Abuse Potential of Electronic Cigarettes and Implications for Users

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Overview—electronic cigarettes:

- What are they?
- Who uses them?
- What is abuse liability or abuse potential?
- How can abuse potential be measured?
- What do we know about the abuse potential of ECIGs?
- Two recently completed studies from VCU
- How could FDA regulations impact abuse potential?
- What does this all mean for youth?
Great variability among members of the class in terms of electrical power, materials, design, and construction. (*Breland et al.*, 2017)
Great variability among members of the class in terms of electrical power, materials, design, and construction (Figure from USDHHS, 2016).
Experience intensely satisfying vapor

TRY NOW
What are e-cigarettes called?

- ECIG
- Vape
- Vape pen
- Mod
- E-hookah
- JUUL
- Pod mods
What are the flavors of electronic cigarettes?
What are the flavors of electronic cigarettes?

**FLAVOR MENU**

**RINGER - BLUE COTTON CANDY**

**HARD CANDY - SWEET TART FLAVOR**

**Gorilla Guts - Banana + Butterscotch**

**APPLE JACKS - LIKE THE CEREAL**

**T.K.O. - RASPBERRY LEMONADE**

**TATER - NEOPOLITAN ICE CREAM**

**FRENCH VANILLA**

**PARADISE - PINEAPPLE, GUAVA, ORANGE**

**F.U.E.S. - VANILLA CUSTARD**

**BULLSEYE - NY CHEESECAKE**

**A-TRAIN - MANGO + PINEAPPLE**

**SWEET MELON - HONEYDEW + MELON**

**DOUBLE TAP - STRAWBERRY + DRAGONFRUIT**

**C4 - BLUEBERRY SHORTCAKE**

**CREAMY STRAWBERRY - CREAM + STRAWBERRY**

**ASTRO - APPLE, PEACH, BERRY**

**LAVA FLOW - PINEAPPLE, COCONUT, PINEAPPLE**

**TIGERS BLOOD - WATERMELON, STRAWBERRY, COCONUT**
What are the concentrations of nicotine available?

- Nicotine Solution - 100mg Gallon
  - Regular Price: $249.99
  - Special Price: $159.99
  - 3 Review(s)

- Nicotine - 100mg - 55 Gallons
  - $7,999.99
  - Add to Cart
Current use among U.S. high school students

Past 30-day product use by year

Data from Jamal et al., 2017 (NYTS).
Current use among U.S. high school students

Past 30-day product use by year

Data from Jamal et al., 2017 (NYTS).
More on JUUL

• JUUL is a relatively new ECIG.
• Becoming increasingly popular (40% or more of ENDS sales, according to Nielsen).
• 10% of 15-24 year olds had used it (online convenience sample; Cantrell et al., 2018 poster at SRNT).
• Among youth who reported ever use of ECIGs, 22% had used JUUL (Jackson et al., 2018 poster at SRNT).
Some ECIG users are never smokers

Some ECIG users progress to cigarettes

- Increasing evidence that youth who initiate with ECIGs progress to combustible cigarettes.
  (e.g., Leventhal et al., 2015; Soneji et al., 2017; Watkins et al., 2018).
What toxicants do ECIGs deliver?

- Nicotine (much more coming up!).
- No carbon monoxide delivery (yet).
- Aerosolized propylene glycol, vegetable glycerin, and flavorants that are intended to be eaten and not inhaled.
- Other toxicants (e.g., formaldehyde) depend on device/liquid combination as well as user behavior (e.g., El-Hellani et al., 2015; Ogunwale et al., 2017; Kosmider et al., 2017; Talih et al., 2017).
- Some liquids contain toxicants (e.g., diacetyl), which are associated with bronchitis obliterans (Allen et al., 2016).
- Concern about effects of ECIGs on human lungs (Chaumont et al., 2018; Ghosh et al., 2018; Reidel et al., 2018).
What is abuse liability and why measure it?

- Increasing use of ECIGs, risk of progression to cigarettes, and ECIG toxicants = reasons to assess the abuse potential of ECIGs.
- Abuse liability is the likelihood that a user will maintain persistent use and dependence (e.g., Carter et al., 2009).
- Abuse potential is predicted abuse liability (terms very similar).
- Contingent on many factors such as the rate of drug delivery, sensory and subjective reinforcing effects, and social acceptability (Balster & Walsh, 2010; Carter et al., 2009; Jaffe & Jaffe, 1989).
Questions to ask about abuse liability

• How much nicotine do ECIGs deliver?
• How do ECIGs compare to cigarettes (high abuse liability) and to NRT (low abuse liability), in terms of abuse liability?
• Are there differences between type of user (cigarette smoker vs experienced ECIG user?) and/or youth and adults?
• Do flavors impact abuse liability?
How can we measure abuse liability in humans?

• Wait and see what happens (not great)
• Assess abuse potential, with studies to assess:
  - Nicotine delivery
  - How reinforcing the product is, using tasks or self-administration
  - Subjective effects (how the product makes people feel) (Great review by Carter et al., 2009)
• Many outcomes can be measured in the human laboratory
Physio recording equipment
Subjective assessments and behavioral tasks
Blood can be drawn
Physio recording equipment
Why measure nicotine delivery?

- Nicotine use leads to the release of dopamine: rewarding effects.
- Nicotine supports dependence: makes quitting very difficult.
- Nicotine causes long-term changes in brain development in adolescents/young adults (Smith et al., 2015; Yuan et al., 2015).
- ECIG use among adolescents has increased dramatically, so nicotine exposure in this population is a very real concern.
- However, adequate nicotine delivery is important for smoking cessation . . .
Do ECIGs deliver nicotine like a cigarette?

• What do you mean “deliver”?
  - Yield: The total amount of nicotine emerging out of the mouth-end of an ECIG
  - Exposure (or delivery): The concentration of nicotine in blood plasma (ng/ml)

• Yield and delivery are related
• Factors that influence nicotine yield and delivery:
  - Liquid nicotine concentration
  - Device power (battery voltage, coil resistance)
  - Puffing behavior
ECIG nicotine delivery varies by product.

Data from Vansickel et al., 2010.
ECIG nicotine delivery varies by product.

ECIG A is a “cigalike” product called “Blu” loaded with two different concentrations of liquid nicotine (16 or 24 mg/mL, both containing 20% propylene glycol and 50% vegetable glycerin). Data are from 23 tobacco cigarette smokers with 7 days experience with the product (Yan & D’Ruiz, 2015).
ECIG nicotine delivery varies by product.

ECIG B is a “cigalike” product called “V2cigs” and ECIG C is a “tank” product called “EVIC” with an “EVOD” heating element; both were loaded with an 18 mg/mL liquid containing 34% propylene glycol and 66% vegetable glycerin. Data are from 23 experienced electronic cigarette users (Farsalinos et al., 2014).

Time of blood sampling, relative to 10-puff use bout
ECIG nicotine delivery varies by product.

ECIG D is a 3.3v “Ego” battery fitted with a 1.5 Ohm dual coil cartomizer (“Smoktech”) and filled with ~1 ml of a 70% propylene glycol 30% vegetable glycerin liquid that varied by liquid nicotine concentration (0, 8, 18, or 36 mg/ml). Data are from 16 experienced electronic cigarette users (Ramôa et al., 2015).
ECIG nicotine delivery varies by product.

ECIG nicotine delivery varies by product.

Data for naïve users are from Lopez et al., 2015.
### Why are ECIG users getting more nicotine?

<table>
<thead>
<tr>
<th>Puff Duration (s)</th>
<th>Bout 1</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>8</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>ECIG-experienced</td>
<td>5.9*+</td>
<td>5.7+</td>
<td>5.0+</td>
<td>4.7+</td>
</tr>
<tr>
<td></td>
<td>(2.4)</td>
<td>(2.2)</td>
<td>(1.9)</td>
<td>(3.9)</td>
</tr>
<tr>
<td>ECIG-naïve</td>
<td>3.3*</td>
<td>3.0*</td>
<td>2.8*</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(1.7)</td>
<td>(1.5)</td>
<td>(1.3)</td>
<td>(0.8)</td>
</tr>
</tbody>
</table>

From Hiler, 2016
ECIG nicotine delivery is highly variable.

ECIG E and F from Wagener et al., 2016.
ECIG nicotine delivery is highly variable.

ECIG E and F from Wagener et al., 2016.
JUUL plasma data

Wynne et al., 2018 (SRNT, 2018 poster); data from 24 adult smokers in New Zealand

5% = 50 mg/ml
More on JUUL

• An analysis of Reddit posts with “JUUL” in them showed that users used positive language, referred to health benefits, and discussed nicotine “buzz” as a reason for JUUL use (Brett et al., 2018 poster at SRNT).
Why use behavioral tasks?

• Behavioral tasks can help determine
  - How hard a participant will work to obtain a drug
  - How much a participant values a drug
  - Participants’ preferences for different drugs or products

• Progressive ratio tasks
• Purchase tasks
• Choice procedures

More on this later!
What do we already know about ECIGs and behavioral tasks?

