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Safety and Drug Utilization Profile of Varenicline as Used in General Practice in England

Interim Results from a Prescription-Event Monitoring Study

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Abstract

Background: Varenicline tartrate (Champix®), a new smoking cessation medicine, was launched in the UK in December 2006. Varenicline is a highly selective partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor ($\alpha_4\beta_2$ receptor). The partial agonistic binding leads to alleviation of symptoms of craving and withdrawal, and simultaneously prevents nicotine from binding to the $\alpha_4\beta_2$ receptor thereby causing reduction in the rewarding and reinforcing effects of smoking. Regulatory concerns have arisen about psychiatric events associated with varenicline, including depression, suicidal ideation and changes in behaviour/emotion.

Aim: To present the interim results of an ongoing study by the Drug Safety Research Unit (DSRU) monitoring the safety of varenicline.

Methods: The observational cohort study is being conducted to study the postmarketing safety of varenicline, using modified prescription-event monitoring (PEM) methodology. Patients are identified from dispensed prescriptions issued by general practitioners (GPs) from December 2006. Demographic, clinical event (during the course and 1 month after stopping varenicline, reasons for discontinuing and suspected adverse drug reactions [ADRs] to varenicline) and drug utilization data are collected from detailed study-specific questionnaires posted to GPs at least 4 months after the date of first prescription for each patient. Event incidence densities (IDs; number of first reports of an event/1000 patient-months of exposure) are calculated.

Results: The interim cohort comprises 2682 patients: median age 47 years (interquartile range [IQR] 38–56), 60.7% females (n = 1627). Nausea/vomiting was the most frequent clinical reason for stopping varenicline (n = 91; 35.3% of clinical reasons) and the most frequently reported suspected ADR to varenicline (n = 60, 50.9% of patients for whom an ADR was reported). The most frequently reported psychiatric events (causality not implied) during treatment included (n; % of cohort): sleep disorder (43; 1.6%), anxiety

(33; 1.2%), depression (29; 1.1%), abnormal dreams (26; 1.0%) and mood change (17; 0.6%). Two cases of attempted suicide were reported during treatment with varenicline (one patient took an overdose of a benzodiazepine with alcohol, the other slashed their wrist). Both these patients had previous history of psychiatric illness and precipitating factors for the event.

Conclusion: This study reflects 'real life' use of varenicline. Nausea/vomiting – the event most frequently reported as an ADR and as reason for stopping treatment – is listed in the UK Summary of Product Characteristics (SPC). The most frequently reported psychiatric events are listed in the UK SPC. All patients with suicidal events either had a past medical history of psychiatric illness prior to starting varenicline and/or a precipitating factor for the event. Clinicians should closely monitor patients with pre-existing psychiatric illness who are taking varenicline. Further evaluation of events of interest including psychiatric events is ongoing. Results presented are expected to change as the cohort size increases. Results of this study should be taken into account together with other clinical and pharmacoepidemiological studies.

Background

Varenicline tartrate (Champix®) is a new smoking cessation medicine that was launched in the UK in December 2006. Varenicline is a highly selective partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor ($\alpha_4\beta_2$ receptor), the receptor that is thought to be responsible for the reinforcing properties of nicotine. Varenicline has a 15-fold higher affinity for this receptor compared with nicotine. Varenicline binding to this receptor is believed to have a dual effect. The partial agonistic binding leads to alleviation symptoms of craving and withdrawal, and simultaneously prevents nicotine from binding to the $\alpha_4\beta_2$ receptor, thereby causing reduction in the rewarding and reinforcing effect of smoking.[1,2]

Concerns arose when reports of depression, suicidal ideation and changes in behaviour/emotion, amongst other psychiatric events, were received.[3,4] These concerns led to changes in the UK Summary of Product Characteristics (SPC) of varenicline, which now includes a warning about depression and suicidal ideation in patients taking varenicline.[5] However, as smoking cessation with or without treatment is associated with psychiatric symptoms[2] such as depressed mood, anger and anxiety, the role of varenicline in these cases is not clear.

The Drug Safety Research Unit (DSRU) is currently conducting a postmarketing safety study on varenicline. This short communication presents the interim results of this ongoing study. The reason for publishing this interim study is to inform the debate on the postmarketing safety of varenicline in view of the regulatory concerns raised about aspects of its safety.

