

# Tobacco Dependence: Best Management Strategies

**Nancy Rigotti, MD**

Professor of Medicine, Harvard Medical School  
Director, Tobacco Research and Treatment Center  
Massachusetts General Hospital, Boston, MA

[nrigotti@partners.org](mailto:nrigotti@partners.org)

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## **Disclosures** – Nancy Rigotti, MD

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# OVERVIEW

- Challenges in treating tobacco users
- Which treatments work?
- Practical strategies for office practice
- Electronic cigarettes

JAMA | Review

# Treatment of Tobacco Smoking A Review

Nancy A. Rigotti, MD; Gina R. Kruse, MD, MS, MPH; Jonathan Livingstone-Banks, PhD; Jamie Hartmann-Boyce, DPhil

*JAMA*. 2022;327:566-577. (Feb. 8, 2022)

# A CASE

- 55 yo man with HTN, BMI 30, depression (*stable SSRI*)
- Smokes 15 cigarettes/day, started at age 18
- *“I know I should quit, but I’ve tried everything and nothing works.”*
- Used nicotine patch for 3 days → *“I still wanted a cigarette”*
- Used bupropion for 1 month → *“I didn’t want to smoke as much... I cut down but couldn’t quit”*
- Chantix? → *“I heard that drug is dangerous!”*
- *“What do you think about the electronic cigarette?”*

# QUESTIONS for us

- Has he *really* tried everything?
- Is varenicline (*Chantix*) really risky?
- What do you say about electronic cigarettes?
  - Recommend or not?
- What's your next step?

# QUITTING IN PERSPECTIVE

National Health Interview Survey - 2015

- 68% of current smokers want to quit
- 55% of smokers try to quit each year
- Few succeed long-term (*quit for 1 year*)
  - ~ 7% succeed without help
  - 25-30% succeed long-term with best treatment
  - Only 31% of those trying to quit seek help

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# Smoking Cessation Treatment Guideline

*2020 US Surgeon General's Report & 2021 US Preventive Services Task Force*

- Effective treatments exist
  - Pharmacotherapy – *targets nicotine addiction*
  - Behavioral support – *targets behavioral components*
    - *deliver in-person, by phone, SMS (web? apps?)*
  - **Combination** is better than either one alone
- More intensive treatment has better outcomes but even brief intervention works

# Pharmacotherapy

*1st Line Medications - 2008 US Public Health Service Guideline*

- **Nicotine replacement**

Skin patch (OTC)

Gum (OTC)

Lozenge (OTC)

Oral inhaler (Rx)

Nasal spray (Rx)

*All are FDA approved for cessation*

*All ~ double quit rate vs. placebo*

- **Bupropion SR** (Zyban, Wellbutrin SR)

- **Varenicline** (Chantix)

