

Seguridad de los fármacos. Vacunas. Cigarrillos electrónicos

F. Javier Ayesta

Oviedo, 28 noviembre 2013

Supertramp

CRISIS! WHAT CRISIS!



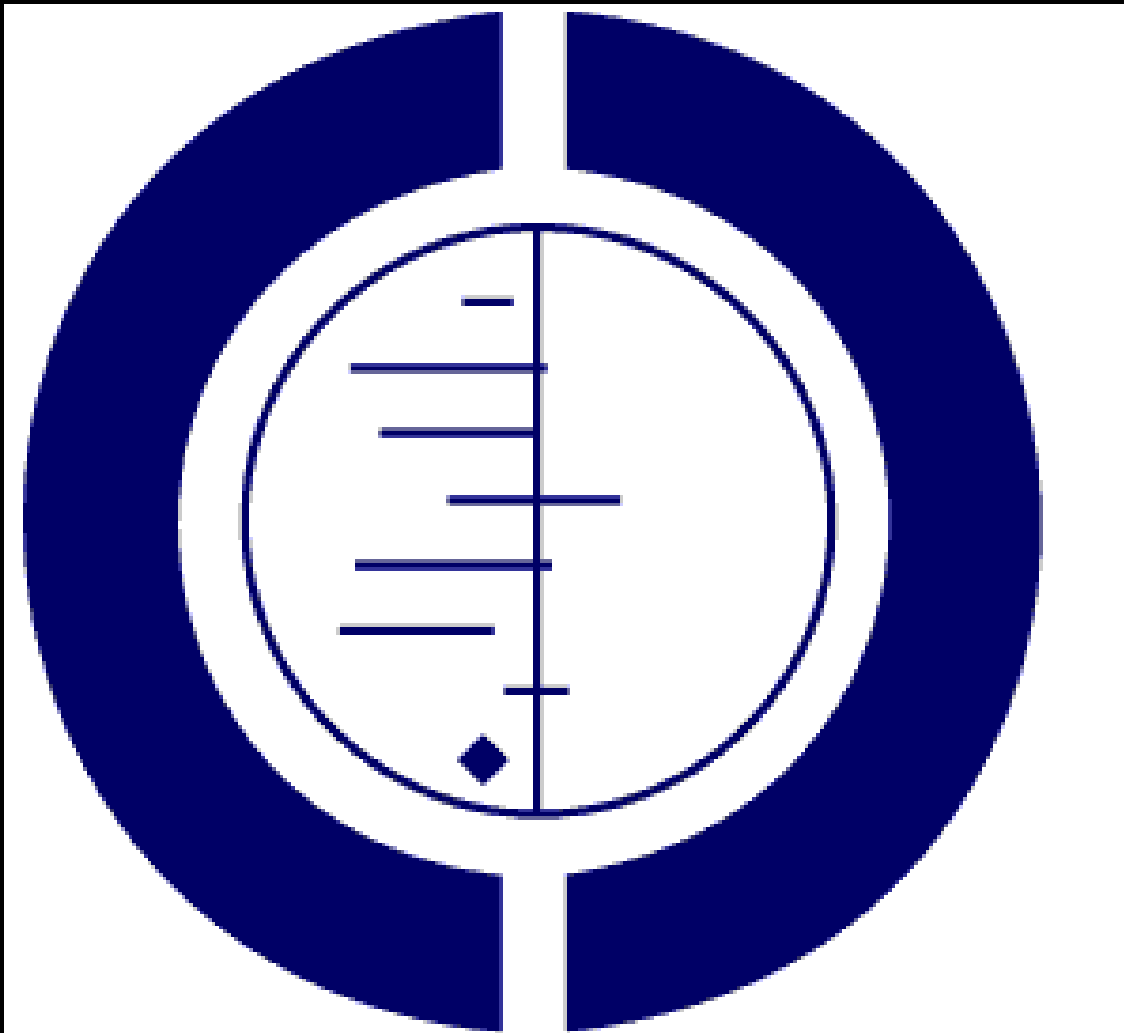
A woman with long dark hair and a pink hoop earring is shown in profile, looking upwards. A fishing hook is stuck in her lower lip, with a thin line extending from the hook towards the top left corner of the frame. The background is a plain, light grey.

NHS

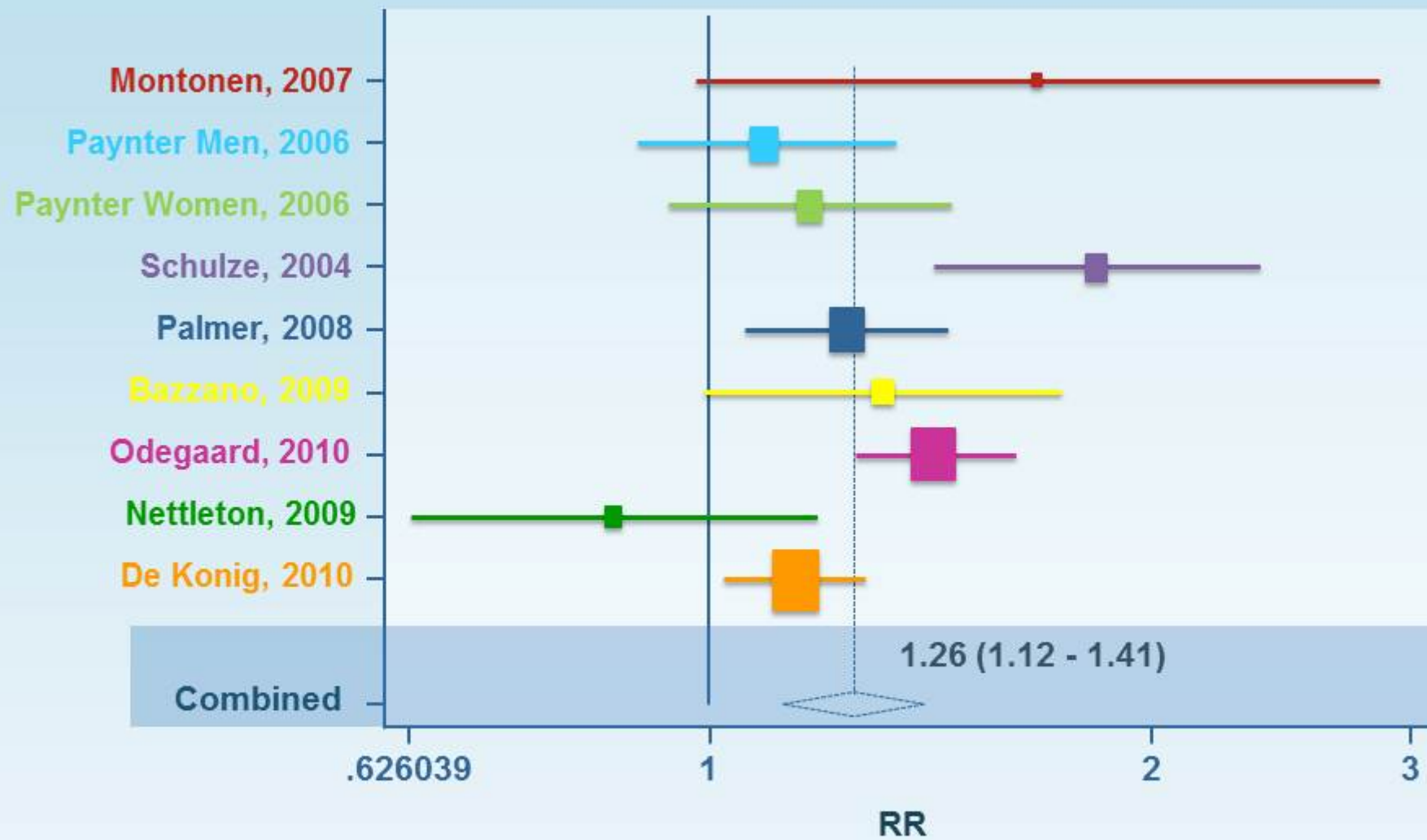
The average smoker needs over five thousand cigarettes a year.

