Factors moderating the relative effectiveness of varenicline and nicotine replacement therapy in clients using smoking cessation services

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Abstract

Background and aims: To assess how far the greater effectiveness of varenicline over nicotine replacement therapy is moderated by characteristics of the smokers or setting in clinical practice.

Design: Observational data between 2013 and 2016 arising from users of Quit-51 smoking cessation service across 11 different health regions in England.

Participants: Clients of smoking cessation service.

Measurements: 4-week Carbon monoxide - validated (primary response) and 12-week self-reported (secondary) quit success/failure.

Methods: We used observational data from 22,472 treatment episodes between 2013 and 2016 from smoking cessation services in England to assess whether differences between varenicline and NRT in 4-week biochemically validated and 12-week self-reported quit rates were moderated by a set of smoker and setting characteristics: level of social deprivation, age, gender, ethnic group, nicotine dependence, and treatment context. From the above, 15,640 episodes were analysed in relation to 4-week quit and 14,273 episodes at 12 weeks. All two-way interactions involving pharmacotherapy were fitted in addition to the main effects and a parsimonious model identified using a backwards stepwise selection procedure.

Findings: At both follow-up points, varenicline was associated with higher success rates overall (adjusted odds ratio varenicline vs NRT = 1.82 [95%CI 1.61, 2.06] and 2.58 [95%CI 2.26,2.94] at 4 and 12 weeks respectively). At 12 weeks, the relative benefits of varenicline were found to be influenced by the setting in which advice was provided (adjusted OR for varenicline × pharmacy setting = 0.53, [95% CI 0.42, 0.69] and for varenicline × General Practice setting = 0.79, [95% CI 0.64,0.98] against a baseline of 1 for varenicline × community setting). The same trends were evident at 4 weeks but this did not translate to statistical significance. There was not conclusive proof for moderating effects with respect to other variables considered.Conclusions: Varenicline use is associated with higher smoking cessation rates than NRT in routine clinical practice, irrespective of a wide range of smoker characteristics but the difference is less in certain intervention settings, most notably pharmacy and GP practice, than the most common prescription of a community setting.

Key words: smoking cessation; NRT; varenicline; epidemiological study; treatment effectiveness; UK

The UK has a national network of smoking cessation services [1]. Similar kinds of support are available in other countries [2]. A range of factors show association with higher success rates in these kinds of services [3]. Among these is the use of varenicline in contrast to nicotine replacement therapy (NRT). However, it is not clear how far the relative benefits of varenicline are influenced by characteristics of smokers or aspects of service delivery. This study looks at the impact on treatment effect of a range of covariates recorded at the individual, temporal and service level.

According to National Institute for Healthcare Excellence (NICE) and National Centre for Smoking Cessation Training (NCSCT) guidelines [4, 5], smoking cessation services provide a programme of counselling sessions with accredited advisers supplemented by tailored pharmacotherapy, using treatments which have shown efficacy in relation to placebo/no treatment [6, 7]. Most often, clients are provided with NRT including skin patches and an oral product [8]. The concurrent use of two forms of NRT has been found to yield improved success rates [3, 9]. Other treatments are available in the form of varenicline (Champix) and bupropion (Zyban). Varenicline has been found to yield higher quit rates than other treatments [10] although combination NRT was estimated to have near parity in a network meta-analysis [11]. The performance of varenicline in a real-world setting is less well understood, although evidence exists to suggest that the benefits seen in randomised controlled trials (RCTs) can be replicated in a clinical setting [12, 13].

It is important to provide treatments for smokers that are tailored to their needs. It may be hypothesised that the effectiveness of pharmacotherapy is to a degree dependent on client characteristics (age, gender, level of dependence). Such effects have been observed in relation to varenicline in the treatment of alcohol dependence [14]. Whilst the benefits of pharmacotherapy in respect of smoking cessation are well known, the potential moderating effect of other variables is at present little understood.

We used data recorded on clients registered with a Quit-51 [15] , a provider of smoking cessation services in England, to assess whether the increased quit rates expected with varenicline versus NRT were moderated by other factors (such as age, gender, ethnic group and features of service provision). An earlier analysis of data from Quit-51 focused on interactions with gender including treatment [16] The current work takes in approximately six months' of further data (up to September 2015 in previous analysis, now up to March 2016) in addition to records from 7 extra regions for which data were not available in earlier analysis. A number of new covariates were

considered in analysis including FTND, IMD and ethnicity. The size of the master dataset in the current analysis was 22,472 in comparison to 11,394 in the afore-mentioned work.

