Electronic Cigarettes and Adolescents:
A Harmless Habit or a Gateway to Smoking?

Image: http://madamenoire.com/557426/teen-e-cigarette-use-rapidly-climbing

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Learning Objectives:
By the end of this presentation, audience members will be able to:

- Compare and contrast the regulations for electronic cigarettes and conventional cigarettes
- Describe current electronic cigarette trends among adolescents and identify major differences in adolescent use vs. adult use of electronic cigarettes
- Discuss the impact that tobacco companies have on influencing adolescents into trying electronic cigarettes
- Evaluate the literature on possible association between electronic cigarette use and initiation of combustible tobacco use in adolescents
- Describe the pharmacist's role on use of electronic cigarettes for smoking cessation

Epidemiology of Smoking in the U.S.

I. Nearly 18 out of every 100 US adults aged 18 years or older currently smoke cigarettes[1-4]
   a. Approximately 42.1 million people
   b. 17.8% of the US population

II. Cigarette smoking is the leading cause of preventable disease and death in the United States[4]
   a. Accounts for more than 480,000 deaths every year (1 out of every 5 deaths)
      i. 42,000 deaths resulting from secondhand smoke exposure
      ii. On average smokers die 10 years earlier than non-smokers
   b. More than 16 million Americans live with a smoking-related disease
   c. Smoking increases risk of:
      i. Lung cancer by 25 times
      ii. Coronary heart disease by 2 to 4 times
      iii. Stroke by 2 to 4 times
      iv. Diabetes by 30-40%

III. Prevalence of Adolescent Smokers[1,3,5]
   a. 9 out of every 10 smokers start by age 18, and 99% started by age 26
   b. Every day, in the United States alone 3,200 people under the age of 18 smoke their first cigarette
   c. Additionally, each day there are 2,100 teens and young adults that transition to smoking daily
      i. Most smokers admitted to have had tried their first cigarette around the age of 11 and become addicted by the time they turn 14
      ii. Only 5% of high school smokers believe that they will still be smoking 5 years after graduation, however research shows that after 8 years, 75% of those smokers will still be using some form of tobacco
   d. In Texas, 14.1% of smokers are high school students (214,800 people)
      i. 24,200 kids (under 18) who become new daily smokers each year
      ii. 43.8 Million packs of cigarettes bought or smoked by kids each year

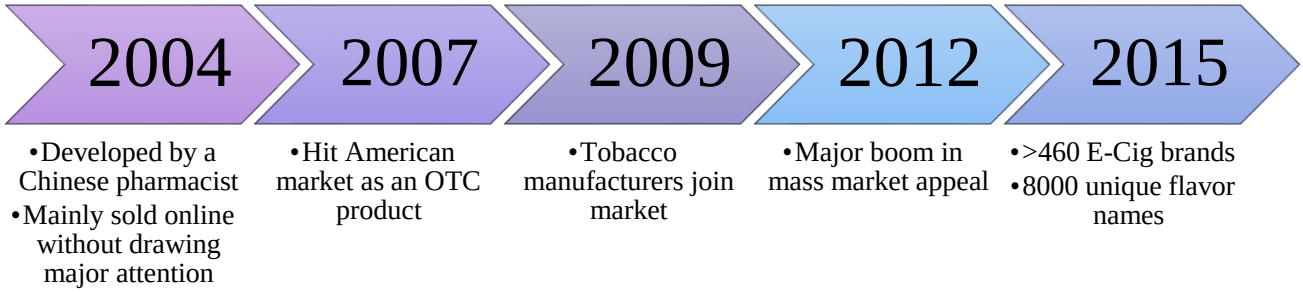
IV. Economic Costs Associated with Smoking[4]
   a. Estimated that smoking-attributed costs nationally exceeds $300 billion annually
      i. $170 billion in direct medical care for adults
      ii. >$156 billion in lost productivity due to premature death and exposure to secondhand smoke
   b. Annual health care costs in Texas directly caused by smoking $8.85 billion

V. Pathophysiology of Nicotine Dependence[4,6]
   a. Nicotine binds to cholinergic receptors in the CNS
   b. Cell bodies in the ventral tegmental area are stimulated directly by nicotine
   c. Increases neuron firing as well as dopamine release in the nucleus accumbens (NAcc)
   d. Widespread neuronal activity results in:
      i. ↑ Pleasure
      ii. ↑ Information processing ability
      iii. ↓ Fatigue
      iv. ↓Anxiety
   e. Tolerance can occur in response to repeated nicotine use
      i. Cholinergic receptors become desensitized to nicotine
      ii. Higher doses of nicotine is required in order to achieve the same level of response

