴¹ conducted an online experiment of the FDA's nicotine warning for e-cigarettes on advertisements testing the impact of warning background and warning size. Exposure to warnings on a red background (vs. white) resulted in greater attention and those who reported greater attention had greater recall but lower perceived relative addictiveness (compared to cigarettes). In this study, warning attention and recall did not differ by warning size. These studies highlight the importance of considering several features when designing warnings including format (text vs. pictorial), size, content, and important design features.

Two studies evaluated the impact of the FDA's *The Real Cost* campaign on adolescents.^{14,72} Exposure to the campaign was high (88% reported seeing or hearing one of the four tested campaign ads). Ad recall was associated with greater perceptions of serious cigarette smoking health consequences.⁷² A second study found that ad recall was associated with ad-targeted beliefs. In addition, adolescents who endorsed campaign beliefs were less likely to intend to smoke.¹⁴

Twelve studies addressed promising themes for health communication about tobacco product use.^{7,8,18,29,31,32,38,128,129,139,143} Several studies noted that there is a significant gap in awareness among youth and young adults of the health harms associated with the use of and the constituents present in the smoke or aerosol of non-cigarette tobacco products.^{8,32,38,139} In particular, studies noted that long-term health consequences were seen as unlikely because of infrequent use of products such as little cigars/cigarillos and hookah/water pipe tobacco.³² Other studies found that youth and young adults had generally positive attitudes towards non-cigarette tobacco products.^{8,32}

Across the studies that tested promising themes, several consistent themes emerged. Promising themes included those focused on

expression of independence,⁷ acute and cosmetic health effects,^{32,139} social stigma,^{7,8} industry targeting practices,¹²⁹ and constituent-based messages.^{29,31,38,128} One study compared loss versus gain-framed messages and generally found loss-framed messages were preferred for health risk themes, addiction, and smoker labeling; however, gain-framed messages were preferred for financial themes.¹⁴³ Although not directly assessing a specific theme, one study found that a health message about smoking risks paired with YouTube videos of youth smoking could be an effective way to counteract peer modeling of smoking.¹⁸

Behavior

Youth and young adult research primarily related to the priority topic of tobacco use behavior included more articles than the other priority areas ($n = 206$), and thus was a key focus of the Centers' research. The articles varied by tobacco product, study design, and population.

However, articles could be grouped under five main subareas: prevalence and trajectories of use ($n = 41$),^{10,53,58,61,75,97,108,130,138,148,149,158,162,169,170,173,181–183,186,188,196,200,202,203,208,210,216,220,221,224,225,231,238,241–243,250,251,252,253} policies related to youth and/or young adults ($n = 6$),^{12,20–22,123,175} intrapersonal factors ($n = 53$),^{8,11,15,28,31,32,36,38,55,56,59,60,62,74,77–79,94,98,102,146,151,155,157,159,163,164–174,177,178,180,187,192–195,197,199,201,204,209,211,214,217,218,223,226,229,230,232,235,254,255} interpersonal factors ($n = 14$),^{19,87,91,132,147,152,161,176,185,189,191,198,205,239} and social–environmental factors ($n = 10$).^{93,119,121,133,134,150,156,206,212,236}

Articles related to prevalence and trajectories of use included subcategories that examined multiple products ($n = 9$),^{53,108,158,169,188,202,203,216,241} e-cigarettes ($n = 16$),^{10,58,61,75,148,162,181–183,186,210,221,231,238,242,251} cigarettes ($n = 5$),^{138,149,170,173,250} and correlates of use ($n = 11$).^{97,130,19,6,200,208,220,224,225,243,252,253} Two of the articles^{108,241} examining multiple products used latent class analyses extending prior literature by including new products, such as e-cigarettes and hookah/water pipe, in addition to other substances. These latent class analyses studies are important in identifying groups of people with similar patterns of behavior. Other articles in this subcategory examined trends in poly-use, associations of tobacco with other substances, and patterns of poly-use and progression to other products. Articles primarily researching cigarettes described trajectories of use, patterns of use, and secondhand smoke exposure.

E-cigarette articles included modeling/trajectory articles and descriptive articles. Eight articles^{58,61,182,183,186,210,231,251} used longitudinal data to determine if e-cigarette use predicted cigarette or other tobacco product use, including one article¹⁸⁶ that showed higher e-cigarette nicotine levels were associated with increased cigarette smoking frequency and intensity. All articles indicated that e-cigarette use predicted future cigarette or combustible product use.

