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ORIGINAL RESEARCH ARTICLE

Neuropsychiatric Events with Varenicline: a Modified Prescription-Event Monitoring Study in General Practice in England

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Abstract

Background Varenicline (Champix®), launched in the UK in December 2006, is indicated for the treatment of smoking cessation in adults (≥18 years of age). In 2008, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK issued a warning suggesting that varenicline was associated with disparate neuropsychiatric symptoms, including depression, suicidal thoughts and behaviour. In response to this regulatory warning, the Drug Safety Research Unit conducted a modified prescription-event monitoring (M-PEM) study to monitor the safety of varenicline.

Objective The aim of this study was to estimate the incidence and examine the pattern of neuropsychiatric events reported to general practitioners (GPs) in England during the immediate postmarketing period for varenicline.

Methods A postmarketing surveillance study was conducted using the observational cohort technique of M-PEM. Patients were identified from dispensed prescriptions issued by primary care physicians between December 2006 and March 2007. Data on exposure, previous history of psychiatric illness and events reported during and after treatment were collected from questionnaires. In order to determine whether hazards for neuropsychiatric events of interest (depression, anxiety, aggression, suicidal ideation, non-fatal self-harm) were non-constant over time (which could indicate a possible association with the drug), the pattern of events was examined by plotting the smoothed hazard function estimate and then fitting a Weibull model. The Weibull model shape parameter (β) and 95 % confidence interval were used as a test for a non-constant hazard function (where a value of 1 indicates a constant hazard over time). In addition to this analysis, the difference in incidence densities (IDs) between month 1 and months 2–3 were calculated and compared.

Results The cohort comprised of 12,159 patients (median age 47 years [interquartile range 19]; 56.9 % [$n = 6924$ female]). The number of events reported during treatment, reason for stopping, adverse drug reactions (ADRs), and the p-value for the Weibull shape parameter were as follows: depression ($n = 94$; 42; 19; $p = 0.144$); anxiety ($n = 94$; 49; 9; $p = 0.009$); aggression ($n = 7$; 4; 2; $p = 0.465$); suicidal ideation ($n = 8$; 4; 1; $p = 0.989$) and non-fatal self-harm ($n = 5$; 1; 0; $p = 0.771$). No differences in the IDs between months 1 and months 2–3 were found for any of the events.

Conclusion Whilst between 7 and 17 % of neuropsychiatric events were attributed to the drug by GPs and approximately 20–50 % were given as reasons for stopping, no signal was raised using the ID differences approach, and only anxiety was flagged as a potential signal for an ADR using the Weibull model. The signal for anxiety requires further evaluation to determine whether the drug plays a part in the development of anxiety or whether it is a withdrawal symptom caused by smoking cessation. Analysis methods will lack power when the numbers of events are low even when a large number of participants are included in the study.

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1 Introduction

Varenicline (Champix®), launched in the UK in December 2006, is indicated for the treatment of smoking cessation in adults (≥18 years of age) [1].

It has been estimated that more than one-third of the world's population over the age of 15 years smokes. Smoking can cause cancer, heart disease, pulmonary disease and premature death, making it the leading cause of preventable death worldwide. The availability of safe and effective therapies to aid smoking cessation is therefore necessary [2].

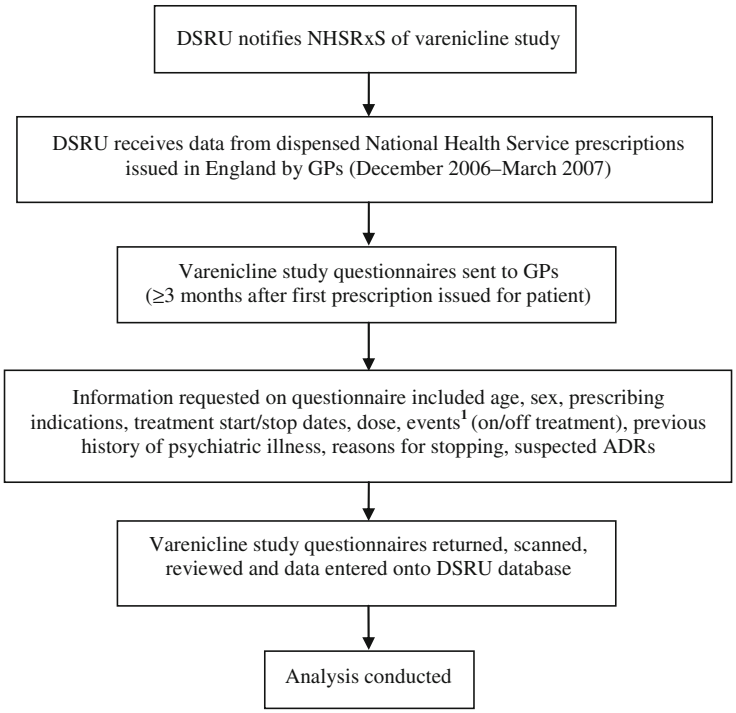
Varenicline tartrate binds with subnanomolar affinity and high selectivity to the α4β2 neuronal nicotinic acetylcholine receptor, where it acts as a partial agonist [3]. When nicotine binds to this receptor, dopamine is released in the nucleus accumbens, the reward centre of the brain thought to be responsible for the reinforcing or addictive properties of nicotine [4]. As a partial agonist with higher affinity and less functional effect than nicotine, the reward properties of nicotine may be diminished and therefore the satisfaction gained from smoking may be reduced. This action may help facilitate the success of a cessation attempt. Furthermore, the partial agonistic activity of varenicline may cause relief from the withdrawal and craving symptoms experienced during smoking cessation [3].

