Modelling continuous abstinence rates over time from clinical trials of pharmacological interventions for smoking cessation

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ABSTRACT

Background and aim   It is useful, for theoretical and practical reasons, to be able to specify functions for continuous abstinence over time in smoking cessation attempts. This study aimed to find the best-fitting models of mean proportion abstinent with different smoking cessation pharmacotherapies up to 52 weeks from the quit date. **Methods**   We searched the Cochrane Database of Systematic Reviews to identify randomized controlled trials (RCTs) of pharmacological treatments to aid smoking cessation. For comparability, we selected trials that provided 12 weeks of treatment. Continuous abstinence rates for each treatment at each follow-up point in trials were extracted along with methodological details of the trial. Data points for each pharmacotherapy at each follow-up point were aggregated where the total across contributing studies included at least 1000 participants per data point. Continuous abstinence curves were modelled using a range of different functions from the quit date to 52-week follow-up. Models were compared for fit using R^2 and Bayesian information criterion (BIC). **Results**   Studies meeting our selection criteria covered three pharmacotherapies [varenicline, nicotine replacement therapy (NRT) and bupropion] and placebo. Power functions provided the best fit ($R^2 > 0.99$, BIC < 17.0) to continuous abstinence curves from the target quit date in all cases except for varenicline, where a logarithmic function described the curve best ($R^2 = 0.99$, BIC = 21.2). At 52 weeks, abstinence rates were 22.5% (23.0% modelled) for varenicline, 16.7% (16.0% modelled) for bupropion, 13.0% (12.4% modelled) for NRT and 8.3% (8.9% modelled) for placebo. For varenicline, bupropion, NRT and placebo, respectively, 55.9, 65.0, 62.3 and 56.5% of participants who were abstinent at the end of treatment were still abstinent at 52 weeks. **Conclusions**   Mean continuous abstinence rates up to 52 weeks from initiation of smoking cessation attempts in clinical trials can be modelled using simple power functions for placebo, nicotine replacement therapy and bupropion and a logarithmic function for varenicline. This allows accurate prediction of abstinence rates from any time point to any other time point up to 52 weeks.

Keywords   Bupropion, continuous abstinence, nicotine replacement therapy, pharmacological interventions, relapse, smoking cessation, smoking cessation aids, varenicline.

INTRODUCTION

Continuous abstinence rates after initiation of a smoking quit attempt follow a negatively decelerating curve over time [1]. This is a common pattern with attempts to stop engaging in addictive behaviours [2]. It is useful to be able to model the curve relating continuous abstinence to time from quit attempt initiation in order to understand the processes underlying smoking relapse and the impact of treatments on these processes, as well as for the more practical goal of predicting long-term abstinence rates from short-term outcomes. This paper synthesizes evidence from clinical trials of pharmacotherapies in smoking cessation to derive best-fitting, up-to-date models of mean continuous abstinence rates as a function of time since the quit attempt started.

Results of clinical trials and cohort studies suggest that with unaided quit attempts, only approximately a quarter of those trying to quit remain abstinent for a week, fewer than one in 10 remain abstinent for 6 months and fewer

than one in 20 remain abstinent at 1 year [1]. Continuous abstinence curves for smokers receiving support for quitting can be derived for a number of individual studies with multiple follow-up points [3–5], but functions describing the shape of the continuous abstinence curve over time have not been specified thus far.

Some studies have specifically addressed the question of whether relapse rates increase when treatment is terminated. A recent synthesis of evidence from trials of varenicline showed a higher relapse rate from the end of 12 weeks of treatment to 24-week follow-up than for placebo [6], but the difference had disappeared by 52-week follow-up. Studies exploring the long-term impact of nicotine replacement therapy (NRT) have found diminishing efficacy in terms of absolute percentage differences from placebo with increased time since quit attempt initiation [7,8]. None of these studies sought to model the shape of the relapse curve, however.

Modelling the shape of continuous abstinence curves in smoking cessation is important for several reasons: (1) if the continuous abstinence curves follow a well-defined and relatively simple mathematical formula, it would allow for prediction of abstinence rates from any time-point to any future time-point, which is important clinically and when assessing health impact [9]. (2) The shape of the curve may help in understanding what drives resumption of smoking at different time-points. It has been suggested that factors affecting early resumption of smoking may differ in kind from those driving later resumption [10]. This, in turn, has implications for interventions that may be effective at different time-points. (3) If the curves follow different shapes with different pharmacotherapies, it suggests that these may operate differentially on factors influencing resumption of smoking. For example, if the curve shows an inflection downwards post-treatment for a given pharmacotherapy, it suggests either that it is not adequately addressing chronic factors that lead to smoking resumption or that the treatment duration was too short.

When seeking to study continuous abstinence curves it is important to have high-quality data with high follow-up rates. Prospective cohort studies can provide valuable information, but often there are limitations with regard to loss to follow-up and inconsistencies in treatment duration that make it difficult to make meaningful comparisons. With greater control over treatment conditions, higher retention rates and data collection occurring at multiple time-points, randomized controlled trials (RCTs) provide an opportunity to examine continuous abstinence following pharmacological interventions for smoking cessation in greater detail. This study therefore aggregated data from high-quality RCTs to describe the shape and parameters of mean continuous abstinence curves associated with different smoking cessation pharmacotherapies. Specifically, we aimed to address the following research questions:

1 What functions best characterize the shape of mean continuous abstinence curves over the first year following quit attempts in smoking cessation RCTs?
2 Do these differ with different pharmacotherapies?

METHOD

Search strategy and study selection

Details of our study search and selection procedure are provided in Fig. 1. We searched the Cochrane Database of Systematic Reviews in the Cochrane Library (from 1990 to March 2017) for reviews with 'smoking' in the title, abstract or keyword fields. The results were assessed by three authors (J.M., H.U., R.W.) in order to identify reviews focusing on pharmacological treatments for smoking cessation; seven were identified as being appropriate for this study [11–17]. The reference lists of these reviews provided a pool of potential studies for inclusion in the present study. Supporting information, Appendix S1 contains an Excel file providing details of all studies considered in case readers wish to undertake their own analyses.

