E-cigarettes: Possible Smoking Cessation Option?

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Learning Objectives
By the end of this presentation, the learner will be able to:
1. Explain the pathophysiology of nicotine dependence, tolerance, and withdrawal
2. Discuss the current available FDA-approved smoking cessation treatment options
3. Describe current electronic cigarettes trends and the potential role they may have in smoking cessation
4. Evaluate the literature on the safety and efficacy of electronic cigarettes as a smoking cessation treatment option
BACKGROUND

I. Smoking Prevalence

A. United States
   1. An estimated 42 million people or 18.1% of all adults (aged 18 years or older)
   2. Overall prevalence declined from 2005 (20.9%) to 2012 (18.1%)
   3. Increased prevalence
      a. Among men (20.5%) vs. women (15.8%)
      b. Persons with mental disorders
      c. Those who have 1st degree relatives who smoke

B. Texas
   1. ~16% of adults in 2013
   2. Ranked 6th in states with lowest rate of cigarette use (Appendix A)

C. El Paso County
   1. ~15% in 2012
   2. Clean Indoor Air Ordinance passed June 2001

II. Smoking Health Effects

A. Leading cause of preventable death in the United States
B. More than 480,000 (1 in 5) deaths each year
C. More than 16 million Americans suffer from a disease caused by smoking
D. Estimated increase risk:
   1. Coronary heart disease by 2 to 4 times
   2. Stroke by 2 to 4 times
   3. Lung cancer by 25 times
   4. Diabetes by 30-40%

III. Economic Costs Associated with Smoking

A. Annual smoking-attributable costs for the years 2009–2012 estimated more than $289 billion
   1. $133 billion for direct medical care of adults
   2. $156 billion+ in lost productivity

B. Exposure to secondhand smoke cost $5.6 billion in lost productivity (2006 data)

IV. Definitions

A. Nicotine Dependence
   1. Tolerance and withdrawal symptoms in characterizes nicotine use
   2. Can occur with cigarette smoking, smokeless tobacco use, cigar/pipe smoking

B. Nicotine Tolerance
   1. Develops as the frequency and dose of nicotine use increases
   2. Requires higher dose of the drug to achieve the same level of response achieved initially

C. Nicotine Withdrawal
   1. Develops when nicotine concentrations fall below individuals accustomed levels
   2. Includes symptoms of dysphoria, insomnia, irritability/frustration, anxiety, difficulty concentrating, restlessness, increased appetite/weight gain
V. Pathophysiology\textsuperscript{5,8} (Appendix B)
   A. Dependence
      1. Nicotine binds to cholinergic receptors in the CNS
      2. Cell bodies in the ventral tegmental area are stimulated directly by nicotine
      3. Increases in neuron firing and dopamine release in the nucleus accumbens (NAcc)
      4. Widespread neuronal activity results in increased pleasure, reduced fatigue, increased
         information-processing ability and reduced anxiety
   B. Tolerance
      1. Occurs in response to repeated nicotine use
      2. Cholinergic receptors become desensitized
   C. Withdrawal
      1. Prolonged periods of nicotine abstinence
      2. Unstimulated nicotine receptors
      3. Reduced dopamine release in the NAcc
      4. Symptoms and cravings

VI. Diagnosis\textsuperscript{7-9}
   A. DSM criteria for nicotine dependence (Appendix C)
      1. Follow those for other forms of substance dependence
      2. DSM-IV-TR criteria for diagnosis of nicotine abuse and dependence
      3. DSM-5 criteria tobacco use disorder
   B. Fagerström Test for Nicotine Dependence (Appendix D)

VII. Common Tobacco Use Monitoring Techniques\textsuperscript{10}
   A. Cotinine: primary metabolite of nicotine
   B. Exhaled carbon monoxide (eCO): detection of cigarette consumption

SMOKING CESSATION OVERVIEW

I. Healthy People 2020 Objectives\textsuperscript{11}
   A. “Increase smoking cessation attempts by adult smokers” (in the past 12 months)
      2. Target (2020): 80%
   B. “Increase smoking cessation success by adult smokers” (smoke free ≥ 6 months)
      1. Baseline (2008): 6%
      2. Target (2020): 8%

II. Benefits of Smoking Cessation\textsuperscript{12}
   A. Reduction in long-term health complications
   B. Short term health benefits
      1. Within 20 minutes your heart rate drops
      2. Within 12 hours blood carbon monoxide levels drop to normal
      3. After 48 hours, sense of smell and taste begin to return to normal
      4. After 1 year, risk of coronary heart disease is half that of a smoker

III. Risks of Smoking Cessation\textsuperscript{13}
   A. Nicotine withdrawal symptoms
   B. Weight gain (~10lbs)
   C. Depression
   D. Cough and mouth ulcers
IV. Behavioral Counseling

