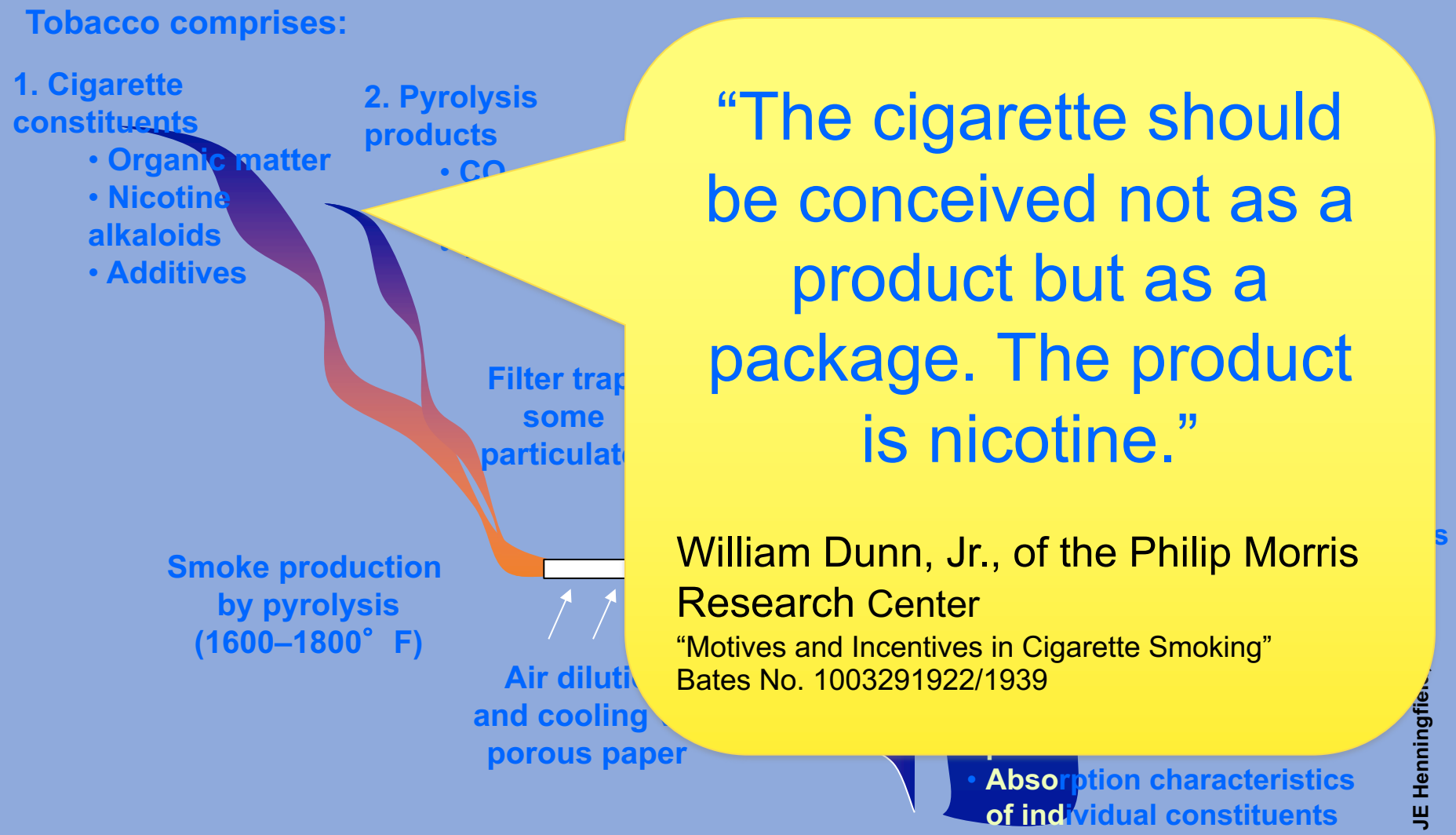
Can E-cigarettes Help Smokers Quit: Exploring the Science, Policy and Future Research Directions

Scott J. Leischow, PhD
Professor of Population Health
Executive Director for Clinical and Translational Science
College of Health Solutions
Arizona State University
scott.leischow@asu.edu

Production and Fate of Cigarette Smoke Constituents



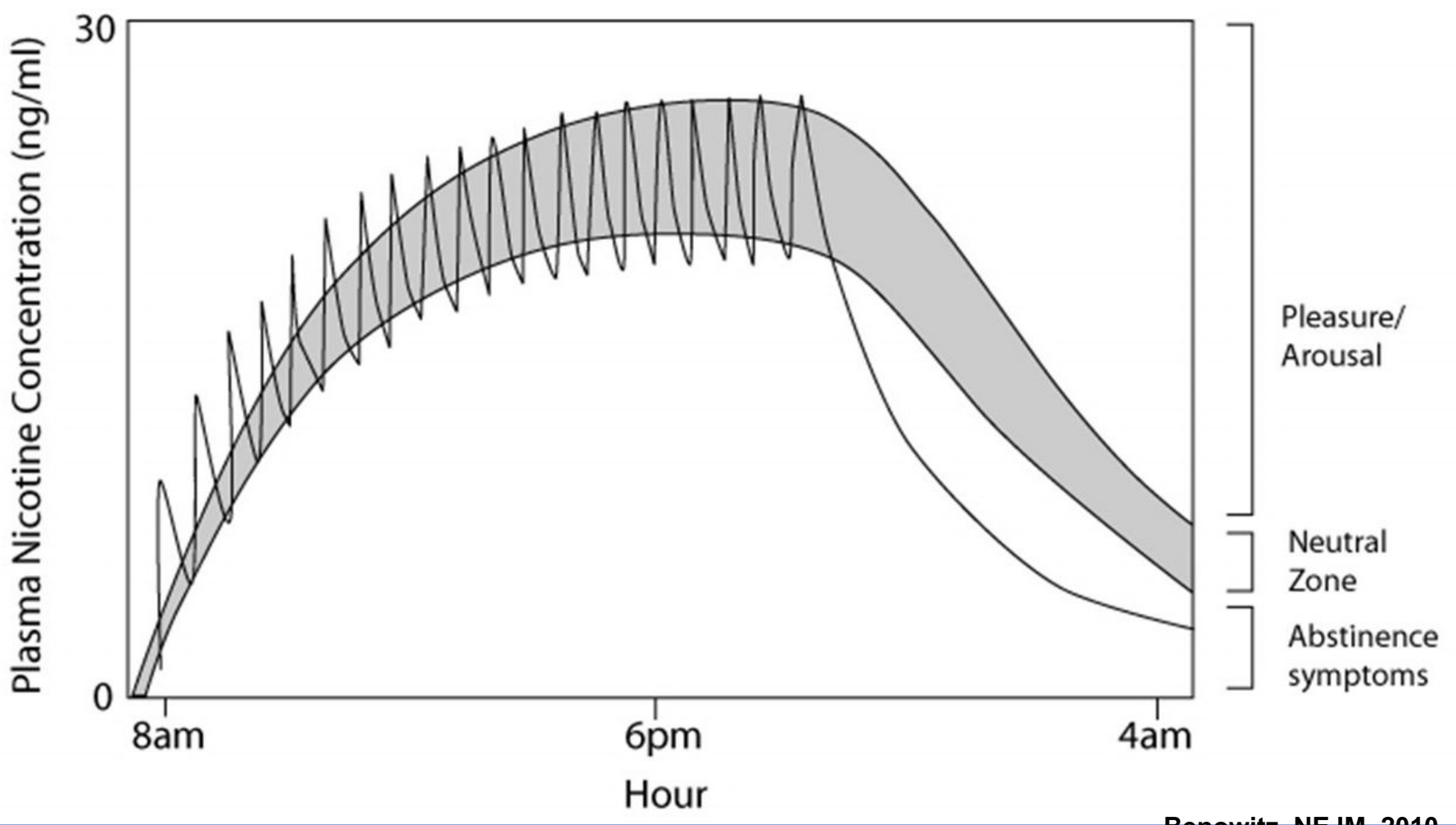
"The cigarette should be conceived not as a product but as a package. The product is nicotine."