Methods

An observational cohort study on the safety profile of varenicline is being conducted in general practice in England, using the technique of 'modified' prescription-event monitoring (PEM). PEM has been described in more detail previously.[6] Modified PEM studies differ from PEM studies in that a more detailed study-specific questionnaire for data collection is sent to primary care physicians/general practitioners (GPs). Furthermore, GPs are paid a small sum of money for completing the questionnaires, unlike PEM where GPs complete relatively simple questionnaires on an unpaid basis.

Prescription Information and Questionnaires

Patients are being identified by means of data from dispensed National Health Service (NHS) prescriptions for varenicline issued by GPs in England from December 2006. This prescription information is supplied in confidence to the DRSU by the Prescription Pricing Division. Modified PEM questionnaires are being sent to prescribing GPs at least 4 months following the first prescription identified by the DSRU for each patient.

Information requested on the questionnaire includes patient demographics; dosage; dates of starting and stopping treatment; clinical event data (during treatment and 1 month after stopping varenicline); reason for discontinuing therapy; and details of the patient's smoking history, past medical history and whether patient continued to smoke after the course of varenicline was completed. GPs are also requested to indicate if they suspect any event to be an adverse drug reaction (ADR) to varenicline. The GPs are paid £20 to cover administrative costs for completing the questionnaires. A reminder letter and duplicate questionnaire are sent to those GPs who have not returned the original questionnaire within 60 days of it being sent.

Data lock was set at the point when >2500 questionnaires with clinical information had been processed (data entered and each questionnaire reviewed by a physician). The data lock point corresponded to 2967 processed questionnaires, of which 2682 (90.4%) questionnaires contained clinical information. The remaining 9.6% (285 of 2967) of questionnaires were classified as void because the questionnaires were either returned completely blank or were incompletely filled with no clinical information; these were excluded from the study cohort and subsequent analysis.

All reported events are 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 'lower level' terms, which are in turn grouped under broader 'higher level' terms, which are linked to the respective SOCs.

Strict confidentiality of patient information is maintained. The anonymous status of the data is ensured by requesting GPs to provide a patient identification number, and all communications are carried out using this number.

Events that require additional information are being followed-up using event-specific questionnaires. This information will be used to assess causal relationship of the event with varenicline. Causality assessments are not presented here, because not all the follow-up questionnaires sent out have been returned to date.

Incidence Density (ID) Analysis

In order to detect any early-onset events with varenicline, the differences between incidence densities (IDs) in month 1 (ID_1) and IDs in months 2–3 of treatment ($ID_{2–3}$) are calculated with 99% confidence intervals (CIs). IDs are expressed per 1000 patient-months of treatment. A positive difference indicates that ID_1 was higher than $ID_{2–3}$. This is done for all events occurring during the treatment period. Patient-months of exposure are based on those patients for whom either the date of stopping the drug is known or who continued to take the drug until the end of the study period.

Ethics

This study is conducted in accordance with *Guidelines for Biomedical Research* (CIOMS/WHO)[7] and those issued by the Royal College of Physicians.[8] The DSRU is noted by the UK General Medical Council as an organization to which relevant information should be provided by physicians, wherever possible, for the purpose of monitoring public health.[9]

Results

The interim cohort comprises 2682 patients. The median age of the cohort is 47 years (IQR 38, 56), and 60.7% (1627 of 2682) of patients are female.

The maintenance dose was specified in 87.5% (2346 of 2682) of the patients. Where this dose was known, 1 mg twice daily was the most

frequent dosage (84.1%; 1974 of 2346). The dose was reported to be reduced in 276 of 2682 (10.3%) patients; the most common reason for reducing the dose was nausea (n = 47).

Reasons for Discontinuing Varenicline, and Suspected ADRs

At the time the GP received our questionnaires, 89.6% (2403 of 2682) of patients had stopped treatment with varenicline. Of these, a reason for discontinuing was given for 89.5% (2151 of 2403) of patients; for the remaining 252 patients, this information was not specified.

The reasons for discontinuing varenicline constituted 321 clinical events and 1935 non-clinical events, with 41 patients in both categories. It is noteworthy that for each patient more than one event (within clinical or non-clinical categories) could have been given as reason for discontinuing varenicline. Specific clinical reasons for discontinuing varenicline are given in table I. The most frequent non-clinical event reported as reason for discontinuing varenicline was 'end of course' (n = 1238; 46.2% of total cohort; 57.6% where reason for discontinuing was specified). Other frequently reported non-clinical reasons were (n; % of cohort) 'no further request' (340; 12.7%); smoking restarted/addiction (88; 3.3%); and smoking cessation (67; 2.5%).

163 events were reported as suspected ADRs to varenicline in 117 patients (4.4% of cohort). For some patients, more than one event was reported as a suspected ADR (table I).

ID Analysis

'Nausea, vomiting' was the event with the highest ID in month 1 ($ID_1 = 81.52$/1000 patient-months of exposure) and for the entire treatment period ($ID_A = 47.98$; total number of events reported = 217). 'Nausea, vomiting' was reported significantly more frequently in the first month of treatment and was considered to be an early-onset event ($ID_1 - ID_{2-3} = 54.19$; 99% CI 33.27, 75.11). Subjects in this cohort for whom a date of stopping varenicline was provided or who continued treatment with varenicline, contributed to a total of 4523 patient-months of exposure. However, for 732 patients (30% of the patients who stopped the drug) the date of stopping varenicline was not known.

Table I. Most frequently reported clinical reasons for discontinuing varenicline and suspected adverse drug reactions (ADRs) reported to varenicline

Event (higher level term)	No. given as reason for discontinuing/total no. reported	Reason for discontinuing (% of cohort)	Frequency[a] of adverse drug reactions in the UK SPC of varenicline[5]
Specific clinical reasons for discontinuing varenicline			
Nausea, vomiting	91/217	3.4	Nausea – very common Vomiting – common
Malaise, lassitude	20/44	0.7	Malaise – uncommon
Headache, migraine	17/48	0.6	Headache – very common
Sleep disorder[b]	17/43	0.6	Sleep disorder – uncommon Insomnia – very common
Anxiety[c]	14/33	0.5	Panic reaction – uncommon
Suspected ADRs to varenicline			
Nausea, vomiting	60/217	2.2	As above
Sleep disorder	9/43	0.3	As above
Headache, migraine	7/48	0.3	As above
Dreams abnormal	6/26	0.2	Abnormal dreams – very common
Constipation	4/17	0.1	Constipation – common

a Frequency as per SPC: very common (1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100).

b The term 'sleep disorder' includes insomnia.

c The term 'anxiety' includes agitation and panic attack.

SPC = Summary of Product Characteristics.

Other Characteristics of the Cohort

For more than half of the patients, GPs either did not know (41.2%; 1105 of 2682) or did not specify (15.3%; 410 of 2682) whether varenicline was stopped abruptly or tapered. Where this information was known, 85.1% (993 of 1167) stopped varenicline abruptly, whereas for 14.9% (174 of 1167) the dose was tapered.

Information on past frequency of smoking and quitting attempts (in the 3 months prior to starting varenicline) are given in table II.

GPs were asked whether their patients were still smoking after the course of varenicline. Where the full course of varenicline was completed (n = 1238), this information was provided for 794 patients: at the time of the most recent consultation 30.6% (243 of 794) were still smoking whereas 69.4% (551 of 794) were not smoking.

Psychiatric Events Reported

A total of 171 psychiatric events have been reported in 142 patients. Of these 142 patients, 92 patients (65.0%) did not have a past medical history (PMH) of psychiatric illness prior to starting varenicline, 44 patients (31.0%) had PMH of psychiatric illness, and for the remaining patients (n = 6; 4.2%), this information was either not known or not specified by the GP.

Suicidal Events

Four events of suicide attempt and two of suicidal ideation have been reported in five patients in this study so far. Two patients attempted suicide during treatment with varenicline (30 days and 47 days after starting varenicline), and the remaining four events occurred after stopping varenicline. Details of these six events are presented in table III.

Other Psychiatric Events

Details of other psychiatric events reported in this cohort are presented in table IV. The most frequently reported event was sleep disorder, which was also the most frequent psychiatric event given as reason for discontinuing varenicline.

Table II. Patients' smoking history in the 3 months prior to starting varenicline

Parameter	No.	% of cohort (where an answer was specified)
Cigarettes per day prior to starting varenicline (n = 2200)		
≤10	287	13.0
11–20	1080	49.1
21–30	558	25.4
>30	275	12.5
Missing[a]	482	
Attempted to quit smoking prior to varenicline (n = 1985)		
Yes	1074	54.1
No	911	45.9
Missing[a]	697	
Method used for quitting smoking (n = 955)		
Bupropion (alone)	96	10.1
Nicotine patches/gum (alone)	614	64.3
Other (alone)	129	13.5
Combination of any of the above	116	12.1

a Missing includes GP answered 'don't know' or did not answer the question.

Discussion

This is an early communication on the safety profile of varenicline. The PEM study on varenicline is ongoing and the final cohort will comprise 10 000–12 000 patients.

