E-cigarettes vs Combination NRT Delivered through State Quitlines on Smoking Outcomes Following a Recent Failed Quit Attempt: A Randomized Trial

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REACH Study Team

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- Kevin Walton
Quitting Smoking is Difficult

- Cessation is the least likely outcome
- FDA-approved smoking cessation products and counseling can double a smoker's chances of staying quit, but not for all or even most smokers
  - >65% want to quit
  - ~50% try to quit each year
  - <10% stay quit for 1 year
- 1 in 3 smokers will die from smoking-related illness
- 480,000 US deaths/yr; 6 million deaths worldwide/yr

*If FDA-approved products and counseling don’t work, what should we do?*

CDC, 2015; Lai et al., 2010; Lancaster & Stead, 2005; Stead et al., 2012
Promise of E-cigarettes

- Are likely to be far less harmful than combustible tobacco cigarettes; a smoker who completely switches to an e-cigarette is exposed to significantly lower levels of toxicants, resulting in some reduced short-term adverse health outcomes.

- Often more appealing and satisfying to smokers than FDA approved nicotine replacement therapies (NRT).

- Smoking cessation with e-cigarettes likely better than NRT
  - E-cigarette: 9-14 out of 100 smokers vs. NRT: 6 out of 100 smokers
    - Walker et al 2019
      - 7% E-cig + Patch (7.6-watt e-cig) > 2% Patch at 6 mo
    - Hajek et al 2019
      - 18% E-cig (14-watt e-cig) > 9.9% Combo NRT at 1 yr
    - Myers-Smith et al 2022
      - 19% E-cig (various e-cigs) > 3% NRT (mono/combo) at 6 mo

2018 NASEM Report; Hartmann-Boyce et al., 2022 Cochrane Database of Systematic Reviews
E-cigarette Evolution

- **2006**: First e-cigarettes introduced in U.S. (cig-a-likes)
- **2008**: Vape pens emerge
- **2010**: Box-mod style e-cigarettes become popular
- **2012**: JUUL is released
- **2014**: Emergence of disposable JUUL-like devices (STIG, Puff Bar)

**Electrical power (wattage)**

**Nicotine concentration and form**

Image from Hickman & Jaspers (2020)
Pod E-cigarettes - Impact on Smoking

Smoking Abstinence

- 6-week: 28.1% (biochemically verified)
- 6-month: 24.0% (not biochemically verified)

Pulvers et al (2020) JAMA Netw Open
Quitlines (QL) on Smoking Cessation

- Are an effective means for treating cigarette dependence, even in populations that have historically been hard to reach
- QL practice is guided by best available evidence
  - Typically, includes counseling and NRT
- To date, QL have not incorporated the use of e-cigarettes as a quit strategy
  - Lack of FDA-approval
  - Few RCTs comparing e-cigarettes vs NRT
  - None examining their efficacy delivered via QL

Brief Question Session 1
Aims & Study Design

Primary Aim

- Among recent QL users who did not successfully quit smoking, we examined the impact of QL counseling + JUUL e-cigarette vs. QL counseling + NRT on:
  - Smoking behavior – CPD, quit attempts, and abstinence
  - Cigarette dependence
  - Withdrawal symptoms
  - Safety

Study Design

- 2-group, randomized (1:1), controlled trial
  - 3 counseling calls, 8 weeks of product (no cost), 3 assessments (baseline, 8, 12 weeks)
  - Daily dairy + iCO

- Outbound recruitment of 372 participants (target) from the Oklahoma Tobacco Helpline and South Carolina Tobacco Quitline
Eligibility Criteria

Inclusion Criteria:

- Participation in the Oklahoma Tobacco Helpline or South Carolina Tobacco Helpline within the last 4-7 months
- ≥ 21 years old
- Currently smoke ≥5 cigarettes per day
- At least minimal interest in switching to an alternative product (> 0 "not at all" on a 0-10 scale)
- English speaking/reading/writing

Exclusion Criteria:

- Report NRT use or making a quit attempt within the last 7 days
- Current daily use of an e-cigarette over last month
- Unstable or significant medical or psychiatric conditions (past and stable conditions allowed)
- History of cardiac event or distress within the past 6 months
- Currently pregnant, planning to become pregnant in next 3 months, or breastfeeding.
- Severe physical reaction to using patch medication or adhesive tape or known allergy to propylene glycol or vegetable glycerin
Study Flow

Screening
- Outbound study recruitment

Baseline Phase
- Baseline Assessment
- Coaching Call 1
- 1st Shipment of study product

Randomized Product Trial Phase
- Coaching Call 2
- 1 Week (~Day 9)
- 1st Shipment of study product

Surveillance Phase
- Coaching Call 3
- 4 Weeks (~Day 28)
- 2nd Shipment of study product
- +8 Weeks
- Follow-up assessment

Post
- Follow-up assessment
- +12 Weeks
- Participant able to re-enroll in Quitline
- +16 Weeks

Daily Diary and iCO assessments for 12-weeks
Study Groups: 3 Coaching Calls + Product

- **E-cigarette Group**
  - Phone + paid service for 16 weeks
  - iCO device
  - Clincard
  - Pamphlet
  - JUUL device with charger
  - 8-week of supply of Menthol 5% or Virginia Tobacco 5% JUUL pods
    - 4-week supply, sent in two shipments

- **Combination NRT Group**
  - Phone + paid service for 16 weeks
  - iCO device
  - Clincard
  - Pamphlet
  - 8-week supply of Generic nicotine patches and Nicorette lozenges
    - 4-week supply, sent in two shipments
Consort Diagram

Actual Recruitment (94.1%)
- multiple events/delays
- funding expenditure

5497 Screened for eligibility
- 5147 Excluded
  - 1457 Declined participation
  - 3665 Ineligible
  - 25 Failed to complete first counseling call

350 Randomized

175 Assigned to e-cigarette
- 129 Completed week 8 visit
  - 12 Missed visit but completed EMA

128 Completed week 12 visit
  - 4 Missed visit but completed EMA

175 Included in the primary analysis

175 Assigned to nicotine replacement
- 127 Completed week 8 visit
  - 8 Missed visit but completed EMA

126 Completed week 12 visit
  - 1 Missed visit but completed EMA

175 Included in the primary analysis
Brief Question Session 2
### Demographics & Baseline Tobacco Use

<table>
<thead>
<tr>
<th></th>
<th>JUUL (n=175)</th>
<th>NRT (n=175)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age mean, SD</strong></td>
<td>55.3</td>
<td>54.2</td>
<td>0.43&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Sex n, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>107</td>
<td>105</td>
<td>0.83&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hispanic n, %</strong></td>
<td>0.99&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Race n, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>21</td>
<td>23</td>
<td>0.93&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>White or Caucasian</td>
<td>125</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Household Yearly Income n, %</strong></td>
<td></td>
<td></td>
<td>0.92&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;$35k</td>
<td>136</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td><strong>Employment n, %</strong></td>
<td></td>
<td></td>
<td>0.16&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unemployed/Unable to work/disabled</td>
<td>96</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td><strong>Cigarettes per Day mean, SD</strong></td>
<td>16.8</td>
<td>17.4</td>
<td>0.48&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Cigarette Dependence Scale mean, SD</strong></td>
<td>19.3</td>
<td>19.2</td>
<td>0.73&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>E-cigarette Use (≥ ‘Monthly’ but &lt; ‘Daily’) n, %</strong></td>
<td>21</td>
<td>11</td>
<td>0.36&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Notes:* <sup>a</sup> Chi-square; <sup>b</sup> Fisher exact test; <sup>c</sup> Wilcoxon rank sum test; <sup>d</sup> t-test
Changes in Cigarettes Per Day

**Figure.** Mean cigarettes per day with corresponding 95% confidence intervals.

Within-subjects: JUUL: 8- and 12-weeks vs Baseline, p<.0001
NRT: 8- and 12-weeks vs Baseline, p<.0001
Changes in Cigarette Dependence

**Figure.** Mean CDS-5 with corresponding 95% confidence intervals.

Within-subjects: JUUL: 8- and 12-weeks vs Baseline, p<.0001
NRT: 8- and 12-weeks vs Baseline, p<.0001
7 Day PPA

Notes: abstinence = no reported smoking and iCO ≤ 8ppm; missing data = smoking
Nicotine Withdrawal Symptoms: Abstainers

<table>
<thead>
<tr>
<th></th>
<th>MNWS-Week 8</th>
<th>MNWS-Week 12</th>
<th>MNWS Craving-Week 8</th>
<th>MNWS Craving-Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUUL Mean Rating</td>
<td>8.7</td>
<td>8.1</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>NRT Mean Rating</td>
<td>10.9</td>
<td>9.6</td>
<td>1.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Mean Ratings with p-values:
- MNWS-Week 8: p=.35
- MNWS-Week 12: p=.56
- MNWS Craving-Week 8: p=.56
- MNWS Craving-Week 12: p=.64

The James
## Intervention Adherence

<table>
<thead>
<tr>
<th></th>
<th>NRT (n=175)</th>
<th>Juul (n=175)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. counseling calls completed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>31</td>
<td>30</td>
<td>0.6204</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td><strong>Use of assigned product</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Weeks</td>
<td>99</td>
<td>112</td>
<td>0.1556</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>71</td>
<td>89</td>
<td>0.0534</td>
</tr>
</tbody>
</table>

1 Participants who did not attend the visit were assumed to not be using the study product.
Study Product Evaluation at 8 weeks

- 68.7% of JUUL users found the product helpful to stop smoking.
- 56.5% of JUUL users found the taste good compared to cigarettes.
- 48.1% of JUUL users found the product satisfying compared to cigarettes.

- 62.2% of NRT users found the product helpful to stop smoking.
- 31.8% of NRT users found the taste good compared to cigarettes.
- 41.7% of NRT users found the product satisfying compared to cigarettes.

- 43% of participants who stopped using JUUL reported wanting more flavor options.