William Dunn, Jr., of the Philip Morris Research Center

"Motives and Incentives in Cigarette Smoking"
Bates No. 1003291922/1939

Plasma Nicotine Concentrations in Smokers

**In a regular smoker, this is repeated every day!!



Benowitz, NEJM, 2010

Tobacco and Nicotine Product Regulation: Two Approaches

- Center for Drug Evaluation and Research (CDER)
  - Comprehensive process for evaluating safety and efficacy of drugs
  - Methodologic standard in human studies is the RCT
  - No requirement to show real world population impact
- Center for Tobacco Products (CTP)
  - Came into existence when the Family Smoking Prevention and Tobacco Control Act became law on June 22, 2009
  - Gives the Food and Drug Administration (FDA) the authority to regulate the manufacture, distribution, and marketing of tobacco products to protect public health, but cannot ban tobacco or nicotine (ie, can reduce/minimize harm, but cannot eliminate them)
  - Can regulate all nicotine/tobacco products, inc. delivery systems, flavors, specific constituents, sales, some marketing
  - Can approve products for sale if the evidence indicates that they are less harmful than combustible cigarettes; new products (eg ecigs) were required to submit for PMTA by May 12, 2020 or be pulled from market
  - Must adopt a public health standard, ie, is there evidence indicating that a tobacco product results in less harm than a combustible cigarette? No evidence for 'efficacy' is required.

FDA CDER-Approved Pharmacotherapy for Tobacco Treatment

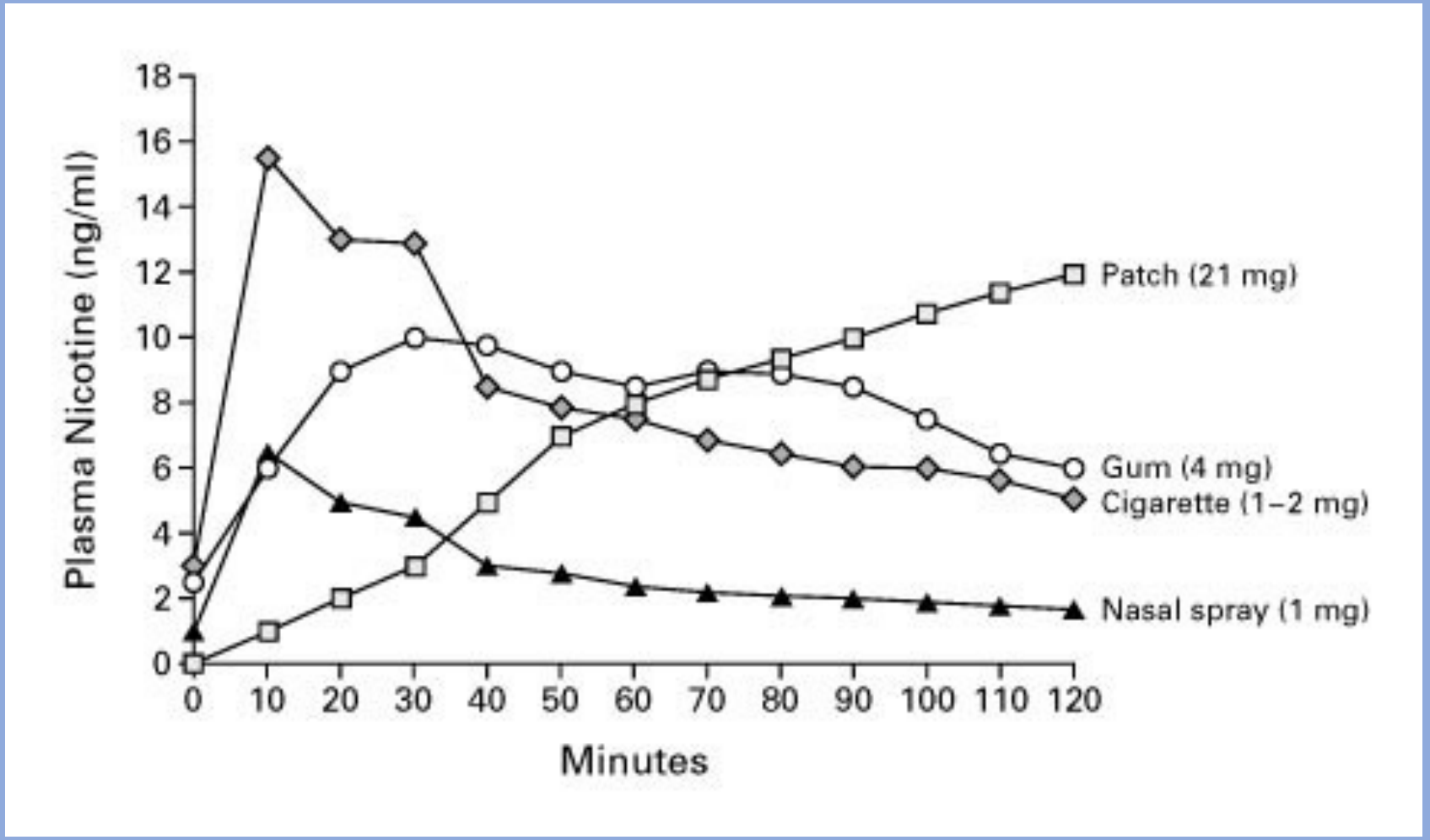
- USPHS Treating Tobacco Use and Dependence: 2008 Update
- Seven first-line medications (5 nicotine and 2 non-nicotine) reliably increase long-term smoking abstinence rates:
  - Bupropion SR
  - Nicotine gum
  - Nicotine inhaler
  - Nicotine lozenge
  - Nicotine nasal spray
  - Nicotine patch
  - Varenicline
- All products work by suppressing withdrawal and craving when smokers quit. The nicotine products are, effectively, harm reduction products

Comparison of FDA-Approved Smoking Cessation Products

Nicotine replacement therapy		Patch	**If >10 cigarettes/day use 21 mg If <10 cigarettes/day use 14 mg or 7 mg**
		Gum	**2 mg or 4 mg (start with 4mg if first tobacco is ≤30 min from waking); max is 20 lozenges or 24 pieces of gum per day**
		Lozenge	
		Nasal spray	**10 mg/mL**
		Oral inhaler	**10 10-mg cartridge (max 6-16 cartridges/day)**
Other pharmacotherapies		Bupropion	**150 mg SR daily (up to twice daily)**
		Varenicline	**0.5 mg daily titrated to 1 mg twice daily**

https://www.acc.org/latest-in-cardiology/articles/2019/03/21/14/39/abcs-of-primary-cv-prevention-2019-update-gl-prevention

Plasma Nicotine Levels from Different Nicotine Delivery Systems



Rigotti, JAMA, 2002

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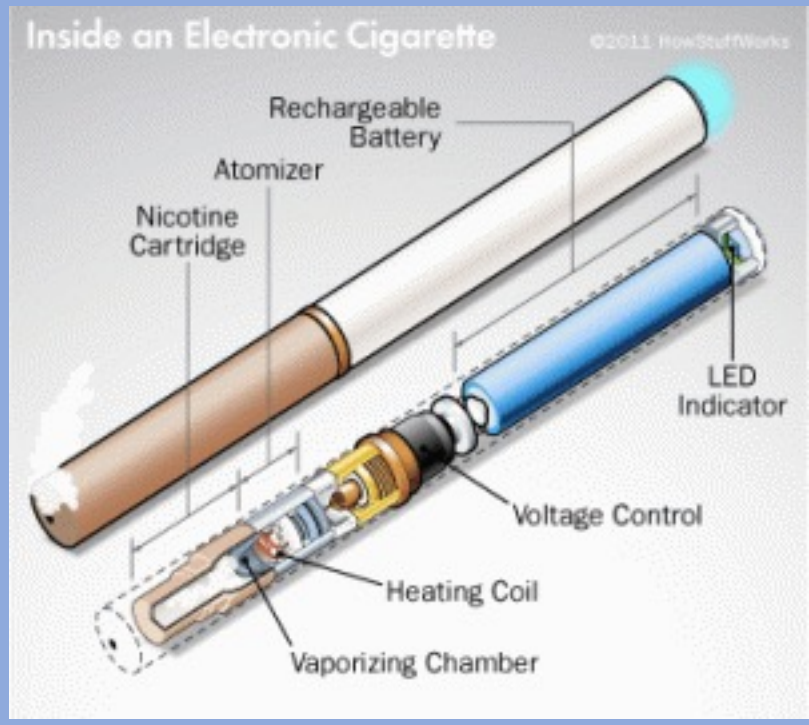
E-Cigarettes: Brief History and Background