# Nicotine Replacement Products

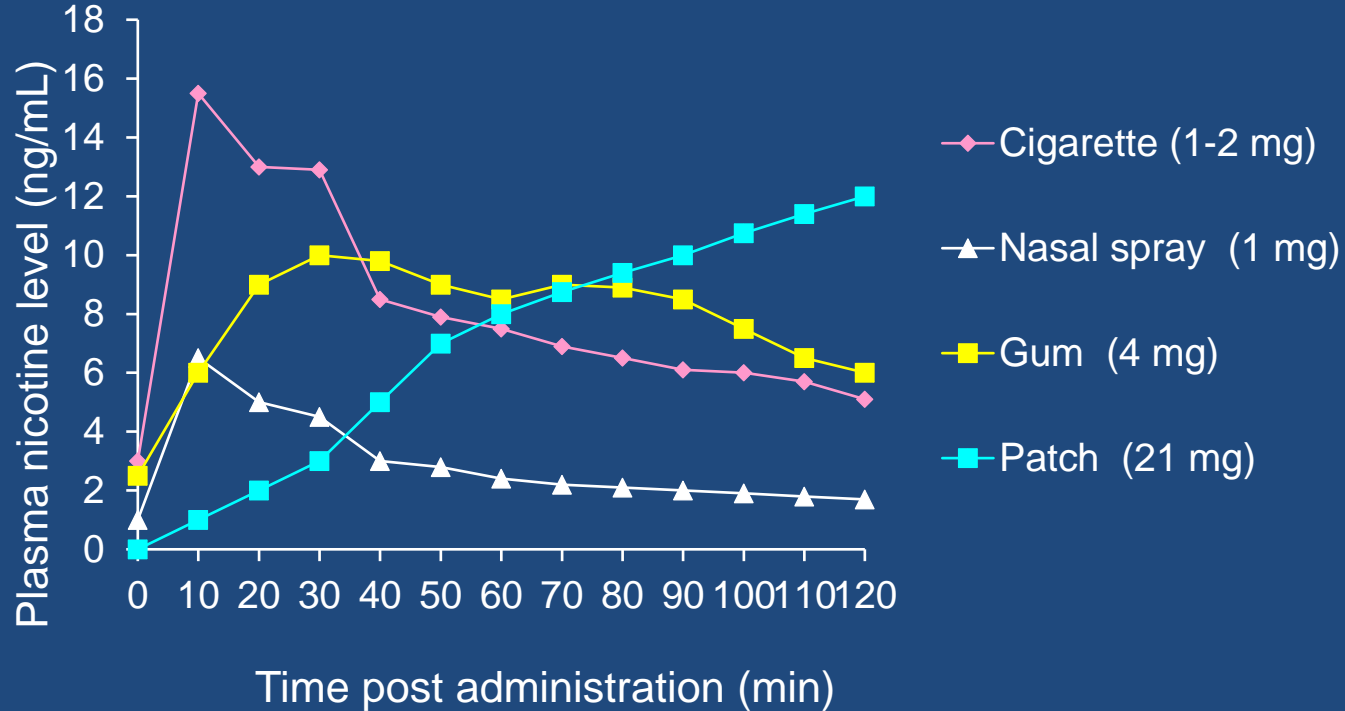
Goal = ↓ nicotine withdrawal

All products ~ equally effective



# Plasma Nicotine Levels

## Cigarettes vs. Nicotine Replacement Products



# Nicotine Replacement Options

**Long-acting, slow onset nicotine delivery** → *skin patch*

- + Constant nicotine level to avoid withdrawal
- + Simplest to use
- User has no control of dose

**Short-acting, faster onset** → *gum, lozenge, inhaler, spray*

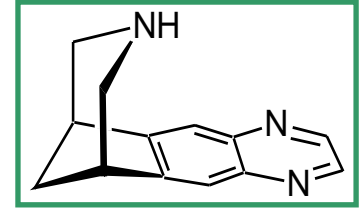
- + User controls dose
- Nicotine blood levels fluctuate more
- Many smokers do not use enough

**Combining long- and short-acting products produces higher quit rates than single forms** -2020 US Surgeon General's Report

# Bupropion SR

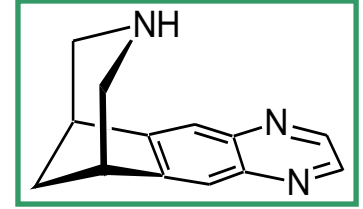
- Atypical antidepressant → ↑ dopamine in CNS
  - Increases cessation rate independent of its antidepressant effect
- Clinical use
  - Start 1 week before quit day (*150 mg qd → bid*)
  - Treat for 3 months, can extend to 6 months
  - Increases seizure risk (*Risk <0.1%*)

# Varenicline



- **Partial agonist at  $\alpha 4\beta 2$  nicotinic receptor**  
Receptor subtype that mediates nicotine dependence
- **Dual mechanism of action**
  - **Partial agonist**  
Stimulates receptor to treat craving, withdrawal
  - **Antagonist**  
Prevents nicotine from binding to the receptor → Blocks reward, reinforcement of smoking

