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Cardiovascular Events in Patients taking Varenicline

A Case Series from Intensive Postmarketing Surveillance in New Zealand

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Abstract

Background: The smoking cessation medicine varenicline has been associated with an increased risk of cardiovascular adverse events compared with placebo in clinical trials. Cases of cardiovascular events, including myocardial infarction (MI) and cardiac dysrhythmias, have been noted from spontaneous reporting systems.

Objective: The aim of this study was to summarize and describe cardiovascular adverse reactions identified in a general population during intensive postmarketing surveillance of varenicline in New Zealand.

Methods: Observational prospective cohort study using prescription event monitoring methods. The patient cohort was established from pharmacy dispensing data sent directly to the Intensive Medicines Monitoring Programme (IMMP) for all New Zealand patients prescribed varenicline. Adverse cardiovascular events were identified from follow-up questionnaires completed by doctors, spontaneous reports and by record linkage to national datasets. Cardiovascular events were organized into clinical groupings for further clinical assessment, and key cases were identified.

Results: All New Zealand patients dispensed a prescription for varenicline from 1 April 2007 to 30 November 2010 were included in this study. At 31 January 2011, the IMMP varenicline events dataset included a total of 172 adverse events in the IMMP circulatory System Organ Class. There were 48 reports of myocardial ischaemia, including 12 reports of MI and 8 reports of angina. Two key cases of myocardial ischaemia suggested that this may have been induced by coronary artery spasm secondary to varenicline treatment. There were 50 reports of hypotensive events, with two key cases having

documented hypotension associated with chest pain/tightness, and a further 27 reports of dysrhythmia events, including two unexplained sudden deaths. **Conclusions:** This paper presents a series of cases of cardiovascular events in patients taking varenicline. Whilst there were multiple confounding factors in some patients, key cases were identified that suggested a possible mechanism of dysregulation of blood pressure leading to vasospasm or hypotension.

Background

Varenicline (Champix®, Pfizer Ltd), is a recent addition to the group of drugs licensed to aid smoking cessation. Varenicline is a partial agonist at the α4β2 nicotinic acetylcholine receptor (nAChR)[1-3] and has been demonstrated to be beneficial for smoking cessation.[2] The partial agonist properties of varenicline at the α4β2 nAChR receptor stimulate the release of dopamine, which may mimic the reward properties of regular smoking. At the same time, varenicline antagonizes the receptor system, which may reduce the psychostimulatory reward for cigarettes smoked during varenicline therapy.[2,4,5]

Efficacy of varenicline has been demonstrated in clinical trials.[6-8] It has superior short-term efficacy to other smoking cessation therapies such as bupropion and nicotine replacement therapy (NRT),[9] although a longer-term study showed varenicline had similar abstinence rates to NRT at 52 weeks.[10] Varenicline therapy has been associated with adverse events; most commonly, headaches, nausea, abnormal dreams and insomnia.[6,11] Other psychiatric effects have also been identified from postmarketing surveillance of varenicline,[12,13] and the product information includes warnings about the risk of neuropsychiatric effects.[14,15]

Recently, the US FDA communicated findings from its review of a clinical trial that included approximately 700 patients with cardiovascular disease,[16] and reported an increased risk of cardiovascular events in patients taking varenicline compared with placebo.[17] Following this, a systematic review and meta-analysis of the risk of serious cardiovascular events associated with varenicline has been published.[18] This systematic review included data from 14 clinical trials and concluded that varenicline was associated with an increased risk of serious adverse cardiovascular events compared with placebo.

In New Zealand, the postmarketing safety of varenicline has been monitored by the New Zealand Intensive Medicines Monitoring Programme (IMMP)[19,20] since 2007 when it was first marketed in this country. Routine review of IMMP adverse event reports for this medicine identified a group of reports of cardiovascular adverse events such as angina, myocardial infarction (MI), hypotension and arrhythmias. In light of recent concerns regarding the cardiovascular safety of varenicline, this paper presents a case series of these reports evaluated by the IMMP, and discusses possible mechanisms to explain these adverse events.