Varenicline is reported to be well tolerated, with nausea being the most commonly reported adverse event during clinical trials [3]. Adverse events were reported to generally occur within the first week of therapy, were mild to moderate in severity, and the incidence of these reactions was not affected by sex, age or race [3]. Other commonly reported adverse events included headache, abnormal dreams and insomnia.

In 2008, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK issued a warning that depression had been reported in patients taking varenicline for smoking cessation, which may include suicidal thoughts or behaviour [5]. In addition, the US FDA issued a warning that varenicline may be associated with serious neuropsychiatric adverse effects. Patients with a previous history of psychiatric disorders, major depressive disorders, psychosis, eating disorders, bipolar disorder or panic disorders were excluded from premarketing clinical trials as well as patients who were taking antidepressants, antipsychotics, anticonvulsants or mood stabilizers. Therefore, the extent of psychiatric illness associated with varenicline is difficult to determine [6]. An analysis of safety results concerning reported psychiatric disorders in ten phase II, III and IV placebo-controlled trials of varenicline showed that there was no difference in the incidence of psychiatric disorders (other than solely sleep disorders and disturbances) between patients treated with varenicline and placebo (10.7 % in the varenicline group vs. 9.7 % in the placebo group; risk ratio 1.02; 95 % confidence interval (CI) 0.86–1.22 [7]. There were no reported cases of suicidal ideation or behaviour in varenicline-treated patients in the ten placebo-controlled studies analysed. However, among an additional three trials that were excluded from the pooled analysis because of their open-label design, two cases of suicidal ideation and one completed suicide were reported in patients who had been treated with varenicline [7]. Results of an observational study by Harrison-Woolrych and Ashton [8], showed that psychiatric adverse events are commonly reported in patients taking varenicline. Approximately 3 % of patients experienced symptoms of depression and the majority of these cases appeared to have a causal association with varenicline.

Prescription-event monitoring (PEM) is a non-interventional observational methodology and typically collects demographic and event information on large inception cohorts of patients exposed to the medication of interest (frequently over 10,000). The prescribing decisions of general practitioners (GPs) are not influenced by this methodology. PEM studies are conducted on a national scale, and include patients prescribed newly marketed medicines in everyday clinical practice. Modified PEM (M-PEM) methodology can be employed to investigate a variety of drug-related issues; for example, additional information on targeted safety issues and subpopulations identified as being at particular risk [9]. During this M-PEM study, patient characteristics, including patient age, dose and pattern of cigarette use, were collected. In addition, information about medical history of psychiatric illness prior to starting treatment with varenicline was collected.

In 2007, the following warning was included in the varenicline Summary of Product Characteristics (SmPC): "Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal. In addition, smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness (e.g. depression)" [32]. The Committee for Medicinal Products for Human use (CHMP) reported that these symptoms had also been reported while attempting to quit smoking with Champix. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly [32]. As a direct response to this inclusion, the Drug Safety Research Unit (DSRU) conducted this M-PEM study. The objective of this study was to examine the pattern of neuropsychiatric events reported during an M-PEM study for varenicline.



1 In PEM an event is defined as 'any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter in the patient's notes'

Fig. 1 Overview of study design. *ADRs* adverse drug reactions, *DSRU* Drug Safety Research Unit, *GPs* general practitioners, *NHSRxS* National Health Service Prescription Services, *PEM* prescription-event monitoring

2 Methods

A retrospective observational study of a primary care inception cohort of patients exposed to varenicline was conducted in England, using the technique of M-PEM, described in more detail previously [9]. In recent years, in parallel with developments in pharmacoepidemiology and the requirements for risk management of medicines, a number of enhancements have been made to the process of PEM. The study questionnaire now facilitates a more targeted post-authorization safety study. The customized questionimprovement) in a concurrent illness, any suspectnaires used in M-PEM are designed to collect supplementary information in order to conduct a more detailed exploration of specific safety or drug utilization issues. In M-PEM, the underlying process remains the same as PEM [10]. The key steps are outlined in Fig. 1.

