I stand with Dr Karl E Lund, who should be at this conference.



EFFECT OF ELECTRONIC CIGARETTES ON SMOKING CESSATION IN SMOKERS WITH NO PLANS TO QUIT: A RANDOMIZED PLACEBO-CONTROLLED TRIAL Jonathan Foulds¹, Ph.D.

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JF has done paid consulting for pharmaceutical companies involved in developing smoking cessation products (e.g. J&J, Pfizer, GSK) and has received a grant and study product from Pfizer. JF has not done paid work of any sort for tobacco or e-cig companies.

TE is a paid consultant in litigation against the tobacco industry and is named on a patent for a device that measures the puffing behavior of electronic cigarette users There is no such thing as "an e-cig". There are many different e-cigs. Most of the early clinical trials used 1st generation e-cigs.



Examples of electronic cigarette devices that have been available on the market (Farsalinos and Polosa, 2014)



Blood Nicotine Levels in Cigarette and E-cigarette Users



First generation e-cigs deliver very little nicotine.

Advanced <u>e-cigs deliver a</u> <u>higher blood nicotine</u> <u>concentration typically less</u> <u>than a cigarette</u>

Some advanced e-cigs can deliver nicotine as rapidly as cigarettes.

Yingst JM, Foulds J, et al. PLoS One. 2019 Jul 25;14(7):e0220300

Objective

The main aim of this RCT was to assess the effects of e-cigs on toxicant exposure, and the primary outcome (reported Cobb et al, Lancet Resp Med, 2021) is urinary concentration of the carcinogen biomarker of tobacco exposure, NNAL.

Here we report on an exploratory analysis of a randomized placebo-controlled trial, examining the effects on quitting smoking of electronic cigarettes (ECIGs) containing different nicotine concentrations among current cigarette smokers with no plans to quit.

Methods:

Current smokers (**N=520**; \geq 10 cigarettes/day [CPD] for \geq 1 year) interested in reducing cigarette intake (but not quitting) were randomized to one of four 6-month conditions and received either an eGO-style ECIG paired with 0, 8, or 36 mg/ml nicotine liquid (double-blind) or a cigarette-shaped plastic tube (CIG-SUB). Self-reported CPD and exhaled carbon monoxide (CO) were measured at all study visits (among other outcomes), enabling analysis of effects on cigarette cessation. The main outcome here is a comparison of intent-to-treat, self-reported 7-day point prevalence cigarette abstinence, biochemically confirmed by exhaled CO of <10ppm at visit 10 (6 months after randomization).

Study Design

 Two-site (VCU, Richmond, VA; N=260; Penn State, Hershey, PA, N=320), four-arm, 6-month parallel group RCT with follow-up to 9 months.

Study Product Arms

• QuitSmart cigarette substitute



- ECIG: 3.3–4.1 V, 1100 mAh rechargeable battery paired with 1.5 Ohm, dual-coil, 510-style cartomizer (SmokTech, Shenzhen, China):
 - 0 mg/ml nicotine concentration (70/30; PG/VG)
 - 8 mg/ml nicotine concentration (70/30; PG/VG)
 - 36 mg/ml nicotine concentration (70/30; PG/VG)
- ECIG conditions were double-blind.
- ECIG cartomizers collected/dispensed at each study visit.

The e-cig and doses used in this trial are capable of delivering a blood nicotine boost of 8 ng/ml (8mg/ml) and 18 ng/ml (36 mg/ml) [Hiler et al 2017]



Minutes Relative to First Puff

Inclusion/Exclusion Criteria

- Aged 21-65
- Smoked ≥10 filtered/machine-rolled cigarettes/day for ≥1 year
- Interested in reducing their cigarette smoking but not planning to quit in the next 6 months
- Expired air CO ≥10 ppm at baseline
- No serious quit attempts in the past 1 month
- No other tobacco use past 7 days and/or use of an ECIG ≥5/28 days
- No unstable/significant medical conditions in past 12 months
- No other medical disorders that could affect primary outcomes
- No use of marijuana/other illegal drugs weekly or more frequently in past 3 months