This study has merit because it presents 'real-life' clinical use of varenicline, without exclusion on the basis of age, sex or co-morbidity. It is a non-interventional study in which the prescribing practices of the GP are not influenced in any way, as patients are identified from dispensed prescriptions, thereby eliminating bias through this route. The study provides clinical event data and also information on drug utilization and other patient characteristics.

One weakness of this interim study is the missing data due to incompletely filled questionnaires. This may be due to the busy schedule of GPs and the time taken in retrieving the data from the computer system. Another weakness of our study is that patients included in this study are restricted to those who were prescribed varenicline by their GPs, therefore patients who were

Table III. Suicidal events[a] reported in this study

Event	Method of suicide/ drug(s) taken in overdose	Age (y)/ sex	Time-to-onset[b] (days)	Past history of psychiatric illness	Precipitating factors for the event	Reason for stopping varenicline	Event related to varenicline? (GP's opinion)
Suicide attempt	Slashed wrist	39/M	On (47)	Depression since 1998	Recent stress of RTA	Yes	Don't know
Overdose[c]	Nitrazepam and alcohol	50/F	On (30)	Depression and alcohol dependence	Longstanding personal stress	No	Don't know
Overdose	Zopiclone and cider	56/F	Off (NK)	Depression in 2003, 2006	Domestic stress	No	No
Overdose	GP not sure (? mirtazapine and clonazepam)	40/F	Off (NK)	Depression	Debt	No	Don't know
Suicidal ideation[c]	NA	50/F	Off (NK)	Depression and alcohol dependence	Longstanding personal stress	No	Don't know
Suicidal ideation	NA	47/F	Off (NK)	No	Domestic stress	No	No

a None of the suicidal events were reported to be fatal.

b During treatment with varenicline (on), after treatment with varenicline had been stopped (off) and not known (NK).

c Both events occurred in the same patient.

F = female; **GP** = general practitioner; **M** = male; **NA** = not applicable; **RTA** = road traffic accident.

prescribed varenicline by the 'stop smoking service' of the NHS are not included. However, we have a large sample of the general population treated by GPs. The varenicline SPC recommends varenicline to be started 1–2 weeks before the decided quit date. However, we did not collect data on when the patient stopped smoking in relation to varenicline treatment, which may have been important for assessment of adverse events.

Furthermore, at this interim stage, it is not possible to determine the actual response rate for the questionnaires returned to date, because the study is ongoing and questionnaires are continuing to be posted in batches, and reminders are sent as required. However, as with all PEM studies, we acknowledge that there will be a proportion of the questionnaires that are not returned, but it is not possible to determine what effect the response rate has had on the results of this study.

Patient Demographics and General Safety

The cohort comprised 61% women and the most frequent age group represented was the middle aged. Regarding the maintenance dose of varenicline, the majority of the patients were prescribed the recommended dosage of 1 mg twice daily. Varenicline questionnaires were sent to GPs at least 4 months after the prescriptions were issued. However, 10% (n = 279) of the patients had not stopped varenicline at the time the GPs received our questionnaires. This could have been because the medication was taken non-continuously. 'End of course' as a reason for discontinuing varenicline was given in 57% of patients where reason for discontinuing was specified, therefore a substantial proportion of patients discontinued varenicline due to other reasons, both clinical and non-clinical.

Nausea/vomiting was the most frequent reason for discontinuing varenicline and the most frequently reported suspected ADR associated with varenicline. It was also detected as an early-onset event with varenicline.

The frequency of clinical events reported as the most frequent reasons for discontinuing varenicline and as suspected ADRs to varenicline did not exceed the frequency of ADRs in the SPC.[5] However, the discontinuation rate due to nausea/

vomiting in this study (3.4%) is higher than that given in the SPC (2.7%).[5] Discontinuation rates for other events in the SPC,[5] i.e. headache (0.6% vs 1.0% for placebo), insomnia (1.3% vs 1.2% for placebo) and abnormal dreams (0.2% vs 0.2% for placebo), were similar to or higher than those reported in this cohort.

Regarding smoking history in the 3 months prior to starting varenicline, where information was known, nearly 50% of patients smoked 11–20 cigarettes per day. The most frequent method used for quitting smoking prior to varenicline was the use of nicotine patches/gum.

