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Psychiatric Adverse Events in Randomized, Double-Blind, Placebo-Controlled Clinical Trials of Varenicline

A Pooled Analysis

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Abstract

Background: Varenicline (Chantix®, Champix®) has shown efficacy and tolerability as an aid to smoking cessation. In postmarketing surveillance, neuropsychiatric symptoms have appeared; however, their incidence and causal relationship to varenicline is not known.

Objective: We assessed the incidence and relative risk (RR) of psychiatric disorders in ten randomized, double-blind, placebo-controlled trials of varenicline for smoking cessation.

Methods: All smoking cessation phase II, III and IV randomized controlled clinical trials of varenicline versus placebo completed as of 31 December 2008, on file with the manufacturer (Pfizer, Inc.), were included. All studies have been published. All 3091 participants who received at least one dose of varenicline and all 2005 participants who received placebo were included in this analysis. These were men and women smoking ≥10 cigarettes/day, aged 18–75 years and without current psychiatric disease who received varenicline or placebo for 6 (one study), 12 (eight studies) or 52 (one study) weeks. Adverse events were recorded at each study visit and classified according to standard Medical Dictionary for Regulatory Activities (MedDRA®) terms (version 11.0).

Results: The incidence of psychiatric disorders other than solely sleep disorders and disturbances was 10.7% in subjects treated with varenicline and 9.7% in subjects treated with placebo, with an RR of 1.02 (95% CI 0.86, 1.22). The RRs (95% CI) versus placebo of psychiatric adverse events with an incidence ≥1% in the varenicline group were 0.86 (0.67, 1.12) for anxiety disorders and symptoms, 0.76 (0.42, 1.39) for changes in physical activity, 1.42 (0.96, 2.08) for depressed mood disorders and disturbances, 1.21 (0.79, 1.83) for mood disorders and disturbances not elsewhere classified and 1.70 (1.50, 1.92) for sleep disorders and disturbances. There were no cases of suicidal ideation or behaviour in varenicline-treated subjects in the ten placebo-controlled studies analysed. However, among three trials that were

excluded from the analysis because of their open-label design, two cases of suicidal ideation and one completed suicide were reported in patients who had been treated with varenicline. With the exception of sleep disorders and disturbances, there was no evidence of dose-responsivity.

Conclusions: There was no significant increase in overall psychiatric disorders, other than sleep disorders and disturbances, in varenicline-treated subjects in this sample of smokers without current psychiatric disorders. Ongoing studies are testing the use of varenicline in psychiatric patients.

Background

Varenicline (known as Chantix® in the US and Champix® in the rest of the world) is a novel drug developed to provide agonist–antagonist effects at the $\alpha_4\beta_2$ nicotinic acetylcholine receptor, thereby reducing withdrawal symptoms associated with smoking cessation.[1] Varenicline has also been shown to reduce the rewarding effects of smoking.[2] Meta-analyses of long-term abstinence data conducted for the Cochrane Database of Systematic Reviews show pooled risk ratios (95% CI) for long-term abstinence versus placebo of 2.33 (1.95, 2.80) for varenicline,[3] 1.75 (1.58, 1.94) for bupropion sustained-release (SR)[3,4] and 1.58 (1.50, 1.66) for nicotine replacement therapy (NRT).[3,5] In head-to-head studies, treatment with varenicline has resulted in higher cessation rates than bupropion SR.[6,7]

Since the initial regulatory approval of varenicline in 2006, there have been several case reports of exacerbation of pre-existing psychiatric disorders in patients receiving varenicline for smoking cessation.[8-13] Similar reports have also appeared in individuals without pre-existing psychiatric disorders.[14]

On 1 July 2009, after alerts and public health advisories issued by the US FDA since November 2007,[15-17] the prescribing information and medication guide for varenicline in the US was revised to include a boxed warning that highlights the risk of serious neuropsychiatric symptoms.[18] These symptoms include changes in behaviour, hostility, agitation, depressed mood, suicidal thoughts and behaviour, and attempted suicide. The added warnings are based on the continued review of postmarketing adverse event reports. These reports included those with a temporal relationship between the use of varenicline and suicidal events and the occurrence of suicidal ideation and suicidal behaviour in patients with no history of psychiatric disease. Some of these cases may have been confounded by symptoms typically seen in people who have stopped smoking and are experiencing withdrawal from nicotine.