- Chinese pharmacist, Hon Lik, patented a device in 2003 and introduced it to the Chinese market the following year. Called them ‘e-cigarettes’

- Current ENDS have three main components:
  - Battery
  - Atomizing Device (ie, heating element)
  - Reservoir for ‘liquid’ (usually nicotine, propylene glycol, glycerin, flavoring, other potential substances)

- When air passes through the atomizing device, heating results in aerosolization of the nicotine mixture and produces a vapor that is ‘inhaled’

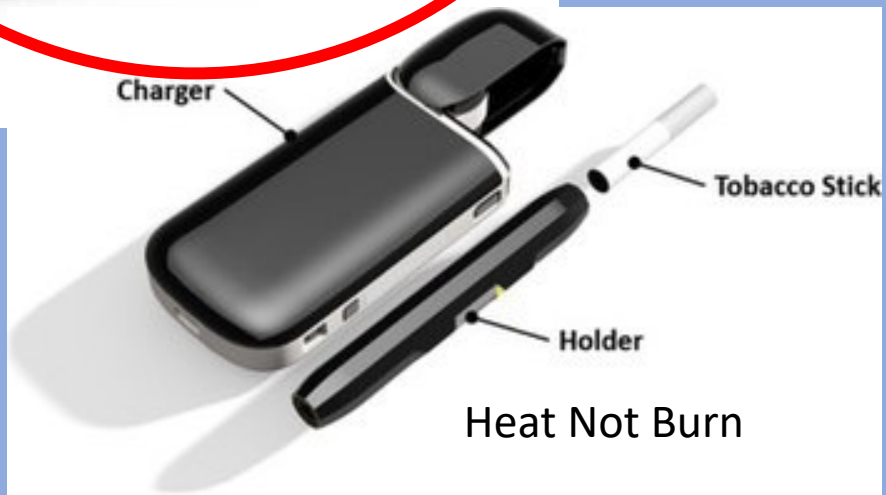
- E-cigarettes are sometimes called “e-cigs,” “vapes,” “e-hookahs,” “vape pens,” “electronic nicotine delivery systems” or “ENDS.”
- Using an e-cigarette is sometimes called “vaping.”

http://www.howstuffworks.com/innovation/everyday-innovations/electronic-cigarette.htm; http://ke.internetforparents.org/blu-electronic-cigarette-harmful.html

Nature of ENDS

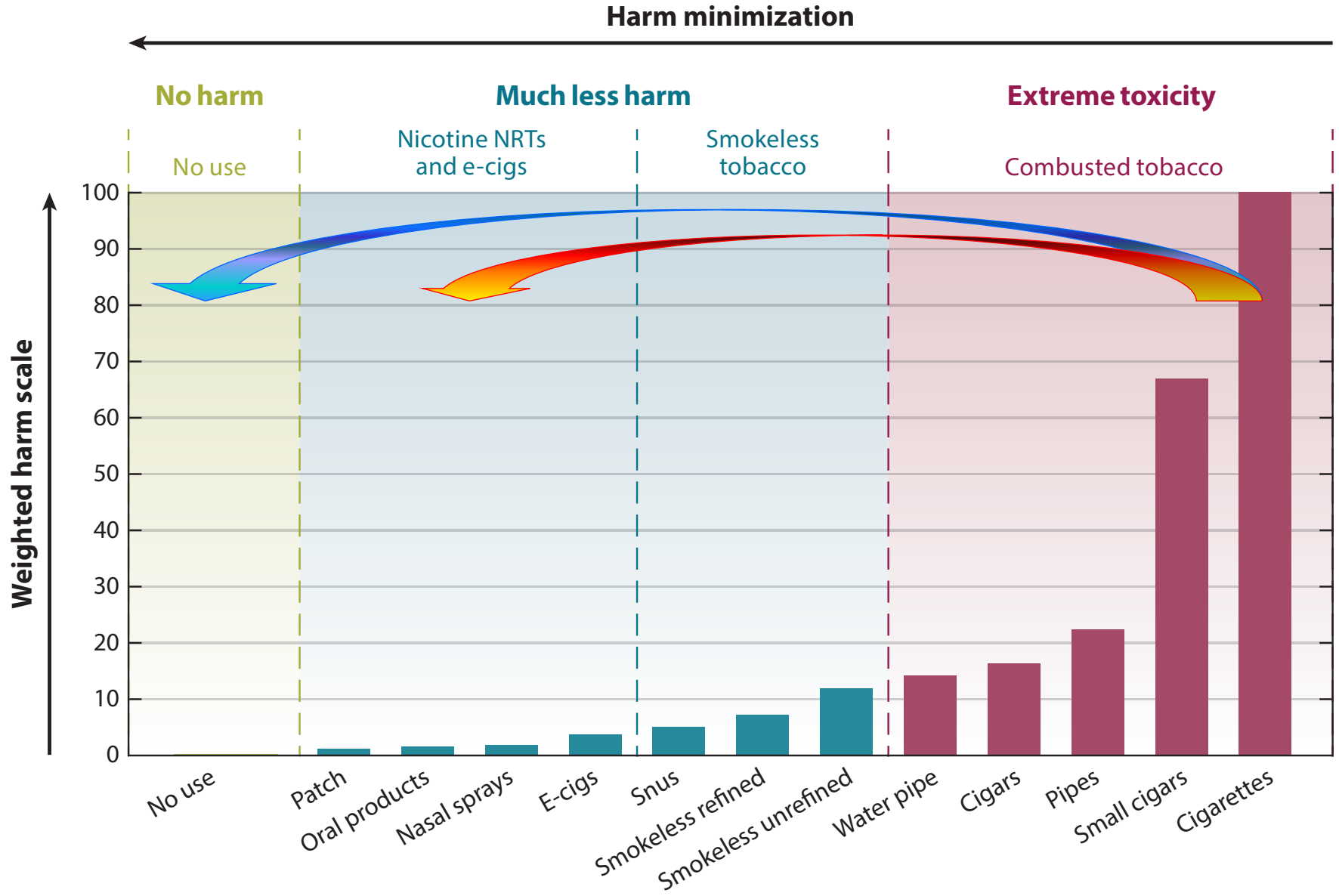
Sample of e-cigarette products. Images are not to scale.

Juul, NJOY, etc: Juul has about 40% of the e-cigarette market



Heat Not Burn

Continuum of Risk



Abrams et al, 2018, *Annu Rev Public Health, with edits by Brandon*

Recent Regulatory Actions to Reduce Youth Use of ENDS

- As of January 2020, it is illegal for a retailer to sell any tobacco product—including cigarettes, cigars and e-cigarettes—to anyone under 21
- FDA intends to implement a policy prioritizing enforcement against certain unauthorized flavored e-cigarette products that appeal to kids, including fruit and mint flavors. They will focus on the following groups of products that do not have premarket authorization:
  - Any flavored, cartridge/pod-based ENDS product (other than a tobacco- or menthol-flavored ENDS product). This does not include e-liquids or cigalikes;
  - All other ENDS products for which the manufacturer has failed to take (or is failing to take) adequate measures to prevent minors' access; and
  - Any ENDS product that is targeted to minors or likely to promote use of ENDS by minors.