We included RCTs that compared continuous abstinence rates between pharmacological interventions, between one intervention and a placebo or between different pharmacotherapy doses and a placebo. We limited our
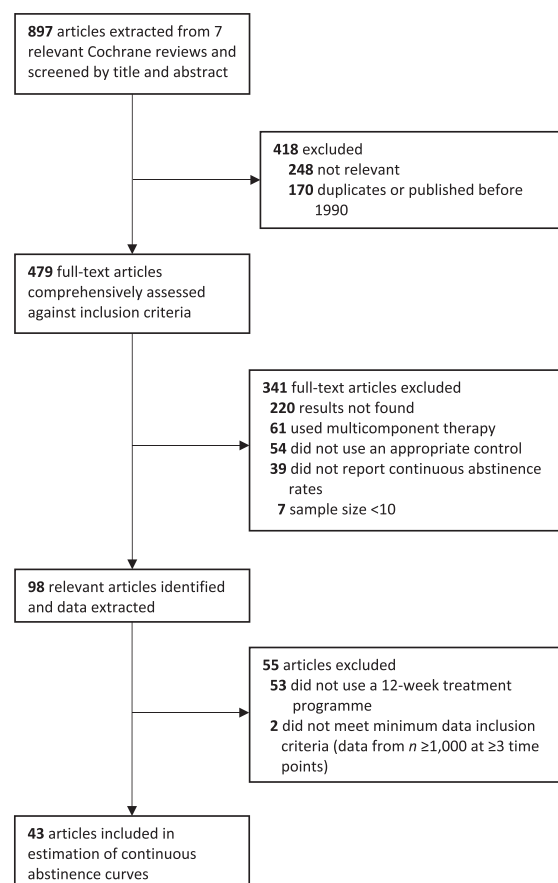
Figure 1 Flow diagram of search strategy and study selection

search to articles published since 1990 because we considered trial reporting and conduct to have improved since then, with agreed reporting criteria for trials such as Consolidated Standards of Reporting Trials (CONSORT) being more widely used [18]. Trials that compared a pharmacological intervention with 'standard care' were excluded, as were studies that focused on a reduction in cigarette consumption, or setting of quit dates rather than abstinence. We also excluded trials of combinations of different pharmacotherapies. Trials that reported only point prevalence (as opposed to continuous) abstinence rates were excluded, because it was not possible to determine whether abstinence was the result of the initial quit attempt. Trials with a sample size < 10 participants were also excluded, because it was judged that these would have been pilot or feasibility trials. We did not exclude any studies by virtue of heaviness of smoking or other smoker characteristics, but the large majority of studies set a minimum of 10 or more cigarettes per day for inclusion.

Due to the stringent criteria of Cochrane Reviews, all included RCTs were considered to be of acceptable standard. Studies awaiting assessments and ongoing studies were included where results were available.

Data extraction

RCTs that met the criteria detailed above were extracted from the relevant Cochrane Reviews. From these trials we extracted information on sample size, pharmacotherapies used, length of pharmacotherapy intervention, start point of follow-up, duration of follow-up and the percentage of participants who were continuously abstinent over time in each condition from a given start point to each follow-up point. Other data extracted from the trials included year of publication, year of trial start and country of origin.

Analyses

There was significant heterogeneity across study samples, methods and presentation of results. In order to standardize results for comparison across different pharmacotherapies while maximizing data available for the estimation of continuous abstinence curves, we selected studies that had used a 12-week treatment programme; this was the modal and median duration of treatments in the 98 studies [4,5,19–115] from which we extracted data. We used Microsoft Excel 2013 to plot the mean continuous abstinence rates weighted by sample size for follow-up points where there were aggregated data from a minimum of 1000 participants for all treatment groups. The resulting graphs describe the mean continuous abstinence rates associated with the different pharmacotherapies, displaying curves from the start of treatment to 52 weeks (the longest

follow-up for which the required data were available). For each treatment group, we compared four function classes (linear, exponential, logarithmic, and power) and fitted the one with the highest R^2. To handle zero values in the case of power functions, the starting time-point was 0.1 week, representing less than 1 day of abstinence. Model selection was confirmed by comparing the Bayesian information criterion (BIC) of each curve (calculated in Stata version 15), with lower BIC values indicating better model fit.

To check how far the relapse curves from the aggregated data matched within-study changes in continuous abstinence rates over time, we superimposed lines between consecutive pairs of time-points with each of the three largest studies, including where there were data available for additional time-points for each pharmacotherapy, onto our continuous abstinence curves to assess whether the curves were a reasonable fit.

RESULTS

Our search and selection procedure (Fig. 1) identified 43 trials eligible for inclusion in the present analysis. Their characteristics are summarized in Table 1. A total of 23 trials used varenicline [4,69–71,74,77,78,80,84–89,91,93,95,98,101,103,109,110,115], 12 used bupropion [4,50,56,63,64,66,69,70,85,90,95,101] and 15 used NRT [4,22,25,28–30,32,48,49,72,88,90,100,105,113], with some studies using more than one of these pharmacotherapies in different treatment groups. A placebo was used as a control in 38 of these trials [4,22,25,28–30,32,48–50,56,63,64,66,69–72,74,77,78,84–87,89,91,93,95,98,100,101,103,105,109,110,113,115], and a further two trials provided only placebo data due to the active comparator failing to meet criteria for inclusion [45,104].

Figure 2 shows the continuous abstinence curves from the quit date to 52-week follow-up for varenicline, bupropion, NRT and placebo. An interactive version of this graph is available in Supporting information, Appendix S2. The shape of the continuous abstinence curve was similar throughout the different pharmacotherapies (including placebo), with relapse rates highest in the initial 3–4 weeks and slowly tapering off after the end of treatment. Comparison of model selection statistics (Table 2) indicated that continuous abstinence data for bupropion, NRT and placebo could best be described by a power function (all $R^2 > 0.99$), while the best-fitting curve for varenicline was logarithmic ($R^2 = 0.99$). Equations for the best-fitting curve for each pharmacotherapy are shown in Fig. 2. The power function for varenicline also fitted well (Supporting information, Fig. S1: $R^2 = 0.94$), but it overestimated the 52-week abstinence rate.

Table 1 Characteristics of included studies.

