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Psychiatric Adverse Events Associated with Varenicline

An Intensive Postmarketing Prospective Cohort Study in New Zealand

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Abstract

Background: Psychiatric adverse events, including depression, suicidal ideation and psychotic reactions have been reported in patients taking the smoking cessation medicine varenicline. However, data regarding the frequency of psychiatric adverse reactions in 'real-life' postmarketing use are limited to date.

Objective: The aim of the study was to calculate the occurrence rates of psychiatric adverse reactions in a nationwide general population prescribed varenicline in New Zealand.

Methods: Observational prospective cohort study using Prescription Event Monitoring methods. All New Zealand patients dispensed a prescription for varenicline from 1 April 2007 to 31 March 2008 were included in this study. Patients were followed up by multiple methods, including linkage to national morbidity and mortality datasets, questionnaires to patients' doctors and assessment of spontaneous reports sent to the Intensive Medicines Monitoring Programme. Main outcome measures were occurrence rates of psychiatric adverse events in the total patient cohort and in the subgroup for whom a follow-up questionnaire was returned (the 'responder population').

Results: The cohort for this study included 3415 patients prescribed varenicline during the first year of monitoring in New Zealand. Follow-up by record linkage was performed for 3353 (98%) patients, and questionnaires were returned for 1394 (42%) of these patients. Of 1394 questionnaires returned, 1310 were valid and defined as the 'responder' population. Sleep disorders, including insomnia, sleep disturbance, dreams and nightmares, were the most frequently reported psychiatric events and were experienced by 56 (4.3%) patients in the responder population. Symptoms of depression were reported by 39 (2.98%) patients in the responder population (24 new-onset depression, 14 worsening of pre-existing depression and 1 report of impaired motivation). Withdrawal reactions after stopping varenicline were reported by 6 (0.46%) patients in the responder population. Serious psychiatric reactions including

suicide (one case), suicidal ideation (two cases) and psychotic reactions (three cases) were also identified. Six self-harm events (one fatal, five non-fatal) were identified in the total cohort, giving an occurrence rate of 0.18% (95% CI 0.06, 0.38) in this population.

Conclusions: This intensive postmarketing study of 3415 New Zealand patients demonstrates 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. Serious psychiatric reactions including suicide, suicidal ideation and psychotic reactions were also identified, but these were less frequently reported.

Background

Varenicline tartrate (Champix®, Chantix®) is a selective nicotinic acetylcholine receptor partial agonist developed as an aid to smoking cessation. It was the first medicine of this new class to be approved in several countries, including New Zealand where it has been monitored by the Intensive Medicines Monitoring Programme (IMMP) since 2007.

Psychiatric adverse events were noted in clinical trials of varenicline[1] and have been reported during postmarketing surveillance.[2] These adverse effects include depression, anxiety, suicidal ideation and self-harm, including suicide.[2-4] A cohort study based on data from the UK General Practice Research Database (GPRD) concluded that there was no clear evidence that varenicline was associated with an increased risk of fatal or non-fatal self-harm,[5] but this observation was challenged as it appeared to contradict observations from spontaneous reporting data in the UK and US.[6] Interim results from an English Prescription Event Monitoring (PEM) study of varenicline were published in 2009[7] and included reports of attempted suicide and other psychiatric adverse events.

More data are now required to quantify the risk of psychiatric adverse events in a general population taking varenicline in 'real-life' clinical use, as this may differ from the risks observed in clinical trials. It is important for patients and prescribers to know the frequency of these adverse events in order to undertake appropriate risk management. This paper summarizes the results from intensive follow-up of patients dispensed varenicline during the first year of marketing in New Zealand.

Methods

The IMMP operates within the New Zealand Pharmacovigilance Centre[8] and performs intensive pharmacovigilance studies of selected medicines using PEM.[9] The IMMP conducts prospective observational cohort studies and its methods have been described in detail previously.[9] In brief, the cohort of patients for each monitored medicine is established from dispensing data collected directly from community and hospital pharmacies throughout New Zealand. Information collected from these dispensing records includes the name, address, National Health Identification (NHI) number (a unique identifier of healthcare users in New Zealand), sex and date of birth of the patient; prescriber and dispensing pharmacy information; and details of the monitored medicine including dispensing dates, dose and quantity dispensed.