Electronic Cigarettes- A General Overview

I. Also referred to as " e-cigarettes, e-Cigs, electronic vaping device, personal vaporizer or electronic nicotine delivery system (ENDS)"[7]

II. Device History[7,8]



III. Device Design[7-10]

a. See Appendix A, Figure 1, pg. 11
b. Delivers nicotine, flavor and other chemicals
c. Major Components: Plastic tube holds a battery, airflow sensor, vaporizer and a nicotine/flavoring cartridge with a chemical component, such as propylene glycol, that turns liquid into vapor
d. Activated when user inhales a "puff", an atomizer to heats up the liquid nicotine (and/or flavored) component inside the cartridge into an aerosol "vapor" which is then inhaled by the user
e. First Generation
    i. Mimics the size and look of traditional cigarettes
    ii. Cartridges are prefilled with liquid
    iii. Contains a small lithium battery that is either disposable or rechargeable
f. Second Generation
    i. Most popular option
    ii. Contains higher capacity lithium battery
    iii. Atomizer is refillable with liquids sold in separate bottles
g. Third Generation
    i. AKA "Mods"
    ii. Contain large-capacity lithium batteries with integrated circuits
    iii. Allows user to change the voltage or power delivered to the atomizer which controls how much nicotine is delivered to the user

IV. Comparing Electronic Cigarettes to Conventional Cigarettes[7,11]

a. Nicotine Delivery:
    i. E-cigarette cartridges contain varying amounts of nicotine strengths ranging from 0-34mg/ml (lasts approx. 300 puffs)
        1. Conventional cigarettes contain ~30 puffs per 1 cigarette
        2. Deliver 1-2mg of nicotine per conventional cigarette
    ii. Highly variable contents between brands and even individual products due to lack of regulation
    iii. Studies had shown high variations between the labelled and measured contents (0-20mg difference) on products
b. Cost:

Table 1. Comparing Costs of Smoking E-Cigarettes Compared to Conventional Cigarettes

	Price	Monthly
Electronic Cigarettes	$30-$100 per Starter Kit	$20-$50
Conventional Cigarettes	$6.69 (approx. $7) Per Single Pack	$220 (1 pack per day)

V. Prevalence of Electronic Cigarette Use in the United States[7,12-14]

a. Currently 4 million people in the U.S. are using e-cigarettes
    i. 1.8 million are under the age of 18

ii. 160,000 students (in grades 6-12) who have never smoked a conventional cigarette tried an e-cigarette in 2014

b. $1.5 billion industry in the U.S. alone (as of 2013)
   i. Sales projected to increase 24.2% per year through 2018
   ii. Projected to surpass conventional cigarettes within the next 10 years

c. 10 states still allow sale of e-cigarettes to minors (including Texas)
   i. There is no regulation over the internet sales of these products, resulting in many teens purchasing e-cigarettes online without having any age verification measures

Electronic Cigarettes: Influence on Adolescents

II. Advertisements of Electronic Cigarettes[13,15-19]

a. Commercial Advertising through TV, internet and radio
   i. Combined, electronic cigarette companies spent $60 million on advertising in 2013
   ii. Currently no regulation on advertising e-cigarettes
      1. Blu® is responsible for 80% of e-cigarette TV ads
      2. Blu® is owned by Lorillard. The tobacco company that also owns Camel, Pall Mall, and New Port
   iii. TV and radio advertising for conventional cigarettes were banned in 1972 and billboard advertisements were banned in 1998

b. Youth events
   i. Tobacco companies are sponsoring public events geared towards youth population such as sporting events and concerts
   ii. Commonly there are free samples given away

c. Celebrity Endorsement
   i. Jenny McCarthy is a paid endorser for Blu®
   ii. Johnny Depp is smoking e-cigarettes in the film "The Tourist"
      1. In the scene he is smoking on train in a "no smoking" area, when questioned about it, he replies that he isn't smoking at all and that e-cigarettes are exempt from the public smoking ban
   iii. Katy Perry, Leonardo DiCaprio, Bradley Cooper and numerous other celebrities have not been paid for endorsements, but have been seen publicly using e-cigarettes

III. Flavors are specifically targeted to attract a younger audience[15,17-18,20]

a. Five main flavor categories:
   i. Tobacco
   ii. Fruit
   iii. Menthol
   iv. Sweet (candy, chocolate, bubble gum, etc.)
   v. Other (coffee, black tea, wine, peanut butter, etc.)