• Four studies in cigarette smokers have suggested that some ECIGs have lower abuse potential than cigarettes (Barnes et al., 2017; Heckman et al., 2018; McPherson et al., 2016; Vansickel et al., 2012).

• Smokers will work harder for flavored ECIGs compared to unflavored ones (Audrain-McGovern et al., 2016).
Why use subjective measures (how people feel)?

• Subjective measures can assess:
  - How well a drug or product reduces abstinence symptoms (i.e., craving)
  - How a drug or product makes a user feel (i.e., how satisfying or pleasant)

• We can measure both easily in the human laboratory
Subjective measures

1. Do you like the drug effects?
2. Do you feel a rush?
3. Is the product satisfying?
4. Is the product pleasant?
What do we already know about the subjective effects of ECIGs?

• Some ECIGs can suppress abstinence symptoms in both smokers and current ECIG users (Dawkins & Corcoran, 2014, Hiler et al., 2017; Vansickel et al, 2010; 2013).

• Participants (young adults) liked a sweet-flavored ECIG more than an unsweet or flavorless ECIGs (Goldenson et al., 2016).
What is already known about whether or not ECIGs produce dependence?

• Some evidence suggests that ECIGs may be associated with less dependence than combustible cigarettes (e.g., Foulds et al., 2015; Etter & Eissenberg, 2015; Rohsenow et al., 2018).

• Little work on ECIG dependence among youth.
Recent work at VCU

• Two recently completed studies at VCU to assess the abuse potential of ECIGs:
  - In adult cigarette smokers (Study 1)
  - In adult experienced ECIG users (Study 2)
Abuse potential of an ECIG in cigarette smokers

- 24 cigarette smokers
- Mean age = 30.9 years (SD = 9.5)
- 75% male
- 46% Black/African-American
- Mean CPD = 16.3 (SD = 6.6)
- Years smoking = 10.1 years (9.1)
- Mean FTND score = 5.2 (SD = 2.0)
- Mean CO level at screening = 20.1 ppm (SD = 5.0)
Abuse potential of an ECIG in cigarette smokers

- Participants completed four sessions:
  - Participants were required to abstain from nicotine/tobacco for $\geq 12$ hours before each clinical laboratory session.
  - Participants were provided with nicotine inhalers (IN) and ECIGs with nicotine levels of 0 mg/ml (ECIG_0) and 36 mg/ml (ECIG_36).
Abuse potential of an ECIG in cigarette smokers

- In each session participants completed:
  - 10 puffs
  - 10 puffs
  - MCP
Choice Procedure

Multiple choice procedure (Griffiths et al., 1993)

Crossover value = measure of the reinforcing efficacy of a drug

<table>
<thead>
<tr>
<th>Please Circle Your Choices:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 10 puffs from ECIG</td>
<td>$0.01</td>
</tr>
<tr>
<td>2. 10 puffs from ECIG</td>
<td>$0.02</td>
</tr>
<tr>
<td>3. 10 puffs from ECIG</td>
<td>$0.04</td>
</tr>
<tr>
<td>4. 10 puffs from ECIG</td>
<td>$0.08</td>
</tr>
<tr>
<td>5. 10 puffs from ECIG</td>
<td>$0.16</td>
</tr>
<tr>
<td>6. 10 puffs from ECIG</td>
<td>$0.32</td>
</tr>
<tr>
<td>7. 10 puffs from ECIG</td>
<td>$0.64</td>
</tr>
<tr>
<td>8. 10 puffs from ECIG</td>
<td>$1.28</td>
</tr>
<tr>
<td>9. 10 puffs from ECIG</td>
<td>$2.56</td>
</tr>
<tr>
<td>10. 10 puffs from ECIG</td>
<td>$5.12</td>
</tr>
<tr>
<td>11. 10 puffs from ECIG</td>
<td>$10.24</td>
</tr>
</tbody>
</table>
Abuse potential of an ECIG in cigarette smokers

• Questions to assess the direct effects of products, e.g.:
  - Was the product pleasant?
  - Was the product satisfying?
  - Did the product taste good?