Authors	Year	Country of origin	Special samples	Pharmacotherapies (italics indicate those not included in modelling)	n (in order of stated pharmacotherapies)	Follow-up points (weeks)
Sachs *et al.* [22]	1993	Sweden	–	NRT patch, placebo	110, 110	6, 12, 18, 26, 52
Imperial Cancer Research fund General practice research group [25]	1994	UK	–	NRT patch, placebo	842, 844	12, 52
Gourlay *et al.* [29]	1995	Australia	–	NRT patch, placebo	315, 314	4, 8, 12, 26
Stapleton *et al.* [28]	1995	UK	–	NRT patch, placebo	800, 400	3, 6, 12, 26, 52
Campbell *et al.* [30]	1996	UK	Hospital patients	NRT patch, placebo	115, 119	12, 52
Sønderskov *et al.* [32]	1997	Denmark	–	NRT patch, placebo	251, 142	4, 8, 12, 26
Wong *et al.* [45]	1999	USA	–	*Naltrexone*, placebo	23, 26	1, 2, 3, 4, 6, 8, 10, 12, 24
Tønnesen *et al.* [49]	2000	Denmark	Lung clinic attenders	NRT patch, NRT inhaler, placebo	104, 118, 109	2, 6, 12, 36, 52
Wallström *et al.* [48]	2000	Sweden	–	NRT sublingual tablet, placebo	123, 124	6, 12, 24, 52
Tashkin *et al.* [50]	2001	USA	Chronic obstructive pulmonary disease	Bupropion, placebo	129, 149	5, 6, 7, 10, 12, 26
Trial ZYB40001 [56]	2003	Canada	–	Bupropion, placebo	141, 143	7, 12
Evins *et al.* [64]	2005	USA	Schizophrenics	Bupropion, placebo	25, 28	12
Wagena *et al.* [63]	2005	Netherlands	At risk for chronic obstructive pulmonary disease	Bupropion, *nortriptyline*, placebo	86, 80, 89	12, 26
Gonzales *et al.* [69]	2006	USA	–	Varenicline, bupropion, placebo	352, 329, 344	12, 24, 52
Jorenby *et al.* [70]	2006	USA	–	Varenicline, bupropion, placebo	344, 342, 341	12, 24, 52
Oncken *et al.* [71]	2006	USA	–	Varenicline, placebo	518, 129	7, 12, 24, 52
Rigotti *et al.* [66]	2006	USA	Hospitalized with acute cardiovascular disease	Bupropion, placebo	124, 123	12, 52
David *et al.* [72]	2007	UK	–	NRT patch, placebo	370, 371	12, 24
Nakamura *et al.* [74]	2007	Japan	–	Varenicline, placebo	465, 154	12, 24, 52
Tsai *et al.* [77]	2007	Korea, Taiwan	–	Varenicline, placebo	126, 124	12, 24
Aubin *et al.* [80]	2008	UK, USA, Belgium, France, Netherlands	–	Varenicline, *NRT patch*[a]	376, 370	12, 52
Niaura *et al.* [78]	2008	USA	–	Varenicline, placebo	157, 155	7, 12, 24, 52
Wang *et al.* [84]	2009	China, Singapore, Thailand	–	Varenicline, placebo	158, 161	12, 24
Fagerström *et al.* [87]	2010	Norway, Sweden	–	Varenicline, placebo	213, 218	12, 26
Fagerström *et al.* [89]	2010	6 Asian countries	–	Varenicline, placebo	447, 446	12, 24

(*Continues*)

Table 1. (Continued)

Authors	Year	Country of origin	Special samples	Pharmacotherapies (italics indicate those not included in modelling)	n (in order of stated pharmacotherapies)	Follow-up points (weeks)
Hays et al. [85]	2010	USA	–	Varenicline, bupropion, placebo	692, 669, 684	12
Rigotti et al. [86]	2010	15 countries	Stable cardiovascular disease	Varenicline, placebo	355, 359	12, 24, 52
Tsukahara et al. [88]	2010	Japan	–	Varenicline, NRT patch	16, 16	12, 24
Bolliger et al. [93]	2011	11 countries	–	Varenicline, placebo	390, 198	12, 24
Tashkin et al. [91]	2011	USA, Spain, France, Italy	Mild/moderate chronic obstructive pulmonary disease	Varenicline, placebo	250, 254	12, 24, 52
Wittchen et al. [90]	2011	Germany	–	Bupropion, NRT	108, 105	52
Xenakis et al. [95]	2011	USA	–	Varenicline, bupropion, placebo	696, 671, 685	12, 52
Rennard et al. [98]	2012	14 countries	–	Varenicline, placebo	493, 166	12, 24
Tønnesen et al. [100]	2012	Denmark, Germany	–	NRT mouth spray, placebo	318, 161	4, 6, 8, 12, 16, 20, 24, 52
Anthenelli et al. [103]	2013	8 countries	Major depression	Varenicline, placebo	256, 269	12, 24, 52
Bullen et al. [105]	2013	New Zealand	–	NRT patch, e-cigarettes, placebo	295, 289, 73	4, 12, 24
Caponnetto et al. [104]	2013	Italy	–	E-cigarettes, placebo	200, 100	12, 52
Cinciripini et al. [101]	2013	USA	–	Varenicline, bupropion, placebo	86, 102, 106	12, 24, 36
Gonzales et al. [110]	2014	8 countries	–	Varenicline, placebo	249, 245	12, 24, 52
Trial NCT01347112 [109]	2014	USA	Alcoholics	Varenicline, placebo	16, 17	12, 24
O'Brien et al. [113]	2015	New Zealand	With and without mental illness	NRT patch, e-cigarettes, placebo	260, 250, 61	24
Anthenelli et al. [4]	2016	16 countries	With and without psychiatric disorders	Varenicline, bupropion, NRT patch, placebo	2037, 2034, 2038, 2035	12, 24
Eisenberg et al. [115]	2016	Canada	Hospitalized patients with acute coronary syndrome	Varenicline, placebo	151, 151	4, 12, 24

All studies involved 12 weeks of pharmacotherapy. [a]Nicotine replacement therapy (NRT) patch was administered for 10 weeks. so results were not included in analyses.

At the end of treatment, 45.1% (41.2% modelled; logarithmic curve) of participants treated with varenicline, 26.3% (24.6% modelled) of those treated with bupropion, 20.8% (20.2% modelled) of those treated with NRT and 16.2% (15.7% modelled) of those treated with placebo were still abstinent. By 52 weeks, abstinence rates had fallen to 22.5% (23.0% modelled) for varenicline, 16.7% (16.0% modelled) for bupropion, 13.0% (12.4% modelled) for NRT and 8.3% (8.9% modelled) for placebo. A total of 49.8% (55.9% modelled) of those treated with varenicline, 63.4% (65.0% modelled) of those treated with bupropion, 62.5% (61.3% modelled) of those treated with NRT and 51.5% (56.5% modelled) of those treated with placebo

who were abstinent at the end of treatment were still abstinent at 52 weeks.

Superimposing lines drawn between continuous abstinence rates from consecutive follow-up points within the three largest studies for each pharmacotherapy showed a good fit to the modelled curves (Supporting information, Fig. S2).

