New evidence on e-cigarettes and other approaches to smoking cessation 2019

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Declaration of interest

- I have no links with any e-cigarette or tobacco manufacturers

- My research into safety and effects of EC is funded by the National Institute of Health Research, Public Health England, UK Centre for Tobacco and Alcohol Studies and UK Medicines Regulatory Agency

Developments in 2018-2019

- E-cigarettes for smoking cessation
    - New data on effects on smokers
    - Varenicline in dual users
- Other smoking cessation findings
    - Medications
    - Tobacco dependence

Electronic cigarettes versus nicotine replacement treatment

Hajek P, Phillips A, Przulj D, Pesola F, Myers K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie H

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

Previous two RCTs, Cochrane verdicts

- EC better than placebo, same as patch

- Achieved with early EC models
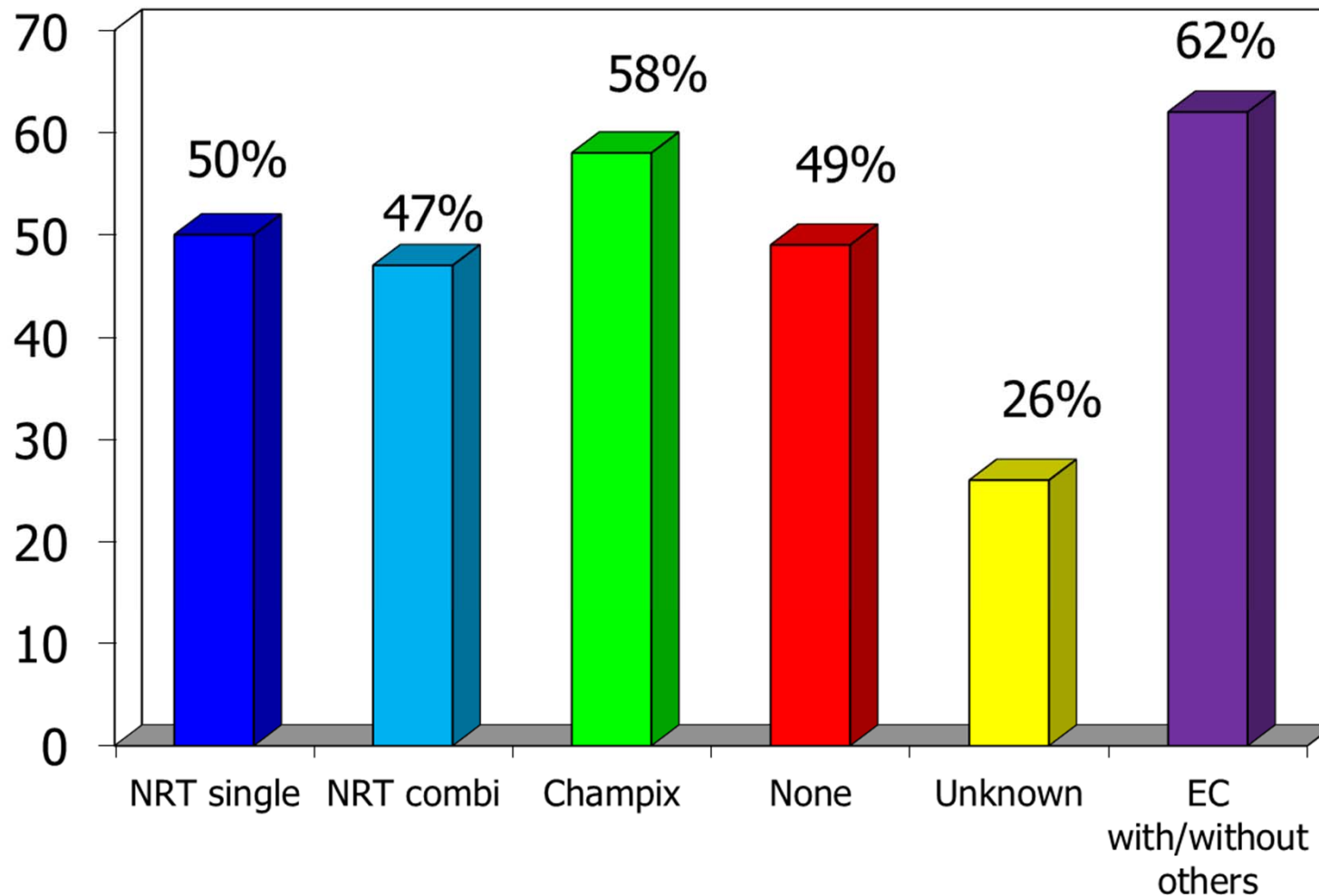 - Poor nicotine delivery, leakage, discontinued

The first small trial with tank EC

- Smokers not intending to quit
- N=32 given refillable EC (18mg/mL)
- N=16 control group – no EC provided
- 2 months CO-validated quit rates
  - 34% vs 0%

Adriaens et al. 2014

Medications efficacy 2017-2018
4-week self-reported quit rate

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TEC trial

- Smokers accessing service with no strong preference for EC or NRT

- Randomised on target quit date (TQD)
  - NRT arm: N=447;   EC arm: N=439

- Followed up for one year, CO validation of abstinence

- Strict outcomes, drop-out or not validated=non-abstainer

NRT arm

- NRT of client choice

- Combinations recommended (88% used NRT combinations)

- Able to switch products (59% did)

- Provided for up to three months

- Guided by clinicians experienced in NRT use

- Mean cost £124

EC arm

- Starter pack: Refillable EC, one bottle of 18mg/ml e-liquid

- Instructed on use

- Advised to try other e-liquids and EC products via vape shops or internet

- Most switched to other e-liquids within a week (popularity of flavours: fruit, tobacco, mint, candy, others)

- Mean cost £20

Sample

- No between-arm differences
  - Mean age 43
  - 48% female
  - 40% entitled to free prescriptions
  - 80%+ tried meds before
  - 15 cigs/day
  - baseline CO=20

Abstinence rates

	EC N=438	NRT N=446	Relative Risk (95% CI)	P-value
Abstinence between weeks 2 and 52, N (%)	79 **18%**	44 **10%**	1.8 (1.3 to 2.6)	.001
Abstinence between weeks 24 and 52, N (%)	93 **21%**	53 **12%**	1.8 (1.3 to 2.4)	<.001

SSS evaluation using the same outcome criteria: 10% one-year quit rate for individual support – but 46% treated with varenicline

Long-term product use

- Abstainers in EC arm: 80% using EC; 3% using NRT

- Abstainers in NRT arm: 9% using NRT; 32% using EC
  - quit rates 20% vs 8% without 'contaminators'

- On-going vaping – good or bad thing?
  - Continuing nicotine use
  - But may alleviate withdrawal symptoms and weight gain and prevent relapse

Other outcomes

- EC received better ratings for helpfulness, satisfaction and taste

- Urges to smoke lower in EC arm at all time points

- Other withdrawal symptoms lower in EC arm in Week 1

Safety

- One death in each study arm (heart disease both)

- More nausea in NRT arm

- More throat/mouth irritation in EC arm

- Mostly mild, no difference in prevalence of severe effects (7% nausea both arms; mouth irritation 6% vs 4%)

Antibacterial effects of vaping?

	EC (N=315) N (%)		NRT (N=279) N (%)		P-value[a]
	Baseline	12 months	Baseline	12 months	
Shortness of breath	120 (38)	66 (21)	92 (33)	64 (23)	.2
Wheezing	102 (32)	74 (24)	97 (31)	59 (21)	.6
Cough	173 (55)	97 (31)	145 (52)	112 (40)	**.005**
Phlegm	137 (44)	79 (25)	122 (44)	104 (37)	**.001**

[a] Logistic regression with symptoms at 12 months regressed onto study arm while adjusting for baseline scores and study centre

Conclusions

- EC are significantly more effective than NRT

- Including EC starter packs among treatment options can improve the efficacy of stop-smoking services

- It also reduces the service cost by some £100 per client who sets a quit date (almost twice as much per quitter)

EC vs usual care (RCT)

- Dental patients, N=80
- EC (as in TEC) vs usual care
- 6M CO-validated: **15% vs 5%, p<0.01**

Holliday R. et al. Pilot and Feasibility Studies 2019

EC vs NRT in pharmacy

- N=115 could chose NRT, EC or both
- 4-6 weeks abstinence:
    - EC (N=37): 62%; EC+NRT (N=13): 62%
    - NRT (N=65): 35%
    - $p<0.01$

Cox et al. Addictive Behaviours, 2019

Effect of EC use on population level smoking cessation

- US CPS-TUS

- 2014-2015 (N=161,054); compared with previous 4 surveys

- Tried to quit? Quit for at least 3M?