# Varenicline



## Clinical use

- Dose up-titration over 1 week to reduce nausea (*0.5 mg qd → 1 mg bid*)
- Start 1-4 weeks before quit date
- Treat for 3 months, can extend to 6 months
- Most common side effects: nausea, vivid dreams
- Now a generic drug
- Supply problems due to possible contaminant\* (*N-nitroso-varenicline*)  
Apo-varenicline (*Canadian generic that FDA has allowed to be sold in US*);  
Par Pharmaceuticals (*FDA approved US generic*)

\*FDA info: <https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-varenicline-products>



# Varenicline: Safety Concerns

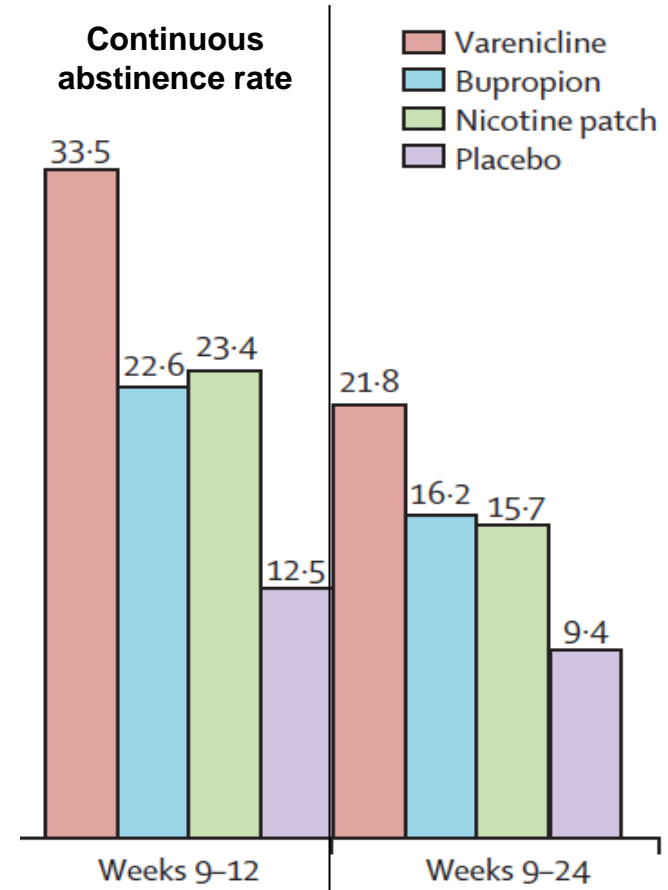
## *FDA Public Health Advisory - July 2009*

- “[Varenicline] or [bupropion] has been associated with reports of changes in behavior such as hostility, agitation, depressed mood, and suicidal thoughts or actions.”
- “FDA is requiring the manufacturers of both products to add a new **Boxed Warning**”

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm169988.htm>

# EAGLES Trial (Anthenelli, Lancet 2016)

- Double-blind placebo controlled RCT
- Nicotine patch vs bupropion vs varenicline vs placebo
- N=8000 smokers  
4000 with + 4000 without diagnosis of mild to moderate psychiatric illness
- Efficacy results provide a rationale for choosing among medications



# EAGLES Trial: Safety Outcome

Anthenelli. Lancet 2016

## Composite neuropsychiatric event endpoint

Non-psychiatric cohort	Non-psychiatric cohort* (n=3984)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)
Primary composite neuropsychiatric endpoint	13 (1.3%)	22 (2.2%)	25 (2.5%)	24 (2.4%)
Estimated primary composite neuropsychiatric adverse events (% [95% CI])	1.25% (0.60 to 1.90)	2.44% (1.52 to 3.36)	2.31% (1.37 to 3.25)	2.52% (1.58 to 3.46)
Difference in risk of composite primary endpoint (RD% [95% CI])				
Versus placebo	-1.28 (-2.40 to -0.15)	-0.08 (-1.37 to 1.21)	-0.21 (-1.54 to 1.12)	..
Versus nicotine patch	-1.07 (-2.21 to 0.08)	0.13 (-1.19 to 1.45)	..	..
Versus bupropion	-1.19 (-2.30 to -0.09)	..	..	..

