

1.1. Overview of varenicline and suicidal behaviour

Introduction

Varenicline (Champix®) is a partial $\alpha 2$ -agonist and is indicated for *smoking cessation therapy* and has been approved for the Dutch market since 2006 [1]. Varenicline binds with high affinity and selectivity at the $\alpha 2$ neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist, with agonistic and antagonistic activity. Nicotine is an agonist of the $\alpha 2$ receptor. Activation of this receptor activates the mesolimbic dopamine system (the 'reward system') and increases the probability of smoking. Varenicline has higher affinity for the receptor but lower intrinsic efficacy than nicotine; therefore, the 'reward system' is less activated and hence the desire for smoking is reduced.

Varenicline is used in the dosage of 1 mg twice a day following a 1-week titration as follows: day 1-3: 0.5 mg once a day; day 4-7: 0.5 mg twice a day; day 8 until the end of treatment: 1 mg twice a day. The patient stops smoking between day 7 and 14. Treatment with varenicline will be continued for 12 weeks [1].

Suicidal ideation and behaviour are among the most serious and common psychiatric emergencies. It is estimated that there are 10 to 40 nonfatal suicide attempts for every completed suicide [2]. Distinction is made between suicidal ideation, suicidal behaviour, suicide attempt and completed suicide. Risk factors for suicide and suicidal behaviour include psychiatric disorders, impulsivity, age and gender [2].

Suicidal ideation is a known ADR of varenicline which is described in the SmPC [1]. The SmPC also indicates in the warning sections that suicide attempts have been reported in patients attempting to quit smoking with varenicline and that depressed mood, rarely including suicidal ideation and suicide attempts, may be a symptom of nicotine withdrawal.

Because of the seriousness of the event, Lareb wishes to inform the Medicines Evaluation Board (MEB) in this overview of the cases of suicide or suicidal behaviour with the use of this drug for the cessation of smoking.

Reports

Between 1 November 2007 and 22 November 2016 Lareb received nine reports (with one duplicate) of suicidal attempt (Table 1) and six reports of completed suicide (Table 2) associated with the use of varenicline, and also 39 reports of suicidal ideation and two reports of suicidal behavior.

Varenicline was also included in the Lareb Intensive Monitoring (LIM) program from 1 December 2008 to 31 March 2012. During this period, 1418 patient signed up for participation in LIM and two reports of suicidal ideation were reported.

Table 1. Reports of suicide attempt with the use of varenicline

Patient, number, sex, age, source	Drug, dosage, smoking at time of event	Concomitant medication	Suspected adverse drug reaction	Time to onset, drug outcome	Relevant medical history
A, 103707, M, unknown, nurse and patient through MAH	Varenicline 0.5mg, dosage unknown, stopped smoking on day 10 but started after a couple of days	sertraline	suicidal ideation, suicide attempt, abnormal behaviour, aggression,	12 days, drug withdrawn, recovered after 1 day	cannabis dependence

Patient, number, sex, age, source	Drug, dosage, smoking at time of event	Concomitant medication	Suspected adverse drug reaction	Time to onset, drug outcome	Relevant medical history
B, 114163, F, 61-70, consumer through MAH	Varenicline 1 mg twice a day, stopped smoking on day 8	sertraline, paracetamol with codeine, salbutamol, adrenaline, desloratadine, two unspecified drugs	suicidal ideation, suicide attempt, feeling abnormal, gait disturbance, visual field defect, disturbance in attention, ill-defined disorder, emotional disorder, feeling jittery, nightmare, pain, fear, impulse-control disorder, nausea, irritable bowel syndrome	13 days for suicide ideation, withdrawn, recovering	depression, post-traumatic stress disorder, borderline
C, 123486, F, 31-40, physician through MAH	varenicline 0.5mg, dosage unknown, the event took place two days after quit smoking	oxazepam	suicide attempt, depression, personality disorder, dependent personality disorder	unknown for suicide attempt, withdrawn, recovered for suicide attempt	alcoholism, divorce for which she received mental health service
D, 108510, F, unknown, pharmacist	Varenicline 1 mg twice a day, smoking unknown	sertraline, zolpidem, oxazepam	suicide attempt	days, unknown, unknown	borderline personality disorder
E, 120685, F, 51-60, general practitioner	varenicline 0.5mg twice a day, smoking unknown	carbamazepine, citalopram, aripiprazol, acetylsalicylic acid, tiotropium, nicotine replacement therapy, algedrate	suicide attempt	5 weeks, unknown, unknown	depression which was well treated, suicide attempt with admission to the hospital one year ago
F, 199427, F, 41-50, specialist doctor	varenicline 0.5 mg and 1 mg, dosage unknown, smoking unknown	quetiapine, mirtazapine, lormetazepam, oxazepam	suicide attempt	7 days, withdrawn, recovered	Psychic disturbance, suicide attempt three years before, depression, alcohol problem
G, 215209, M, 41-50, general practitioner	varenicline 0.5mg twice a day, smoking unknown		suicide attempt, intentional overdose with multiple drugs	14 days, withdrawn, recovered with sequel after 1 day	
H, 73236 = 82962, M, 31-40, physician through MAH	Varenicline 0.5mg, dosage unknown, smoking unknown		intentional overdose, suicide attempt	unknown, unknown	unspecified psychological disease and emotional problems specified as suicidal thoughts

Table 2. Reports of completed suicide with the use of varenicline

Patient, number, sex, age, source	Drug, dosage, smoking at time of event	Concomitant medication	Suspected adverse drug reaction	Time to onset, drug outcome	Relevant medical history
I, 218207, F, 31-40, consumer	varenicline 0.5+1mg, dosage unknown, smoking unknown		depression completed suicide	Less than a month, fatal	
J, 229638, F, 51-60, general practitioner through MAH	varenicline 0.5+1mg, dosage unknown, smoking unknown		completed suicide	unknown, fatal	
K, 159994, F, 22-30, General practitioner	varenicline 1mg twice a day, smoking unknown	ethinylestradiol/levonorgestrel	depressed mood completed suicide	2 weeks for depressed mood, 10 days after drug withdrawal for completed suicide, fatal	
L, 218000, F, 51-60, General practitioner	varenicline 0.5 mg twice a day, smoking unknown	esomeprazole sotalol carbasalate calcium rosuvastatin diltiazem	completed suicide	12 Weeks after start and 2 weeks after drug withdrawal, fatal	depression since 8 years, but no symptoms during screening
M, 89643, M, unknown, physician through MAH	varenicline 0.5mg dosage unknown, smoking unknown		completed suicide	unknown time after drug withdrawal, fatal	depression
N, 221111, F, unknown, consumer through MAH	varenicline 0.5+1 mg, dosage unknown, smoking unknown		depression completed suicide	unknown for both events, fatal	depression which was stable for years

The concomitant medication and medical history was started or present before the start of varenicline.

Other relevant information per patient:

B. Symptoms of suicidal ideation resulting in a suicidal attempt started after increasing the dose from 1 mg a day to 2 mg a day. Laboratory investigation revealed the patient has a very fast nicotine metabolism.

C. Past drug therapy included varenicline with unknown duration, which was withdrawn one year before the restart of varenicline and venlafaxine with indication depression at an unknown date. Following the event the patient was diagnosed with an adaptation disorder with fear and depression, and a dependent personality disorder. It was unknown whether the patient had a familial history of psychological problems.

E. The patient used a half dosage of varenicline. Because of the risk of aggravated depression the patient was seen by the general practitioner every week. The suicide attempt was impulsive. After the suicide attempt the patient seemed psychotic at admission to the hospital.

G. Possible other causes included psychosocial stress factors.

H. The patient took 10 pills of varenicline. According to the general practitioner, there was no reasonable possibility that the event was related to varenicline.

J. The family is not sure if the patient had taken varenicline at the moment of suicide.

K. During the treatment with varenicline, she had relational problems. At the time of withdrawal, the patient has no suicidal ideation. The patient used varenicline before without any relevant events.

M. After drug withdrawal, the patient was admitted to a closed institution and treated for a month, but committed suicide. The physician stated that there was no relationship with varenicline.

Other sources of information

SmPC

The Dutch SmPC of varenicline mentions suicidal ideation with an incidence of 0.001% - 0.01% in section 4.8 [1]. Furthermore, section 5.1 of the SmPC, mentions a randomised and double blind placebo controlled study with varenicline in patients with and without psychiatric disorders. The endpoint was the number of neuropsychiatric events. Among them were suicidal thoughts, suicidal behaviour, suicide attempt or completed suicide. For the non-psychiatric cohort, these events when using varenicline were equal to or lower than the use of placebo. For the psychiatric cohort, more psychiatric events were mentioned when using varenicline compared to placebo, but this was not statistically significant. Almost all of these events were suicidal thoughts [1].

Also, independent observational studies showed no indications for a higher risk of serious neuropsychiatric events when varenicline was compared with nicotine replacement therapy or bupropion [1].

Section 4.4 of the SmPC mentions that behavioural changes like suicidal thoughts or attempts are reported post marketing in patients who used varenicline as smoking cessation therapy. Stopping with varenicline is also associated with a higher risk on depression and irritability. Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly. [1].

Literature

Several studies in the literature describe the occurrence of suicide while using varenicline. In the latest and largest study from Anthenelli et al. [3], neuropsychiatric events using varenicline, bupropion or nicotine replacement therapy were compared with placebo among smokers who wanted to quit smoking. A psychiatric and non-psychiatric cohort was followed and suicidal ideation, suicidal behavior were followed. Results showed that the risk of suicidal ideation of behavior was greater in the psychiatric cohort and similar across treatments.

In an observational study from Molero et al. [4] 69,757 varenicline users are selected from a database and compared to a non-treated cohort, which are people who were not treated with varenicline. Information on psychiatric events came from the Patient Register, which includes diagnoses from both hospital admissions and outpatient visits in specialized care. This also includes the definitions of suicide attempts and suicide as emergency hospital visits or death due to intentional self-harm. The authors tested potential confounding by nicotine withdrawal syndrome by a 'between person Cox proportional hazards regression' between the use of varenicline or bupropion. Patients treated with varenicline had significantly less risk of mood conditions than bupropion users corrected for nicotine withdrawal (Hazard ratio (HR) 0.63, 0.55-0.74).

The authors find no evidence for a causal relationship between the use of varenicline and the risk of suicidality for non-psychiatric patients. However, an increased risk of mood conditions during varenicline treatment was found for psychiatric patients (HR 1.31, 1.06-1.33) versus non-psychiatric patients (HR 1.17, 0.86-1.60). However, the analysis did not take time varying confounding factors into account (e.g. non-adherence to other drugs), which may lead to increased risk of new psychiatric conditions [4].

The results of the Lareb Intensive Monitoring Study (LIM) showed that a total of 504 psychiatric ADRs were reported while using varenicline, with depressed mood (78 times) and mood swings (13 times) reported most. Two patients mentioned serious depression, one of these two patient also suffered from suicidal ideation. This study concluded that the number of reports on psychiatric ADRs was small, compared with the incidence rates mentioned in the SmPC of varenicline [5].

The Farmacotherapeutisch Kompas [6], which is frequently used by doctors of all specialties, mentions that care should be taken in case of severe psychiatric conditions such as schizophrenia, bipolar disorder and severe depressions, because the safety is not assessed.

Databases

Table 3. Reports of suicidal expressions associated with the use of varenicline in the Lareb database [7].

Drug	PT	Number of reports	ROR (95% CI)
Varenicline	Suicidal ideation	39	8.4 [6.0-11.7]
Varenicline	Suicidal behavior	2	Number of reports too low to calculate ROR
Varenicline	Suicide attempt	8	9.1 [4.5-18.5]
Varenicline	Completed suicide	6	13.1 [5.8-29.8]

Table 4. Reports of suicidal expressions associated with the use of varenicline in the Eudravigilance and WHO database [8,9].

PT	Number of reports EV	ROR EV (95% CI)	Number of reports WHO	ROR WHO (95% CI)
Suicidal ideation	4510	9.4 [9.0-9.7]	5221	25.6 [24.9-26.4]
Suicidal behaviour	345	13.3 [11.9-15.0]	353	41.6 [37.0-46.7]
Suicide attempt	2187	4.8 [4.6-5.0]	2360	13.5 [12.9-14.0]
Completed suicide	795	1.7 [1.6-1.9]	857	3.9 [3.7-4.2]

WHO database: 50.1% of all reports mentioned depression as relevant medical history. Also, intentional overdose (11.6%) and depressed mood (4.8%) were mentioned.

Prescription data

According to the drug Information System of the Dutch Health Care Insurance Board [10], varenicline is not included in the Dutch drug reimbursement system (genesmiddelenvergoedingssysteem (GVS)). However, some insurances seem to reimburse varenicline but this varies per insurance and year [11,12]. The GIP-databank has no information about varenicline. However, the Dutch Stichting Farmaceutische Kengetallen (SFK), noticed 260,000 prescriptions of varenicline in the Dutch pharmacies in 2011 [10].

Mechanism

The mechanism behind suicidal ideation, behavior or attempt is unclear. Depressed mood, in rare cases with suicidal thoughts and suicide attempts, can be a symptom of nicotine withdrawal. Varenicline intervenes with the reward system, on which it has an antagonistic effect, causing less dopamine to come available [1]. Less dopamine is, together with a decrease in serotonin and noradrenalin, associated with the occurrence of depression [13].

Discussion and conclusion

After introduction of varenicline on the market, reports of suicidality emerged in post-marketing surveillance and led to warnings in Europe [14] and United States [15]. The Netherlands Pharmacovigilance Centre Lareb received 39 reports of suicidal ideation, two reports of suicidal behavior, nine reports of suicidal attempt and six reports of completed associated with the use of varenicline. Also, two reports of suicidal ideation were reported with the LIM program. The association of varenicline and suicidal expressions is supported by a statistically significant disproportionality in the database of Lareb, WHO and Eudravigilance.

Most reports on suicide attempts or completed suicide included psychiatric illness or medication during the event, except for patients G, I and K. Patients L and M had depression in the past with was stable for years. Patients K, L and M committed suicide after withdrawal of varenicline.

The association between varenicline and suicidal ideation or behaviour is known in the SmPC [1]. The SmPC also warrants that care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly. [1].

The association between varenicline and suicidal ideation or behaviour is also well known in literature, especially in psychiatric patients [1,3,4]. However, some data came from Patient Registers, which included diagnoses from hospital admissions. Only outcomes serious enough would end up in the registers [4]. Therefore it is likely that the number of patients is underestimated. Among the reports Lareb received were serious reports with e.g. hospitalization, but also reports where no healthcare professional was seen.

Suicidal ideation, behaviour or attempt is supported by a hypothetical mechanism of less dopamine due to nicotine withdrawal. Also, nicotine withdrawal could affect pharmacokinetics of pharmacodynamics of concomitant medication by an increase of substrates of CYP1A2 [1]. However none of the patients used relevant concomitant medication [16].

The association between varenicline and suicidal behaviour is well known, The possibility of this association is further substantiated by a total of 56 reports of suicidal ideation or behaviour, suicide attempt of completed suicide received by Lareb. Despite all warnings in information for healthcare professionals and patients available, additional vigilance with close monitoring of these patients is needed for this association, especially in patients with a psychiatric medical history.

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This overview was published on April 3 2017. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl