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Original article

Evaluation of smoking cessation drug use and outcomes in the Netherlands

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Abstract

Objective:
Several pharmacological therapies are available to help smokers quit. The aim was to investigate the utilisation and effectiveness of smoking cessation drugs in daily practice in the Netherlands.

Methods:
Subjects aged ≥18 years with a pharmacy prescription of varenicline, bupropion, nicotine replacement therapy (NRT) or nortriptyline between March 2007 and September 2008 were identified from the PHARMO data warehouse, which includes drug dispensing, hospitalisation and other data from approximately 2.5 million residents in the Netherlands. Using an encrypted methodology, corresponding non-person-identifiable dispensing IDs were linked to a web-based system for patient-reported data collection. Corresponding pharmacists asked the subjects to participate in the study and complete a web-based questionnaire on smoking history and cessation, including utilisation of (pharmaco) therapies.

Results:
Of 2,684 invited subjects, 698 responded (26%), of whom 612 were included in the analyses. Bupropion was the most frequently used smoking cessation drug (35% of patients), followed by varenicline (28%), bupropion + NRT (12%) and varenicline + NRT (9%). Overall, 51% of patients also reported behavioural therapy. A total of 53% of bupropion users, 51% of varenicline users, 42% of NRT users and 20–40% of patients using multiple drugs reported to not smoke at the time of questionnaire. Median (interquartile range) number of days between time of questionnaire and start date of last quit attempt ranged from 271 (104–432) for varenicline + bupropion to 356 (205–518) for bupropion. Mean duration of drug use ranged from 42 to 53 days among quitters and from 19 to 42 days among relapsers.

Conclusion:
In this study up to 50% of patients who obtained smoking cessation drugs at the pharmacy stopped smoking. Better access to smoking cessation drugs as recommended in guidelines will help to further decrease smoking prevalence.

Introduction

Smoking is the leading preventable risk factor for premature mortality, causing about 1.6 million deaths per year in the European Region[1]. Smoking cessation is associated with a substantial improvement in cardiovascular and lung function and decreased morbidity and mortality[2–4]. Time frames for risk reduction differ across outcomes, with most of the excess cardiovascular risk being eliminated rapidly and within 20 years for lung diseases[4]. On a population level even a small decrease in smoking prevalence is clinically relevant and cost effective because of the very large health gains that accrue from stopping smoking[5].

In 2005, on average 40% of men and 18% of women in Europe smoked[1]. While most smokers recognise the significant health risks associated with

smoking, many attempts at quitting remain unsuccessful due to the high level of relapse[6]. Among Dutch smokers, 64% have tried to quit but did not succeed[7].

Several pharmacological therapies are available to help smokers quit and decrease the risk of relapse: nicotine replacement therapy (NRT), bupropion and varenicline. Additionally, nortriptyline is used off-label in smoking cessation. All these drugs reduce symptoms of nicotine withdrawal. Also, varenicline decreases the reinforcing effects of smoking satisfaction and psychological reward that are often associated with nicotine use[8]. In numerous trials effectiveness of these drugs has been proven, with reported long-term rates of quitting (up to 1 year) generally twice those of placebo[9,10]. However, there is a need for further effectiveness and safety evaluation, particularly in those with comorbid conditions.

In the Dutch College of General Practitioners' guideline for smoking cessation, issued in July 2007[11], NRT is recommended as first-choice drug; nortriptyline and bupropion are listed as second-choice treatments. Use of varenicline is not yet recommended because the drug has only been studied in healthy patients and its long-term effects are still unclear. The aim of this study was to determine characteristics of use and effectiveness of smoking cessation drugs in daily practice in the Netherlands

Patients and methods

Study population

Potential study participants were identified using community pharmacy data from PHARMO data warehouse, a population-based patient-centric data tracking system including high quality and complete information linked on a patient level of, among other things, patient demographics and drug dispensing from approximately 2.5 million community-dwelling inhabitants of 48 geo-demographic areas in the Netherlands. Specifically, all subjects aged 18 years and older with one or more dispensing(s) of a smoking cessation drug (varenicline, bupropion, NRT and nortriptyline) between March 2007 and September 2008 were identified. This period was chosen because varenicline was introduced into the Netherlands in March 2007, and to ensure sufficient follow-up time. Using an encrypted automated methodology, ePRO-LINK, the non-person-identifiable dispensing IDs corresponding to these identified subjects were anonymously linked to an advanced web-based system for longitudinal patient-reported data collection. The ePRO-LINK system was developed in collaboration with Prospective Medical Data International (PMDI), a data and technology services company for data collection, validation and dissemination in medical research. In January 2009, associated pharmacies were asked to invite the patients corresponding to the identified dispensing IDs to participate in the study using the ePRO-LINK system. The patient invitation letters contained a personal login account by which they could log on to their study portal to read study information and complete an informed consent document and a questionnaire.