- No difference among drugs in rates of psychiatric adverse events in either stratum

## Psychiatric cohort

Psychiatric cohort	Psychiatric cohort* (n=4074)			
	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Primary composite neuropsychiatric endpoint	67 (6.5%)	68 (6.7%)	53 (5.2%)†	50 (4.9%)
Estimated primary composite neuropsychiatric adverse events (% [95% CI])	6.42% (4.91 to 7.93)	6.62% (5.09 to 8.15)	5.20% (3.84 to 6.56)	4.83% (3.51 to 6.16)
Difference in risk of composite primary endpoint (RD% [95% CI])				
Versus placebo	1.59 (-0.42 to 3.59)	1.78 (-0.24 to 3.81)	0.37 (-1.53 to 2.26)	..
Versus nicotine patch	1.22 (-0.81 to 3.25)	1.42 (-0.63 to 3.46)	..	..
Versus bupropion	-0.20 (-2.34 to 1.95)	..	..	..

**FDA removed Black Box warning  
(Dec. 2016)**

## 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment

# Selecting a Smoking Cessation Medication

## *An Evidence-based Protocol*

1 <sup>st</sup> line	Varenicline OR combination NRT
2 <sup>nd</sup> line	Bupropion OR single NRT product
If single agent is insufficient	Combine categories of FDA-approved drugs: Varenicline + NRT Varenicline + bupropion Bupropion + NRT

# Initiating Pharmacologic Treatment in Tobacco-Dependent Adults

## An Official American Thoracic Society Clinical Practice Guideline

*Leone et al, May 2020*

### Initial medication choice

- Varenicline > nicotine patch, bupropion, or e-cigarettes
- Even in smokers with psychiatric illness
- Use >12 weeks

### Combine medications with different mechanisms?

- Varenicline + nicotine patch > varenicline alone (conditional)

Start treatment with varenicline if smoker is not ready to quit

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- **Practical strategies for office practice**
- Electronic cigarettes

# TREATING TOBACCO IN HEALTH CARE

*2008 U.S. Public Health Service Guidelines – 5A's*

- Routine advice to quit is effective
- Brief counseling is more effective than advice only
- Evidence-based 5 step (5A) Guideline
  - **ASK**                      all patients about smoking
  - **ADVISE**                all smokers to quit
  - **ASSESS**                smoker's readiness to quit
  - **ASSIST**                smokers to quit
  - **ARRANGE**            follow-up care

# Reconsidering ASSESS:

## Moving to an “Opt Out” model of treatment

- If tobacco use is a chronic disease
  - Don't ask a if a smoker is ready to quit
  - Just offer treatment:
    - “Quitting smoking can be hard, but there is good treatment and I can help you. Can we talk about what options you could try?”*



# Treating Tobacco in the Office: A Practical Strategy

## *3 Step Model – Ask / Advise / Act*

- **ASK**      *Do you ever smoke tobacco?*  
*Are you exposed to smoke at home or at work?*
- **ADVISE**      *Stopping smoking is key to stay (or become) healthy.*
- **ACT**      Offer treatment to all smokers  
Prescribe pharmacotherapy  
Connect to internal or community resources for behavioral support

# Free behavioral support programs to recommend to patients

## Telephone Quitline *1-800-QUIT NOW*

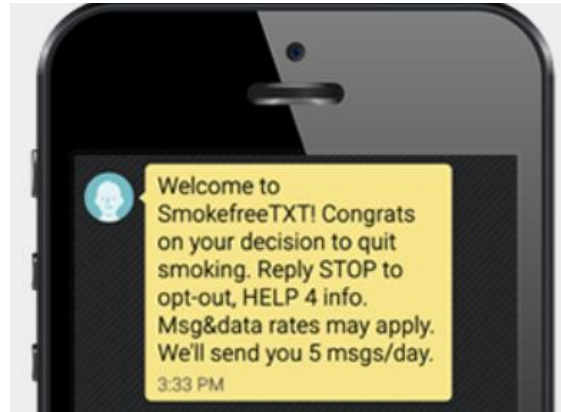
- Multi-session counseling by appointment: Convenient, private, free
- Most offer free samples of nicotine patch, gum, or lozenge
- **Make an active referral from your office** (*eReferral, web enroll*)