- EC users quit rate: 8.2%; non-users: 2.5%-4.8%

- Population quit rate significantly increased

Zhu et al. BMJ 2019

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Natural experiment update: Australia vs US+UK

UK, US, Australia 18y+ smoking rates 2010-2018

Data: UK Office of National Statistics | US: NHIS | Australia: NDSHS; NHS
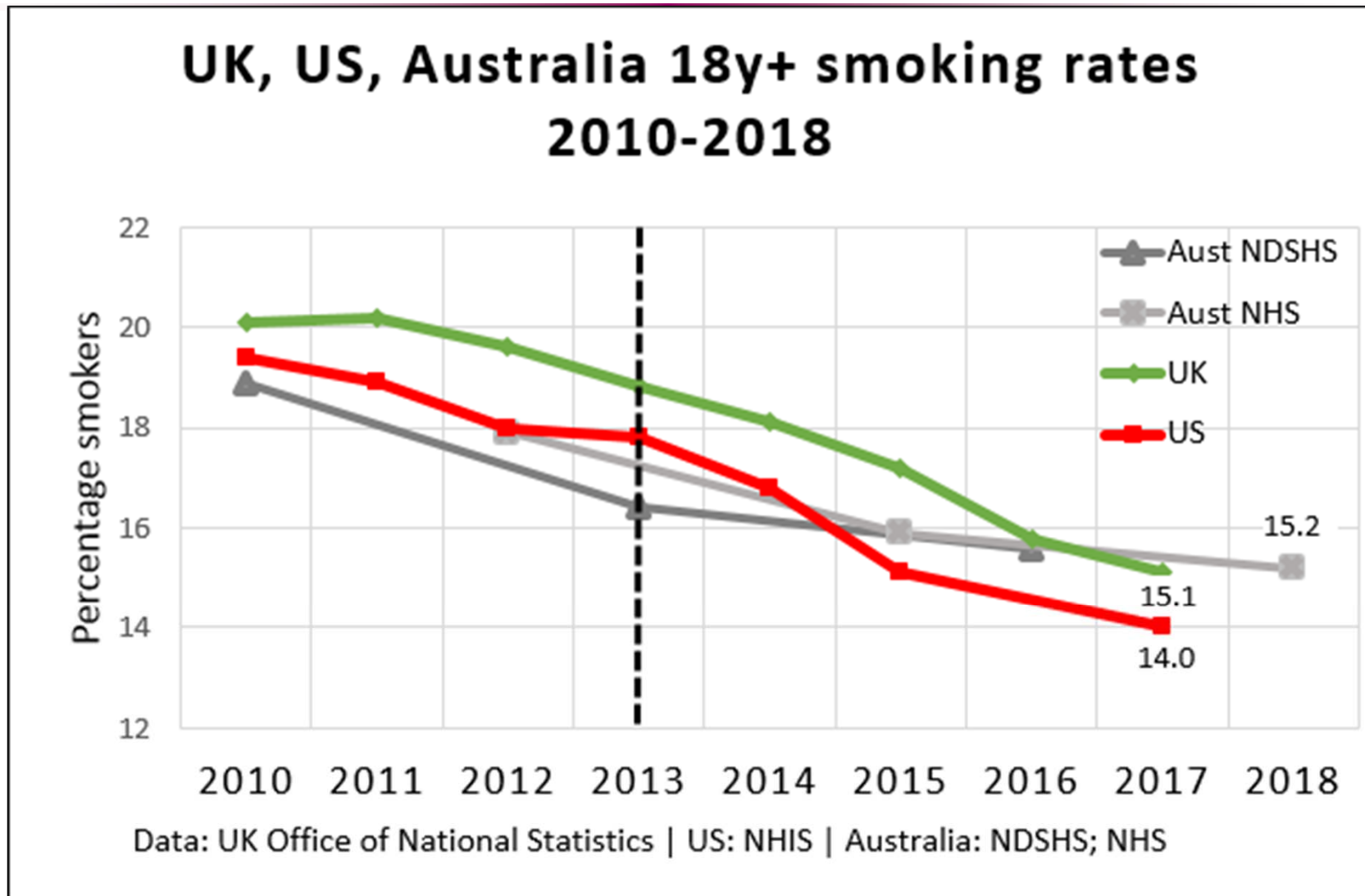
Rapid decline in smoking in young people (18-24) in US
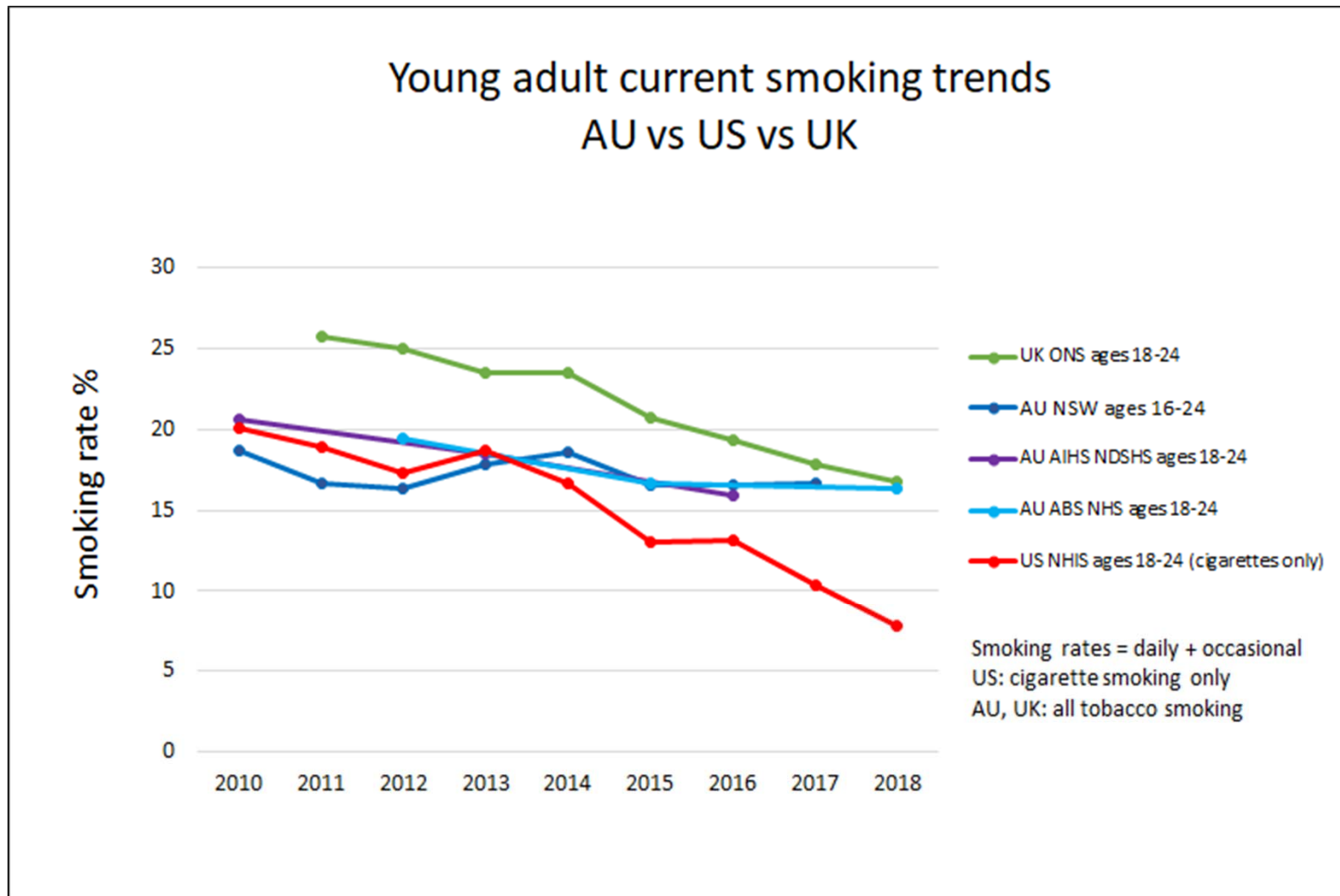
Conclusions

- In clinical context, there is strong evidence that EC help smokers quit

- On the population level, EC use is associated with a reduction in smoking prevalence, but a formal analysis of time trends has not been done and other factors may be contributing

Interest in varenicline and its effects in people who both smoke and vape

Hajek, Peerbux, Phillips, Smith, Pittacio, Przulj

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Background

- Smokers try e-cigarettes (EC) to limit risks of smoking

- Some switch fully, some abandon vaping

- Some become dual users – find EC helpful enough to smoke less, but not good enough to replace smoking altogether

- Nothing is known about interest among dual users in stop-smoking medications and whether they can help them

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DUO study

- Longitudinal study of dual users (N=204)

- **Interest in and reactions to varenicline**
  - NRT is of less interest in this context

Wanted: Vapers who also smoke

If you use **both e-cigarettes and regular cigarettes**, and are willing to help us with an important study, please call us on

020 7882 5948

Or email

health-research@qmul.ac.uk

Barts and The London
School of Medicine and Dentistry

TEC advertisements v3.0, 01 July 2015

Study procedures

- First contact: Study info, eligibility check; If eligible, consent, questionnaires (including medical history), saliva kit and £20 posted
  - Q included: Interested in v to stop smoking?
- On receipt of Q and saliva sample, those wanting v were called to confirm if eligible (all were) and to ask them to call on receipt before starting use

Study procedures

- V users advised over the phone on v and quitting and started v; TQD 1-2 weeks later; weekly support calls over 4 weeks, then optional calls every 2 weeks for up to 12 weeks

- All participants (v or no-v) called/e-mailed to provide data at 3, 6 and 12 M; posted saliva samples plus £10 at 3 and 6 and £20 at 12M

What % of dual users are interested in varenicline?