Given these concerns, we thought it important to analyse safety results from the existing randomized, double-blind, placebo-controlled trials of varenicline. One reason for this is that although retrospective epidemiological studies and case reports can be important indicators of safety concerns they do not provide a reliable estimate of the incidence of adverse events or whether such events are causally related to varenicline, whereas randomized controlled clinical trials can also be used to characterize this. The only prospective incidence study reported 3.6% of 2862 smokers who developed a psychiatric, non-sleep-related adverse event within 4 months of filling a prescription for varenicline; however, the study lacked a control group.[19] We analysed the incidence and risk of reported psychiatric disorders in ten phase II, III and IV placebo-controlled trials of varenicline that had similar inclusion criteria and standards of monitoring. Some of these trials reported such events in the primary publication; however, a comprehensive analysis of the data on file across all ten studies provides a more precise and generalizable estimate by capturing adverse events that might not have been reported previously in the study publications due to low incidence. We also describe cases of suicidal ideation and behaviour reported in all phase II, III and IV clinical studies (13 studies in all).

Methods

Included Studies

Study inclusion criteria were randomized, placebo-controlled studies of varenicline for smoking cessation. At the time of this report, the only phase II, III and IV randomized, double-blind, placebo-controlled studies of varenicline were sponsored by Pfizer. All studies completed by 31 December 2008 were identified. A total of 13 studies were found, of which ten were randomized, double-blind, placebo-controlled studies of varenicline and were eligible for inclusion. All ten studies have been published in full.[6,7,20-27]

Three Pfizer-sponsored clinical trials did not qualify because their open-label design would not permit a rigorous treatment comparison.[28-30] These were an open-label study of varenicline 1 mg twice daily versus NRT,[29] an open-label pilot study in 30 patients in Japan (varenicline 0.5 mg twice daily for 7 weeks)[30] and a maintenance study in smokers who began with 12 weeks of open-label varenicline 1 mg twice daily.[28] These three studies were included in a search for cases of suicidal ideation or behaviour and all such cases are presented using a descriptive narrative.

Participants

Eligible subjects were male and female cigarette smokers aged 18–75 years who smoked ≥10 cigarettes/day within the past year. In nine studies, the smoker was required to be motivated to quit smoking,[6,7,20-24,26,27] while one study did not specify this requirement.[25] Smokers were required not to have been abstinent from smoking for more than 3 months in the past year and, in nine of the studies, to be in good health. The tenth study examined smoking cessation in patients with cardiovascular disease (other than hypertension) that had been diagnosed more than 2 months before study entry.[27] Smokers receiving treatment for depression at study initiation or within the past 12 months, and individuals with a past or present history of panic disorder, psychosis, bipolar disorder or who had alcohol or drug abuse/dependency within the past year (except nicotine or marijuana) were excluded from all studies. Smokers who had a diagnosis of depression that did not require treatment at study initiation or within the previous 12 months were included. The trials did not systematically elicit the presence of past psychiatric problems.

Length of Treatment

The length of treatment with varenicline or placebo (table I) was 12 weeks in eight studies,[6,7,20,21,23,24,26,27] 6 or 7 weeks in one study[22] and 52 weeks in one study.[25] In one study,[20] 42 of 618 subjects received an additional course of varenicline.[30] The dosage of varenicline ranged from 0.3 mg once daily to 1 mg twice daily. In all studies, subjects were randomized to treatment with varenicline 1 mg twice daily; four of these studies also randomized subjects to lower dosages.[20-23] Subjects were followed up after randomization for up to 6 months[24,26] or 1 year.[6,7,20-23,25,27]

Adverse Event Collection and Classification

At each study visit during the treatment phase with varenicline or placebo the study investigators were required to ask whether subjects had experienced any adverse events. Visits typically occurred weekly (table I), except for one study in which visits were weekly to week 4 and then every 2 weeks, [24] and another study in which visits were weekly to week 8 and then monthly.[25] All observed or volunteered adverse events were collected and graded according to severity (mild, moderate or severe) and seriousness of outcome or risk (serious or non-serious). Investigators also recorded start and end dates of each adverse event, their clinical judgement about the relationship of the adverse event to treatment or other causes, action taken and outcomes. All adverse events occurring during the treatment phase or up to 30 days following the end of treatment, regardless of whether the investigators considered them as being related to the study drug, were included in the analysis. Adverse events that were considered serious were those that were life-threatening or that resulted in death, hospitalization, significant disability or birth

Table I. Design of ten randomized, placebo-controlled studies of varenicline[a]

Study	Study sites	Active treatment	Dosing period (wk)	Frequency of clinical visits during treatment phase
Nides et al.[22]	US	Varenicline 0.3 mg od, 1.0 mg od, 1.0 mg bid Bupropion SR 150 mg bid	6 7	Weekly Weekly
Oncken et al.[23]	US	Varenicline 0.5 mg bid, 1.0 mg bid	12	Weekly
Gonzales et al.[6]	US	Varenicline 1.0 mg bid Bupropion SR 150 mg bid	12	Weekly
Jorenby et al.[7]	US	Varenicline 1.0 mg bid Bupropion SR 150 mg bid	12	Weekly
Niaura et al.[21]	US	Varenicline 0.5–2.0 mg/day	12	Weekly
Nakamura et al.[20] b	Japan	Varenicline 0.25 mg bid, 0.5 mg bid, 1.0 mg bid	12	Weekly
Tsai et al.[24]	Korea, Taiwan	Varenicline 1.0 mg bid	12	Weekly up to week 4, then every 2 weeks
Wang et al.[26]	China, Singapore, Thailand	Varenicline 1.0 mg bid	12	Weekly
Rigotti et al.[27]	Argentina, Australia, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Mexico, the Netherlands, Republic of Korea, Taiwan, UK, US	Varenicline 1.0 mg bid	12	Weekly
Williams et al.[25]	US, Australia	Varenicline 1.0 mg bid	52	Weekly through week 8 and then monthly

a Subjects were followed for 52 weeks, with the exception of Tsai et al.[24] (24 weeks), Wang et al.[26] (24 weeks) and Williams et al.[25] (53 weeks).

b In an extension of the study by Nakamura et al.,[20] 42 of 618 subjects received an additional course of therapy.[31]

bid = twice daily; **od** = once daily; **SR** = sustained release.

defect and were reported immediately to the sponsor.

The verbatim terms used by the investigators to report adverse events were captured in the database and automatically coded through a computerized programme to standard terms according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 11.0.[32] MedDRA is a pragmatic medical terminology used to standardize data entry, retrieval, analysis and display, and is used widely around the world by regulatory agencies and drug manufacturers. It was developed by the International Conference on Harmonization and the International Federation of Pharmaceutical Manufacturers and Associations, and is maintained by the Maintenance and Support Services Organization. Adverse events were summarized according to larger categories called system organ classes (SOC) and were then further classified into more discrete 'high-level group terms'. Data regarding all high-level group terms under the SOC 'psychiatric disorders' are presented and hereafter referred to as 'psychiatric disorders'. Subjects who reported more than one psychiatric disorder are counted separately under each specific high-level group term. Data for subjects who reported solely sleep disorders and disturbances and no other psychiatric disorders are reported separately as varenicline is known to cause sleep disorders.[2,33] Data for subjects who reported sleep disorders and disturbances together with other psychiatric disorders remain included in the overall analysis.

Statistical Analyses

Subjects who took at least one dose of the study drug (active or placebo) were included in

the analyses. Incidence rates for psychiatric disorders were summarized for varenicline (all doses) and placebo based on pooled data from the ten studies. The incidence rates for varenicline were compared with placebo using the relative risk (RR) from a Cochrane-Mantel-Haenszel analysis and the risk difference (RD) from a Mantel-Haenszel analysis, both using study as a stratification factor to account for any confounding due to interstudy differences, including unequal randomization ratios.[34] Respective nominal 95% CIs were calculated from these RR and RD point estimates. To investigate a dose relationship, psychiatric disorders were also summarized for varenicline 1 mg twice daily, <1 mg twice daily and placebo based on pooled data from the subset of four studies that included varenicline <1 mg twice-daily regimens.

The severity and seriousness of the incidence of adverse events, together with adverse event resolutions (e.g. discontinuation from study) were summarized. The onset and prevalence of psychiatric events by week were also summarized. SAS version 9.0 (SAS Institute, Cary, NC, USA) was used for the analyses.

Results

In the ten studies, 3091 subjects treated with varenicline and 2005 subjects treated with placebo took at least one dose of the study drug. The majority of participants were White (63.8%), with 6.1%, 25.7% and 4.5% being African American, Asian or other ethnicity, respectively. Baseline characteristics of participants, given in table II, were similar for varenicline and placebo.

The incidences of all adverse events, discontinuations due to adverse events and adverse events classified as psychiatric disorders are shown in table III. The percentage of participants reporting at least one psychiatric adverse event other than only sleep disorders and disturbances was similar in the varenicline and placebo groups (10.7% vs 9.7%), with an RD (varenicline vs placebo) of 0.24% (95% CI −1.49, 1.96), and the RR for reporting at least one psychiatric adverse event other than only sleep disorders and disturbances was 1.02 (95% CI 0.86, 1.22) for varenicline versus placebo. The RR for such events rated as moderate and severe was 1.11 (95% CI 0.85, 1.45) for varenicline versus placebo. When sleep disorders and disturbances are included, more subjects (30.6%) reported at least one psychiatric adverse event in the varenicline group than in the placebo group (20.8%), with an RD of 9.03% (95% CI 6.60, 11.47) and an RR of 1.43 (95% CI 1.29, 1.58).

There were three reports of serious psychiatric adverse events. These included one case of a varenicline-treated subject who did not report a history of psychiatric disease but was hospitalized for acute psychosis.[7] This subject had increased alcohol consumption during the study. There were two reports of serious psychiatric events in placebo-treated subjects. These were a suicide attempt[23] with paracetamol (acetaminophen) and diphenhydramine, and an acute exacerbation of psychosis in a patient with schizophrenia that was not disclosed at study entry.[6]

Table II. Baseline characteristics of subjects for each treatment

Baseline characteristic	Varenicline (n = 3091)	Placebo (n = 2005)
Sex (male; %)	61.0	66.9
Mean age [y (SD)]	44.1 (12.0)	44.4 (12.3)
Race (White; %)	63.7	63.8
Mean total number of years smoked (SD)	26.2 (12.4)	26.7 (12.5)
Mean average number of cigarettes per day in past month (SD)	22.4 (9.6)	22.4 (9.5)
FTND, mean total score (SD)	5.4 (2.1)	5.5 (2.1)
First cigarette within 5 min of waking (%; from FTND)	36.2	37.2
Living with a smoker (%)	32.2	34.9
≥1 serious previous quit attempts (%)	73.8	67.2

FTND = Fagerström Test for Nicotine Dependence.[35]

Table III. Subjects with all adverse events, psychiatric adverse events and discontinuations

Category	Varenicline (n = 3091) [n (%)]	Placebo (n = 2005) [n (%)]
All adverse events		
Subjects with any adverse event	2587 (83.7)	1473 (73.5)
Subjects with serious adverse events[a]	66 (2.1)	45 (2.2)
Subjects discontinued due to adverse events	326 (10.5)	133 (6.6)
Subjects discontinued for any reason[b]	821 (26.6)	608 (30.3)
Psychiatric adverse events		
Subjects with any psychiatric adverse events	946 (30.6)	418 (20.8)
Subjects with solely sleep disorders and disturbances	615 (19.9)	224 (11.2)
Subjects with any psychiatric adverse events other than solely sleep disorders and disturbances		
all severities (mild, moderate, severe)	331 (10.7)	194 (9.7)
moderate and severe only	152 (4.9)	81 (4.0)
Subjects with psychiatric serious adverse events	1 (<0.1)	2 (0.1)

a A serious adverse event was defined for the investigators as any untoward medical occurrence at any dose that results in death, is life-threatening (immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in congenital anomaly/birth defect.

b Any reason includes adverse events, lost to follow-up and refusal to continue.

Table IV shows that, other than for sleep disorders and disturbances, and anxiety disorders and symptoms, the incidence and RR for each event was low in the varenicline and placebo groups. RDs and CIs for overall psychiatric adverse events other than solely sleep disorders and disturbances, and for each psychiatric disorder for varenicline versus placebo, are shown in figure 1. Sleep disorders and disturbances increased by 10.09% (95% CI 7.88, 12.30) but other increases were small, e.g. the next highest increase was for depressed mood disorders (0.80% [95% CI –0.06, 1.67]).

The incidence rates of psychiatric disorders for varenicline 1 mg twice daily, <1 mg twice daily and corresponding placebo based on the four studies that included both dose regimens are presented in table V. The incidence of sleep disorders and disturbances was significantly higher in subjects treated with varenicline <1 mg twice daily (22.2%) than placebo (13.4%) with an RR of 1.68 (95% CI 1.32, 2.13), and numerically higher for subjects treated with varenicline 1 mg twice daily (27.5%) than subjects treated with varenicline <1 mg twice daily with an RR of 1.13 (95% CI 0.95, 1.33). For all other psychiatric disorders the incidence rates were similar, with no trend suggesting a dose effect.

The onset of psychiatric adverse events by week is shown in figure 2a (varenicline) and figure 2b (placebo). The onset of sleep disorders and disturbances reached a peak for both treatments in week 1 and decreased to approximately 1% of the study population per week after week 5 (varenicline) and week 4 (placebo). The onset of anxiety disorders was most frequent in weeks 1 and 2 (varenicline) and week 2 (placebo). For all other psychiatric disorders, the onset occurred in <1% of the study population in any week.

Suicidal and Self-Injurious Behaviours

No cases of suicidal or self-injurious behaviours were reported in varenicline-treated subjects in the ten placebo-controlled studies. In those treated with placebo, one case of suicidal ideation was reported and another subject made a suicide attempt (intentional drug overdose) [table IV].

In the other three studies (excluded from the analysis because of their open-label design), two cases of suicidal ideation and one completed suicide were reported in patients treated with varenicline. One case of suicidal ideation was reported in a subject who resumed smoking and stopped taking varenicline after 73 days of treatment.[28] The second

report of suicidal ideation occurred in one subject on day 11 after stopping varenicline.[29] The suicide occurred 27 days after the last dose of varenicline.[28]

Discussion

This analysis was undertaken to estimate the incidence of and to better characterize psychiatric adverse events from the use of varenicline. A systematic, quantitative review of ten placebo-controlled trials of smokers with no current or recent psychiatric disorder found that, with the exception of sleep disorders and disturbances, psychiatric adverse events were uncommon. The incidence of both sleep- and non-sleep-related adverse events in the varenicline groups among these randomized controlled trials was very similar to that observed in a prospective study of prescriptions for varenicline among clinical practices in the UK.[19] Importantly, in the current analysis, there was no significant increase in several types of psychiatric adverse events in subjects treated with varenicline compared with placebo. Furthermore, suicidal ideation or behaviour was rare, with no cases in the varenicline-treated subjects in the ten studies analysed, and two suicidal ideations and one completed suicide in the three open-label trials. For sleep disorders and disturbances, an RD of 10.09% (95% CI 7.88, 12.30) between varenicline and placebo was reported. Among other psychiatric disorders, the next greatest RD was 0.80% (95% CI –0.06, 1.67) for depressed mood disorders and disturbances. In summary, psychiatric adverse events are

Table IV. Incidence of psychiatric disorders[a]

Psychiatric disorders[b]	Varenicline (n = 3091) [n (%)]	Placebo (n = 2005) [n (%)]	Relative risk[c] (95% CI)
Adjustment disorders	0 (0.0)	1 (0.1)	NA
Anxiety disorders and symptoms	138 (4.5)	101 (5.0)	0.86 (0.67, 1.12)
Changes in physical activity (including restlessness)	33 (1.1)	20 (1.0)	0.76 (0.42, 1.39)
Cognitive and attention disorders and disturbances	0 (0.0)	1 (0.1)	NA
Communication disorders and disturbances	0 (0.0)	1 (0.1)	NA
Deliria (confusional state, disorientation)	3 (0.1)	2 (0.1)	1.07 (0.14, 8.12)
Depressed mood disorders and disturbances (including agitated depression, anhedonia, depressed mood, depression, depressive symptoms)	88 (2.8)	38 (1.9)	1.42 (0.96, 2.08)
Dissociative disorders	7 (0.2)	3 (0.2)	0.68 (0.18, 2.54)
Disturbances in thinking and perception (including hallucination)	13 (0.4)	2 (0.1)	3.29 (0.73, 14.81)
Manic and bipolar mood disorders and disturbances	2 (0.1)	0 (0.0)	NA
Mood disorders and disturbances NEC (including anger, apathy, frustration)	73 (2.4)	30 (1.5)	1.21 (0.79, 1.83)
Personality disorders and disturbances in behaviour (including aggression, hostility)	5 (0.2)	5 (0.2)	0.81 (0.21, 3.06)
Psychiatric and behavioural symptoms NEC (hypervigilance)	0 (0.0)	1 (0.1)	NA
Psychiatric disorders NEC (including nicotine dependence)	16 (0.5)	6 (0.3)	2.37 (0.91, 6.21)
Schizophrenia and other psychotic disorders	1 (<0.1)	1 (0.1)	0.99 (0.06, 15.74)
Sexual dysfunctions, disturbances and gender-identity disorders	18 (0.6)	10 (0.5)	1.07 (0.49, 2.34)
Sleep disorders and disturbances	776 (25.1)	291 (14.5)	1.70 (1.50, 1.92)
Somatoform and factitious disorders (conversion disorder)	0 (0.0)	1 (0.1)	NA
Suicidal and self-injurious behaviours NEC (suicidal ideation, suicide attempt)	0 (0.0)	2 (0.1)	NA

a Subjects could have reported >1 psychiatric disorder, hence the sum of the incidence of individual psychiatric disorders does not equal the incidence of all psychiatric disorders in table III.

b Adverse events were programmatically coded to standard terms according to the MedDRA® version 11.0.[32]

c Relative risk estimates for varenicline vs placebo were stratified by study. Relative risks were not calculated for high-level group terms with zero incidence.

MedDRA = Medical Dictionary for Regulatory Activities; **NA** = not applicable; **NEC** = not elsewhere classified.

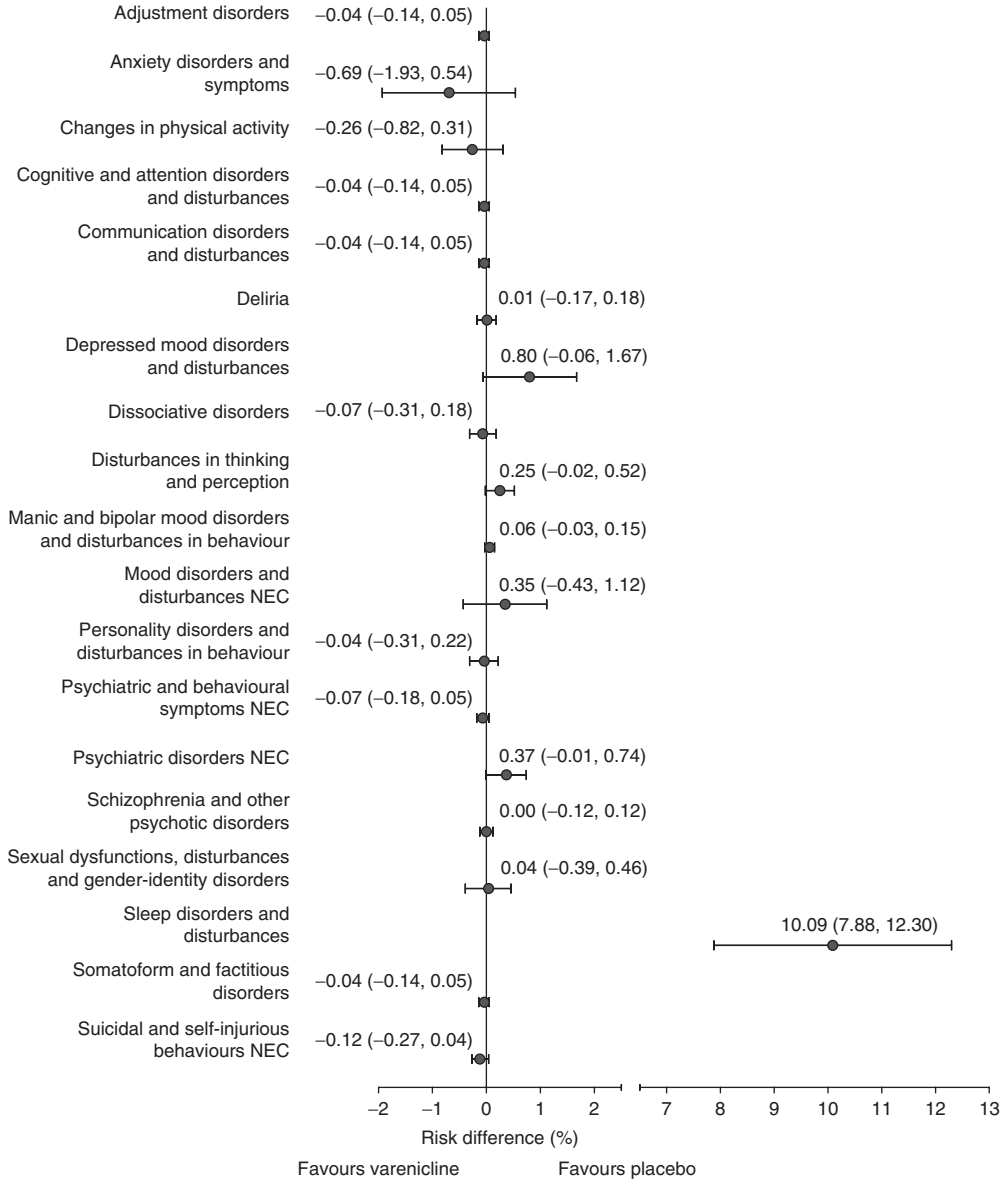

Fig. 1. Risk differences [% (95% CI)] of psychiatric disorders for varenicline vs placebo. T-bars represent 95% CIs. Adverse events were programmatically coded to standard terms according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 11.0.[32] **NEC** = not elsewhere classified.

uncommon and do not appear to be caused by varenicline *per se*. Varenicline is highly selective for $\alpha_4\beta_2$ nicotinic receptors and, at therapeutic levels,[36] does not bind to other neurotransmitter receptors and transporters,[37] including those implicated in mental disorders.[38] Some have interpreted the association of nicotine use and psychiatric disorders to indicate that nicotine itself causes mental disorders.[39] In contrast, other data suggest this association is due to self-medication,

i.e. the use of nicotine to treat pre-existing psychiatric problems.[40] In addition, nicotine decreases serotonin levels,[41] which has been associated with anger and depression.[42] In contrast, other studies have suggested that nicotine agonists and antagonists are antidepressants.[43]

The strengths of this analysis include the randomized, prospective and placebo-controlled design of the studies, the blinding of clinicians, subjects and sponsor, the standardized monitoring for adverse events, and the use of a computerized programme to assign adverse events to predefined MedDRA® groups. All of these factors minimized bias.

Some of the neuropsychiatric adverse events may have been due to nicotine withdrawal, e.g. depressed mood, irritability/frustration/anger and anxiety are symptoms of nicotine withdrawal[44] and can last for several weeks.[45] Since varenicline significantly increased abstinence compared with placebo, any increase in adverse events with varenicline could be due to enhanced quitting activity in actively treated subjects. Unfortunately, measurements in the ten studies do not allow us to separate abstinence effects from medication effects.

The incidence of psychiatric adverse events was based on subject report; these symptoms were not assessed systematically through scales or interviews, whether at baseline or during treatment. A detailed interview questioning psychiatric symptoms or completion of validated depression scales before versus after quitting, and on versus off varenicline, may be useful in future trials to delineate whether a true risk of psychiatric adverse events exists and whether the psychiatric adverse events are attributable to varenicline or the increased rate of quitting in varenicline-treated subjects.

The current analysis is limited by the fact that the ten studies excluded patients with psychiatric co-morbidities or who used psychiatric medications. This is common practice in studies of smoking cessation medications and was carried out because these symptoms could interact in unknown ways with the medication being studied, confound the treatment effect, decrease compliance and thus make it difficult to interpret the results. In addition, a further potential limitation of the current analysis is that nine of the ten studies included in the analysis were designed

Table V. Incidence of psychiatric disorders in studies that included both varenicline 1 mg twice daily (bid) and <1 mg bid dose regimens (based on four studies)[20-23]

Psychiatric disorders[a]	Varenicline 1 mg bid (n = 603) [n (%)]	Varenicline <1 mg bid (n = 901) [n (%)]	Placebo (n = 553) [n (%)]
Adjustment disorders	0 (0.0)	0 (0.0)	1 (0.2)
Anxiety disorders and symptoms	22 (3.6)	45 (5.0)	30 (5.4)
Changes in physical activity	12 (2.0)	14 (1.6)	6 (1.1)
Deliria	1 (0.2)	0 (0.0)	0 (0.0)
Depressed mood disorders and disturbances	12 (2.0)	29 (3.2)	12 (2.2)
Dissociative disorders	4 (0.7)	3 (0.3)	3 (0.5)
Disturbances in thinking and perception	2 (0.3)	5 (0.6)	1 (0.2)
Manic and bipolar mood disorders and disturbances	1 (0.2)	0 (0.0)	0 (0.0)
Mood disorders and disturbances NEC	22 (3.6)	23 (2.6)	17 (3.1)
Personality disorders and disturbances in behaviour	1 (0.2)	0 (0.0)	0 (0.0)
Psychiatric and behavioural symptoms NEC	0 (0.0)	0 (0.0)	1 (0.2)
Psychiatric disorders NEC	0 (0.0)	3 (0.3)	0 (0.0)
Sexual dysfunctions, disturbances and gender-identity disorders	5 (0.8)	3 (0.3)	3 (0.5)
Sleep disorders and disturbances	166 (27.5)	200 (22.2)	74 (13.4)
Suicidal and self-injurious behaviours NEC	0 (0.0)	0 (0.0)	1 (0.2)

a Adverse events were programmatically coded to standard terms according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 11.0.[32]

NEC = not elsewhere classified.

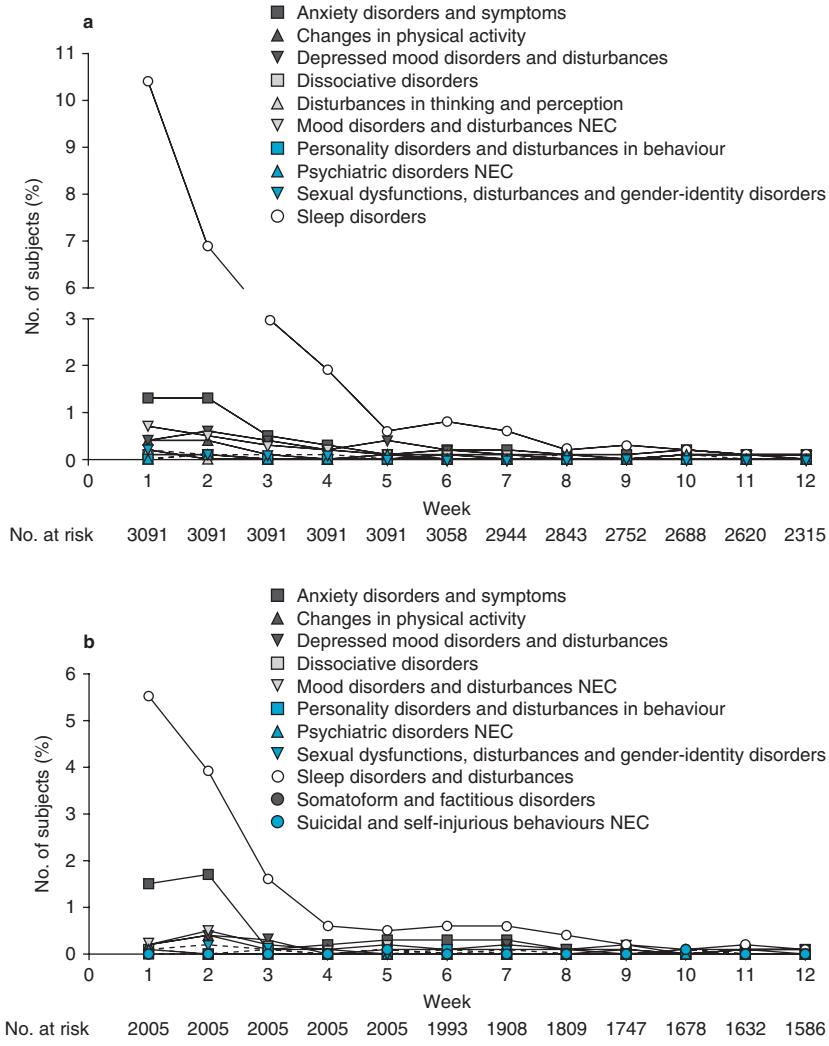

Fig. 2. Onset of treatment-emergent psychiatric adverse events by week for (**a**) varenicline-treated group and (**b**) placebo group. Adverse events were programmatically coded to standard terms according to the MedDRA® version 11.0.[32] **MedDRA** = Medical Dictionary for Regulatory Activities; **NEC** = not elsewhere classified.

to assess efficacy rather than safety and only one of the trials was designed to assess long-term safety.[25]

Since these ten trials, several studies on the safety of varenicline have been conducted. Three open-label studies conducted independently of the manufacturer have tested varenicline in smokers with current psychiatric disorders,[46-48] none of which raised a particular concern. A retrospective analysis of the General Practice Research Database (GPRD) in the UK found the incidence of suicide and depression was no greater in users of varenicline than in users of NRT or bupropion.[49] A study by Stapleton et al.[48] found that the use of varenicline in smokers with current mental illness was not associated with an increased risk of adverse psychiatric events. In addition to these studies, the FDA conducted a postmarketing safety review of varenicline and bupropion using the Adverse Event Reporting

System (AERS) to identify cases of suicidality.[50] The report suggested a possible association between suicidal events and the use of varenicline or bupropion, but stated that it was unclear if such events were caused by either medication, and urged close monitoring of patients taking these medications for neuropsychiatric symptoms. Our study did not examine the safety of varenicline specifically in smokers with psychiatric co-morbidity. Given the high incidence of psychiatric co-morbidity among smokers seeking treatment,[51] further studies of the safety of varenicline in such smokers are clearly needed. In fact, several such studies are ongoing (www.clinicaltrials.gov).

No cases of suicidal ideation and behaviour were reported in the ten placebo-controlled studies; however, one case of completed suicide was reported in all subjects receiving varenicline in all phase II, III and IV studies. Even though the population in this analysis includes approximately 3000 smokers exposed to varenicline, this is a relatively small sample size for the detection of rare potential adverse events. Large pharmacoepidemiology trials that collect adverse events in a more standard format than the often minimal spontaneous postmarketing reports, may provide a more accurate assessment of the occurrence of psychiatric adverse events with varenicline.

Finally, benefit-risk evaluations should evaluate estimates of both risks and benefits. In clinical trials, approximately one in ten smokers who otherwise would not have quit, did quit with varenicline.[3,15] While studies with follow-up beyond 1 year are not available for varenicline, the benefit of quitting smoking was demonstrated in, for example, the Lung Health Study where smokers with airway obstruction were followed for up to 14 years. Sustained quitters experienced a decrease of all-cause mortality (6.04 per 1000 person-years) compared with continuing smokers (11.09 per 1000 person-years).[52]

Conclusions

This quantitative analysis of ten placebo-controlled studies of varenicline among smokers with no current psychiatric problems found that, with the exception of sleep disorders and disturbances, psychiatric adverse events were rare and were not significantly associated with varenicline use. Further studies of varenicline in at-risk samples are currently underway.

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