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Fifty-two-week continuous abstinence rates of smokers being treated with varenicline versus nicotine replacement therapy

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ABSTRACT

Background and aims Cross-study comparisons of effect sizes suggest that varenicline is more effective than nicotine replacement therapy (NRT) in aiding smoking cessation, but evidence from direct comparisons is limited. This study compared biochemically verified 52-week sustained abstinence rates in smokers attending the same clinical service according to whether they used varenicline or NRT in their quit attempt. **Methods** This was a prospective cohort study of 855 smokers attending a large smoking cessation clinic who used their choice of NRT product or varenicline in their quit attempt. All received the same behavioural support programme and chose their medication option ($n = 519$ varenicline; $n = 336$ NRT). The primary outcome measure was self-report of 52 weeks' abstinence following the target quit date confirmed by expired air carbon monoxide concentration. Baseline measures included socio-demographic variables, mental health diagnoses, measures of smoking, cigarette dependence and past use of NRT or varenicline. **Results** The 52-week abstinence rates were 42.8% versus 31.0% in those using varenicline versus NRT, respectively ($P < 0.001$). After adjusting for all baseline variables, the odds of remaining abstinent for 52 weeks were 2.03 (95% CI 1.46–2.82), $P < 0.001$ times higher in those using varenicline than those using NRT. **Conclusions** Smokers in the same behavioural support programme who use varenicline appear to have a greater probability of achieving long-term abstinence than those using their choice of nicotine replacement therapy options, even after adjusting for potentially confounding smoker characteristics.

Keywords: NRT, smoking cessation, varenicline.

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INTRODUCTION

Identifying optimal treatment to aid smoking cessation is of considerable clinical and public health importance. Even small differences in effectiveness are highly important clinically [1]. Varenicline has been found to be more effective than bupropion [2–5], but there is uncertainty about whether it is more effective than nicotine replacement therapy (NRT) [3,6]. A recent systematic review concluded that this is the case [7], but this was based largely on cross-study comparisons of effect sizes. This is a useful source of evidence but weaker than direct comparisons within identified samples, because of the potential for differences across studies in terms of key variables that might influence outcomes. Moreover, there are many different NRT products and effectiveness can vary according to usage patterns and context.

It is unlikely at this stage in the development of either varenicline or NRT that randomized controlled trials (RCTs) will be conducted to assess relative efficacy. Even were such a study to be conducted, application of the findings to routine clinical practice would be limited because NRT can be used in different ways that might alter effectiveness (e.g. with more than one form of NRT

used concurrently) [8]. Given this, the best evidence that is likely to be obtained is from comparisons of success rates in smokers using the medications in clinical services. While selection bias may occur in terms of those smokers who use varenicline versus NRT, potential confounders can be adjusted for statistically, thus increasing confidence in the comparability of the samples using each form of treatment. Thus, while such studies cannot provide definitive evidence or relative efficacy individually, collectively they are important in contributing to an answer to what is an extremely important clinical question.

Two recent studies that assessed short-term success rates found that 4-week biochemically verified abstinence rates were higher in smokers using varenicline than those using NRT, after adjusting for a range of potential confounding variables [9,10]. Another study has found smokers' clinic clients using varenicline to be more likely to remain abstinent for at least 52 weeks compared with those using NRT [11]. In that study, it remains possible that differences in the kind of behavioural support provided to smokers may account at least partially for the superiority of varenicline. There is evidence that stop-smoking practitioners differ widely in their effectiveness [12], and those with greater knowledge and skill may have also been more likely to recommend varenicline.

A smoker's clinic with high throughput of patients has been running in Prague since 2005, and has been collecting data on key baseline variables and evaluating long-term smoking cessation outcomes rigorously. The clinic provides smokers with a choice of medications, including varenicline and most forms of NRT. The fact that all smokers receive the same behavioural support package, provide information on key personal characteristics and that there is rigorous assessment of long-term abstinence rates provided an opportunity to answer the following question: do smokers' clinic clients who use varenicline have a higher probability of long-term success at stopping smoking than those who receive the same behavioural support but use nicotine replacement therapy instead, after adjusting for smoker characteristics that may influence outcome?

METHODS

Design

This was a prospective observational study in which smokers attending a hospital-based smokers' clinic in Prague were followed-up for 52 weeks after their target quit date. Smokers who used varenicline were compared in terms of 52-week continuous abstinence rates with those who used one or more of a range of NRTs (including fast-acting forms and patches).