Get unhooked. Call 0800 169 0 169 or visit getunhooked.co.uk

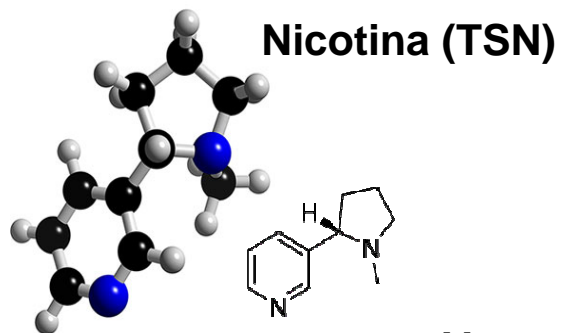

SMOKEFREE



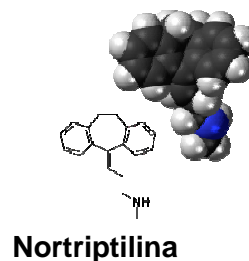
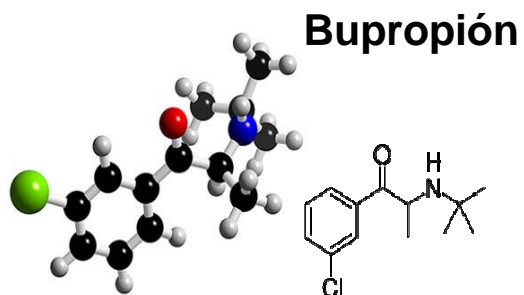
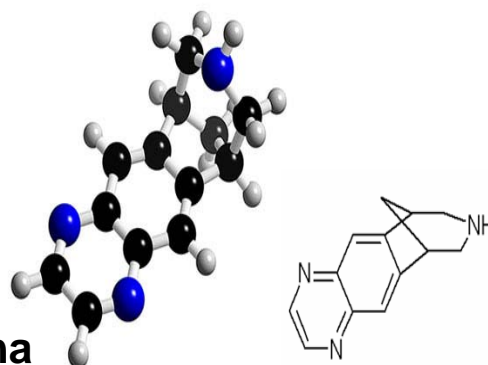
**THE COCHRANE
COLLABORATION®**



Adapted from Malik et al. Diabetes Care 2010;33:2477-83



Vareniclina



En tabaquismo disponemos de unos de los fármacos que objetivamente son más seguros.

¿Cuál es nuestro problema entonces?





Población “sana”

Cesación “limpia”

Pregunta de un curso *online* de formación de profesionales sanitarios en tabaco (2012)

4. ¿Cuál de las siguientes no es una contraindicación para el uso de la vareniclina para dejar de fumar?

- a) Pacientes psicóticos
- b) Pacientes con enfermedad afectiva activa
- c) En los pacientes que han sufrido enfermedades del corazón
- d) Pacientes con antecedentes familiares de suicidio

4 de julio de 2011

Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis

ABSTRACT

Background: There have been postmarketing reports of adverse cardiovascular events associated with the use of varenicline, a widely used smoking cessation drug. We conducted a systematic review and meta-analysis of randomized controlled trials to ascertain the serious adverse cardiovascular effects of varenicline compared with placebo among tobacco users.

Methods: We searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, websites of regulatory authorities and registries of clinical trials, with no date or language restrictions, through September 2010 (updated March 2011) for published and unpublished studies. We selected double-blind randomized controlled trials of at least one week's duration involving smokers or people who used smokeless tobacco that reported on cardiovascular events (ischemia, arrhythmia, congestive heart failure, sudden death or cardiovascular-related death) as serious

adverse events associated with the use of varenicline.

Results: We analyzed data from 14 double-blind randomized controlled trials involving 8216 participants. The trials ranged in duration from 7 to 52 weeks. Varenicline was associated with a significantly increased risk of serious adverse cardiovascular events compared with placebo (1.06% [52/4908] in varenicline group v. 0.82% [27/3308] in placebo group; Peto odds ratio [OR] 1.72, 95% confidence interval [CI] 1.09–2.71; $P = 0\%$). The results of various sensitivity analyses were consistent with those of the main analysis, and a funnel plot showed no publication bias. There were too few deaths to allow meaningful comparisons of mortality.

Interpretation: Our meta-analysis raises safety concerns about the potential for an increased risk of serious adverse cardiovascular events associated with the use of varenicline among tobacco users.

Primer comprimido **sin nicotina**
que actúa sobre los componentes biológicos
de la adicción a la nicotina

Primer comprimido sin la estructura pirrolidín-piridina
que actúa sobre los componentes biológicos
de la adicción a la nicotina

Primer comprimido sin nicotina
que actúa sobre los componentes biológicos
de la adicción a la nicotina

DOUBT **IS** **THEIR** **PRODUCT**

**How Industry's Assault on Science
Threatens Your Health**

David Michaels



ACSH is a tobacco industry-funded front group that now advocates e-cigs as harm-reduction

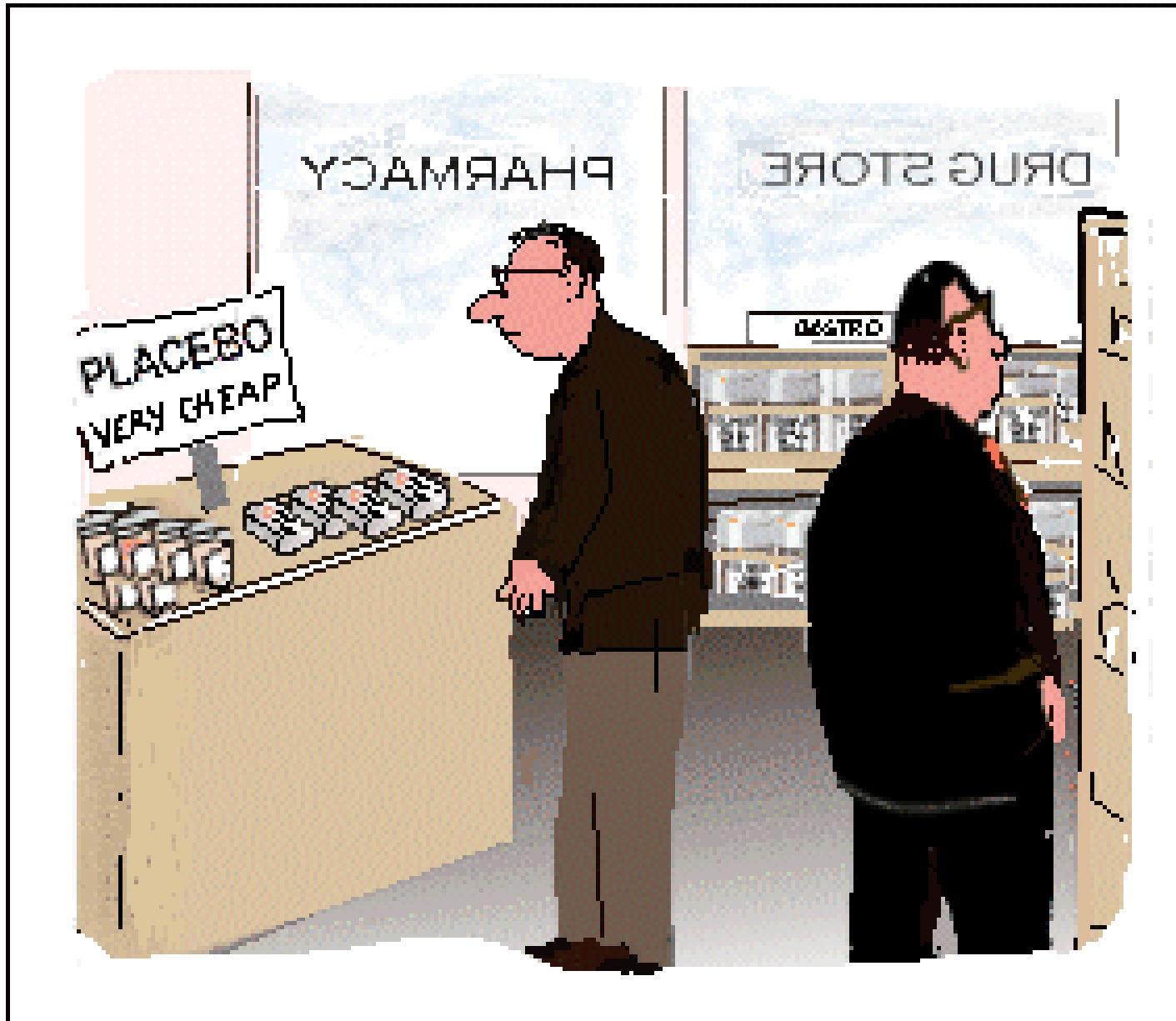
<http://www.motherjones.com/politics/2013/10/american-council-science-health-leaked-documents-fundraising>

ACSH describes itself as "group of scientists...concerned that many important public policies related to health and the environment did not have a sound scientific basis." They have 501(c)(3) status and often oppose environmentalists/consumer rights advocates. In the past, they have defended fracking, fought NYC's attempt to ban big sugary sodas, dismiss concerns about bisphenol-A, etc. Their finances have been kept private since the 90s, but in spite of their stated intent "to remain free from financial ties with corporations with a financial interest in the topics we are investigating," leaked documents reveal that they're on the payroll of the likes of McDonalds, Coca-Cola, Chevron, Altria, and American Petroleum, as well as the International Formula Council, which advocates for infant formula. In fact, the newly leaked documents reveal that "ACSH staffers should approach potential corporate financial backers with pitches geared toward specific issues." Recently, however, ACSH's agenda has run parallel to Big Tobacco's, often touting e-cigarettes as a [safer alternative to smoking](#) (also [here](#)). It's likely no coincidence that ACSH received \$338,200 from the tobacco industry between July 2013 and June 2013.