DISCUSSION

There were sufficient data to enable reliable estimation of mean continuous abstinence rates for end of treatment (12-week post-quit date), 26- and 52-week time-points.
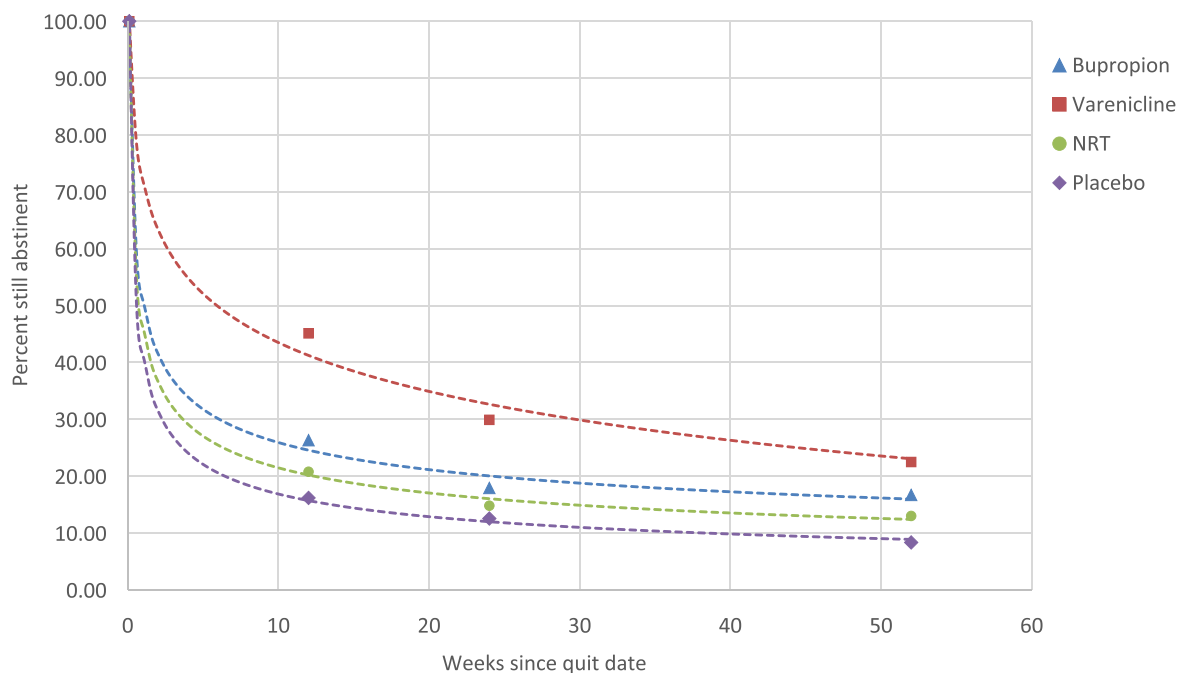
Figure 2 Continuous abstinence rates with best-fitting curves estimated from continuous abstinence rates from randomized controlled trials (RCTs) of 12-week treatment with smoking cessation pharmacotherapies. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 Model selection statistics for continuous abstinence curves from 0 to 52 weeks.

	Varenicline		Bupropion		NRT		Placebo	
	R^2	BIC	R^2	BIC	R^2	BIC	R^2	BIC
Linear	0.669	37.01	0.516	39.60	0.499	40.12	0.503	40.44
Exponential	0.817	31.53	0.619	31.97	0.613	30.73	0.678	28.78
Logarithmic	0.994	21.16	0.984	25.88	0.980	27.23	0.980	27.55
Power	0.940	26.69	0.991	16.92	0.996	11.75	0.998	7.29

BIC = Bayesian information criterion; NRT = nicotine replacement therapy.

The shape of the function relating these to time could best be modelled by power functions for placebo, NRT and bupropion and a logarithmic function for varenicline.

Being able to describe continuous abstinence curves using a simple function, in theory, provides a basis for predicting relapse from one time-point to any other time-point. This is useful when one only has short-term follow-up data available, or when interpolating back from long-term data. In UK stop-smoking services, for example, it is common to use 4- or 12-week abstinence rates in targets because limited resources make it impracticable to collect accurate longer-term data. Unfortunately, there were not sufficient data to estimate continuous abstinence rates prior to 12 weeks, so it is possible that more complex functions during the treatment period may have been missed. However, we were able to provide precise estimates of mean relapse rates following end of treatment for the different pharmacotherapies.

The finding that a single function starting at the quit date was able to capture abstinence rates at the end of treatment, as well as 26- and 52-week abstinence rates, suggests that a single relapse process is in operation during and after treatment. This appears to conflict with studies suggesting that different processes may be in operation. However, it remains possible that different processes are in operation, but their combined effects remain the same. This is a topic that merits further investigation.

We did not see evidence for a point of inflection in the curves at the end of treatment with the active pharmacotherapies, which also suggests that by 12 weeks from the quit date these pharmacotherapies have had whatever effect they are going to have. This accords with findings from trials with NRT which have not found clear evidence for a benefit of extending treatment beyond 12 weeks [5,7]. It conflicts with findings from a large RCT with varenicline, which showed a benefit from extending treatment for a

further 12 weeks [116]. However, this benefit appeared to occur with participants who had not managed to attain abstinence early on and had only been abstinent for a short while when the 12-week course of treatment ended [117]. This suggests an optimum treatment regimen for varenicline of 12 weeks if smokers are able to abstain during the first week, but 24 weeks if they only manage to abstain after a few weeks—the aim being to ensure that they receive approximately 12 weeks of pharmacotherapy from the point at which they initiate abstinence.

Of the four functions we fitted to the data, power functions provided the best fit for continuous abstinence from all treatments with the exception of varenicline, which was better described by a logarithmic curve. This difference was driven by the higher 12-week abstinence rate observed in participants treated with varenicline. Methodological differences between trials of varenicline and other pharmacotherapies may account for at least some of this variance. Varenicline trials typically measure continuous abstinence from week 9 rather than from the target quit date, so the figure may be somewhat inflated, given that varenicline recruits smokers into abstinence for several weeks after the target quit date [118]. The results suggest that there is no benefit in recruiting these additional smokers into abstinence, as they are more likely to relapse between the end of treatment and 52-week follow-up compared with those treated with other pharmacotherapies.