NOT ALLOWED:

ALLOWED:

https://www.fda.gov/tobacco-products; Campaign for Tobacco Free Kids

Premarket Tobacco Product Application (PMTA)

Must include scientific data that demonstrates a product is appropriate for the protection of public health

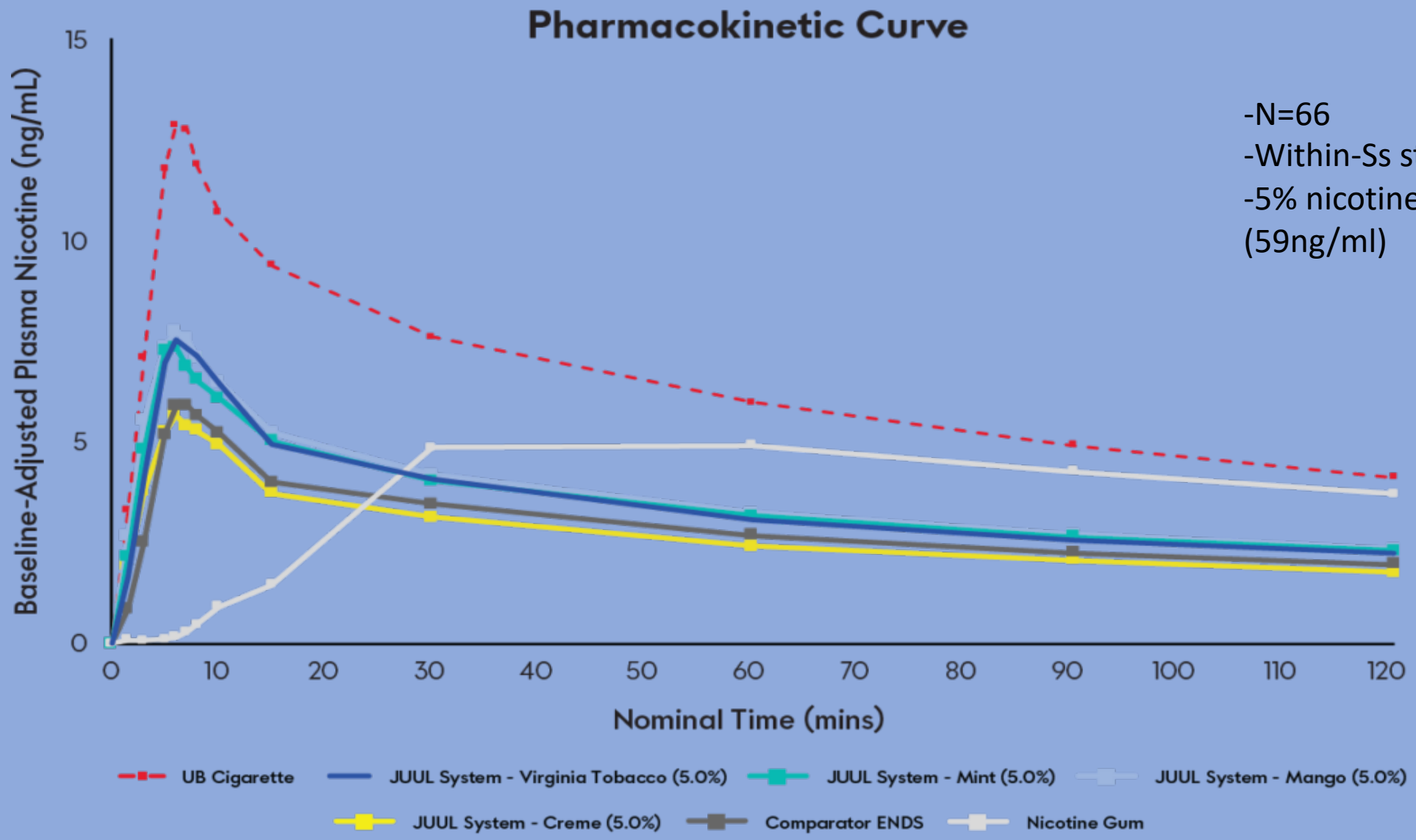
- Companies were required to submit for PMTA by May 12, 2020 or be pulled from market. The FDA had to determine:
  - Risks and benefits to the population as a whole, including people who would use the proposed new tobacco product as well as nonusers;
  - Whether people who currently use any tobacco product would be more or less likely to stop using such products if the proposed new tobacco product were available;
  - Whether people who currently do not use any tobacco products would be more or less likely to begin using tobacco products if the new product were available; and
- Over 500 companies submitted PMTA requests covering more than 6.5 million products. On 9 Sept 2021, FDA ordered 4.5 million products removed, but did not address the largest e-cigarette companies (eg Juul, NJOY, etc). All flavors except menthol banned. Per the FDA, the products "failed to provide sufficient evidence" that the benefits to adult smokers, for whom vapes are a less-damaging alternative to traditional tobacco, outweigh the "documented risks to youth."

https://www.politico.com/news/2021/09/09/fda-electronic-cigarettes-off-market-510967

Why Does Juul Dominate the Adult Smoker Market?

- Developed an approach where nicotine salts are created by combining nicotine in its purest form with an organic acid such as benzoic acid. This boosts nicotine delivery and reduces harshness of nicotine base.
- Each 5% (nicotine-by-weight) cartridge contains approximately 40 mg nicotine per pod and is ‘approximately equivalent to about 1 pack of cigarettes
- Seven studies measured nicotine delivery via vaping-machine generated aerosols, varying in puffing regimes and equipment. Across 200 puffs/pod, they delivered 14.4–32.8 mg of nicotine per pod with equivalence to 13–30 cigarettes
- A study measuring nicotine levels in JUUL users during a 5-day controlled switch found equivalence to 18 cigarettes (closer to one pack)

Why Are Recent Vape Products So Popular? *Nicotine Delivery Rate and Amount*



-N=66
-Within-Ss study
-5% nicotine concentration (59ng/ml)

Goldenson et al, Drug and Alcohol Dependence, Vol 217, Dec 2020

Plausibility as Tobacco Cessation Devices

To merit review as a potential treatment for tobacco dependence, e-cigarettes need to deliver nicotine in sufficient quantities to suppress craving and withdrawal.

Do They??

Schroeder MJ, Hoffman AC. Tob Control. 2014

Plausibility as Tobacco Cessation Devices

1. Inexperienced E-Cigarette Users: Plasma nicotine levels ranged from 0.0 (early studies) to 7.2 ng/mL[1]
2. Experienced E-Cigarette Users: Plasma nicotine levels ranged from 0.74 – 10.3 ng/mL[1]
3. Most studies found that use of e-cigarettes resulted in reduced craving and other withdrawal symptoms[2]