## SmokefreeTXT *Text “quit” to 47848* if ready to set a quit date in 1 mo

- *Text “GO” to 47848* if not

## Smokefree.gov *website*

- Mobile app (quitSTART)
- Web-based information
- SmokefreeTXT, Quitline



# Smokefree.gov

I Want to Quit

My Quit Day

I Recently Quit

Staying Quit

## Tools & Tips

Learn about different tools to help you quit and how to use them.



Smokefree  
Texting  
Programs



Build Your Quit  
Plan



Using Nicotine  
Replacement  
Therapy



Smokefree  
Social Media



Smokefree  
Apps

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- **Electronic cigarettes**

# Electronic Cigarette

*A nicotine delivery device that looks like a cigarette*



***Nicotine +  
propylene glycol or glycerin ±  
flavoring***

## **No tobacco burned → Safer than cigarettes?**

- Nicotine is what keeps smokers smoking
- Products of combustion of tobacco products are what kills

Abstinence from all tobacco use is the goal, but many smokers are unable to achieve it → *Harm reduction*



# Electronic Cigarette

*A nicotine delivery device that looks like a cigarette*



***Nicotine +  
propylene glycol or glycerin ±  
flavoring***

No tobacco burned → Safer than cigarettes?

**The devices are new and changing rapidly**



# The Evolution of Electronic Cigarettes



Disposable  
e-cigarettes



E-cigarettes with  
prefilled pods  
Rechargeable



Tanks or Mods  
(refillable)  
More powerful  
batteries



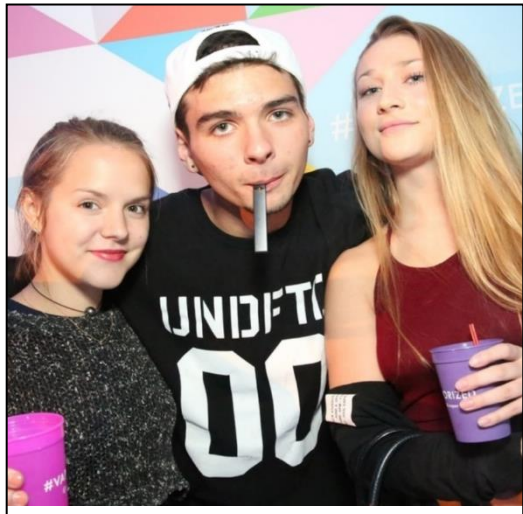
Pod Mods  
(prefilled pods;  
nicotine salts)  
Sleek design  
Easy to conceal