Between December 2006 and March 2007 all dispensed National Health Service (NHS) prescriptions for varenicline, issued by GPs in England, were identified, and data supplied in confidence to the DSRU by the NHS Prescription Services (NHSRxS) [a part of the NHS Business Services Authority]. Hospital prescriptions were not included in this study. At least 3 months after the initial prescription for each patient, varenicline study questionnaires were sent to prescribing GPs. Three months' observation was used because this is the recommended treatment period for varenicline [3]; however, for some patients, GPs may have reported information beyond 3 months, and this information is reported as the total number of events on treatment but not included in the analysis. Information on clinical events[1] (during course and 1 month after stopping varenicline), reasons for discontinuing if therapy was stopped, suspected adverse drug reactions (ADRs) to varenicline, drug utilization and patient demographic details were among the data collected. In addition, information about history of psychiatric illness prior to starting varenicline was requested. This study collected information on known confounding factors for psychiatric illness (age, sex, previous medical history of

[1] The term 'event', as used in PEM, is defined as "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's notes."

psychiatric illness [Y/N]); however, collection of risk factors for neuropsychiatric events was limited because of the retrospective methods of data collection and the length of the study. Information on patients for whom a varenicline study questionnaire was returned was included in this study regardless of the dose or frequency of administration of varenicline, and irrespective of whether any medicines were concurrently administered. Patients for whom any of the following applied were not included in the study: patient/doctor could not be identified (e.g. patient not registered or cannot be traced, doctor has moved), incorrectly identified (e.g. no record of drug having been prescribed) and insufficient data (e.g. questionnaire returned with no clinical information) [Fig. 2].

All reported events were entered onto the DSRU database using the DSRU event dictionary which has a hierarchical structure arranged by System Organ Class (SOC). The terminology used by the GP (doctor summary term) is grouped under a 'lower-level' term, which is subsequently grouped under a broader 'higher-level' term (HLT) and this is then linked to the respective SOC. An event was coded as a suspected ADR if the GP indicated on the varenicline study questionnaire that the event was attributable to the drug (this was in the GP's own estimation that the event was drug-related, and there was no validation of this attribution of causality). All returned varenicline study questionnaires were reviewed by a DSRU research fellow. GPs were offered £20 as reimbursement for administration costs for completing the study questionnaires. This study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the CIOMS in collaboration with the WHO (2002) [11].

3 Analysis

All analyses were pre-specified and conducted according to the study protocol. The neuropsychiatric events, which occurred during treatment with varenicline, included in this analysis are depression, anxiety, aggression, suicidal ideation and non-fatal self-harm (the non-fatal self-harm group includes events such as suicide attempt, overdose and self-injury). Analyses of event data for examining the pattern of time to onset of the selected events (for purposes of signal detection) included comparing event rates for selected time periods (incidence density [ID] differences) and also exploring the application of a parametric 'time-to-event' model (Weibull model) to test for non-constant hazards, which has been previously proposed as a signal detection method for cohort data [12]; the power of this method has also been quantified [13]. Specific details for each approach are provided in Sects. 3.1 and 3.2.