STOP

MAKING
EXCUSES



MOLÉCULAS EN FASE EXPERIMENTAL para el tratamiento del tabaquismo

Taranabant (MK0364)	Merck & Co.	CB ₁ R antagonist and/or inverse agonist	Phase II
EVT 302	Evotec	MAOB inhibitor	Phase II
Selegiline	NIDA	MAOB inhibitor	Phase II
D-cycloserine	Boston University	NMDA receptor agonist (also used as broad-spectrum antibiotic)	Phase II
GSK598809	GlaxoSmithKline	DRD3 antagonist	Phase II
Nalmefene	Somaxon Pharmaceuticals	Opioid receptor antagonist	Phase II
Naltrexone (naltrexone HCl)	University of Chicago	Opioid receptor antagonist	Phase II
NAL2762 (nicotine ODF)	NAL Pharmaceuticals	nAChR ligand	Phase II
Meclizine (meclizine hydrochloride)	Duke University/ Philip Morris USA	Antihistamine	Phase II
X-22 (nicotine)	22nd Century Group	Kit of VLN cigarettes	Phase IIb

CB₁R, cannabinoid 1 receptor; DRD3, dopamine D3 receptor; MAO, monoamine oxidase; nAChR, nicotinic acetylcholine receptor; NIDA, US National Institute on Drug Abuse; NMDA, N-methyl-D-aspartate; ODF, orally dissolvable film; VLN, very low nicotine. Sources: ClinicalTrials.gov website, scientific literature and company reports.

Smoking cessation drugs market

Basharut A. Syed and Kritika Chaudhari

La siguiente diapositiva muestra los diversos tratamientos del tabaquismo que se encuentran en fase II.

Fase II es aquella en la que, tras haberse comprobado su mínima seguridad en humanos, se administra el fármaco a individuos que presentan la enfermedad para la que se ha concebido su empleo. No se suelen incluir más de 100 a 200 individuos. Su finalidad consiste en realizar mediciones preliminares de la relación eficacia terapéutica/toxicidad (ventana terapéutica), así como establecer la dosis óptima o sus límites de variación en la condición a tratar.

Aunque no es el tema que nos toca hoy, vemos cómo se están investigando moléculas como el antagonista CB1 taranabant, algunos IMAOs tipo B, un ligando nicotínico (quizá del tipo de la vareniclina) y cigarrillos con muy bajo contenido en nicotina. Investigados también en otros trastornos adictivos también están un antagonista de los receptores dopaminérgicos D3 y dos antagonistas opioides.

No voy a decir nada sobre ellos. Quizá en la discusión, si alguna persona está especialmente interesada.

En esta tabla de hace tres meses se recogen las vacunas actualmente en fase de experimentación. Todas están en fase II; se está intentando determinar su eficacia. Hasta el momento los resultados publicados podrían describirse como un tanto decepcionantes (*disappointing*).

VACUNAS nicotínicas en fase de experimentación

TA-NIC (nicotine butyric acid covalently linked to recombinant cholera toxin B)	Celtic Pharmaceuticals	Therapeutic vaccine	Phase II
Niccine	Independent Pharmaceutica	Therapeutic vaccine	Phase II
NIC-002	Cytos Biotechnology/ Novartis	Therapeutic vaccine	Phase II
NicVAX (3-aminomethyl nicotine hapten) plus Champix (varenicline)	Nabi Biopharmaceuticals	Therapeutic vaccine combination product	Phase II

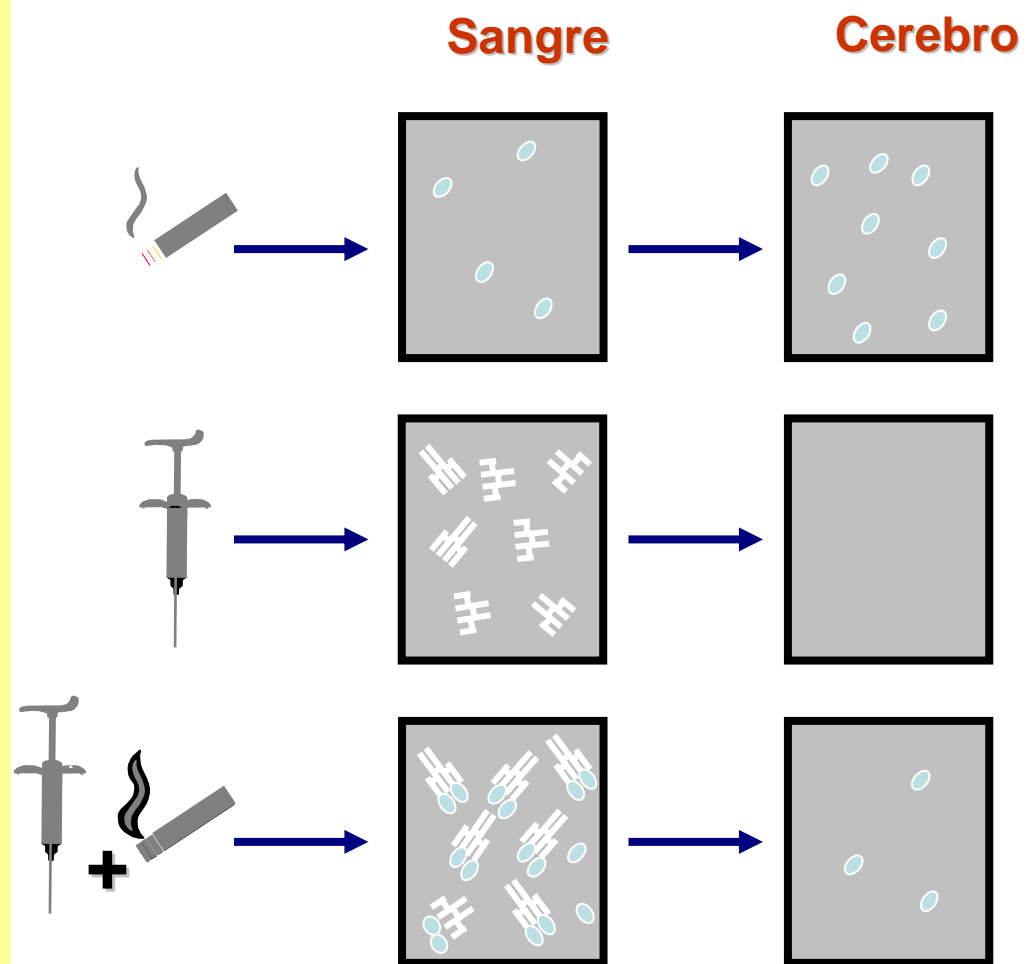
Smoking cessation drugs market

Basharut A. Syed and Kritika Chaudhari

El mecanismo básico de acción de las vacunas sería: 1) en condiciones normales las moléculas de nicotina pasan la BHE y llegan a cerebro donde actúan; 2) los anticuerpos anti-nicotina desarrollados son de gran tamaño y no cruzan la BHE; 3) al fumar en estas condiciones, la **mayor parte** de las moléculas de nicotina son retenidas en la circulación periférica.

Quienes nunca han fumado, experimentarían inicialmente efectos mínimos y tendrían más dificultad en volverse dependientes. A quienes intentan dejarlo, podría servirles para extinguir condicionamientos, ya que apenas perciben los efectos.

En cualquier caso, siempre puede acabarse contrarrestando la protección de la vacunación a base de fumar mucho (... aunque esto conlleva sus riesgos).



Potenciales usos de las vacunas

Tratamiento de la dependencia.

Su uso disminuiría la acción reforzadora del consumo y se facilitaría la extinción de asociaciones.

Prevención de recaídas.

En personas motivadas y en fase de mantenimiento.

Uso preventivo.

- Prevención de inicio en adolescentes vacunados por menor respuesta a nicotina.
- Prevención de daño al feto, ya que no pasa la barrera placentaria (Ag-Ac).

Conclusiones a día de hoy

“Unfortunately, the only vaccine tested in two large, randomized phase III trials, 3'-amino-methyl-nicotine r-exoprotein A conjugate vaccine (NicVAX®, Nabi Bio-pharmaceuticals, MD, USA), **did not demonstrate efficacy**” (Goniewicz ML, Delijewski M. Nicotine vaccines to treat tobacco dependence. *Hum Vaccin Immunother* 2013; 9:13-25. doi: 10.4161/hv.22060).

