Eur J Clin Pharmacol (2012) 68:1065–1072
DOI 10.1007/s00228-012-1220-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Epistaxis and other haemorrhagic events associated with the smoking cessation medicine varenicline: a case series from two national pharmacovigilance centres

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Received: 29 June 2011 / Accepted: 13 January 2012 / Published online: 8 February 2012

Abstract
Purpose To present a case series of haemorrhagic events associated with varenicline identified from the New Zealand (NZ) and Netherlands national pharmacovigilance centres and propose a possible mechanism for these adverse events.
Methods Reports of epistaxis and other haemorrhagic events (in all system organ classes excluding gynaecological) associated with varenicline were identified and assessed in both the NZ Intensive Medicines Monitoring Programme (IMMP) and the Netherlands Pharmacovigilance Centre Lareb (Lareb). Additional reports were identified from the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) datasets, and these also underwent causality assessment.
Results A total of 30 reports of haemorrhagic events were identified by the NZ IMMP (16 reports) and Lareb (14 reports). Six cases of epistaxis were identified, and four patients had a positive dechallenge on withdrawal of varenicline, suggesting a causal association. Another five reports of gingival bleeding were identified, with three patients having a positive dechallenge. Another patient who experienced haemoptysis while taking varenicline had a positive dechallenge and a positive rechallenge. In the WHO datasets, a further 49 reports of epistaxis, 39 reports of haemoptysis and 21 reports of thrombocytopenia were identified. A plausible mechanism for haemorrhagic events associated with varenicline may be a result of interaction with the serotonin (5-HT) receptor system and transporter.
Conclusions This is the first specific investigation of haemorrhagic events associated with varenicline. The results of our assessment of reports identified by two national pharmacovigilance centres suggest that there may be causal relationship between varenicline and these adverse events.

Keywords Varenicline · Epistaxis · Bleeding · Adverse events · Haemorrhage

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Introduction

Varenicline tartrate (Champix, Chantix) is a selective nicotinic acetylcholine receptor partial agonist which is approved in several countries as a smoking cessation aid. It was the first medicine of this new class to be approved in New Zealand, where it has been marketed since 2007, and in the Netherlands, where it was licensed through a centralised procedure in 2006.

In clinical trials varenicline was shown to be more effective in assisting patients with smoking cessation than placebo [1, 2], bupropion [2] and nicotine patches [3]. However, safety issues have been identified during the post-marketing period, including the risk of psychiatric adverse reactions

[4–6] which are now listed on the varenicline product information [7, 8]. Despite these concerns, varenicline has become a popular treatment for smoking cessation, and its recent subsidisation in NZ [9] is likely to result in further increases in its use.

In New Zealand (NZ), varenicline has been monitored during the post-marketing period by the Intensive Medicines Monitoring Programme (IMMP) [10] of the NZ Pharmacovigilance Centre. In the Netherlands, varenicline has been monitored through the spontaneous reporting system since the start of marketing and also by the intensive monitoring system of the Netherlands Pharmacovigilance Centre Lareb (Lareb) since December 2008. Routine review of adverse event reports by the IMMP identified cases of epistaxis (nose-bleeding) and other reports of bleeding in patients taking varenicline. These were presented at the World Health Organisation (WHO) National Pharmacovigilance Centres meeting in 2010. Subsequent review of the Lareb dataset identified additional cases of haemorrhagic events. This report summarises the data from both the IMMP and Lareb and proposes a possible mechanism to explain the occurrence of these adverse events in patients taking varenicline.

Methods

Assessment of reports of epistaxis and other haemorrhagic events associated with varenicline was undertaken in both the NZ and Netherlands pharmacovigilance centres as described below. Both centres reviewed reports of bleeding in any system organ class (SOC; see below for further detail). Reports of gynaecological bleeding were excluded from further analysis as the mechanism and regulation of menstrual bleeding is different to other types of haemorrhage. Additional reports of epistaxis, haemoptysis and thrombocytopenia were identified from the WHO Uppsala Monitoring Centre (WHO-UMC) datasets as detailed below.

New Zealand IMMP

The IMMP operates within the NZ Pharmacovigilance Centre (NZPhvC), which is the national pharmacovigilance centre for New Zealand [11]. The NZPhvC is based at the University of Otago and works under contract to the NZ Ministry of Health (Medsafe). The IMMP performs prospective observational cohort studies on selected medicines using prescription event monitoring (PEM) methods that have been described in detail previously [10]. In brief, the cohort of patients for each monitored medicine is established from dispensing data collected directly from pharmacies throughout NZ. Patients dispensed the monitored medicines are then 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. The IMMP also undertakes record linkage to the NZ National Collections databases to identify deaths and adverse events resulting in hospitalisation [10]. Additional information is received from spontaneous reports (yellow cards) sent to the NZPhvC by health professionals, pharmaceutical companies and patients [11]. Based on this procedure, the IMMP is able to identify reports of adverse events from multiple sources and has processes in place to check for any duplicate reports.

Varenicline study

Monitoring of varenicline began in April 2007 when marketing of this medicine commenced in New Zealand. Prescription data have now been entered for all NZ patients dispensed varenicline from 1 April 2007 to 30 November 2010. Follow-up questionnaires for this study were based on previous IMMP questionnaires, with the main purpose to ask doctors to record all new clinical events since the patient started varenicline. Doctors recorded clinical events in an open table (i.e. there was no check-list of adverse events) which included columns to record the date of each event and the clinical outcome.

Returned questionnaires, record linkage data, spontaneous reports and any other follow-up information are assessed by clinical staff at the IMMP as the monitoring study progresses. All adverse events occurring while the patient was taking the medicine and for 1 month after the last dose are coded using terms from a specialised dictionary based on the WHO adverse reaction terminology (WHOART) [10]. Causality assessments are performed in line with standard methods used at the NZPhvC [11, 12], the purpose of which is to determine the strength of the relationship between a medicine and a particular adverse event [reference: http://www.who-umc.org/Graphics/24734.pdf]. Once coded, adverse events are grouped into SOCs for analysis. At the time this study was performed, the follow-up of patients in the varenicline cohorts was still ongoing.

Assessment of cases of epistaxis and other bleeding disorders

The IMMP SOC 'Haematological' was reviewed for all adverse events identified and entered into the dataset by 31 January 2011. Adverse events for other SOCs were also reviewed by a clinician to identify any other reports of haemorrhagic events (for example, cerebral haemorrhage events are coded in the 'Circulatory' SOC). A haemorrhagic event was defined as any bleeding event (e.g. epistaxis, gum bleeding or haemoptysis) or an event clinically considered to be a risk factor for bleeding (e.g. thrombocytopenia). All

reports identified were reviewed, and causality assessments were performed by clinical assessors. For haemorrhagic events identified in this study, key factors considered in the causality assessments included the calculation of time to onset of the bleeding event after starting varenicline and the assessment of confounding factors, such as disease or concomitant medicines, the result of withdrawal of varenicline on the bleeding symptoms (dechallenge) and the result of rechallenge with varenicline if available. Causality assessments were based on the information provided on each report, with additional information sought as required (and when possible) from individual reporters.

Netherlands Pharmacovigilance Centre Lareb

The Netherlands Pharmacovigilance Centre Lareb is responsible for the collection and analysis of reports submitted to the spontaneous reporting system in the Netherlands. In the Netherlands, doctors, pharmacists and patients can submit reports to the spontaneous reporting system. Lareb also receives reports from the marketing authorisation holders. Lareb is not a part of the regulatory authority and can therefore not undertake any regulatory action. Instead, quarterly reports are sent to the regulatory authority, the Dutch Medicines Evaluation Board, with new signals identified. In 2006, the Lareb intensive monitoring (LIM) system was introduced as a compliment to the spontaneous reporting system [13].

Lareb intensive monitoring of varenicline

Patients eligible for inclusion in the varenicline study are identified in the pharmacy upon filling of the first prescription of varenicline. A first prescription signal is generated by the pharmacy computer software if the patient has not filled a prescription of that particular drug in the previous 12 months. The patient is informed about the study and asked to participate. An information flyer is handed to the patient, together with a specific code, which is used when the patient signs up for the study online. Upon registration, patients are asked for an e-mail address that can be used for further correspondence. The patient is asked to provide personal information, such as gender, date of birth, height and weight, as well as information on use of the study drug, including start date, strength, product code, dosage, administration form and indication for use. This information is also collected for all concomitant medication. After registration, the patient receives questionnaires by e-mail at specific points in time which include questions on possible adverse drug reactions, seriousness of event [Council for International Organisations of Medical Sciences (CIOMS) criteria], start date of event, action taken with the study drug (stopping/dose reduction/no dose change) and outcome of the event. If the patient states that he/she has stopped the medicine, no further questionnaires will be sent.

All data are stored in an Oracle database. The indication and reported adverse events are coded with a Medical Dictionary for Regulatory Activities (MedDRA) lower level term (LLT) by a qualified assessor. Study drug and co-medication are coded using the Dutch drug dictionary (Z-index). If a report is considered to be serious according to the CIOMS criteria, a copy of the report is exported to the national database containing all spontaneous reports, where it is handled according to the regulations regarding serious adverse drug reaction reports. The LIM methodology has been described in detail previously [14].

Assessment of cases of epistaxis and other bleeding disorders

The Lareb database and the LIM database were searched on 31 March 2011. All reports coded as MedDRA preferred term ‘epistaxis’ were identified. In addition, all other reports where varenicline was reported as the suspect or interacting drug were reviewed by LH in order to identify other reports of haemorrhagic events. The definition of a haemorrhagic event was defined in the same way as for the NZ IMMP database. All reports identified were reviewed and causality assessments performed. Factors considered in the causality assessments for bleeding events were similar to those used at the NZ IMMP and as outlined above.

WHO-UMC data

The WHO-UMC enters spontaneous reports received from all national pharmacovigilance centres into the UMC Vigibase dataset. To date, this database contains more than 6 million reports from more than 100 countries. The WHO dataset was searched for reports of epistaxis, haemoptysis and thrombocytopenia. All cases were reviewed by clinical assessors at the IMMP (MHW and MT) to determine if they had sufficient data for assessment. This was defined as having enough information to verify that the haemorrhagic event occurred after the patient had started taking varenicline. Causality assessments were then performed for the WHO reports with sufficient information for analysis.

Results

IMMP cases

In the IMMP ‘Haematological’ SOC on 31 January 2011 there were 18 adverse event reports concerning patients either taking varenicline at the time of the adverse event or who were within 1 month of stopping the medicine. Of

these, 12 events were clinically assessed as haemorrhagic events and included three reports of epistaxis, two reports of haemoptysis, two reports of bleeding gums, one report of subungual haematoma, one report of scrotal haematoma, one report of bowel bleeding, one report of thrombocytopenia and one report of splenic rupture. A further report of acute sub-arachnoid haemorrhage was identified in the 'Circulatory' SOC. There were also two reports of rectal bleeding in the 'Alimentary' [gastrointestinal (GI)] SOC, and one report of sub-conjunctival haemorrhage was identified in the 'Eye' SOC.

Of the 16 haemorrhagic events identified, nine were assessed as having a causal relationship with varenicline, and these cases are summarised in Table 1. A key case was that of a 44-year-old asthmatic women who experienced haemoptysis and dysphonia (see Patient 'S', Table 1) which was spontaneously reported to the IMMP. This patient began coughing blood 10 days after starting varenicline (expected dose at day 10=2 mg daily). The haemoptysis and dysphonia resolved upon stopping varenicline, and her doctor reported that the symptoms re-occurred when varenicline was commenced again (positive rechallenge).

Of the 16 haemorrhagic events identified by the IMMP, two had a fatal outcome. The first concerned a female patient, aged 65 years who died from an acute subarachnoid haemorrhage within 7 days of stopping varenicline. This patient had a prior history of a benign brain tumour, but this had been successfully treated with radiotherapy 11 years earlier (her general practitioner reported she was stable during this time). In addition to the subarachnoid haemorrhage, a right-sided cerebrovascular accident (CVA) was also listed as a cause of death. The second concerned a 46-year-old man with chronic lymphocytic leukaemia who was dispensed a Starter Pack (14 days treatment) of varenicline. About 3 weeks after the last dose (estimated from IMMP dispensing records), this patient developed liver capsule distension, was admitted to hospital and subsequently died from a ruptured spleen. He was reported to have thrombocytopenia before he died, but it was unclear when this developed during the course of his illness.

Lareb cases

On 31 March 2011 the Netherlands Pharmacovigilance Centre Lareb had received 13 reports via the spontaneous reporting system concerning epistaxis and other haemorrhagic events associated with the use of varenicline. Two duplicate reports were identified, bringing the total number of unique cases to 11. An additional three reports were retrieved through the LIM system. In total, Lareb identified three reports of epistaxis, three reports of bleeding gums, three reports of haematochezia, two reports of CVA and one report of thrombotic thrombocytopenic purpura, one report of 'blood-filled blisters' in the mouth and one report of bleeding in the mouth. For more details on these 14 cases, see Table 1.

WHO-UMC cases

A further 49 reports of epistaxis associated with varenicline were identified in the WHO-UMC dataset. Of these, 21 reports (43%) had sufficient data to verify that epistaxis occurred after the patient had started taking varenicline and were therefore included in this analysis. Nine reports were from the USA, seven from the UK, two from Australia and one each from Mexico, Switzerland and Finland. Of the 21 reports with sufficient information for assessment, the time to onset of epistaxis ranged from 1 to 85 days, with an average onset interval of 20.4 days. Varenicline was reported to have been withdrawn in 14 of the patients mentioned in these reports, but outcome was reported as unknown for 12 of these patients. For the remaining two patients, epistaxis was reported to have abated when varenicline was withdrawn (positive dechallenge); consequently, these cases were assessed as having a probable relationship.

The WHO-UMC database contained 39 reports of haemoptysis associated with varenicline, with five (13%) reports containing sufficient information for assessment. Of the five patients concerned, four cases were assessed as having a possible relationship with varenicline.

Twenty-one reports of thrombocytopenia were identified in the WHO-UMC database, of which eight (38%) contained sufficient information to ascertain that thrombocytopenia had developed after the patient had started taking varenicline. Two of these patients died. Causality assessment of the eight reports with sufficient information suggested a possible relationship of thrombocytopenia with varenicline for seven patients. However, two of these patients were taking other medicines (spironolactone, metoprolol and imiquinod) which have been reported to cause thrombocytopenia.

Discussion

This investigation of two national pharmacovigilance centre datasets has identified a case series of haemorrhagic events in patients taking varenicline for smoking cessation. The IMMP and Lareb identified a total of six cases of epistaxis, with four of these cases having a positive dechallenge—i.e. the patient's nose bleeding resolved upon the withdrawal of varenicline. An additional five reports of gingival bleeding were identified, with three of these reports containing evidence of positive dechallenge, suggesting a causal association with varenicline. There were also seven reports suggestive of other bleeding from the GI tract (4 reports of

Table 1 Reports of haemorrhagic events identified from the datasets of the New Zealand Intensive Medicines Monitoring Programme and Netherlands Pharmacovigilance Centre Lareb assessed as having a causal association[a] with the use of varenicline

Patient (sex, age)[b]	Suspected adverse drug reaction	Concomitant medication	Time to onset	Action with drug, outcome	Causality assessment[a]	Notes
A (F, 76)	Epistaxis	Nifedepine, metoprolol, furosemide, calcium carbonate	12 days	Drug withdrawn, recovered	Possible	Epistaxis first treated with nose sponge, but 3 days later patient hospitalised and treated with coagulants.
B (F, 47)	Epistaxis, night sweats pruritus	None reported	14 days	Drug withdrawn, recovered	Probable	
C (M, 35)	Epistaxis	None reported	1 day	Dose not changed. recovered	Possible	
D (M, 39)	Epistaxis	None	27 days	Drug withdrawn, recovered	Probable	No relevant medical history
E (M, 47)	Epistaxis, dizziness	Lacetylsalicylic acid, metformin, glibenclamide, cilazapril, simvastatin	15 days	Drug withdrawn, recovered	Probable	Patient had diabetes and hypertension
F (F, 21)	Epistaxis, vomiting, abnormal dreams	Medroxyprogesterone	16 days after last dose	Outcome not reported	Possible	Patient required cautery to treat bleeding
G (F, 56)	Gingival bleeding, haematochezia, diarrhea	None reported	35 days	Action taken with the drug is unknown, not recovered	Possible	No haemorrhoids or constipation
H (M, 47)	Gingival bleeding	None reported	2 months	Drug withdrawn, recovered	Probable	
I (F, 49)	Gingival bleeding	None reported	16 days	Drug withdrawn, recovering	Probable	
J (F, 46)	Gingival bleeding	Warfarin, citalopram	Unknown	Drug withdrawn, recovered	Probable	No problems with bleeding before start of varenicline
K (F, 56)	Gingival bleeding muscle spasms	None reported	Unknown	Dose not changed, unknown	Possible	
L (F, 58)	Haematochezia, hypermenorrhea, anger	None reported	3 days	Drug withdrawn, recovered	Probable	No menstruation for previous 5 months, but during varenicline use menstruated heavily
M (F, unknown)	Haematochezia, abnormal sensation of limbs, flatulence, taste alteration	None reported	Within 1 month	Dose not changed, unknown	Possible	
N (F, unknown)	Haematochezia, gastric disorder	None reported	Within 1 month,	Unknown, unknown	Possible	
O (F, 39)	Thrombotic thrombocytopenic purpura	Ibuprofen	1 month	Drug withdrawn, recovered	Possible	Thrombo's 17* 10E9/l. Patient was treated with high dose prednisolone and plasmafereses
P (F, 71)	Thrombocytopenia	Acetylsalicylic acid, atorvastatin, clizapril/ thiazide, thyroxine, amitriptyline, omeprazole	26 days	Dose not changed, unknown	Possible	
Q (M, 72)	CVA, headache, nausea, bad mood	Nitroglycerin, acetylsalicylic acid, metoprolol, tiotropium, omeprazole	1 week	Drug withdrawn, recovered	Possible	Patient had known cardiovascular disease
R (M, 49)			2 days	Drug withdrawn, recovered with sequelae	Possible	CVA caused by bleeding in the left thalamus. Patient smoked 50 cigarettes a day.

Table 1 (continued)

Patient (sex, age)[b]	Suspected adverse drug reaction	Concomitant medication	Time to onset	Action with drug, outcome	Causality assessment[a]	Notes
S (F, 46)	Haemoptysis, dysphonia	Thyroxine, oestradiol, nortriptyline, naproxen, omeprazole, asthma medications	10 days	Drug withdrawn, recovered	Definite	Positive rechallenge
T (F, 47)	Sub-conjunctival haemorrhage, blood pressure increased	None reported	44 days, 1 day after cessation	Recovered	Possible	
U (F, 64)	Subungual haematoma	Estradiol patch	3 days	Dose not changed, unknown	Possible	
V (F, 53)	Bloodfilled blisters in the oral mucosa		6 weeks	Drug withdrawn, recovering	Possible	
W (M, 46)	Bleeding in the mouth, cough, throat pain	Acetylsalicylic acid, atorvastatin	3 days	Dose not changed, recovered	Possible	

CVA, Cerebrovascular accident

[a] Causality assessments were performed in accordance with standard methods, using the terms defined in 'The use of the WHO-UMC system for standardised case causality assessment' (http://www.who-umc.org/Graphics/24734.pdf)

[b] Sex (F, female; M, male) and age (in years) are given in parenthesis

haematochezia in Lareb plus 3 reports of GI bleeding in IMMP). Although one of these seven patients had a positive dechallenge, information was lacking or there were confounding issues (e.g. constipation) for the other six patients which made causality assessment difficult. A further confounding issue in this case series was concomitant medicines. Of the 23 patients summarised in Table 1, seven had been taking concomitant medications that could possibly affect coagulation. It is possible therefore, that bleeding in these patients was exacerbated by an additive, accumulative or interactive effect of the concomitant medicine with varenicline.

A key case in this study was the report of haemoptysis submitted to the IMMP, in which the patient experienced a positive rechallenge. The reporting doctor did not initially suspect any relationship of the patient's symptoms with varenicline, as respiratory tract infections and other causes of coughing blood are common in smokers. However, there was no evidence of other pathology, and when varenicline was restarted the patient began to cough blood again. This history, including the positive rechallenge, suggested a causal relationship with varenicline. There were no reports of haemoptysis to Lareb, but this may be an under-reported adverse effect of varenicline as physicians (and patients) may assume this symptom is due to underlying pathology associated with a history of smoking.

Supporting data obtained from the WHO-UMC dataset identified a further 49 cases of epistaxis associated with varenicline reported from other countries. However, less than half of these cases had sufficient information for assessment, with dechallenge information only available for two cases, which limited the usefulness of the WHO data. Likewise, the majority of the WHO case reports of haemoptysis and thrombocytopenia contained insufficient information for assessment, and while it is interesting to note these cases as supporting data, further detailed assessment to determine causality was not possible for most reports.

Insufficient clinical information for assessment in some cases is a limitation of this study and is a recognised issue with adverse reaction case reports submitted to national pharmacovigilance centres. The lack of clinical data provided by reporting doctors may affect the performance of causality assessments in some cases. However, the intensive monitoring methods used by the IMMP [10] and Lareb [13] in addition to spontaneous reporting are helpful in overcoming such limitations. Both centres usually obtain detailed information from healthcare professionals (and patients), and cases are often followed up for more information. Thus, the IMMP or Lareb cases with insufficient information for assessment represent a minority of cases in this series.

Fatal cases

In this case series, the IMMP identified two patients who died from haemorrhagic events shortly after stopping varenicline. One patient died from cerebral bleeding, but this case was confounded by the past medical history of a brain tumour. The other patient died from a ruptured spleen and thrombocytopenia, but this case was confounded by the

patient's chronic lymphocytic leukaemia. The presence of serious medical conditions which may affect bleeding, as well as the fact that both patients had stopped taking varenicline, suggested that there was unlikely to be a causal relationship between the bleeding event and varenicline. However, this assessment does not completely eliminate varenicline from having any role in these fatal haemorrhagic events. It is possible that by mechanistic effects (see section 'Possible mechanism') varenicline contributed to the dysfunction of the coagulation system which occurred in these patients.

Other evidence

A literature search for previous publications reporting epistaxis or other bleeding events associated with varenicline did not identify any papers which have specifically investigated this issue. However, one study of consumer reports of suspected adverse reactions to varenicline identified several unlabelled adverse effects, including epistaxis [15]. Epistaxis is not labelled in the European Summary of Product Characteristics (SPC) [8], and the NZ datasheet for varenicline/Champix does not include mention of epistaxis or other bleeding events [7].

Possible confounding effect of smoking cessation

While the causality assessments for the IMMP and Lareb cases of epistaxis, gingival bleeding and haemoptysis suggested a causal relationship between the event and varenicline in the majority of cases, it is important to consider any possible confounding effect of smoking cessation. Bleeding and haemostasis is regulated by several plasma proteins which make up the coagulation cascade, and activation of this cascade generates thrombin, which converts fibrinogen to fibrin to form a clot [16]. Smoking has been associated with increases in circulating fibrinogen [17]. In one study, male smokers had a 2.4% mean increase in plasma fibrinogen levels compared to non-smokers, which was statistically significant [18]. During smoking cessation, fibrinogen levels have been demonstrated to decrease by 3.7% [19], and it may take years for these to return to non-smoker levels [20–23].

Since coagulation requires the conversion of fibrinogen to fibrin, it could be hypothesised that an acute drop in plasma fibrinogen during smoking cessation may disrupt the otherwise tightly controlled balance between haemorrhage and coagulation and lead to bleeding disorders. However, the reported changes in fibrinogen levels during smoking cessation may not be clinically relevant as there does not appear to be evidence of clinically significant bleeding disorders in patients giving up smoking.

Two studies have demonstrated that smoking has a strong suppressive effect on gingival bleeding and that this phenomenon is dose dependent—i.e. more predominant in patients who were heavy smokers (>10 cigarettes a day) [24, 25]. This is an interesting observation, which might imply an increased tendency for gum bleeding on smoking cessation.

Possible mechanism

Our study identified reports of haemorrhagic events in several different SOCs in patients taking varenicline. Thus, it is feasible to hypothesise that there may be a common mechanism leading to an increased likelihood of bleeding. Thrombocytopenia, defined as a platelet count of $<100\ L^{-9}$, is listed as an adverse event in the varenicline product information [7]. Low platelets counts are associated with an increased bleeding tendency which, if severe, may be life-threatening. Blood count data were not available for the majority of patients in this case series of haemorrhagic events, but other cases of thrombocytopenia associated with varenicline were identified in the Lareb, IMMP and WHO datasets.

Platelets contain up to 99% of the serotonin in the circulation, and this is released at sites of vascular injury to promote and amplify platelet aggregation and further activate the haemostatic system [26]. Decreased levels of platelet serotonin may lead to impaired platelet aggregation and therefore increase the risk of bleeding and bruising. Serotonin re-uptake inhibitors are associated with cases of bruising and bleeding, which have been mechanistically related to decreased uptake of serotonin by platelets, leading to thrombocytopenia [27, 28]. It has been hypothesised that varenicline may affect serotonin re-uptake [29]. Studies in rodents have demonstrated that varenicline had a low affinity for both the 5HT receptor system as well as the 5HT transporter [30]. Varenicline is an α-7 nicotinic receptor agonist, and human platelets express these receptors [31]. However, to date, no studies have looked at the possible relationship of varenicline with changes in coagulation, and further studies are required to investigate this possibility.

Conclusions

This paper describes a case series of haemorrhagic events associated with varenicline that were retrieved from the datasets of two national pharmacovigilance centres. The majority of reports of nose and gum bleeding were clinically assessed as having a causal relationship with varenicline as there was evidence of resolution of the event after varenicline was withdrawn. In one case of haemoptysis there was evidence of a positive rechallenge. However, in all of the

cases reported there may be a potential confounding effect of smoking cessation itself on the haematological system, which in turn may increase the likelihood of bleeding. The identification of haemorrhagic events in several different organ classes suggested there may be a common mechanism for these adverse events. Varenicline has been reported to cause thrombocytopenia, which may explain the occurrence of haemorrhagic events in some patients.

Acknowledgements The IMMP and Lareb would like to thank all the doctors, other healthcare professionals and patients in both countries who submitted reports which have been included in this study. We also acknowledge the help of the WHO-UMC in gaining access to the reports in their dataset. The NZ IMMP part of this work was funded by the NZ Ministry of Health (Medsafe). Lareb received no additional funding for the work reported in this paper.

Conflict of interest None.

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