The sample size and basis for choosing different forms of NRT (see below) did not permit distinguishing between different NRT products or single-form versus a combination of different forms (dual-form) of NRT. However, additional exploratory analyses comparisons were made between single- and dual-form NRT and between varenicline and each of these.

We also undertook a set of exploratory analyses to rule out self-selection or therapist selection as an explanation. Varenicline was introduced into the clinic in 2007. If self-selection or therapist accounted for the findings, there should be no overall increase in success rates from before to after introduction of varenicline. If varenicline were responsible for any improvement in success rates there would be no increase pre- to post-varenicline introduction in those using NRT. Thus, those using varenicline would be more successful than those using NRT both pre- and post-varenicline introduction. The power to detect differences with the reduced sample sizes was low, but the results could help with interpretation of the main study findings.

Study sample

The sample consisted of 855 smokers attending the Prague smokers' clinic for help with stopping between 2005 and 2011 who used either NRT or varenicline as part of their treatment and who used no other form of medication (e.g. bupropion) and did not use both NRT and varenicline, and for whom complete data were available for all baseline variables of interest. Varenicline was introduced in 2007. These were drawn from a larger pool of 2414 smokers attending the clinic, of whom 764 either used no medication, used bupropion or used combinations of NRT and varenicline; 795 smokers had data missing on at least one baseline variable. Of the 855 smokers included in the analysis, 188 were treated before varenicline was available and 667 afterwards.

Of the 855 participants, 519 used varenicline and 336 used NRT. Of those using NRT, 125 used one or more combinations of faster-acting forms (gum, lozenge or inhalator), 51 used transdermal patch and 160 used a combination of patch and a faster-acting form. Of those treated after varenicline became available, 148 used NRT. Table 1 shows the sample characteristics.

Compared with those using NRT, participants using varenicline were more likely to be in employment, older, had a higher baseline carbon monoxide concentration (CO) reading at baseline and were less likely to have used NRT previously. None of the participants had used varenicline previously.

Measures

The primary outcome measure was self-report of continuous abstinence from the quit date to the 52-week

Table 1 Characteristics of the study sample.

Variable	*NRT group (n = 336)*	*Varenicline group (n = 519)*	*Total (n = 855)*	*P-value for difference*[a]
Mean (SD) age	46.4 (16.11)	43.5 (13.25)	44.6 (14.51)	0.004
Percentage (*n*) female	48.8 (164)	43.0 (223)	45.3 (387)	0.106
Percent (*n*) with college-level education	28.6 (96)	27.6 (143)	28.0 (239)	0.712
Percentage (*n*) with employment status of				0.012
In employment	66.4 (223)	75.7 (393)	72.0 (616)	
Pensioner	18.2 (61)	11.0 (57)	13.8 (118)	
Student	7.1 (24)	4.6 (24)	5.6 (48)	
Unemployed	3.3 (11)	2.7 (14)	2.9 (25)	
Other	5.1 (17)	6.0 (31)	5.6 (48)	
Percentage (*n*) married	38.4 (129)	41.2 (214)	40.1 (343)	0.651
Percentage (*n*) with diagnosis of current anxiety disorder	0.3 (1)	1.5 (8)	1.1 (9)	0.097
Percentage (*n*) with diagnosis of current depressive disorder	3.3 (11)	6.2 (32)	5.0 (43)	0.077
Percentage (*n*) with diagnosis of current schizophrenia	0.6 (2)	0.4 (2)	0.5 (4)	0.648
Mean (SD) daily cigarette consumption	23.9 (10.90)	24.7 (9.58)	24.4 (10.10)	0.230
Mean (SD) expired air carbon monoxide concentration (ppm)	13.7 (9.19)	21.1 (19.57)	18.2 (16.70)	<0.001
Percentage (*n*) stopping for health reasons	62.2 (209)	58.0 (301)	59.6 (510)	0.226
Percentage (*n*) who had used NRT before	11.6 (39)	0.2 (1)	4.7 (40)	<0.001
Percentage (*n*) who had used varenicline before	0.0 (0)	0.0 (0)	0.0 (0)	–
Mean (SD) FTCD score (0–10)	4.2 (3.03)	4.4 (3.22)	4.3 (3.14)	0.277
Mean (SD) previous longest period of abstinence (days)	55.3 (113.71)	43.6 (94.62)	48.2 (102.64	0.102
Mean (SD) number of previous attempts to stop smoking	1.8 (0.62)	1.8 (0.60)	1.8 (0.61)	0.262

[a]By χ^2 test for proportions and *t*-test for means. NRT: nicotine replacement therapy; FTCD: Fagerstrom Test for Cigarette Dependence; SD: standard deviation.

follow-up, confirmed at 52 weeks by an expired air CO of fewer than 10 parts per million (ppm), as specified in the Russell Standard [13]. As recommended by the Russell Standard, smokers lost to follow-up were counted as having relapsed.