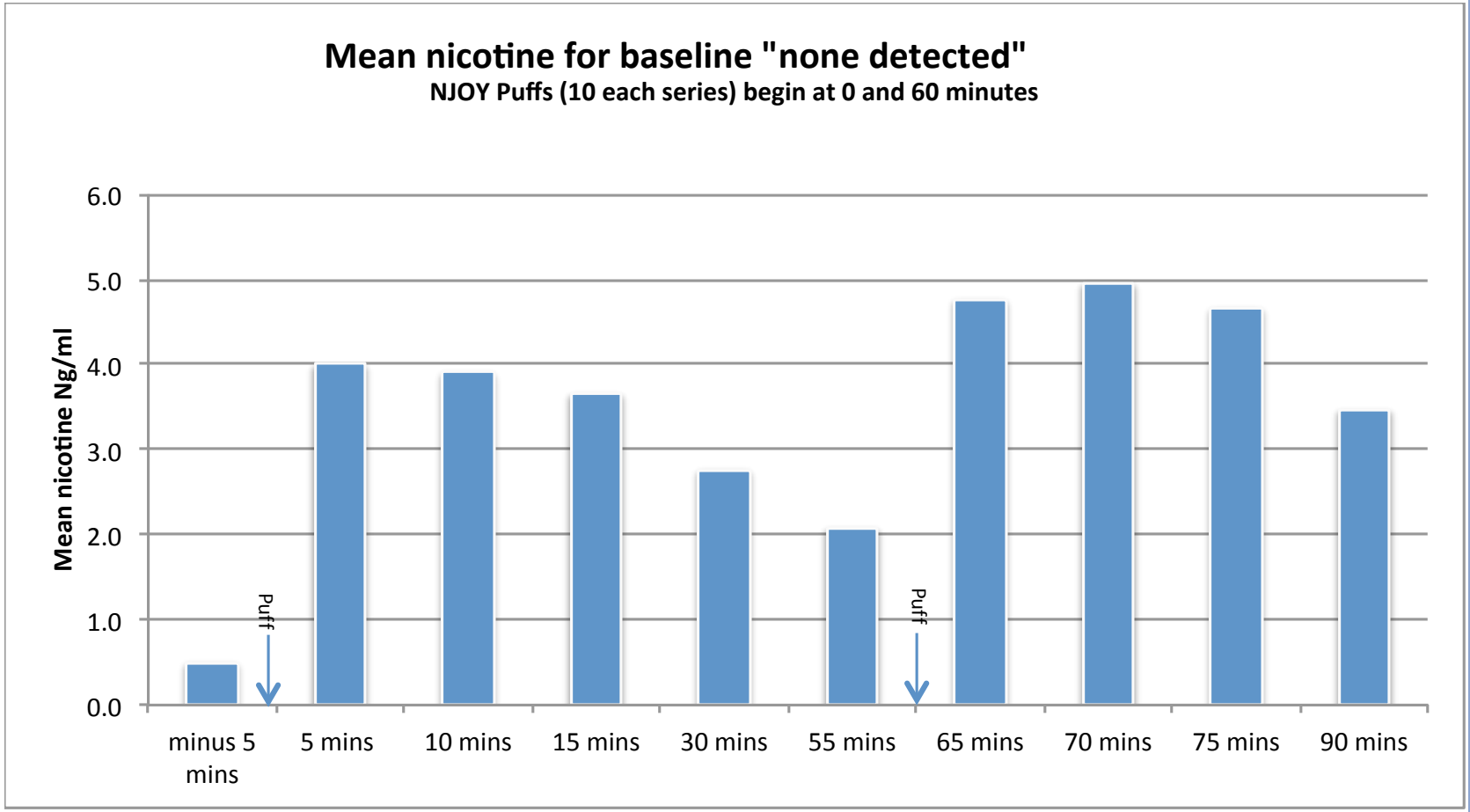
1. Schroeder MJ, Hoffman AC. Tob Control. 2014;
2. Evans SE, Hoffman AC. Tob Control. 2014

Our Research: Nicotine Levels and Short-term Smoking Reduction with an ENDS

- Evaluated nicotine delivery from the currently marketed NJOY® King Bold ENDS (4.5% nicotine) and its short-term potential for smoking reduction or cessation.
- One week of ad libitum use was followed by measurements of plasma nicotine, heart rate, and craving and withdrawal after 12 hours of nicotine abstinence in adult smokers not interested in quitting
- ENDS dosage for the pharmacokinetic/pharmacodynamic testing consisted of 2 series of 10 puffs of the ENDS, with a 30-second inter-puff interval (IPI). The second series of puffs began one hour after the start of the first series. A 4-mL blood sample was drawn into a lavender-top tube 5 minutes before and 5, 10, 15, and 30 minutes after the first puff of each series.
- Self report measures (eg craving) also collected

Nides. Leischow et al., 2013.

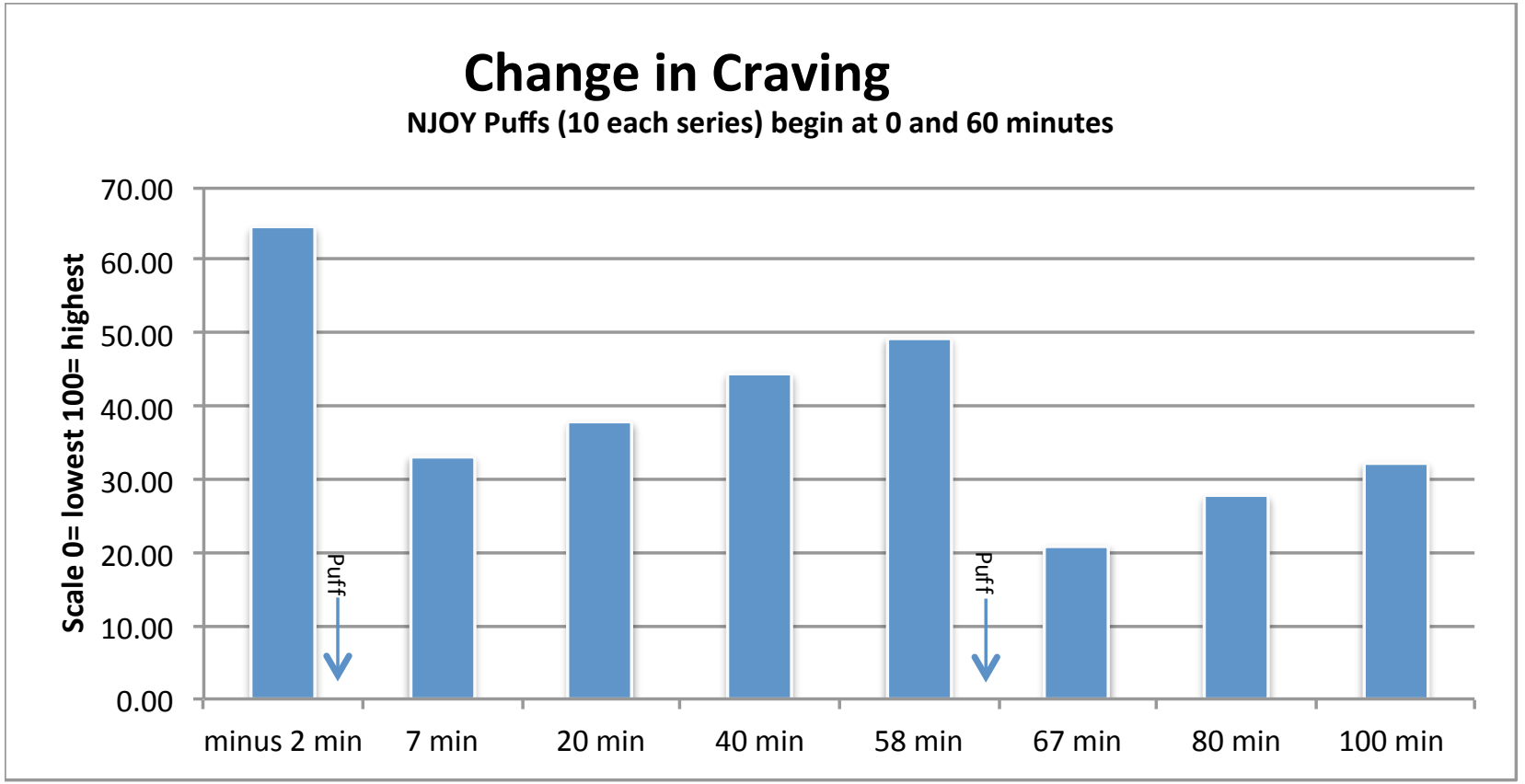
Blood Nicotine Levels



(Note: Mean changes from baseline were statically significant at all times (paired t test, p < .002)

