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ORIGINAL RESEARCH ARTICLE

Experiences with the Use of Varenicline in Daily Practice in the Netherlands: A Prospective, Observational Cohort Study

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Abstract

Background Although a concise overview of adverse drug reactions (ADRs) to varenicline is available, little is known about the use of varenicline in daily practice and time-related information about ADRs.

Objective The aim of this study was to gain insight in the safety and use of varenicline in daily practice.

Methods A prospective, observational, non-interventional cohort study was performed. The study population was defined as first-time users recruited through participating pharmacies between 1 December 2008 and 31 March 2012. Patients could sign up for the study on a dedicated website. Web-based questionnaires were sent after 1, 2 and 6 weeks, 3 months and 4 months after patients started to use varenicline. Questions were asked about drug use and ADRs. Information about the ADR, its seriousness and the action taken when experiencing an ADR was gathered.

Results A total of 1,418 patients signed up for the study. The response rates for the various questionnaires varied from 31.3 to 62.5 %. At least one ADR was reported by 58.8 % of the patients. The most frequently reported ADRs were nausea (30.8 %), abdominal pain (11.2 %) and abnormal dreaming (10.4 %). Most patients did not stop taking varenicline when they experienced these ADRs. The median latency times for ADRs reported more than 50 times were 3–7 days, with an exception for depressed mood, which had a latency time of 10 days.

Conclusion This prospective cohort study has given insight into latency time and action taken with varenicline when ADRs occur during treatment with varenicline in daily practice. It confirms the ADR pattern detected prior to marketing of the drug.

Key Points

Nausea, abdominal pain and abnormal dreaming are the most frequently experienced adverse drug reactions in patients using varenicline

Most patients do not stop taking varenicline when they have adverse drug reactions

In this study, the median latency times for nausea, abdominal pain and abnormal dreaming were 3–7 days, and the median latency time for depressed mood was 10 days

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1 Background

When drugs are approved for marketing, their benefits must outweigh the impact of possible adverse drug reactions (ADRs). Although, at the time of marketing, the majority of frequently occurring ADRs are known and are

mentioned in the Summary of Product Characteristics (SmPC), little is known about the use of drugs in daily practice and the occurrence of rare ADRs over time.

In the Netherlands, the Pharmacovigilance Centre Lareb is responsible for collecting and analysing ADR reports through a spontaneous reporting system. Both healthcare professionals and consumers can report possible ADRs. In this way, signals of hitherto unknown ADRs can be detected, which may lead to regulatory actions such as amendment of the SmPC or, in exceptional cases, to withdrawal of the drug from the market [1]. However, because of the relatively small number of reports per association, the spontaneous reporting system is less valuable for gaining in-depth knowledge about ADRs and the circumstances in which they occur.

Especially for drugs that are new chemical entities, additional information is needed about their ADRs, since this information is still limited because of the relatively small size and homogenous population of the pre-marketing trials. In 2006, the Lareb Intensive Monitoring programme (LIM) was started in the Netherlands as a complement to the spontaneous reporting system. With this web-based system, it is possible to follow users of a specific drug over time and obtain insight into their drug use and possible ADRs in a prospective, observational, non-interventional manner [2]. In comparison with clinical trials, the strength of an intensive monitoring system is that all users can be included. Since this methodology uses patient-reported outcomes, the data reflect the information about possible ADRs from the patients' perspective. In addition, the incidence of ADRs can be estimated in the participating group [1].

Drugs that have previously been monitored by LIM are pregabaline [2] and duloxetine [3]. Currently, the antidiabetic drugs are being monitored. In 2008, Lareb started to monitor the safety of varenicline with LIM. Varenicline is registered in the European Union for smoking cessation in adults. Varenicline is an alfa-4-beta-2 ($\alpha 4\beta 2$) partial agonist.

Nicotine is an agonist of the alfa-4-beta-2 receptor. Activation of this receptor activates the mesolimbic dopamine system (the 'reward system') and increases the probability of a certain behaviour—in this instance, smoking. Varenicline has higher affinity for the receptor but lower intrinsic efficacy than nicotine; therefore, the 'reward system' is less activated and hence the desire for smoking is reduced [4].