Two articles^{162,183} showed that e-cigarette use occurred in youth who would not have initiated the use of other tobacco products. Many articles described e-cigarette use, including device type, nicotine levels, and specific behaviors (eg, dripping). Eleven articles assessed correlates of use, many of which have been researched thoroughly for cigarettes, yet most of this literature extended the scientific base to include new and emerging products.^{97,130,196,200,208,220,224,225,243,252,253} These articles have been particularly important for regulatory efforts as they clearly demonstrate the co-occurrence of all tobacco products, their use with other substances, and the progression of e-cigarette use to combustible tobacco product use, particularly cigarettes.

Among the six articles that were related to policies, two examined raising legal purchasing age to 21,^{123,175} two used global data to

assess potential advertising bans and point of sale,^{20,21} one examined how the flavored cigarette ban influenced adolescent tobacco use,¹² and one used national data to determine how medical marijuana legalization could affect cigarette use.²² All articles examined effects of these policies among youth, not young adults. Of these policies, the FDA has direct authority to ban flavors and to implement regulations around marketing. These articles provide evidence about how these regulations may influence behavior, particularly the positive impact on tobacco use by raising the legal purchasing age to 21 and reducing point-of-sale access through monitoring and enforcement.

Fifty-three articles were categorized as examining intrapersonal factors related to youth and young adult tobacco use. Overall, 23 articles focused on adolescents, 22 focused on young adults, and 8 had both youth and young adult samples in their studies. Articles were further subcategorized: weight control ($n = 2$),^{155,204} susceptibility ($n = 3$),^{74,157,229} reasons to use ($n = 4$),^{15,209,230,235} mental health ($n = 7$),^{59,60,187,174,192,193,223} sensation seeking and impulsivity ($n = 3$),^{194,195,232} subjective experiences ($n = 3$),^{177,211,217} life transition ($n = 2$),^{178,180} attitudes/beliefs ($n = 5$),^{146,163,199,226,254} and perceptions ($n = 21$).^{8,11,28,32,36,38,55,62,77–79,94,98,151,159,164,197,201,214,218,255} Of the 21 perception articles, 12 articles focused on harm perceptions or perceptions of risk.^{11,32,77,78,94,98,159,164,197,201,218}

The majority of the articles found that new and emerging products were perceived as less harmful and were associated with fewer risks. Only one article used longitudinal data to examine changes in harm perceptions and the association with future use.⁷⁸ The remaining nine were product specific: hookah/water pipe ($n = 2$),^{151,255} e-cigarettes ($n = 4$),^{8,28,55,62} cigarettes ($n = 2$),^{36,214} new and emerging products ($n = 1$), examining benefits and harm perceptions.³⁸ Targeted and tailored interventions, including communication campaigns, have been shown to be key in reducing tobacco product use and initiation among youth and young adults.²⁵⁶ These studies provide specific factors on which these interventions can be built; for example, understanding the reasons that young people use specific products and perceptions of these products can inform FDA how to tailor their communication campaigns to youth and young adult populations.

Of the fourteen articles related to interpersonal factors, eight focused on flavors,^{19,87,91,147,176,185,205,239} five on social networks,^{152,161,189,191,198} and one on cigarette warning labels.¹³² Articles related to flavors mostly focused on e-cigarettes ($n = 7$).^{19,87,147,176,185,205,239} The articles on flavors indicate that youth and young adults find flavors of tobacco products appealing, including e-cigarettes and smokeless tobacco. Further, youth and young adults disproportionately use flavored e-cigarettes. Together, these articles add to the scientific base to support the FDA's proposed regulations to ban flavors in all tobacco products. Regarding social networks, all of the articles found that peer use is associated with tobacco product use in adolescence and young adulthood.

The remaining articles ($n = 10$) related to social–environmental factors including access ($n = 4$),^{93,150,212,236} specific opinions/views ($n = 3$),^{121,133,156} and social media ($n = 3$).^{119,134,206} Only one article looked at these factors in young adults.¹¹⁹ It is within the purview of the FDA to limit where tobacco products are sold and how they are advertised. These articles indicate that youth are likely to obtain tobacco products, particularly new and emerging products, from online and retail environments and that social media provides unique exposure to tobacco advertising and promotional activities for young people.

Discussion

Given the short time period of this review (Fall 2013–Spring 2018), the TCORS, CENIC, and COMET investigators published a notable

number of peer-reviewed publications relevant to the priority areas of the FDA, with 258 articles relevant to youth and young adult tobacco use, the cornerstone of the FDA's mandate from the TCA. These articles will provide and have provided important guidance for the regulatory efforts of the FDA.

The TCORS mechanism is unique in that it represents the first-ever attempt of the FDA on this scale to support external scientists to inform its regulatory decisions. When the FDA was granted authority to regulate tobacco products in the United States in 2009, the agency was forced to set aside its traditional "safe and effective" standard, used for the regulation of food and medicine, and create an entirely new paradigm for tobacco regulation.²⁵⁷ Tobacco regulatory science and the TCORS Centers were developed under an ambitious and innovative strategy to carry out this new charge for the FDA. Thus, although ultimately the Centers' work will be considered with other research, it is instructive to review what this unique mechanism has been able to accomplish.

Table 2 summarizes the main findings from each of the FDA's priority areas. Each of these findings are derived from two or more publications. Together, the Centers accelerated research that can guide the FDA in its efforts to reduce youth and young adult tobacco use. Several themes emerge from this review. The first involves the importance of *perceptions and attitudes* about tobacco products. Youth and young adults may have misperceptions or are uncertain about the constituents of tobacco products, and the short- and long-term consequences of use, including addiction. Changing these perceptions and attitudes—through *marketing or communication campaigns*—can increase or decrease the attractiveness of tobacco products for youth and young adults. For example, promising themes for health communication directed at youth and young adults include those focused on the expression of independence, acute and cosmetic health effects, social stigma, and industry targeting practices. Yet, many of these themes also are used in marketing tobacco products, making the products more attractive to young people. Importantly, the use of *different tobacco products co-vary*, and multiple studies reviewed show that e-cigarette use leads to cigarette use in this population. Fortunately, *anti-smoking campaigns* have been successful in changing perceptions and attitudes and reducing social acceptability of smoking. It is important that these strategies now be used with other new and emerging tobacco products, particularly e-cigarettes.

The FDA has proposed specific actions to reduce tobacco use, including e-cigarette use, among youth. In November 2018, the FDA Commissioner proposed new limits to flavored tobacco products, including having flavored tobacco products in age-restricted locations, banning cigar product flavors, and restricting marketing aimed at youth.²⁵⁸ In addition, in December 2018, the US Surgeon General issued a public health advisory concerning e-cigarette use as an epidemic among youth.²⁵⁹ These actions were likely bolstered by the scientific evidence not only from the Centers for Disease Control and Prevention^{260,261} but also from the publications from the 16 Centers that were cited in this review.

As examples, results from articles reviewed provide support for the proposed banning of flavors based on the findings that youth and young adults find flavors particularly appealing^{91,176,185} and disproportionately use flavored products compared to adults.^{147,239} Further, the FDA Youth Tobacco Prevention Plan²⁶² focuses on preventing access to products, curbing marketing of the products, and educating youth of the dangers of using any tobacco product. Findings from the studies in this review provide key insights into the targets for educational opportunities, for example, correcting misperceptions

about specific products or constituents of the products.^{30,31,36,38} In addition, results from articles on marketing and health communications provide important evidence for the FDA to continue with their plan to curb the tobacco industry's marketing aimed at youth.^{14,17,29,32} Finally, articles included in this review all add to the cumulative scientific evidence for future regulatory efforts that may reduce and prevent youth and young adult tobacco use.

This review was limited by the short time frame of TCORS 1.0, the reliance on the principal investigators to report all publications from their Centers, and the overlap within the FDA priorities so that many articles were categorized under more than one priority area. Also, as noted earlier, the Centers' research will be part of the cumulative evidence that is considered by the FDA and does not represent the entirety of articles published on these themes over these 5 years. Still, the importance of these articles at a time of significant growth in e-cigarette use among youth and young adults is noteworthy, as data are already available from these studies to guide the current efforts to reduce e-cigarette use among youth. The dynamics of the tobacco company marketplace suggests that ongoing surveillance and research relevant to these young populations must continue so that the FDA's mandate to reduce tobacco use is expedited and successful.

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