Electronic Nicotine Delivery Systems (ENDS)

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Goals & Objectives

• Understand the mechanics of ENDS
• Summarize the data regarding ENDS & nicotine delivery
• Define the known health risks of ENDS
• Know the rates of ENDS use of among adolescents
• Recall what summary reports expert recommendations exist on ENDS
## Disclosures

### Relevant Financial Relationship(s)

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Relationship</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jon Ebbert, M.D.</td>
<td>Consultant</td>
<td>Nesmah</td>
</tr>
<tr>
<td></td>
<td>Stock Shareholder (self-managed)</td>
<td>Al Kaif</td>
</tr>
</tbody>
</table>

### Off Label/Investigational Usage

None
“Vaping” - Technically Aerosolization
Simple Anatomy of the Electronic Cigarette

- NiCad
- NiMh
- Li-poly
- LiMn

- Liquid-filled cartridge inhaler
- Atomizing device and heater
- Lithium battery chamber and components
- LED indicator light

Vapor draw
ENDS Evolution

1ST GENERATION
- ‘cig-a-like’
- Cartridge, atomiser and battery

2ND GENERATION
- ‘Vape pens’
- Tank and battery
- Refillable

3RD GENERATION
- Mechanical ‘mods’
- Variable power options
Vape Pens

eGo AIO
All-in-One Style

LET YOU COLORS SHINE
2ML TANK / CHILDEPROOF / LEAKPROOF
Pod Systems

THE ANATOMY OF A POD VAPE

- E-JUICE POD
- LED POWER INDICATOR
- BATTERY
- CHARGE CONNECTOR
Pod System - Juul
Vaping “Archetypes”

Sub-Ohm Vaping with Mod Systems

“Low-profile” Vaping with Pod Systems
Aerosolization With Heat: “It’s All About The Coil”

1. Kanthal (chromium-iron-aluminum)
2. Nichrome (nickel-chrome)
3. Stainless steel
4. Nickel
5. Titanium

Mod Systems

Pod Systems
Mod System Coils
Pod System Coil
Coil Mechanics Drive Aerosol Production
E-Juice or E-Liquid (7,700 Flavors*)
E-LIQUID COMPONENTS

- flavoring
- nicotine
- vegetable glycerin
- propylene glycol
### E-liquid Flavorings

<table>
<thead>
<tr>
<th>Chemical Group</th>
<th>Flavoring Chemical</th>
<th>CAS Number</th>
<th>Flavor Type</th>
<th>Flavor Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehydes</td>
<td>Geranial</td>
<td>141-27-5</td>
<td>Citrus</td>
<td>Citrus, lemon</td>
</tr>
<tr>
<td></td>
<td>Benzaldehyde</td>
<td>100-52-7</td>
<td>Fruity</td>
<td>Almond, fruity, powdery, nutty, and benzaldehyde-like</td>
</tr>
<tr>
<td></td>
<td>Cinnamaldehyde</td>
<td>104-55-2</td>
<td>Spicy</td>
<td>Sweet, spice, cinnamon red, hots, warm</td>
</tr>
<tr>
<td></td>
<td>Vanillin</td>
<td>121-33-5</td>
<td>Vanilla</td>
<td>Sweet, vanilla, creamy, chocolate</td>
</tr>
<tr>
<td>Ketones</td>
<td>Diacetyl</td>
<td>431-03-8</td>
<td>Buttery</td>
<td>Sweet, creamy, buttery, pungent, with a pungent caramellic nuance</td>
</tr>
<tr>
<td></td>
<td>Acetyl propionyl</td>
<td>600-14-6</td>
<td>Buttery</td>
<td>Buttery, nutty, toasted, caramelic, diacetyl and acetoin notes</td>
</tr>
<tr>
<td></td>
<td>Raspberry ketone</td>
<td>5471-51-2</td>
<td>Fruity</td>
<td>Sweet, berry jam, raspberry, ripe, floral</td>
</tr>
<tr>
<td>Heterocycles</td>
<td>Furfural</td>
<td>98-01-1</td>
<td>Bready</td>
<td>Brown, sweet, woody, bready, nutty, caramelic with a burnt astringent nuance</td>
</tr>
<tr>
<td></td>
<td>5-Methylfurfural</td>
<td>620-02-0</td>
<td>Caramelic</td>
<td>Sweet, caramelic, bready, brown, coffee-like</td>
</tr>
<tr>
<td></td>
<td>Maltol</td>
<td>118-71-8</td>
<td>Caramelic</td>
<td>Sweet, caramel, cotton candy, jam, fruity, baked bread</td>
</tr>
<tr>
<td></td>
<td>2-Acetopyrazine</td>
<td>22047-25-2</td>
<td>Popcorn</td>
<td>Musty, roasted, corn chip, popcorn, nutty, potato-like</td>
</tr>
</tbody>
</table>
Solvent Carrier: Vegetable Glycerin ("VG")