During the first week of use, the patient's dosage is titrated from 0.5 to 1 mg daily while the patient continues to smoke. At the end of week 1, the patient has to stop smoking. From day 8 until the end of the treatment (mostly after 3 months), 2 mg of varenicline daily is used [4].

The efficacy and safety of varenicline were investigated in clinical trials prior to its registration [4]. In an observational cohort study conducted in the UK, the post-marketing safety of varenicline was studied, using a modified prescription-event monitoring (PEM) methodology. A total of 2,682 patients were identified from dispensed prescriptions issued by general practitioners (GPs) from December 2006. Among other variables, data on all events considered to be ADRs to varenicline were collected from GPs during the treatment course and 1 month after stopping varenicline. Nausea and vomiting were the most frequent clinical reasons for stopping varenicline and the most frequently reported suspected ADRs associated with varenicline. The most frequently reported psychiatric events were sleep disorders, anxiety, depression, abnormal dreaming and mood changes [5].

In a prospective cohort study, the effectiveness and safety of varenicline in comparison with nicotine replacement for smoking cessation among patients with mental illness was evaluated in a clinical setting. A total of 412 patients received routine care with either nicotine replacement therapy or varenicline. The extent of verified abstinence or withdrawal symptoms, as well as the incidence and severity of ADRs, were compared. The investigators found a higher incidence of ADRs among those taking varenicline, but these were tolerated by most smokers [6].

The aim of this study was to gain insight into the safety and use of varenicline in daily practice. Our study adds knowledge to the existing literature, since 'real-life' data from patients using varenicline were used instead of data gathered through GPs or in a clinical setting. Information about varenicline and the experiences with possible ADRs can be used for more dedicated advice to patients who start using this drug.

2 Methods

A prospective, observational, non-interventional cohort study was conducted, in which patients were sent web-based questionnaires at regular time intervals.

2.1 Study Population

The study population was defined as first-time users of varenicline in the period between 1 December 2008 and 31 March 2012, who collected their prescription in one of the 1,296 Dutch pharmacies, corresponding to 65.4 % of all Dutch pharmacies, who registered for the Intensive Monitoring programme.

First-time users of varenicline were defined as patients who had not collected a prescription for varenicline in

the previous 12 months, using the first-prescription signal in that particular pharmacy. Patients in the Netherlands use only one pharmacy, which makes it possible to identify first-time users. When the first-prescription signal for varenicline is shown, a special LIM signal is shown as well, which instructs the pharmacist to inform the patient about the study and give him/her an information leaflet. This leaflet contains a specific code with which the patient can sign up for the study via a specific website.

2.2 Inclusion and Exclusion Criteria

All first-time users of varenicline in the LIM participating pharmacies were invited to participate in the study. Patients who had no access to the internet, or who had no one else available to complete the questionnaires on the internet, were not able to participate in the study. Upon registration, patients were asked to specify the date on which they started using varenicline. Patients who had started using varenicline more than 1 month earlier were excluded from the study.

2.3 Questionnaires

Upon registration, information was sought regarding patient characteristics (sex, birth date, weight and height), the use of varenicline (start date, dosage and indication) and any concomitant medication being used.

After registration, patients received five questionnaires by e-mail 1 week, 2 weeks, 6 weeks, 3 months and 4 months after they started using varenicline. This study period was chosen to cover the entire treatment duration of 3 months and one additional month to be able to capture withdrawal symptoms.

On the basis of an open list, patients were asked if they had experienced a possible ADR and, if so, a short description was requested. Also, information was gathered about the seriousness of the reaction, the start and stop dates, and the outcome of the reaction. For an overview of the questionnaire, see Table 1. The seriousness of the reaction was defined by the current criteria for seriousness, as defined by the Council for International Organizations of Medical Sciences (CIOMS) Working Party [7]. These include (prolonged) hospitalization, congenital abnormalities,

Table 1 Overview of the questions in the questionnaire

General questions
Confirmation of previously mentioned patient characteristics (e-mail address, age, sex)
Do you still use varenicline?
If yes: confirmation of the previously mentioned dosage and strength
If no: stop date, reasons for cessation (problem is resolved, drug does not work, occurrence of ADR, other reasons [with optional text field])
Confirmation of the previously mentioned concomitant medication (dosage, strength, start date, stop date)
Is there any new concomitant medication?
If yes: drug, start date, dosage, strength
ADR questions
If ADRs were previously mentioned: the following ADR(s) was/were mentioned earlier. Are they still current? [confirmation of the previous answers]
Have you experienced any new ADRs? If yes:
Short description of the ADR
Start date of the ADR
Has this ADR led to one of the following situations: congenital abnormality, disability, life-threatening reaction, hospitalization, death?
What is the outcome: recovering, recovered, not recovered, recovered with sequelae)?
If recovered: recovery date
Action after occurrence of the ADR (none, dose reduced with/without advice from doctor, drug withdrawal with/without advice from doctor)
Specific questions for the varenicline study
Did you read (part of) the patient leaflet?
How many cigarettes did you smoke?
For how long did you smoke?
On what date did you quit smoking?
Have you smoked since that date?
Have you had any of the following diseases: COPD, asthma, cardiac disorders, mood swings, depression with the use of any medication, psychiatric diseases?

ADR adverse drug reaction, *COPD* chronic obstructive pulmonary disease

life-threatening events and reactions that are disabling, and fatal reactions. Patients who stopped using varenicline during the study period were asked to give their reasons for stopping the drug. These patients were considered to have completed the study and were not invited to complete subsequent questionnaires.

If needed, a reminder of the questionnaire was sent after 5 days. If a patient did not fill in the questionnaire, he was considered lost to follow-up for that specific questionnaire. The patient was then invited to complete subsequent questionnaires.

2.4 Data Collection

All data were stored in an Oracle database. The reported indication and ADRs were coded by a qualified assessor using the Medical Dictionary for Regulatory Activities (MedDRA) terminology [8]. The concomitant medication was coded using the Dutch drug dictionary (Z-Index [9]). If an ADR was reported as serious by the patient and was also considered serious according to the CIOMS criteria [7] by the assessor, a copy of the report was stored in the national database of the Netherlands Pharmacovigilance Centre Lareb and handled in the same way as all other spontaneous reports of serious ADRs. A flow diagram of the Lareb Intensive Monitoring system can be found in Fig. 1.

To check if the study population was a reflection of all varenicline users in the Netherlands, the results were compared with information from the Dutch Foundation for Pharmaceutical Statistics (SFK). This foundation collects prescription data from 94.5 % of the community pharmacies in the Netherlands [10].

2.5 Data Analysis

Data extraction was performed using Microsoft Access 2010. Descriptive analysis was performed for the patient characteristics. Response rates were calculated. The varenicline population was compared with the total population of varenicline users in the Netherlands for sex and age, using the SFK data [10]. Patients whose ages were unspecified were excluded from the dataset. Age and sex were compared using a χ^2 test (for sex) and a t test (for age). Statistical significance was based on $p < 0.05$. The statistical software package SPSS version 17.0 (IBM SPSS Statistics Microsite, Chicago, IL, USA) was used for analysis purposes.

The number of patients reporting an ADR was calculated. When a patient reported the same reaction in several questionnaires, this reaction was counted only once for calculation of the incidence of ADRs. The reported ADRs were classified as 'labelled' or 'not labelled', on the basis of the current SmPC of varenicline [4]. Reported ADRs not labelled in the SmPC or those of interest were analysed on a case-by-case basis. The reported latency times were calculated, as well as the number of patients who stopped using varenicline. Since the latency time was not normally distributed, the median latency time was used instead of the mean latency time. The number of patients who mentioned an ADR in the separate questionnaires was determined, as well as the action taken with the drug after experiencing an ADR, and the outcome when the patient stopped or continued the use of varenicline.

3 Results

3.1 Response Rates

Between 1 December 2008 and 31 March 2012, 1,418 patients signed up for participation in the varenicline study. Of those, 1,182 (83.4 %) filled in at least one questionnaire. Of the patients who were still using varenicline at the time when they completed the subsequent questionnaire, the response rates for the first up to the fifth questionnaire were 46.9, 61.6, 62.5, 49.6 and 31.3 %, respectively. An overview of all response rates can be found in Fig. 2.

3.2 Patient Characteristics

More than half of the patients (n = 860, 60.6 %) were female. The average age was 49.7 years (standard deviation [SD] 10.9, range 15–87 years). One patient was under the age of 18 years. Smoking cessation therapy was the most frequently reported indication (98.3 %). Other

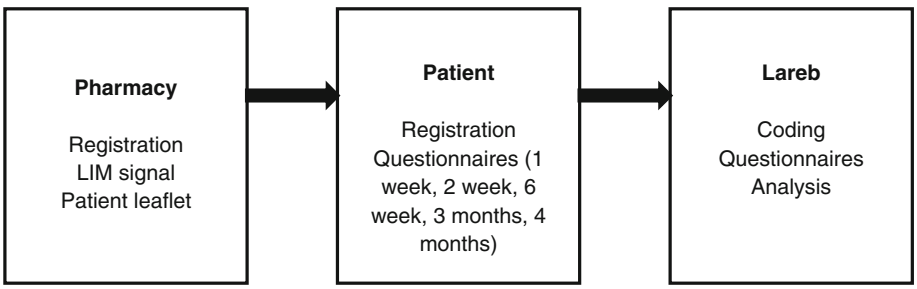

Fig. 1 Flow diagram of the Lareb Intensive Monitoring (LIM) system

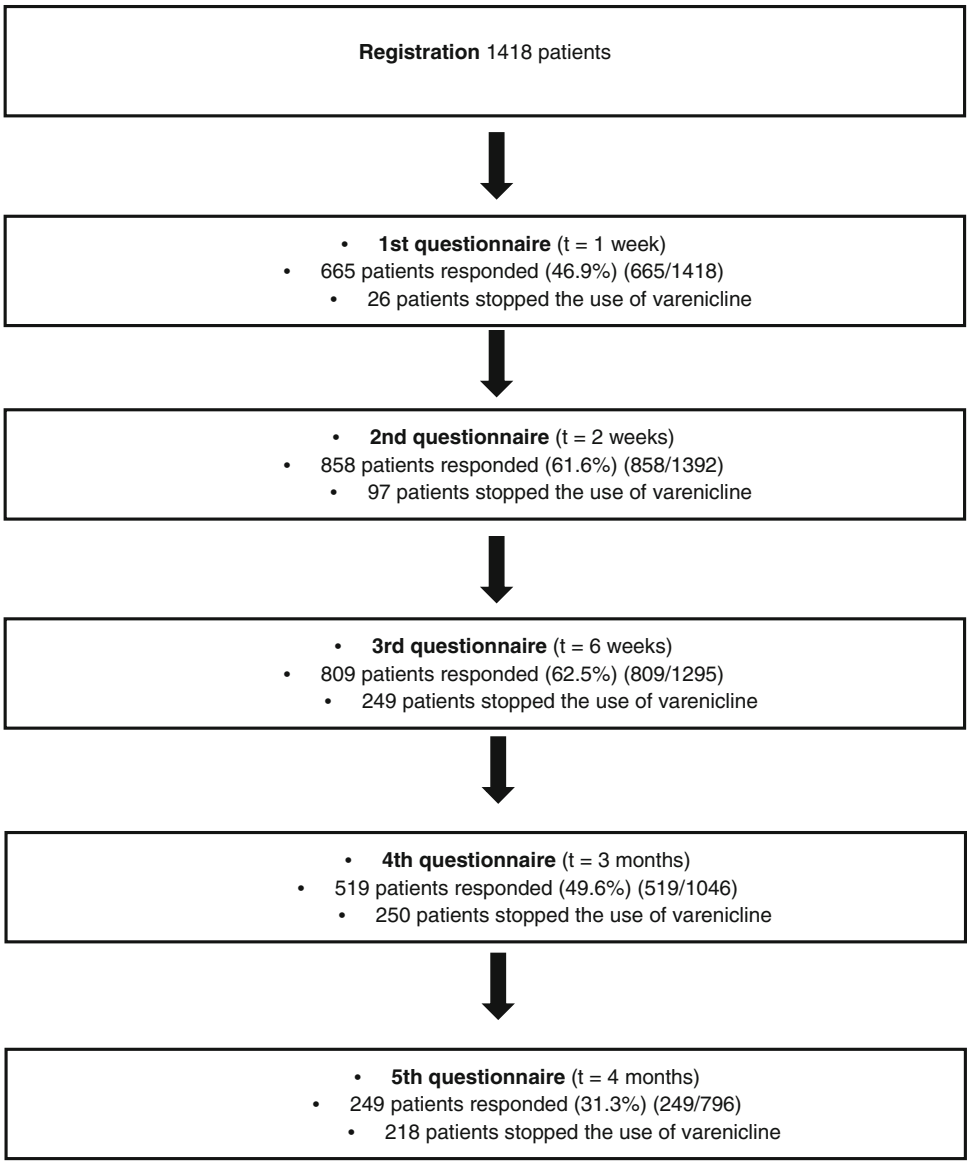

Fig. 2 Response rate per questionnaire

mentioned indications all related to the negative impact that smoking has on health.

The patients had been smoking for an average of 31 years (SD 11.3, range 1–65, median 32 years) and approximately 22 cigarettes daily (SD 8.9, range 2–76, median 20 cigarettes).

Concomitant medication was used by 675 (47.6 %) of the included patients; the most commonly used medications (13.3 %) were sympathomimetic drugs for inhalation (short- and long-acting beta-agonists). Also, proton pump inhibitors (11.9 %), statins (11.3 %) and thrombocyte aggregation inhibitors (10.5 %) were frequently used.

In the Netherlands, 94.5 % of all pharmacies collaborate with the SFK [10]. During the inclusion period, there were 155,024 first prescriptions of varenicline issued by these pharmacies. This population included a lower proportion of female patients (51.1 %) and was younger (48.4 years) than the studied population. These differences were statistically significant ($p = 0.013$ for age and $p < 0.001$ for sex).

3.3 Adverse Drug Reactions

At least one ADR was reported by 834 patients (58.8 %), who reported a total of 2,271 individual ADRs. The most frequently reported ADRs were nausea (30.8 %), abdominal pain (11.2 %) and abnormal dreaming (10.4 %), which are mentioned in the SmPC of varenicline [4]. An overview of reactions reported more than 50 times is shown in Table 2. All 2,271 individual ADRs are shown in the Electronic Supplementary Material (ESM).

One month after varenicline treatment was stopped, the fifth questionnaire was sent. No drug withdrawal reactions were reported. Among the reported ADRs, there were no ADRs that needed extra attention or indicated a new signal after case-by-case analysis.

Serious ADRs, according to the CIOMS criteria, were reported by three patients. In two of these cases (one male and one female), depression was reported as a serious, life-threatening reaction, one of which involved suicidal tendency. Both patients stopped using varenicline. The male patient, who had suicidal tendency and depression, had a medical history of mood swings and depression, and he recovered from the reported ADRs after drug withdrawal. The female patient was recovering at the time of the report. The third report concerned a female patient with chest pain, which necessitated hospitalization. The patient was treated with a sublingual spray. Her medical history included a myocardial infarction 4 months prior to the ADR.

Of the ADRs shown in Table 2, the reported median latency times were all between 3 and 7 days, except for depressed mood, which had a median latency time of 10 days (Table 3). During the questionnaire period of the study, the percentage of patients who experienced an ADR increased for some of the most frequently reported ADRs (nausea, abdominal pain, abnormal dreaming, sleep disorders) but remained the same for other ADRs, such as constipation and dry mouth. The spectra between the three questionnaires were broadly the same with respect to the reported possible ADRs (Table 4).