* p<.0001
p=.27
p=.30
## Adverse Events at 8 weeks

<table>
<thead>
<tr>
<th>Condition</th>
<th>NRT (n=128)</th>
<th>JUUL (n=131)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sore or dry mouth and throat</strong></td>
<td>26 (20.3)</td>
<td>33 (25.2)</td>
<td>1.32 (0.74, 2.37)</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>17 (13.3)</td>
<td>13 (9.9)</td>
<td>0.72 (0.33, 1.55)</td>
</tr>
<tr>
<td><strong>Gingivitis/gum bleeding</strong></td>
<td>1 (0.8)</td>
<td>2 (1.5)</td>
<td>1.97 (0.18, 21.99)</td>
</tr>
<tr>
<td><strong>Mouth or tongue sores/inflammation</strong></td>
<td>10 (7.8)</td>
<td>7 (5.3)</td>
<td>0.67 (0.25, 1.81)</td>
</tr>
<tr>
<td><strong>Black tongue</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Nose bleeding</strong></td>
<td>4 (3.1)</td>
<td>0 (0.0)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>13 (10.2)</td>
<td>43 (32.8)</td>
<td>4.32 (2.19, 8.53)*</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>18 (14.1)</td>
<td>5 (3.8)</td>
<td>0.24 (0.09, 0.67)*</td>
</tr>
<tr>
<td><strong>Sleepiness</strong></td>
<td>9 (7.0)</td>
<td>3 (2.3)</td>
<td>0.31 (0.08, 1.17)</td>
</tr>
<tr>
<td><strong>Sleeplessness</strong></td>
<td>25 (19.5)</td>
<td>11 (8.4)</td>
<td>0.37 (0.18, 0.80)*</td>
</tr>
<tr>
<td><strong>Heart Palpitations</strong></td>
<td>6 (4.7)</td>
<td>4 (3.1)</td>
<td>0.64 (0.18, 2.32)</td>
</tr>
<tr>
<td><strong>Breathing Difficulties</strong></td>
<td>4 (3.1)</td>
<td>10 (7.6)</td>
<td>2.56 (0.78, 8.39)</td>
</tr>
<tr>
<td><strong>Allergies</strong></td>
<td>13 (10.2)</td>
<td>0 (0.0)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Chest Pain</strong></td>
<td>4 (3.1)</td>
<td>7 (5.3)</td>
<td>1.75 (0.50, 6.13)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>9 (7.0)</td>
<td>5 (3.8)</td>
<td>0.52 (0.17, 1.61)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>NRT (n=125)</td>
<td>Juul (n=130)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Sore or dry mouth and throat</td>
<td>24 (19.2)</td>
<td>24 (18.5)</td>
<td>0.95 (0.51, 1.79)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (10.4)</td>
<td>7 (5.4)</td>
<td>0.49 (0.19, 1.27)</td>
</tr>
<tr>
<td>Gingivitis/gum bleeding</td>
<td>3 (2.4)</td>
<td>2 (1.5)</td>
<td>0.64 (0.10, 3.87)</td>
</tr>
<tr>
<td>Mouth or tongue sores/inflammation</td>
<td>7 (5.6)</td>
<td>2 (1.5)</td>
<td>0.26 (0.05, 1.29)</td>
</tr>
<tr>
<td>Black tongue</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>--</td>
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<td>0 (0.0)</td>
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<td>3.22 (1.44, 7.19)*</td>
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<tr>
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<td>2 (1.5)</td>
<td>0.47 (0.09, 2.63)</td>
</tr>
<tr>
<td>Sleeplessness</td>
<td>15 (12.0)</td>
<td>6 (4.6)</td>
<td>0.35 (0.13, 0.95)*</td>
</tr>
<tr>
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<td>1 (0.8)</td>
<td>4 (3.1)</td>
<td>3.94 (0.43, 35.72)</td>
</tr>
<tr>
<td>Breathing Difficulties</td>
<td>2 (1.6)</td>
<td>9 (6.9)</td>
<td>4.57 (0.97, 21.61)</td>
</tr>
<tr>
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<td>8 (6.4)</td>
<td>2 (1.5)</td>
<td>0.23 (0.05, 1.10)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>0.48 (0.04, 5.32)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.2)</td>
<td>3 (2.3)</td>
<td>0.71 (0.16, 3.26)</td>
</tr>
</tbody>
</table>
Changes in Cigarettes Per Day: Non-abstainers

**Figure.** Subset of participants smoking ≥ 1 CPD at week 12 with corresponding 95% CI.

Within-subjects: JUUL: 8- and 12-weeks vs Baseline, p<.0001
NRT: 8- and 12-weeks vs Baseline, p<.0001
Changes in Cigarette Dependence: Non-abstainers

**Figure.** Mean CDS-5 with corresponding 95% CI.

Within-subjects: JUUL: 8- and 12-weeks vs Baseline, p<.0001
NRT: 8- and 12-weeks vs Baseline, p<.0001
24-hour Quit Attempts (past 30 days): Non-abstainers

Within-subjects: JUUL: 8- and 12-weeks vs Baseline, p<.0001
NRT: 8- and 12-weeks vs Baseline, p<.0001
Conclusions & Next Steps

- Like previous studies comparing e-cigs to NRT both were effective:
  - increasing smoking abstinence
  - reducing cigarettes smoked per day
  - reducing cigarette dependence

- No significant difference found between e-cigs and NRT though e-cigs may be slightly more effective, especially earlier in the intervention

- E-cigs and NRT had a similar side effect profile

- Importantly, these effects were seen in the context of reengagement with a state tobacco QL after an unsuccessful QL quit attempt

- E-cigs generally received more positive ratings of appeal – notably participants were often requesting other e-cig flavors

- Next steps: Non-tobacco flavors are preferred by smokers wanting to switch – will they further increase abstinence?
Thank You!