**Puff Bar**  
Disposable  
(nicotine salts)  
Sleek design  
Easy to conceal

# JUUL Phenomenon

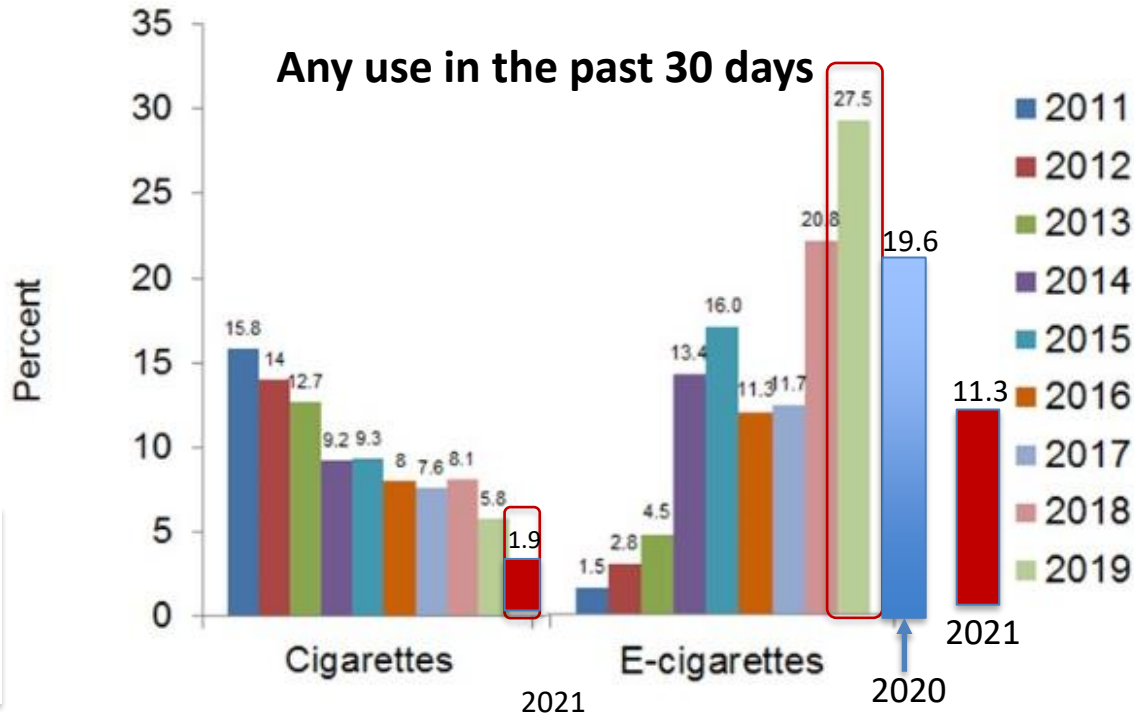
- Sleek high-tech design
- Better nicotine delivery
- Social media marketing





# NATIONAL YOUTH TOBACCO SURVEY\*:

CDC:  
Methodologic  
differences in  
2021 data  
collection due  
to COVID  
“prevent  
year-to-year  
comparisons”



# Electronic Cigarette

*A nicotine delivery device that looks like a cigarette*



*Nicotine +  
propylene glycol or glycerin ±  
flavoring*

No tobacco burned → Safer than cigarettes?

The devices are changing rapidly

**Not FDA regulated → Many knowledge gaps**



# Public Health Impact of E-Cigarettes – Balance of 3 factors

## Potential Benefit

- Help more smokers to quit smoking

## Potential Risks

- Attract nonsmokers → nicotine dependence → transition to smoke
- Possible health risks of vaping
  - Adult smokers: Risks are relative to smoking
  - Youth, nonsmokers: Avoid any risk

# E-Cigarettes - Summary of the Evidence

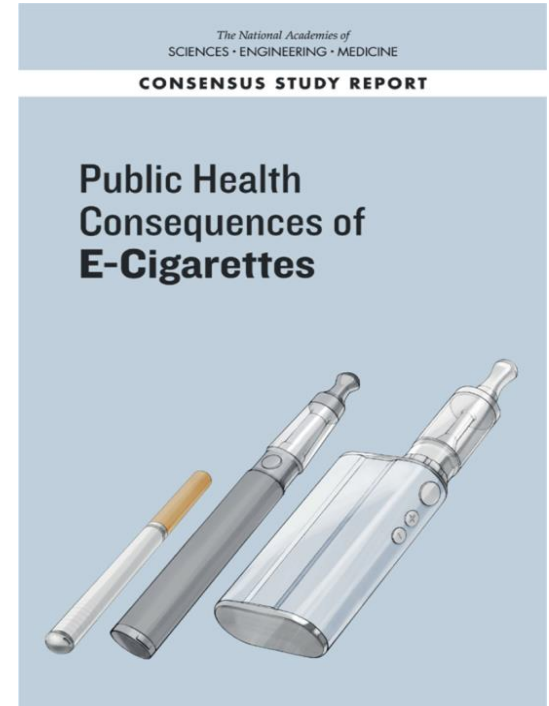
*2018 National Academy of Science, Engineering and Medicine Report*