Patients dispensed the monitored medicines are followed up by 'intensive' (i.e. multiple) methods in order to obtain information from several sources. Questionnaires requesting information on all new clinical events since the patient started the monitored medicine are sent to prescribing doctors – usually the patient's general practitioner.

Additional follow-up information is obtained from spontaneous reports (yellow cards) sent to the New Zealand Pharmacovigilance Centre by health professionals, pharmaceutical companies and patients.[8] As a further measure to identify deaths and adverse events resulting in hospitalization – particularly in patients for whom a follow-up questionnaire is not returned – the IMMP also undertakes record linkage to the New Zealand Health Information Service (NZHIS) National Collections databases.[9] Procedures are in place at the IMMP to identify any duplicate reports and, when this occurs, information from all reports for the same patient is combined into one report for assessment.

Varenicline Study

Monitoring of varenicline began in April 2007 when marketing of this medicine commenced in New Zealand. Data were entered for all New Zealand patients who were dispensed varenicline from 1 April 2007 to 31 March 2008. All patients in this cohort with an identifiable doctor were followed up by IMMP questionnaires sent to doctors in June 2008.

The follow-up questionnaires for this study were based on previous IMMP questionnaires, with the primary aim being to identify new clinical events since the patient started varenicline. On the questionnaire doctors were asked to record any clinical events in an open table, which also had columns for the date and the outcome of each event. Additional specific questions were included: past smoking history, previous attempts at smoking cessation, past psychiatric history, concomitant medicines and other questions relating to utilization of varenicline.[10]

For every patient with a valid NHI number, record linkage to the NZHIS datasets was performed for a period of 6 months after the last dose of varenicline (the date of each patient's last dose was calculated from IMMP dispensing data records) in order to identify deaths and hospital admission events.

Returned questionnaires were defined as 'valid' if they included any assessable information about the patient. Questionnaires, record linkage data and any other follow-up information (e.g. spontaneous reports) were assessed by clinical staff at the IMMP. All adverse events occurring whilst the patient was taking the medicine and for 1 month after the last dose were coded using terms from a specialized dictionary based on the WHO Adverse Reaction Terminology (WHO-ART).[9] Causality assessments were performed using standard methods[11,12] and adverse events were grouped into System Organ Classes (SOCs) for analysis. Events within the psychiatric SOC were placed into clinical subgroups for further assessment.

Analyses

Analyses were performed to determine the occurrence rates of psychiatric adverse events per 100 patients (%) exposed to varenicline and two denominators were used for these calculations: (i) the total cohort**:** all patients in the first-year cohort; and (ii) the 'responder' cohort, which was a sub-group of the total cohort, defined as all patients for whom a valid IMMP follow-up questionnaire was received**.** Use of this 'responder population' group as a denominator was considered to give the most accurate rates for adverse events that do not usually result in hospitalization or death.

The follow-up/observation period for each patient was defined as the time from when varenicline was first dispensed to the date the questionnaire was completed (for patients in the responder population), the date the record linkage was performed (for other patients in the cohort for whom a questionnaire was not returned) or the date other information about adverse events (e.g. spontaneous reports) was received. The datalock point for this study was 30 September 2010 (to allow sufficient time for adverse events to be identified and entered into the IMMP datasets) and any adverse events identified after this time were not included in these analyses.

Results

From 1 April 2007 to 31 March 2008, 3415 patients in New Zealand were dispensed 7817 prescriptions for varenicline. Sex was identified

for 3409 patients and of these, 1769 (52%) were female and 1640 (48%) male. Age of the varenicline total cohort at the time of their first prescription ranged from 17 to 88 years with a median age of 49 years (interquartile range [IQR] 40–57 years).