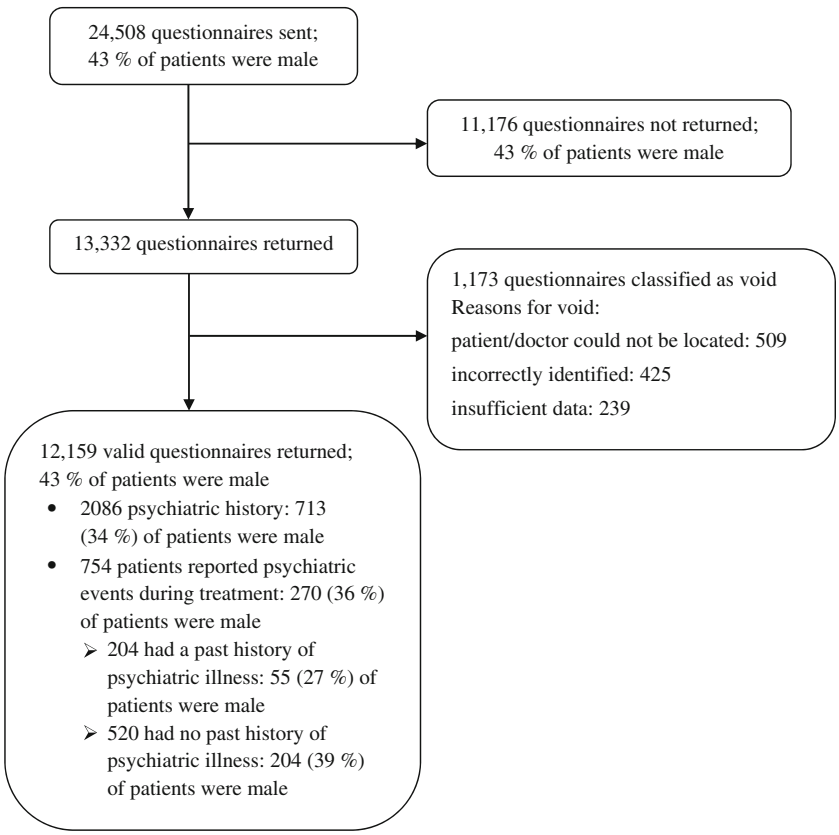


Fig. 2 Study flow diagram

3.1 Incidence Density (ID) Differences Analysis

IDs were calculated separately for events of depression, anxiety, aggression, suicidal ideation and non-fatal self-harm reported in the 3 months after starting treatment with varenicline. The denominator used in calculating IDs during treatment was the number of patient-months of treatment for the specific time period, e.g. the denominator for the first month (D_1) relates to the first month of treatment for individual patients. For each reported event, the difference between the IDs in the first month of treatment and the IDs for months 2–3 ($ID_1 - ID_{2-3}$) was calculated; this allowed the examination of the null hypothesis that the rate for the event was not increasing or decreasing between the two time periods. A CI (99 %) was applied to the difference in the rates between months as specified above.[2] If a patient experienced recurrent events, only the incident event was included in the analysis.

3.2 Time-to-Event Analysis

It is possible to explore the time of occurrence of an event by using statistical methods termed 'time-to-event' analysis. Using these methods, a hazard function can be estimated which shows the instantaneous risk of an event over time. In order to determine whether hazards for a selected number of events were non-constant, the baseline hazard function was modelled using the Weibull distribution, which has a shape parameter (β). When the shape parameter is equal to 1, the hazard is estimated to be constant over time; this null hypothesis is a similar principle to ID differences analysis but without the disadvantage of having to categorize the treatment time arbitrarily and therefore will have greater statistical power. If β is greater than 1 the hazard is increasing, if β is less than 1 the hazard is decreasing over time. A hazard function was regarded to be non-constant if the 95 % CI excluded the value 1. Smoothed estimates of the empirical hazard function were plotted using an epanechnikov kernel with a half width of 10 days (Stata version 11, StataCorp LP, College Station, TX, USA).

During this study, events of depression, anxiety, aggression, suicidal ideation and non-fatal self-harm (where event dates were provided) were modelled by plotting the estimated hazard function over the 3-month treatment period for this study. Patients who used varenicline for longer than 3 months were treated as censored after this period.

[2] This is the standard confidence interval used for signal detection procedures within the DSRU.

4 Results

4.1 Study Cohort

Of the 24,508 patients identified who had questionnaires posted to GPs, 12,159 were completed and returned, thus giving a response rate of 49.6 %. The cohort consisted of 5235 males (43.1 %) and 6924 females (56.9 %). The median age of the cohort was 47 years, with an interquartile range of 38–57 years, with no difference in age distribution between males and females. A history of psychiatric illness prior to starting varenicline was reported in 17.7 % of patients (2086/11772; where specified by the GP). After 3 months, 3118 (25.6 %) of the cohort were still using varenicline.

4.2 Events Reported Within the Psychiatric System Organ Class

A total of 913 incident psychiatric events were reported during treatment in 754 patients. Malaise/lassitude was the most common psychiatric event (HLT) reported ($n = 186$; 1.5 % of the cohort), followed by sleep disorder ($n = 132$; 1.1 % of the cohort).

Of the five events of interest, anxiety was the most frequent ($n = 129$); 103 of these occurred in the first 3 months of therapy (one patient had two events reported on the same day, and for ID calculations only one was counted) and 94 were included in the time-to-event analysis (see footnote b in Table 1). This was followed by depression ($n = 124$); 103 of these occurred in the first 3 months of therapy and 94 were included in the time-to-event analysis). There were 12 reports of aggression (9 of these occurred in the first 3 months of therapy and 7 were included in the time-to-event analysis); eight reports of suicidal ideation (all of these occurred in the first 3 months of therapy and were included in the time-to-event analysis); and five reports of non-fatal self-harm (all of these occurred in the first 3 months of therapy and were included in the time-to-event analysis).

Of the 754 patients, 204 patients (27 %) had a previous medical history of psychiatric illness, 520 patients (69 %) did not have a previous medical history of psychiatric illness prior to starting varenicline, and for the remaining patients ($n = 30$; 4 %) this information was either not known or not specified by the GP.

There were no events of completed suicide reported during treatment with varenicline.

4.3 IDs, Adverse Drug Reactions and Reasons for Stopping

The frequencies and IDs for month 1 compared with months 2–3 for the events of interest can be seen in

Table 1 Time-to-event analysis for specific events occurring during treatment in the first 3 months after starting varenicline

Event group term	HLT dictionary terms	LLT dictionary terms	Total number of events on treatment	No. of events reported on treatment in first 3 months after starting[a]	No. of events included in time-to-event analysis	Weibull Model		
						p	95 % CI	p-value
Depression	Depression	Depression	124	103	94[c]	1.145	0.955, 1.372	0.144
Anxiety	**Anxiety**	**Anxiety, Aerophagia**	**129**	**102[b]**	**94[c]**	**1.271[d]**	**1.062, 1.522**	**0.009**
Aggression	Aggression	Aggression	12	9	7[c]	1.280	0.661, 2.477	0.465
Suicidal ideation	Suicidal ideation	Suicidal ideation	8	8	8	0.996	0.532, 1.863	0.989
Non-fatal self-harm	Suicide, suicide attempt, drug overdose	Suicide attempt	1	1	5	1.124	0.512, 2.471	0.771
		Overdose 'other drug'	2	2				
	Self-injury	Overdose 'unknown drug'	1	1				
		Self-injury	1	1				