A. 5 A's of Quitting: Five-step algorithm

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ask</td>
</tr>
<tr>
<td>2.</td>
<td>Advise</td>
</tr>
<tr>
<td>3.</td>
<td>Assess</td>
</tr>
<tr>
<td>4.</td>
<td>Assist</td>
</tr>
<tr>
<td>5.</td>
<td>Arrange</td>
</tr>
</tbody>
</table>

- Ask about tobacco use
- Advise to quit
- Assess willingness to make a quit attempt
- Assist in quit attempt
- Arrange followup

Figure 1: 5 A’s of Quitting: Five-step algorithm

B. Stages of Change

Figure 2: Stages of Change

C. Direct patient-clinician encounters
D. Group-based therapy

V. Nicotine Replacement Therapies (NRTs) (Appendix E)

A. Five FDA approved forms of NRTs (1st line)
   1. OTC: patch, gum, lozenge
   2. Rx Only: nasal spray, inhaler

B. NRTs work by delivering nicotine into the body to ease withdrawal while allowing the smoker to break behavioral habits
C. Nicotine Product Kinetics

<table>
<thead>
<tr>
<th>Product</th>
<th>Time to Peak Concentration</th>
<th>Total Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette</td>
<td>5-10 min</td>
<td>1-2 mg / cig</td>
</tr>
<tr>
<td>Nasal Spray</td>
<td>5-10 min</td>
<td>1 mg / 2 sprays</td>
</tr>
<tr>
<td>Electronic Cigarette</td>
<td>20 min</td>
<td>1-2 mg / 30 puffs</td>
</tr>
<tr>
<td>Gum</td>
<td>30 min</td>
<td>1 or 2 mg / piece</td>
</tr>
<tr>
<td>Inhaler</td>
<td>30 min</td>
<td>4 mg / cartridge</td>
</tr>
<tr>
<td>Patch</td>
<td>6 hrs</td>
<td>0.3-0.9 mg/hr</td>
</tr>
</tbody>
</table>


VI. Non-Nicotine Medications\(^\text{16}\) (Appendix F)

A. FDA approved medications (1\(^{\text{st}}\) line)

1. Varenicline (Chantix\(^\text{®}\))
   a. Initial Dose: Day 1-3: 0.5 mg daily, Day: 4-7: 0.5 mg BID
   b. Maintenance Dose: 1mg BID
   c. MOA
      i. Partial neuronal α4β2 nicotinic receptor agonist
      ii. Stimulates dopamine activity
   d. Advantages
      i. Highest abstinence rate for single therapy
      ii. No significant drug interactions
   e. Disadvantages
      i. Nausea
      ii. Vivid/Strange dreams
      iii. Black Box Warning: Suicidality/depression

2. Bupropion SR (Zyban\(^\text{®}\), Wellbutrin SR\(^\text{®}\))
   a. Initial Dose: 150 mg daily for 3 days
   b. Maintenance Dose: 150 mg BID
   c. MOA
      i. Weak inhibitor of norepinephrine and dopamine reuptake
      ii. Nicotinic acetylcholine receptor antagonist
   d. Advantages
      i. Antidepressant activity
      ii. Delays weight gain
      iii. Can combine with NRTs
   e. Disadvantages
      i. Seizure risk (dose-dependent; >450 mg)
      ii. Drug Interactions (e.g., MAOIs, SSRIs, cimetidine, phenobarbital)
      iii. Black Box Warning: Suicidality/depression

B. Off-label Smoking Cessation Medications (2\(^{\text{nd}}\) line) (Appendix F)

1. Clonidine
2. Nortriptyline
VII. Abstinence Rates

A. 70% of smokers report wanting to quit; 46% attempt to quit each year
B. Treating Tobacco Use and Dependence Guidelines

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated Abstinence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch + ad lib NRT (e.g., gum)</td>
<td>36.5</td>
</tr>
<tr>
<td>Varenicline (2 mg/day)</td>
<td>33.2</td>
</tr>
<tr>
<td>Nasal Spray</td>
<td>26.7</td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>26.1</td>
</tr>
<tr>
<td>Nicotine Inhaler</td>
<td>24.8</td>
</tr>
<tr>
<td>Clonidine</td>
<td>25.0</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>24.2</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>23.4</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>22.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.8</td>
</tr>
</tbody>
</table>


ELECTRONIC CIGARETTE OVERVIEW

I. Electronic Cigarette Devices

A. Developed and introduced in China in 2004
B. Design
   1. Deliver nicotine, flavor and other chemicals
   2. Consist of a cartridge, atomizer, and battery
   3. Convert chemicals into an aerosol or “vapor” inhaled by the user
   4. Include components

![E-cigarette components](image)

Figure 2: Electronic cigarette components

C. First-Generation
   1. Mimics the size and look of traditional cigarettes
   2. Cartridges are prefilled with liquid
   3. Contains small lithium battery (disposable or rechargeable)