- **Glycerol** from vegetables
- Sweetener - 60% as sweet as sucrose
- Food preservative
- Gel capsule component
- Personal care products to make them “smooth”
Solvent Carrier: Propylene glycol ("PG")

- Pharmaceutical solvent
- Food additive
- Additive in moisturizer, cosmetics toothpaste, hand sanitizer
- Non-toxic antifreeze (toxic = ethylene glycol)
- Asthma inhaler & nebulizer component
Comparing Propylene Glycol (Pg) and Vegetable Glycerin (Vg):

- **Popularity**
  - High
  - Moderate
  - Low

- **Viscosity**
  - High
  - Moderate
  - Low

- **Gunk Build Up**
  - High
  - Moderate
  - Low

- **Allergy Risk**
  - High
  - Moderate
  - Low

- **Flavor Intensity**
  - High
  - Moderate
  - Low

- **Throat Hit**
  - High
  - Moderate
  - Low

- **Vapor Density**
  - High
  - Moderate
  - Low

- **Vapor Temperature**
  - High
  - Moderate
  - Low

- **Wick Material Absorption Time**
  - Quick
  - Slow
Nicotine Delivery By Device Type

What is a “Nicotine Salt”? 

**Salt:**
- Smoother taste
- Higher concentration delivered

**Free Base:**
- Harsher taste
- Limits concentration delivered

**Add:**
- Benzoic acid
- Salicylic acid
- Malic acid

**Make:**
- Nicotine benzoate
- Nicotine salicylate
- Nicotine malate

Lower pH

![Chemical structure of nicotine](image)

$p\text{K}_a = 3.04$ (Di-protonated Nicotine)

![Graph showing pH vs. nicotine concentration](image)
Nicotine Salt Delivers More Nicotine

- Requires a higher temperature to properly vaporize (Pod system)
- Relative nicotine content
  - E-liquids (non salts)
    - 0, 3, 6, 12, and 18 mg/mL
  - Juul
    - 5% nicotine by weight (59 mg/mL)
    - 3% nicotine by weight (35 mg/mL)
Blood nicotine (ng/mL) vs. Time after first puff (min)

- **Combustion cigarette**
- **Traditional e-liquid**
- **PAX Labs platform - as tested**
- **PAX Labs platform - commercial version**

*Data calculated using PBPK model*
Mean blood serum nicotine levels for cigarette and ENDDs users

Median urinary cotinine concentration measured in participants who used pods was **244.8 ng/mL** (IQR 8.4–1255.8), higher than **155.2 ng/mL** (IQR: 68.8–579.2) in 55 adolescents (ages 13–19 years) who regularly smoked conventional tobacco cigarettes.