CI confidence interval, *HLT* higher-level term, *LLT* lower-level term

[a] Only events where event dates were specified were included in the analysis

[b] One patient had both events reported on the same day; for counts on incident events in the first 3 months, only one count was included

[c] Neuropsychiatric events occurring on day 0 were excluded because of reporting bias on day 0 as these are episodes of pre-existing disease rather than new occurrences: nine depression, eight anxiety and two aggression (there were no events reported on day 0 for suicidal ideation or non-fatal self-harm event group)

[d] The hazard for 'Anxiety' was seen to increase over the 3 months of the study (in bold text)

Table 2 Incidence density analysis for the neuropsychiatric events of interest

Higher-level term	N_1	$N_{2–3}$	ID_1	$ID_{2–3}$	$ID_1 - ID_{2–3}$	CI (min)	CI (max)	N_A (%)	ID_A	RFS	ADR
Depression	55	48	5.75	4.28	1.47	−1.08	4.02	124 (1.0)	4.36	42	19
Anxiety	43	60	4.50	5.35	−0.85	−3.36	1.65	129 (1.0)	4.53	49	9
Aggression	4	5	0.42	0.45	−0.03	−0.77	0.72	12 (0.1)	0.42	4	2
Suicidal ideation	3	5	0.31	0.45	−0.13	−0.83	0.56	8 (0.06)	0.28	4	1
Non-fatal self-harm	1	4	0.10	0.36	−0.25	−0.78	0.28	5 (0.04)	0.18	1	0

ADR adverse drug reaction, *CI* confidence interval, *D* denominator, ID_1 incidence density for each event during the first month of treatment (D = 9566 patient-months of treatment), $ID_{2–3}$ incidence density for each event during treatment months 2–3 (D = 11,223 patient-months of treatment), $ID_1 - ID_{2–3}$ arithmetic difference between ID_1 and $ID_{2–3}$; 99 % CI = 99 % CIs for $ID_1 - ID_{2–3}$, ID_A incidence density for each event for the total treatment period (D = 28,471 patient-months of treatment), N_1 total number of reports of each event during the first month of treatment, $N_{2–3}$ total number of reports of each event during treatment in months 2–3, N_A *(%)* total number of reports of each event during the total treatment period (proportion of total cohort), *RFS* reason for stopping varenicline (total no. reports = 10,925 in 9852 patients [81.0 % of cohort])

Table 2. No significant differences in IDs between the two time periods were found for any of the events; this can be seen by the 99 % CIs which all contain zero (the value of no difference).

There were 103 reports of depression during the 3-month observation period (including events where no event date was supplied by the GP); 42 of these were also recorded as reasons for stopping varenicline and 19 were reported as ADRs. There were also 102 incident reports of anxiety during the study (one patient had two events reported on the same day, only one was counted), 49 of which were recorded as reasons for stopping varenicline and 9 as ADRs. There were nine reports of aggression, four of which were recorded as reasons for stopping and two as ADRs, eight reports of suicidal ideation, four of which were recorded as reasons for stopping and one as an ADR, and five reports of non-fatal self-harm, one of which was as a reason for stopping varenicline (Table 2).

4.4 Time-to-Event Analysis

Table 1 lists the events and event groups of interest that were identified *a priori* and listed in the protocol.

Because of the ongoing nature of depressive, suicidal ideation and anxiety events, those reported on the prescription start date were considered as pre-existing ongoing episodes rather than 'new' episodes and were therefore not included in the estimate of the background hazard function.

The graphs of the smoothed empirical hazard function for each event can be seen in Figs. 3, 4, 5, 6, 7. The predicted hazard function using a Weibull model will be a monotonic function. Whilst it can be seen from the plot that the hazard function is not monotonic, the Weibull model is being utilized as a signal detection tool and the model fit is not of primary interest. The hazard function was modelled separately for five events (depression, anxiety, aggression, suicidal ideation and non-fatal self-harm). The resulting estimated model shape parameters and 95 % CIs can be seen in Table 1. No evidence was found that the hazard of depression, aggression, suicidal ideation and non-fatal self-harm were either significantly increasing or decreasing over the 3-month study period as assessed by the Weibull shape parameter at the 5 % level. However, the shape parameter for anxiety events was found to be significantly greater than the value 1 ($p = 0.009$), indicating the hazard of anxiety increased over the 3-month study period. This increase may indicate a possible association to varenicline treatment (Table 1).