This study had several limitations. First, there was substantial heterogeneity in trial methods and study samples which may have introduced noise to the data points. Secondly, there were only sufficient data to plot abstinence rates for 12, 24 and 52 weeks after the start of treatment. It would have been useful to have data available on a greater number of time-points to incorporate into our continuous abstinence curves, particularly in the early weeks where relapse rates were very high. Thirdly, we were only able to include three pharmacotherapies and placebo in our analysis. There were insufficient data available on combination NRT and other popular and emerging pharmacological aids to smoking cessation, such as e-cigarettes, nortriptyline and cytisine, and it is possible that the continuous abstinence curves associated with these treatments may differ from those observed here. Fourthly, we pre-specified a small number of functions, and it may be that another function would be more appropriate. Although the fit of the selected function was very high, there was only a small number of follow-up points. With more follow-up points, a better-fitting function might emerge. Fifthly, while a power function provided a very good fit in most cases, the y value is infinite at $x = 0$ rather than 100%, so the starting point for time has to be a number above 0. We chose 0.1 weeks (representing less than 1 day) as a value close to 0, and this provided a very close fit to the data. However, a more mathematically sound

function with a similar shape may be preferable. Finally, we limited follow-up to 52 weeks because of the scarcity of data points after that point. Studies with longer-term follow-up have been conducted, and these suggest that approximately 30% of those who abstain for 52 weeks relapse at some point within the next 10 years [7]. This suggests that the power function, which has a very shallow slope after 52 weeks, may be an adequate fit to the longer-term continuous abstinence curve.

In conclusion, this study indicates that a power function, or a function very close to it in shape, provides a very close fit to mean continuous abstinence from smoking in studies of smokers trying to quit using placebo, nicotine replacement therapy or bupropion. For varenicline, a logarithmic function appears to provide a better fit.

Declaration of interests

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References

1. Hughes J. R., Keely J., Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004; **99**: 29–38.
2. Kirshenbaum A. P., Olsen D. M., Bickel W. K. A quantitative review of the ubiquitous relapse curve. *J Subst Abuse Treat* 2009; **36**: 8–17.
3. Dobbie F., Hiscock R., Leonardi-Bee J., Murray S., Shahab L., Aveyard P. *et al.* Evaluating long-term outcomes of NHS stop smoking services (ELONS): a prospective cohort study NIHR Journals Library. *Health Technol Assess* 2015; **19**: 1–156.
4. Anthenelli R. M., Benowitz N. L., West R., Aubin L. S., McRae T., Lawrence D. *et al.* Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016; **387**: 2507–20.
5. Tønnesen P., Paoletti P., Gustavsson G., Russell M. A., Saracci R., Gulsvik A. *et al.* Higher dosage nicotine patches increase one-year smoking cessation rates: results from

the European CEASE trial. Collaborative European anti-smoking evaluation. European Respiratory Society. *Eur Respir J* 1999; **13**: 238–46.

6. Agboola S. A., Coleman T., McNeill A., Leonardi-Bee J. Abstinence and relapse among smokers who use varenicline in a quit attempt—a pooled analysis of randomized controlled trials. *Addiction* 2015; **110**: 1182–93.

7. Etter J.-F., Stapleton J. A. Nicotine replacement therapy for long-term smoking cessation: a meta-analysis. *Tob Control* 2006; **15**: 280–5.

8. Rosen L. J., Galili T., Kott J., Goodman M., Freedman L. S. Diminishing benefit of smoking cessation medications during the first year: a meta-analysis of randomized controlled trials. *Addiction* 2018; **113**: 805–16.

9. West R., Coyle K., Owen L., Coyle D., Pokhrel S. Estimates of effectiveness and reach for 'return on investment' modelling of smoking cessation interventions using data from England. *Addiction* 2018; **113**: 19–31.

10. Herd N., Borland R., Hyland A. Predictors of smoking relapse by duration of abstinence: findings from the International Tobacco Control (ITC) Four Country Survey. *Addiction* 2009; **104**: 2088–99.

11. Hartmann-Boyce J., Cahill K., Hatsukami D., Cornuz J. Nicotine vaccines for smoking cessation. *Cochrane Database Syst Rev* 2012; **8**: CD007072.

12. Hartmann-Boyce J., McRobbie H., Bullen C., Begh R., Stead L. F., Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2016; **9**: CD010216.

13. Cahill K., Stead L. F., Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012; **4**: CD006103.

14. Stead L. F., Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev* 2012; **10**: CD008286.

15. Cahill K., Ussher M. H. Cannabinoid type 1 receptor antagonists for smoking cessation. *Cochrane Database Syst Rev* 2011; **3**: CD005353.

16. Hughes J. R., Stead L. F., Hartmann-Boyce J., Cahill K., Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2014; **1**: CD000031.

17. Stead L. F., Perera R., Bullen C., Mant D., Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008; **1**: CD000146.

18. Begg C., Cho M., Eastwood S., Horton R., Moher D., Olkin I. *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; **276**: 637–9.

19. Tonnesen P., Norregaard J., Simonsen K., Säwe U. A. Double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med* 1991; **325**: 311–5.

20. Christen A., Beiswanger B., Mau M., Walker C., Hatsukami D., Allen S. *et al.* Transdermal nicotine for smoking cessation: six-month results from two multicenter controlled clinical trials. *JAMA* 1991; **266**: 3133–8.

21. Sutherland G., Stapleton J. A., Russell M. A., Jarvis M. J., Hajek P., Belcher M. *et al.* Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992; **340**: 324–9.

22. Sachs D. P., Säwe U., Leischow S. J. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med* 1993; **153**: 1881–90.

23. Russell M. A., Stapleton J. A., Feyerabend C., Wiseman S. M., Gustavsson G., Sawe U. *et al.* Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ* 1993; **306**: 1308–12.

24. Hjalmarson A., Franzon M., Westin A., Wiklund O. Effect of nicotine nasal spray on smoking cessation. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1994; **154**: 2567–72.

25. Group BMJP Randomised trial of nicotine patches in general practice: results at one year. *BMJ* 1994; **308**: 1476–7.

26. Herrera N., Franco R., Herrera L., Partidas A., Rolando R., Fagerström K. O. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. *Chest* 1995; **108**: 447–51.

27. Schneider N. G., Olmstead R., Mody F. V., Doan K., Franzon M., Jarvik M. E. *et al.* Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. *Addiction* 1995; **90**: 1671–82.

28. Stapleton J. A., Russell M. A., Feyerabend C., Wiseman S. M., Gustavsson G., Sawe U. *et al.* Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction* 1995; **90**: 31–42.

29. Gourlay S. G., Forbes A., Marriner T., Pethica D., McNeil J. J. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ* 1995; **311**: 363–6.

30. Campbell I. A., Prescott R. J., Tjeder-Burton S. M. Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study. *Respir Med* 1996; **90**: 47–51.