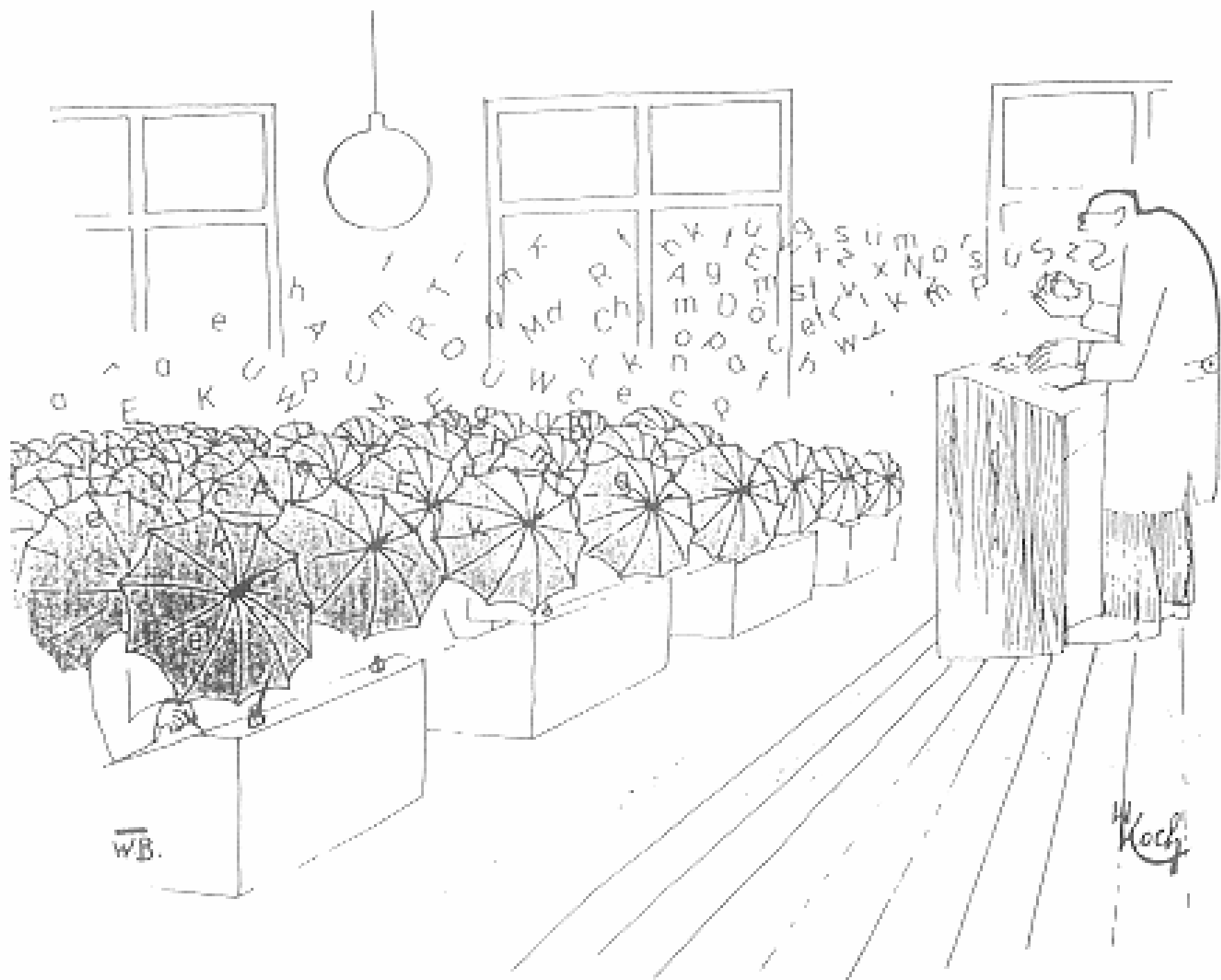
Esta falta de eficacia es la razón por la que ahora se está estudiando su posible utilidad en su asociación con vareniclina.

“Existing evidence indicates that nicotine vaccination is well tolerated and capable of inducing an immune response **but its effectiveness in increasing smoking abstinence has not been shown so far**” (Fahim RE, Kessler PD, Kalnik MW. Therapeutic vaccines against tobacco addiction. *Expert Rev Vaccines* 2013; 12:333-42. doi: 10.1586/erv.13.13).

En definitiva, aún no han mostrado eficacia.

VACUNAS

- 2002
Santander
- 2008
Portland
- 2012
Helsinki

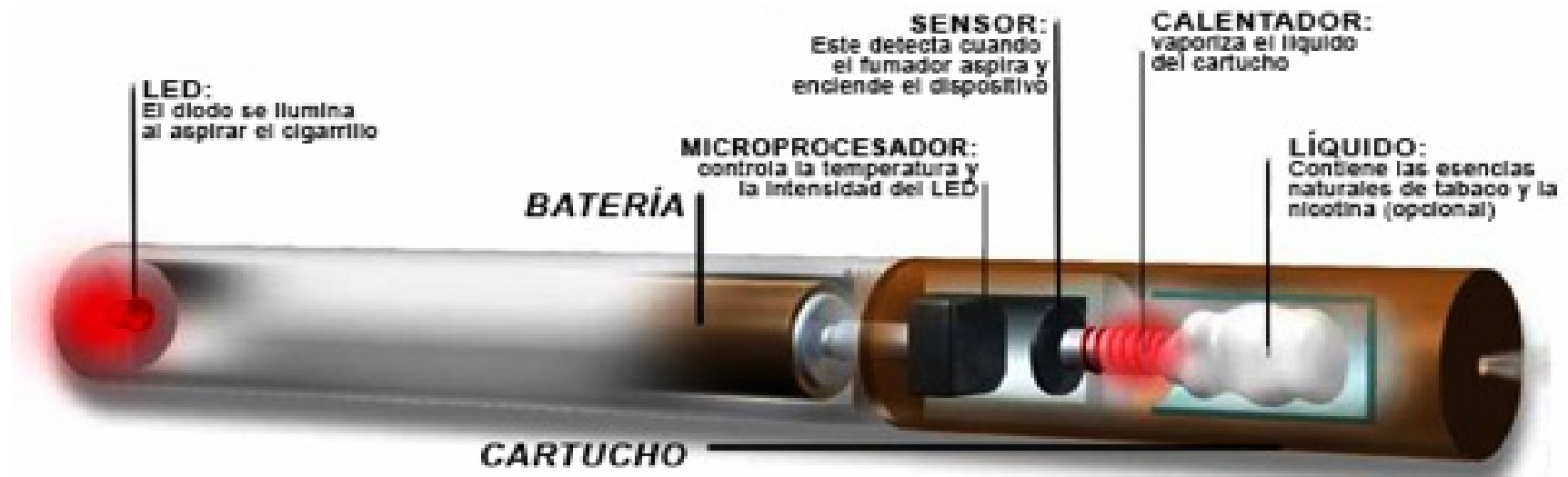




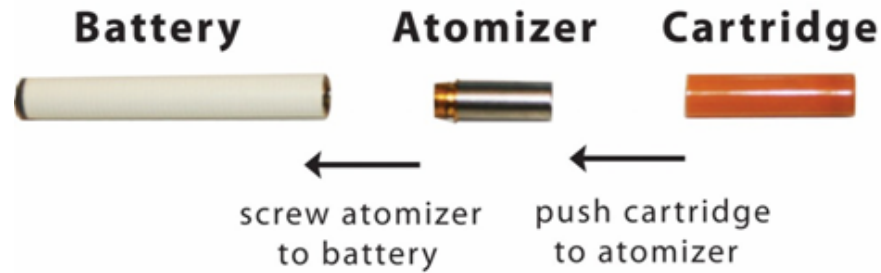
- Fenómeno social creciente
- Innovación
- Plantea dudas en términos de seguridad
- Puede socavar avances obtenidos
- Debate sobre su pertinencia como estrategia de reducción de daños
- Riesgos “ocultos” – maniobra IT
- Vacío legal
- Se requiere proceso de regulación

ENDS (*Electronic nicotine delivery systems*)

Los sistemas electrónicos de administración de nicotina (ENDS) constituyen una categoría de productos de consumo diseñados para liberar nicotina en los pulmones tras introducir en la boca el extremo de un cilindro de plástico o metálico, de manera similar a un cigarrillo o un puro, e inhalar con objeto de extraer una mezcla de aire y vapores del dispositivo y liberarla en el aparato respiratorio.



