Effectiveness of stop-smoking medications: findings from the International Tobacco Control (ITC) Four Country Survey

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ABSTRACT

Aim   To evaluate the population effectiveness of stop-smoking medications while accounting for potential recall bias by controlling for quit attempt recency. **Design**   Prospective cohort survey. **Setting**   United Kingdom, Canada, Australia and the United States. **Participants**   A total of 7436 adult smokers (18+ years) selected via random digit dialling and interviewed as part of the International Tobacco Control Four Country Survey (ITC-4) between 2002 and 2009. Primary analyses utilized the subset of respondents who participated in 2006 or later ($n = 2550$). **Measurements**   Continuous abstinence from smoking for 1 month/6 months. **Findings**   Among participants who recalled making a quit attempt within 1 month of interview, those who reported using varenicline, bupropion or nicotine patch were more likely to maintain 6-month continuous abstinence from smoking compared to those who attempted to quit without medication [adjusted odds ratio (OR) 5.84, 95% confidence interval (CI) (2.12–16.12), 3.94 (0.87–17.80), 4.09 (1.72–9.74), respectively]; there were no clear effects for oral NRT use. Those who did not use any medication when attempting to quit tended to be younger, to be racial/ethnic minorities, to have lower incomes and to believe that medications do not make quitting easier. **Conclusions**   Consistent with evidence from randomized controlled trials, smokers in the United Kingdom, Canada, Australia and the United States are more likely to succeed in quit attempts if they use varenicline, bupropion or nicotine patch. Previous population studies that failed to find an effect failed to control adequately for important sources of bias.

Keywords   Nicotine replacement therapy, population effectiveness, recall bias, smoking cessation, stop-smoking medication, varenicline.

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INTRODUCTION

Numerous randomized, placebo-controlled clinical trials have demonstrated that nicotine replacement therapy [1,2], bupropion [3] and varenicline [4] are efficacious in increasing the odds of smoking cessation, and clinical practice guidelines recommend the use of pharmacotherapy as a first-line agent for treating nicotine dependence [5,6]. Despite the recommendations, the majority of smokers who attempt to quit do so without the aid of stop-smoking medications (SSMs) [7–9], although the use of SSMs has been increasing over time [10–13].

It is important to assess the 'real-world' effectiveness of SSMs in the contexts in which they are being used, because compliance with medication use instructions in the controlled trial setting is probably higher than it is in the population setting, and because subjects who are selected to participate in clinical trials may not be representative of the self-selected smokers who ultimately use the medications [14]. The real-world effectiveness of

varenicline and bupropion as quitting treatments has not yet been assessed widely in population studies, and studies of the effectiveness of nicotine replacement therapies (NRT) have produced mixed results [15–26]. For example, Pierce & Gilpin reported that NRT is ineffective since becoming available over-the-counter (OTC) [17], Hyland *et al.* found nicotine patch quit rates to be lower after becoming available OTC [18], but Thorndike *et al.* found quit rates among those using NRT to be nearly identical during the period before and after the medication became available OTC [19]. Studies evaluating the effectiveness of NRT without focusing on the impact of OTC availability have also produced mixed results [20–26]. For example, Shiffman *et al.* reported that use of NRT was associated with decreased rates of smoking cessation, and pointed to bias inherent in retrospective surveys to account for this finding [20]. Similarly, Alberg *et al.* found that NRT users were less likely to quit smoking than were those who never used NRT [21]. Recently, Alpert *et al.* concluded, surprisingly, that NRT is not effective for long-term smoking cessation because they found relapse rates between those who quit with and without NRT to be equivalent in a period of a year or more after use ceased [22], which does not relate to the question of medication effectiveness. Others have found positive effects [23–26]. West & Zhou, using data collected every 3 months, reported that cessation rates were two to three times higher among NRT users compared to nonusers [23]. Similarly, a prospective evaluation of the New York State Smokers' Quitline program to give away free nicotine patches showed quit rates among those who received the patches to be nearly two times higher than rates observed prior to the implementation of the program [24,25]. Additionally, Gilpin *et al.* found a cessation advantage among NRT users living in smoke-free homes, and suggested that medication may be more effective among those who are more motivated to quit [26].