Methods

The IMMP performs postmarketing observational cohort studies on selected medicines using prescription event monitoring (PEM) methods, which have been described in detail previously.[20] 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 multiple 'intensive' methods.

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 (GP). 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.[21] As a further measure to identify deaths and adverse events resulting in hospitalization, the IMMP also undertakes record linkage to the New Zealand National Collections databases.

Varenicline Study

Monitoring of varenicline began in April 2007 when marketing of this medicine commenced in New Zealand. Follow-up questionnaires for varenicline were first sent to doctors in June 2008 and were then sent out every 4 months. Questionnaires for this study were based on previous IMMP questionnaires, with the primary aim being for doctors to record new clinical events since the patient started varenicline. Doctors recorded clinical events in an open table (i.e. there was no checklist of adverse events) that included columns to record the date of each event and the clinical outcome. Additional specific questions were included, including past smoking history, previous attempts at smoking cessation, past history of cardiovascular disease, and concomitant medications. For every patient in the IMMP cohort with a valid NHI number, record linkage to national datasets was performed to identify deaths and hospital admission events occurring from the time of starting varenicline to 1 month after the last dose (the date of each patient's last dose was calculated from the IMMP dispensing data records).

Returned questionnaires, record linkage data and other follow-up information were assessed by clinical staff at the IMMP. In line with routine practice 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).[22] Causality assessments were performed in line with standard methods[23] used at the New Zealand Pharmacovigilance Centre,[21] and adverse events were grouped into System Organ Classes (SOCs) for analysis.

Selection and Assessment of Cardiovascular Event Cases

Varenicline event reports coded in the IMMP circulatory (cardiovascular) SOC and entered into the IMMP database by 31 January 2011 were reviewed by clinical assessors. All reports in the circulatory SOC were included if the patient was taking varenicline at the time of the adverse event or within 1 month of their last dose (as determined from the IMMP dispensing data). Events in other SOCs that may have indicated a cardiovascular event (e.g. 'chest pain' initially coded in the IMMP musculo-skeletal SOC) were reviewed again by clinical assessors and further information was sought from reporters where necessary. If there was clinical evidence that the adverse event was due to a cardiovascular cause, reports were re-coded into the circulatory SOC. Likewise, further information obtained on events initially coded in the circulatory SOC that indicated the event was not a cardiovascular event, resulted in re-coding of the event into the appropriate SOC.

All event reports in the circulatory SOC were organized into the following clinical subgroups: myocardial ischaemia, heart failure, cerebrovascular events, cardiac dysrhythmias, hypotensive events, hypertensive events, thromboembolic events and 'other'. Further clinical assessment was undertaken of the cases of myocardial ischaemia, hypotensive and hypertensive events (in order to identify possible mechanisms for the myocardial ischaemic events) and cardiac dysrhythmias. Specific cases of clinical interest were selected to present as key/index cases.

Results

At 31 January 2011, the IMMP varenicline events dataset included a total of 2813 adverse events in all SOCs, with the highest proportion of events (699 events, 24.8% of all events) in the

IMMP alimentary SOC. In the circulatory SOC there were 172 adverse events (6.1% of all events) that occurred in 154 patients. The numbers of cardiovascular events in each clinical subgroup are shown in table I.

At 31 January 2011, the varenicline cohort included 15 847 New Zealand patients who had been dispensed varenicline between 1 April 2007 and 30 November 2010. At the time this study of cardiovascular events was conducted, IMMP follow-up questionnaires had been sent for 13 716 patients and a review of responses was ongoing, but incomplete. Full follow-up (review of responses to questionnaires and linkage to national datasets for all patients, including non-responders) had been completed for 8446 patients.

Table I. Cardiovascular events in the Intensive Medicines Monitoring Programme (IMMP) varenicline cohort

Clinical subgroup	Cardiovascular adverse event	No. of events
Myocardial ischaemia	Angina	8
	Chest pain	14
	Chest heaviness	2
	Chest tightness	2
	Chest pain worse[a]	7
	Myocardial infarction	11
	Ischaemic heart disease	2
	Myocardial re-infarction	1
	Coronary insufficiency worse[a]	1
	Subgroup total	*48*
Heart failure	Heart failure	2
	Heart valve disorder	2
	Oedema	3
	Subgroup total	*7*
Hypotensive events	Dizziness	36
	Faintness	3
	Hypotension	4
	Syncope	6
	Circulatory collapse	1
	Subgroup total	*50*
Hypertensive events	Elevated blood pressure	5
	Hypertension	8
	Hypertension worse[a]	3
	Subgroup total	*16*
Cardiac dysrhythmias	Tachycardia	2
	Palpitations	12
	Palpitations worse[a]	1
	Irregular pulse	1
	Atrial fibrillation	3
	Arrhythmia	1
	Heart block	1
	Prolonged QT interval	1
	Ventricular tachycardia	2
	Ventricular fibrillation	1
	Cardiac arrest	1
	Sudden death	1
	Subgroup total	*27*
Cerebrovascular events	Stroke	2
	Subarachnoid haemorrhage	1
	Subgroup total	*3*

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Case Reports of Myocardial Ischaemia

Of the 48 event reports clinically assessed as indicating myocardial ischaemia, 12 reports were confirmed as MI and a further 8 were confirmed as angina from the details on the case reports and follow-up information. One patient experienced angina followed by an MI; therefore, these 20 events occurred in 19 patients. These cases are summarized in table II.

One of the 12 cases of MI had documented evidence of coronary artery spasm as the likely cause of the infarction. This patient, a 48-year-old man with no significant medical history, had been taking varenicline for 22 days when he was hospitalized with chest pain described in the report as "ischaemic sounding". Investigations revealed ECG changes and a raised troponin level of 1.83 ng/mL; a diagnosis of non-ST elevation MI was made. Angiography reported occlusion of the right coronary artery caused by spasm rather than atherosclerosis and a normal left coronary arterial system. A stent was inserted and the patient recovered.

In addition to the cases of MI, there was a further interesting case of newly diagnosed ischaemic heart disease (IHD). A 62-year-old man with no past history of IHD presented to his GP with severe epigastric pain, nausea and headache on the 53rd day of taking varenicline. His doctor reported that the patient's symptoms

Table I. Contd

Clinical subgroup	Cardiovascular adverse event	No. of events
Thromboembolism	Thrombophlebitis	1
	Venous thrombosis	1
	Pulmonary embolism	1
	Arterial thromboembolism	1
	Mesenteric artery thrombosis	1
	Subgroup total	*5*
Other	Cardiomyopathy	1
	Unspecified cardiac disease	1
	Pericardial effusion	1
	Flushing	1
	Intermittent claudication worse[a]	1
	Peripheral vascular disease	4
	Atherosclerosis	1
	Vascular occlusion	2
	Arterial aneurysm	1
	Aortic aneurysm	2
	Aortic stenosis	1
	Other total	*16*
Total		**172**

a 'Worse' is the IMMP term applied to events that the patient may have experienced prior to starting the monitored medicine, but which recurred with increased frequency or intensity after starting the medicine.

were relieved on withdrawal of varenicline (positive dechallenge) and recurred on taking one varenicline tablet 1 week later (positive rechallenge). The patient was referred for investigations and a positive exercise stress confirmed a diagnosis of IHD. A stent was inserted the following month and the patient recovered. Clinical presentation of this case was not typical, but it was clearly documented that there was sufficient concern about the nature of the symptoms after starting varenicline for cardiac investigations to be requested.

Hypotension and Collapse

There were 50 event reports classified as hypotensive events (see table I), and the most commonly reported event in this group was dizziness. For these 36 cases, time to onset of event was reported for 32 patients, 22 (69%) of whom experienced dizziness within 14 days of starting varenicline.

In the hypotensive events group only four patients had confirmed hypotension (i.e. recorded by a medical practitioner). One of these cases was a 62-year-old man who presented to his GP with hypotension 1 day after starting varenicline. Two days later he complained of severe substernal chest pain, sweating associated with rigors and intense fatigue, which kept him away from work for 4 days. The following day varenicline was discontinued and he recovered (positive dechallenge). Another female patient (age not reported) experienced hypotension, dizziness, nausea and abnormal dreams after about 8 weeks of varenicline. Reducing the dose of varenicline to 0.5 mg daily was followed by some improvement.

There was also a report of circulatory collapse in a 56-year-old male patient with a history of hypertension who collapsed after consuming two bottles of beer. He had been taking varenicline 0.5 mg daily for 4 days; the report indicated that prior to taking varenicline this patient had not previously collapsed after drinking this amount of alcohol. The collapse was reported as 'severe', but the patient recovered after cessation of varenicline. In another case report, a 51-year-old woman taking varenicline 1 mg daily experienced chest tightness associated with feeling hot, sweating and neck/back pain shortly after consuming a small amount of alcohol and 'one puff' of marijuana. She had restarted varenicline 12 hours before this episode after stopping it for 3–4 days. The patient's symptoms were relieved by oxygen, and after admission to hospital she recovered quickly and was discharged the following day.

Hypertension

There were eight reports of documented new-onset hypertension, a further five of elevated blood pressure and three reports of worsening of hypertension in patients known to have had hypertension prior to starting varenicline. There was little data on dechallenge as some patients were treated for their hypertension and some

Table II. Cases of angina and myocardial infarction (MI) in the Intensive Medicines Monitoring Programme varenicline (var) cohort

Age (y)/sex	Medical history	Event	Time to onset	Time from last dose	Varenicline withdrawn	Outcome	Concomitant medicines
54/M	Previous MI	Angina	74 d	On med	No	Recovered. Var cont.	No information
59/M	Previous MI	Angina	30 d	17 d	NA	Recovered	No information
56/F	Depression	Angina	70 d	28 d	NA	Recovered	No information
50/F	IHD	Unstable angina	5 d	On med	Yes	Recovered	Aspirin (acetylsalicylic acid), metoprolol
60/M	IHD	Unstable angina	20 d	On med	Yes	Recovered. Stent inserted	Aspirin, doxazosin, metoprolol, simvastatin, cilazapril
40/M	Peripheral atherosclerosis	Unstable angina	22 d	On med	No	Recovered. Developed MI 2 mo after stopping var	Simvastatin, aspirin
64/F	Aortic stenosis	Unstable angina	63 d	On med	Yes	Recovered	No information
55/M	Stable aortic valve replacement	MI and new-onset angina 1 wk before	52 d	23 d	NA	Died within minutes	Simvastatin
57/F	Hypertension	MI	16 d (second course)	On med	Yes	Recovered	Doxazosin, bendroflumethiazide, amlodipine, potassium chloride, fluoxetine
48/M	Nil	MI	22 d	On med	Yes	Recovered. Stent inserted	Nil
58/M	Peripheral atherosclerosis	MI	22 d (second course)	On med	No	Recovered. Var cont.	Nil
61/M	No information	MI	38 d	On med	No	Recovered. Var cont.	No information
48/M	No information	MI	43 d (second course)	On med	Yes	Recovered	No information
48/M	IHD, hypertension, hyperlipidaemia, migraine	MI (during stent procedure)	63 d	On med	No	Recovered. Var cont.	Cilazapril, nortriptyline, simvastatin, metoprolol, pantoprazole, clopidogrel, aspirin
51/M	No information	MI	16 d	2 d	NA	Recovered	No information
67/F	Hypertension, hypercholesterolaemia, CVA 5 d prior to MI and diagnosed with ovarian cancer concurrently	MI	42 d	5 d	NA	Died 25 d after MI from ovarian cancer	Felodipine, quinapril/hydrochlorothiazide, metoprolol, simvastatin
50/M	No information	MI	101 d	5 d	NA	Recovered	No information
56/M	Nil of note	MI	23 d	9 d	NA	Recovered	Nil
61/F	Previous MI	Myocardial re-infarction	6 d	On med	No	Recovered. Var cont.	No information

cont. = continued; **CVA** = cerebrovascular accident; **F** = female; **IHD** = ischaemic heart disease; **M** = male; **med** = medication; **NA** = not applicable.

continued varenicline. There were no reports of new-onset or aggravated hypertension in association with serious events.

Cardiac Dysrhythmias and Sudden Death

The clinical subgroup 'cardiac dysrhythmias' included 27 event reports, which occurred in 23 patients (four patients had two dysrhythmia events each). There were 12 reports of new-onset palpitations, but none of these patients had a documented arrhythmia. A 40-year-old male patient with known non-obstructive hypertrophic cardiomyopathy and receiving long-term treatment with metoprolol for palpitations, complained of worsening palpitations 21 days after starting varenicline. Holter monitoring detected episodes of ventricular tachycardia associated with the patient's palpitations. The patient discontinued varenicline and the dose of metoprolol was increased from 47.5 mg to 95 mg daily. About 5 months later he restarted varenicline and 1 month later was admitted to hospital with chest pain, but no further information was available regarding this hospital admission.

Two patients in the cardiac dysrhythmia subgroup had a fatal outcome and their case reports are described below:

Case 1: A 39-year-old man taking varenicline for 22 days was hospitalized with ventricular fibrillation and a cardiac arrest. He had no history of cardiac disease or any family history of premature heart disease. His only concomitant medicine was celecoxib 200 mg taken 'occasionally' for the treatment of ankylosing spondylitis. Following admission to hospital he died with no definitive underlying cause identified for his fatal cardiac arrest.

Case 2: A 49-year-old man who had been taking varenicline for 32 days was found dead at his home. He had a history of hypertension and hyperlipidaemia and was taking lipid-lowering medication. One month before his death he was treated for 'pleurodynia of probable viral origin' with amoxicillin 500 mg three times daily and naproxen 550 mg twice daily. Post-mortem examination revealed left ventricular hypertrophy and severe focal coronary artery disease with 75% stenosis of the left anterior descending and right coronary arteries. However, no thrombosis was noted and it was reported that the stomach contents smelled strongly of alcohol.

Discussion

This intensive postmarketing surveillance study has identified a number of cardiovascular adverse events in New Zealand patients taking the smoking cessation medicine varenicline. At first review, the observation of reports of myocardial ischaemia and other types of cardiovascular event was not unexpected in the varenicline IMMP cohort. Cigarette smoking is a major risk factor for cardiovascular disease, which is the leading cause of death in smokers.[24] Smokers have a background risk of cardiovascular disease that is greater than non-smokers for men from age 35 years and for women from age 45 years, even in the absence of other risk factors. The 5-year absolute cardiovascular risk can increase to over 20% as hypertension and dyslipidaemia develop, and may be even higher if the patient becomes diabetic.[25]

Careful and repeated clinical assessment of the case reports in this study identified a series of new-onset cardiovascular events, some of which appeared to have a causal association with varenicline. Three of four patients who developed unstable angina after starting varenicline recovered after varenicline was withdrawn, and this observation of positive dechallenge (and the temporal association with varenicline administration) supported a causal association. However, assessment of one of these cases was confounded by the treatment of the unstable angina by placement of a stent, and this may have been the reason for the patient's recovery, rather than the withdrawal of varenicline. In addition to this issue, dechallenge assessment was not always appropriate for completed cardiovascular events such as MI, or terminal events such as cardiac arrest/sudden death.

This study identified 48 reports of symptoms of myocardial ischaemia in patients taking varenicline (or within 1 month of stopping varenicline treatment). This number is likely to be an underestimate due to underreporting, which is a

recognized limitation of spontaneous reporting programmes and, to a lesser extent, PEM studies.[26] However, the multiple methods of follow-up used by the IMMP should reduce the effect of underreporting. A further limitation of our study was that the IMMP clinical assessments were based on information provided by the reporters. As a national reporting centre, the IMMP receives secondary information from reporting doctors and clinical detail about some of the cases was limited, even after attempts to follow up cases further.

Awareness of the multiple confounding issues in many of the patients included in this series was an important consideration during the clinical assessments and causality assessments performed in this study. All patients in the IMMP varenicline cohort had a history of smoking and some had other documented history of cardiovascular disease. It is also possible that patients with no reported evidence of previous cardiovascular disease did in fact have pre-existing disease, possibly undiagnosed at the time they started varenicline. The IMMP cohort of patients taking varenicline represented 'real-life' postmarketing use of this medicine and there were no exclusion criteria as in pre-licensing clinical trials. In this general population, our study identified patients with no known history of cardiovascular disease who experienced cardiovascular events for the first time after starting varenicline. This prompted further clinical assessment of the event reports in the IMMP datasets and identification of some key cases that suggested a causal association with varenicline.

Other Evidence Regarding Varenicline and Cardiovascular Events

Regulatory authorities in other countries using spontaneous reporting systems have identified reports of cardiovascular events, including MI and arrhythmias in patients taking varenicline.[27] In 2010, the results of a multicentre, randomized clinical trial of varenicline in patients with pre-existing cardiovascular disease were published.[16] This Pfizer-sponsored study showed that 7.1% and 5.7% of patients in the varenicline and placebo groups, respectively, experienced a cardiovascular event.[16] This increased risk with varenicline led the US FDA to release a safety alert for varenicline regarding the risk of cardiovascular events.[17]

More recently, a meta-analysis of 14 double-blind, placebo-controlled trials demonstrated a significantly increased risk of serious cardiovascular adverse events in patients prescribed varenicline compared with placebo.[18] In this meta-analysis, the risk of serious cardiovascular adverse events was 1.06% (52/4908) in varenicline patients compared with 0.82% (27/3308) in patients given placebo. The primary outcome measure in all the studies included in this meta-analysis was efficacy of varenicline, and the trials excluded patients with a recent history (in the last 6 months) of cardiovascular disease (eight studies), unstable cardiovascular disease (two studies) or any history of cardiovascular disease (four studies).

The evidence from these clinical trials, which have the advantage of including a randomized, placebo-controlled group of patients, suggests that varenicline increases the likelihood of cardiovascular events, both in patients with known cardiovascular disease and those without such a history. These results are consistent with the findings of our postmarketing observational study, but it is not clear how varenicline may induce these effects. There is some evidence that MI may be induced by various triggers in susceptible patients,[28] and it is possible that varenicline acts as another trigger for cardiovascular events in patients already at risk because of their smoking history and because of their already compromised cardiovascular systems.

Possible Mechanisms

In order to consider our observations further, the cardiovascular events identified in this study were separated into clinical groups based on the type of event experienced (recognizing that one patient may have experienced more than one event) and the possible mechanisms that might explain the cardiovascular adverse event.

The clinical histories of two key cases of myocardial ischaemia in this series suggested that varenicline may have induced spasm of the cor-

onary arteries. Coronary spasm is a temporary narrowing of the coronary artery, which can induce an MI.[29] Furthermore, coronary spasm may also lead to sudden death, syncope and life-threatening arrhythmias such as ventricular fibrillation, ventricular tachycardia or atrioventricular block.[30-32] Thus, this mechanism might also explain some of the cases of dysrhythmias and sudden death in the IMMP cohort. Smoking is an independent risk factor for developing coronary spasm[33,34] and it is possible that varenicline, via its action on the α3β4 receptors in the peripheral ganglia[35] leading to release of acetylcholine, may add to this risk or trigger coronary spasm in susceptible individuals. Acetylcholine is used clinically to provoke coronary artery spasm (acetylcholine provocation test);[36] hence, acetylcholine release induced by varenicline may increase the risk of coronary spasm. Interestingly, two cases of cerebral vasospasm associated with varenicline have been presented at a recent neurology meeting,[37] with both patients having formal angiography to demonstrate the vasospasm. It is possible that, by a common mechanism, varenicline may induce vasospasm in different regions of the cardiovascular system.

An alternative (or additional) mechanism to explain the cases of cardiac arrhythmias and sudden death in this series (and other reports[27]) may be via varenicline-induced release of catecholamines. Nicotine produces a significant increase in plasma levels of dysrhythmogenic catecholamines.[38] Varenicline, by its action on nicotinic receptors partially agonizing the release of dopamine, may also induce release of arrhythmogenic catecholamines. In addition, patients may continue to smoke cigarettes during treatment with varenicline, and this dual enhancement of catecholamine release may lead to cardiac arrhythmias.

Whilst it is recognized that chronic hypertension is a risk factor for cardiovascular events, including MI and stroke,[39-41] our case-series study produced only a weak signal of increased blood pressure with varenicline use and did not identify a signal of cases of new-onset hypertension associated with cardiovascular events. However, the Champix® product information indicates that blood pressure was elevated in clinical trials of varenicline more often than with placebo,[14] and this is supported by animal studies of increased renal sympathetic activity with an α7-agonist.[42] Small-to-moderate increases in blood pressure may not be relevant to the onset of serious cardiovascular events with varenicline as courses of treatment are usually 3–6 months or less.

In contrast, the observation of a cluster of cases suggesting hypotension associated with varenicline (mainly during the first 2 weeks of treatment), and key cases in which patients who experienced hypotension followed by (or associated with) chest pain, led us to consider whether this might be a mechanism to explain cardiovascular events such as myocardial ischaemia, especially in susceptible patients. Such a mechanism may also explain the large number of reports in the US FDA datasets of 'sudden loss of consciousness' in patients taking varenicline.[27] When varenicline (1 mg twice daily) and NRT (transdermal 21 mg/day) were coadministered to smokers (n = 24) for 12 days, there was a statistically significant decrease in average systolic blood pressure.[14] Thus, it is possible that patients continuing to smoke at the start of varenicline therapy (the product information advises patients to stop smoking on day 8 of treatment[14]), or at other times when taking varenicline, may be at higher risk of hypotensive events.

Studies have demonstrated that nAChRs are present in key areas of the CNS that regulate blood pressure. The brainstem, nucleus tractus solitarius, rostral ventrolateral medulla and caudal ventrolateral medulla express functional α4β2 and α7 nAChR receptors.[43,44] Studies have demonstrated that pharmacological manipulation with α4β2 and α7 nAChR agonists and antagonists significantly affected arterial blood pressure and heart rate in an animal model.[42] In the mammalian brain, the brainstem plays a vital role in peripheral cardiovascular autonomic function[45-47] and therefore it can be hypothesized that varenicline, with its partial and full agonist properties at α4β2 and α7 nAChRs, respectively, may centrally influence blood pressure homeostasis.

Conclusions

This case-series study presents a summary of 172 adverse cardiovascular events identified in 154 varenicline patients in an intensive postmarketing study in New Zealand. Adverse events were organized into clinical groupings, including myocardial ischaemia, hypotension and dysrhythmias, and repeated clinical review identified cases considered to have a causal relationship with varenicline. Whilst there were difficulties with assessment of cardiovascular events in patients with multiple confounding factors, we identified some key cases that suggested a possible mechanism of dysregulation of blood pressure leading to vasospasm or hypotension to explain the occurrence of these events in varenicline patients. Further studies of varenicline with the primary endpoint of adverse cardiovascular events are needed to confirm or refute the association with cardiovascular events.

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