First Generation ECs (‘cigalikes’)



- Disposable
- Re-chargeable with pre-filled cartridges



Second Generation ECs



- Refillable with liquids



Third Generation ECs ('mods')



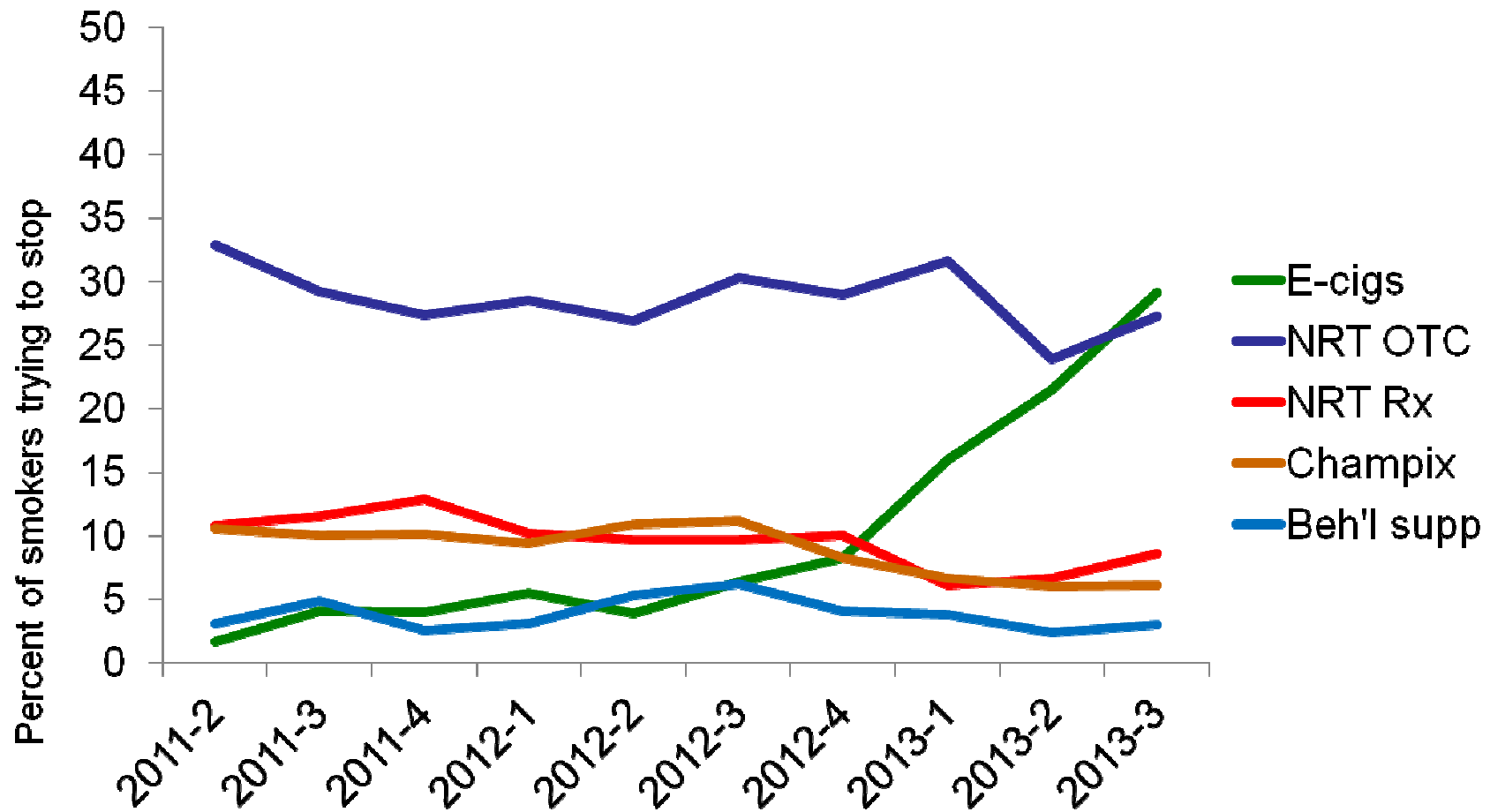


Contents

- Propylene glycol and/or Vegetable glycerine (glycerol)
- Nicotine (in mg/ml; ranging from 0-36)
- Flavourings (e.g. tobacco, mint, fruit)
- Additives



Aids used in most recent quit attempt

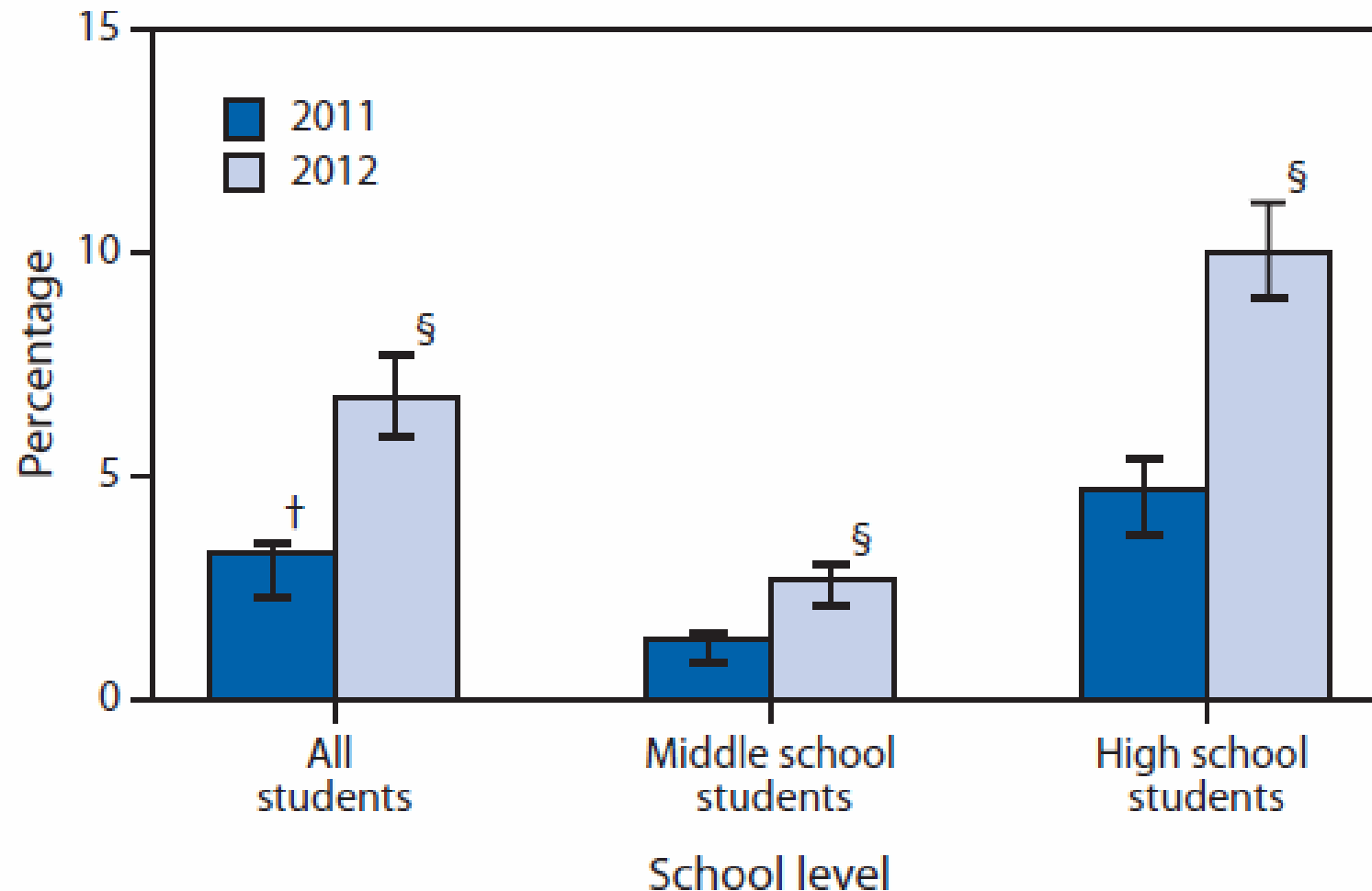


N=4,164 adults who smoke and tried to stop or who stopped in the past year

UK prevalence

- An estimated 1 in 6 smokers and recent ex-smokers use electronic cigarettes and 1 in 10 use them daily
- Almost 1 in 3 quit attempts involve use of electronic cigarettes
- There has been a decrease in use of other aids to smoking cessation
- Motivation to stop smoking has increased slightly
- Quit rates have increased slightly
- Per capita cigarette consumption has shrunk but per capita consumption of all nicotine products appears to have shrunk less

FIGURE. Ever electronic cigarette use* among middle and high school students, by year — National Youth Tobacco Survey, United States, 2011–2012

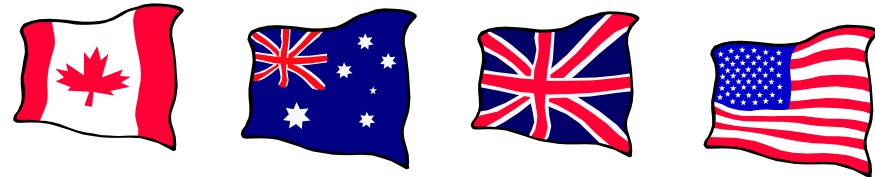


* Ever electronic cigarette use defined as having ever used electronic cigarettes, even just one time.