Within the context of the widespread observation that population level quit rates have not increased over time despite increases in usage of stop-smoking medications [10,11,27,28], some have taken the failure to consistently find positive effects of NRT as evidence that it is not effective in the real world [17,29]. However, others have pointed to confounders inherent in population-based survey designs that might explain the lack of compelling real-world evidence for effectiveness [15,16,20,30–36]. First, medication users in the general population are systematically different from non-users in important characteristics, such as being more heavily addicted to nicotine, which predisposes medication users to be unsuccessful in quitting [7,20,30–32]. Secondly, retrospective survey designs may be subject to biased recall of failed quit attempts [20,33–36]. It has been shown that the likelihood of recalling a quit attempt

decreases with increasing time since the quit attempt [35]. In addition, Borland *et al.* found that, compared to those who attempted to quit with medication, those who attempted to quit without medication recalled their last unsuccessful quit attempts as starting more recently, with a significantly greater proportion of unaided attempts being reported in the previous month [36]. Adjusted for nicotine dependence to equate groups on the likelihood of making a recent quit attempt, this association demonstrates that failed quit attempts occurring longer ago are more likely to be forgotten by those who did not use medication.

The presence of these confounders requires that population-based evaluations of SSM effectiveness control for systematic differences between self-selected medication users and non-users, as is carried out routinely in population studies, and be limited to respondents for whom systematic recall bias is minimal (i.e. those who recalled their last quit attempts as occurring recently relative to survey date), which has not yet been carried out methodically in population studies. The purpose of this study was to evaluate the real-world effectiveness of SSMs while accounting for previously considered confounders, as well as recall bias. We also describe the characteristics of medication users, such that the comparability of our sample to previous population-based samples can be considered.

METHODS

Participants

Participants were adults (aged 18 years or older) who were interviewed as part of the International Tobacco Control Four Country Survey (ITC-4). The ITC-4 is an ongoing prospective cohort survey designed initially to evaluate the psychosocial and behavioral impacts of various national-level tobacco control policies. Beginning in 2002, nationally representative samples of smokers from the United Kingdom, Canada, Australia and the United States were surveyed using standardized data collection methods and measurements. Detailed descriptions of the survey procedures can be found elsewhere [37–40]. Random digit dialing was used to recruit smokers within strata defined by geographic region and community size to complete the 45-minute survey. Response rates ranged from 26% in the United States to 50% in Canada, which are comparable with other telephone surveys in these countries. Previous analyses have demonstrated good correspondence between the demographic characteristics of those who responded to this survey and the characteristics of respondents from national benchmark surveys, indicating that non-response is not a source of systematic bias in this study

[38]. Participants were re-contacted approximately annually to complete follow-up surveys, and those lost to attrition (~30% on average) were replenished each year to maintain a sample size of ~2000 participants per country [39]. Previous analyses of attrition rates have indicated that age, gender and racial/ethnic groups vary with respect to retention [40]; thus, we compared those lost to follow-up with those who were retained in the sample, and we performed sensitivity analyses of medication effectiveness supposing that those lost to attrition went back to smoking.

This study used data collected during the first eight survey waves (2002–09). Analyses were restricted to respondents who participated in at least two consecutive survey waves and reported making a quit attempt between waves, yielding a total sample eligible for analysis of 7436 individuals. The primary medication effectiveness analyses utilized the subset of respondents who participated in 2006 (i.e. wave 5) or later ($n = 2550$).

Measures

Smoking status

To be eligible for enrolment in the ITC survey, respondents had to report smoking at least 100 cigarettes during their life-times and had to smoke at least once in the 30 days preceding the baseline survey. Smoking status was assessed at first follow-up interview among those who had the opportunity to reach the cessation end-points, which were defined as 1 month/6 months continuous abstinence from smoking. The smoking status of those who attempted to quit less than 1 month/6 months prior to the first follow-up interview, and thus did not have the opportunity to reach these end-points at interview, was determined using the following question asked at the next follow-up interview: 'How long were you quit for, on your quit attempt that had started on [Quit Date from Last Survey Date (LSD)]?'. Respondents who attempted to quit within the end-point window and were not contacted during the following wave were excluded from primary analyses, even if they were known to have relapsed at first follow-up wave.

Quit attempts

During each follow-up wave, participants who were smokers in the previous wave were asked: 'Have you made any attempts to stop smoking since we last talked with you?'. All analyses were restricted to respondents who reported making a quit attempt between waves.

In order to address confounding of the association between medication use and smoking cessation due to differential recall of failed quit attempts, a recency of last quit attempt variable was derived using questions asked in waves 5–7. Quitters were asked: 'When did your most recent quit attempt start?', while smokers were asked: 'How long ago did your most recent quit attempt end?' and 'How long were you quit for, on your most recent quit attempt?'. The number of days elapsed since the start of the most recent quit attempt (calculated as the sum of days since the end of the most recent quit attempt and length of the most recent quit attempt for smokers) was used to indicate quit attempt recency.

Use of stop-smoking medications

During each survey wave, respondents were asked to recall their use of medications since the last survey, and those who reported using medications were asked a series of questions regarding the medications indicated, including: 'What was the main reason you used [the medication]?'. Only those who reported using medication in an attempt to stop smoking completely were considered to be medication users for the purpose of these analyses. The actual wording of all questions used in the different ITC survey waves can be found at: http://www.ITCproject.org[41].

A separate medication use variable was created for each of four types of medication: nicotine gum/other oral forms of NRT (i.e. lozenges and sublingual tablets), nicotine patch, bupropion (i.e. Zyban or Wellbutrin) and varenicline (waves 5–7 only). Respondents who indicated that they used more than one type of medication at the same time were excluded from analyses used to evaluate the effectiveness of individual medications (but were included in analyses evaluating the effectiveness of any medication use), and were included in analyses used to describe the characteristics of medication users (where they contributed to analyses predicting use of each of the four most common types of medication indicated).

The order in which medication use questions were asked differed between waves 2–4 and waves 5–7; therefore, criteria for inclusion in analyses differed between these sets of waves as follows: for waves 2–4, medication users were defined as those respondents who: (i) reported having made an attempt to quit smoking since LSD; (ii) reported that [type of medication] was the most recent medication used (since LSD); and (iii) reported that [type of medication] was used to stop smoking completely. For waves 5–7, medication users were defined as those who: (i) reported having made an attempt to quit smoking since LSD; and (ii) reported using [type of medication] the last time a medication was used to quit (since LSD). For all waves, non-users were defined as those who reported having made an attempt to quit smoking since LSD, and had not used any SSM (for any reason) since LSD.

Demographic and smoking-related characteristics

The following baseline variables were included in the analyses: country (i.e. United Kingdom, Canada, Australia and United States), gender and identified majority/minority group (based on the primary means of identifying minorities in each country, i.e. racial/ethnic group in the United Kingdom, Canada and the United States, and English language spoken at home in Australia).

The following time-varying demographic variables were also included in the analyses: age group (i.e. 18–24, 25–39, 40–54 and 55+ years), level of education (defined as 'low' if respondent completed high school or less in Canada, United States and Australia, or secondary/vocational or less in the United Kingdom, 'moderate' if respondent completed community college/trade/technical school/some university (no degree) in Canada and the United States, college/university (no degree) in the United Kingdom or technical/trade/some university (no degree) in Australia, or 'high' if respondent completed university or postgraduate in all countries), and annual household income (defined as 'low' if it was less than US$30 000 (United States, Canada and Australia) or less than £30 000 (United Kingdom), 'moderate' if it was between US$30 000 and US$59 999 (or £30 000 and £44 999 in the United Kingdom) or 'high' if it was equal to or greater than US$60 000 (or £45 000 in the United Kingdom); respondents who did not provide this information (~5%) were included in adjusted analyses as a valid unknown group).

The following time-varying smoking-related characteristics and beliefs, assessed while respondents were still smoking, were also examined: nicotine dependence (measured with the heaviness of smoking index (HSI), a short form of the Fagerström tolerance questionnaire [42]), self-efficacy [assessed with the item: 'If you decided to give up smoking completely in the next 6 months, how sure are you that you would succeed?'. Response options were collapsed to: not at all sure + slightly sure (low self-efficacy), moderately sure (moderate), very sure + extremely sure (high)], and belief about medication effectiveness [assessed with the item 'Stop smoking medications make it easier to quit'. Response options were collapsed to indicate agreement (i.e. strongly agree/agree) versus other (i.e. strongly disagree/disagree/neither agree nor disagree)].