Questionnaire

The questionnaire contained questions on smoking history, smoking cessation, comorbidity and basic demographics. Regarding smoking history, participants were asked about their smoking frequency, duration, main form of tobacco use and six items from the Fagerström Test for Nicotine Dependence (FTND)[12]. Regarding smoking cessation, participants were asked for the number of quit attempts and to report on their last quit attempt: reason for quitting, type and duration of smoking cessation therapy and the outcome of the last quit attempt. It should be noted that this last quit attempt may have been a later attempt than that for which they were identified in the PHARMO data warehouse as: (1) the last attempt may have been after September 2008, (2) NRT are also available over-the-counter at the chemists and (3) patients may have used behavioural therapy only. The questionnaire took on average 10 minutes for completion. A financial incentive was provided for each completed questionnaire.

Data handling and analyses

All participants who reported having used any smoking cessation drug in their last quit attempt and had filled out all relevant questions were included in the analyses.

Regarding patients' smoking history, pack-years were calculated by multiplying smoking duration with daily tobacco consumption[13]. One pack-year was defined as 20 cigarettes each day over the course of 1 year. Regarding nicotine dependence, the total scores for the FTND were calculated according to the instruction manual[14]. A score of 0 to 2 was defined 'very slightly dependent', a score of 3 'slightly dependent', a score of 4 'moderately dependent', a score of 5 'dependent' and a score of 6 to 10 'highly dependent'. Reasons for quitting smoking (19 answer categories) were grouped into: medical reasons, advice from healthcare professionals, financial reasons, aesthetic reasons and other reasons. Duration of use of smoking cessation drugs was calculated for patients who had stopped treatment at the time of the questionnaire and was presented separately for patients who remained abstinent and those who had relapsed at the time of the questionnaire. Differences in duration of use between these two groups were tested using the *t*-test. In cases when multiple drugs were used, no information was available on timing of

Table 1. Characteristics of study patients, stratified by reported smoking cessation drug at last quit attempt.

	All $n=612$ *n* (%)	Smoking cessation drug at last quit attempt*			
		Varenicline $n=173$ *n* (%)	Bupropion $n=216$ *n* (%)	NRT $n=31$ *n* (%)	Combination of drugs $n=176$ *n* (%)
Gender					
Male	286 (47)	76 (44)	107 (50)	11 (35)	82 (47)
Female	326 (53)	97 (56)	109 (50)	20 (65)	94 (53)
Age (years, mean ± SD)	48 ± 11	47 ± 11	48 ± 12	52 ± 11	49 ± 11
Reported comorbidities					
Cardiovascular diseases	83 (14)	20 (12)	29 (13)	5 (16)	28 (16)
Asthma	53 (9)	22 (13)	8 (4)	6 (19)	17 (10)
COPD	110 (18)	33 (19)	26 (12)	4 (13)	43 (24)
Diabetes mellitus	39 (6)	9 (5)	12 (6)	3 (10)	12 (7)
Psychiatric disorders	84 (14)	25 (15)	20 (9)	7 (23)	30 (17)
Pack-years smoked (median (IQR))	30 (16–41)	30 (16–41)	27 (14–38)	29 (25–44)	30 (19–45)
Nicotine dependence level					
Very slightly dependent	75 (12)	17 (10)	29 (13)	5 (16)	23 (13)
Slightly dependent	59 (10)	12 (7)	26 (12)	3 (10)	15 (9)
Moderately dependent	92 (15)	23 (13)	34 (16)	6 (19)	27 (15)
Dependent	116 (19)	29 (17)	45 (21)	6 (19)	32 (18)
Highly dependent	270 (44)	92 (53)	82 (38)	11 (36)	79 (45)
Number of quit attempts					
1	68 (11)	26 (15)	27 (13)	2 (7)	12 (7)
2–3	276 (45)	79 (46)	111 (51)	17 (55)	61 (35)
4–5	151 (25)	35 (20)	52 (24)	5 (16)	55 (31)
6–7	34 (6)	15 (9)	5 (2)	1 (3)	13 (7)
More than 7	83 (14)	18 (10)	21 (10)	6 (19)	35 (20)