b. Youthful names of flavors
   i. Cherry crush
   ii. Lovely bubbly (bubble gum)

c. Flavors themselves are geared towards a more youthful demographic
   i. Snicker Doodle
   ii. Gummy Bear

d. Flavored cigarettes were banned by the FDA in 2009 due to the fact that they were targeting teens

IV. Trends of E-Cigarette Use In Adolescents[7,14,21]

a. The Centers for Disease Control and Prevention shows a threefold increase in the number of young people who had tried an e-cigarette in 2013
   i. From roughly 79,000 in 2011 to more than 263,000 in 2013

b. That number tripled from 2013 to 2014 with 450,000 current adolescent e-cigarette users

c. According National Youth Tobacco Survey (NYTS) e-cigarettes became the most commonly used tobacco product among middle (3.9%) and high (13.4%) school students in 2014
d. The Monitoring the Future study found that in 2014, 8.7% of 8th graders, 16.2% of 10th graders and 17.1% of 12th graders had used e-cigarettes in the past 30 days
e. Demographic for use tends to be more male and Caucasian adolescents. E-cigarettes are used in conjuncture with conventional cigarettes (dual use); never used as smoking cessation tools, which is a common use in the adult population

Literature Review on Electronic Cigarettes in the Adolescent Population

Table 2. E-cigarette use among Texas youth: Results from the 2014 Texas Youth Tobacco Survey[5] Cooper M, Case KR, Loukas A. *Addict Behav*. 2015; 50: 173-177.		
Objective	Determine prevalence of e-cigarette use, including rates of concurrent use with other tobacco products among Texas youth Describe the demographic and tobacco use differences between e-cigarette current users and non-users	
Hypothesis	E-cigarette use will be higher among students who are in high school, white, male and who have a family member who smokes conventional cigarettes Students who use e-cigarettes in the past 30 days or in their lifetime will be more likely than those who have not used e-cigarettes to have used other tobacco products	
Trial Design	Descriptive statistics were generated from the 2014 Texas Youth Tobacco Survey (TYTS) to determine prevalence of e-cigarette use Logistic regression analyses were conducted to examine differences in demographic characteristics	
Patient Selection	**Inclusion Criteria:** 13,602 students (6th-12th grade) who completed the 2014 Texas Youth Tobacco Survey	
Results	Baseline patient characteristics: • 49.9% female • 43.9% Non-Hispanic white, 5.8% African-American, 41.1% Hispanic • Mean age 14.49 (SD=1.98) • 36.9% of all students had someone in their home who was a current smoker of conventional cigarettes Results: • See Appendix B Table 5, pg. 13 • 14.0% of middle and high school students reported current use (last 30 days) of electronic cigarettes (23.6% lifetime use) • Demographic: male, non-Hispanic white, high school student with a family member being a current smoker of conventional cigarettes • Current e-cigarette users significantly more likely to report other tobacco use as well (see Appendix C, Table 6, pg 13)	
Author's Conclusion	Need to include e-cigarettes in tobacco prevention programs Need to restrict sales to minors; regulate advertising of e-cigarettes	
Strengths & Limitations	Authors Noted:	Presenter's Noted:
	Limitations: • Sample limited to Texas students (may not necessarily be generalizable to other populations) • Design is cross-sectional, which prohibits making causal inferences/understanding the directionality of relationships	Strengths: • Able to determine the population demographic for e-cigarette use in adolescents • Demonstrated trying flavored tobacco is linked to current e-cigarette use Limitations: • Did not distinguish if "flavored tobacco product" includes e-cigarettes

Presenter's Conclusion	Demonstrates that more adolescents are using e-cigarettes and concurrently using other tobacco products, however more research is needed to understand if this correlation is a causal relationship

Table 3. Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence[22] Leventhal, AM et al. *JAMA*. 2015;314(7):700-707.		
Objective	To evaluate whether e-cigarette use among 14 year old adolescents who have never tried combustible tobacco is associated with risk of initiating use of 3 combustible tobacco products	
Trial Design	Longitudinal repeated assessment of a school-based cohort at baseline (fall 2013, 9th grade), 6 month follow-up (spring 2014, 9th grade) and a 12-month follow-up (fall 2014, 10th grade)	
Patient Selection	**Inclusion Criteria:** 9th grade English-speaking students not enrolled in special education classes throughout 10 public high schools in Los Angeles, CA.	**Exclusion Criteria:** Student as well as their parents must assent to be participate in the survey

Methods	Students that assented to partake in the study were sent surveys regarding their background and previous electronic cigarette use in the past 6 months as well as any combustible tobacco use in the past 6 months. Students then partook in a 6 month follow up survey and a 12 month follow up survey.
	