Other variables measured at baseline were: age, gender, marital status, employment status (in employment, pensioner, student, unemployed, other), level of education (college level versus below), number of cigarettes smoked per day, Fagerstrom Test for Cigarette Dependence (FTCD) [14,15], expired-air CO concentration (ppm), whether stopping for health reasons, number of quit attempts that had lasted longer than 24 hours and longest time having stopped previously. A diagnosis of current anxiety, depression or schizophrenia was also recorded.

Other data collected by the clinic but not included in this study comprised blood pressure, heart rate, body mass index, liver function assays and lung function.

Interventions

All participants received support to help them stop smoking following a regimen adapted from the Maudsley model and the Mayo Nicotine Dependence Center. The first screening visit lasted for approximately 1 hour, mainly with a nurse, but some time was also spent with a physician. During the visit, socio-demographic data, anthropometric data, family and medical history were gathered. A second visit was then scheduled with a nurse, lasting approximately 2 hours. It included motivational assessment and advice on becoming smoke-free, prevention of weight gain and coping with typical smoking situations. Smokers were assessed for contraindications for stop-smoking medications and offered one or more of those for which they were eligible. Barring contraindications, the choice as to which medication to use was made by the smokers. If they chose varenicline, they were prescribed the standard course of 1 mg twice a day, although in rare cases this could be reduced because of nausea. If they chose NRT, they could use it singly or in combination. They could also choose to switch medications at any time or add a medication. Only those who used solely NRT or solely varenicline were included into the present study. Smokers were advised to use their medication for at least 3 months. They had to fund it themselves, and the cost was broadly similar to that of smoking. The quit date was set at the second visit, usually for a date within the next 2 weeks. The next follow-up visit occurred usually within 2 weeks and was then offered monthly, although frequency of attendance was at the discretion of the patient. Smoking status and expired-air CO was assessed at each visit.

Statistical analysis

It was calculated that the available sample size would have greater than 80% power to detect an odds ratio (OR) of 1.5 or greater for varenicline versus NRT, which is the lower bound of the figure that would be suggested from the existing research. The unadjusted difference in 52-week success rates was evaluated by Fisher's exact test and logistic regression. The primary analysis involved a logistic regression in which self-reported continuous abstinence from the quit date to the 52-week follow-up, verified by expired air CO, was regressed onto medication type (varenicline versus NRT) adjusting for all baseline variables. The secondary analyses also involved multiple logistic regression analyses comparing relevant groups on the primary outcome measure while adjusting for all baseline covariates. A sensitivity analysis was undertaken examining the unadjusted OR for the comparison between varenicline and NRT in the larger sample, which included smokers who had missing data on covariates.

RESULTS

The overall 52-week abstinence rate was 38.1% (326); in those using varenicline it was 42.8% ($n = 222$) compared with 31.0% ($n = 104$) for those using NRT (Fisher's exact test $P < 0.001$). An unadjusted logistic regression analysis gave an OR of 1.67 [95% confidence interval (CI): 1.25–2.23], $P < 0.001$.

The sensitivity analysis, including all smokers for whom there were data on medication use and outcome but possibly missing data on one or more covariates, yielded very similar differences between varenicline and NRT: OR = 1.59 (95% CI: 1.29–1.958), $P < 0.001$, $n = 1650$.

Table 2 shows the results of the multiple logistic regression analysis including all baseline covariates. The adjusted OR for varenicline versus NRT was 2.03 (95% CI: 1.46–2.82), $P < 0.001$. Aside from medication use, predictors of abstinence were being older, college education, being male, a lower baseline expired air CO and a shorter duration of abstinence in the past. FTCD did not predict abstinence significantly.