<div style="text-align: center;">Methods</div>

Participants, Design and Setting: We used data recorded by Quit-51 on clients using the service between March 2013 and March 2016 within the following 11 English regions: Leicester, Lincoln, Sandwell, Solihull, Stoke, Surrey, East Sussex, Telford & Wrekin, Walsall, West Cheshire and Worcester. At the outset, this comprised 22,472 observations, but this number was reduced (including two of the original regions) as a result of some records being omitted prior to statistical analysis (Figure 1).

Data recorded by Quit-51 are wide-ranging, including client-level information (age, gender, metrics relating to tobacco dependence etc.), details on support provided (pharmacotherapy, whether counselling was on a group basis at a GP or pharmacy or one-to-one etc.), information on sessions attended (date, duration etc.) in addition to measures of success/failure of quit attempt. The primary motivation of this work was to identify the relationship between pharmacotherapy and quit success (at 4 and 12 weeks) and to investigate whether this relationship was moderated by other covariates. Awareness of such relationships may be informative in deciding on individual treatment regimes for users of smoking cessation services.

Measures: Our primary outcome measure was Carbon Monoxide (CO)–validated quit [17]in line with NHS guidelines at 4 weeks and this was supported by analysis of self-reported quit at 12 weeks (CO readings were only taken at the 4 week time point). A number of additional variables were extracted or derived from master data, namely: gender, age at quit date (4 categories: 13-19 years, 20-39 years, 40-59 years, 60 years and above), pharmacotherapy (NRT/ varenicline), intervention setting – a categorical variable describing the setting in which client met with practitioner for advisory sessions (the original categories are described here [18] but these were reduced to community, GP practice, pharmacy, Stop Smoking Service [SSS] and other), year, yearly quarter (January/February/March = 1, April/May/June = 2, July/August/September = 3, October/November/December = 4), ethnic group (6 categories derived from original data - White; British & Irish, White; Other, Asian, Black, Other, Unknown), nicotine dependence based on the Fagerstrom Test for Nicotine Dependence, or FTND [19], whereby a higher score denotes greater dependence.

Social deprivation was assessed using the Index of Multiple Deprivation, or IMD [20], which is an areal deprivation score mapped to postcode and scored on a scale of 1-10 inclusive, with lower

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scores indicating greater deprivation. In order to facilitate interpretation when talking of a deprivation effect, these scores were inverted so that 1 = least deprived/most affluent area with increasing score indicating a greater degree of deprivation (maximum=10). Summary statistics for both deprivation and FTND are presented for each score up to 10 (i.e. as a categorical variable) but in statistical analyses these were treated as continuous variables.

Data preparation: Preliminary restrictions were applied to the master dataset. Instances where bupropion had been prescribed were removed as the number (N=80) was considered too low to be able to make a meaningful comparison with the other treatments. Clients recorded as pregnant were left out of analysis. In some instances, more than one treatment was recorded as having been prescribed. These cases were removed as it was not possible to compare treatment effect in addition to there being uncertainty as to whether this information had been recorded correctly. Cases where age was recorded outside the range 13-89 inclusive were also removed as it was considered possible that these may have been misreported. The above restrictions gave rise to a dataset of 20,463 observations (Dataset 2, Figure 1) which was used for the derivation of summary statistics.

In addition to the main analysis, frequencies are presented in the subgroups prescribed (i) NRT (ii) varenicline for a group of factors which were not considered in regression models. Included here are the binary variables "live with other smokers (no/yes)" and "live with children (no/yes)". Furthermore, a number of morbidities were identified from the variable "medical condition" (text field consisting of a theoretically unlimited list of conditions) which may have influenced choice of treatment. From these, three binary variables were derived: psychological condition (where original field included "anxiety disorder", "schizophrenia", "depression", "mental illness", "manic-depressive disorder" or "eating disorder"); heart condition (from "angina", "heart disease", "heart attack", "heart failure", "acute cardiovascular event within the last 4 weeks" or "CHD") and lung condition (from "bronchitis", "emphysema", "collapsed lung", "COPD" or "persistent cough or breathlessness"). Whilst these figures may point to imbalance in the two treatment groups, there was uncertainty as to the robustness of their recording and none of these were included in regression models.