	Covariates:
	• Sociodemographics
	  ○ Age, sex, race/ethnicity, highest parental education
	• Environmental Factors
	  ○ Family living situation, family history of smoking, peer smoking
	• Intrapersonal Factors
	  ○ Mental health, personality traits, psychological processes linked with experimentation, risky behavior and smoking	

Outcomes	Any use during the prior 6 months of: • Any combustible tobacco product • Combustible cigarettes • Cigars (full sized, little cigars or blunts- composite variable due to infrequent use of individual cigar products) • Hookah • Total number of combustible tobacco products used among cigarette, cigar and hookah categories	
Statistical Measures	Chi squared, 2 tailed alpha set to 0.05 significance Missing data on covariates were accounted for using a multiple-imputation approach	

Results	• Baseline characteristics:
	  • N=4100-Students were eligible to participate
	  • N=3383-Students (and parents) assented and had data collected at baseline
	  • N=3293-Data collected at 6 month follow-up
	  • N=3283-Data collected at 12 month follow-up
	  • Average Age: 14.1 years
	
	• See Appendix C, Table 6, pg. 14
	
	• Baseline e-cigarette use was associated with greater likelihood of use of any combustible tobacco product averaged across the 2 follow-up periods (6 months and 12 months respectively) in the unadjusted analyses (OR, 4.27 [95% CI, 3.19-5.71]	

<table>
<tr><td></td><td colspan="2">Adjusted analyses for sociodemographic, environmental, and intrapersonal risk factors for smoking also demonstrated that electronic cigarette use was associated with greater likelihood of combustible tobacco use (OR, 2.73 [95% CI, 2.00-3.73]
Past 6 month use of any combustible tobacco product at the 6 month follow-up was more frequent in students that had identified as e-cigarette users at baseline (30.7% vs 8.1%), difference in prevalence rates 22.7% [95% CI, 16.4%-28.9%]
Past 6 month use of any combustible tobacco product at the 12 month follow-up also demonstrated more frequent use in students identified as e-cigarette users at baseline (25.2% vs. 9.3%) difference between the groups was 15.9% [95% CI, 10.0-21.8%]
Product specific analyses showed that (averaged across both follow-up periods) baseline e-cigarette use was positively associated with:
Combustible cigarette (OR 2.65 [95% CI, 1.73-4.05])
Cigar (OR, 4.85 [95% CI, 3.38-6.96])
Hookah (OR, 3.25 [95% CI, 2.29-4.62])
Number of different combustible products used (OR, 4.26 [95% CI, 3.16-5.74])</td></tr>
<tr><td>Author's Conclusion</td><td colspan="2">Among high school students in Los Angeles, those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year. Further research is needed to understand whether this association may be causal</td></tr>
<tr><td rowspan="2">Strengths & Limitations</td><td>Authors Noted:</td><td>Presenter's Noted:</td></tr>
<tr><td>Strengths:
Demographically diverse sample
Repeated measures of tobacco use
Exclusion of ever smokers at baseline
High follow-up rate
Limitations
E-cigarette use was measured only as an any use (no frequency) and product characteristics (nicotine strength/flavor) were not assessed</td><td>Strengths:
Statistically adjusting to covariates which also influence a person's decision to begin smoking
Prospective cohort
Limitations:
Longer duration of follow-up (ideally throughout all 4 years of high school)
Survey questions were not designed to allow open-ended responses (not able to study why students were beginning to smoke more combustible tobacco)</td></tr>
<tr><td>Presenter's Conclusion</td><td colspan="2">Data was able to provide evidence that e-cigarette use is prospectively associated with an increase use of combustible tobacco in early adolescents. Data from this study along with numerous other reports of growing rates of e-cigarette use among adolescents is enough to warrant concern among health care professionals.</td></tr>
</table>

The Pharmacist's Role on Electronic Cigarette Use

I. Educating Physicians[23,24]
   a. Study shows that most physicians routinely screen adolescent patients for conventional cigarette smoking, but few routinely screen for electronic cigarette use (86% vs 14%)
   b. Many physicians (41%) would, if asked, tell patients that e-cigarettes are less harmful than conventional cigarettes and a safe alternative
      i. Routine counseling to avoid conventional cigarette smoking than for avoiding e-cigarettes (79% vs. 18%)
   c. Physician-specific resources on electronic cigarettes are available

II. Counseling Patients[24,25]

a. Electronic Cigarettes are extremely popular and we as pharmacists need to be prepared to offer the appropriate counseling for patients (most often in regards to smoking cessation)
b. Evidence on E-cigarettes for smoking cessation
    i. Conflict of interest is influencing methods, results and conclusions of currently published studies
        1. Some prospective studies show very promising results however…
    ii. Meta-analysis found that e-cigarette users were significantly less likely than non-users to have stopped smoking
    iii. Survey found that only 1% of e-cigarette users achieved permanent abstinence from combustible tobacco after 1 year
c. Using current available evidence, clinicians must be circumspect in recommending e-cigarettes
    i. They have not demonstrate superiority over FDA-approved medications for smoking cessation
    ii. Lack of regulations of the products
    iii. Short term data has demonstrated that they can cause airway reactivity

Table 4. Electronic Cigarettes for Smoking Cessation: a Randomized Controlled Trial
Bullen C, et al. *Lancet.* 2013;382(9905):1629-1637.[25]

Objective	Determine if electronic cigarettes were more effective at smoking cessation than nicotine patches	
Hypothesis	Nicotine e-cigarettes would be more effective than patches and placebo e-cigarettes for smoking reduction, tobacco dependence and relief of withdrawal symptoms	
Trial Design	Randomized controlled superiority trial	
Patient Selection	**Inclusion Criteria:** 18 or older Smoked 10 or more cigarettes per day for the past year, Patients wanting to quit smoking and could provide consent	**Exclusion Criteria:** Women who were pregnant or breastfeeding, People currently using cessation drugs or an existing cessation program, those who reported heart attack, stroke or severe angina in the previous 2 weeks and those with poorly controlled medical disorders, allergies or other chemical dependence.
Methods	289 randomized into e-cigarette group (16mg/ml), 295 to 21mg/24hr patches and 73 to placebo e-cigarette group	
Outcomes	Primary Outcome: Continuous smoking abstinence 6 months after quit day verified by exhaled breath carbon monoxide measurements (allowing for <5 cigarettes in total) Secondary Outcome: Continued abstinence at 1,3 and 6 months post quit day, 7-day post prevalence abstinence (absolutely no smoking of tobacco cigarettes in the past 7 days) Withdrawal symptoms	
Statistical Measures	80% power, two sided alpha set at 0.05 significance to detect an absolute difference of 10% in quit rates between the groups using chi-squared test Intent to treat analysis	
Results	See Appendices D-E, pg. 15-16 Verified continuous abstinence at 6 months after quit day was highest in nicotine e-cigarette group (7.3%), followed by the nicotine patches (5.8%) and placebo e-cigarette group (4.1%) • Insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or placebo • No difference in adverse events	
Author's Conclusion	E-cigarettes, with or without nicotine were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches and few adverse events	
Strengths & Limitations	Authors Noted:	Presenter's Noted:
	Strengths: conservative primary outcome measure and rigorous trial conduct to mitigate risk of bias	Strengths: to date, most realistic trial done on effectiveness of e-cigarettes for smoking cessation (long duration, no behavioral therapy)

	Limitations: sample size too small to detect difference, modest abstinence rate for nicotine e-cigarettes	Limitations: though data was unbiased, authors were clearly biased on clinical impact
Presenter's Conclusion	Data is lacking on showing a clear superiority of e-cigarettes to other nicotine replacement therapy for smoking cessation. Due to uncertainty regarding overall safety of e-cigarettes, and known data that use in adolescents is increasing use of conventional cigarettes. pharmacists should not be recommending these products	

Upcoming Trials[26, 27]

I. E-cigarettes and Adolescents-Recruiting Trials
   a. Effects of E-cigarettes on Lung Biology
   b. Flavors and E-cigarette Effects in Adolescent Smokers
   c. Korean Youth Smoking Cessation Study
   d. Comparison of Smoking and Vaping in Families

II. Smoking Cessation Aids (Adults)
   a. In combination with nicotine patches
   b. Standard counseling in addition with no nicotine e-cigarettes

III. Environmental Impact of E-cigarettes
   a. Evaluation of Environmental Emissions from electronic-cigarettes and tobacco-burning cigarettes

Conclusion

I. Electronic cigarettes have been growing exponentially in popularity since 2009

II. Most of the adult population is seen using electronic cigarettes for smoking cessation tools, however the adolescent population is using e-cigarettes in conjuncture with conventional cigarettes (dual use)

III. Lack of Regulation
   a. Tobacco companies are free to advertise products targeting younger populations
      i. TV/internet ads
      ii. Flavors
      iii. Celebrities
      iv. Youth Events
   b. Most products have varying amounts of nicotine
      i. Products differed from labelling by as much as 20mg
      ii. Even products marketed as "0 nicotine" had measureable amounts of nicotine
   c. No age restrictions in 10 states (including Texas)
   d. No restrictions on where you are allowed to smoke e-cigarettes
      i. Adolescents are beginning to re-normalize smoking

IV. Studies demonstrate that e-cigarette use is associated with initiating combustible tobacco products

V. Proper education on e-cigarettes to other health care professionals will be key in reducing rates of electronic cigarette use in the adolescent population

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Appendices

Appendix A:

Figure 1

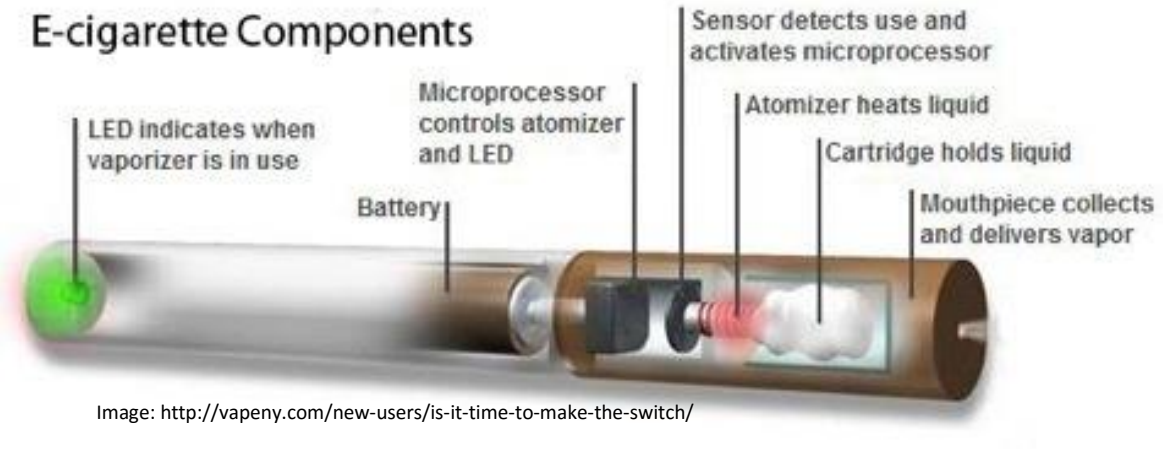

Image: http://vapeny.com/new-users/is-it-time-to-make-the-switch/

Appendix B[5]:

Table 5

Table 2
Difference between E-cigarette lifetime users and non-users, by tobacco use behaviors, adjusting for gender, grade level, and race/ethnicity—2014 Texas Youth Tobacco Survey.

	E-cigarette lifetime users[a] ($n = 2519$)	Non-users ($n = 10,806$)	p
	Percentage (95% CI)	Percentage (95% CI)	
Tobacco use behavior			
Current use			
% Cigarette	38.82 (33.54, 44.11)	2.38 (1.80, 2.95)	<.001
% Chew	25.09 (20.63, 29.56)	1.59 (0.79, 2.39)	<.001
% Snus	15.72 (11.93, 19.51)	0.85 (0.56, 1.15)	<.001
% Hookah	31.59 (25.99, 37.19)	2.11 (1.36, 2.86)	<.001
% Flavored[b]	34.27 (29.64, 38.90)	2.38 (1.47, 3.28)	<.001
% Any tobacco	60.99 (55.18, 66.80)	4.70 (3.59, 5.81)	<.001
Lifetime use			
% Cigarette	74.74 (70.47, 79.02)	9.57 (7.03, 12.10)	<.001
% Chew	38.08 (32.91, 43.25)	4.84 (3.45, 6.24)	<.001
% Snus	28.08 (24.45, 31.72)	1.46 (0.88, 2.04)	<.001
% Hookah	45.28 (39.45, 51.11)	3.36 (2.60, 4.12)	<.001
% Flavored[c]	56.98 (52.19, 61.77)	4.15 (3.35, 4.96)	<.001
% Any tobacco	93.04 (89.66, 96.42)	13.54 (9.83, 17.26)	<.001

[a] Lifetime users included individuals who were current e-cigarette users.
[b] Current flavored tobacco product use was defined as using a tobacco product that was flavored on any day in the past 30 days.
[c] Lifetime flavored tobacco product use was defined as ever trying a tobacco product that was flavored.

Adapted from: Cooper M, et al. *Addict Behav*. 2015; 50: 173-177.

Appendix C[21]:

Table 6

Table 2. Prevalence and Cross-sectional Association of Baseline e-Cigarette Use and Combustible Tobacco Use[a]

	Combined Sample (n = 3326)[b]	Never Use of e-Cigarettes (n = 2709)	Ever Use of e-Cigarettes (n = 617)	Difference in Prevalence Rates, % (95% CI)
Ever Use				
Any combustible tobacco product	768 (23.1)	376 (13.9)	392 (63.5)	49.7 (45.6-53.7)
Combustible cigarettes (n = 3320)[c]	349 (10.5)	153 (5.7)	196 (32.0)	26.4 (22.6-30.2)
Cigars (n = 3324)[c]	419 (12.6)	168 (6.2)	251 (40.8)	34.6 (30.6-38.6)
Hookah (n = 3304)[c]	501 (15.2)	220 (8.2)	281 (46.5)	38.3 (34.2-42.4)
No. of different combustible tobacco products				
0	2558 (76.9)	2333 (86.1)	225 (36.5)	
1	401 (12.1)	245 (9.0)	156 (25.3)	
2	233 (7.0)	97 (3.6)	136 (22.0)	
3	134 (4.0)	34 (1.3)	100 (16.2)	

Adapted From: Leventhal AM, et al. *JAMA*. 2015;314(7):700-707.

Appendix D[25]:

Figure 2

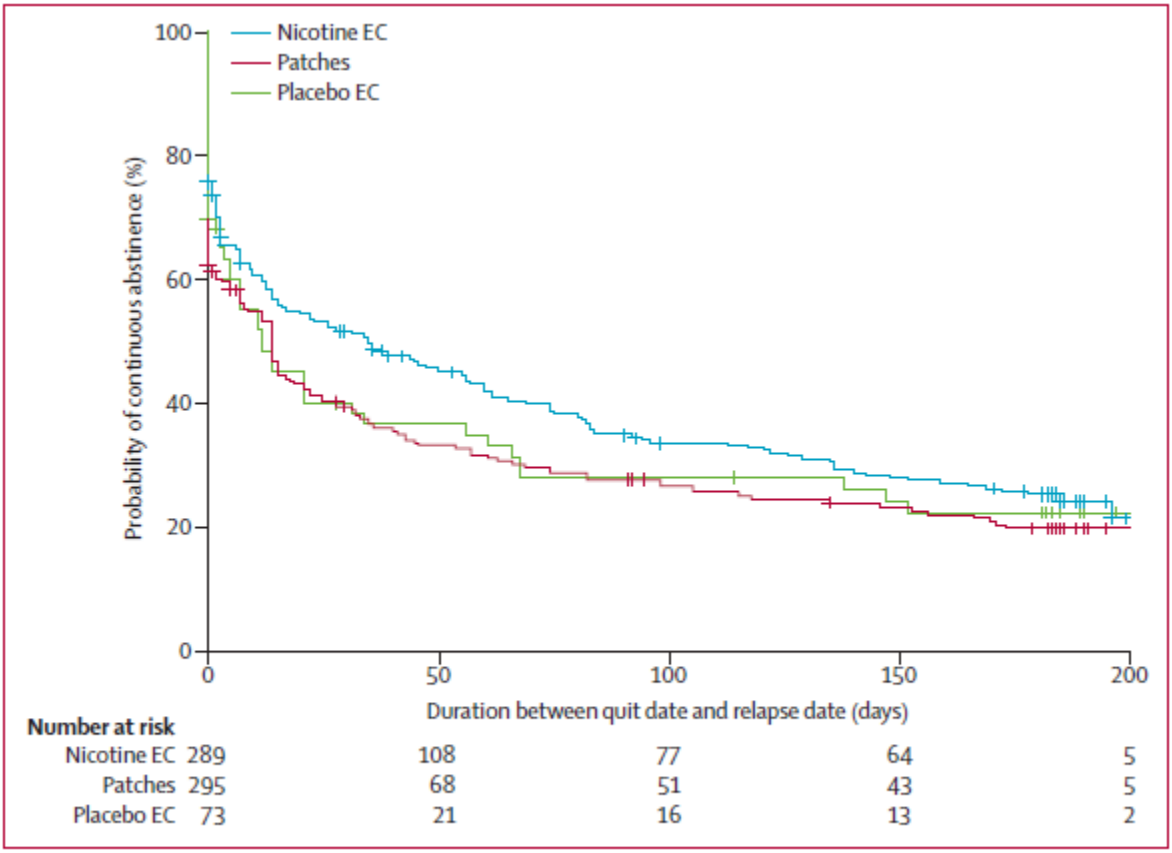

***Figure 2*: Kaplan-Meier analysis of time to relapse**
EC=e-cigarettes.

Adapted from: Bullen C, et al.. *Lancet*. 2013;382(9905):1629-1637.