5 Discussion

This study examined the 'real life' use of varenicline in 12,159 patients who were issued prescriptions by GPs in

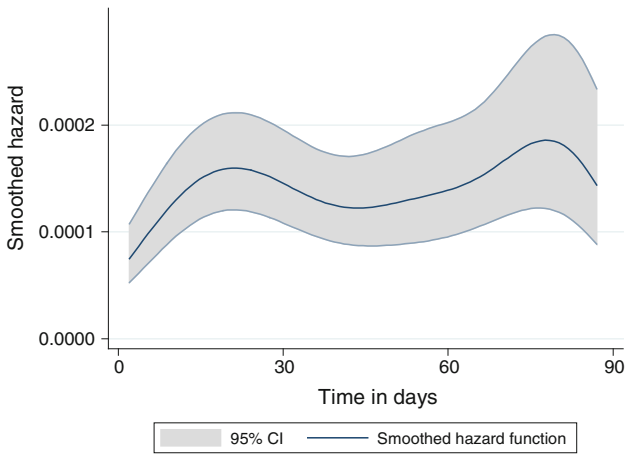


Fig. 3 Plot of smoothed hazard function with 95 % CIs for depression events occurring after starting treatment with varenicline

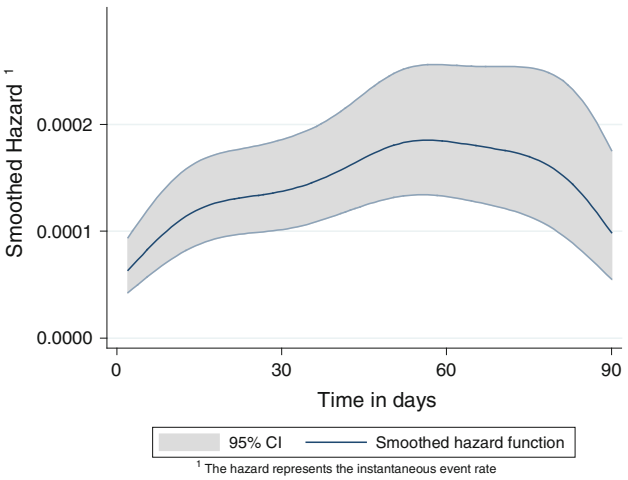


Fig. 4 Plot of smoothed hazard function with 95 % CIs for anxiety events occurring after starting treatment with varenicline

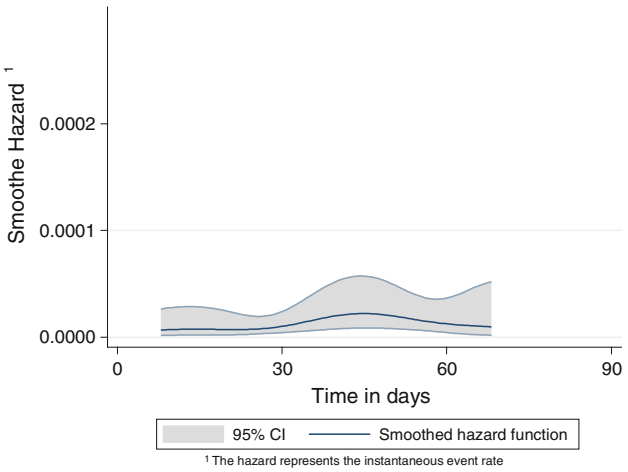


Fig. 5 Plot of smoothed hazard function with 95 % CIs for aggression events occurring after starting treatment with varenicline

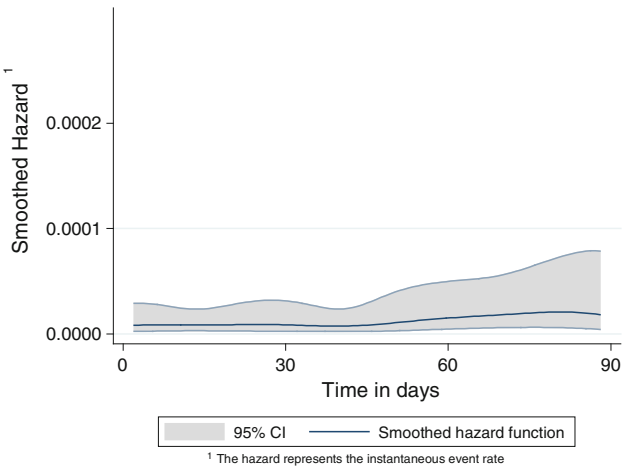


Fig. 6 Plot of smoothed hazard function with 95 % CIs for suicidal ideation events occurring after starting treatment with varenicline