Four week analysis: Further sequential restrictions were applied before analysis of quit at 4 weeks. Specifically (i) removal of observations where the quit date fell after 31/1/16 (ii) omission of records where the intervention setting field is empty (iii) retention of either the first chronological observation where all analytical data were available or the first chronological observation if no such "comprehensive" record was available. The first of these was carried out to ensure as far as possible

that 4-week quit information was not incomplete, i.e. that the client was not in the middle of a cessation attempt at the time of data compilation. The second step ensured that each individual contributed one record only as there was a small degree of client replication as can be ascertained from Figure 1.

Analyses: Analysis was carried out on 4-week CO-validated quit (0/1) using a Generalised Linear Mixed Model (GLMM) procedure [21]. Explanatory variables fitted were: gender, age, pharmacotherapy, intervention setting, year, yearly quarter, ethnic group, IMD and FTND. A logit transform was applied to the response variable (4-week and 12-week quit) and dispersion fixed at 1. The region where the client was based was incorporated as an unstructured random effect. A backwards stepwise procedure was applied starting with a model including all of the above explanatory variables as main effects and all two-way interactions involving pharmacotherapy and the other explanatory variables. At each step, the main effect/interaction with the highest p-value (based on χ^2 Wald tests) was identified and removed from the model if above an *a priori* threshold of 0.05. This process was concluded where all remaining effects had $p < 0.05$, giving rise to a most parsimonious model. For clarity of interpretation, three-way interactions were not considered but the possibility of their existence cannot be ruled out (or at higher levels) and the final model selected should not be interpreted as the "best amongst all models". Main effects were not considered for removal until interactions involving the relevant variable had been eliminated.

Missing data: By default, a complete-case analytical approach was adopted. Since data were missing to varying degrees for a number of variables in the model, the *de facto* size of the dataset was reduced accordingly. The extent of missing data in some cases was sufficient to potentially undermine the generalisability of the results. The variables identified as missing a significant level of data were (i) pharmacotherapy (ii) FTND (iii) IMD as can be ascertained from Table 1.

In order to address concerns over possible consequences on the results arising from missing data, the optimal model identified from the original analysis was repeated after data were imputed in respect of the three variables listed above. Values were imputed through regression based on the following explanatory variables: age, gender, occupation, ethnicity and intervention setting. This process was repeated three times in order to allow for uncertainty in the imputation process and from these, averages were derived of parameter estimates and Wald statistics. Details on the imputation are provided in Supplementary File 1. Regression results from the optimal model identified were compared between (i) the original dataset and (ii) the same supplemented with imputed data as described above. Subject to reasonable agreement in this regard, results presented

and inference are based on results arising from analysis of imputed data. For the purposes of comparison, the results from original complete-case analyses are presented in Supplementary File 2.

The same procedure was repeated for analysis of self-reported quit at 12 weeks except that the cut-off date used for inclusion was now 9/12/15. All analyses were carried out in GenStat 18.0 [22].

<p align="center">clientclientclientclient<u>Results</u></p>

Table 1 shows the frequencies of records in the different subgroups for key variables, in addition to the frequency and percentage of varenicline prescription using the sample that was followed up at 4 weeks. Table 2 looks at the frequencies of subgroups of potentially influential factors which were not included in analysis.

With respect to the analysis of 4-week CO-validated quit, the selected model retained all main effects except ethnic group (and by extension the interaction between ethnic group and treatment). Most of these translated to significant effects when imputed data were included in analysis except for (i) gender (ii) treatment × intervention setting (iii) treatment × FTND, although the direction of these effects was the same in both cases. Model parameters for the analysis of supplemented data at this timescale are provided in Table 3. Clients using varenicline were significantly more likely to quit than those using NRT (adjusted odds ratio [OR] for a successful quit and 95% confidence interval [CI] for varenicline vs NRT = 2.07 [1.85-2.23]). The odds of a successful quit at 4 weeks was found to improve progressively with age group (Table 3). Clients who were provided counselling in a community setting had a higher quit rate than all other categories and a significantly higher odds ratio than all except the "other" category (Table 3). The probability of a successful quit was observed to decrease with baseline tobacco dependence and people living in deprived areas were less likely to quit than those in more affluent areas (OR and CI below 1 in both instances, see Table 3).