† 95% confidence interval.

§ Statistically significant difference between 2011 and 2012 (chi-square, $p < 0.05$).

Barriers to implementation: Beliefs about nicotine



	Canada	Aust.	U.K.	U.S.
Nicotine causes most cancer (% answering "true")	41%	45%	49%	44%
Nicotine causes most cancer (% answering "true") LOW INCOME	46%	52%	57%	51%
NRT might harm health (% agree strongly + somewhat)	37%	33%	25%	33%



Source: Siahpush et al, Tobacco Control 2006;(Suppl III):iii65-70.

Clinical studies

Effects on cardiac function

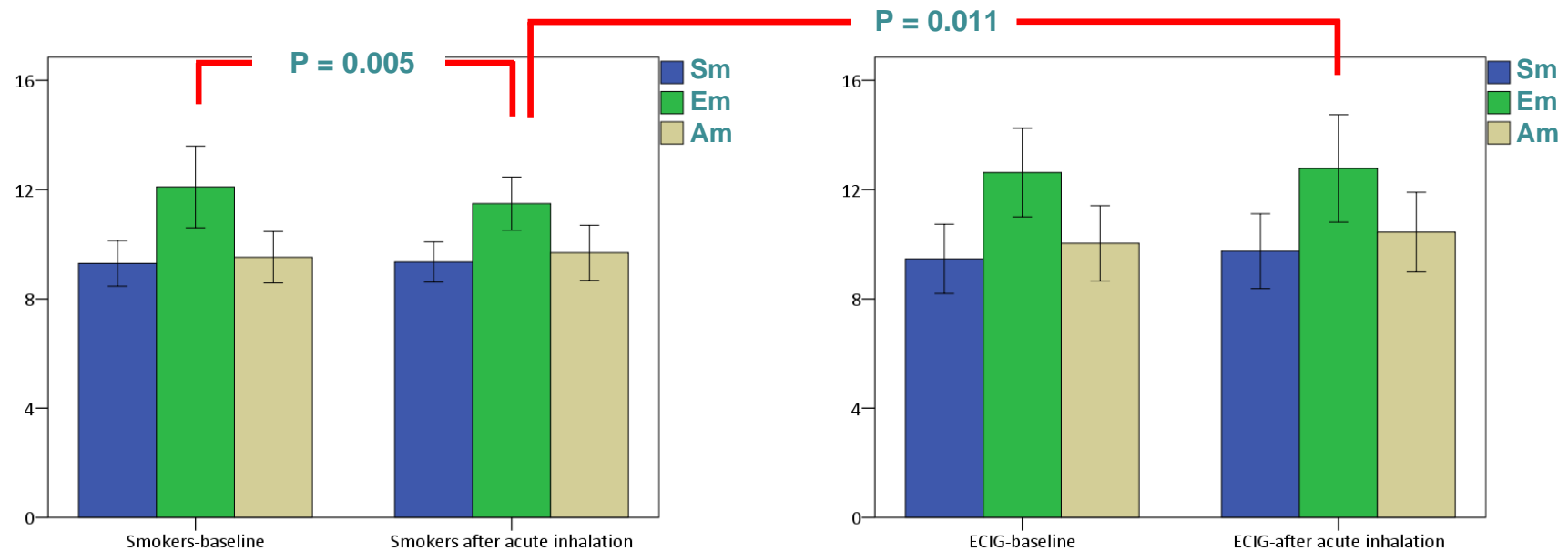
Hemodynamic changes

Post-use

	Smokers (n=20)	ECIG users (n=22)	P-value (smokers intra-group)	P-value (ECIG users intra- group)	P-value (inter- group after inhalation)
SBP (mmHg)	135 ± 7	128 ± 10	< 0.001	0.433	0.028
DBP (mmHg)	80 ± 7	81 ± 6	< 0.001	0.001	0.57
HR bpm	74 ± 8	68 ± 10	< 0.001	0.245	0.055
Ejection fraction (%)	60 ± 4	62 ± 4	0.317	0.224	0.571