During the prescribed treatment with varenicline for 3 months, 622 patients (43.9 %) stopped using varenicline.

Table 2 Adverse drug reactions (ADRs) reported more than 50 times in this study

ADR	Reported incidence	
	In this study [% (*n*)][a]	In the SmPC [%]
Nausea	30.8 (437)	28.6
Abdominal pain	11.2 (159)	0.001–0.01
Abnormal dreaming	10.4 (147)	>10
Headache	9.9 (141)	>10
Sleep disorder	8.3 (118)	0.1–1
Dizziness	7.4 (105)	1–10
Fatigue	7.3 (104)	1–10
Depressed mood	5.5 (78)	0.1–1
Insomnia	5.3 (75)	>10
Flatulence	4.2 (59)	1–10
Constipation	3.7 (53)	>10
Dry mouth	3.7 (52)	0.01–0.1

SmPC Summary of Product Characteristics

[a] Where a patient reported the ADR in multiple questionnaires, this was counted as one report

Table 3 Reported adverse drug reactions (ADRs) and their median latency times

ADR	Latency time	
	Median [days]	Range [days]
Nausea	4	0–88
Abdominal pain	7	0–83
Abnormal dreaming	5	0–46
Headache	4	0–49
Sleep disorder	7	0–77
Dizziness	4	0–76
Fatigue	3	0–64
Depressed mood	10	0–81
Insomnia	5	0–46
Flatulence	6	0–32
Constipation	7	0–35
Dry mouth	3	0–29

The reasons given for stopping varenicline were the occurrence of ADRs (42.2 %), quitting smoking successfully (21.5 %), ineffectiveness of varenicline (5.1 %) and other unspecified reasons [multiple answers were possible] (40.0 %). The proportions of patients who stopped using varenicline because the smoking cessation therapy was successful were 0.0, 11.3, 20.1 and 29.2 % in questionnaires 1–4, respectively. One month after the prescribed treatment for 3 months, 37.2 % of the patients mentioned that they had stopped using varenicline because they had successfully quit smoking. The proportions of patients who stopped using varenicline because of ADRs were 80.8, 43.3, 48.2, 32.0 and 17.0 % in questionnaires 1–5, respectively.

However, for the three most frequently reported ADRs (nausea, abdominal pain and abnormal dreaming), most patients took no action after experiencing the ADR (Table 5). When the patients decided to stop using varenicline, the majority of them had recovered or were recovering at the time when they filled in the next questionnaire.

4 Discussion

4.1 Patient Characteristics

The results of this study provide insight into the occurrence of possible ADRs and into the use of varenicline in daily practice. To our knowledge, this study is the first prospective cohort study that has collected data directly from patients in the post-marketing setting. The average age in the studied population was 49.7 years and differed significantly from the SFK data concerning the general population (48.4 years). However, the absolute difference in age

Table 4 Reported adverse drug reactions (ADRs) over time

ADR	Questionnaire 1, $t = 1$ week [% (n)][a]	Questionnaire 3, $t = 6$ weeks [% (n)][a]	Questionnaire 5, $t = 4$ months [% (n)][a]
Nausea	38.9 (259)	42.6 (345)	43.0 (107)
Abdominal pain	5.4 (36)	9.1 (74)	11.2 (28)
Abnormal dreaming	12.0 (80)	14.6 (118)	15.8 (39)
Headache	13.1 (87)	13.0 (105)	10.8 (27)
Sleep disorder	9.9 (66)	12.6 (102)	18.9 (47)
Dizziness	9.6 (64)	10.1 (82)	10.8 (27)
Fatigue	9.5 (63)	9.9 (80)	7.2 (18)
Depressed mood	5.3 (35)	7.3 (59)	6.8 (17)
Insomnia	6.0 (40)	8.0 (65)	6.8 (17)
Flatulence	5.1 (34)	5.9 (48)	7.2 (18)
Constipation	4.4 (29)	5.8 (47)	5.6 (14)
Dry mouth	5.4 (36)	4.4 (36)	5.6 (14)

[a] The percentages were calculated on the basis of the response rate in each questionnaire

Table 5 Action taken with the drug after experiencing an adverse drug reaction (ADR), and outcome of the reaction, depending on whether the drug was withdrawn or not

Action or outcome	Nausea	Abdominal pain	Abnormal dreaming
Action taken with the drug after experiencing an ADR [% (n)][a,b]			
No action	49.5 (319)	56.0 (98)	59.4 (107)
Dose reduced after consultation	6.8 (44)	11.4 (20)	8.3 (15)
Drug withdrawn after consultation	5.4 (35)	4.0 (7)	4.4 (8)
Dose reduced on patient's own initiative	9.1 (59)	5.7 (10)	6.7 (12)
Drug withdrawn on patient's own initiative	12.6 (81)	8.6 (15)	13.3 (24)
Other action	16.6 (107)	14.3 (25)	7.8 (14)
Outcome of the ADR after stopping varenicline use [% (n)][a,b]			
Recovered after stopping	41.9 (90)	40.0 (2)	48.6 (35)
Recovering after stopping	18.1 (39)	40.0 (2)	18.0 (13)
Did not recover after stopping	27.9 (60)	20.0 (1)	27.8 (20)
Unknown after stopping	12.1 (26)	0.0 (0)	5.6 (4)
Outcome of the ADR after continuing varenicline use [% (n)][a,b]			
Recovered after continuing	19.6 (100)	26.9 (7)	17.7 (27)
Recovering after continuing	30.4 (155)	42.3 (11)	23.7 (36)
Did not recover after continuing	48.4 (247)	30.8 (8)	57.9 (88)
Unknown after continuing	1.6 (8)	0.0 (0)	0.7 (1)

[a] Because not all patients answered all questions, the numbers of patients listed for the different questions are not always constant

[b] Because more answers could be chosen in subsequent questionnaires, the total number of answers can exceed the number of patients

was small and probably not clinically relevant. With regard to sex, the difference was more prominent: 60.6 % of patients in this study were female, versus 51.1 % of varenicline users in the Netherlands. It is possible that women are generally more likely to participate in this type of study.

Data on weight and height were not necessarily reported by the patients, because a free text field was used. As a consequence, it was not possible to use these data in the analysis. In the future, adaptations will be made in the system to obtain more reliable data on weight and height.

The Central Bureau for Statistics (CBS) in the Netherlands has reported that people smoke, on average, for 15–20 years before quitting. The average number of cigarettes consumed each day is 12, but 30 % of smokers consume more than 20 cigarettes daily [11]. The patients included in our study had smoked for an average of 31 years and consumed approximately 22 cigarettes daily. It is most likely that the patients in this study were heavier smokers who had already tried more conventional methods in order to quit smoking.

4.2 Response Rates

Altruism is the main motive of patients for participation in an intensive monitoring study [12]. A previous study

showed that experiencing ADRs in the past or negative experiences were not important motives for patients to participate [12]. In the current study, 83.4 % of the patients filled in at least one questionnaire. The response rates in the other studies included in this intensive monitoring programme were 76.5 % in a study of pregabaline [2] and 76.1 % in a study of duloxetine [3]. The reason for this relatively high response rate remains unknown, but it is possible that patients make a well-considered decision to use varenicline because the more regular methods for quitting smoking have not worked so far. During most of the study period, the cost of varenicline was not reimbursed by health insurance, and patients had to pay for the varenicline themselves. It is possible that these patients were more motivated to participate in a study about their drug use and ADRs.

The response rates were highest for questionnaires 2 and 3 (after 1 and 5 weeks of varenicline use), and 58.8 % of the patients mentioned that they had experienced at least one ADR. It is to be expected that patients who experienced an ADR with the use of varenicline would be willing to complete the questionnaires.