Although the overall quit rate at 12 weeks was lower than at 4 weeks (mean quit rate was 56.0% and 28.8%% for 4 and 12 weeks respectively), the overall pattern in terms of odds ratios at 12-week quit (Table 4) were broadly similar to the above with a few notable exceptions. The set of variables identified by initial complete-case backwards stepwise regression was the same as for 4 weeks except for the removal of the interaction between treatment and dependence (FTND). On this occasion, all effects were also found to be significant when analysis was repeated on supplemented data.   At this time interval, significant differences among the levels associated with the interaction between treatment and setting were found (Table 4). This manifested itself through an elevated

<p align="center">7</p>

odds ratio when varenicline was used in conjunction with community setting (all other combinations involving varenicline were estimated at less than unity) and consideration of the corresponding confidence intervals indicates that this difference was significant in relation to (i) varenicline in conjunction with (i) pharmacy (ii) "other" setting categories. .

Discussion

In an analysis of data on clients using a smoking cessation service, varenicline use was found to improve the odds of a successful quit relative to NRT and furthermore, the magnitude of this phenomenon was found to depend on the setting in which counselling was provided when quit was measured at 12 weeks. In contrast to much of the research in this area, the data originate from a real-world setting where we might expect these effects to be attenuated in relation to those observed in the idealised environment of scientific trials [23].

Nicotine replacement therapy was prescribed almost three times more often than varenicline. Furthermore, men were prescribed varenicline more often than women. This difference cannot be attributed to non-use of this treatment amongst pregnant women [8] as records associated with this subgroup were removed from the dataset before analysis. Prescription of varenicline is not prescribed to the under 18s and this is reflected in the low rate of use in the youngest age group. Unlike in the other age groups, there are more males than females in the teenage group.

The difference in quit rate between the two treatments presented here is striking and of a greater magnitude than that reported elsewhere at the same [24] and different points in time [25]. Comparison of quit rates at specific times is complicated by the fact that the agreed quit date coincides with the start of treatment with respect to NRT, but is fixed 8 to 14 days after start of treatment for those using varenicline Therefore, there tends to be a longer gap between initial registration and 4-week quit date for varenicline users. This difference in the schedule could potentially influence estimates of treatment effect in unforeseen ways. For example, the extended period between registration and scheduled follow-up dates could hypothetically increase the risk of drop-out in the intervening period (although there is no evidence here of that here since the cessation rate is higher in varenicline users).

The chance of quit success was also found to be influenced by the session setting, with the highest levels of success seen in relation to community setting at 4 weeks, although this did not emerge as the "best" setting at 12 weeks. At both 4 and 12 weeks, GP practice fared worse than other settings. The observation that men have a greater chance of quitting than women has been reported elsewhere [26, 27] as has the link between socio-economic deprivation and low quit rates [28-30].

Statistical analysis of the initial data (pre-imputation) suggested the presence of interactions between pharmacotherapy and (i) intervention setting (ii) tobacco dependence at 4 weeks and just intervention setting at 12 weeks. However, these effects were no longer found to be statistically significant at 4 weeks once imputed data were included. The interaction between treatment and setting was significant at 12 weeks after including the additional data and it was notable that at both time points the benefit of varenicline was most diminished in conjunction with pharmacy setting. The low quit rate associated with varenicline in conjunction with pharmacy suggest that more intensive support may be required for clients within this treatment pathway in order for the effects of this medication to be optimised.

In contrast, the relatively low quit rates observed in relation to varenicline in conjunction with pharmacy suggest that more support may be required for clients within this treatment pathway.

In an age where the internet is increasingly accessible, there may in future be greater emphasis on online smoking cessation services [31] which have been found to increase quit rates, especially in conjunction with medication such as varenicline [27]. This may represent an appealing option for a younger age group who are generally more engaged with internet media and in the current service do not achieve as high quit rates as older age groups..

Even allowing for the significant interactions, varenicline was associated with higher quit rates across the different levels of all factors. Thus whilst there may be counter-arguments to prescribing varenicline to individuals where there is concern over severity of side-effects or possible health consequences (e.g. in the case of teenage smokers) there is no evidence here to suggest that NRT will outperform varenicline in any of these subgroups in enhancing cessation rates .