D. Second-Generation (most popular)
   1. Contains higher capacity lithium battery
   2. Atomizer is refillable with liquids sold in separate bottles
E. Third-Generation “Mods”
   1. Contains large-capacity lithium batteries with integrated circuits
   2. Allows user to change the voltage or power delivered to the atomizer

F. Examples of electronic cigarette devices currently available

<table>
<thead>
<tr>
<th>1st generation device</th>
<th>2nd generation device</th>
<th>3rd generation device</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="1st generation device" /></td>
<td><img src="image2" alt="2nd generation device" /></td>
<td><img src="image3" alt="3rd generation device" /></td>
</tr>
</tbody>
</table>

Figure 3: Examples of electronic cigarette devices currently available

G. Nicotine Delivery in Electronic Cigarettes (2nd generation)
   1. Cartridges can contain a variety nicotine strengths (0-24mg)
   2. 30 puffs is generally considered equivalent to one conventional cigarette
      a. 1-2mg of nicotine per traditional cigarette
      b. Actual amount of nicotine delivered depends on the device
   3. Can receive ~300 puffs from one nicotine electronic cigarette cartridge
   4. Time to peak concentration is ~20 minutes

II. Electronic Cigarettes Users\(^{19, 20}\)
   A. From 2010 to 2013
      1. Awareness grew to 80% of adults
      2. Use of electronic cigarettes among smokers increased from 9.8% to 36.5%
   B. Compared with non-users, electronic cigarette users tend to be
      1. Younger
      2. Better educated
      3. Higher income
      4. No clear association with gender

II. Regulation of Devices\(^{19, 21-23}\)
   A. Introduced in US as an OTC product in 2007
   B. Manufactured mostly by tobacco companies
   C. Currently:
      1. Center for Tobacco Products (CTP) regulates cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco (not electronic cigarettes)
      2. Center for Drug Evaluation and Research (CDER) regulates only electronic cigarettes marketed for therapeutic purposes
      3. Regulation is entrusted to local and state governments
D. Proposed regulations issued by FDA (April 2014) would extend the CTP’s authority to cover electronic cigarettes
   1. Federal prohibition on sales to minors
   2. Federal prohibition on free sampling
   3. Federal warning label requirements

III. Potential Advantages of Electronic Cigarettes\textsuperscript{21, 24, 25}
A. Tobacco free
B. No combustion (not exposed to harmful tobacco smoke constituents)
C. Less Expensive
   1. Electronic Cigarettes
      a. Starter Kit (containing cigarette, battery, and cartridges) between $60-$150
      b. Refill cartridges about $2 each when purchased in bulk
      c. Estimated $600-$850 per pack-year equivalent
   2. Traditional Cigarettes
      a. $7/pack in Texas $2500 per pack-year
      b. $3.30/pack in Mexico $1200 per pack-year

D. Properties of both pharmacological and behavioral smoking cessation interventions
   1. Mimics the action of smoking
   2. Mitigates withdrawal symptoms
E. Variety of nicotine strength cartridges (allows for tapering)

IV. Potential Risks of Electronic Cigarettes\textsuperscript{21, 23}
A. Inconsistent manufacturing practices
   1. Study analyzing 16 popular brands found nicotine content in 9 of 20 cartridges varied by more than 20% from the labeled content
   2. Concerns that toxins, carcinogens, and impurities may be present
      a. Ethylene glycol
      b. Tobacco-specific nitrosamines
   3. Electrical accidents and fires
B. Possible adverse events voluntarily reported to FDA: pneumonia, congestive heart failure, disorientation, seizure, hypotension
C. Unknowns of “second-hand vaping”
D. Heavy metals content similar to those found in nicotine inhalers (Appendix G)

V. Public Health Concerns\textsuperscript{26}
A. May weaken the effect of clean indoor air policies on smokers
B. Smokers may use e-cigs instead of proven-effective smoking cessation treatments
C. Gateways to cigarette smoking for non-smokers (specifically youth)
   1. Novel device
   2. Flavored products
LITERATURE REVIEW