The exploratory analyses yielded the following results. No difference was observed between those who used dual-form versus single-form NRT: adjusted OR = 0.81 (95% CI: 0.49–1.35), $P = 0.421$, $n = 336$, reference = single-form. Outcomes were significantly better for varenicline than single- and dual-form NRT: single-form NRT comparison adjusted OR = 1.39 (95% CI: 1.13–1.72), $P = 0.002$, $n = 695$; dual-form NRT comparison adjusted OR = 2.19 (95% CI: 1.44–3.35), $P < 0.001$, $n = 679$. There was an overall improvement in clinic success rates following introduction of the varenicline option: adjusted OR = 1.91 (95% CI: 1.31–2.79), $P = 0.001$, reference = preintroduction of varenicline. This improvement was not seen when only those using NRT after the introduction of varenicline were included: adjusted OR = 1.22

Table 2 Results of logistic regression of 52-week abstinence adjusting for baseline variables.

Variable	*Odds ratio*	*Confidence interval*	*P-value*
Used varenicline (ref = NRT)	2.03	1.46–2.82	<0.001
Age	1.02	1.00–2.33	0.037
Female versus male (ref)	0.71	0.52–0.97	0.033
Education level versus basic (ref)			
College	0.51	0.28–0.94	0.032
High school	0.76	0.55–1.0	0.104
Employment status versus other (ref)			
In employment	0.85	0.46–1.60	0.619
Pensioner	0.86	0.29–2.49	0.774
Student	0.84	0.37–1.88	0.668
Unemployed	0.40	0.14–1.14	0.086
Married versus not married (ref)	1.07	0.73–1.56	0.743
Expired air carbon monoxide concentration (ppm)	0.98	0.96–0.99	0.001
Stopping for health reasons versus other reasons (ref)	0.96	0.71–1.28	0.962
Used NRT before versus not (ref)	1.07	0.51–2.27	0.852
FTCD score	0.97	0.92–1.02	0.193
Previous longest period of abstinence	0.99	0.99–1.00	0.03
Number of previous attempts to stop smoking	0.81	0.64–1.03	0.086
Current anxiety	0.55	0.14–2.24	0.404
Current depression	0.82	0.41–1.65	0.581
Current schizophrenia	Not evaluable	–	–

NRT: nicotine replacement therapy; FTCD: Fagerstrom Test for Cigarette Dependence; ppm: parts per million.

(95% CI: 0.68–2.18), $P = 0.503$, $n = 335$, reference = preintroduction of varenicline. Including only smokers who were treated after the introduction of varenicline, this medication was associated with better outcomes than NRT: adjusted OR = 1.90 (95% CI: 1.19–3.04), $P = 0.007$, $n = 667$.

DISCUSSION

Smokers using varenicline to help them stop smoking in the context of an intensive behavioural support programme were more likely to remain abstinent for at least 52 weeks than those using a flexible NRT regimen, and this difference remained after adjusting for a range of potential confounding variables. The OR was slightly higher than might be expected from previous research. Exploratory analysis showed that when varenicline was introduced into the clinic overall success rates improved, and this was completely attributable to better success rates in those using varenicline.

Unique features of this study include: involving smokers in a European country with a high smoking prevalence and a clinical context that has not been evaluated previously; long-term abstinence with CO verification at every follow-up point; comparison with a flexible NRT dosing regimen; a sample of smokers who were having to fund the medication costs themselves; and ability to adjust for a large number of potentially relevant confounding variables, including the FTCD and expired air CO as markers of cigarette dependence, whether or not the participants had used NRT or varenicline previously and mental health status. Showing that the introduction of varenicline improved clinic outcomes ruled out the possibility that differences from NRT were due to patient selection bias.

There is always the risk in an observational study that potential confounding variables may have been missed. For example, this study did not measure motivation to quit. However, there is no reason to believe that this would have differed sufficiently between those using varenicline versus NRT to explain our findings, given that its association with successful abstinence in clinical settings has been found to be modest, at best [11,16]. Moreover, the historical and temporal analyses rule out self-selection as a plausible explanation of the findings.

The success rates, even among those using NRT, were high compared with what has been observed in clinical trials [8,17] and monitoring of clinical services [12]. This could be due to a number of factors. Most obviously, the intensity of the behavioural support was substantially greater than is provided typically. The first two sessions took up to 3 hours whereas, for example, in the English stop-smoking services, they would usually take less than 1 hour. The model adopted by the clinic is very medically orientated, with a large number of assessments. This might create a stronger 'placebo' response, with smokers having greater confidence in the 'treatment' than if, for instance, it were more informal. Having to pay for the medication may increase success rates by restricting access in lower-income smokers or those who have a lower commitment to the treatment programme. Also, there may be less of a smoking cessation culture in the Czech republic, so that those attending have not already tried and failed many times which is more the norm in, for example, the United Kingdom [11,18,19].