Although not included in analysis, summary statistics show a disproportionate tendency to prescription of NRT rather than varenicline in clients diagnosed with a psychological condition (but not notably in relation to other additional factors considered). This may have had some bearing on the results, although the number of clients in this group is relatively small and the discrepancy in frequency not great (approximately 4%). With the data being observational in nature, the potentially distorting effects of covariates, both measured and unmeasured, cannot be ignored and further evidence from similar analysis of extraneous data would be valuable in drawing conclusions regarding treatment effects and associated moderators.

There are likely to be interactive effects in relation to a range of variables in addition to those considered here, for example gender and financial strain as identified by Reitzel et al. [32]. This provides scope for further research, both through RCTs and observational cohorts. This could also incorporate further experimentation around an optimal regime for the various pharmaceutical agents. For example, Hajek et al. [33] observed that both quit success and a number of measures recorded in relation to nicotine withdrawal discomfort showed favourable results when smokers were preloaded with varenicline for 4 weeks before the quit date, a period longer than the current prescription in the UK of 2 weeks. It would also be instructive to learn how such variations in medication regime are moderated (if at all) by other factors.

Conclusions

In an analysis of data from a smoking cessation service, varenicline was found to outperform NRT as an aid to cessation, men quit with higher probability than women and the percentage of successful quits increased with age. The setting for counselling with practitioner was also found to influence the chance of quitting. Furthermore, significant interactions were observed between (i) pharmacotherapy and setting. Varenicline was found to be least effective in conjunction with pharmacy intervention setting. Notwithstanding interactions, varenicline was found to enhance quit rates relative to NRT across all subgroups, suggesting a universality of effect. Being observational data, the potentially distorting effects of covariates, both measured and unmeasured, cannot be ignored and further evidence from extraneous datasets would be valuable.

Acknowledgements

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Table 1: Frequency of observations in different subgroups of key categorical variables with corresponding frequency and percentage of recorded varenicline prescription (Dataset 2, N=20,463).

Variable	N missing	Subgroup	n	% prescribed varenicline
Gender	0			
		Male	9740	25.0 %
		Female	10723	22.4 %
Age in years (mean = 44.8, S.D. = 15.6)	0			
		13-19	996	5.6 %
		20 - 39	6879	26.0 %
		40 - 59	8557	25.5 %
		60 - 89	4031	20.3 %
Ethnicity	0			
		White (British & Irish)	18253	24.0 %
		White (other)	608	37.4 %
		Asian	598	11.7 %
		Black	392	12.1 %
		Other	187	20.9 %
		Unknown	425	16.2 %

Treatment	3321			
		NRT	13090	-
		Varenicline	4052	-
Setting	59			
		Community	8775	27.1%
		GP practice	4829	31.9%
		Other	1784	13.1%
		Pharmacy	4392	14.7%
		SSS	624	10.3%
Year	0			
		2013	1010	6.9 %
		2014	5207	13.1 %
		2015	10578	28.5 %
		2016	3668	27.7 %
Quarter	0			
		Jan-Mar	6260	21.8 %
		Apr-Jun	4425	26.4 %
		Jul-Sep	5055	23.4 %
		Oct-Dec	4723	24.1 %
FTND (mean=4.68, S.D. = 2.24)	8626			
		0	479	20.1 %

		1	580	22.8 %
		2	971	30.9 %
		3	1537	27.7 %
		4	1885	25.9 %
		5	2022	27.9 %
		6	1806	26.3 %
		7	1287	23.6 %
		8	792	21.4 %
		9	367	21.1 %
		10	111	20.9 %
Deprivation index (mean = 6.54, S.D. = 2.73)	1687			
		1	732	38.8%
		2	1088	34.7%
		3	1560	32.3%
		4	1668	30.2%
		5	1674	27.5%
		6	1725	24.0%
		7	1850	29.0%
		8	2508	24.0%
		9	2938	16.1%

		10	3033	17.3%

Table 2: Frequency of levels of factors which may be expected to influence choice of prescribed treatment. These frequencies are presented separately for clients prescribed (i) NRT (ii) varenicline. Figures derived from Dataset 2.

Variable	Category	n/N (%) occurrence	
Live with other smoker(s)?		NRT	varenicline
	No	4995/8421 (59.3%)	1805/3021 (59.7%)
	yes	3426/8421 (40.7%)	1216/3021 (40.3%)
Live with children?			
	No	5427/8292 (65.4%)	1811/3021 (59.9%)
	Yes	2865/8292 (34.5%)	1210/3021 (40.1%)
Psychological condition?			
	No	11395/13090 (87.1%)	3695/4052 (91.2%)
	Yes	1695/13090 (12.9%)	357/4052 (8.8%)
Heart condition?			
	No	12564/13090 (96.0%)	3928/4052 (96.9%)
	Yes	526/13090 (4.0%)	124/4052 (3.1%)
Lung condition?			
	No	12031/13090 (91.9%)	3737/4052 (92.2%)
	yes	1059/13090 (8.1%)	315/4052 (7.8%)

Table 3: Percentage quit rate (for categorical variables), model coefficients (both for main effects only and full model), odds ratios (adjusted for model covariates) and significance test results for all main effects and interactions included in the optimal GLMM, at 4 weeks after quit date. Model results are based on analyses of supplemented data incorporating imputed values (N=15,640).

Variable		Quit rate - n/N (%)	B (main effects only)	B (logit)	Adjusted OR (95% CI)	Wald-statistic (d.f.)	p-value
						Multiple regression model	
Gender						1.7 (1)	0.2
	Male	4257/7523 (56.6%)	0	0	1		
	Female	4504/8117 (55.5%)	-0.043	-0.044	0.96 (0.90,1.02)		
Age						117.3 (3)	<0.001
	13-19	338/860 (39.3%)	0	0	1		
	20-39	2896/5355 (54.1%)	0.59	0.57	1.77 (1.51,2.08)		
	40-59	3674/6406 (57.4%)	0.73	0.72	2.05 (1.74,2.40)		
	60+	1853/3019 (61.4%)	0.89	0.88	2.41 (2.03,2.86)		
Treatment						87.5 (1)	<0.001
	NRT	5140/9748 (52.7%)	0	0	1		
	varenicline	2043/3059 (66.8%)	0.54	0.60	1.82 (1.61,2.06)		
Setting						114.8 (3)	<0.001

	community	3960/6350 (62.4%)	0	0	1		
	GP practice	1836/3763 (48.8%)	-0.57	-0.55	0.58 (0.52,0.64)		
	pharmacy	1918/3503 (54.8%)	-0.16	-0.12	0.89 (0.80,0.98)		
	SSS	289/559 (51.7%)	-0.34	-0.34	0.71 (0.57,0.89)		
	other	758/1465 (51.7%)	-0.12	-0.12	0.88 (0.77,1.02)		
Year						79.8 (3)	<0.001
	2013	490/930 (52.7%)	0	0	1		
	2014	2746/4634 (59.3%)	-0.31	-0.31	0.74 (0.62,0.87)		
	2015	5015/9016 (55.6%)	-0.51	-0.50	0.60 (0.51,0.72)		
	2016	510/1060 (48.1%)	-1.10	-1.10	0.33 (0.26,0.43)		
Quarter						60.7 (3)	<0.001
	1	1871/3287 (56.9%)	0	0	1		
	2	2317/3992 (58.0%)	-0.27	-0.27	0.76 (0.67,0.86)		
	3	2429/4413 (55.0%)	-0.44	-0.44	0.64 (0.57,0.72)		
	4	2144/3948 (54.3%)	-0.38	-0.38	0.68 (0.61,0.77)		
FTND			-0.048	-0.048	0.95 (0.94,0.97)	32.0 (1)	<0.001
IMD (deprivation)			-0.052	-0.047	0.95 (0.94,0.97)	41.7 (1)	<0.001
Treatment*Setting						6.6 (4)	0.2
	NRT*community	2416/4067 (59.4%)	-	0	1		
	NRT*GP	742/1763 (42.1%)	-	0	1		

	practice						
	NRT*pharmacy	1150/2263 (50.8%)	-	0	1		
	NRT*SSS	229/451 (50.8%)	-	0	1		
	NRT*other	603/1204 (50.1%)	-	0	1		
	varenicline *community	1114/1539 (72.4%)	-	0	1		
	varenicline *GP practice	504/858 (58.7%)	-	-0.068	0.93 (0.77,1.13)		
	varenicline* pharmacy	261/419 (62.3%)	-	-0.25	0.78 (0.62,0.99)		
	varenicline* SSS	39/57 (68.4%)	-	0.15	1.17 (0.66,2.08)		
	varenicline *other	125/186 (67.2%)	-	0.11	1.15 (0.79,1.58)		
Treatment*FTND							
	NRT*FTND		-	0	1	3.05 (1)	0.08
	varenicline *FTND		-	-0.03	0.97 (0.94,1.01)		

Table 4: Percentage quit rate (for categorical variables), model coefficients (both for main effects only and full model), odds ratios (adjusted for model covariates) and significance test results for all main effects and interactions included in the optimal GLMM, at 12 weeks after quit date. Model results are based on analyses of supplemented data incorporating imputed values (N=14,273).

Variable		Quit rate - n/N (%)	B (main effects only)	B (logit)	Adjusted OR (95% CI)	Wald-statistic (d.f.)	p-value
					Multiple regression model		
Gender						10.1 (1)	0.001
	Male	2076/6485 (30.3%)	0	0	1		
	Female	2041/7428 (27.5%)	-0.12	-0.12	0.88 (0.82,0.95)		
Age						150.0 (3)	<0.001
	13-19	181/806 (22.5%)	0	0	1		
	20-39	1256/4901 (25.6%)	0.39	0.37	1.45 (1.19,1.78)		
	40-59	1737/5826 (29.8%)	0.68	0.66	1.94 (1.59,2.38)		
	60+	943/2740 (34.4%)	0.97	0.96	2.61 (2.11,3.22)		
Treatment						197.5 (1)	<0.001
	NRT	2562/8832 (29.0%)	0	0	1		
	varenicline	1274/2709 (47.0%)	0.77	0.95	2.58 (2.26,2.94)		
Setting						33.7 (4)	<0.001

	community	1609/5769 (27.9%)	0	0	1		
	GP practice	867/3431 (25.3%)	-0.36	-0.27	0.76 (0.67,0.87)		
	pharmacy	1034/3184 (32.5%)	-0.088	0.063	1.06 (0.94,1.20)		
	SSS	225/559 (45.6%)	0.21	0.31	1.37 (1.08,1.73)		
	other	352/1330 (26.4%)	-0.043	0.015	1.02 (0.85,1.21)		
Year						29.0 (2)	<0.001
	2013	418/932 (44.8%)	0	0	1		
	2014	1010/4639 (21.8%)	-0.47	-0.45	0.64 (0.54,0.76)		
	2015	2689/8702 (30.9%)	-0.32	-0.30	0.74 (0.62,0.89)		
Quarter						29.0 (3)	<0.001
	1	643/2231 (28.8%)	0	0	1		
	2	1278/4003 (31.9%)	-0.05	-0.053	0.64 (0.54,0.76)		
	3	1139/4424 (25.7%)	-0.29	-0.29	0.74 (0.62,0.89)		
	4	1057/3615 (29.2%)	-0.11	-0.12	0.89 (0.78,1.02)		
FTND			-0.043	-0.044	0.96 (0.94,0.97)	24.9 (1)	<0.001
Deprivation			-0.043	-0.043	0.96 (0.94,0.97)	25.3 (1)	<0.001
Treatment*Setting						24.6 (4)	<0.001
	NRT*community	880/3701 (23.8%)	-	0	1		
	NRT*GP practice	434/1562 (27.8%)	-	0	1		

	NRT*other	269/1091 (24.7%)	-	0	1	
	NRT*pharmacy	776/2027 (38.3%)	-	0	1	
	NRT*SSS	203/451 (45.0%)	-	0	1	
	varenicline *community	674/1348 (50%)	-	0	1	
	varenicline *GP practice	343/769 (44.6%)	-	-0.23	0.79 (0.64,0.98)	
	varenicline* pharmacy	152/367 (41.4%)	-	-0.63	0.53 (0.42,0.69)	
	varenicline*SSS	35/57 (61.4%)	-	-0.18	0.83 (0.47,1.46)	
	varenicline *other	70/168 (41.7%)	-	-0.12	0.88 (0.61,1.27)	