*Only mono-pharmacotherapy groups larger than ten respondents are listed separately. All drug combinations are included in one group. Frequently used combinations were: zyban + NRT ($n=73$), champix + NRT ($n=53$), champix + zyban ($n=21$). No information was available on timing of multiple therapies, so they could have been used sequentially.
SD, standard deviation; IQR, interquartile range (i.e., range of the middle 50% of the data).

therapies, so the drugs may have been used (partly) simultaneously or sequentially. Duration of use was conservatively based on the drug with the longest reported duration of use (i.e., assuming simultaneous use)

All analyses were conducted using SAS Enterprise Guide version 4.0 (SAS Institute Inc., Cary, NC, USA) on UNIX with SAS version 9.1.

Results

A total of 9,627 potential study patients at 230 pharmacies were identified from the PHARMO data warehouse. In all, 78 pharmacists indicated their willingness to participate (pharmacy response rate: 34%) and sent out 2,684 invitation letters to eligible patients. A total of 698 respondents filled out the questionnaire (patient response rate: 26%). Of these, 612 patients reported to have used any smoking cessation drug in their last quit attempt and answered all the relevant questions, and were included in the analyses. Among these study patients bupropion was the most frequently used smoking cessation drug (35% of patients), followed by varenicline (28%), bupropion + NRT (12%) and varenicline + NRT (9%). 51% of study patients also reported behavioural therapy, mainly counselling. The median number of days between time of questionnaire and start date of last quit attempt was 318 days (InterQuartile Range (IQR): 190–483). The proportion of patients with at least 6 or 12 months of follow-up after their last quit attempt was 77% and 42%, respectively.

Characteristics of study patients are shown in Table 1. Overall, mean age was 48 years and presence of cardiovascular disease, COPD and psychiatric disorders were each reported by 14–18% of patients. The median number of pack-years smoked was 30. Nearly all study patients (96 to 100%, not included in the table) (had) smoked (own rolled) cigarettes. A total of 38% of bupropion users, 36% of NRT users and 53% of varenicline users were or had been highly nicotine dependent. Two-thirds of varenicline users to three-quarters of bupropion users had made two to five quit attempts. At least 90% of study patients reported a medical reason for their last quit attempt (Table 2). 'Being independent of nicotine' was the most frequently reported 'other reason' for quitting smoking (41% of all patients).

Table 3 shows the effectiveness of smoking cessation drugs and the duration of drug use stratified by outcome. For the different monotherapies, 53% of bupropion users, 51% of varenicline users and 42% of NRT users reported to not smoke at the time of questionnaire. The median number of days between time of questionnaire and start date of last quit attempt ranged from 306 days

Table 2. Reason quitting smoking, stratified by reported smoking cessation drug at last quit attempt.

Reason for quitting smoking*		Smoking cessation drug at last quit attempt			
	All $n=612$ n (%)	Varenicline $n=173$ n (%)	Bupropion $n=216$ n (%)	NRT $n=31$ n (%)	Combination of drugs $n=176$ n (%)
Medical reason	561 (92)	156 (90)	195 (90)	28 (90)	166 (94)
Advice from healthcare professional	197 (32)	61 (35)	52 (24)	12 (39)	64 (36)
Financial reason	252 (41)	63 (36)	92 (43)	9 (29)	79 (45)
Aesthetic reason	183 (30)	50 (29)	66 (31)	8 (26)	52 (30)
Other reason	309 (50)	81 (47)	115 (53)	14 (45)	91 (52)

*Percentages count up to more than 100% because of multiple answers to this question.

Table 3. Effectiveness of smoking cessation drugs and duration of use stratified by outcome of last quit attempt.

Smoking cessation drug at last quit attempt†		Outcome last quit attempt*						p-value for difference duration use
		Remained abstinent			Relapsed			
	N	N (%)	n‡	Duration of use in days§ (mean ± SD)	N (%)	n‡	Duration of use in days§ (mean ± SD)	
Varenicline	173	88 (51%)	84	53 ± 30	85 (49%)	82	40 ± 29	<0.01
Bupropion	216	115 (53%)	114	42 ± 26	101 (47%)	99	35 ± 27	<0.05
NRT	31	13 (42%)	11	44 ± 25	18 (58%)	18	19 ± 16	<0.01
Varenicline + NRT	53	21 (40%)	20	46 ± 33	32 (60%)	31	42 ± 33	0.65
Bupropion + NRT	73	23 (32%)	23	42 ± 31	50 (68%)	50	40 ± 27	0.72
Varenicline + bupropion	21	4 (19%)	3	63 ± 37	17 (81%)	15	42 ± 32	0.33

*Self-report of smoking status at the time of questionnaire, i.e. at a median 318 days after the last quit attempt.
†Only drugs and drug combinations used by more than ten respondents are listed.
‡Number of respondents who had stopped treatment yet at the time of questionnaire. Duration of use was calculated over this number of respondents.
§In case of drug combinations no information was available on timing of therapies, so drugs could have been used (partly) simultaneously or sequentially. Duration of use was conservatively based on the drug with the longest duration of use (i.e., assuming simultaneous use).
SD, standard deviation.

(IQR: 190–430) for varenicline to 356 days (IQR: 205–518) for bupropion. To properly determine quit rates, patients should preferably be followed for at least 6 months after their quit attempt[15]. Restricting the analyses to patients with at least 6 months of follow-up (bupropion $n=177$, varenicline $n=134$, NRT $n=21$) yielded similar quit rates (53%, 54% and 38%, respectively). Quit rates may also differ with additional behavioural therapy. Only among varenicline and bupropion users did available patient numbers allowed for a stratified analysis: in the presence of additional behavioural therapy the quit rate was 43% compared to 60% without such therapy.

The mean duration of drug use among varenicline/bupropion/NRT users who remained abstinent was significantly longer than among varenicline/bupropion/NRT users who relapsed (Table 3). In case the last quit attempt started more than 1 year before the time of questionnaire, the reported duration of use may have been less reliable due to recall bias. Restricting the analyses to patients with a recall period of less than 12 months (varenicline $n=46$ quitters and 52 relapsers, bupropion $n=54$ quitters and 50 relapsers, NRT not applicable due to too few patients) yielded similar mean durations of use (53 ± 30 and 39 ± 25 days for varenicline quitters and relapsers, respectively, 40 ± 24 and 33 ± 29 days for bupropion quitters and relapsers, respectively).

Those with multiple drug use reported lower quit rates of 20–40% (Table 3). The median follow-up after the last quit attempt ranged from 271 days (IQR: 104–432) for varenicline + bupropion to 314 days (IQR: 186–460) for varenicline + NRT. Similar quit rates were observed when restricting the analyses to patients with at least 6 months of follow-up (data not shown). Mean duration of drug use did not differ significantly between users of multiple drugs who remained abstinent and those who relapsed.

Discussion

In this population-based study among users of smoking cessation drugs, quit rates ranged from about 52% with use of varenicline or bupropion to 20–40% with use of multiple drugs and NRT. Duration of drug use was shorter than recommended in the guidelines.

Quit rates in the current study were based on self-report of smoking status at the time of questionnaire, i.e. at a median 318 days after the last quit attempt. Population-based quit rates reported in the literature are limited, with different follow-up periods and varying means of assessing abstinence rate. The latest statistics from the NHS stop smoking services in the UK show that 46% of NRT users, 49–50% of bupropion, bupropion + NRT or varenicline + NRT users and 61% of varenicline users compared to 49% of those who did not receive pharmacotherapies had not smoked at all since 2 weeks after the quit date[16]. Data from the Smoking Cessation Center at Parma, Italy show that the percentage of abstainers after 6 months was 31% for NRT, 37% for bupropion and 46% for bupropion + NRT[17]. Available data for varenicline, i.e. 62% abstainers, are restricted to 3 months follow-up. Among smokers attending two smoking cessation clinics in Barcelona, Spain and receiving varenicline plus cognitive-behavioural intervention, the continuous abstinence rate after 12 weeks was 58%[18]. In the current study, quit rates with varenicline or bupropion use plus behavioural therapy was 43% compared to 60% without such therapy. This difference in quit rates does not seem to be related to the extent of nicotine dependence; mean FTND score was similar among patients with and without additional behavioural therapy. However, for varenicline, but not for bupropion, the proportion of patients with six or more quit attempts was larger among patients who also had behavioural therapy (27% compared to 11%).

According to the Dutch College of General Practitioners' guideline for smoking cessation, NRT are first-choice drug, nortriptyline and bupropion are listed as second-choice treatments and use of varenicline is not yet recommended[11]. In the present study, however, nortriptyline monotherapy was used by only 1% of patients, compared to 35% of patients using bupropion monotherapy, and varenicline monotherapy was used by 28% of patients. Furthermore, about 14% of patients using varenicline or bupropion used this drug at their first quit attempt. In addition, about 30% of patients used a combination of drugs, although this had not been recommended. However, it is not known whether multiple drugs were used (partly) simultaneously or sequentially. In the most recent 'Treatment of tobacco dependence'-guideline developed by the Dutch Institute for Healthcare[19], nortriptyline, bupropion as well as varencline are recommended as second-choice treatments after NRT.

Furthermore, varenicline is recommended to be used for 12 weeks and bupropion for 7–9 weeks, while reported mean durations of use were much lower, namely 53 and 42 days, respectively for patients who remained abstinent and 40 and 35 days, respectively for patients who relapsed. The observation that quitters showed a higher duration of therapy than relapsers highlights the importance of counselling and patient monitoring for drug adherence and successful outcome. This is also underlined by the trial by Tonstad *et al.*[20] in which the benefit of an additional 12 weeks of varenicline treatment in preventing relapses was demonstrated.

Some methodological remarks should be made to the present study. First, the response rate to the study's web-based survey was 26%. It can be argued that participating patients may not have differed from non-responders and were representative for potential study patients. Due to privacy constraints, information of non-responding subjects was automatically deleted from the portal and consequently characteristics of these patients were unknown. However, age and gender were available of all potential study patients identified in the PHARMO data warehouse, which is representative for the Netherlands. Mean age of all patients who were either not recruited or non-responding ($n = 9{,}015$) was 50 ± 14 years and 46% were male, which is similar to the mean age and gender distribution of the study patients. However, only 2% of study patients was older than 70 years compared to 7% of the not recruited/non-responders. Second, because of the retrospective study design, for 42% of patients the period between time of questionnaire and start date of last quit attempt was more than 1 year. Reported duration of drug use may then have been less reliable due to recall bias. However, restricting the analysis to patients with a recall period of less than 12 months yielded similar mean durations of use. On the other hand, for 23% of patients the period between time of questionnaire and start date of last quit attempt was less than 6 months, which is too short to properly determine quit rates. However, restricting the analyses to patients with a follow-up of at least 6 months yielded similar quit rates. Third, study patients were restricted to those obtaining smoking cessation drugs at the pharmacy. NRTs however, are also available, and widely obtained, over-the-counter at the chemists. The distribution of smoking cessation drugs observed in the present study therefore will not reflect the distribution of these drugs in daily practice. Similarly, the NRT users included in this study may not be representative for NRT users in general. Fourth, related to the aforementioned limitation, results for NRT are based on only 31 patients. Similarly, results for drug combinations are based on small numbers. Because of these small patient numbers, different length of follow-up as well as the observational design of the current study, observed quit rates cannot be compared between smoking cessation drugs.

Governments throughout the world have recognised the importance of tobacco control and many are now seriously addressing tobacco control in all its facets by taxation, advertising control, mandatory health warnings on packages, smoking bans in public places and cessation interventions for smokers. Regarding the latter, use of smoking cessation drugs and behavioural therapy will increase long-term quit rates[9,10]. In the present study, up

to 50% of users of smoking cessation drugs in daily practice stopped smoking. However, only 23% of smokers in the Netherlands use any type of therapy at their quit attempt[7]. This low proportion is related to the costs of these therapies; only behavioural therapies are reimbursed. To decrease smoking prevalence, and benefit from corresponding large health gains, the Dutch Health Care Insurance Board advises that the cost of smoking cessation drugs should be reimbursed as part of a smoking cessation program. A pilot study has shown that such a program will increase the use of smoking cessation therapies, especially the use of smoking cessation drugs[21].

Conclusion

In this study up to 50% of users of smoking cessation drugs in daily practice stopped smoking. Better access to these drugs as recommended in smoking cessation guidelines, which is likely to be achieved by reimbursed smoking cessation programs, will help to further decrease smoking prevalence.

Transparency

Declaration of funding

This study was financially supported by an unrestricted grant from Pfizer B.V., the Netherlands. No limitations were set with regard to the conduct of the study and the writing of the manuscript.

Declaration of financial/other relationships

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