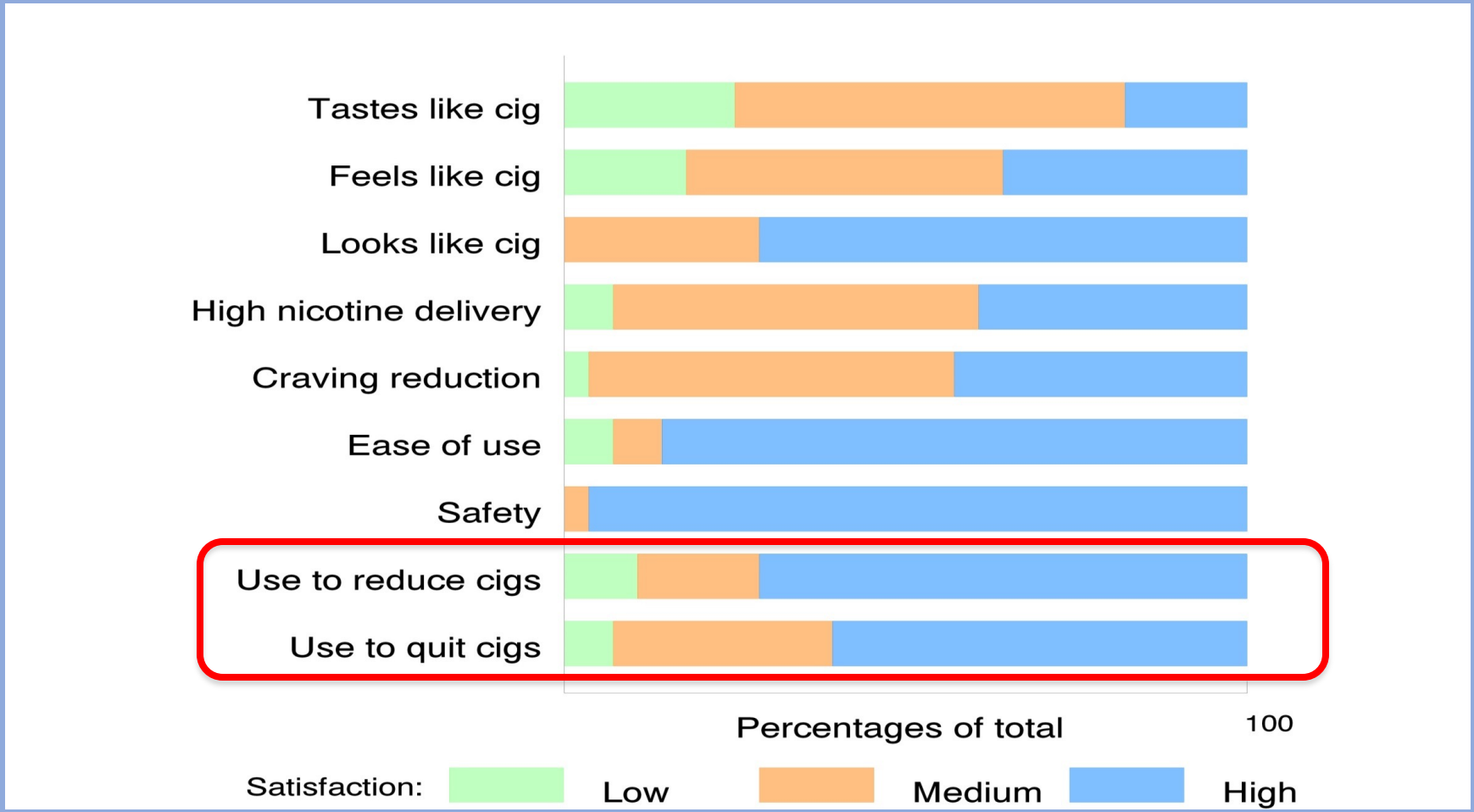
Nides. Leischow et al., 2013.

Change in Craving



Nides. Leischow et al.; AJHB; 2013.

Product Perceptions after Sampling Week



(Note: Percentage of subjects with responses to the perception questionnaire in the categories of low (0-1), medium (2-4), and high (5-6) on the 7-point scale ranging from 0 for "not at all satisfied" to 7 for "extremely satisfied."

Nides. Leischow et al.; AJHB; 2013.

Cochrane Review: Nicotine E-Cigarettes Compared to NRT for Smoking Cessation

Patient or population: People who smoke
Setting: New Zealand, UK, USA
Intervention: Nicotine EC
Comparison: NRT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NRT	Risk with Nicotine EC				
Smoking cessation at 6 months to 1 year Assessed with biochemical validation	Study population 6 per 100	9 per 100 (7 to 12)	RR 1.53 (1.21 to 1.93)	1924 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
Adverse events at 4 weeks to 6 months Assessed by self-report	Study population 45 per 100	44 per 100 (36 to 53)	RR 0.98 (0.80 to 1.19)	485 (2 RCTs)	⊕⊕⊖⊖ LOW[b]	-
Serious adverse events at 4 weeks to 1 year Assessed via self-report and medical records	Study population 5 per 100	7 per 100 (4 to 10)	RR 1.30 (0.89 to 1.90)	1424 (4 RCTs)	⊕⊕⊖⊖ LOW[c]	1 study reported no events; effect estimate based on the three studies in which events were reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on assumed quit rates for NRT assuming receipt of limited behavioral stop-smoking support (as per Hartmann-Boyce 2018a). The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

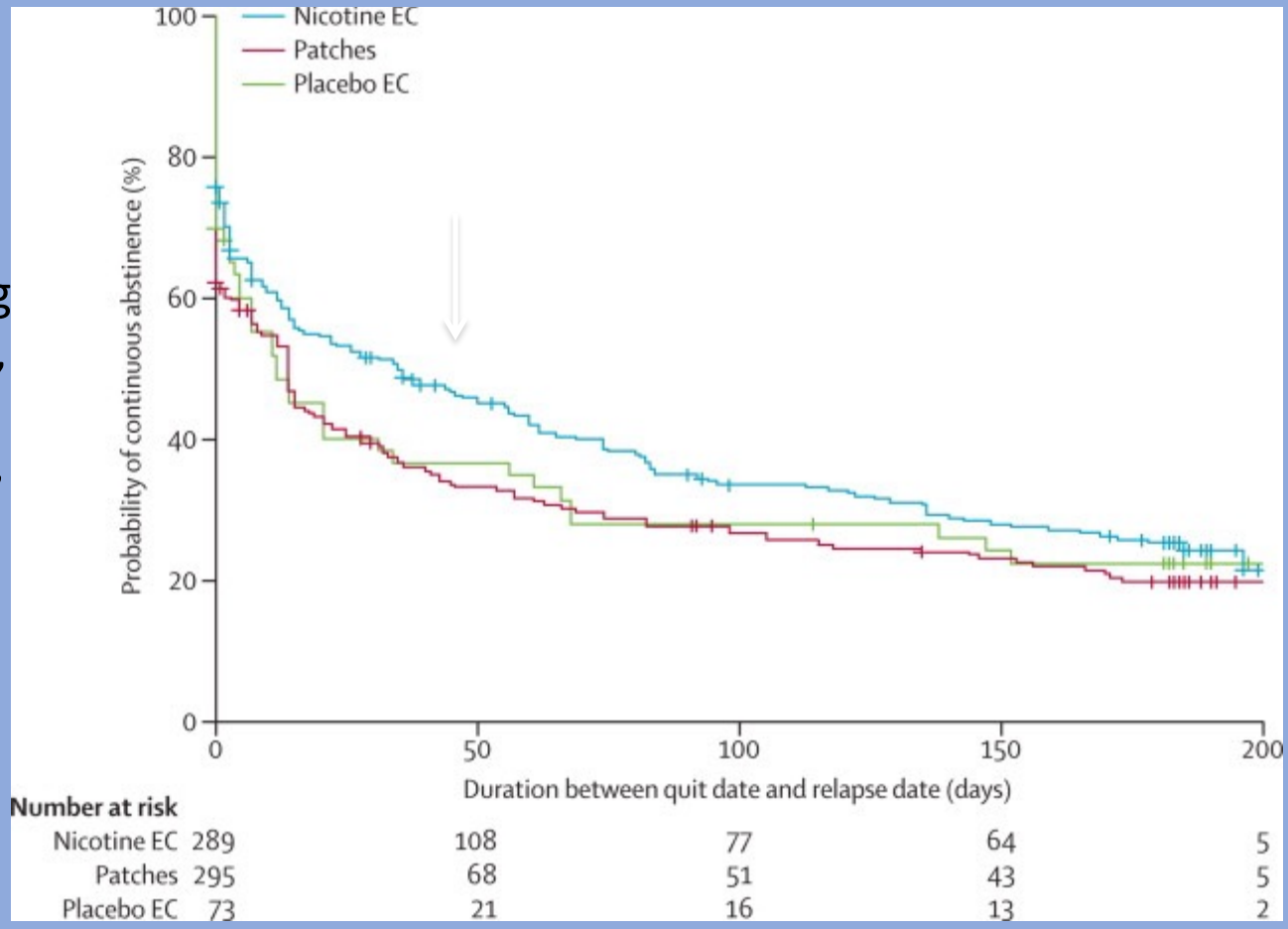
CI: Confidence interval; **RCT:** randomized controlled trial; **RR:** Risk ratio