31. Schneider N. G., Olmstead R., Nilsson F., Mody F. V., Franzon M., Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. *Addiction* 1996; **91**: 1293–306.

32. Sønderskov J., Olsen J., Sabroe S., Meillier L., Overvad K. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. *Am J Epidemiol* 1997; **145**: 309–18.

33. Hurt R. D., Sachs D. P., Glover E. D., Offord K. P., Johnston J. A., Dale L. C. *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997; **337**: 1195–202.

34. Richmond R. L., Kehoe L., de Almeida Neto A. C. Effectiveness of a 24-hour transdermal nicotine patch in conjunction with a cognitive behavioural programme: 1-year outcome. *Addiction* 1997; **92**: 27–31.

35. Blöndal T., Franzon M., Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *Eur Respir J* 1997; **10**: 1585–90.

36. Hjalmarson A., Nilsson F., Sjöström L., Wiklund O. The nicotine inhaler in smoking cessation. *Arch Intern Med* 1997; **157**: 1721–8.

37. Ahluwalia J. S., McNagny S. E., Clark W. S. Smoking cessation among inner-city African Americans using the nicotine transdermal patch. *J Gen Intern Med* 1998; **13**: 1–8.

38. Stapleton J. A., Sutherland G., Russell M. A. H. How much does relapse after one year erode effectiveness of smoking cessation treatments? Long term follow up of randomised trial of nicotine nasal spray. *BMJ* 1998; **316**: 830–1.

39. Davidson M., Epstein M., Burt R., Schaefer C., Whitworth G., McDonald A. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. *Arch Fam Med* 1998; **7**: 569–74.

40. Hall S. M., Reus V. I., Muñoz R. F., Sees K. L., Humfleet G., Hartz D. T. *et al.* Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Arch Gen Psychiatry* 1998; **55**: 683–90.

41. Hays J. T., Croghan I. T., Schroeder D. R., Offord K. P., Hurt R. D., Wolter T. D. *et al.* Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled, and open label trials. *Am J Public Health* 1999; **89**: 1701–7.

42. Jorenby D. E., Leischow S. J., Nides M. A., Rennard S. I., Johnston J. A., Hughes A. R. *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999; **340**: 685–91.

43. Daughton D. M., Fortmann S. P., Glover E. D., Hatsukami D. K., Heatley S. A., Lichtenstein E. *et al.* The smoking cessation efficacy of varying doses of nicotine patch delivery systems 4 to 5 years post-quit day. *Prev Med* 1999; **28**: 113–8.

44. Hughes J. R., Lesmes G. R., Hatsukami D. K., Richmond R. L., Lichtenstein E., Jorenby D. E. *et al.* Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tob Res* 1999; **1**: 169–74.

45. Wong G. Y., Wolter T. D., Croghan G. A., Croghan I. T., Offord K. P., Hurt R. D. A randomized trial of naltrexone for smoking cessation. *Addiction* 1999; **94**: 1227–37.

46. Wisborg K., Henriksen T. B., Jespersen L. B., Secher N. J. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstet Gynecol* 2000; **96**: 967–71.

47. Multi-Center, Double-Blind, Double-Dummy, Placebo-Controlled, Randomized, Parallel Group, Dose response evaluation of a new chemical entity (NCE) and ZYBAN (bupropion hydrochloride) sustained release (300mg/day) versus placebo as aids to smoking cessation [internet]. Study ID SMK20001; 2000. Available at: www.gsk-clinicalstudyregister.com/study/SMK20001 (accessed 1 December 2018) (Archived at http://www.webcitation.org/75UsNvnm2 on 17 January 2019).

48. Wallström M., Nilsson F., Hirsch J. M. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. *Addiction* 2000; **95**: 1161–71.

49. Tønnesen P., Mikkelsen K. L. Smoking cessation with four nicotine replacement regimes in a lung clinic. *Eur Respir J* 2000; **16**: 717–22.

50. Tashkin D., Kanner R., Bailey W., Buist S., Anderson P., Nides M. *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; **357**: 1571–5.

51. Gonzales D. H., Nides M. A., Ferry L. H., Kustra R. P., Jamerson B. D., Segall N. *et al.* Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001; **69**: 438–44.

52. Gonzales D., Bjornson W., Durcan M. J., White J. D., Johnston J. A., Buist A. S. *et al.* Effects of gender on relapse prevention in smokers treated with bupropion SR. *Am J Prev Med* 2002; **22**: 234–9.

53. Glover E. D., Glover P. N., Franzon M., Sullivan C. R., Cerullo C. C., Howell R. M. *et al.* A comparison of a nicotine sublingual tablet and placebo for smoking cessation. *Nicotine Tob Res* 2002; **4**: 441–50.

54. George T. P., Vessicchio J. C., Termine A., Bregartner T. A., Feingold A., Rounsaville B. J. *et al.* A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry* 2002; **52**: 53–61.

55. Shiffman S., Dresler C. M., Hajek P., Gilburt S. J. A., Targett D. A., Strahs K. R. Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 2002; **162**: 1267–76.

56. A randomized, double-blind, placebo-controlled, 12-week smoking cessation trial of Zyban (150 mg bid) in adult smokers previously treated with Zyban [internet]. Study ID ZYB40001; 2003. Available at: https://www.gsk-clinicalstudyregister.com/study/ZYB40001?search=study&#rs (accessed 1 December 2018) (Archived at http://www.webcitation.org/75UsScUim on 17 January 2019).

57. Hughes J. R., Novy P., Hatsukami D. K., Jensen J., Callas P. W. Efficacy of nicotine patch in smokers with a history of alcoholism. *Alcohol Clin Exp Res* 2003; **27**: 946–54.

58. Tønnesen P., Tonstad S., Hjalmarson A., Lebargy F., Van Spiegel P. I., Hider A. *et al.* A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003; **254**: 184–92.

59. Tonstad S., Farsang C., Klaene G., Lewis K., Manolis A., Perruchoud A. P. *et al.* Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. *Eur Heart J* 2003; **24**: 946–55.

60. Lerman C., Kaufmann V., Rukstalis M., Patterson F., Perkins K., Audrain-McGovern J. *et al.* Individualizing nicotine replacement therapy for the treatment of tobacco dependence: a randomized trial. *Ann Intern Med* 2004; **140**: 426–33.

61. Aubin H. J., Lebargy F., Berlin I., Bidaut-Mazel C., Chemali-Hudry J., Lagrue G. Efficacy of bupropion and predictors of successful outcome in a sample of French smokers: a randomized placebo-controlled trial. *Addiction* 2004; **99**: 1206–18.