<table>
<thead>
<tr>
<th>Study Objective</th>
<th>“To measure the short-term effects of an electronic nicotine delivery device on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Single blind randomized repeated measures cross-over trial; New Zealand</td>
</tr>
</tbody>
</table>
| Patient Population | Inclusion Criteria:  
|                  | • 18-70 years old  
|                  | • Smokes ≥ 10 cigs/day for ≥ 1 yr  
|                  | • Smokes 1st cigarette within 30 minutes of waking  
|                  | • Not currently attempting to quit |
| Methods         | After overnight abstinence, each study day participants were randomized to use:  
|                  | • 16 mg nicotine e-cigarette, placebo e-cigarette, 10 mg nicotine inhaler, own cigarettes  
|                  | • Blinded only to 16mg vs placebo e-cigarette  
|                  | • 3-day wash out period between each of the 4 study days  
|                  | • 1° Endpoint: Change in desire to smoke (measured as “AUC” on 11-point visual analogue scale before and at intervals over 1 hr of use)  
|                  | • 2° Endpoints: Withdrawal symptoms, acceptability, adverse events, serum nicotine levels |
| Statistics      | For 90% power at a two-sided significance level of 5%, need estimated n=48 to detect a one-point difference in desire to smoke on the 11-point scale  
|                  | • Intention-to-treat (ITT) method; multiple comparisons were adjusted for using Tukey-Kramer  
|                  | • Assessed withdrawal using 3 items from the Minnesota Nicotine Withdrawal Scale (i.e., irritability, restlessness, difficulty concentrating) |
| Results         | Baseline characteristics were similar (n=40)  
|                  | • Mean age = 47.6 yrs; 53% female  
|                  | • Mean Fagerström level of dependence = 5.4; mean cigs/day=20  
|                  | • 1° Endpoint:  
|                  | • Statistically significant decrease desire to smoke favoring nicotine e-cigarette group (-2.6 units) over e-cigarette placebo (1.8 units, p=0.006)  
|                  | • No significance with inhaler (p=0.99)  
|                  | • 2° Endpoints:  
|                  | • No difference in withdrawal symptoms between nicotine e-cigarette and inhaler  
|                  | • Nicotine e-cigarette:  
|                  | ▪ Rated higher for pleasantness of use than the inhaler by 1.49 units (p=0.016)  
|                  | ▪ Less irritation of the mouth or throat than with inhaler (p<0.001)  
|                  | • Tmax/Cmax of nicotine concentration: Usual cigarette (14.3 min; 13.4ng/ml), nicotine e-cigarette (19.6 min; 1.3ng/ml), inhaler (32.0 min; 2.1ng/ml) → p=0.01 |
| Author's Conclusions | 16 mg e-cigarette alleviated desire to smoke after overnight abstinence; was well tolerated and had a pharmacokinetic profile more like the inhaler than a tobacco cigarette  
|                  | • Evaluation of the e-cigarette for long-term safety, potential for long-term use, and efficacy as a cessation aid is needed |
| Reviewer's Conclusions | **Strengths:** Cross-over design, Direct comparison with approved smoking cessation option  
|                  | • **Limitations:** Smokers not intending to quit, statistically powered to detect 16 vs 0 mg e-cigarette (not inhaler), sample size not achieved, possible inadequate e-cigarette inhaling sessions  
|                  | • Preliminary findings suggests e-cigarettes exhibit a more similar reduction in the desire to smoke and pharmacokinetic profile to inhalers rather than usual cigarettes without excess adverse events |

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>“To evaluate smoking reduction, smoking abstinence, and adverse events in smokers not intending to quit using two different strengths of e-cigarettes”</th>
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</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Prospective 12-month, three-arms double-blind, controlled, randomized trial; Italy</td>
</tr>
<tr>
<td>Patient Population</td>
<td></td>
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</tbody>
</table>
| Inclusion Criteria: | • Smokes ≥ 10 cigs/day for ≥ 5 yrs  
• 18-70 years old  
• Good health  
• Not currently attempting to quit |
| Exclusion Criteria: | • Cardiovascular disease  
• Respiratory disease  
• Psychotropic medication use  
• Current or past alcohol abuse  
• Use of smokeless tobacco/NRT  
• Pregnancy/Breastfeeding |
| Methods | • Randomized 1:1:1 ratio  
  A. 7.2 mg nicotine electronic cigarette x 12 weeks  
  B. 7.2 mg nicotine electronic cigarette x 6 weeks, then 5.4 mg x 6 weeks  
  C. Placebo electronic cigarette x 12 weeks  
• Efficacy and safety evaluated at follow-up visits at 24- and 52-weeks  
• 1° Endpoint: ≥50% reduction in the number of cig/day since baseline  
• 2° Endpoints: Self-reported abstinence, eCO levels (confirm abstinence), adverse events |
| Statistics | • Proof-of-concept pilot study; no previous data available for power calculation  
• For 95% power, estimated n=93 with a p value of <0.05 reaching statistical significance  
• Per-protocol and ITT analysis (lost to follow-up classified as failures)  
• Wilcoxon signed-rank test; categorical data tested by χ² test |
| Results | • Baseline characteristics were similar (n=300)  
  o Mean age = 44 and 63% male  
  o Mean cigs/day=20  
• Per-Protocol Evaluation  
  o ≥50% reduction in cig/day use from baseline n = 31/300 (10.3%); p<0.0001  
  o Significant reduction in eCO levels from baseline (p<0.0001)  
  o No difference was found between group (p<0.001) (including placebo e-cigarette group)  
• Intent-to-treat Analysis  
  o Quitters (traditional cigarettes) = 26/300 (8.7%)  
  o Complete quitters (including electronic cigarettes) = 19/300 (6.3%)  
• Most frequently reported adverse events included cough (26%), dry mouth (22%), shortness of breath (20%), throat irritation (17%), and headache (17%) |
| Author’s Conclusions | • Electronic cigarette use can cause the persistent modification of smoking behavior among smokers not intending to quit, resulting in important smoking reduction and abstinence  
• Data is not definitive; more research about long-term safety is still required |
| Reviewer’s Conclusions | • Strengths: Titration design, evaluated long-term efficacy & safety  
• Limitations: Smokers not intending to quit, lack of control group, did not evaluate withdrawal symptoms, use of underperforming electronic cigarette model  
• Provides suggestive evidence that electronic cigarettes can lead to smoking reduction and abstinence in smokers not intending to quit |