Of the 3415 patients in the first-year cohort, 3353 (98%) had an identifiable NHI number, and record linkage to the NZHIS datasets was performed for all these patients. IMMP follow-up questionnaires were sent for 3340 (98%) of the 3415 patients in the first-year cohort. By March 2010 follow-up responses had been received for 1394 patients (42% return rate) and of these, 1310 were defined as valid and formed the 'responder' population.

Adverse Events

Assessment of adverse events identified by record linkage, from follow-up questionnaires and from spontaneous reports, identified 513 reports for 502 patients (15%) in the first-year cohort. These patients experienced a total of 828 events. The numbers of adverse events in each IMMP SOC are shown in table I.

The results in table I show that psychiatric events were the second most frequent group of adverse events and accounted for 25% of all adverse events identified in this cohort.

Table I. Adverse events by system organ class (SOC) in the first-year Intensive Medicines Monitoring Programme (IMMP) varenicline cohort

IMMP SOC	Number of events	Percentage of total events
Alimentary	225	27
Psychiatric	206	25
Circulatory	51	6
Respiratory	50	6
Neurological	37	5
Musculoskeletal	33	4
Accidents	31	4
Urogenital	30	4
Endocrine/metabolic	27	3
Skin	21	3
Autonomic	20	2
Neoplasms	19	2
Ear, nose and throat	18	2
General side effects	14	2
Eyes	13	2
Infections	10	1
Other	23	3
Total	**828**	**100**

Psychiatric Adverse Events

Of the 3415 patients in the IMMP first-year cohort, 138 (4%) patients experienced a psychiatric adverse effect. Of these patients, 89 (64.5%) were women and 49 (35.5%) were men, with a mean age of 52 years (IQR 46–59 years). The detailed age and sex distribution of patients who experienced a psychiatric adverse event are shown in table II.

These 138 patients experienced a total of 206 psychiatric events. The numbers and occurrence rates (shown as a proportion of the total and responder cohorts) of these events are shown in table III.

Most Frequent Psychiatric Events

Sleep disorders were the most commonly reported adverse effects in the psychiatric SOC and were experienced by 56 (4.28%) patients in the 'responder' population. The most frequent sleep disorder was insomnia, which was reported by 29 (2.21%) of the responder cohort. Other types of sleep disturbance, nightmares and dreams were also reported (see table III) and all of these adverse events were assessed as having a causal association with varenicline. In every case of nightmares (n = 13 patients), these resolved when varenicline was stopped (positive dechallenge).

Depression

There were 27 reports of new onset symptoms of depression in patients in the total first-year cohort (n = 3415). Information regarding time to onset of these symptoms was available for 13 of these patients and ranged from 2 to 120 days. Causality assessments were performed for 26 of the 27 patients (one had insufficient information for assessment) and of these, 17 (65%) patients had a positive dechallenge. There were also 15 reports of worsening depression (or relapse of a previously stable depressive illness) in patients

who had pre-existing depressive illness. Causality assessments were performed for these 15 patient reports: 6 (40%) patients had a positive dechallenge, and for the remaining 11 patients the relationship of their symptoms with varenicline was assessed as 'possible'.

In addition to the above reports of depression, there was one report of impaired motivation and a further five reports of impaired concentration, both of which may be symptoms of depression. One of these patients also reported low mood, one also experienced sleep disturbance, one had somnolence, one had symptoms of depersonalization and one had no other adverse events. Four of the five patients with impaired concentration stopped taking varenicline because of this and all had a positive dechallenge.

Suicide and Self-Harm Events

One case of suicide was identified in the total cohort, but details of the case were scant and it was not possible to perform a causality assessment because of insufficient information about potential confounding factors. There were two reports of suicidal ideation. The first patient was a woman aged 62 years who had a history of depression, but was not on antidepressant medication at the time of starting varenicline. After 1 month the patient reported to her doctor that she was 'feeling great' and a further varenicline prescription was given. The patient later reported that she became increasingly agitated and anxious and then 'proceeded to spiral into depression very quickly' with marked sleep disturbance and suicidal ideation. Varenicline was stopped and she was referred for specialist care. The second patient with suicidal ideation was a 44-year-old man with no history of depression. He reported having to stop varenicline after 12 weeks of treatment because of very low mood, irritability and suicidal ideation. These symptoms resolved after cessation of varenicline.

Table II. Age and sex distribution of patients with a psychiatric event

Age group (y)	Females	Males	Total (%)
20–29	1	5	6 (4.3)
30–39	7	3	10 (7.3)
40–49	27	16	43 (31.2)
50–59	32	13	45 (32.6)
60–69	17	9	26 (18.8)
70+	5	3	8 (5.8)
Total (%)	**89 (64.5)**	**49 (35.5)**	**138 (100.0)**

Two cases of non-fatal overdose were identified – one from record linkage to hospital admission datasets and one reported on an IMMP follow-up questionnaire. A female patient aged 53 years took an overdose 23 days after starting varenicline, and a male patient aged 38 years took an overdose 38 days after varenicline was dispensed. Both of these events were assessed as having a possible causal relationship with varenicline.

Agitation, Aggression and Psychotic Reactions

There were two reports of agitation and a further three reports of aggressive behaviour in the total first-year cohort. The three case reports of aggression were assessed as causally related to varenicline and two of these patients had a positive dechallenge. Both patients (one male, one female), developed aggressive behaviour during the 12th week of treatment.

A further three reports included adverse events that were clinically assessed as having a psychotic component. The first report was of a 24-year-old man who was admitted to hospital with a non-organic psychosis 2 weeks after starting varenicline. This patient had no known history of psychiatric illness. The second report was another 24-year-old man who developed hallucinations (type not specified) after 1 week of treatment. This patient stopped varenicline and the hallucinations resolved. The third report was a 48-year-old man who developed paranoia as part of a reaction involving anxiety, panic and sleep disturbance. These symptoms began 8 days after starting varenicline and resolved on cessation of treatment.

Varenicline Withdrawal Reactions

Five patients were reported to have experienced psychiatric adverse events after stopping varenicline. Two patients experienced agitation or anxiety, two reported feeling very depressed

Table III. Psychiatric events reported with varenicline in the Intensive Medicines Monitoring Programme (IMMP) cohort

Clinical subgroup adverse event	Total cohort[a] (n = 3415)		Responder population[b] (n = 1310)	
	number of events	proportion total cohort[c] [% (95% CI)]	number of events	proportion responder cohort [% (95% CI)]
Sleep disorders				
Insomnia	31	0.91 (0.62, 1.29)	29	2.21 (1.48, 3.18)
Sleep disturbance	14	0.41 (0.22, 0.69)	10	0.76 (0.37, 1.40)
Dreams	9	0.26 (0.12, 0.50)	7	0.53 (0.21, 1.10)
Nightmares	13	0.38 (0.20, 0.65)	10	0.76 (0.37, 1.40)
Subgroup total	*67*	*1.96 (1.52, 2.49)*	*56*	*4.28 (3.23, 5.55)*
Tiredness events				
Fatigue	15	0.44 (0.25, 0.72)	12	0.92 (0.47, 1.60)
Somnolence	4	0.12 (0.03, 0.30)	3	0.23 (0.05, 0.67)
Malaise	3	0.09 (0.02, 0.26)	3	0.23 (0.05, 0.67)
Weakness	1	0.03 (0.0001, 0.16)	0	NA
Subgroup total	*23*	*0.67 (0.43, 1.01)*	*18*	*1.37 (0.81, 2.17)*
Depression events				
Depression	27	0.79 (0.52, 1.15)	24	1.83 (1.17, 2.73)
Depression worse	15	0.44 (0.25, 0.72)	14	1.69 (0.58, 1.79)
Motivation impaired	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Subgroup total	*43*	*1.26 (0.91, 1.70)*	*39*	*2.98 (2.12, 4.07)*
Suicide and self-harm				
Suicide	1	0.03 (0.0001, 0.16)	0	NA
Overdose (non-fatal)	2	0.06 (0.01, 0.21)	1	0.08 (0.002, 0.43)
Self-injury worse	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Suicidal ideation	2	0.06 (0.01, 0.21)	1	0.08 (0.002, 0.43)
Subgroup total	*6*	*0.18 (0.06, 0.38)*	*3*	*0.23 (0.05, 0.67)*
Mood disorders				
Mood swings	5	0.15 (0.05, 0.34)	4	0.31 (0.08, 0.78)
Mood elevation	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Hypomania	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Subgroup total	*7*	*0.21 (0.08, 0.42)*	*6*	*0.46 (0.17, 1.00)*
Anxiety disorders				
Anxiety	10	0.29 (0.14, 0.54)	7	0.53 (0.21, 1.10)
Anxiety worse	4	0.12 (0.03, 0.30)	4	0.31 (0.08, 0.78)
Irritability	5	0.15 (0.05, 0.34)	4	0.31 (0.08, 0.78)
Panic	5	0.15 (0.05, 0.34)	2	0.15 (0.02, 0.55)
Stress reaction	4	0.12 (0.03, 0.30)	4	0.31 (0.08, 0.78)
Restlessness	2	0.06 (0.01, 0.21)	1	0.08 (0.002, 0.43)
Subgroup total	*30*	*0.88 (0.59, 1.25)*	*22*	*1.68 (1.05, 2.54)*
Aggressive reactions				
Agitation	2	0.06 (0.01, 0.21)	2	0.15 (0.02, 0.55)
Aggression	3	0.09 (0.02, 0.26)	3	0.23 (0.05, 0.67)
Subgroup total	*5*	*0.15 (0.05, 0.34)*	*5*	*0.38 (0.12, 0.89)*

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Table III. Contd

Clinical subgroup adverse event	Total cohort[a] (n = 3415)		Responder population[b] (n = 1310)	
	number of events	proportion total cohort[c] [% (95% CI)]	number of events	proportion responder cohort [% (95% CI)]
Cognitive changes				
Depersonalization	7	0.21 (0.08, 0.42)	6	0.46 (0.17, 1.00)
Concentration impaired	5	0.15 (0.05, 0.34)	5	0.38 (0.12, 0.89)
Thinking abnormal	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Confusion	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Subgroup total	*14*	*0.41 (0.22, 0.69)*	*13*	*0.99 (0.53, 1.70)*
Psychotic events				
Hallucinations	1	0.03 (0.0001, 0.16)	0	NA
Psychosis	1	0.03 (0.0001, 0.16)	0	NA
Paranoia	1	0.03 (0.0001, 0.16)	0	NA
Subgroup total	*3*	*0.09 (0.02, 0.26)*	*0*	*NA*
Withdrawal symptoms				
Withdrawal anxiety	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Withdrawal depression	2	0.06 (0.01, 0.21)	2	0.15 (0.02, 0.55)
Withdrawal symptoms	3	0.09 (0.02, 0.26)	3	0.23 (0.05, 0.67)
Subgroup total	*6*	*0.18 (0.06, 0.38)*	*6*	*0.46 (0.17, 1.00)*
Other				
Memory impairment	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Anorexia	1	0.03 (0.0001, 0.16)	1	0.08 (0.002, 0.43)
Total	*206*[d]	*6.03 (5.24, 6.91)*	*170*	*12.98 (11.10, 15.08)*

a The total cohort was defined as all patients with a varenicline dispensing from 1 April 2007 to 31 March 2008 and events in this column may have been identified from IMMP follow-up questionnaires, record linkage or spontaneous reports (see Methods section).

b The responder cohort is a subgroup of the total cohort and was defined as all patients for whom a valid follow-up questionnaire was received; therefore, the events in this column were identified from follow-up questionnaires only.

c Indicates percentage of patients in the cohort who experienced each adverse event.

d The total number of events is greater than the number of patients who experienced any psychiatric event (n = 138) because patients may have experienced more than one adverse event.

NA = not applicable.

and the remaining patient reported feeling "moody, unwell and craving cigarettes" after cessation of treatment. Two of these five patients who experienced withdrawal effects restarted varenicline at 0.5 mg daily and increased the dose until their symptoms were controlled. Once this had been achieved, the dose was gradually decreased before stopping varenicline.

Discussion

This intensive postmarketing study of varenicline showed that psychiatric events were a commonly-reported adverse effect of this smoking cessation medicine. The most frequent effects were sleep disorders, including insomnia, nightmares, dreams and other types of sleep disturbance. A key observation was that new-onset symptoms of depression were reported by approximately 2% of patients for whom a follow-up questionnaire was returned and a further 1% of patients in this group experienced a worsening or relapse of pre-existing depression. This finding translates to an important clinical message that at least three patients in every hundred prescribed varenicline are likely to experience symptoms of depression. Whilst it may be argued that smoking cessation itself may result in depression in some patients, assessment of the individual case reports in this study showed the majority of patients who developed

depression recovered on cessation of varenicline, which supports a causal association with this medicine.

Identification of psychiatric adverse events in this postmarketing study of patients taking varenicline was not unexpected. Clinical trials – including those conducted before varenicline was approved for marketing in New Zealand – reported psychiatric disorders as treatment-emergent adverse events.[13,14] However, there has been some debate regarding the relationship of these psychiatric reactions with varenicline. A pooled analysis of clinical trials funded by Pfizer (the marketing authorization holder for Champix®) concluded ''psychiatric events are uncommon and do not appear to be caused by varenicline *per se*''.[1] However, whilst this analysis reported ''no significant increase in several types of psychiatric adverse events'' in subjects treated with varenicline compared with placebo, it did show a significantly increased risk of sleep disorders and more patients taking varenicline experienced depressed mood disorders than those taking placebo.[1]

The incidence of depressed mood disorders in approximately 3000 varenicline patients included in several different company-sponsored clinical trials was 2.8%,[1] which is approximately similar to the rate reported in our study. Whilst it is interesting to evaluate how rates of adverse events in postmarketing studies compare with results from pre-marketing clinical trials, such comparisons must be undertaken with caution. Clinical trials are conducted in select populations and may exclude patients at risk of adverse reactions (for example those with a history of psychiatric illness), which may lead to an underestimation of risk in these studies. Postmarketing observational studies such as our nationwide cohort study include all patients prescribed the medicine in 'real-life' clinical use, where contraindications and warnings listed on datasheets are not always adhered to and thus the occurrence rates of psychiatric events may be expected to be higher than in clinical trials. However, underreporting of adverse events – either by the patient to their doctor, or by the doctor not reporting adverse events – is a limitation of our study that may result in an underestimation of the occurrence rates of adverse events in 'real-life' use. To reduce this possible effect – and compensate for the low return rate of questionnaires in this IMMP study – we used multiple follow-up methods, which included record-linkage to national morbidity and mortality datasets for virtually every patient in the varenicline cohort to identify serious, life-threatening and fatal adverse events.

A further limitation of our study was that there was no comparator group. Observational cohort studies do not usually include a placebo group as in clinical trials and whilst the IMMP has performed comparative studies,[15] this requires another similar medicine to have been monitored, preferably over the same time period. Unfortunately the IMMP has not monitored any other smoking cessation medicines and therefore comparison of results from this study is limited to other similar studies. Interim results from the English varenicline PEM study showed similar rates of some psychiatric events; for example, 1.2% of patients in the responder population of the English study reported anxiety[7] compared with 1.7% of patients in the IMMP responder group. However, our study identified a higher occurrence rate of new-onset depression – about 2% of the IMMP responder population reported this compared with about 1% in the English study.[7] There may be several reasons for this difference, including higher reporting rates of depressive events from New Zealand doctors and patients, better methods for identification of these adverse events in New Zealand, or reporting bias in New Zealand. The IMMP study was performed slightly later than the English study and doctors may have been aware of early postmarketing data on depression and suicide associated with varenicline.

In 2009, the US FDA approved a boxed warning for varenicline regarding the risk of serious neuropsychiatric events following receipt of spontaneous reports of psychotic events, severe agitation and aggression, and reports of suicidal ideation and completed suicide.[16] Our study also identified serious psychiatric events associated with varenicline, but the incidence of self-harm events in the first-year IMMP cohort was low: approximately 2 per 1000 patients, and the rate of

psychotic reactions was <1 per 1000. Thoughts and acts of aggression and violence associated with varenicline have been reported in other countries.[17] Whilst the IMMP identified three reports of aggressive behaviour, there were no reports of homicidal ideation or other serious thoughts or acts of violence towards others. The absence of reports of serious acts of violence in the responder population in our study might be explained by ascertainment bias, if the physician completing the questionnaire was unaware of the patient's thoughts/acts of violence. However, psychiatric events in the total cohort for our study also included those identified from spontaneous reporting, which was the method used to identify such reactions in the US,[17] and hospital admission events identified from national datasets. The use of multiple methods of event identification should reduce ascertainment bias, but is unlikely to eliminate it for adverse events such as thoughts of violence, which may not be reported to health professionals.

The risk of suicide associated with varenicline continues to be a controversial topic. This study identified one case of completed suicide, giving a rate of 3/10 000 (95% CI 0.07/10 000, 16/10 000), which was reported earlier in the study,[18] although, because of limited information for this case, a causal association with varenicline has not been proven. The English PEM study of 2682 varenicline patients identified five suicide attempts but none was fatal;[7] however, this study did not perform record linkage to mortality datasets as in our study and therefore completed suicides in the English cohort may have been missed. In ten company-sponsored clinical trials of varenicline, which included approximately 3000 patients randomized to varenicline, there were no cases of suicidal behaviour.[1] A British cohort study within the GPRD found there was no clear evidence that varenicline was associated with an increased risk of fatal or non-fatal self-harm compared with other smoking cessation therapies.[5]

In contrast with the findings from these studies, a significant number of cases of suicide and self-harm associated with varenicline use have been spontaneously reported to national monitoring programmes in the US[6] and Australia.[3] This apparently contradictory finding has been discussed in the letters pages of an international journal[6] and it is recognized that each pharmacovigilance study method has its limitations. There may be reporting bias in spontaneous reporting systems and the rate of suicide in varenicline patients cannot be calculated because the exposed population is not accurately known. Cohort event monitoring studies – such as this IMMP study – determine the exposed population from pharmacy dispensing data (which are more accurate than prescription records as some prescriptions are never dispensed[19]) and, by using intensive follow-up of all patients, we believe this study provides a reasonably accurate estimate of the risk of fatal and non-fatal self-harm events in patients taking varenicline.

This study is the first to report the frequency of varenicline withdrawal reactions, although there have been published case reports of withdrawal-induced hallucinations[20] and psychosis associated with varenicline withdrawal.[21] Our study did not identify any cases of acute psychosis induced by withdrawal of varenicline, but one case of withdrawal depression was reported as 'severe' and other cases of anxiety and agitation were reported as being significant to the patient. The New Zealand datasheet for varenicline includes mention of withdrawal-induced reactions, but states ''dose tapering of Champix is not required at the end of treatment''.[4] The results of our study suggest that doctors prescribing varenicline should warn patients of the risk of withdrawal reactions on stopping this medicine, although as yet there is no published guidance on how to treat such reactions.

Conclusions

This intensive postmarketing study of 3415 New Zealand patients demonstrates that psychiatric adverse events are commonly reported in association with varenicline. Approximately 3% of patients experienced symptoms of depression and the majority of these cases appeared to have a causal association with varenicline. Serious psychiatric reactions, including suicide, suicidal ideation

and psychotic reactions, were also identified, but these were less frequently reported.

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Privacy issues and ethics approval: The IMMP is a longstanding national medicines surveillance programme and its processes and practices have been approved by the New Zealand Privacy Commissioner. This study was carried out under the existing and ongoing IMMP ethical approval granted by the Otago Ethics Committee (Reference OTA/04/32/CPD).

Data access: Both authors of this study had access to the raw data collected in the study and take full responsibility for the material included.

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