62. Dalsgareth O. J., Hansen N.-C. G., Søes-Petersen U., Evald T., Høegholm A., Barber J. *et al.* A multicenter, randomized, double-blind, placebo-controlled, 6-month trial of bupropion hydrochloride sustained-release tablets as an aid to smoking cessation in hospital employees. *Nicotine Tob Res* 2004; **6**: 55–61.

63. Wagena E. J., Knipschild P. G., Huibers M. J. H., Wouters E. F. M., van Schayck C. P. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. *Arch Intern Med* 2005; **165**: 2286–92.

64. Evins A. E., Cather C., Deckersbach T., Freudenreich O., Culhane M. A., Olm-Shipman C. M. *et al.* A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *J Clin Psychopharmacol* 2005; **25**: 218–25.

65. Holt S., Timu-Parata C., Ryder-Lewis S., Weatherall M., Beasley R. Efficacy of bupropion in the indigenous Maori population in New Zealand. *Thorax* 2005; **60**: 120–3.

66. Rigotti N. A., Thorndike A. N., Regan S., McKool K., Pasternak R. C., Chang Y. *et al.* Bupropion for smokers hospitalized with acute cardiovascular disease. *Am J Med* 2006; **119**: 1080–7.

67. Nides M., Oncken C., Gonzales D., Rennard S., Watsky E. J., Anziano R. *et al.* Smoking cessation with Varenicline, a selective α4β2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med* 2006; **166**: 1561–8.

68. Haggsträm F. M., Chatkin J. M., Sussenbach-Vaz E., Cesari D. H., Fam C. F., Fritscher C. C. A controlled trial of

nortriptyline, sustained-release bupropion and placebo for smoking cessation: preliminary results. *Pulm Pharmacol Ther* 2006; **19**: 205–9.

69. Gonzales D., Rennard S. I., Nides M., Oncken C., Azoulay S., Billing C. B. *et al.* Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006; **296**: 47–55.

70. Jorenby D. E., Hays J. T., Rigotti N. A., Azoulay S., Watsky E. J., Williams K. E. *et al.* Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006; **296**: 56–63.

71. Oncken C., Gonzales D., Nides M., Rennard S., Watsky E., Billing C. B. *et al.* Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 2006; **166**: 1571–7.

72. David S. P., Munafò M. R., Murphy M. F. G., Walton R. T., Johnstone E. C. The serotonin transporter 5-HTTLPR polymorphism and treatment response to nicotine patch: follow-up of a randomized controlled trial. *Nicotine Tob Res* 2007; **9**: 225–31.

73. Fossati R., Apolone G., Negri E., Compagnoni A., La Vecchia C., Mangano S. *et al.* A double-blind, placebo-controlled, randomized trial of bupropion for smoking cessation in primary care. *Arch Intern Med* 2007; **167**: 1791–7.

74. Nakamura M., Oshima A., Fujimoto Y., Maruyama N., Ishibashi T., Reeves K. R. Efficacy and tolerability of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers. *Clin Ther* 2007; **29**: 1040–56.

75. Prapavessis H., Cameron L., Baldi J. C., Robinson S., Borrie K., Harper T. *et al.* The effects of exercise and nicotine replacement therapy on smoking rates in women. *Addict Behav* 2007; **32**: 1416–32.

76. David S. P., Strong D. R., Munafò M. R., Brown R. A., Lloyd-Richardson E. E., Wileyto P. E. *et al.* Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. *Nicotine Tob Res* 2007; **9**: 1251–7.

77. Tsai S.-T., Cho H.-J., Cheng H.-S., Kim C.-H., Hsueh K.-C., Billing C. B. Jr. *et al.* A randomized, placebo-controlled trial of varenicline, a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. *Clin Ther* 2007; **29**: 1027–39.

78. Niaura R., Hays J. T., Jorenby D. E., Leone F. T., Pappas J. E., Reeves K. R. *et al.* The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial. *Curr Med Res Opin* 2008; **24**: 1931–41.

79. Cornuz J., Zwahlen S., Jungi W. F., Osterwalder J., Klingler K., van Melle G. *et al.* A vaccine against nicotine for smoking cessation: a randomized controlled trial. *PLOS ONE* 2008; **3**: e2547.

80. Aubin H.-J., Bobak A., Britton J. R., Oncken C., Billing C. B., Gong J. *et al.* Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax* 2008; **63**: 717–24.

81. Vinnikov D., Brimkulov N., Burjubaeva A. A double-blind, randomised, placebo-controlled trial of Cytisine for smoking cessation in medium-dependent workers. *J Smok Cessat* 2008; **3**: 57–62.

82. Simon J. A., Duncan C., Huggins J., Solkowitz S., Carmody T. P. Sustained-release bupropion for hospital-based smoking cessation: a randomized trial. *Nicotine Tob Res* 2009; **11**: 663–9.

83. Piper M. E., Smith S. S., Schlam T. R., Fiore M. C., Jorenby D. E., Fraser D. *et al.* A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch Gen Psychiatry* 2009; **66**: 1253–62.

84. Wang C., Xiao D., Chan K. P. W., Pothirat C., Garza D., Davies S. Varenicline for smoking cessation: a placebo-controlled, randomized study. *Respirology* 2009; **14**: 384–92.

85. Hays J. T., Leischow S. J., Lawrence D., Lee T. C. Adherence to treatment for tobacco dependence: association with smoking abstinence and predictors of adherence. *Nicotine Tob Res* 2010; **12**: 574–81.

86. Rigotti N. A., Pipe A. L., Benowitz N. L., Arteaga C., Garza D., Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation* 2010; **121**: 221–9.

87. Fagerström K., Gilljam H., Metcalfe M., Tonstad S., Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *BMJ* 2010; **341**: c6549.

88. Tsukahara H., Noda K., Saku K. A randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers: efficacy, safety and withdrawal symptoms (the VN-SEESAW study). *Circ J* 2010; **74**: 771–8.

89. Fagerström K., Nakamura M., Cho H.-J., Tsai S.-T., Wang C., Davies S. *et al.* Varenicline treatment for smoking cessation in Asian populations: a pooled analysis of placebo-controlled trials conducted in six Asian countries. *Curr Med Res Opin* 2010; **26**: 2165–73.

90. Wittchen H.-U., Hoch E., Klotsche J., Muehlig S. Smoking cessation in primary care - a randomized controlled trial of bupropione, nicotine replacements, CBT and a minimal intervention. *Int J Methods Psychiatr Res* 2011; **20**: 28–39.