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>“To assess whether e-cigarettes with cartridges containing nicotine were more effective for smoking cessation than nicotine patches”</th>
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<tbody>
<tr>
<td>Study Design</td>
<td>Pragmatic, three parallel group, randomized controlled 12-week trial; New Zealand</td>
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<thead>
<tr>
<th>Patient Population</th>
<th>Inclusion Criteria:</th>
<th>Exclusion Criteria:</th>
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<tbody>
<tr>
<td></td>
<td>• 18 years of age or older</td>
<td>• Pregnancy/Breastfeeding</td>
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<td></td>
<td>• Smoked 10+ cigarettes/per day for the past year</td>
<td>• Current use of cessation drugs</td>
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<td></td>
<td>• Desire to quit smoking</td>
<td>• MI/Stroke in previous 2 weeks</td>
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<tr>
<td></td>
<td></td>
<td>• Poorly controlled medical disorders</td>
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<tr>
<td></td>
<td></td>
<td>• Other chemical dependence</td>
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<table>
<thead>
<tr>
<th>Methods</th>
<th>• Stratified randomization: 4:4:1 ratio (16mg nicotine e-cigarettes, 21mg nicotine patches, or placebo e-cigarettes)</th>
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<tbody>
<tr>
<td></td>
<td>• 1° Endpoint: Continuous smoking abstinence 6 months after quit day (verified by exhaled breath carbon monoxide measurements)</td>
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<td>• 2° Endpoints: # of tobacco cigarettes smoked/day, # of participants reducing tobacco smoking, time to relapse to tobacco smoking, # of patches/cartridges used, adherence, adverse events</td>
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| Statistics | • n=657 conferred 80% power with two-sided p=0.05 |
|            | • Endpoints: ITT and per-protocol method; X² tests w/ multivariate regression; Kaplan-Meier |

<table>
<thead>
<tr>
<th>Results</th>
<th>• Baseline characteristics were similar (n=657)</th>
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<tbody>
<tr>
<td></td>
<td>• Mean age = 43yrs; 62% female</td>
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<td></td>
<td>• Average 18 cigs/day at baseline</td>
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<tr>
<td></td>
<td>• Overall loss to follow up 22% (Nicotine e-cigs 17% vs. Patches 27%)</td>
</tr>
<tr>
<td></td>
<td>• Primary Endpoint:</td>
</tr>
<tr>
<td></td>
<td>• Continuous abstinence at 6 months</td>
</tr>
<tr>
<td></td>
<td>• Nicotine e-cigarette (n=21/289, 7.3%)</td>
</tr>
<tr>
<td></td>
<td>• Complete abstainers (including e-cigarettes) (n=13/289, 4.5%)</td>
</tr>
<tr>
<td></td>
<td>• Placebo (n= 3/73, 4.1%; p=0.44)</td>
</tr>
<tr>
<td></td>
<td>• Patch (n=17/295, 5.8%, p=0.46)</td>
</tr>
<tr>
<td></td>
<td>• Achievement of abstinence lower than anticipated; insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches/placebo e-cigarettes</td>
</tr>
<tr>
<td></td>
<td>• Quit rates were initially high then decreased in all groups</td>
</tr>
<tr>
<td></td>
<td>• Secondary Endpoints:</td>
</tr>
<tr>
<td></td>
<td>• % of participants reduced daily cigarettes by at least half at 6 months</td>
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<tr>
<td></td>
<td>• Nicotine e-cigarette (57%), Patch (41%, p=0.002), Placebo (45%, p=0.08)</td>
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<tr>
<td></td>
<td>• Time to relapse (days)</td>
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<tr>
<td></td>
<td>• Nicotine e-cigarette (35day), Patch (14day, p&lt;0.0001), Placebo (12day, p=0.09)</td>
</tr>
<tr>
<td></td>
<td>• Change in # of cigarettes consumed/day from baseline</td>
</tr>
<tr>
<td></td>
<td>• Nicotine e-cigarette (-11cig), Patch (-9.1cig, p&lt;0.002), Placebo (no data)</td>
</tr>
<tr>
<td></td>
<td>• Adherence significantly higher for nicotine e-cigarette group compared with patches and placebo group (p&lt;0.0001 for both)</td>
</tr>
<tr>
<td></td>
<td>• Nicotine e-cigarette users: 1.3 cartridges/day at 1 month; 0.7 cartridges/day at 6 months</td>
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<tr>
<td></td>
<td>• No significant difference in the incidence of adverse events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author’s Conclusions</th>
<th>• E-cigarette, with or without nicotine, were modestly effective at helping smokers quit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• E-cigarette seem to have no greater risk of adverse effects when compared to patches</td>
</tr>
</tbody>
</table>