- We estimated a maximum of 20%
- 61% (N=124) expressed interest
  - Expression of interest can be misleading, some lost contact or changed their mind
- 42% (N=85) confirmed interest and received varenicline
- **39% (N=80) started treatment**
  - Of 5 not starting: not the right time to quit (stress) - 3; quit in the meantime - 1; lost the meds and dropped out - 1

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Do the two groups differ?

	Used varenicline (N=80)	Did not use v. (N=124)	Difference
Age (SD)	33.6 (11.6)	30.4 (11.2)	p=0.053
Women (%)	29%	31%	NS
FTND	4.9	4.1	P=0.012
Months of vaping	16.8	16.8	NS
CPD (SD) now	11.7 (5.2)	9.2 (5.9)	P=0.003
CPD (SD) before vaping	20.7 (10.1)	22.4 (8.9)	NS
Nicotine strength (mg/ml)	13.8 (n=67)	9.5 (n=112)	P=0.001
Enjoyment smoking	6.2	6.1	NS
Enjoyment vaping	7.2	7.5	NS
Refillable EC (%)	75 (94%)	111 (95%)	NS

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What proportion of dual users quit vaping at 1, 3 and 6 months?

	Used varenicline (N=80)	Did not use varenicline (N=124)	Difference
4 weeks	16%		
3 months (PP)	24%	2%	P<0.001
6 months (PP)	24%	3%	P<0.001
6 months (sustained)	13%	2%	P=0.002

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What proportion of dual users quit smoking at 1, 3 and 6 months?

	Used varenicline (N=80)	Did not use varenicline (N=124)	Difference
4 weeks	34%		
3 months (PP)	44%	9%	P<0.001
6 months (PP)	31%	11%	P<0.001
6 months (sustained)	18%	5%	P=0.003

What proportion of dual users quit both at 1, 3 and 6 months?

	Used varenicline (N=80)	Did not use varenicline (N=124)	Difference
4 weeks	16.3% (13/80)		
3 months (PP)	20% (16/80)	2% (2/124)	P<0.001
6 months (PP)	16% (13/80)	2% (2/124)	P<0.001
6 months (sustained)	10% (8/80)	2% (2/124)	P=0.007

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Changes in enjoyment of smoking and vaping

	Used varenicline	Did not use varenicline	Diff
Enjoyment of vaping in those still vaping at 3M	-0.8 (n=46)	-0.17 (n=99)	p=0.032
Enjoyment of smoking at 3M	-1.3 (n=28)	-0.6 (n=90)	NS
Enjoyment of vaping at 6M	-0.4 (n=30)	-0.02 (n=82)	NS
Enjoyment of smoking at 6M	-0.96 (n=26)	-0.6 (n=70)	NS

Conclusions

- Almost half of dual users are keen to use varenicline (more dependent smokers using stronger e-liquid)

- There is a clear signal that varenicline helps them stop smoking (and vaping)

- Clinicians can advise dual users that there is some evidence that varenicline can help them stop smoking (would it work for HNB?)

- A randomised study is needed to provide definitive evidence

Other smoking cessation methods

Progressive nicotine patch dosing prior to quitting smoking

ADDICTION

RESEARCH REPORT

SSA · SOCIETY FOR THE STUDY OF ADDICTION

doi:10.1111/add.14483

Progressive nicotine patch dosing prior to quitting smoking: feasibility, safety and effects during the pre-quit and post-quit periods

Dunja Przulj[1], Luis Wehbe[2], Hayden McRobbie[1] & Peter Hajek[1]

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Efficacy of NRT is modest

Long-term abstinence rates

Risk Ratio=1.60
95% CI: 1.53-1.68

Pre-cessation NRT use

Long-term abstinence rates

Risk Ratio=1.18; 95% CI: 0.98-1.41

- Pre-cessation NRT
- NRT post quit date

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Increasing nicotine dose

Long-term abstinence rates

Risk Ratio=1.43
95% CI: 1.12-1.83

Nicotine Gum
4mg 2mg

Long-term abstinence rates

Risk Ratio=1.14
95% CI: 1.01-1.29

Nicotine Patch
High dose Standard dose

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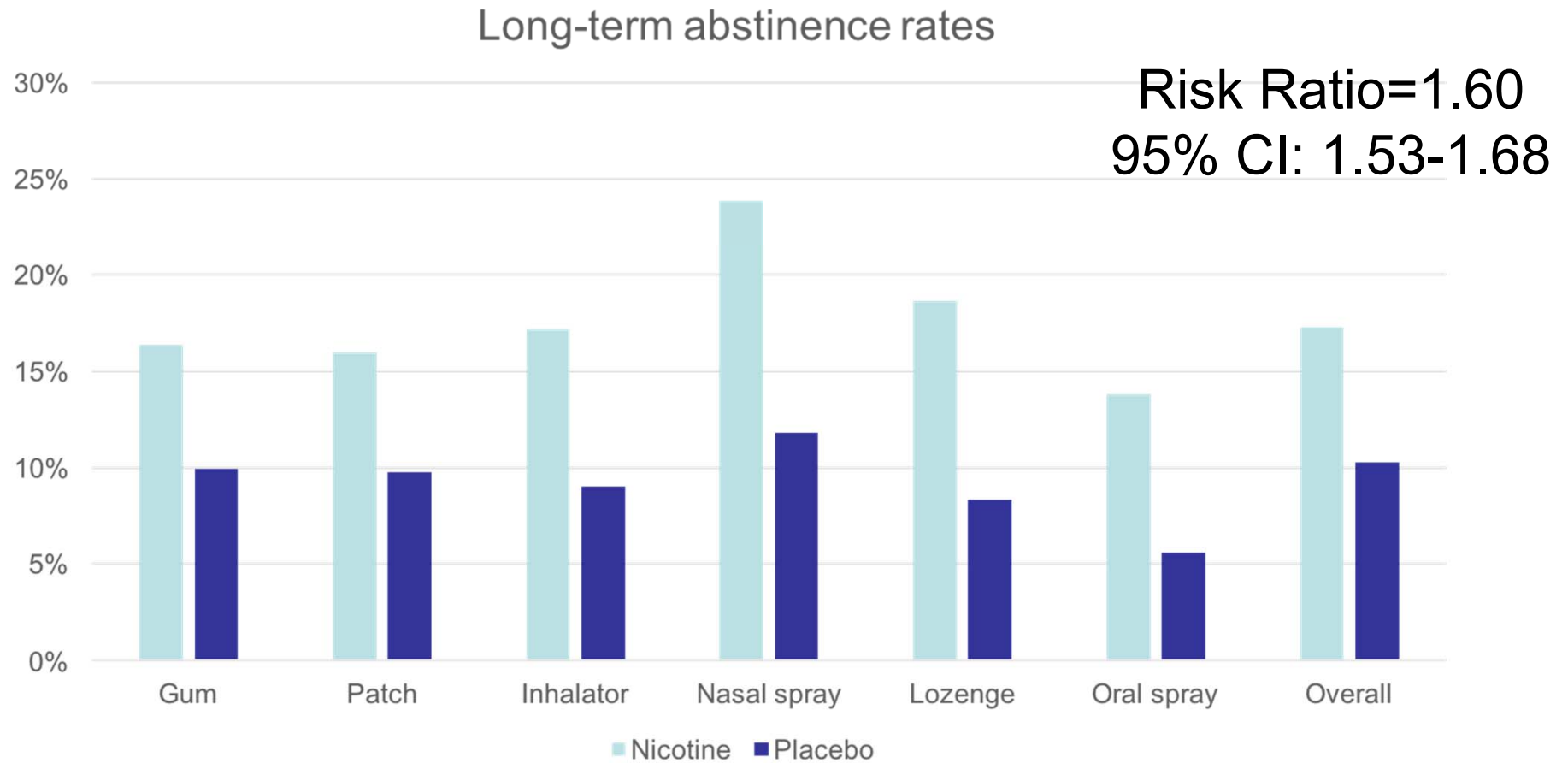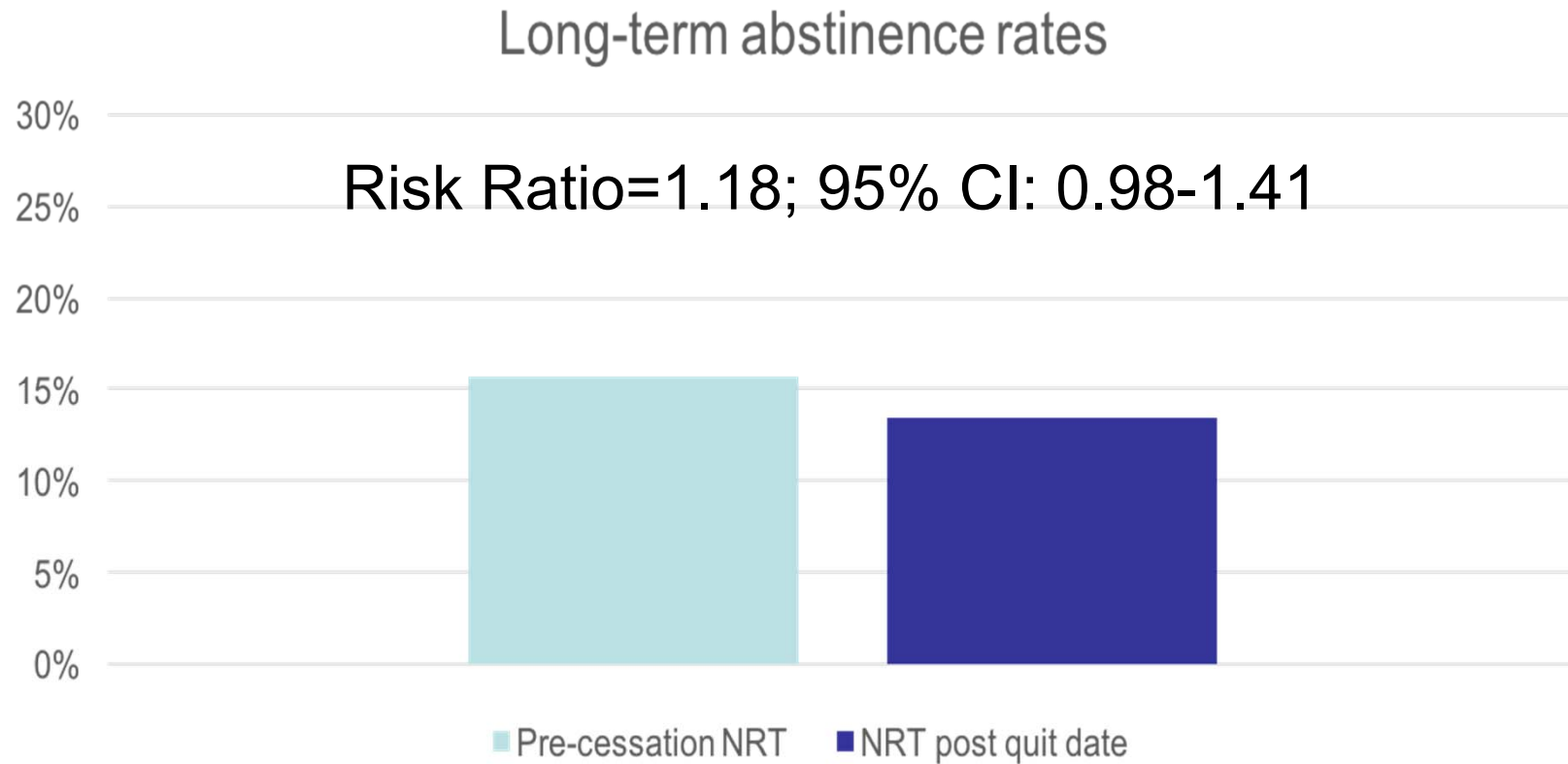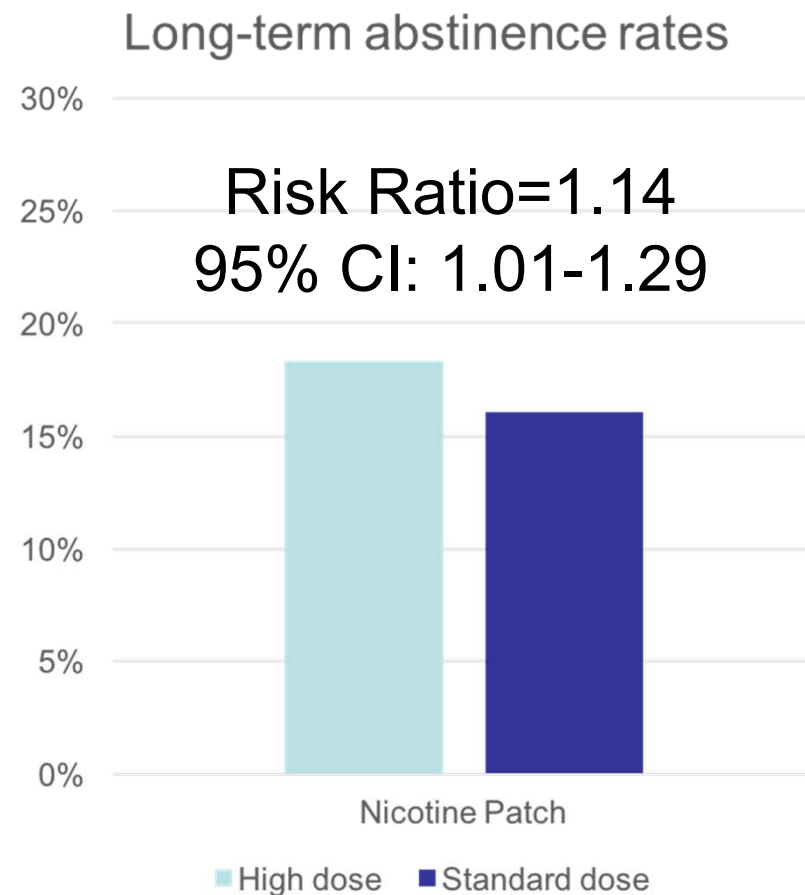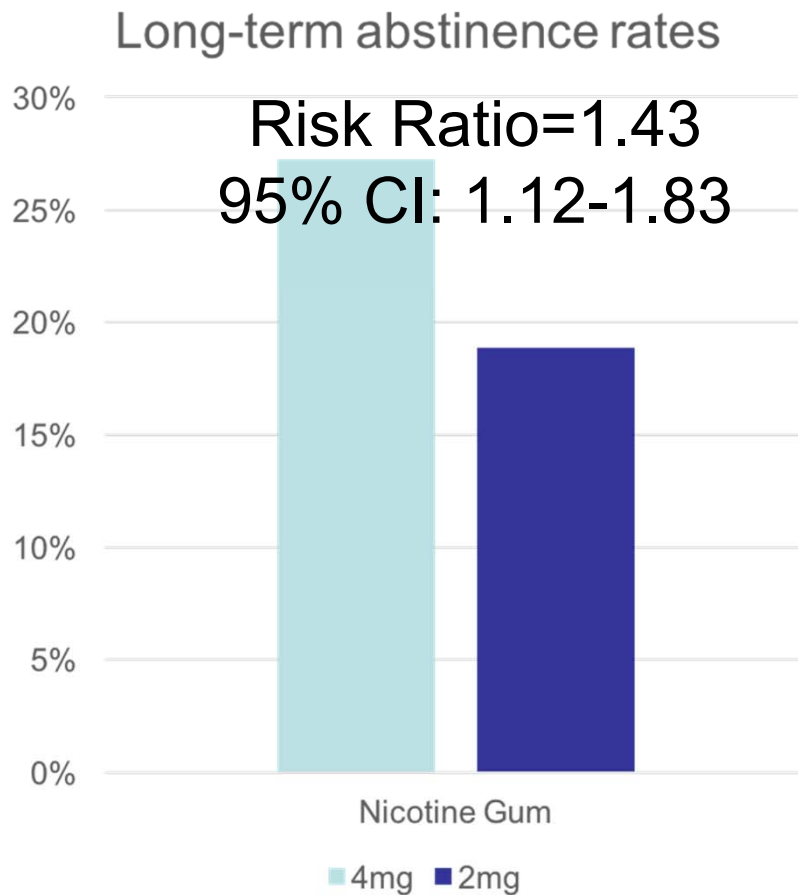
Increasing nicotine dose Combination NRT