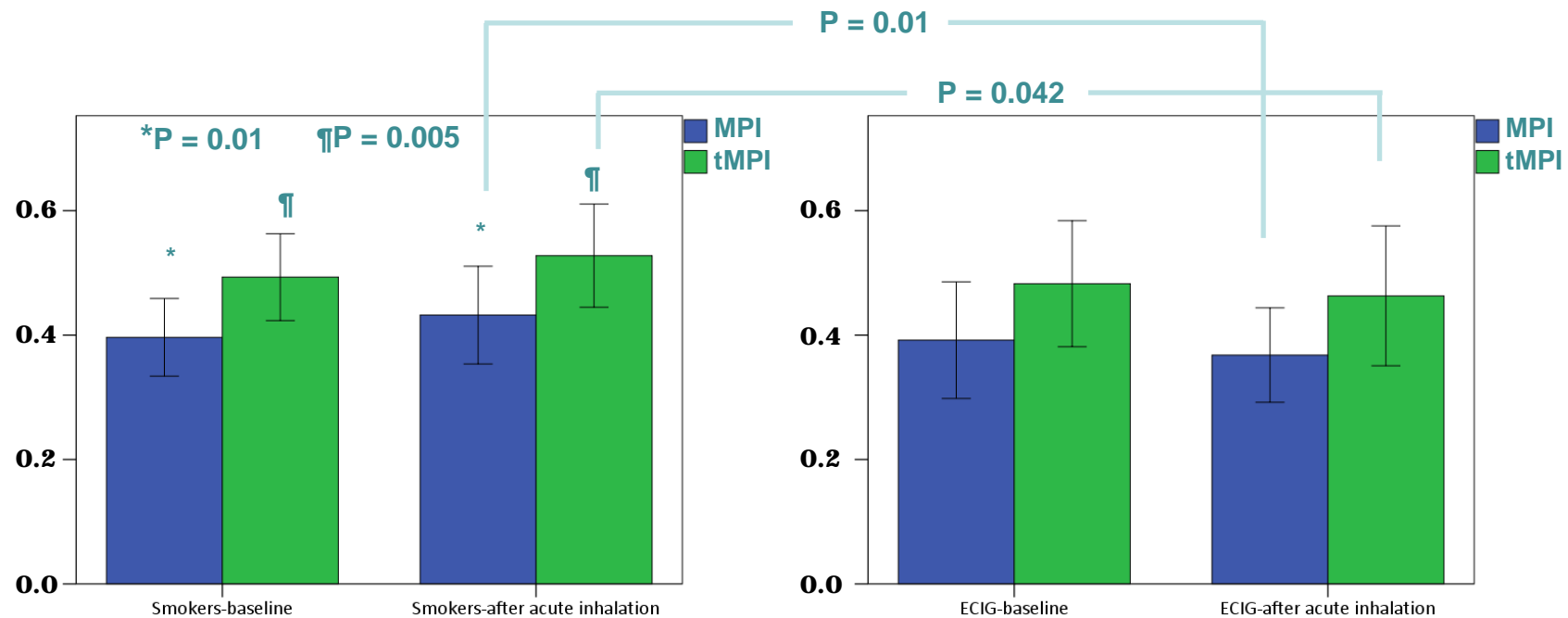
Clinical studies

Effects on cardiac function



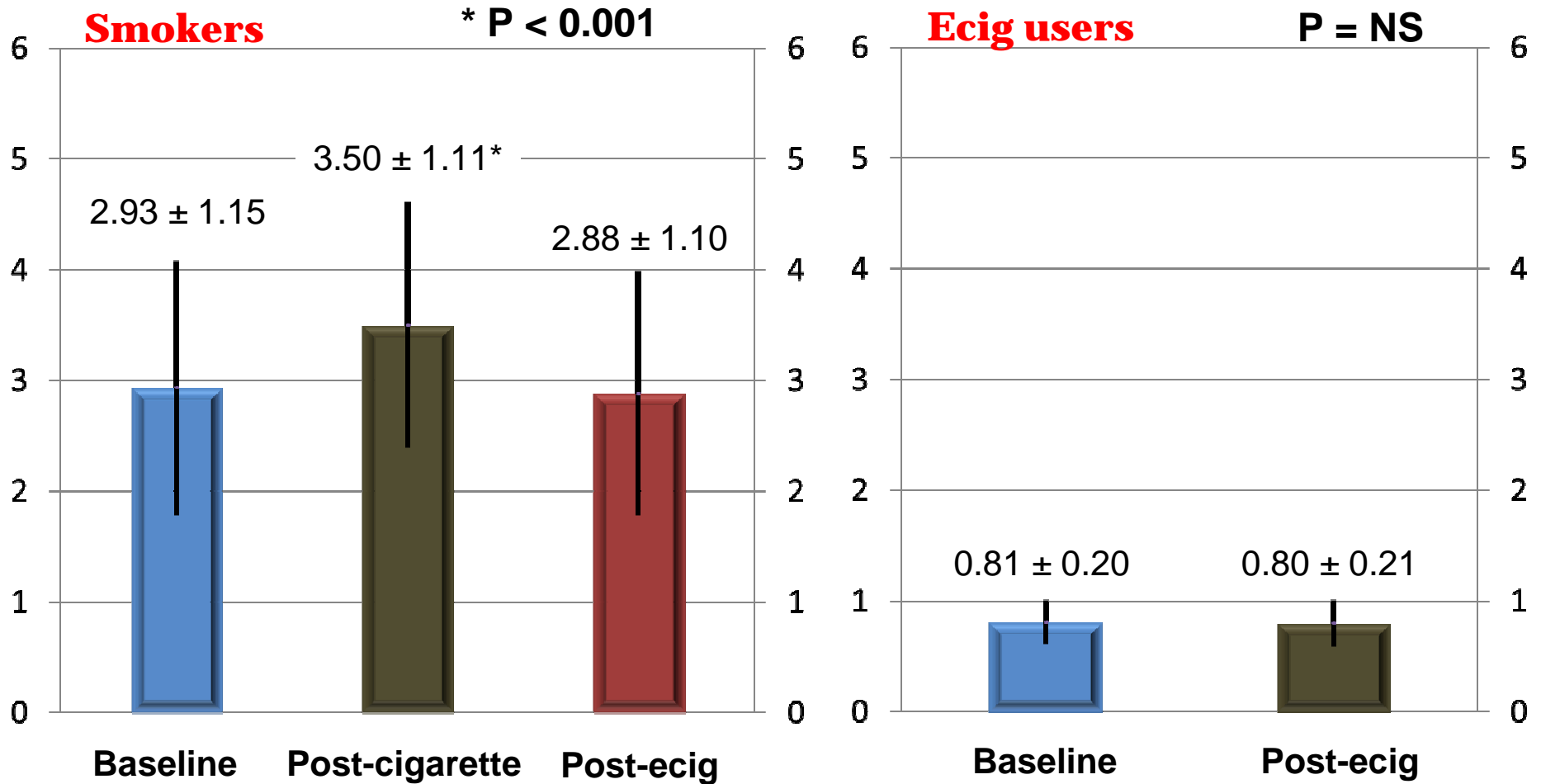
Clinical studies

Effects on cardiac function



Clinical studies

Carboxyhemoglobin



Farsalinos et al, *ESC 2013-Amsterdam*

Electronic cigarettes for smoking cessation: a randomised controlled trial

www.thelancet.com Published online September 7, 2013 [http://dx.doi.org/10.1016/S0140-6736\(13\)61842-5](http://dx.doi.org/10.1016/S0140-6736(13)61842-5)

Christopher Bullen, Colin Howe, Murray Laugesen, Hayden McRobbie, Varsha Parag, Jonathan Williman, Natalie Walker

Summary

Background Electronic cigarettes (e-cigarettes) can deliver nicotine and mitigate tobacco withdrawal and are used by many smokers to assist quit attempts. We investigated whether e-cigarettes are more effective than nicotine patches at helping smokers to quit.

Methods We did this pragmatic randomised-controlled superiority trial in Auckland, New Zealand, between Sept 6, 2011, and July 5, 2013. Adult (≥ 18 years) smokers wanting to quit were randomised (with computerised block randomisation, block size nine, stratified by ethnicity [Māori; Pacific; or non-Māori, non-Pacific], sex [men or women], and level of nicotine dependence [>5 or ≤ 5 Fagerström test for nicotine dependence]) in a 4:4:1 ratio to 16 mg nicotine e-cigarettes, nicotine patches (21 mg patch, one daily), or placebo e-cigarettes (no nicotine), from 1 week before until 12 weeks after quit day, with low intensity behavioural support via voluntary telephone counselling. The primary outcome was biochemically verified continuous abstinence at 6 months (exhaled breath carbon monoxide measurement <10 ppm). Primary analysis was by intention to treat. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000866000.

Findings 657 people were randomised (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) and were included in the intention-to-treat analysis. At 6 months, verified abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8% (17 of 295) with patches, and 4.1% (three of 73) with placebo e-cigarettes (risk difference for nicotine e-cigarette vs patches 1.51 [95% CI -2.49 to 5.51]; for nicotine e-cigarettes vs placebo e-cigarettes 3.16 [95% CI -2.29 to 8.61]). Achievement of abstinence was substantially lower than we anticipated for the power calculation, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes. We identified no significant differences in adverse events, with 137 events in the nicotine e-cigarettes group, 119 events in the patches group, and 36 events in the placebo e-cigarettes group. We noted no evidence of an association between adverse events and study product.

Interpretation E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events. Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels.

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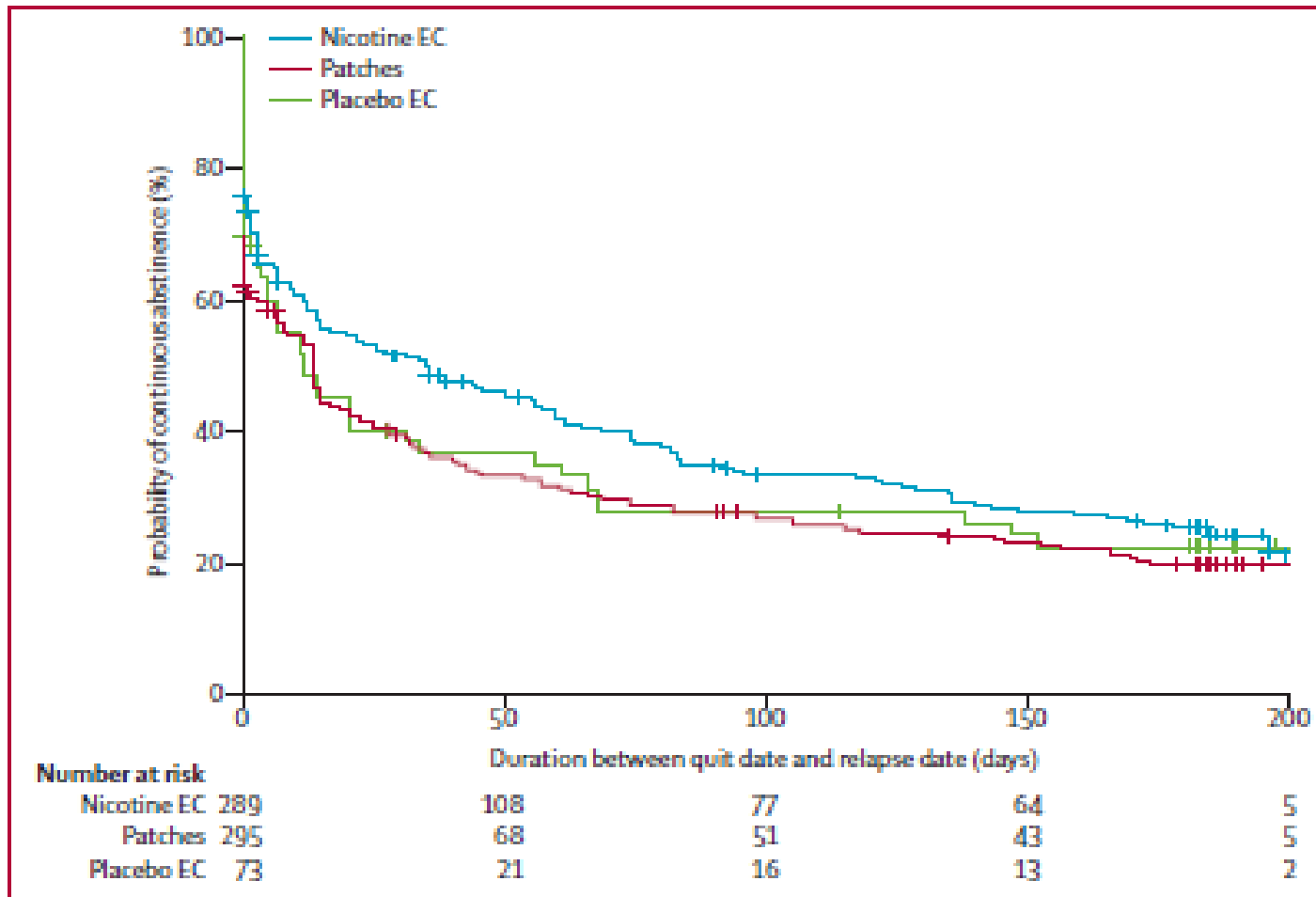


Figure 2: Kaplan-Meier analysis of time to relapse
EC=e-cigarettes.