Health Effects of ENDS
TSNAs Levels in 105 ENDS Replacement Liquids

ENDS Fluid & Cytotoxicity

• Embryonic and adult cells & refill fluids
  • Cytotoxicity varied among fluids and was correlated with the number and concentration of chemicals used to flavor fluids
  • Cytotoxicity was not due to nicotine

Carbonyl Compounds Created By Oxidation of E-Juice From Contact with the Heated Nichrome Wire (>350ºC)


**Aerosolization - Up to 18 additional compounds**
Carbonyl Compounds in Ecig Vapor by Voltage & Heat


Carbonyl Production Associated with Coil Metal & Coil Age

Formaldehyde (FA), acetaldehyde (AA), acetone (Acet), acrolein (Acr), propionaldehyde (PA), butyraldehyde (BA), glyoxal (GA), and methylglyoxal (MGA)
ENDS: Health Effects

• 30 healthy smokers (Athens, Greece)
  • Minimum of 5 pack-years
  • Aged 19-56 years
  • 14 male
• Ecigarettes for 5 minutes
• Ecigarettes associated with a significant increase in airway resistance

ENDS & Lipoid Pneumonia

- Ecigarettes x 7 months
- SOB, fevers, cough
- Chest CT showed opacities consistent with lipoid pneumonia.
- Macrophages in bronchoalveolar lavage fluid were loaded with lipid.
- Patient stopped Ecigarettes
- Hypothesized condition may have been caused by inhaling Ecigarette aerosol.

Lithium Battery Explosions
“Thermal Runaway”

Injury types:
• Flame
• Chemical
• Blast


Conclusion 7-2. There is substantial evidence that components of e-cigarette aerosols can promote formation of reactive oxygen species/oxidative stress. Although this supports the biological plausibility of tissue injury and disease from long-term exposure to e-cigarette aerosols, generation of reactive oxygen species and oxidative stress induction is generally lower from e-cigarettes than from combustible tobacco cigarette smoke.

Conclusion 10-4. There is substantial evidence that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes.
Conceptual Framework for Transition from ENDS Use Initiation and Progression

Estimated percentage of high school students who currently use any tobacco product,* any combustible tobacco product,† ≥2 tobacco product types,§ and selected tobacco products — National Youth Tobacco Survey, 2011–2018¶,**,††

**Juul released June, 2015
Estimated percentage of middle school students who currently use any tobacco product, any combustible tobacco product, ≥2 tobacco product types, and selected tobacco products — National Youth Tobacco Survey, 2011–2018.

**Juul released June, 2015**
Tobacco product use among high school students—2018

### Probability of Cigarette Smoking Initiation, %

<table>
<thead>
<tr>
<th>Source</th>
<th>Ever e-Cigarette Users</th>
<th>Never e-Cigarette Users</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miech et al.⁵ 2017</td>
<td>31.1</td>
<td>6.8</td>
<td>6.09 (1.57-24.63)</td>
<td>4.78 (1.91-11.96)</td>
<td>11.1</td>
</tr>
<tr>
<td>Spindle et al.⁹ 2017</td>
<td>29.4</td>
<td>10.6</td>
<td>3.50 (2.41-5.09)</td>
<td>3.37 (1.91-5.94)</td>
<td>18.1</td>
</tr>
<tr>
<td>Primack et al.²² 2016</td>
<td>37.5</td>
<td>9.0</td>
<td>6.06 (2.15-17.10)</td>
<td>6.82 (1.65-28.22)</td>
<td>5.9</td>
</tr>
<tr>
<td>Barrington-Trimis et al.⁸ 2016</td>
<td>40.4</td>
<td>10.5</td>
<td>5.76 (3.12-10.66)</td>
<td>6.17 (3.29-11.57)</td>
<td>16.6</td>
</tr>
<tr>
<td>Wills et al.⁷ 2016</td>
<td>19.5</td>
<td>5.4</td>
<td>4.25 (2.74-6.61)</td>
<td>2.87 (2.03-4.05)</td>
<td>23.9</td>
</tr>
<tr>
<td>Primack et al.⁶ 2015</td>
<td>37.5</td>
<td>9.6</td>
<td>5.66 (1.99-16.07)</td>
<td>8.30 (1.19-58.00)</td>
<td>3.5</td>
</tr>
<tr>
<td>Leventhal et al.⁵ 2015</td>
<td>8.8</td>
<td>3.1</td>
<td>2.65 (1.73-4.05)</td>
<td>1.75 (1.10-2.78)</td>
<td>20.8</td>
</tr>
<tr>
<td>Total</td>
<td>23.2</td>
<td>7.2</td>
<td>3.83 (3.74-3.91)</td>
<td>3.50 (2.38-5.16)</td>
<td>100</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.13; Q_6 = 13.79; P = .03; I^2 = 56\%