• Questions about abstinence symptom suppression, e.g.:
  - Craving for a cigarette
  - Urge to smoke a cigarette
Plasma nicotine: cigarette smokers

![Bar chart showing nicotine levels in plasma for different conditions: OB, ECIG_36, ECIG_0, IN. The chart compares Bout 1 and Bout 2 with error bars indicating variability. Asterisks denote statistical significance.]
MCP crossover point: cigarette smokers
Subjective effects: cigarette smokers

![Bar chart showing subjective effects of different brands of cigarettes. The x-axis represents different brands: OB, ECIG_36, ECIG_0, IN. The y-axis represents the score on a scale from 0 to 100. The chart compares 'Taste Good' and 'Satisfying' with and without statistical significance indicated by symbols.](image-url)
Conclusions from Study 1

• In cigarette smokers, the ECIGs examined in this study may have a lower abuse liability than OB.
• However, the ECIG_36 delivered substantial amounts of nicotine to participants that did not statistically differ from OB.
• ECIGs were found to be more reinforcing than IN.
• This could suggest that ECIGs are a potential cigarette alternative or that nicotine-containing ECIGs could produce dependence in users.
Abuse potential of two ECIGs in ECIG users

- 24 ECIG-experienced men
- Mean age = 28.6 years (SD = 7.4)
- 71% Caucasian
- Duration of ECIG use = 18.0 months (SD = 13.1)
- Cigarettes per day = 0.04 (SD = 0.2)
- Mean CO level at screening = 3.3 ppm (SD = 3.5)
- Mean liquid concentration (mg/ml) = 9.3 (SD = 4.1)
- Mean volume liquid used/day = 6.1 ml (SD = 4.9)
Abuse potential of two ECIGs in ECIG users

• Sessions differed by product used (all in participants’ preferred flavors):

  - Participants were required to abstain from nicotine/tobacco for ≥ 12 hours before each clinical laboratory session.
Abuse potential of an ECIG in ECIG users

• In each session participants completed:

10 puffs

10 puffs

MCP
Abuse potential of an ECIG in ECIG users

• Questions to assess the direct effects of products, e.g.:
  - Was the product pleasant?
  - Was the product satisfying?

• Questions about abstinence symptom suppression, e.g.:
  - Craving for an e-cigarette
  - Urge to use an e-cigarette
Plasma nicotine, ECIG users

Mean = 12.5 mg/ml nicotine
Mean = 9.3 mg/ml nicotine
MCP crossover value, ECIG users

- OWN
- EGO\_highest
- EGO\_0
- Inhaler
Subjective effects: ECIG users

Was the product satisfying?

Score

OWN  EGO_highest  EGO_0  Inhaler

Bout 1  Bout 2

+  +  +  +  +  *

*  *  *  *  *  *
Conclusions from Study 2

• In male ECIG users, OWN and EGO\_highest conditions delivered similar amounts of nicotine.
• OWN more reinforcing and more satisfying than EGO\_highest.
• Factors beyond nicotine delivery may influence ECIG abuse potential.
• ECIGs tested had a higher abuse potential than the Nicotrol inhaler.
• Findings from both studies fit with other literature.
• More work must be done with other products.
Conclusions: Overall

• Electronic cigarettes are a constantly evolving class of products with great variability in terms of electrical power, nicotine delivery, and design.

• In U.S. high school students, electronic cigarette use is more prevalent than tobacco cigarette use.

• Some electronic cigarettes deliver the drug nicotine that causes dependence and can also alter brain development in adolescents.

• Increasing evidence suggests that youth who try ECIGs are more likely to initiate cigarette use.

• There are concerns about the toxicants ECIGs can deliver.
Conclusions: Overall

• In cigarette smoking adults, ECIGs may have less abuse potential than cigarettes, but more than a nicotine inhaler.

• In ECIG-experienced adults, ECIGs have more abuse potential than a nicotine inhaler.

• FDA has the ability to put specific product standards in place; some standards could reduce the abuse potential of ECIGs. Some ideas:
  - Restrict nicotine flux (what comes out of the mouth end of an ECIG, over unit time)
  - Possibly restrict/eliminate flavors

• Human lab studies can also be used as a model for measuring the effects of different product standards.
Conclusions: What does this mean for youth?

- In adults, ECIGs associated with some abuse potential, although may be less than cigarettes.
- However, ECIGs associated with fewer negative subjective experiences than cigarettes and cigars (Mantey et al., 2017).
- Some cigarette smokers do not progress because of aversive first experience (Balster & Eissenberg, 2009).
- In youth, will a less aversive product that delivers nicotine with sweet flavors actually be MORE likely to be abused?
- More use/abuse = more exposure to toxicants.
Conclusions: More on JUUL

• Abuse liability connected to nicotine delivery and appeal, so concerns with JUUL.
• JUUL may have potential to help smokers quit, if it can reliably deliver nicotine to adult cigarette smokers.
• BUT high nicotine delivery and flavors could mean increased risk for abuse/dependence for users.
• MUCH more work is needed to assess the abuse potential of ECIGs in youth, including with products like JUUL.
Thanks for listening!