4.3 Adverse Drug Reactions

Although a causality assessment was not performed, we decided not to use the term 'adverse events' but to use the term 'possible ADRs' because patients were asked only to report symptoms that they believed were associated with the use of varenicline. Most of the reported ADRs had a median latency time of 3–7 days, and they were mentioned with the same overall frequency as in the SmPC of varenicline [4]. Smoking cessation symptoms mostly started within the first 3 days after the patients stopped smoking, and they subsided over the next 3 or 4 weeks [13]. Because the median time of the first occurrence of ADRs is before the stopping smoking date on day 7, the reported symptoms seemed to be ADRs. The fact that the reported ADRs did not subside during treatment with varenicline and that patients were recovering or recovered after stopping varenicline strengthens this hypothesis.

In 2008, varenicline was found to be associated with depression and suicidal thoughts, and the SmPC was updated with this information [14]. In our study, a total of 504 psychiatric ADRs were reported, and depressed mood (reported 78 times) was reported with a higher incidence than was mentioned in the SmPC of varenicline. The only other psychiatric ADR that was reported more than 10 times and is not shown in Table 2 was mood swings (reported 13 times). Other psychiatric symptoms were reported only a few times—for example, agitation and anxiety (both reported 6 times), panic attacks (reported 4 times) and aggression (reported 3 times). Two patients reported serious depression (one with suicidal tendency) with the use of varenicline. However, there is no evidence of an increased risk of suicidal behaviour in patients using varenicline, compared with the use of nicotine replacement therapy [15]. Besides depressed mood, the number of reports on psychiatric ADRs was small, compared with the incidence rates mentioned in the SmPC of varenicline [4].

4.4 Strengths and Limitations of the Study

Spontaneous reporting systems and intensive monitoring programmes both detect ADRs in daily use. In this intensive monitoring study, the use of a drug by patients who were prescribed that drug for the first time was monitored closely. Because the patients were asked for information on ADRs at specific points in time, other information became available, whereas in a spontaneous reporting system, patients or healthcare professionals report information on ADRs only if they are actually experienced. In this intensive monitoring study, patients who did not experience an ADR were also monitored, yielding another type of information beyond that obtained by spontaneous reporting.

In future studies, we can focus on more differentiated questionnaires with conditional logic, which can be used to obtain more specific information about ADRs in an efficient way.

Web-based intensive monitoring using patients as a source of information has strengths and limitations. The pharmacies played an important role in informing the patients about the existence of this study, and thus they facilitated the inclusion of patients in the study. Since the exact number of pharmacies participating in the varenicline study was, unfortunately, unknown, and the number of patients obtaining a first prescription for varenicline in each particular pharmacy was lacking, the actual proportion of patients included in the study cannot be determined. In future studies, it would be interesting to investigate how many pharmacies indeed approach patients for study participation. A previous study in the LIM database concluded that patients are willing to participate in LIM when they are informed and invited by the pharmacy [16]. The number of actual inclusions was used to calculate the response rates in this study. It is possible that the selection of the study population did not reflect the real-life situations among smokers. Selection bias could not completely be ruled out.

The patient's role in pharmacovigilance is increasing. New legislation [17] states that both marketing authorization holders and national pharmacovigilance centres should accept reports from patients. This varenicline study used patients as the most important source of information. Since the patients completed several questionnaires over a period of time, recall bias would be limited because every questionnaire asked about the occurrence of ADRs. It may be

bothersome for patients to make a proper assessment of the causal relationship between varenicline and the possible ADR they experienced, and medical confirmation may be needed in cases of syndromes or complex diagnoses. If needed, the treating physician could be contacted via the patient.

5 Conclusion

This is the first prospective cohort study in the Netherlands that has focused on the use of varenicline in daily use and collected data directly from patients. It confirms the previous pre-marketing detection of ADRs. The median reported latency times were mostly 3–7 days, except for depressed mood, which had a latency time of 10 days. The reported spectrum of ADRs in the various questionnaires was comparable over time. After experiencing nausea, abdominal pain or abnormal dreaming as possible ADRs, patients usually do not stop using varenicline.

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