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Effectiveness of Varenicline as an Aid to Smoking Cessation in Primary Care: An Observational Study

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Key Words
Observational study · Primary care · Smoking cessation · Varenicline

Abstract
Aims: Although varenicline is commonly prescribed in primary care, information on smoking-related comorbidities and the effectiveness of varenicline in this context in Germany is scarce. This study assessed the efficacy and safety of varenicline in a large sample of patients seeking smoking cessation treatment through their general practitioners. The frequency of comorbidities was also evaluated. ***Methods:*** This was a 12-week, prospective, observational, non-comparative phase IV trial conducted in Germany. Abstinence rates at week 12 were evaluated by verbal reporting using the nicotine use inventory. ***Results:*** Overall, 1,391 subjects were enrolled; 1,177 received study medication and were evaluated for effectiveness and safety. At the end of the study, 71.1% (95% confidence interval 68.5–73.7) of subjects were abstinent. There were a total of 205 all-causality adverse events; 2.2% were classified as serious or severe. There were no fatal adverse events. At inclusion, 66.7% of participants had at least 1 concurrent comorbidity, with chronic obstructive pulmonary disease (35.5%), hypertension (29.6%) and depression (10.4%) being the most commonly reported. ***Conclusion:*** These real-world data indicate that varenicline is an effective and well-tolerated smoking cessation treatment when used in the primary care setting including patients with smoking-related comorbidities.

Introduction

Randomized controlled studies (RCTs) are the gold standard in proving efficacy of one pharmacotherapy over another or over placebo. While RCTs have excellent internal validity, their external validity is limited, in particular, by the exclusion of patients with severe physical or mental disorders, which limits the translation of results into the real world. Therefore, phase IV effectiveness studies are useful to confirm the findings of RCTs in the real-world setting [1].

Varenicline has demonstrated efficacy versus placebo in a number of RCTs [2–6]. According to a meta-analysis, at the recommended dose of 1 mg twice daily, varenicline increases the chances of successful long-term smoking

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cessation between 2- and 3-fold compared with pharmacologically unassisted quit attempts [7].

Postmarketing safety data have included reports of depressed mood, agitation and suicidal behavior or ideation, and the varenicline prescribing information has been updated to include this information. Based on these post-marketing reports, questions have been raised about a possible association between varenicline and neuropsychiatric adverse events [8, 9], although such data suffer from limitations and are not sufficient to establish a causal relationship. Furthermore, surveillance reports and secondary analyses of trial data lend little support to a causal relationship [7]. To further assess the neuropsychiatric safety of varenicline, a large, randomized, double-blind placebo controlled study is ongoing (clinicaltrials.gov identifier: NCT01456936). The prescribing information for varenicline has also been updated to include information about a small numeric increase in the incidence of certain cardiovascular events in patients taking varenicline compared with those taking placebo in a study of patients with stable cardiovascular disease [4]. While a meta-analysis of cardiovascular events in varenicline studies has raised questions about cardiovascular risk [10], regulators have not drawn robust conclusions from that analysis [11]. A second meta-analysis did not report a clinically or statistically significant increase in the incidence of cardiovascular events in varenicline-treated versus placebo-treated subjects [12].

Smoking-related diseases such as chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease, diabetes mellitus and arterial hypertension are very common, particularly among the aging population [13]. Smoking cessation is known to reduce mortality in patients with COPD [14], and has a profoundly positive impact on asthma, cardiovascular disease [15], diabetes mellitus [16], arterial stiffness and presumably arterial hypertension [17]. Furthermore, many patients with mental disorders smoke. Although it may be particularly difficult, these individuals can successfully quit smoking when they receive appropriate treatment [18]. Assessment of smoking status and counseling of smokers are core tasks in primary care. Routine assessment of smoking habits is a recommended component of regular checkups and also forms part of disease management programs for patients with coronary artery disease, diabetes [19] and COPD [14]. Opportunistic assessment of smoking status can be conducted in patients consulting with symptoms or diseases related to cigarette smoking. While even brief advice delivered by a physician has a small but significant effect on cessation rates [20], success rates can be significantly enhanced by more intense counseling and use of pharmacotherapy [7, 21, 22]. Although there is convincing evidence on the effectiveness of smoking cessation therapies in the primary care setting [23–26], there is currently very little information available on use in patients with smoking-related comorbidities in the real-world setting.

The aim of this real-life study was assessment of the 12-week cessation rate and safety profile of varenicline in a large sample of patients including patients with multiple comorbidities seeking a smoking cessation intervention with varenicline through their general practitioners.

Methods

Study Design and Population

This study was a 12-week, prospective, observational, non-comparative phase IV trial conducted in 459 mostly primary care practices in Germany between 27 May 2010 and 30 March 2011. The study (clinicaltrials.gov identifier: NCT01104636) was approved by the Ethical Board of the Freiburger Ethik Kommission International and written informed consent was obtained prior to the subjects entering the study. A schematic overview of the study design is shown in figure 1.

Screening and Eligibility

Subjects were eligible for inclusion in this study if they were of legal age to smoke, were regular smokers (mainly cigarettes), if they were motivated and willing to quit and were, according to the clinical judgment of their personal physician, suitable candidates for treatment with varenicline for smoking cessation. There were no restrictions on prior or concomitant medications or comorbidities apart from the usual prescribing information in the European Summary of Product Characteristics.

Study Medication

Participants were prescribed varenicline for at least 12 weeks. The smoker determined a quit date and received a prescription for study medication to commence treatment up to 2 weeks before the quit date. Since smoking cessation is not covered by statutory health insurance in Germany, the cost of the drug was covered by the patient.

Clinical Evaluations

Data were collected at three time points: baseline (week 0, administration of the first dose of varenicline), an optional interim visit, and at the end of study (week 12) (fig. 1). Demographic data, smoking history, comorbidities, medication, history of nicotine use, concurrent smoking-related illnesses and proposed behavioral support were recorded at enrollment. Nicotine dependence was also assessed at enrollment using the Fagerström Test of Nicotine Dependence (FTND), which comprises six questions. The primary end point was the 7-day point prevalence of abstinence rate at weeks 11–12 based on verbal reporting using a nicotine use inventory (NUI). The NUI consisted of the following two questions: 'Has the subject smoked any cigarettes (even a puff) in the

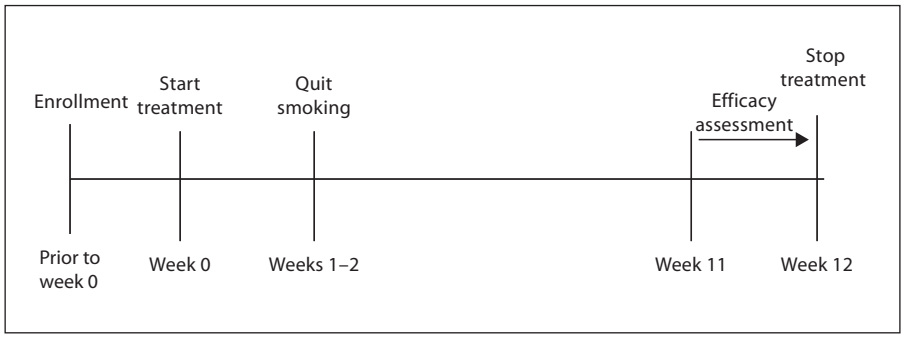

Fig. 1. Study design.

last 7 days?' and 'Has the subject used any other tobacco products (e.g. pipe, cigars, snuff, chewing tobacco) in the last 7 days?'. NUI assessments were also carried out at interim visits, if applicable.

Safety Evaluations

Adverse events reported by investigators were coded automatically using the Medical Dictionary for Regulatory Activities and summarized descriptively. Investigators recorded all observed or volunteered adverse events (including severity: mild, moderate or severe) and also their opinion of the relationship to the study treatment on case report forms. Adverse events included adverse drug reactions, illnesses with onset during the study and exacerbation of previous illnesses.

Statistical Analysis

This study was non-comparative, and analyses were descriptive and exploratory. The analysis included all enrolled participants who had documented evidence of receiving at least one dose of study medication. Descriptive summaries were provided as counts and percentages for categorical variables, and as means and standard deviations for continuous variables. Evaluations were performed according to the intention-to-treat principle [27]. Patients who were lost to follow-up were counted as smokers. The success rate for smoking cessation was calculated using the number of subjects who were considered to be responders for the 7-day point prevalence of abstinence as a proportion of the number of subjects included in the study, reported with Clopper-Pearson 95% confidence limits and determined based on the binominal distributions. No dosing data were recorded for 214 subjects enrolled in this study. Consequently, these subjects were excluded from the main analyses. To ensure that exclusion of these subjects did not bias the results, an additional sensitivity analysis was performed including all subjects irrespective of whether dosing data were recorded.

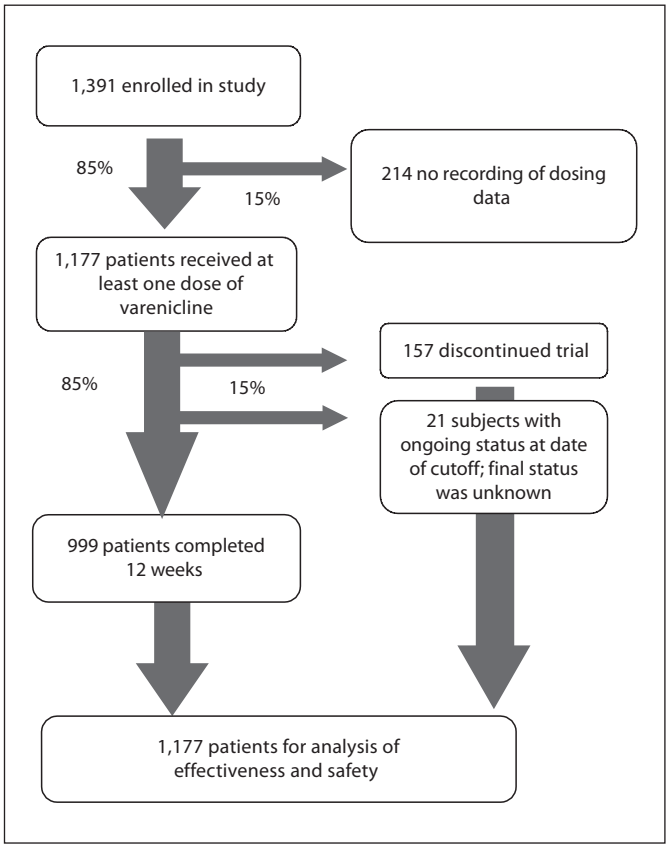

Fig. 2. Subject disposition. The 214 patients with no recording of dosing data were included in an additional sensitivity analysis.

Results

Baseline Demographics

Subject disposition is detailed in figure 2. Overall, 1,391 subjects were enrolled in this study, of whom, 1,177 received study medication and were evaluated for effectiveness and safety.

A total of 999 (84.9%) subjects completed the study, and 157 (13.3%) subjects discontinued. The most common reasons for discontinuation were insufficient clinical response (43 subjects, 3.7%) and other (including cost, desire to smoke, side effects; 43 subjects, 3.7%). Forty-nine subjects (4.2%) discontinued due to adverse

Table 1. Baseline sociodemographic data (n = 1,177)

	Subjects[1]	
Sex	1,172	
Male		669 (57%)
Female		503 (43%)
Age, years	1,161	
Mean		49.4 (12)
Range		18.0–81.0
Weight, kg	1,146	77.5 (15.8)
Body mass index, kg/m^2	1,144	25.9 (4.4)
Marital status	1,112	
Married		62.1%
Educational level	886	
Without education (up to 9 years)		105 (11.9%)
With education (9–17 years)		748 (84.4%)
University degree (>17 years)		33 (3.7%)
Employment status	1,102	
Full-time		737 (66.9%)
Part-time		101 (9.2%)
Not employed		264 (24.0%)

Figures in parentheses for age, weight and body mass index indicate SD. [1] Number of subjects with available data.

events. Twenty-one subjects were ongoing at the cutoff date (i.e. those with unknown final status at end of the study). The mean age of the participants was 49.4 years, and 57% were male. Sociodemographic characteristics of the participants are shown in table 1. The mean number of years of smoking was 26.6; the average number of cigarettes smoked per day over the past year was 22.1, and subjects had, on average, attempted to quit 3.6 times in their lifetime. The most frequently used methods for quitting were: 'cold turkey' (36.3%), nicotine patch (29.3%) and nicotine gum (21.1%). The main reasons stated for wanting to quit this time were: health (88.4%), for family/friends (39.7%) and money/cost (39.7%). The mean score on the Fagerström Test of Nicotine Dependence was 5.3.

Comorbidities and Concomitant Medications

In total, 66.7% of participants were reported to have at least one current comorbidity, the most common of which included COPD (35.5%), hypertension (29.6%), cardiovascular disorder (10.5%), depression (10.4%), diabetes mellitus (8.2%) and asthma (7.9%). The most common concomitant medications used during the study were: simvastatin (6.6%), acetylsalicylic acid (6.4%), ramipril (6.3%) and tiotropium bromide (6.1%).

Duration of Study Medication

The median duration of treatment was 85 days (range: 1–463). 430 of the total 1,177 participants (36.5%) took varenicline for a duration of between 61 and 90 days, and 398 participants (33.8%) took study treatment for ≥91 days. The recommended treatment period for the majority of subjects (874 subjects, 84.9%) was ≥12 weeks. A total of 823 of 1,057 participants (77.9%) received smoking cessation counseling in addition to study medication; 11.4% received minimal (<3 min) counseling, and 44.8% received low-intensity (3–10 min) counseling. 1,066 of the 1,177 treated subjects (90.6%) attended optional interim visits during weeks 3–11.

Abstinence Rates

In the 7-day period between weeks 11 and 12 (end of study), 837 of the 1,177 participants (71.1%; 95% confidence interval 68.5–73.7) were abstinent. Additional analyses were performed to include the 214 subjects for whom no dosing data were recorded and who were excluded from the main analysis. For subjects with no dosing data recorded, the earliest case report form date was used as the subject's dosing date to include them in the treated population. A total of 1,391 subjects were included in these additional sensitivity analyses; 1,040 (74.8%) subjects completed the study, and 191 (13.7%) subjects discontinued. The results of these additional sensitivity analyses were similar to the results from the main analyses. The proportion of responders at week 12 was 62.5% (n = 869/1,391; 95% confidence interval 59.9–65.0).

Safety

A total of 205 all-causality adverse events were reported in 130 subjects (11.0%) during the study, of which 189 (in 122 participants, 10.4%) were considered treatment-related.

Forty-nine subjects (4.2%) permanently discontinued due to adverse events; 3.7% were considered treatment-related by the investigators. Most adverse events were classified as mild (42/1,177, 3.6%) or moderate (126/1,177, 10.7%) in severity. Mild adverse events were defined as those that did not interfere with subject's usual function, moderate as those which interfered to some extent with subject's usual function, and severe as those that interfered significantly with subject's usual function. Severe adverse events were reported in 19 participants (1.6%). Severe adverse events included suicidal ideation, depression and hallucination. Seven participants (0.6%) experienced 17 serious adverse events (14 of which were considered treatment related by the investigators: aggression,

Table 2. Incidence of treatment-emergent adverse events (all-causality) occurring in ≥1% of all participants (n = 1,177)

	Total	Mild	Moderate	Severe
Nausea	41 (3.5)	14 (1.2)	18 (1.5)	9 (0.8)
Depression	24 (2.0)	1 (0.1)	21 (1.8)	2 (0.2)
Headache	16 (1.4)	4 (0.3)	12 (1.0)	0 (0.0)
Flatulence	15 (1.3)	0 (0.0)	15 (1.3)	0 (0.0)
Hyposomnia	15 (1.3)	0 (0.0)	15 (1.3)	0 (0.0)

Figures in parentheses indicate percentages.

Table 3. Incidence of treatment-emergent psychiatric adverse events (all-causality; n = 1,177)

	Total	Mild	Moderate	Severe
Depression/ depressed mood	25 (2.1)	1 (0.1)	22 (1.9)	2 (0.2)
Sleep disorders and disturbances	32 (2.7)	6 (0.5)	24 (2.0)	2 (0.2)
Apathy	3 (0.3)	0 (0.0)	2 (0.2)	1 (0.1)
Hallucination	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)
Aggression	2 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)
Suicidal ideation	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)
Nervousness	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Panic attack	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Psychotic disorder	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Mood swing	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)

Figures in parentheses indicate percentages.

depression/depressed mood, suicidal ideation (each n = 2); apathy, abnormal dreams, hallucination, loss of consciousness, mood swings, myalgia, nausea, road traffic accident (each n = 1). There were no fatal adverse events. The most frequently reported (≥1%) treatment-emergent adverse events (all-causality) are summarized in table 2, and all neuropsychiatric adverse events are summarized in table 3.

Discussion

This was an observational study designed to assess the efficacy and safety of varenicline when used in the real-world setting in Germany. At the end of the treatment period (week 12), the 7-day point prevalence of abstinence was 71.1%. Varenicline was generally well tolerated, and no new safety concerns were identified. Most adverse events were mild in severity, and around 4% of participants discontinued the study because of adverse events. Severe adverse events were observed in 1.6% of subjects. It is important to note that there was a high percentage of smoking-related disease in this study population; 35.5% of participants had COPD, 10.5% had cardiovascular disorder, 8.2% had diabetes mellitus, 10.4% had depression and 7.9% had asthma.

In this real-world study, the end-of-treatment 7-day point prevalence of abstinence in smokers who received varenicline (71%) was higher than abstinence rates observed in RCTs. The reported 7-day point prevalence of abstinence rate at week 12 was approximately 50% in RCTs of varenicline healthy smokers [2, 3], 54% in a cohort with cardiovascular disease [4], and 48% in a population of smokers with COPD [5]. In a recent 12-week, observational, non-comparative study of varenicline conducted in 566 participants from four European countries, 64.6% of participants had successfully quit smoking by the end of the treatment phase at week 12 [26], and similarly, other studies reported 12-week, point prevalence of abstinence rates of 64 [28] and 62% [29].

According to results of a meta-analysis, smoking cessation rates are approximately twice as high when varenicline treatment is administered for 24 weeks versus 6 weeks [30]. In the present study, varenicline was not reimbursed, and the costs for a 4-week treatment initiation pack or a 4-week maintenance pack were EUR 109.96. Despite this, the median duration of treatment with varenicline was 85 days and comparable with that of previous RCTs [2–5] (median duration, 84 days). Similarly, in the European observational study mentioned above, the median duration of treatment was 82.5 days [26].

The observed high smoking cessation rate in our cohort could be explained by selection of subjects with relatively high motivation to quit smoking, for example owing to the presence of symptomatic morbidity or because they were responsible for meeting the costs of medication, which their counterparts in phase III studies were not. It has been shown that copayment has strong deterrent effect on smoking [31]. Selection of motivated individuals for interventions is a typical pragmatic approach in primary care.

The most commonly observed adverse event in varenicline RCTs was nausea, which was reported at rates in the range of 29 [2, 3] to 40% [32], with attributable discontinuation rates ranging from 2.5 to 7.6% [7]. Other adverse effects associated with varenicline include insom-

nia, headache and abnormal dreams [7]. In the two phase III RCTs comparing varenicline, bupropion and placebo, an average of 9.5% of participants in the varenicline groups discontinued treatment owing to adverse events (but remained in the trial for follow-up), compared with an average of 8% in the placebo groups [7]. In a European observational study with over 500 subjects that had a similar design to the present study, 19 participants (3.4%) discontinued the study owing to treatment-related adverse events. The most frequently reported adverse events for the total population were nausea (8.9%), insomnia (2.9%), and sleep disorders (2.2%) [26]. In a study comparing three forms of behavioral support for smoking cessation in over 1,000 patients receiving varenicline for smoking cessation, after 1 month, 17% of participants had discontinued varenicline, the majority (53%) because of adverse events [33], which may have been attributed to the Web- and telephone-based interventions being investigated. In the present study, nausea was reported in only 3.5% of subjects and depression in 2.0% of subjects (only one subject had reports of depression in their medical history or at baseline). Although nausea was less commonly reported than in previous studies, other than the well-known fact that in general adverse events are often underreported in observational studies, we do not have an explanation for this finding. Similar to studies included in the recent Cochrane meta-analysis [7] and similarly to the European observational study [26], no fatal adverse events were recorded in the present study.