Reference: Hartmann-Boyce, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 021, Issue 9. Art. No.: CD010216; Sept. 2021

Effectiveness in Quitting: Clinical Trials

Bullen C., et al. Lancet. 2013

Adult smokers wanting to quit were randomized to 16 mg nicotine e-cigarettes, nicotine patches (21 mg patch, one daily), or placebo e-cigarettes (no nicotine) for 12 weeks after quit day



	Nicotine e-cigarettes (n=289)	Placebo e-cigarettes (n=73)	Difference Fisher's exact p value	Relative risk (95% CI)	Risk difference (95% CI)
Continuous abstinence					
1 month*	67 (23·2%)	12 (16·4%)	0·21	1·41 (0·81 to 2·46)	6·74 (–3·06 to 16·54)
3 months*	38 (13·1%)	5 (6·8%)	0·14	1·92 (0·78 to 4·70)	6·30 (–0·68 to 13·28)
6 months (primary outcome)	21 (7·3%)	3 (4·1%)	0·44	1·77 (0·54 to 5·77)	3·16 (–2·29 to 8·61)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D., Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc., Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D., Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D., Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.

Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI)†
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)

Cochrane Review: Nicotine E-Cigarettes Compared to Non-Nicotine E-Cigarettes for Smoking Cessation

Patient or population: People who smoke cigarettes
Setting: Canada, Italy, New Zealand, UK, USA
Intervention: Nicotine EC
Comparison: Non-nicotine EC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-nicotine EC	Risk with Nicotine EC				
Smoking cessation at 6 - 12 months Assessed with biochemical validation	Study population		RR 1.94 (1.21 to 3.13)	1447 (5 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	-
	7 per 100	14 per 100 (9 to 23)				
Adverse events at 1 week to 6 months Assessed via self-report	Study population		RR 1.01 (0.91 to 1.11)	601 (3 RCTs)	⊕⊕⊕⊖ MODERATE[c]	-
	35 per 100	35 per 100 (31 to 38)				
Serious adverse events at 1 week to 1 year Assessed via self-report and medical records	Study population		RR 1.06 (0.47 to 2.38)	792 (5 RCTs)	⊕⊕⊖⊖ LOW[d]	3 studies reported no events; effect estimate based on the 2 studies in which events were reported
	2 per 100	2 per 100 (1 to 4)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on receipt of moderate-intensity behavioral stop-smoking support. The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

Reference: Hartmann-Boyce, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 021, Issue 9. Art. No.: CD010216; Sept. 2021

Cochrane Review: Nicotine E-Cigarettes Compared to Behavioral Support Only/No Support for Smoking Cessation

Patient or population: People who smoke
Setting: Canada, Italy, UK, USA
Intervention: Nicotine EC
Comparison: Behavioural support only/no support

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with behavioral support only/no support	Risk with Nicotine EC				
Smoking cessation at 6 to 12 months Assessed using biochemical validation	Study population		RR 2.61 (1.44 to 4.74)	2886 (6 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b]	-
	4 per 100	10 per 100 (6 to 19)				
Adverse events at 12 weeks to 6 months Assessed via self-report	Study population		RR 1.22 (1.12 to 1.32)	765 (4 RCTs)	⊕⊕⊖⊖ LOW[a]	-
	60 per 100	73 per 100 (67 to 79)				
Serious adverse events at 4 weeks to 6 months Assessed via self-report and medical records	Study population		RR 1.51 (0.70 to 3.24)	1303 (7 RCTs)	⊕⊖⊖⊖ VERY LOW[a,c]	4 of the 7 studies reported no SAEs; MA is based on pooled results from 3 studies
	1 per 100	2 per 100 (1 to 3)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on receipt of limited stop-smoking support. The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

CI: Confidence interval; **MA:** meta-analysis; **RCT:** randomized controlled trial; **RR:** Risk ratio

Reference: Hartmann-Boyce, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 021, Issue 9. Art. No.: CD010216; Sept. 2021

Cochrane Conclusions, and Limitations

- Nicotine e-cigarettes probably do help people to stop smoking for at least six months. They probably work better than nicotine replacement therapy and nicotine-free e-cigarettes.
- They may work better than no support, or behavioral support alone, and they may not be associated with serious unwanted effects.
- However, we need more evidence to be confident about the effects of e-cigarettes, particularly the effects of newer types of e-cigarettes that have better nicotine delivery than older types of e-cigarettes.
- But...Small number of studies

Reference: Hartmann-Boyce, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 021, Issue 9. Art. No.: CD010216; Sept. 2021

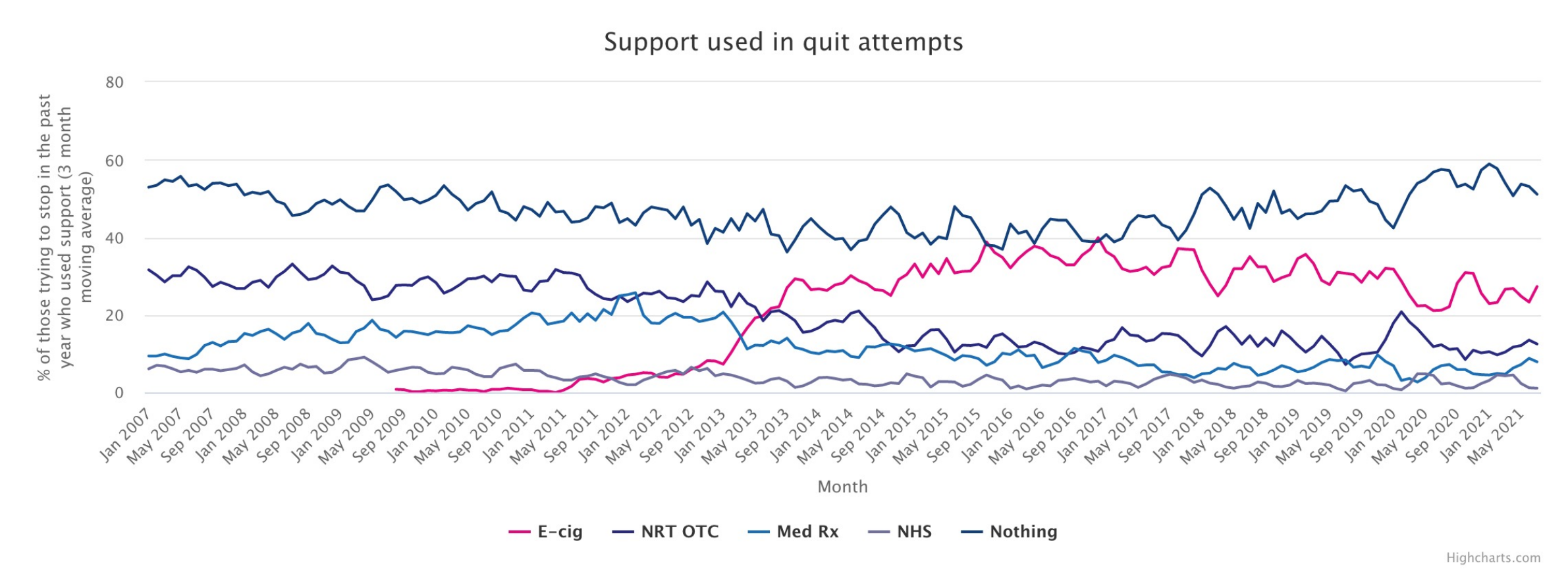
UK Smoking Toolkit Study – Real World Tracking in the UK