Study Design Overview



The ECIG consists of a 3.3 V, 1100 mAh battery (SmokTech; Shenzhen, China) with a 1.5 Ohm, dual-coil, 510-style cartomizer (SmokTech; Shenzhen, China) that is purchased without any liquid in it. Study staff load the cartomizer with 1 ml of a flavored (tobacco or menthol) 70 % propylene glycol/30 % vegetable glycerin liquid containing nicotine concentrations of 0, 8, or 36 mg/ml.



Participants

	CIGSUB	ECIG-	ECIG-	ECIG-	OVERALL	р
		0 mg/ml	8 mg/ml	36 mg/ml		
Ν	130	130	130	130	520	
Age, years	46.1±12.4	45.7±11.4	45.6±11.7	47.4±11.1	46. 2±11.6	0.578
Gender (female), % (n)	60.8 (79)	61.5 (80)	61.5 (80)	51.5 (67)	58.9 (306)	0.279
Race/Ethnicity, % (n)						0.942
Caucasian/White NH	63.9 (83)	70.8 (92)	66.9 (87)	67.7 (88)	67.3 (350)	
African American/Black NH	30.0 (39)	25.4 (33)	28.5 (37)	27.7 (36)	27.9 (145)	
Other	6.2 (8)	3.9 (5)	4.6 (6)	4.6 (6)	4.8 (25)	
Hispanic, % (n)	0.8 (1)	0	2.3 (3)	3.1 (4)	1.5 (8)	0.166
Education, % (n)						0.716
Less than 12th grade/No diploma	9.2 (12)	14.6 (19)	10.0 (13)	9.2 (12)	10.8 (56)	
High school graduate/GED	32.9 (42)	30.0 (39)	26.2 (34)	30.0 (39)	29.6 (154)	
Some college/no degree	29.2 (38)	33.9 (44)	36.2 (47)	31.5 (41)	32.7 (170)	
Associate's degree	15.4 (20)	13.1 (17)	11.5 (15)	13.1 (17)	13.3 (69)	
Bachelor's degree or higher	13.9 (18)	8.5 (11)	16.2 (21)	16.2 (21)	13.7 (71)	
Visit 2 Average CPD (7-day TLFB)	18.4±7.1	18.8±8.3	19.4±8.7	17.8±6.5	18.6 ±7.7	0.348
Visit 2 Penn State Cigarette Dependence Index	13.4±3.0	13.7±2.7	13.2±3.0	13.2±3.2	13.4 ±3.0	0.457
Visit 2 CO, ppm	23.6±12.5	23.4±12.2	21.8±9.8	21.9±10.5	22.7 ±11.3	0.444

Note. CPD=cigarettes per day, 7-TLFB=7 day timeline-follow-back method, CO=carbon monoxide, ppm=parts per million; N=25 missing Visit 2 Penn State Cigarette Dependence Scale score.

At pre-randomization baseline, across groups participants were on average 46 years old, 41% male, 67% White, and smoked 19 CPD with no significant between-group differences.

Results

Quit Rates at Visit 10 (24 weeks post-randomization):

36mg/ml – 14/130 (10.8%) 8mg/ml – 6/130 (4.6%) 0mg/ml – 1/130 (0.8%) CIG SUB – 4/130 (3.1%)

Significant Differences (Fisher's Exact Test) between:

- 36mg/ml vs. 0mg/ml p=.0007
- 36mg/ml vs. CIG SUB p=.025

The mean exhaled CO among self-reported quitters was <3ppm for all groups (compared to 23ppm at baseline).



Results

At visit 9 (4 weeks prior, week20) quit rates were:

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36mg/ml – 12/130 (9.2%)
8mg/ml – 5/130 (3.1%)
0mg/ml – 1/130 (0.8%)*
CIG SUB – 2/130 (1.5%)* (both sig < 36 mg/ml)
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At visit 10, 86%, 83%, 0%, and 0% of those same groups who were abstinent, were still using their study product.