91. Tashkin D. P., Rennard S., Hays J. T., Ma W., Lawrence D., Lee T. C. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. *Chest* 2011; **139**: 591–9.

92. Tonstad S., Holme I., Tønnesen P. Dianicline, a novel α4β2 nicotinic acetylcholine receptor partial agonist, for smoking cessation: a randomized placebo-controlled clinical trial. *Nicotine Tob Res* 2011; **13**: 1–6.

93. Bolliger C. T., Issa J. S., Posadas-Valay R., Safwat T., Abreu P., Correia E. A. *et al.* Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. *Clin Ther* 2011; **33**: 465–77.

94. Hatsukami D. K., Jorenby D. E., Gonzales D., Rigotti N. A., Glover E. D., Oncken C. A. *et al.* Immunogenicity and smoking-cessation outcomes for a novel nicotine immunotherapeutic. *Clin Pharmacol Ther* 2011; **89**: 392–9.

95. Xenakis J. G., Kinter E. T., Ishak K. J., Ward A. J., Marton J. P., Willke R. J. *et al.* A discrete-event simulation of smoking-cessation strategies based on varenicline pivotal trial data. *Pharmacoeconomics* 2011; **29**: 497–510.

96. West R., Zatonski W., Cedzynska M., Lewandowska D., Pazik J., Aveyard P. *et al.* Placebo-controlled trial of Cytisine for smoking cessation. *N Engl J Med* 2011; **365**: 1193–200.

97. Coleman T., Cooper S., Thornton J. G., Grainge M. J., Watts K., Britton J. *et al.* A randomized trial of nicotine-

replacement therapy patches in pregnancy. *N Engl J Med* 2012; **366**: 808–18.

98. Rennard S., Hughes J., Cinciripini P. M., Kralikova E., Raupach T., Arteaga C. *et al.* A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. *Nicotine Tob Res* 2012; **14**: 343–50.

99. Heydari G., Talischi F., Tafti S. F., Masjedi M. R. Quitting smoking with varenicline: parallel, randomised efficacy trial in Iran. *Int J Tuberc Lung Dis* 2012; **16**: 268–72.

100. Tønnesen P., Lauri H., Perfekt R., Mann K., Batra A. Efficacy of a nicotine mouth spray in smoking cessation: a randomised, double-blind trial. *Eur Respir J* 2012 Sep; **40**: 548–54.

101. Cinciripini P. M., Robinson J. D., Karam-Hage M., Minnix J. A., Lam C., Versace F. *et al.* Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. *JAMA Psychiatry* 2013; **70**: 522–33.

102. Stein M. D., Caviness C. M., Kurth M. E., Audet D., Olson J., Anderson B. J. Varenicline for smoking cessation among methadone-maintained smokers: a randomized clinical trial. *Drug Alcohol Depend* 2013; **133**: 486–93.

103. Anthenelli R. M., Morris C., Ramey T. S., Dubrava S. J., Tsilkos K., Russ C. *et al.* Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. *Ann Intern Med* 2013; **159**: 390–400.

104. Caponnetto P., Campagna D., Cibella F., Morjaria J. B., Caruso M., Russo C. *et al.* EffiCiency and safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLOS ONE* 2013; **8**: e66317.

105. Bullen C., Howe C., Laugesen M., McRobbie H., Parag V., Williman J. *et al.* Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013; **382**: 1629–37.

106. Evins A. E., Cather C., Pratt S. A., Pachas G. N., Hoeppner S. S., Goff D. C. *et al.* Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA* 2014; **311**: 145–54.

107. A study to evaluate the efficacy and safety of Varenicline compared to placebo for smoking cessation through reduction [internet]. Study ID NCT01370356; 2014. Available at: https://clinicaltrials.gov/ct2/show/NCT01370356 (accessed 1 December 2018) (Archived at http://www.webcitation.org/75UsW0LGZ on 17 January 2019).

108. Walker N., Howe C., Glover M., McRobbie H., Barnes J., Nosa V. *et al.* Cytisine versus nicotine for smoking cessation. *N Engl J Med* 2014; **371**: 2353–62.

109. Varenicline treatment for active alcoholic smokers [internet]. Study ID NCT01347112; 2014. Available at: https://clinicaltrials.gov/ct2/show/NCT01347112 (accessed 1 December 2018) (Archived at http://www.webcitation.org/75UsZDMTK on 17 January 2019).

110. Gonzales D., Hajek P., Pliamm L., Nackaerts K., Tseng L.-J., McRae T. D. *et al.* Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. *Clin Pharmacol Ther* 2014; **96**: 390–6.

111. Cooper S., Taggar J., Lewis S., Marlow N., Dickinson A., Whitemore R. *et al.* Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. *Lancet Respir Med* 2014; **2**: 728–37.

112. Ebbert J. O., Hughes J. R., West R. J., Rennard S. I., Russ C., McRae T. D. *et al.* Effect of Varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA* 2015; **313**: 687–94.

113. O'Brien B., Knight-West O., Walker N., Parag V., Bullen C. E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. *Tob Induc Dis* 2015; **13**: 5.

114. Selegiline for smoking cessation [internet]. Study ID NCT00439413; 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT00439413 (accessed 1 December 2018) (Archived at http://www.webcitation.org/75UsaTik3 on 17 January 2019).

115. Eisenberg M. J., Windle S. B., Roy N., Old W., Grondin F. R., Bata I. *et al.* Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation* 2016; **133**: 21–30.

116. Tonstad S., Tønnesen P., Hajek P., Williams K. E., Billing C. B., Reeves K. R. *et al.* Effect of maintenance therapy with Varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006; **296**: 64–71.

117. Hajek P., Tønnesen P., Arteaga C., Russ C., Tonstad S. Varenicline in prevention of relapse to smoking: effect of quit pattern on response to extended treatment. *Addiction* 2009; **104**: 1597–602.

118. Coe J. W., Brooks P. R., Vetelino M. G., Wirtz M. C., Arnold E. P., Huang J. *et al.* Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005; **48**: 3474–7.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Excel file containing details of all studies considered for inclusion.

Appendix S2 Interactive graph showing abstinence rates with best-fit curves estimated from continuous abstinence rates from RCTs of 12-week treatment with smoking cessation pharmacotherapies.

Figure S1 Continuous abstinence rates with power curve for varenicline estimated from continuous abstinence rates from RCTs of smoking cessation.

Figure S2 Continuous abstinence rates with best-fit curves estimated from continuous abstinence rates from RCTs of 12-week treatment with (A) bupropion, (B) varenicline, (C) nicotine replacement therapy and (D) placebo, with consecutive pairs of data points from the three largest studies for each treatment.