## Exposure:

- E-cigarettes contain fewer (and lower levels) of toxic substances than conventional cigarettes

## Health Effects:

- **While not without health risks, they are likely to be far less harmful than smoking combustible tobacco cigarettes**
- Long-term health effects of e-cigarettes are not yet clear



# Vaping-Associated Lung Injury (EVALI)

- 2807 cases (68 deaths) by February 18, 2020
  - Bilateral pulmonary infiltrates
  - Hypoxia – many need mechanical ventilation
- Most cases in adolescents or young adults
- Exposure: 85% vaped THC (13% used only nicotine)
- **Culprit: Vitamin E acetate in illicit THC vaping products**
  - **Not commercial e-cigarettes**



# A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Hajek P et al. N Engl J Med. Feb. 14, 2019.

## Participants

- 886 adult smokers (15 cig/d) attending British NHS Stop Smoking clinics
- No preference for NRT vs. e-cigarette to quit

## Interventions

- Choice of type of NRT (combination recommended) – 3 mo. OR
- E-cigarette starter pack (refillable device + 1 bottle e-liquid)  
(All got 4 weekly counseling visits)

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI) <sup>†</sup>	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46) <sup>‡</sup>

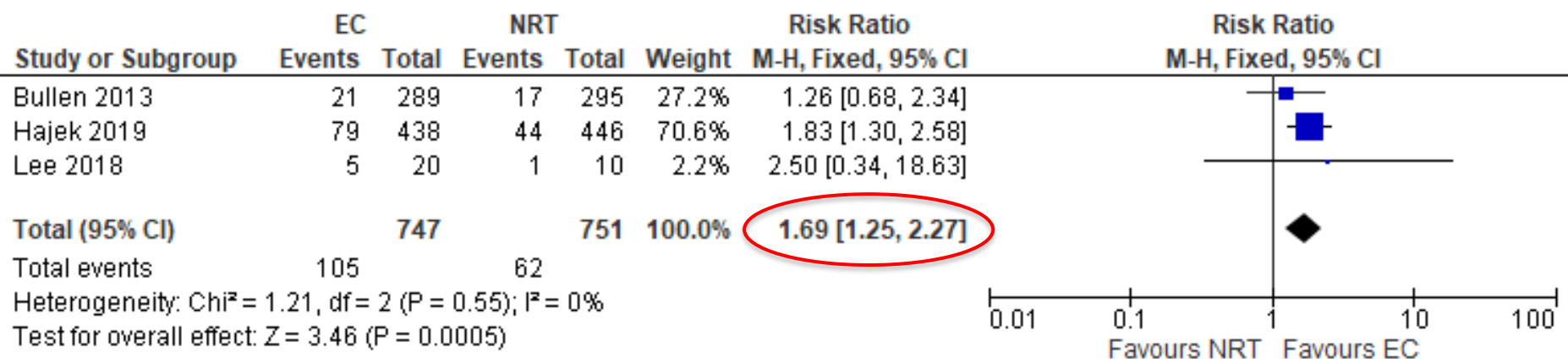
Among those who were quit at 1 year: 80% in e-cig group were still using e-cigs  
9% in NRT group were still using NRT

# Electronic cigarettes for smoking cessation

✉ Jamie Hartmann-Boyce, Hayden McRobbie, Nicola Lindson, Chris Bullen, Rachna Begh, Annika Theodoulou, Caitlin Notley, Nancy A Rigotti, Tari Turner, Ailsa R Butler, Thomas R Fanshawe, Peter Hajek Authors' declarations of interest

Version published: 29 April 2021 [Version history](#)