Políticas de reducción de daños

- **1. INTRODUCCIÓN**
- **2. ESTRATEGIAS DE REDUCCIÓN DE DAÑOS**
 - **2.1. ESTRATEGIAS CLÍNICAS**
 - **2.1.1. Reducción del número de cigarrillos**
 - **2.1.2. Reducción gradual de nicotina y alquitrán**
 - **2.1.3. Terapia sustitutiva de nicotina (tsn)**
 - **2.2. ESTRATEGIAS DE LA INDUSTRIA TABACALERA**
 - **2.2.1. Cigarros puros o pipa**
 - **2.2.2. Cigarrillos con filtro**
 - **2.2.3. Cigarrillos bajos en alquitrán y nicotina (cigarrillos “light”)**
 - **2.3. OTROS PRODUCTOS DE RIESGO POTENCIAL REDUCIDO (PREPS)**
 - **2.3.1. Tabaco sin humo (smokeless)**
 - **2.3.2. Cigarrillos modificados**
- **3. VENTAJAS E INCONVENIENTES DE LAS ESTRATEGIAS DE REDUCCIÓN DE RIESGOS**
- **4. BIBLIOGRAFÍA**

Documents tell us that ...

- TTCs considered smokeless tobacco:

could provide the opportunity to make new profits rather than cannibalise existing profits from cigarettes.

- smokers that (due to health concerns) considered quitting
 - smokers in smokefree environments
 - new generation of 'better educated' not interested in smoking

- Interest was driven by concern about threat of regulation (smokefree) & consumers' health concerns driving a decline in cig sales

“The objective”

We have no wish to aid or hasten any decline in cigarette smoking. Deeper involvement in smokeless is strategically defensible.

*Extract BAT internal marketing briefing to its Tobacco Executive Committee, 21 Sept 1981
(available from: <http://legacy.library.ucsf.edu/tid/hxf18a99>)*

To market the range to younger, urban consumers as an alternative way to enjoy tobacco.

*Extract BAT internal marketing briefing to its Tobacco Executive Committee, 25 June 1984
(available from: <http://legacy.library.ucsf.edu/tid/hywd38a99>)*

Esta historia me suena...

- Menos tóxico
- ¿Es una moda transitoria?

Harm reduction:

- Salvar millones de vidas
- Los tratamientos no funcionan
- Estamos perdiendo la batalla



Seleccionar idioma | ▼

yo vapeo.es

CIGARROS ELECTRÓNICOS

Buscar...



INICIO

NOSOTROS

PREGUNTAS FRECUENTES

CONTACTO

ENVIOS Y DEVOLUCIONES

- LÍQUIDOS
- BASES Y AROMAS
- KITS MODs
- KITS CIGARRILLOS
- KITS PIPAS Y CIGARROS
- ACCESORIOS
- ATOS REPARABLES
- CLAROS Y CARTOS
- DRIP- TIPS
- BRICO E-LIQUID
- BRICO E- CIG
- FUNDA E-BOOK

Estás en: Inicio / LÍQUIDOS / LÍQUIDOS ATMOSLAB / BOTES DE 30 ML / BEBECA 30 ml

BEBECA 30 ml



Bebeca

Uno de los sabores más queridos y elegidos por los vapers que imita al Tribeca de Halo, ahora en la interpretación de AtmosLab.

Un dulce sabor del tabaco, con toques de algodón de azúcar, apto para vapear todos los días. Un golpe definitivo.

REVISIÓN (VIDEO 23)

Argumentos

- **A favor**
 - Balance de riesgos favorable respecto a fumar tabaco
 - No hay evidencia riesgos importantes
 - Estimula abandono
 - Preferible a TSN
 - “Harm reduction”
- **En contra**
 - Dudas en relación seguridad
 - Retrasa/impide cesación
 - Existencia prod, sanitarios regulados (TSN...)
 - Socava avances obtenidos (como espacios sin humo)
 - Marketing agresivo /mercado desregulado

WHO Technical Report Series
955

WHO STUDY GROUP ON TOBACCO PRODUCT REGULATION

Report on the Scientific Basis
of Tobacco Product Regulation:
Third Report of a WHO Study Group



- Fenómeno social creciente
- Innovación
- Plantea dudas en términos de seguridad
- Puede socavar avances obtenidos
- Debate sobre su pertinencia como estrategia de reducción de daños
- Riesgos “ocultos” – maniobra IT
- Vacío legal
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SOCIETY FOR RESEARCH ON



NICOTINE AND TOBACCO

SRNT Europe **16th Annual Meeting**

September 18-20, 2014

Santiago de Compostela

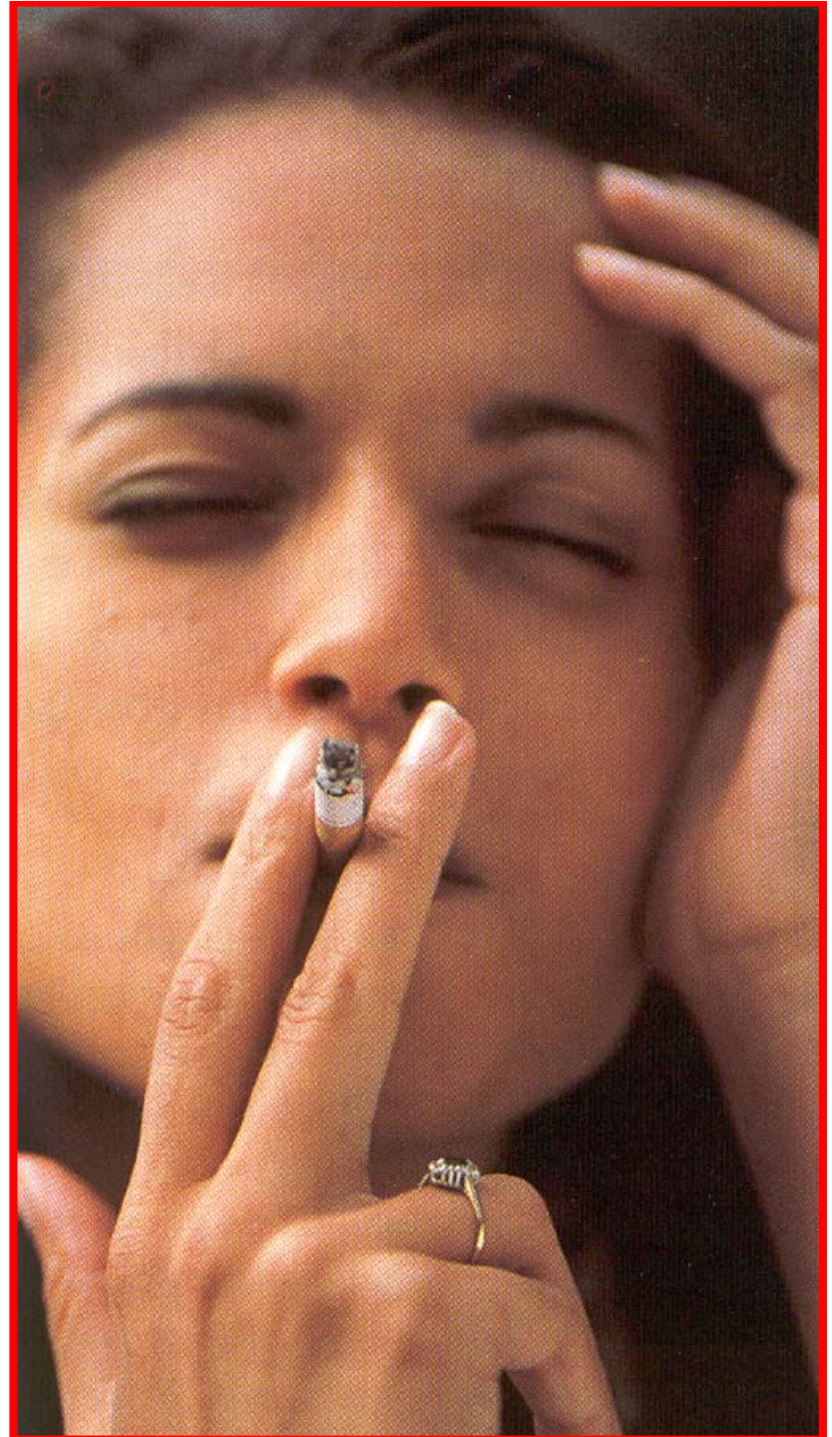
Galicia - Spain

www.2014srnt.eu



RESUMEN

- 1.Podemos ayudar a nuestros pacientes
- 2.Intervenciones útiles y fármacos seguros
- 3.Poco futuro vacunas
- 4.E-cig: necesitamos datos



Muchas gra

ayestaf@unica