Statistical analyses

All analyses were conducted using STATA version 11 [43]. The generalized estimating equations (GEE) approach was used to evaluate the association between medication use and smoking cessation overall, as well as specifically among those for whom increasing amounts of

confounding due to systematic recall bias were removed (i.e. those who recalled their most recent quit attempts as occurring within the last 3 months, 2 months and 1 month of interview), and to identify the characteristics of those who used each of the four most common types of medication when attempting to quit smoking.

Specifically, repeated longitudinal logistic regression analyses were performed such that medication effectiveness analyses were adjusted for smoking behavior characteristics measured prior to the quit attempt, and predictors of medication use were measured prior to the assessment of use. Repeated analyses via GEEs allowed for individuals who were present in multiple pairs of waves to contribute multiple observations (if applicable), while accounting for the inherent correlated nature of data within individuals over time [44,45]. All models included a specification for the binomial distribution of the dichotomous dependent variables, a specification for the unstructured within-person correlation matrix, and all confidence intervals were computed using the robust Huber ('sandwich') estimator of variance. Model covariance parameters were set at a maximum of 100 iterations and convergence tolerance for the coefficient vector was set at 1e-6.

Analyses were adjusted for country, gender, age group, majority/minority group, education, income, HSI and self-efficacy. Analyses utilizing data from the entire study period were adjusted additionally for the change in instrument that occurred between waves 4 and 5, and analyses assessing medication effectiveness were restricted to daily smokers of 10+ cigarettes (i.e. the typical criterion for medication use). Medication effectiveness analyses were performed using both unweighted data and weighted data, and both sets of analyses produced the same conclusions. As the structure of our database renders no single set of longitudinal weights to be suitable for all respondents, necessitating multiple sets of weighted analyses, we present only results produced from the unweighted analyses.

Ethics approval

The study protocol was approved by the institutional review boards or research ethics boards of the University of Waterloo (Canada), Roswell Park Cancer Institute (United States), University of Strathclyde (United Kingdom), University of Stirling (United Kingdom), The Open University (United Kingdom) and The Cancer Council Victoria (Australia).

RESULTS

The odds of 1-month and 6-month continuous abstinence from smoking as a function of medication use are

presented in Table 1, both overall (i.e. since the previous wave—around 1 year), and stratified by quit attempt recency (i.e. within 3, 2 and 1 month of interview). In the analyses using the full interwave interval, there was only a small and inconsistent positive effect for NRT, effectively replicating previous findings of no or smaller effects. However, among those who recalled their last quit attempts as occurring within 1 month of interview (i.e. the stratum that excluded the most recall bias), vareni-cline users were nearly six times more likely to be quit for 6 months (adjusted OR = 5.84, 95% CI = 2.12–16.12), bupropion users were nearly four times more likely to be quit for 6 months (adjusted OR = 3.94, (95% CI = 0.87–17.80) and nicotine patch users were four times more likely to be quit for 6 months (adjusted OR = 4.09, 95% CI = 1.72–9.74), compared to those who attempted to quit without medication. Indeed, as increasing amounts of recall bias were removed, the odds ratios for these medications increased to be higher than those found from meta-analyses of randomized controlled trials. However, there were only non-significant associations for oral NRT users, regardless of the recall time-frame.

As shown in Table 2, those who attempted to quit without medication were generally more likely to be male, to be younger, to be minorities, to have lower incomes, to be less heavily addicted to nicotine and to have higher self-efficacy compared to those who attempted to quit with medication. Those who agreed that SSMs make it easier to quit were approximately two to three times more likely to use medication.

DISCUSSION

Generally consistent with results from clinical trials, findings from this study show that use of varenicline, bupropion or the nicotine patch is associated with increased quit rates compared to quit rates among those attempting to quit without medication. Among those for whom systematic recall bias was largely minimized, those who used any of these medications exhibited a threefold or greater increase in 6-month continuous abstinence, with varenicline users experiencing a nearly sixfold increase. Given the limited power, no clear conclusions can be drawn about oral NRT use, but any effects appear smaller than those found for the other products. Results also suggest that failure to control for differential recall of unsuccessful quit attempts between medication users and non-users may explain the inconsistent results of previous population-based studies; as we tightened control over recall effects, the size of the positive effects for medications increased and the effect for NRT patches became significant. Lastly, our sample resembles samples from previous population studies, in that many smokers did not use medication when attempting to quit, and this was particularly true of younger smokers, minorities, those with low incomes and those, understandably, who did not believe medications make quitting easier.

These findings should be interpreted in light of the following study limitations: reliance on self-reported smoking status (although it is unlikely that successful quitters in the real world, who were neither compelled nor compensated to use medication, would misrepresent how they achieved cessation), no control over potential differences in motivation to quit or differences in relevant policy changes (e.g. increases in cigarette prices), the possibility that some subgroups of the population may have been under-represented, absence of an assessment of medication side effects and reduced sample sizes when analyses were restricted to recent quit attempters (which left insufficient power to detect cross-country differences in effectiveness, $P > 0.05$ for all country interaction terms).

Also, prior to wave 6, we could not ascertain whether medication was used specifically during a respondent's last quit attempt, meaning that results presented in Table 1 indicate estimated effect sizes for those known to have used medication at some point during the preceding year. However, beginning in wave 6, an additional item was added to the survey allowing for smoking cessation to be assessed as a direct function of medication use/non-use during the last quit attempt in particular, and analyses based on this subset of respondents ($n = 1731$) indicate that all recall bias-reduced estimates of medication effectiveness are higher when assessed as a direct function of respondents' last quit attempts. We also further restricted these analyses to respondents whose quit attempt lasted for at least 1 day, in an effort to exclude short quit attempts that some might not consider to be serious, and found that although effectiveness estimates were somewhat attenuated, the conclusions drawn from these results were the same as those drawn from Table 1.

We carried out several additional analyses to address the representativeness of our effectiveness findings, including: (i) performing analyses using longitudinally weighted data, which produced the same conclusions as those drawn from Table 1; (ii) statistically comparing those who were lost to follow-up (~30%) with those who were retained in the sample in terms of demographic, smoking-related and medication usage variables, and found these groups to be statistically indistinguishable on all variables; and (iii) performing sensitivity analyses in which we supposed that all those who were lost to follow-up did not quit smoking, and though the effect sizes for nicotine patch effectiveness and varenicline effectiveness were somewhat attenuated, the conclusions drawn from these results were the same as those drawn from Table 1.

Table 1 Odds of smoking cessation as a function of medication use, stratified by recalled recency of last quit attempt.

	Type of medication																												
	No medication (ref)			Any medication[a]					Nicotine gum/other oral NRT					Nicotine patch					Bupropion					Varenicline				
Recency of quit attempt (QA)	n_{indiv}	n_{QA}	% quit	n_{indiv}	n_{QA}	% quit	OR	(95% CI)	n_{indiv}	n_{QA}	% quit	OR	(95% CI)	n_{indiv}	n_{QA}	% quit	OR	(95% CI)	n_{indiv}	n_{QA}	% quit	OR	(95% CI)	n_{indiv}	n_{QA}	% quit	OR	(95% CI)
1-month abstinence																												
QA since last wave[b]	2956	3706	21	2201	2798	24	1.21**	(1.07–1.36)	423	477	22	1.06	(0.83–1.34)	1260	1523	24	1.19*	(1.02–1.38)	313	357	23	1.21	(0.93–1.57)	286	291	33	1.88***	(1.41–2.52)
QA within the last 3 months[c]	652	720	16	525	560	22	1.47***	(1.10–1.96)	89	91	15	0.96	(0.52–1.76)	236	247	21	1.26	(0.87–1.83)	41	41	29	2.08	(0.97–4.48)	125	127	30	2.61***	(1.64–4.14)
QA within the last 2 months[c]	405	446	14	326	340	23	1.96**	(1.33–2.89)	55	56	16	1.27	(0.59–2.77)	157	163	23	1.96**	(1.22–3.15)	27	27	26	2.14	(0.76–6.04)	67	67	30	3.34***	(1.71–6.54)
QA within the last month[c]	292	313	12	219	227	23	2.56***	(1.56–4.19)	39	40	18	1.84	(0.73–4.61)	98	101	25	2.53***	(1.31–4.90)	20	20	25	3.35*	(1.02–11.07)	47	47	27	3.76**	(1.60–8.79)
6-month abstinence																												
QA since last wave[b]	2750	3473	14	2042	2609	16	1.17*	(1.01–1.35)	393	444	14	1.02	(0.76–1.36)	1151	1405	15	1.15	(0.96–1.36)	289	332	14	1.09	(0.77–1.53)	276	281	26	1.76**	(1.28–2.41)
QA within the last 3 months[c]	624	690	8	503	538	12	1.57*	(1.07–2.31)	86	88	7	0.90	(0.37–2.20)	226	237	11	1.37	(0.82–2.29)	41	41	15	2.06	(0.78–5.45)	117	119	17	2.73**	(1.51–4.94)
QA within the last 2 months[c]	393	434	6	316	330	13	2.47**	(1.45–4.20)	53	54	6	0.89	(0.25–3.13)	151	157	13	2.65**	(1.38–5.09)	27	27	15	3.42	(0.93–12.54)	65	65	18	4.48**	(1.91–10.53)
QA within the last month[c]	287	308	5	217	225	14	3.59***	(1.79–7.19)	39	40	8	1.42	(0.36–5.56)	98	101	16	4.09**	(1.72–9.74)	20	20	15	3.94	(0.87–17.80)	47	47	19	5.84**	(2.12–16.12)

Analyses were adjusted for country, sex, age group, majority/minority group, education, income, heaviness of smoking index (HSI) and self-efficacy. Analyses were restricted to those who were daily smokers of 10+ cigarettes prior to quitting; *n*s are given for number of individuals and number of quit attempts; percentages include multiple quit attempts per individual; continuous abstinence was determined using second follow-up data among those who attempted to quit within the abstinence end-point window when interviewed at first follow-up. [b]Based on data collected during waves 2–8. [c]Includes those who used more than one type of medication. [d]Based on data collected during waves 5–8. CI: confidence interval; NRT: nicotine replacement therapy; OR: odds ratio.
*P < 0.05; **P < 0.01; ***P < 0.001.

Table 2 Predictors of using medication when attempting to quit smoking.

Predictors	Nicotine gum n = 5447 (10% use overall)			Nicotine patch n = 6432 (27% use overall)			Bupropion n = 5394 (8% use overall)			Varenicline n = 2683 (13% use overall)		
	n	% used	OR	n	% used	OR	n	% used	OR	n	% used	OR
Country												
United Kingdom	1248	13	Referent	1563	35	Referent	1165	4	Referent	514	6	Referent
Canada	1415	10	0.68**	1660	26	0.64***	1434	10	2.66***	662	12	1.95**
Australia	1492	9	0.60***	1779	26	0.72***	1492	8	2.22***	784	9	1.77***
United States	1292	9	0.54***	1430	19	0.45***	1303	9	2.26***	723	24	4.46***
Sex												
Female	3069	10	Referent	3682	29	Referent	3036	9	Referent	1533	15	Referent
Male	2378	9	0.87	2750	25	0.76***	2358	7	0.74**	1150	11	0.64***
Age group (years)												
18–24	634	6	Referent	680	14	Referent	622	3	Referent	177	2	Referent
25–39	1662	9	1.33	2000	26	2.02***	1655	7	2.16**	664	10	4.90*
40–54	1887	11	1.38	2305	31	2.13***	1876	10	2.39***	987	15	5.70***
55+	1449	11	1.37	1701	27	1.73***	1409	8	2.09**	901	16	6.16***
Majority/minority group												
Majority	4738	10	Referent	5675	28	Referent	4699	8	Referent	2371	14	Referent
Minority	709	8	0.85	756	16	0.59***	695	5	0.57**	312	7	0.41***
Education												
Low	2766	9	Referent	3338	28	Referent	2755	8	Referent	1310	11	Referent
Moderate	1818	10	1.26*	2115	26	1.00	1807	9	1.08	898	15	1.26
High	913	12	1.41**	1039	24	0.92	881	7	0.85	497	15	1.35
Income												
Low	1715	9	Referent	2011	27	Referent	1678	7	Referent	823	12	Referent
Moderate	1925	10	0.87	2288	26	1.05	1919	8	1.14	904	14	1.33*
High	1649	11	1.12	1982	28	1.23*	1634	9	1.57***	844	15	1.93***
HSI												
Low	3153	8	Referent	3560	19	Referent	3097	5	Referent	1457	8	Referent
High	2652	13	1.54***	3422	35	1.84***	2637	11	1.84***	1342	20	2.40***
Self-efficacy												
Low	2664	12	Referent	3220	29	Referent	2596	9	Referent	1306	16	Referent
Moderate	2183	9	0.85	2677	28	1.06	2163	8	1.04	982	13	0.97
High	1507	7	0.73**	1729	20	0.85*	1486	5	0.80	672	8	0.57**
Medications make quitting easier												
Disagree/neither agree nor disagree	2177	5	Referent	2370	13	Referent	2139	3	Referent	953	7	Referent
Agree	3699	13	1.92***	4590	34	2.49***	3658	11	3.08***	1822	17	2.48***

Analyses were adjusted for country, sex, age group, majority/minority group, education, income, heaviness of smoking index (HSI), longest time off smoking and instrument change. Predictors were measured one wave prior to the measurement of recalled medication use; *n*s indicate number of unique individuals within cells; percentages consider multiple observations per individual. OR: odds ratio. *P < 0.05; **P < 0.01; ***P < 0.001.

Balanced against the above study limitations are several strengths, including: (i) the large sample of smokers compared to some other studies; (ii) the breadth of the sample (representative from four countries); (iii) the cohort design, which allowed for longer term outcomes to be evaluated at subsequent survey waves; (iv) use of GEEs, which allowed for repeat longitudinal analyses to be performed while accounting for repeated measurements within individuals over time; and (v) measurement of time to recalled events and adjustment for numerous potential confounders of medication effectiveness.

The association between medication use and recall of failed quit attempts requires that population-based evaluations of medication effectiveness account for quit attempt recency [36]. Indeed, results reported in the present study show that the estimated magnitude of effectiveness decreases with decreasing quit attempt recency. Reduction of recall bias can be achieved by using prospective cohorts and timely assessments, or by controlling, statistically, for time elapsed between events and measurement of events. Failure to address this bias may account for some of the previous inconsistencies observed in the literature; retrospective studies evaluating quit attempts occurring within 1 year of interview generally found NRT to be ineffective [17–21], while a study using assessments occurring every 3 months and a fully prospective study found NRT to be effective [23,24]. Gilpin *et al.*, using a retrospective design, did find a cessation benefit of NRT for smokers living in smoke-free homes, and suggested that NRT is more effective among those who are more motivated to quit [26].

Although there was a suggestion that oral NRT users may experience higher continuous abstinence rates than non-users, these rates were statistically indistinguishable from those of non-users. Although our power to detect a significant effect was limited, it remains possible that there is no long-term benefit of oral NRT when used in the population setting. We found that more than 80% of nicotine gum users reported using fewer than the recommended eight pieces per day [46], as have other studies [47,48], and it remains plausible that insufficient use contributed to reduced effectiveness.

The bias-reduced estimates of varenicline, bupropion and nicotine patch effectiveness shown in our study are somewhat higher than the clinical trial estimates of medication efficacy [1–4]. This could be due to chance effects but could, plausibly, be real; in real-life settings we are testing the combined effect of the drug and non-specific effects. To the extent that non-specific effects accompany the drug (e.g. the belief that it will help), success rates should be greater than those estimated from randomized controlled trials. Thus, if our estimates are representative, more medication users are helped than many conventional studies suggest.

CONCLUSIONS

Consistent with the findings of clinical trials, results from this study indicate that smoking cessation rates are higher among those using varenicline, bupropion or the nicotine patch compared to those attempting to quit without medication; however, no clear effects for oral NRT use were found. Despite the cessation advantage gained by using varenicline, bupropion or the nicotine patch, however, many of those making quit attempts do so without the aid of any medication. Thus, in theory, population quit rates could be increased by promoting use of demonstrably effective stop-smoking medications. However, even among those using these medications to help them stop smoking, relapse to smoking remains the norm, thus reinforcing the need for efforts to develop and deliver more effective treatments to help smokers to quit.

Declarations of interest

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