| Reviewer’s Conclusions | • Strengths: Direct comparison with approved smoking cessation option, smokers with desire to quit smoking, continued abstinence defined at 6-months |
|                       | • Limitations: Small sample size (did not meet power), higher loss to follow up/withdrawal rate for those assigned to patch group |
|                       | • Provides suggestive evidence of the efficacy of e-cigarettes for smoking cessation |
I. Numerous trials registered with the U.S. National Institute of Health regarding electronic cigarettes\textsuperscript{21,29}
   A. Trials recruiting to evaluate efficacy for smoking cessation or reduction
      1. Electronic cigarettes versus nicotine inhaler
      2. Smoking cessation and reduction in depression (electronic cigarette vs. Inhaler)
   B. Trials recruiting to evaluate safety
      1. Cardiovascular assessment of the effects of tobacco and nicotine delivery products
      2. Evaluation of environmental emissions from electronic cigarettes versus tobacco-burning cigarettes
   C. Recently completed trials (awaiting data)
      1. 5-year follow-up study of the efficacy and safety of electronic cigarettes
      2. 2-year study evaluating the safety of electronic vapor products

CONCLUSION

I. Approved cessation aids currently available are not reliably effective for many
   a. Continued abstinence rates at best around 36.5%
   b. Need for alternative options
II. Electronic cigarettes are currently not a viable smoking cessation option
III. Further randomized controlled research is needed to establish
   a. Overall safety
   b. Efficacy for smoking cessation
IV. If regulated, government can enforce good manufacturing practices to make sure that products made are safe and uniform, with minimal chemical toxins and impurities
V. In the future, pending government regulation, these devices may have a place in therapy
Appendix A: States with the Lowest/ Highest Rates of Cigarette Use in 2013³

<table>
<thead>
<tr>
<th>Lowest 5 States</th>
<th>Percentage (%)</th>
<th>Highest 5 States</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utah</td>
<td>10.3</td>
<td>Arkansas</td>
<td>25.9</td>
</tr>
<tr>
<td>California</td>
<td>12.5</td>
<td>Mississippi</td>
<td>24.8</td>
</tr>
<tr>
<td>Hawaii</td>
<td>13.3</td>
<td>Tennessee</td>
<td>24.3</td>
</tr>
<tr>
<td>Connecticut</td>
<td>15.5</td>
<td>Oklahoma</td>
<td>23.7</td>
</tr>
<tr>
<td>New Jersey</td>
<td>15.7</td>
<td>Louisiana</td>
<td>23.5</td>
</tr>
</tbody>
</table>

Appendix B: Simplified Scheme Showing Effects of Nicotine, Withdrawal, Varenicline, and Bupropion³⁰

### Appendix C: Tobacco-related Disorders according to DSM-IV-TR vs. DSM-5

<table>
<thead>
<tr>
<th>DSM-IV-TR</th>
<th>DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicotine Abuse</strong> at least one of the following criteria within the same 12 months period:</td>
<td><strong>Tobacco Use Disorder</strong> maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:</td>
</tr>
<tr>
<td>1. Severe problems regarding family, home, profession or school due to substance use</td>
<td>1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home</td>
</tr>
<tr>
<td>2. Substance use in dangerous situations</td>
<td>2. Recurrent substance use in situations in which it is physically hazardous</td>
</tr>
<tr>
<td>3. Legal problems due to substance use</td>
<td>3. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance</td>
</tr>
<tr>
<td>4. Social and/or interpersonal problems due to substance use</td>
<td>4. Tolerance, as defined by either of the following: a) the need for markedly increased amounts of the substance to achieve intoxication or desired effect b) markedly diminished effect with continued use of the same amount of the substance</td>
</tr>
<tr>
<td>The symptoms have never fulfilled the criteria for substance addiction of the respective substance class.</td>
<td>5. Withdrawal, as manifested by either of the following: a) the characteristic withdrawal syndrome for the substance; b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms</td>
</tr>
<tr>
<td>at least three of the following criteria within the same 12 months period:</td>
<td>6. The substance is often taken in larger amounts or over a longer period than was intended</td>
</tr>
<tr>
<td>1. Development of tolerance</td>
<td>7. There is a persistent desire or unsuccessful efforts to cut down or control substance use</td>
</tr>
<tr>
<td>2. Withdrawal symptoms</td>
<td>8. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects</td>
</tr>
<tr>
<td>3. Substance use longer or in larger quantities than intended</td>
<td>9. Important social, occupational, or recreational activities are given up or reduced because of substance use</td>
</tr>
<tr>
<td>4. Permanent wish or failure to control substance use</td>
<td>10. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance</td>
</tr>
<tr>
<td>5. Time-consuming procurement, use and recovery from substance</td>
<td>11. Craving or a strong desire or urge to use a specific substance.</td>
</tr>
<tr>
<td>6. Important social, professional or recreational activities are given up or limited due to substance use</td>
<td></td>
</tr>
<tr>
<td>7. Continued substance use despite physical or psychic problems</td>
<td></td>
</tr>
</tbody>
</table>