Depression as an adverse event after quitting was reported in about 2% of the patients in this study, although comorbid depression was present in about 10% on inclusion. This is less than the >20% incidence previously reported in patients with a history of major depression (who had not used antidepressant medicine for 6 months) [34] and figures reported in a recent meta-analysis of suicidal behavior and depression in individuals using smoking cessation therapy [9]. It is not possible to definitively determine whether these findings are due to the patients included or an underreporting known to be present in observational studies.

Compared with the subject populations enrolled in the phase III studies investigating smoking cessation pharmacotherapy in healthy smokers [2, 3, 32, 35], participants in the present study had a high prevalence of COPD, cardiovascular disease and other comorbidities. It is well established that the pathogenesis of these noncommunicable diseases is linked to cigarette smoking and, as such, smoking cessation is a crucial factor in the treatment of these diseases [36]. In previous studies of comparable design with the present study, comorbidity data have been scarcely reported. In the recently published European observational study, the most commonly reported prior or concomitant comorbidities were hypertension (20.0%), COPD (18.2%), depression (9.4%) and other psychiatric disorders (3.3%) [26]. According to data from a representative US survey, persons with a mental disorder consume more than 40% of the total cigarettes smoked, the highest percentage in patients suffering from depression [37]. In a large UK smoking cessation cohort, a history of mental health disorder was present in 4% of participants, and 25% were receiving antidepressant therapy [24]. In the present study, 10.4% of participants had depression, and 5.7% had other mental disorders. The results of the present study confirm previous findings showing that patients with mental disorders including depression can successfully quit smoking with the aid of smoking cessation pharmacotherapy [18].

Strengths and Limitations

This is the largest observational study of the efficacy and safety of varenicline for smoking cessation. Strengths of this study are that it included patients with multiple comorbidities who were not included in the initial clinical trials of smoking cessation, and the low level of support received by the patients adds to the generalizability of the results. Several limitations have also to be acknowledged. We do not have biologic confirmation of smoking status, for example through measurement of carbon monoxide concentration in exhaled breath. However, self-report has been shown to reliably capture smoking status [38, 39]. Furthermore, follow-up was only 12 weeks, whereas a follow-up of 56 weeks would have been superior and is standard in RCTs [27]. The comorbidity as reported by the practices was not confirmed by an independent investigator. However, we have no reason to assume that the provided data on comorbidity are not valid.

Although the present study sample comprises participating practices which are likely highly motivated to assess patients for smoking cessation, it is unlikely that the patient population in this study differs from other practices. Selection bias of patients highly motivated to quit smoking is possible, but motivation to quit is considered a prerequisite for all pharmacologic intervention for this addiction. It should also be acknowledged that in our study, patients had to pay for the medication themselves, and this may limit extrapolation of our findings to other healthcare settings.

Conclusions

The results of this study demonstrate that varenicline is an effective and well-tolerated smoking cessation therapy when used in ambulatory care including patients with frequent comorbidities. The quit rates observed in this real-life study in patients treated with varenicline were higher than in RCTs; however, inter-study comparisons should be interpreted with caution. Future studies should assess the long-term effectiveness of varenicline beyond 12 weeks.

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Disclosure Statement

S.A. received lecture honoraria from Pfizer and participated in a previous Pfizer study on smoking cessation. J.F.C. has no conflicts of interest. R.D. and S.P. are employees of Pfizer. K.M. has received research grants from Alkermes, Lundbeck, McNeil, MundiPharma and Merck Sharp & Dohme. He was a consultant to Alkermes and Desitin and is currently a consultant to Lundbeck and Pfizer.

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