Long-term abstinence rates

Risk Ratio=1.34,   95% CI: 1.18-1.51

Combination   Single product
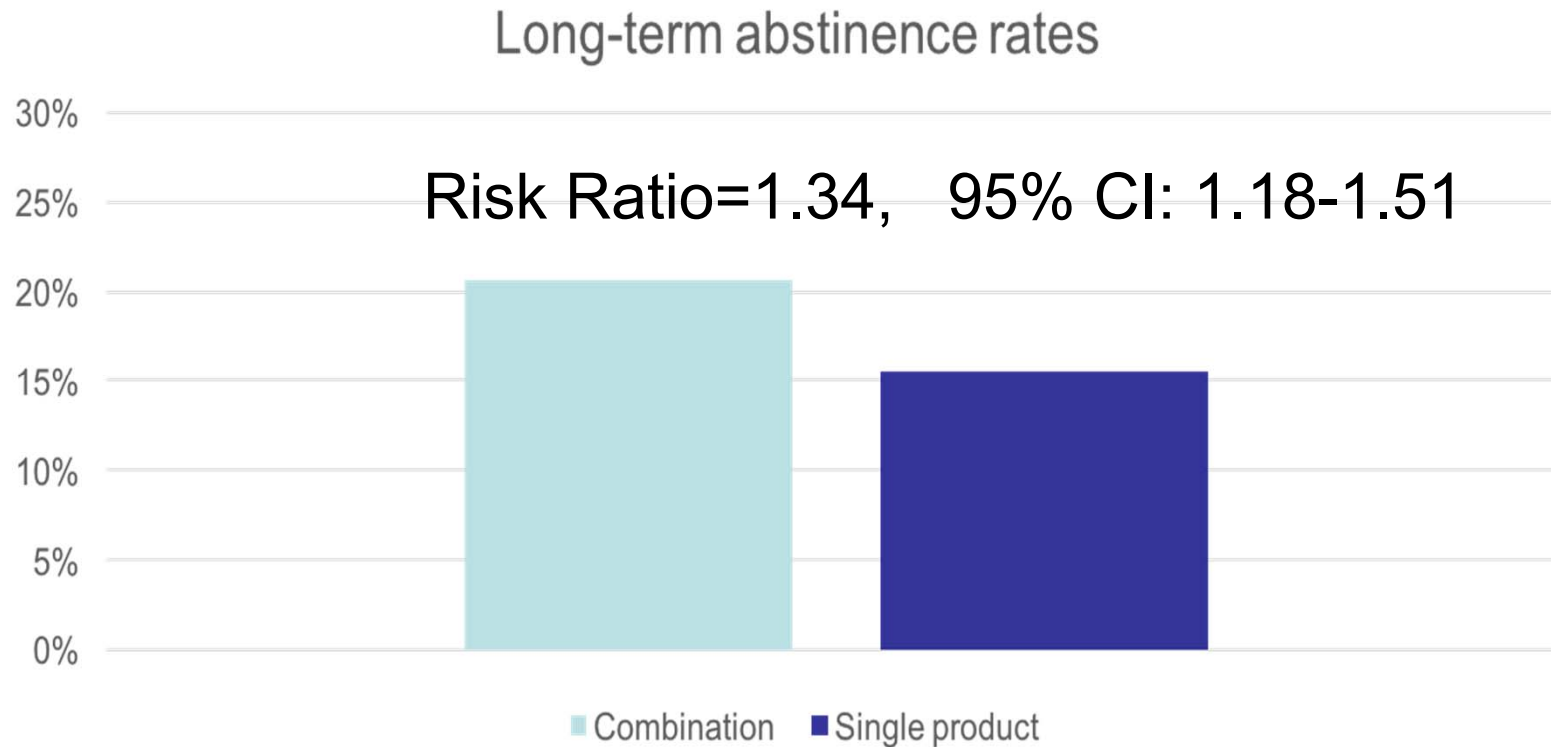
High dose NRT & cigarette consumption
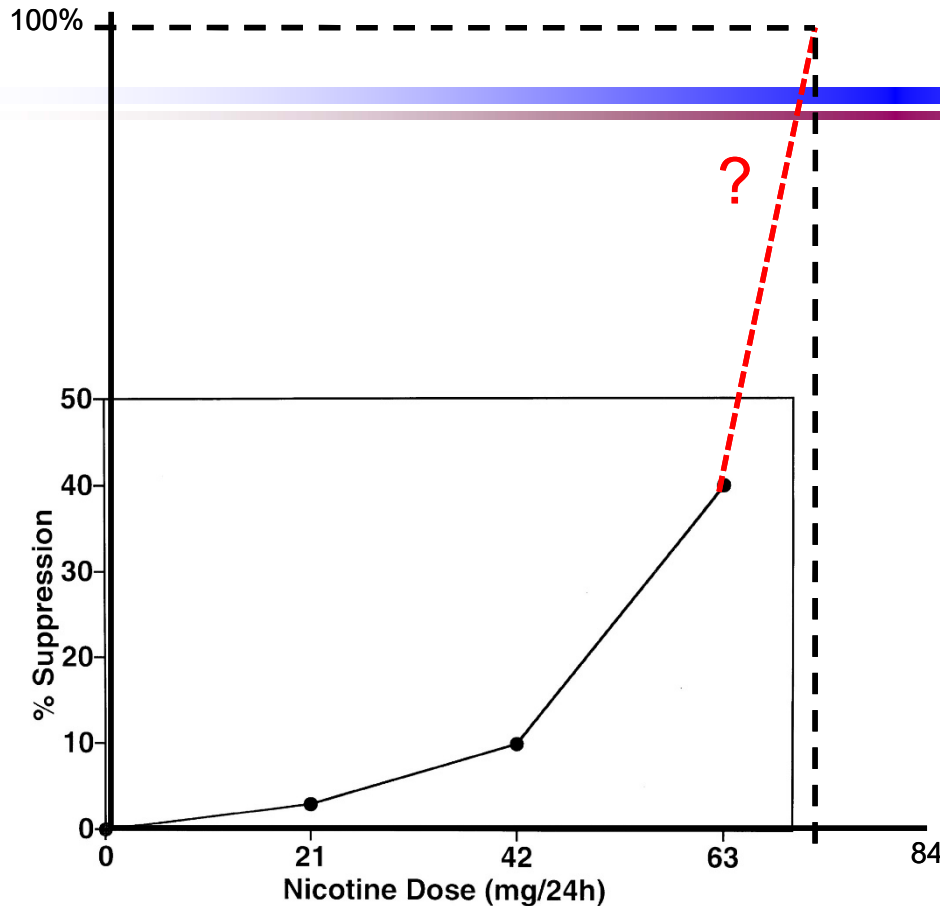
Could a higher dose result in better suppression of smoking?

Mechanism of action:
- Desensitization of nicotinic acetylcholine receptors?
- People feel sick if they smoke?

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Mayo Clinic approach

- Aims for 100% nicotine replacement and uses doses of NRT that are titrated to the clients' blood cotinine levels while smoking
  - Higher percentage cotinine replacement (achieved with 42mg patches) has been shown to be associated with higher 8-week quit rates[1]
- A recent report from the NDC shows maximum patch dose of 84mg/day[1]
  - In this report six-month point prevalence abstinence rates are as high as 59%

1. Dale, Hurt, Offord et al (1995). JAMA 274(17): 1353-8
2. Ebbert, Burke, Hays, Hurt. Combination treatment with varenicline and nicotine replacement therapy. *Nicotine Tob Res* 2009;11(5):572-6

Safety of higher dose NRT

- Incidence of adverse events with combination NRT is not significantly greater than that with single NRT used alone

- Smokers capable of titrating their nicotine intake

- Two case reports of attempted suicide with NRT
    - 44 year old man tried to induce an AMI with 7 patches and smoking
    - 15 year old girl used 14 patches simultaneously
    - Both survived

Montalto N, Brackett CC, Sobol T: Use of transdermal nicotine systems in a possible suicide attempt. J Am Board Fam Pract 1994; 7:417-420.

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ADONIS Trial

- Nicotine doses adjusted for salivary cotinine from smoking

- Highest dose as 162 mg

- Prolonged 12-week abstinence similar in the tailored and standard NRT arma (30% vs. 26%, ns)

- However, the first dose increase at 2 weeks after the quit date !!!

- The initial withdrawal period decides abstinence, dose increase likely instigated too late

46   Berlin et al *Addiction.* 2011;106(4):833-843.

Current cohort study to see if smokers tolerate higher doses

- **Study Design**
  - 50 smokers recruited at a smokers clinic in Mar del Plata, Argentina

•over 18 years of age •daily smokers seeking help to quit smoking •willing to use nicotine patches.	Exclusion criteria • pregnant/breastfeeding • CVD or other serious medical condition

Visits and patch dose

Visit	1	2	3	4	5	6	7	8	9
Week	-4	-3	-2	-1	TQD	1	2	3	4
Patch dose (mg)	21	42	63	84	84	63	42	21	-

The dose not increased (and could be decreased) if participants
- felt nauseous
- had other adverse effects
- did not wish to increase the dose

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Study endpoints

- Proportion progressing through each stage of the dosing schedule

- Patch adherence and ratings

- Adverse effects

- Changes in CO, enjoyment of smoking and cigarette consumption

- Abstinence rates at 4 weeks post-TQD

Participant characteristics

N=50	%
% male	50%
% Employed	86%
	Mean (SD)
Age (SD)	49 (9.5)
Cigarettes per day (SD)	20 (8.4)
FTCD (SD)	4.9 (2.3)
Expired CO (SD)	19.3 (8.5)

Patch dose progression

Week	N of participants administered dose				N of participants adhering to dose				Mean (SD) number of days used
	21mg	42mg	63mg	84mg	21 mg	42mg	63mg	84mg	
-4	50				49				6.9
-3		49				48			6.9
-2			48				45		6.9
-1				43				36	6.9
TQD				36				34	6.9
1			43				42		6.9
2		47				47			6.9
3	48				47				6.8

☐ Participants progressing to the maximum patch dose (n=36), versus those who did not (n=13)

- ☐ smoked more cigarettes per day (22 vs 15, $p=0.012$)
- ☐ had higher baseline CO (21 vs 16, $p=0.049$)

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Pre-quit Changes

Significant (p<0.001) change over time

Significant (p<0.001) change over time

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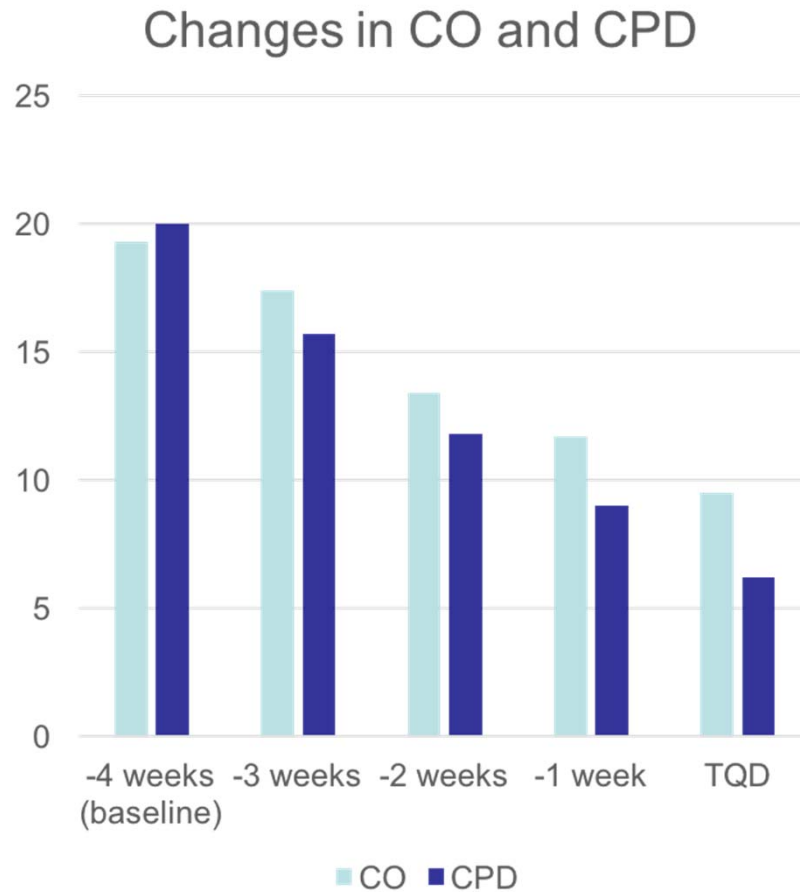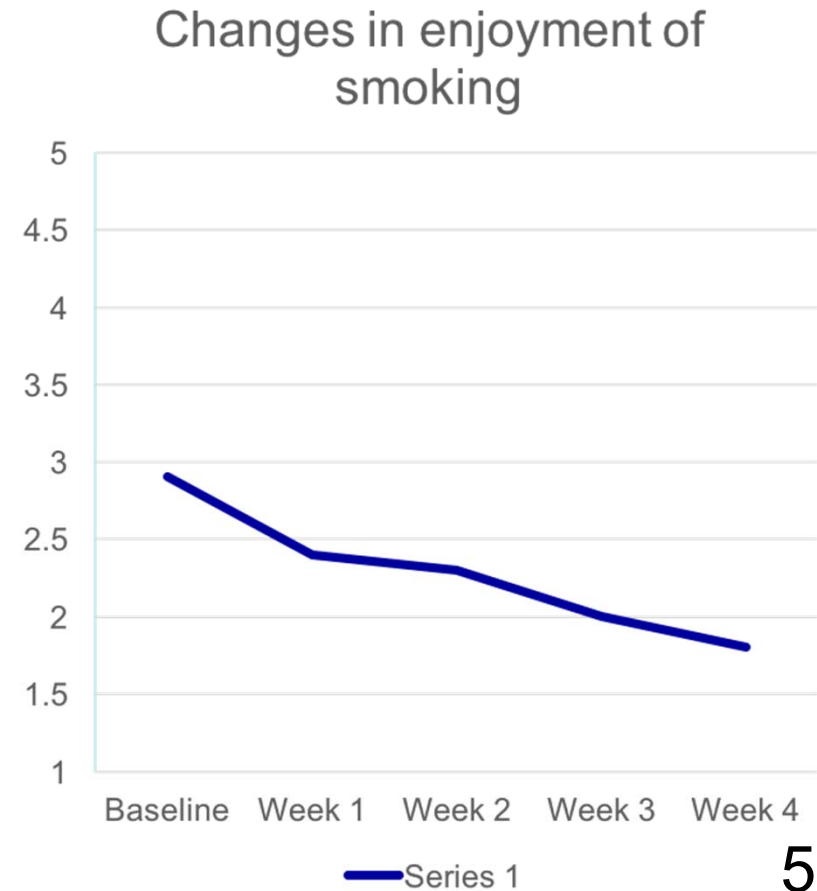
Adverse Effects

Dose	N (%)	Type of AE's (number of reports)
21mg	3/50 (6%)	Bitterness in mouth (N=1) Skin rash/local itching (N=1) Headache (N=1)
42mg	12/49 (24%)	Nausea (N=4) Vomiting (N=2) Skin rash/local itching (N=4) Headache (N=1) Sleepiness (N=1)
63mg	14/48 (29%)	Nausea (N=12) Vomiting (N=2) Skin rash/local itching (N=1) Headache (N=2) Bitterness in mouth (N=1) Insomnia (N=1) Low blood pressure (N=2) Blurry vision (N=1)
84mg	22/43 (51%)	Nausea (N=13) Vomiting (N=6) Skin rash/local itching (N=3) Headache (N=1) Insomnia (N=3) Low blood pressure (N=1)

Around 25% reported nausea at higher patch dose

There was a small but significant increase in nausea ratings from baseline to TQD (p<0.001) though the ratings remained low (<2/5)

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Abstinence rates and helpfulness

- Abstinence
  - 41/50 (82%) were abstinent at 4 weeks post-TQD.
  - 37/50 (74%) continuously abstinent

- Helpfulness
  - 59% rated the patch pre-loading as 'very useful' in helping them prepare for their quit day
  - None of the participants said it was 'not at all' useful

Conclusions

- Higher dose patches were well tolerated
  - 90% progressed to 3 patches and 66% to 4
- The intervention was acceptable and adherence was high (only 6% dropped out)
- Current NRT labelling (post-quit use and low doses) is suboptimal, dosing can be much higher and pre-loading can probably boost effects
- A controlled trial is now warranted

Nicotine patch pre-treatment

Aveyard, Hajek, Lewis et al.

RESEARCH

Effects on abstinence of nicotine patch treatment before quitting smoking: parallel, two arm, pragmatic randomised trial

The Preloading Investigators

Preloading- short-term abstinence

Study or Subgroup	Pre-quit NRT Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hughes 2010	39	297	60	299	17.6%	0.65 [0.45, 0.95]
Bullen 2010	132	549	143	551	41.9%	0.93 [0.75, 1.14]
Etter 2009	61	154	65	160	18.7%	0.98 [0.74, 1.28]
Rose 1998	16	40	14	40	4.1%	1.14 [0.65, 2.02]
Schuurmans 2004	29	100	19	100	5.6%	1.53 [0.92, 2.54]
Rose 1994	10	24	6	24	1.8%	1.67 [0.72, 3.86]
Rose 2009	44	191	24	188	7.1%	1.80 [1.15, 2.84]
Rose 2006	24	48	11	48	3.2%	2.18 [1.21, 3.94]
Total (95% CI)		**1403**		**1410**	**100.0%**	**1.05 [0.92, 1.19]**
Total events	355		342			

Heterogeneity: Chi² = 22.66, df = 7 (P = 0.002); I² = 69%
Test for overall effect: Z = 0.69 (P = 0.49)

For patch alone RR=1.17 (95% CI = 1.00, 1.37)
For gum/lozenge RR=0.82 (95% CI = 0.66, 1.02),
$p = 0.009$ for the difference in RRs.

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Long-term abstinence

Study or Subgroup	Pre-quit NRT Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hughes 2010	12	297	21	299	10.9%	0.58 [0.29, 1.15]
Bullen 2010	99	549	97	551	50.6%	1.02 [0.79, 1.32]
Etter 2009	32	154	31	160	15.9%	1.07 [0.69, 1.67]
Rose 1994	6	24	4	24	2.1%	1.50 [0.48, 4.65]
Rose 2006	10	48	6	48	3.1%	1.67 [0.66, 4.22]
Schuurmans 2004	22	100	12	100	6.3%	1.83 [0.96, 3.50]
Rose 2009	28	191	15	188	7.9%	1.84 [1.01, 3.33]
Rose 1998	12	40	6	40	3.1%	2.00 [0.83, 4.81]
Total (95% CI)		1403		1410	100.0%	1.16 [0.97, 1.38]
Total events	221		192			

Heterogeneity: Chi² = 11.50, df = 7 (P = 0.12); I² = 39%
Test for overall effect: Z = 1.63 (P = 0.10)

Risk Ratio M-H, Fixed, 95% CI
0.2   0.5   1   2   5
Favours control   Favours pre-quit NRT

For patch alone RR=1.26 (95% CI = 1.03, 1.55),
For gum/lozenge RR=0.87 (95% CI = 0.60, 1.26),
$p = 0.09$ for difference between in RRs

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Patch pre-loading trial: Participants

	Control n=893 n (%)	Intervention n=899 n (%)
Cigarettes per day	18.7	19.1
Dependence (FTND)	5.2	5.2
CO reading	24	24
Longest previous abstinence	Median 90	Median 90
Sought help in last 6 months	34 %	31 %

Aveyard et al. BMJ 2018

The preloading trial

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                    ┌─────────────────┐
                    │ Randomised      │
                    │ n=1792          │
                    └────────┬────────┘
              ┌──────────────┴──────────────┐
┌───────────────────────────┐   ┌───────────────────────────┐
│ Preloading n=899          │   │ Control n=893             │
│ -4 week assessment        │   │ -4 week assessment        │
└─────────────┬─────────────┘   └─────────────┬─────────────┘
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│ AE & mechanistic          │   │ AE & mechanistic          │
│ assessment -3 weeks       │   │ assessment -3 weeks)      │
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│ assessment +1 week        │   │ assessment +1 week        │
└─────────────┬─────────────┘   └─────────────┬─────────────┘
┌───────────────────────────┐   ┌───────────────────────────┐
│ Follow ups 4 weeks, 6     │   │ Follow ups 4 weeks, 6     │
│ month, 12 month           │   │ month, 12 month           │
└───────────────────────────┘   └───────────────────────────┘
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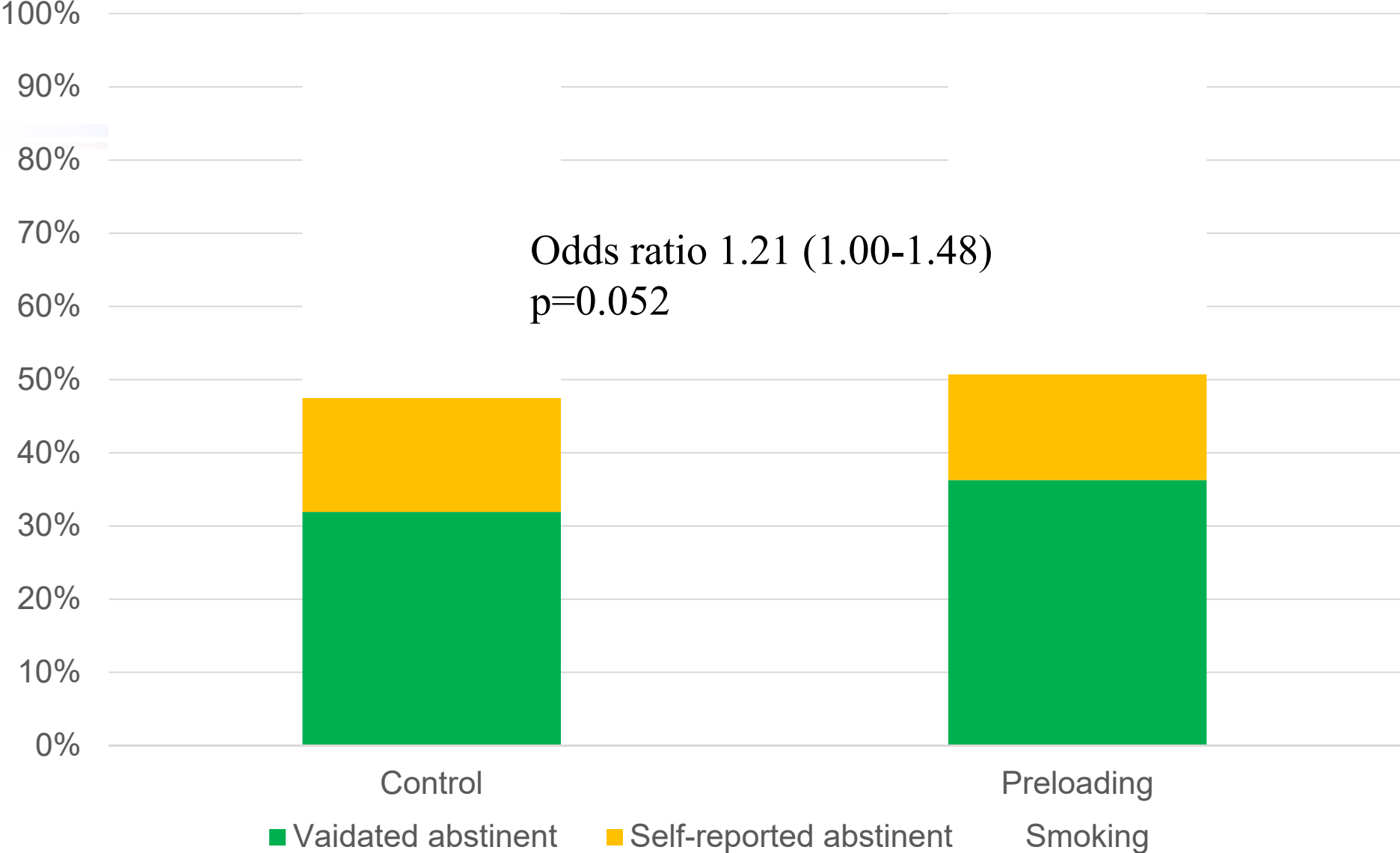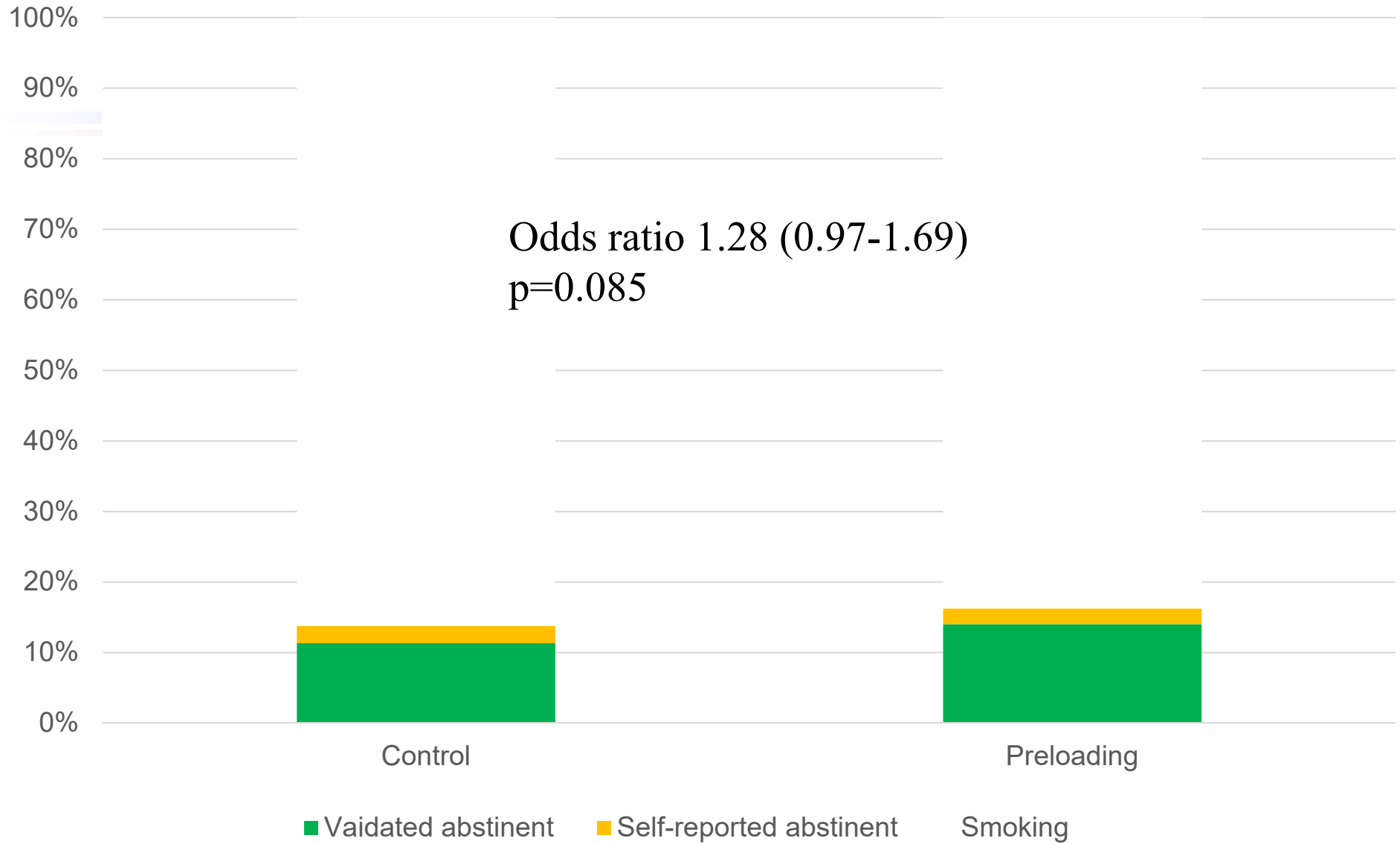
Patch use

- Patch use at 1 week after baseline
  - 75% used it daily

- In the subsequent 3 weeks of preloading
  - 80% used it daily

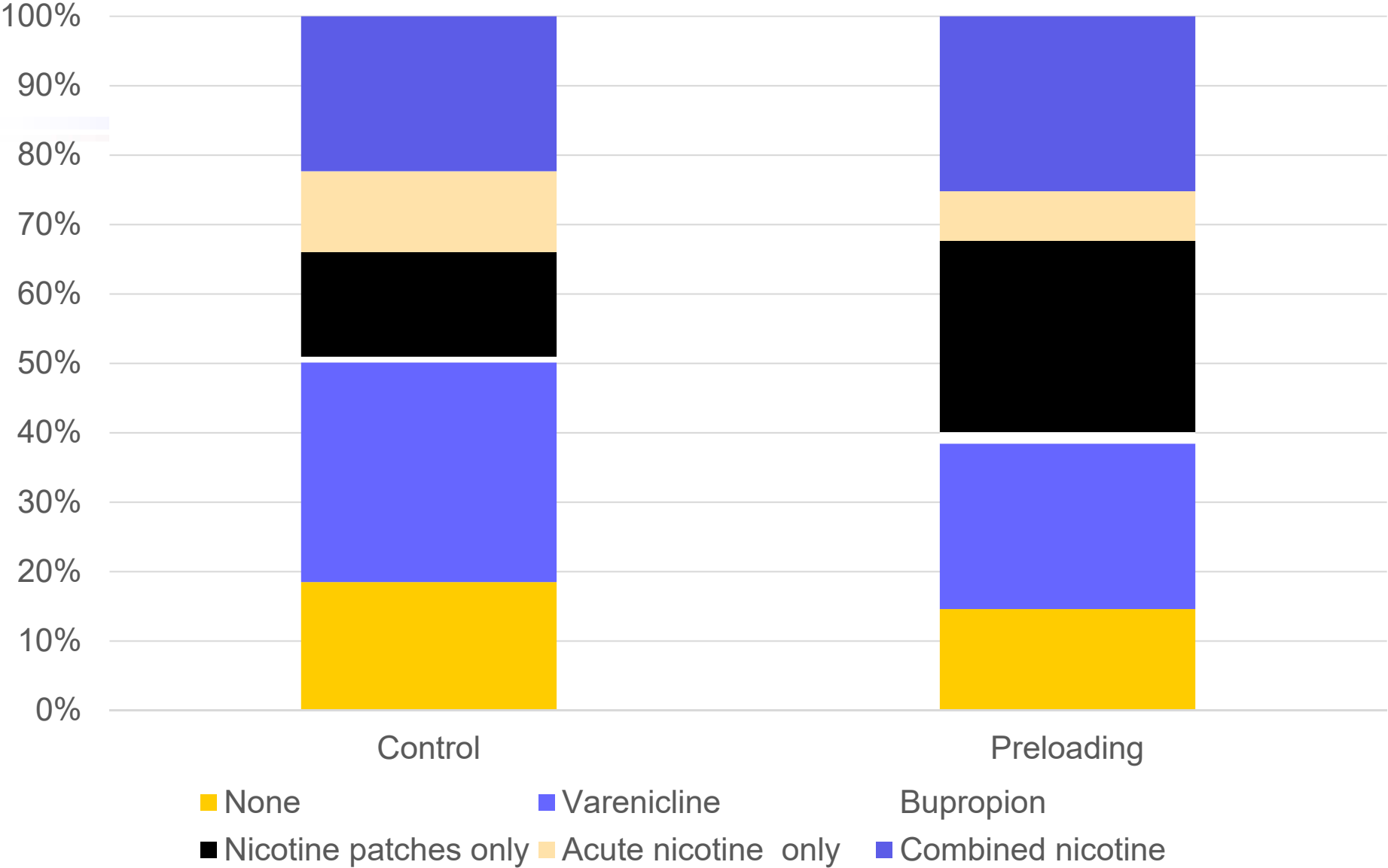- Only 6% stopped using preloading prematurely

4-week abstinence

Odds ratio 1.21 (1.00-1.48)
p=0.052

Control

Preloading

■ Vaidated abstinent   ■ Self-reported abstinent   Smoking

12-month prolonged abstinence

Odds ratio 1.28 (0.97-1.69)
p=0.085

Legend: ■ Vaidated abstinent ■ Self-reported abstinent Smoking

Categories: Control, Preloading

Medication use one week after quit day

Legend: None, Varenicline, Bupropion, Nicotine patches only, Acute nicotine only, Combined nicotine

Results adjusted for varenicline use

- 4-week abstinence   OR 1.3 (1.1-1.6); p=0.007

- 6-month abstinence OR 1.3 (1.0-1.7); p=0.028

- 12-month abstinence OR 1.4 (1.0-1.8); p=0.036

How does it work?

○ Mediation analysis checking effects on 1) positive reward from smoking, 2) negative reward (alleviating boredom, calming effects, etc.), 3) the intensity of urges to smoke, 4) smoking stereotypy, 5) cigarette consumption and smoke intake, 6) self - efficacy, 7) nausea and aversion to smoking, 8) post - TQD urges to smoke and cigarette withdrawal symptoms and 9) post - TQD medication use

Hajek et al. Addiction 2018

Results

Preloading affected a number of variables (enjoyment, reward, nausea etc), but only three mediated abstinence

- Reduced smoke intake
- Reduced urges to smoke pre-quit
- Reduced urges to smoke post-quit

Conclusions

- NRT preloading has an effect, but it depends on not deterring use of varenicline (pre-loading with varenicline would make more sense)

- Safe and well-tolerated

- It works by reducing smoking during pre-quit and urges to smoke throughout

Nicotine and pain

Nicotine and pain

- Previous studies suggested that nicotine has analgesic effects; and quitting increases pain sensitivity acutely

- Recent study confirmation: Abstaining smokers had lower pain threshold pre-surgery (hepatic resection), more post-op pain, and needed more analgesics than non-smokers

Shen et al. Addict Behav 2017

Stopping smoking and pain

- N=165, 12-24h deprivation or not
- Pain induction via topical capsaicin
- Abstinence increases pain sensitivity
- Correlates with other withdrawal symptoms
- Growing evidence that this is an important withdrawal symptom
- Smoking increases sensitivity to pleasure, quitting increases sensitivity to pain

Ditre at al. J Abnorm Psychol 2018

Various

Weight management: During quitting, or later?

- RCT, N=2,504 quitline callers

- Weight management (WM) via telephone coaching

- A) Coaching calls for both smoking and weight for two months

- B) Weight calls only after quit calls finished

- **Neither WM had any effect on weight**

- **A) undermined quitting**

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Bush et al. BMC Public Health 2018

More Swedes now dependent on coffee than on cigarettes

Random sample, N=3,001	Uses cigarettes	Uses coffee
Daily use	7%	71%
Would be very hard to give up	36%	18%
Absolute numbers finding it very hard to give up	**72**	**380**

Fagerstrom, Int J Environ Res Public Health. 2018