## Nicotine e-cigarette vs. nicotine replacement: Quitting at 6+ months

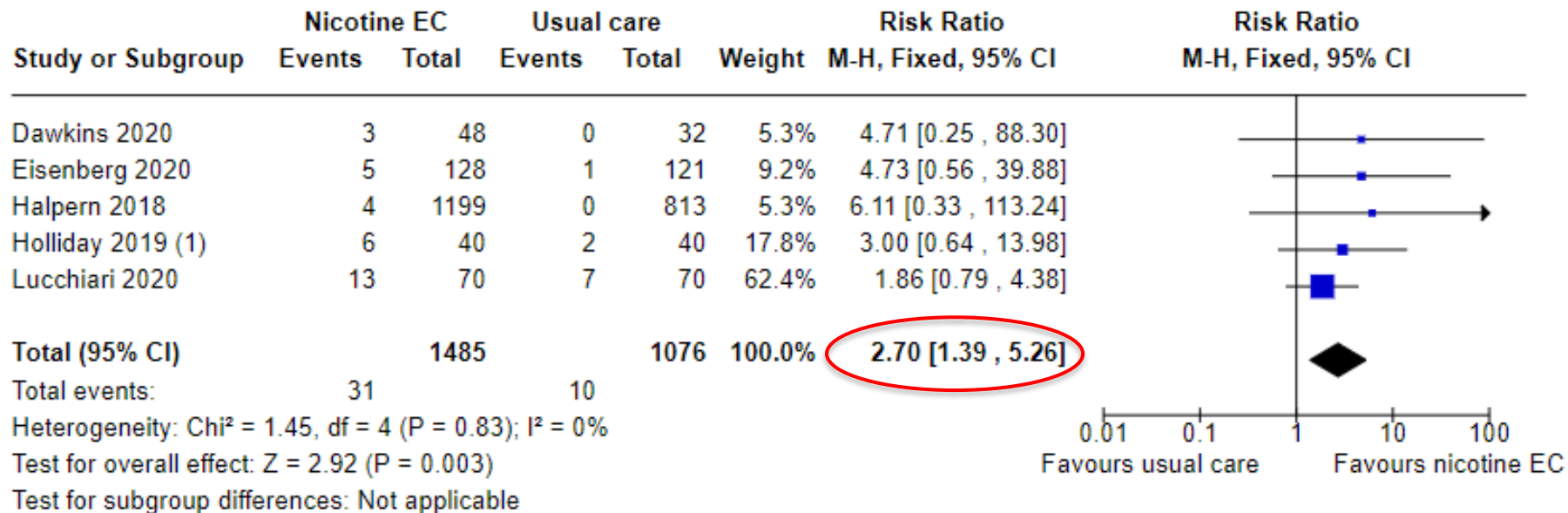


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## Nicotine e-cigarette vs. behavioral support only/no support: Quitting at 6+ months





# Electronic Cigarettes *What should you say to a smoker?*

- Many unanswered questions about safety and efficacy
- They are likely less harmful than smoking combustible cigarettes
- Recommend FDA-approved safe, effective treatments first
- If a smoker uses e-cigarettes
  - Switch completely – stop smoking cigarettes
  - Plan to quit e-cigarettes eventually too
  - Monitor yourself for respiratory symptoms
  - Use commercial e-cigarettes and don't tamper with them

*Consistent with ACC Consensus Document, 2018*

# *F.D.A. Authorizes E-Cigarettes to Stay on U.S. Market for the First Time*

Oct. 12, 2021

The agency approved three Vuse vaping products and said their benefits in helping smokers quit outweighed the risks of hooking youths.

- Approved tobacco flavored product only, no decision on the menthol version yet
- Many flavored e-cig applications were rejected



# Key Points

- Treat tobacco use like a chronic disease – keep trying
- Varenicline or combination NRT are 1<sup>st</sup> line medications  
Single NRT or bupropion are 2<sup>nd</sup> line
- Combinations of treatments produce higher quit rates  
Combine drugs AND combine drugs + counseling
- Make active referrals to free resources  
Quitlines **(1-800-QUIT NOW)**, [www.Smokefree.gov](http://www.Smokefree.gov)
- Ask about vaping and be ready to address questions