Psychiatric Events

The 'public health advisory' issued by the US FDA warned about the possibility of severe changes in mood and behaviour, and symptoms such as anxiety, nervousness, depressed mood and thinking about or attempting suicide in patients taking varenicline. The FDA's assessment revealed that these could be worsening of current psychiatric illness or recurrence of old psychiatric illness as well as new-onset psychiatric symptoms.[4,10]

The spontaneous suspected ADRs reported to the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK (through the yellow card scheme) for varenicline have been dominated by psychiatric adverse events (77% of all ADRs reported; 2286 of 2974). These include 344 reports of depression, 187 suicidal ideations, 14 suicide attempts and eight completed suicides.[11]

Health Canada described seven cases of suicidal tendencies after starting varenicline. Time-to-onset ranged from 11 days to 72 days after starting treatment. Only one of the seven patients had a known history of psychiatric condition; for four there was no known history of psychiatric condition and for the remaining two this information was not known.[12]

A number of case reports of exacerbation of psychiatric illnesses after starting varenicline have been published recently. These include exacerbation of depression in a patient with history of recurrent major depressive disorder, previously stable on fluoxetine;[13] psychotic relapse in a patient with schizophrenia;[14] a manic episode in a patient with a history of bipolar disorder, previously stable on valproic acid;[15]

Table IV. Other psychiatric events reported in this study

Event (higher level term)	No. (% of cohort)	Median age (y)	Sex (male/female)	Time-to-onset in days (median unless otherwise specified)	Past medical history of psych illness (% of events reported)	Reason for stopping varenicline
Sleep disorder	43 (1.6)	48	14/29	35	9 (21.0)	17
Anxiety[a]	33 (1.2)	50	11/22	42	16 (48.5)	14
Depression	29 (1.1)	46	4/25	44	14 (48.3)	2
Dreams abnormal	26 (1.0)	52	9/17	35	4 (15.0)	6
Mood change[b]	17 (0.6)	44	6/11	43	6 (35.3)	3
Delirium[c]	5 (0.1)	49	4/1	35	2 (40.0)	3
Alcoholism[d]	3 (0.07)	47	2/1	14, 71[e]	0	0
Aggression	2 (0.07)	52, 61	2/0	7, 163	1 (50.0)	1
Hyperactive	2 (0.07)	38, 49	1/1	50	0	1
Hallucination	1 (0.04)	47	1/0	34	0	1

a The term 'anxiety' includes agitation and panic attack.

b The term 'mood change' includes emotional disturbance.

c The term 'delirium' includes confusion.

d Alcoholism pre-dated the use of varenicline in all three patients; however the general practitioners did not report a past medical history of psychiatric illness.

e Time-to-onset was not known in one patient with alcoholism.

and mixed mood and psychotic episode in a patient with a past history of depression.[16] Exacerbation of psychiatric illness occurred as early as the first week of treatment with varenicline in two of the patients. Dechallenge was positive in all the cases. These reports emphasize that clinicians should exercise caution when prescribing varenicline to patients with established psychiatric disorders.

In this study, suicidal events were reported in five patients. This included one male patient and four female patients; all were middle-aged. All the patients had a past medical history of psychiatric illness and/or a precipitating factor for the suicidal event. None of the suicide attempts was fatal. The GPs either answered 'no' or 'don't know' when asked whether the suicidal event was related to varenicline. This could be because assessment of causal association can be difficult due to confounding factors such as past medical history of psychiatric illness, precipitating factors for the events, and the fact that smoking cessation with or without treatment may be associated with various symptoms such as depressed mood, anger and anxiety.[5]

Among the other psychiatric events reported, 'sleep disorder' and anxiety were the most frequently reported events and also the most frequently reported psychiatric reasons for discontinuing varenicline. Median time-to-onset for most of the psychiatric events was 6–7 weeks of treatment. For events such as anxiety, depression and aggression, nearly 50% of the patients had no past medical history of psychiatric illness, whereas for patients who were reported to have sleep disorder and abnormal dreams, 80% did not have a past medical history of a psychiatric illness. Although the commonly reported psychiatric events in this study are listed in the UK SPC, some of the psychiatric events (delirium, aggression, hallucination) reported in this study are not listed in the SPC.[5] However, the frequency of these events was very small.

Conclusions

This study reflects 'real life' use of varenicline. Nausea/vomiting – the event most frequently reported as an ADR and reason for stopping treatment – is listed in the UK SPC. Although the frequently reported psychiatric events in this study are listed in the UK SPC, a small number of low frequency psychiatric events are not listed. All patients with suicidal events had a past medical history of psychiatric illness prior to starting varenicline and/or precipitating factors for the event. Clinicians should closely monitor patients with pre-existing psychiatric illness who are taking varenicline. Further evaluation of events of interest including psychiatric events is ongoing. Results presented are expected to change as the cohort size increases. Results of this study should be taken into account together with other clinical and pharmacoepidemiological studies.

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