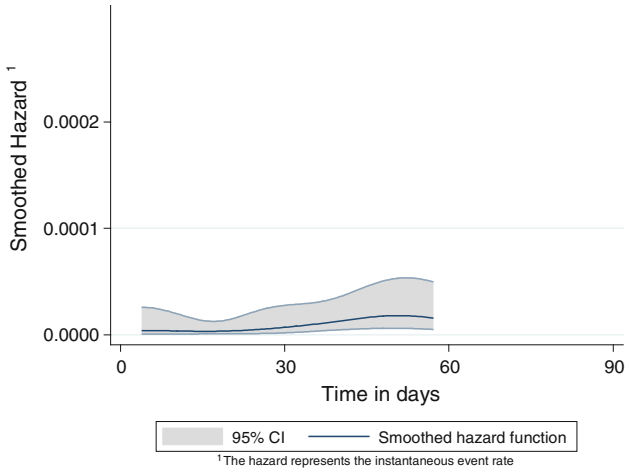


Fig. 7 Plot of smoothed hazard function with 95 % CIs for non-fatal self-harm events occurring after starting treatment with varenicline

England. This study focuses on the pattern of neuropsychiatric events reported during the course of the M-PEM study.

Varenicline is indicated for smoking cessation in adults ≥18 years of age [3]. The cohort comprised of patients who were prescribed varenicline between December 2006 and March 2007. Postmarketing reports have highlighted concerns regarding psychiatric events in patients taking varenicline and in 2008 the CHMP recommended changes to the SmPC and warnings were put in place to discontinue the drug if any psychiatric adverse events were experienced while the patients were taking varenicline [3, 14]. Smoking cessation, with or without pharmacological intervention, may be associated with an increased risk of psychiatric symptoms and therefore it is difficult to determine if the drug is involved in the aetiology of the psychiatric symptoms. During this study, 17.2 % ($n = 2086$) of patients had a previous history of psychiatric illness (where previous history was defined by the GP as any previous history of psychiatric illness recorded in the patient's notes, either recently or at any time in the past). This may contribute to an increase in the risk of patients developing psychiatric events after starting treatment with varenicline. Smokers with a previous history of psychiatric illness may be at an increased risk of developing neuropsychiatric symptoms after starting varenicline compared with smokers with no psychiatric history, however this is difficult to determine [15].

An association between psychiatric morbidity and dependence on nicotine, alcohol and drugs has been reported elsewhere [16], and the characteristics of patients included in this M-PEM study are similar to another recent study conducted in general practice in the UK [17]. During this M-PEM study, the most frequently reported psychiatric events (at HLT) during treatment with varenicline were malaise, lassitude ($n = 186$), followed by sleep disorders ($n = 132$), anxiety ($n = 129$) and depression ($n = 124$). Sleep disorders and depression were also among the most frequently reported adverse psychiatric events during a recent postmarketing prospective cohort study [8]. The incidence of depression in this study was approximately 10 per 1000 (124/12,159), while the incidence of suicidal ideation was approximately 0.7 per 1000 (8/12,159). The incidence of suicidal ideation reported in this study is similar to the study by Harrison-Woolrych and Ashton [8] (1/1310 of responders); however, the incidence of depression was approximately 20 per 1000 (27/1310) compared with 10 per 1000 in this M-PEM study. The introduction of warnings about depression into the SmPC in February 2008 may have influenced reporting in the study by Harrison-Woolrych and Ashton [8] as this study was conducted between April 2007 and March 2008, whereas data for the M-PEM study was collected between December 2006 and March 2007, before the warnings were introduced. In addition, the M-PEM study only collected data for the first 12 weeks of treatment, compared with the first year of treatment in the prospective cohort study.

In July 2008, the MHRA issued advice about an association between varenicline and suicidal behaviour [5]. Up to March 2008, 129 reports of suicidal thoughts or behaviour were received for varenicline in the UK. Because of this, a warning was issued suggesting patients should stop taking varenicline if they experience any suicidal behaviour [5]. However, in a recent publication by Gunnell et al., there was no clear evidence for an increased risk of both fatal and non-fatal self-harm associated with varenicline [17]. In a recently conducted observational prospective cohort study based in New Zealand using PEM methods, psychiatric events were commonly reported with the use of varenicline [8]. Serious psychiatric adverse effects such as suicide and suicidal ideation were also reported but less commonly. It is difficult to quantify the risk of suicide in this population as smokers may be at an increased risk of suicide compared with non-smokers [18]. In our study we did not find an association between varenicline and suicidal ideation or non-fatal self-harm using both ID analysis and time-to-event modelling. In a recent study by Moore et al. [19] using spontaneous reporting data, 13 % (1819/13.243) of reports for varenicline reflected suicidal ideation/self-harm. This study used disproportionality analysis to compare suicidal/self-injurious behaviour or depression between different smoking cessation treatments. Treatment with varenicline showed a substantial statistically significant increased risk of reported depression and suicidal/self-injurious behaviour compared with nicotine replacement. The limitations of spontaneous reporting should be considered in interpreting the results from this study. Solicited reporting influenced

by media interest or changes to the product information may have influenced the reporting rates. In addition, there were more consumer reports for nicotine replacement compared with varenicline. A recent study comparing healthcare professional reporting with patient reporting found that healthcare professionals tended to report more serious reactions that resulted in hospitalization, were life-threatening or caused death [20]. This may have affected the study results and the ability of the study to detect differences between the different smoking cessation agents.