Test for overall effect: \( z = 6.34; P < .001 \)

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The odds ratios (OR) for the studies are adjusted for a study-specific set of demographic, psychosocial, and behavioral risk factors. The size of the point estimate (black square) is proportional to the weight of the study in the random-effects meta-analysis model. The weights add to 99.9% and not 100% because of rounding. \( Q \) indicates Cochrane \( Q \).
Substantial evidence: good-quality observational studies or controlled trials with few or no credible opposing findings.

• Conclusion 16-1. There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.
Reasons for ENDS Use Among Adolescents: Characteristics of 12th Graders With a History of Vaping

- Monitoring the Future (MTF) study: annual cross-sectional surveys of nationally representative samples of 12th grade students in public and private schools across the contiguous United States
- Completed 2015 and 2016 surveys

<table>
<thead>
<tr>
<th>Reasons for vaping</th>
<th>% (weighted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment</td>
<td>54.59</td>
</tr>
<tr>
<td>Tastes good</td>
<td>36.66</td>
</tr>
<tr>
<td>Boredom</td>
<td>21.83</td>
</tr>
<tr>
<td>Good time</td>
<td>20.27</td>
</tr>
<tr>
<td>Relax</td>
<td>18.88</td>
</tr>
<tr>
<td>Looks cool</td>
<td>13.34</td>
</tr>
<tr>
<td>Get high</td>
<td>6.81</td>
</tr>
<tr>
<td>Help quit cigarettes</td>
<td>8.55</td>
</tr>
<tr>
<td>Cigarettes not permitted</td>
<td>5.16</td>
</tr>
<tr>
<td>Hooked</td>
<td>.92</td>
</tr>
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</table>

Summary Reports & Expert Recommendations
E-Cigarette Use Among Youth and Young Adults

A Report of the Surgeon General

Executive Summary

U.S. Department of Health and Human Services
## Draft: Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adults</td>
<td>The USPSTF recommends that clinicians ask all adults about tobacco use and provide U.S. Food and Drug Administration (FDA)–approved pharmacotherapy or behavioral interventions (alone or in combination) for cessation in adults who use tobacco.</td>
<td>A</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>The USPSTF recommends that clinicians ask all pregnant women about tobacco use and provide behavioral interventions for cessation in pregnant women who use tobacco.</td>
<td>A</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women.</td>
<td>I</td>
</tr>
<tr>
<td>All adults who smoke tobacco</td>
<td>The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety (see above).</td>
<td>I</td>
</tr>
</tbody>
</table>
Expert Panel Conclusions & Recommendations

• American Cancer Society
  • “…switching to the exclusive use of e-cigarettes is preferable to continuing to smoke combustible products.”

• American Heart Association
  • “If a patient has failed initial treatment, has been intolerant to or refuses to use conventional smoking cessation medication, and wishes to use e-cigarettes to aid quitting, it is reasonable to support the attempt.”

• American Lung Association
  • “If smokers are ready to quit smoking for good, they should call 1-800-QUITNOW or talk with their doctor about finding the best way to quit using proven methods and FDA-approved treatments and counseling.”
“Smokers who have tried other methods of quitting without success could be encouraged to try e-cigarettes (EC) to stop smoking and stop smoking services should support smokers using EC to quit by offering them behavioral support.” – Public Health England
Goals & Objectives

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• Summarize the data regarding ENDS & nicotine delivery
• Define the known health risks of ENDS
• Know the rates of ENDS use of among adolescents
• Recall what summary reports expert recommendations exist on ENDS