Aside from the fact that smokers were not allocated randomly to receive varenicline or NRT, the main limitations of this study were those that are inherent with use of routine clinical data. For example, data on medication side effects and usage were not recorded in such a manner as to enable assessment of how far these might have influenced the findings. However, previous research has found that, if anything, the side effect profile of varenicline is slightly less favourable than NRT, with nausea and sleep disturbance being relatively common [3,20], and adherence rates have been found to be similar to those for NRT [4,21,22]. Therefore, it is unlikely that differences in medication adherence and side effect profile could explain the findings.

The issue of relative real-world effectiveness of different medication options for smoking cessation will continue to be of considerable public health importance. Even small differences in effectiveness can mean preventing or failing to prevent many tens of thousands of premature deaths each year internationally. This study increases confidence that varenicline, in particular contexts, probably yields higher success rates than NRT. However, more research needs to be conducted to establish the generalizability of this finding. For example, it remains to be seen whether varenicline is more effective than NRT in the context in which it is most often used, i.e. when prescribed by physicians with minimal additional support.

Declaration of interest

R.W. undertakes research and consultancy for companies that manufacture smoking cessation medications, including Pfizer, who manufacture varenicline and J&J and GSK, who manufacture nicotine replacement therapy.

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References

1. West R. The clinical significance of 'small' effects of smoking cessation treatments. *Addiction* 2007; **102**: 506–9.
2. Aubin H. J., Bobak A., Britton J. R., Oncken C., Billing C. B. Jr, Gong J. *et al*. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax* 2008; **63**: 717–24.
3. Cahill K., Stead L. F., Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012; **4**: CD006103. doi: 10.1002/14651858.CD006103.pub6.
4. 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.
5. Wu P., Wilson K., Dimoulas P., Mills E. J. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. *BMC Public Health* 2006; **6**: 300.
6. Hughes J. R., Stead L. F., Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007; CD000031.
7. Mills E. J., Wu P., Lockhart I., Thorlund K., Puhan M., Ebbert J. O. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. *Ann Med* 2012; **44**: 588–97.
8. Stead L. F., Perera R., Bullen C., Mant D., Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008; CD000146. doi: 10.1002/14651858.CD000146.pub3.
9. Brose L. S., West R., McDermott M. S., Fidler J. A., Croghan E., McEwen A. What makes for an effective stop-smoking service? *Thorax* 2011; **66**: 924–6.
10. Stapleton J. A., Watson L., Spirling L. I., Smith R., Milbrandt A., Ratcliffe M. *et al*. Varenicline in the routine treatment of tobacco dependence: a pre–post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction* 2008; **103**: 146–54.
11. Bauld L., Ferguson J., McEwen A., Hiscock R. Evaluation of a drop-in rolling-group model of support to stop smoking. *Addiction* 2012; **107**: 1687–95.
12. Brose L. S., McEwen A., West R. Does it matter who you see to help you stop smoking? Short-term quit rates across specialist stop smoking practitioners in England. *Addiction* 2012; **107**: 2029–36.
13. West R., Hajek P., Stead L., Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005; **100**: 299–303.
14. Heatherton T. F., Kozlowski L. T., Frecker R. C., Fagerstrom K. O. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991; **86**: 1119–27.
15. Fagerstrom K. Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine Tob Res* 2012; **14**: 75–8.
16. Vangeli E., Stapleton J., Smit E. S., Borland R., West R. Predictors of attempts to stop smoking and their success in adult general population samples: a systematic review. *Addiction* 2011; **106**: 2110–21.
17. Ebbert J., Montori V. M., Erwin P. J., Stead L. F. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev* 2011; CD004306. doi: 10.1002/14651858.CD004306.pub4.
18. Kotz D., West R. Explaining the social gradient in smoking cessation: it's not in the trying, but in the succeeding. *Tob Control* 2009; **18**: 43–6.
19. Vangeli E., West R. Sociodemographic differences in triggers to quit smoking: findings from a national survey. *Tob Control* 2008; **17**: 410–5.
20. Leung L. K., Patafio F. M., Rosser W. W. Gastrointestinal adverse effects of varenicline at maintenance dose: a meta-analysis. *BMC Clin Pharmacol* 2011; **11**: 15.
21. Catz S. L., Jack L. M., McClure J. B., Javitz H. S., Deprey M., Zbikowski S. M. *et al*. Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine Tob Res* 2011; **13**: 361–8.
22. 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.