All 14 in the 36mg/ml group who were abstinent at v10, were using their assigned product when they first achieved abstinence, an average of 95 days earlier.

Results

Those randomized to 36 mg/ml as compared to CigSub or Omg/ml were (a) sig more likely to quit smoking for 1 day+ (22.3%, 26.2% v 41.5%)

(b) likely to achieve significantly more days of cigarette abstinence overall(5.3, 4.7 v 15.6).

E-cigarettes with nicotine delivery approaching that of a cigarette are more effective in enabling ambivalent smokers to abstain from cigarettes.

Conclusion

When smokers seeking to reduce smoking try ECIGs, very few spontaneously quit in the short term.

However, if smokers continue to use an ECIG with high nicotine delivery for over 3 months, a greater proportion succeed in completely switching to ECIGs, as compared with placebo or no ECIG.

Full details of this study at:

Foulds J, Cobb C et al. Effect of an electronic nicotine delivery systems on cigarette abstinence in smokers with no plans to quit: Exploratory analysis of a randomized placebo-controlled trial. **Nicotine Tob Res 2022**, 24 (7): 955–961. (also in medRxiv, 2021)

Cobb C, Foulds J, and the CSTP-Randomized Control Trial Methods Workgroup. Effect of an electronic nicotine delivery system with 0, 8, or 36 mg/ml liquid nicotine versus a cigarette substitute on tobacco-related toxicant exposure: a randomized controlled trial **Lancet Respiratory Medicine 2021** Aug;9(8):840-850

Yingst J, Wang et al. Changes in nicotine dependence among smokers using electronic cigarettes to reduce cigarette smoking in a randomized trial. **Nicotine Tob Res. (online, June 2022**).

Safer Nicotine Wiki 2021

Closing the life-saving escape route that smokers can have in snus and e-cigarettes is a bit like closing the door to the fire escape because the steps may be slippery.

Karl E Lund, PhD Senior Researcher Norwegian Institute of Public Health



Recruitment and Retention









Expired air CO - MI (adjusted)

Instructions at Day 0, randomization

"As you learned during the consent process, you are being asked to reduce your traditional cigarette consumption throughout this study. <u>Tomorrow</u>, you will cut back on the number of cigarettes you smoke per day by half. This means that if you smoke 20 cigarettes per day, you will now smoke no more than 10 cigarettes per day....

Remember the study product that we just discussed? You should use that study product to replace the cigarettes that you normally smoke.."

Instructions at Day 7 (visit 3)

"During the next 7 days, continue to smoke only half of the cigarettes that you normally smoked before. This means you should maintain the same reduction in the total number of cigarettes smoked as you did last week."

Instructions at Day 14 (visit 4)

"During the next 14 days, you will be asked to reduce your cigarette consumption a bit more. Previously, we asked you to reduce your cigarette consumption by half. Now we are going to ask that you reduce your cigarette consumption by 75% compared to your baseline level. This means that if you smoked 20 cigarettes per day at the start of this study, you will now try to smoke only 5 cigarettes per day.

We ask that you continue to use only the study product provided to you and your usual brand of cigarettes....etc."

Instructions at Day 28 (visit 5)

"During the next 28 days, continue to smoke only a quarter of the number of cigarettes you used to smoke, (i.e. for you, that would be no more than x cigarettes per day). Also, continue to use your study product in the place of those cigarettes you are cutting out. In fact, use the study product whenever you want, consistent of course with local rules and regulations regarding clean indoor air."

Instructions at Day 56 (visit 6 etc)

"During the next 28 days, we want you to make sure you continue to attempt/maintain your 75% reduction in your cigarette consumption. You have done really well so far so that is awesome. We also want to encourage you to continue to use your study product to replace the cigarettes you have cut out. If you want to continue to reduce the number of cigarettes smoked per day even further, that would be excellent."