Appendix E[25]:

Table 7

	Nicotine e-cigarettes (n=289)	Patches (n=295)	Difference χ^2 p value	Relative risk (95% CI)	Risk difference (95% CI)
Continuous abstinence					
1 month	67 (23·2%)	47 (15·9%)	0·03	1·46 (1·04 to 2·04)	7·25 (0·84 to 13·66)
3 months	38 (13·1%)	27 (9·2%)	0·12	1·44 (0·90 to 2·33)	4·00 (–1·10 to 9·10)
6 months (primary outcome)	21 (7·3%)	17 (5·8%)	0·46	1·26 (0·68 to 2·34)	1·51 (–2·49 to 5·51)
Sensitivity analyses for 6 months continuous abstinence data					
Complete case analysis*	21/241 (8·7%)	17/215 (7·9%)	0·76	1·10 (0·60 to 2·03)	0·80 (–4·27 to 5·87)
Per-protocol analysis 1†	21/231 (9·1%)	15/207 (7·2%)	0·48	1·25 (0·66 to 2·37)	1·84 (–3·28 to 6·96)
Per-protocol analysis 2‡	20/211 (9·5%)	13/151 (8·6%)	0·78	1·10 (0·57 to 2·14)	0·87 (–5·10 to 6·84)
Per-protocol analysis 3§	12/147 (8·2%)	12/138 (8·7%)	0·87	0·94 (0·44 to 2·02)	–0·54 (–7·00 to 5·92)
Including not biochemically verified¶	30 (10·4%)	21 (7·1%)	0·16	1·46 (0·86 to 2·49)	3·26 (–1·32 to 7·84)
Repeated measures analysis‖					
Overall treatment effect	..	..	0·05	1·61 (1·00 to 2·57)	..
1 month effect	..	..	0·004	1·87 (1·23 to 2·85)	..
3 months effect	..	..	0·12	1·52 (0·89 to 2·58)	..
6 months effect	..	..	0·21	1·46 (0·81 to 2·62)	..
7 day point prevalence abstinence					
1 month	69 (23·9%)	51 (17·3%)	0·05	1·38 (1·00 to 1·91)	6·59 (0·05 to 13·13)
3 months	62 (21·5%)	50 (17·0%)	0·17	1·27 (0·91 to 1·77)	4·50 (–1·88 to 10·88)
6 months	61 (21·1%)	46 (15·6%)	0·09	1·35 (0·96 to 1·91)	5·52 (–0·75 to 11·79)

All analyses are intention to treat unless otherwise specified (assumes participants with missing smoking status were smoking). Data are n (%) or n/N (%) unless otherwise specified. *Complete case analysis: excludes 128 participants with missing 6 month visits (withdrawn or lost to follow-up; 48 in nicotine e-cigarettes group and 80 in patches group), and includes 456 participants (241 in nicotine e-cigarettes group and 215 in patches group). †Per-protocol analysis 1: excludes protocol violations: pregnancy, death, quitters who did not have biochemical verification, undisclosed medication ineligibility, withdrew, and lost to follow-up at 6 months. ‡Per-protocol analysis 2: excludes protocol violations from per-protocol analysis 1 plus: cross-overs, use of other or combined nicotine replacement therapy products, and use of non-nicotine replacement therapy (eg, varenicline). §Per-protocol analysis 3: excludes protocol violations from per-protocol analysis 2 plus: participants still using product to which they were randomised at 6 months. ¶Continuous abstinence including not biochemically verified: eight participants in nicotine e-cigarettes group: one moved, two refused, four did not attend appointment, one adverse event (birth) did not want to attend; four participants in patches group: one moved, three refused. ‖Output for repeated measures analysis is difference in least squares means, not relative risk.

Table 2: **Continuous smoking abstinence and 7 day point prevalence, nicotine e-cigarettes versus patches**

Adapted from: Bullen C, et al.. *Lancet*. 2013;382(9905):1629-1637.