### Appendix D: Fagerström Test for Nicotine Dependence

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How soon after waking do you smoke your first cigarette?</strong></td>
<td>Within 5 minutes</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5-30 minutes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31-60 minutes</td>
<td>1</td>
</tr>
<tr>
<td><strong>Do you find it difficult to refrain from smoking in places where it is forbidden? e.g., Church, library, etc.</strong></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td><strong>Which cigarette would you hate to give up?</strong></td>
<td>The first in the morning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any other</td>
<td>0</td>
</tr>
<tr>
<td><strong>How many cigarettes/day do you smoke?</strong></td>
<td>10 or less</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31 or more</td>
<td>3</td>
</tr>
<tr>
<td><strong>Do you smoke more frequently in the morning?</strong></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td><strong>Do you smoke even if you are sick in bed most of the day?</strong></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td><strong>Score (level of dependence) 1-2 = low 3-4 = low to moderate 5-7 = moderate 8+ = high</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

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### Appendix E: Nicotine Replacement Therapies

<table>
<thead>
<tr>
<th>Product</th>
<th>Nicotine Patches (OTC)</th>
<th>Nicotine Gum (OTC)</th>
<th>Nicotine Lozenge (OTC)</th>
<th>Nicotine Inhaler (Rx)</th>
<th>Nicotine Nasal Spray (Rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>&gt;10 cig/d: 21 mg Wk 1-6: 21 mg Wk 7-8: 14 mg Wk 9-10: 7 mg</td>
<td>2 mg: &lt; 25 cig/d 4 mg: ≤ 25 cig/d Wk 1-6: 1 q 1-2 hr Wk 7-9: 1 q 2-4 hr Wk 10-12: 1 q 4-8 hr</td>
<td>2 mg: 1st cig &gt; 30 min after waking 4 mg: 1st cig ≤ 30 min after waking Wk 1-6: q 1-2 hrs Wk 7-9: q 2-4 hrs Wk 10-12: q 4-8 hrs</td>
<td>6-16 10 mg cart/d (4 mg nicotine) Use min of 6 cart/d x 3-6 wks, then: continue x 3 mths • taper 6-12 wks</td>
<td>1-2 0.5 mg sprays per nostril/hr Dose ~ 2 sprays</td>
</tr>
<tr>
<td>≤ 10 cig/d: Wk 1-6: 14 mg Wk 7-8: 7 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>~8-10 wks (~2 mths)</td>
<td>~12 wks (3 mths)</td>
<td>~12 wk (3 mths)</td>
<td>~18-24 wks (4-6 mths)</td>
<td>~12 wks (3 mths)</td>
</tr>
<tr>
<td>Max Dose</td>
<td>21 mg/day</td>
<td>24 pieces/d</td>
<td>5 lozenges/ 6 hrs or 20 lozenges/day</td>
<td>16 cartridges/d</td>
<td>5 sprays/hr or 40 sprays/d</td>
</tr>
<tr>
<td>Common Side Effects</td>
<td>• Sleep disturbances/ abnormal dreams (w/24 hr use) • Local skin reactions • Headache • Hypersensitivity to skin</td>
<td>• Jaw soreness • Hiccups • N/V • H/A • Mouth/throat sore • Bad taste • Indigestion</td>
<td>• Tingling • Hiccups • N/V • Heartburn</td>
<td>• Bad taste in mouth • Cough • Rhinitis • Hiccups • Dyspepsia • Headache • Local irritation in throat/mouth</td>
<td>• Hot/peppery sensation in nose/throat • Sneezing • Coughing • Watery eyes • Runny nose</td>
</tr>
<tr>
<td>Pregnancy Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advantages</td>
<td>• Steady release of medication • Fewer compliance problems</td>
<td>• Delays weight gain • May satisfy oral craving • May be useful in pregnancy</td>
<td>• Responds to cravings</td>
<td>• Mimics act of smoking • Responds to cravings</td>
<td>• Easy to titrate • Responds to cravings</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>• Allergic reactions to adhesive • Cannot titrate dose</td>
<td>• Dentures • Proper chewing technique</td>
<td>• Side effects (~1 wk) • Dependence</td>
<td>• Uncomfortable use • Dependence • Wait 5 minutes before driving</td>
<td></td>
</tr>
<tr>
<td>Est. Costs</td>
<td>$168-420 (8-12 wks) 1 patch / d</td>
<td>$336-588 (8-12 wks) Avg: 12 pieces / d</td>
<td>$420 (12 wks) Avg: 10 lozenges /d</td>
<td>$504-1,008 (8-12 wks) Avg: 10 cart/d</td>
<td>$280- 504 (8-12 wks) Avg: 12 doses/d</td>
</tr>
</tbody>
</table>