Whilst between 7 and 17 % of the neuropsychiatric events in this study were attributed to the drug by GPs, and approximately 20–50 % were given as reasons for stopping, only anxiety was flagged as a potential signal for an ADR using the Weibull model. ID calculations did not reveal any associations between the neuropsychiatric events and drug exposure. The fact that no significant differences were found does not necessarily mean that none existed; both methods used will have low power with few events and therefore may have not been powerful enough to detect a difference. For events such as depression, anxiety, aggression, suicidal ideation and non-fatal self-harm, the time of reporting may not accurately reflect the occurrence or onset of these events and this may increase the variability of the observations and contribute to a reduction in the power of the statistical tests. However, given the large cohort size, if there was an increased risk that was not detected then the absolute risk would have been small. The inconsistencies between the results for the ID calculations and the time-to-event analysis for anxiety is due to using different levels of significance (99 % CIs and 95 % CIs) and different methods to analyse the data. While statistical methods did not reveal any associations between varenicline and neuropsychiatric events, these events were frequently reported as reasons for stopping or as reasons for ADRs to varenicline by GPs. There were 124 reports of depression, 42 of which were also reported as reasons for stopping varenicline (34 %) and 19 were reported as ADRs, 12 reports of aggression, four of which were reported as reasons for stopping varenicline (33 %), and eight reports of suicidal ideation, four of which were reported as reasons for stopping (50 %). This information, as well as results from the signal detection analysis, is important to take into account when considering the association between varenicline and neuropsychiatric events. In this study, both descriptive and comparative methods of signal detection were considered when determining an association between varenicline and neuropsychiatric events.

This signal for anxiety requires further evaluation because of the complexity of determining whether the drug plays a part in the development of anxiety or whether it is a withdrawal symptom caused by smoking cessation. It has been previously reported that smoking cessation can cause increased anxiety [21]. However, in a longitudinal study of smoking cessation, stopping smoking did not appear to increase the risk of symptoms of depression or anxiety in those free from symptoms when they stop [22]. In recent studies using spontaneous reporting data, varenicline was associated with increased reporting of violence or aggression when compared with other smoking cessation drugs, as well as other psychoactive medications [23–25]. In this study, there were 12 reports of aggression, two of which were reported as ADRs and four as reasons for stopping varenicline.

This M-PEM study included patients who were prescribed varenicline by GPs in England, including patients who would have been excluded from clinical trials because of various co-morbidities. Patients with the following underlying psychiatric conditions were excluded from clinical trials for varenicline: major depression requiring treatment, previous history of alcohol or drug abuse, psychosis and bipolar disorder [26–28].

Limitations of this study design include non-return of questionnaires, return of questionnaires with incomplete information, and patient compliance with treatment. Of the M-PEM questionnaires sent (24,508), 12,159 valid questionnaires (49.6 %) were returned. This study did not assess the impact of non-response bias. However, the response rate is comparable to response rates reported elsewhere for GP postal surveys [29]. Of the valid M-PEM questionnaires that were returned, 8.8 % ($n = 1173$) were classified as void. Of these, 43.4 % ($n = 509$) were void because the patients were no longer registered at the GP practice. It is difficult to estimate accurately the exact rate of patient migration between GP practices in the UK; however, the latest figures available show a net increase in both interregional and international migration in the UK [30]. Compliance with varenicline was not measured during this study, as with any other observational study. Measurement of compliance with varenicline would be difficult in the observational setting. Non-compliance must be considered when interpreting the incidence values of specific events in observational studies. The events collected were reported to the GP and the study outcomes were reliant on the GP reporting events. It is therefore possible that events of malaise and depression are more likely to be reported by patients compared with aggression.

Time-to-event analysis was conducted on neuropsychiatric events of interest using the Weibull shape parameter estimate. The purpose of this model was to simply detect whether hazards were thought to be non-constant, it was not our aim to model the hazards accurately. This model has previously been used to detect associations between drug use and time-dependent adverse events [31]. As with any epidemiological study, there are inherent limitations to

the use of this model as a signal detection tool. The hazard is assumed to be monotonically increasing or decreasing over time, and this assumption may not always be valid. The ability of this model to detect changes where the hazard might be high in the middle of the study period (i.e. when the hazard function is symmetrical) is lower than if the hazard is associated to shortly after starting treatment or towards the end of the study period (i.e. when the hazard function is asymmetrical) [13].

6 Conclusion

There was some evidence that anxiety events were time-dependent and thus possibly related to varenicline use. This signal requires further evaluation. No signal for depression was raised despite 34 % of events being classed as reasons for stopping by GPs. The other neuropsychiatric events were rare and thus it was not possible to reliably comment on distribution of their occurrence; however, approximately 33 % of aggression events and 50 % of suicidal ideation events were reported as the reasons for stopping varenicline. No signal was detected using ID differences analyses. Analysis methods will lack power when the numbers of events are low.

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