Methods

- Data collected during monthly household survey
- Each month involves a new representative sample of 1700-1800 adults (16 and over)
- Due to the pandemic:
- The March 2020 survey did not complete face-to-face collection at short notice and is missing
- To present trends, March is interpolated as the average of Feb and April
- From April 2020, surveys were conducted by telephone and among adults aged 18 and over until face-to-face collection is possible
- Running since November 2006 and has accumulated more than 290,000 respondents of whom more than 60,000 are ‘last-year smokers’
- Fidler, et al., 2011. 'The smoking toolkit study': a national study of smoking and smoking cessation in England. BMC Public Health 11:479

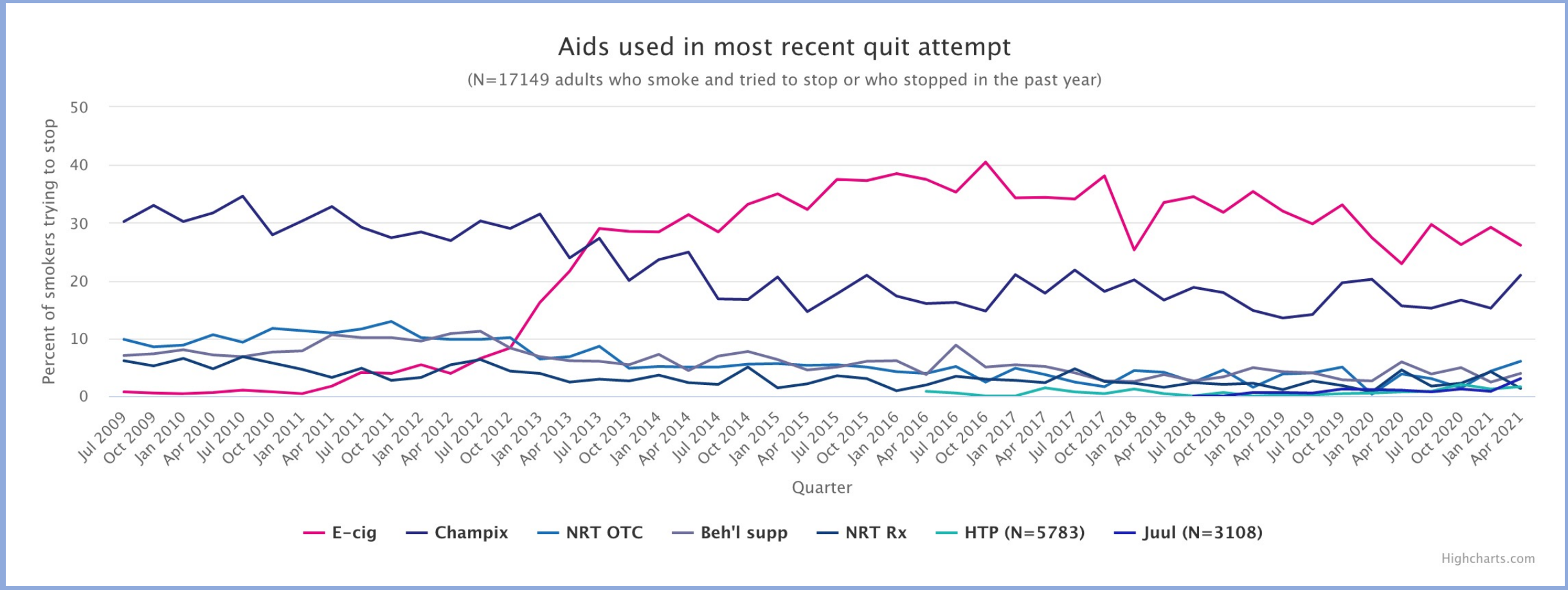
https://smokinginengland.info/graphs/monthly-tracking-kpi

Support Used to Quit



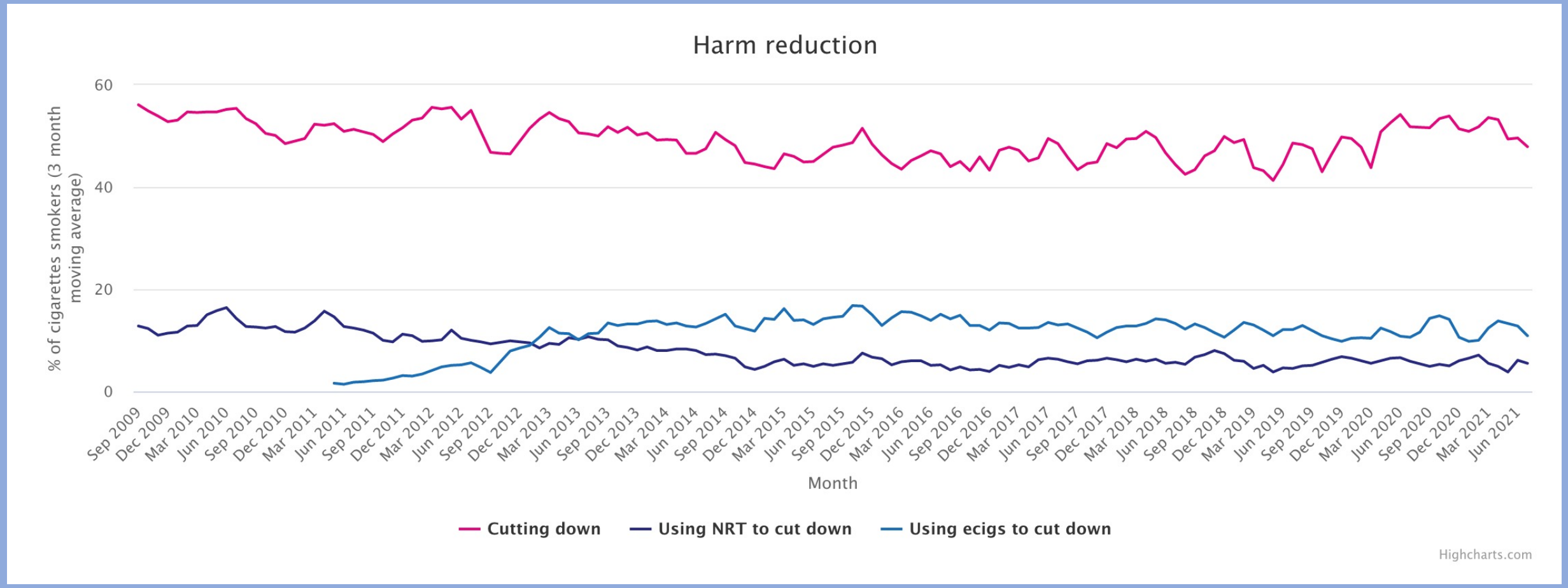
https://smokinginengland.info/graphs/monthly-tracking-kpi

Aids Used in Most Recent Quit Attempt



https://smokinginengland.info/graphs/monthly-tracking-kpi

Harm Reduction Approaches



https://smokinginengland.info/graphs/monthly-tracking-kpi

ClinicalTrials.gov: E-cigarette Studies

- 31 studies returned under search term “Electronic cigarettes”
- 16 are not yet recruiting or are currently recruiting
- 1 study in Canada; 6 in the UK; 9 in Italy; 13 in the United States
- Areas of study include:
  - E-cigarettes vs. traditional Nicotine Replacement Therapy
  - Effect on nicotine concentrations
  - Use by mental health patients
  - 5-year Longitudinal study

Planning for a pilot study

- Work with local vape shop to identify smokers who want to quit using e-cigarettes
- Vape shop provides web link regarding study to any that purchase with the intent to quit. This provides info on the study and consent
- Protocol: Randomize participants such that half receive free nicotine patches and the other half gets no additional pharmacotherapy
- Assess smoking status at weeks 3, 6 and 12. Biochemical verification of smoking status from those who claim to have quit combustibles

Thank you!

Tucson, Arizona by SJL