Appendix F: Non-Nicotine Smoking Cessation Medications\textsuperscript{16, 32-34}

<table>
<thead>
<tr>
<th>Product</th>
<th>Varenicline (Rx)</th>
<th>Bupropion SR (Rx)</th>
<th>Clonidine (Rx)</th>
<th>Nortriptyline (Rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name</td>
<td>Chantix®</td>
<td>Zyban®</td>
<td>Catapres®</td>
<td>Pamelor®</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Partial neuronal α(_4) β(_2) nicotinic receptor agonist; stimulates dopamine activity</td>
<td>Weak inhibitor of norepinephrine and dopamine reuptake; nicotinic acetylcholine receptor antagonist</td>
<td>α2-adrenergic agonist that acts on the CNS to decrease sympathetic outflow; counteract CNS features of nicotine withdrawal, including craving and anxiety.</td>
<td>Noradrenergic effects replace those of nicotine; nicotine receptor antagonist</td>
</tr>
<tr>
<td>Dosing</td>
<td>Day 1-3: 0.5 mg/day Day 4-7: 0.5 mg BID Maintenance: 1 mg BID</td>
<td>150 mg qday x 3day Then ↑ 150 mg bid</td>
<td>0.15-0.75 mg / day po (start 0.1 mg bid) 0.1-0.2 mg / day patch</td>
<td>Initiate 25 mg/day up to 75-100 mg/day</td>
</tr>
<tr>
<td>Patient Counsel</td>
<td>• Start med 1 wk before quit date • Do not use with NRT</td>
<td>• Quit date: 1-2 wks after start bupropion • May be used with NRT</td>
<td>• Initiate up to 3 days before (or on) the quit date • Taper dose over 2-4 days to avoid rebound HTN (rapid ↑ BP, agitation, confusion, tremor)</td>
<td>• Start 10-28 days before quit date</td>
</tr>
<tr>
<td>Duration</td>
<td>~12 wks (may cont. 12 more wks)</td>
<td>~8-12 wks (2-3 mths)</td>
<td>~3-10 wks</td>
<td>12 wks (3 mths)</td>
</tr>
<tr>
<td>Common Side Effects</td>
<td>• Nausea • Insomnia • Headache • Abnormal Dreams • Flatulence • Constipation</td>
<td>• Dry mouth • Insomnia • Nervousness • Difficulty concentrating • Rash • Constipation • Seizure-risk 1:1000</td>
<td>• Dry mouth • Drowsiness • Dizziness • Sedation • Constipation • ↑ BP</td>
<td>• Sedation • Dry mouth • Blurred vision • Lightheadedness • Shaky hands</td>
</tr>
<tr>
<td>Pregnancy Category</td>
<td>C</td>
<td>B</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Est. Costs</td>
<td>$224 – 336 (8-12wks)</td>
<td>$168-336 (8-12 wks)</td>
<td>$20-30 (8-12wks)</td>
<td>$22-35 (8-12wks)</td>
</tr>
</tbody>
</table>


Appendix G: Levels of Toxicants in E-Cigarette Aerosol Compared With Nicotine Inhaler and Cigarette Smoke\textsuperscript{35}

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Range in content in aerosol from 12 e-cigarette samples per 15 puffs</th>
<th>Range in content in conventional cigarette micrograms in mainstream smoke from 1 cigarette</th>
<th>Content in nicotine inhaler mist per 15 puffs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde, µg</td>
<td>0.2–5.61</td>
<td>1.6–52</td>
<td>0.200</td>
</tr>
<tr>
<td>Acetaldehyde, µg</td>
<td>0.11–1.36</td>
<td>52–140</td>
<td>0.110</td>
</tr>
<tr>
<td>Acrolein, µg</td>
<td>0.07–4.19</td>
<td>2.4–62</td>
<td>ND</td>
</tr>
<tr>
<td>Toluene, µg</td>
<td>ND–0.63</td>
<td>8.3–70</td>
<td>ND</td>
</tr>
<tr>
<td>Cadmium, ng</td>
<td>ND–0.022</td>
<td>…</td>
<td>0.003</td>
</tr>
<tr>
<td>Nickel, ng</td>
<td>0.011–0.029</td>
<td>…</td>
<td>0.019</td>
</tr>
<tr>
<td>Lead, ng</td>
<td>0.003–0.057</td>
<td>…</td>
<td>0.004</td>
</tr>
</tbody>
</table>

ND= Not detectable

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REFERENCES: