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RESEARCH

Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database

D Gunnell, professor of epidemiology,[1] D Irvine, pharmacoepidemiologist,[2] L Wise, senior pharmacoepidemiologist,[2] C Davies, senior pharmacovigilance assessor,[2] R M Martin, professor of clinical epidemiology[1]

[1]University of Bristol, Department of Social Medicine, University of Bristol, Bristol BS8 2PS

[2]Vigilance and Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency, London SW8 5NQ

Correspondence to: D Gunnell
d.j.gunnell@bristol.ac.uk

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ABSTRACT

Objective To determine whether varenicline, a recently licensed smoking cessation product, is associated with an increased risk of suicide and suicidal behaviour compared with alternative treatments bupropion and nicotine replacement therapy.

Design Cohort study nested within the General Practice Research Database.

Setting Primary care in the United Kingdom.

Participants 80 660 men and women aged 18-95 years were prescribed a new course of a smoking cessation product between 1 September 2006 and 31 May 2008; the initial drugs prescribed during follow-up were nicotine replacement products (n=63 265), varenicline (n=10 973), and bupropion (n=6422).

Main outcome measures Primary outcomes were fatal and non-fatal self harm, secondary outcomes were suicidal thoughts and depression, all investigated with Cox's proportional hazards models.

Results There was no clear evidence that varenicline was associated with an increased risk of fatal (n=2) or non-fatal (n=166) self harm, although a twofold increased risk cannot be ruled out on the basis of the upper limit of the 95% confidence interval. Compared with nicotine replacement products, the hazard ratio for self harm among people prescribed varenicline was 1.12 (95% CI 0.67 to 1.88), and it was 1.17 (0.59 to 2.32) for people prescribed bupropion. There was no evidence that varenicline was associated with an increased risk of depression (n=2244) (hazard ratio 0.88 (0.77 to1.00)) or suicidal thoughts (n=37) (1.43 (0.53 to 3.85)).

Conclusion Although a twofold increased risk of self harm with varenicline cannot be ruled out, these findings provide some reassurance concerning its association with suicidal behaviour.

INTRODUCTION

There are growing concerns that varenicline, a smoking cessation product licensed in the UK since September 2006, may be associated with an increased risk of suicide. Varenicline is a partial agonist that binds at the nicotinic α4β2 receptor, and it seems to be the most effective smoking cessation product currently available.[1] As it acts on the central nervous system and its effects include the stimulation of dopamine release, it is possible that it may have an impact on mood and suicide risk.[2 3]

In December 2007, after reports of depression and suicidal thoughts among people prescribed varenicline, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a warning concerning possible increased risks,[4] with further warnings issued in July and November 2008. Similar warnings have been issued by regulatory authorities worldwide, and warnings have been added to the prescribing information and information for patients. In July 2009, the US Food and Drugs Administration (FDA) required the manufacturers of both varenicline and bupropion to add a new "boxed warning" (the strongest warning that the FDA requires) to the product labelling based on the continued review of postmarketing adverse event reports. By June 2008, almost half a million people had been prescribed varenicline in the UK. The rate of reported suicide related events tripled in the months immediately after regulatory warnings in the UK (see figure), a phenomenon known as "stimulated reporting." By April 2009, yellow card reports relating to 14 suicides in people taking varenicline had been received by the MHRA, although causal links were not confirmed.

Although clinician and patient reports of adverse events associated with varenicline suggest the possibility of serious side effects, controlled studies are required to quantify the degree of risk, distinguish the side effects of varenicline from the effects of smoking cessation, and take account of the characteristics of people who decide to stop smoking (confounding by indication). To our knowledge, no previous large population studies have investigated this issue.

Investigation of these concerns is challenging because people who smoke have a twofold to threefold increased risk of suicide.[5 6] The underlying mechanism for this increased risk is unclear, although confounding by alcohol misuse and mental illness seems to explain much of the association.[2] One way of distinguishing any increased risk associated with varenicline from that associated with smoking cessation per se is to compare the risk of self harm among people taking

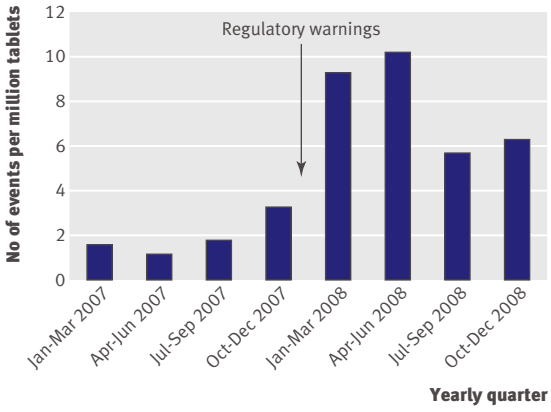

Fig 1 | Rate of suicide related adverse events reported for varenicline per million tablets prescribed in 2007-2008. (Data source MHRA yellow cards and data derived from IMS HEALTH Midas database)

varenicline with the risk associated with other smoking cessation products—nicotine replacement therapy and bupropion. In this paper we report a cohort study using the UK General Practice Research Database (GPRD) to investigate this issue.

METHODS

Cohort identification

The GPRD records demographic, consultation, prescribing, referral and health outcome data from almost 500 general practices (about 3.6 million active patients) throughout the United Kingdom (www.gprd.com/home/default.asp). Data quality are checked and validated by the GPRD Group, and previous studies confirm good completeness of recording of clinical data.[7 8] It is likely that almost all prescriptions issued by the general practitioners are recorded on the database, as they generate prescriptions using their computer, and these are automatically captured in the computer record.

We identified all patients aged 18 years and over with GPRD records who were prescribed either varenicline (recommended treatment duration 12 weeks), bupropion (recommended treatment duration 7-9 weeks), or a nicotine replacement product (transdermal patch, inhaler, nasal spray, gum, sublingual tablet or lozenge—variable recommended treatment durations, approximate range 3-6 months) between 1 September 2006 and 31 May 2008. We chose 18 years as the lower age limit for inclusion in our study as the drug is licensed for use only in adults. We excluded all patients (n=1376) who took a particular smoking cessation product for more than twice the recommended treatment duration.

The date of the first prescription defined entry to the cohort. We obtained electronic patient records for care over the period of the prescription and for three months after the date of the last prescription. We excluded patients with GPRD records of <365 days before their first recorded prescription. We used only those patients classified as "acceptable" by the GPRD and restricted the analysis to practices that were designated as "up to standard" by the GPRD Group. This procedure was implemented to maximise the quality and completeness of the data. Patients were categorised to the three exposure groups (varenicline, bupropion, or nicotine replacement therapy) based on the drug they were first prescribed in the follow-up period. Subsequent treatment episodes were not included in the analysis, but we identified patients who received other smoking cessation treatments after the index prescription and censored follow-up at the time of switching or adding products. We did a sensitivity analysis by dropping all people who commenced other smoking cessation products.

Power calculations based on preliminary data extracts from the GPRD indicated we had sufficient (80%) power (5% level of statistical significance) to detect twofold increases in risk of self harm with varenicline compared with other products.

Outcome measures

Our primary outcome was fatal and non-fatal self harm. This was defined based on more than 70 Read codes and Oxford Medical Information System (OXMIS) medical terms using an algorithm used in a previous GPRD study.[9] Read and OXMIS are coding systems used by general practices to enter diagnoses: the codes used included terms such as "poisoning self-inflicted", "intentional self-harm by hanging, strangulation/suffocation", "intentional self-harm by sharp object", and "attempted suicide" (the full list is available from the authors). Suicide deaths were identified from death details and postmortem findings recorded on GPRD. We did not obtain death certificates for all deaths.

We also examined associations of smoking cessation products with suicidal thoughts, depression, and all cause mortality, again using relevant Read and OXMIS terms; we defined depression as the start of antidepressant therapy and excluded from this analysis people who had been prescribed antidepressants at any time in the six months before starting smoking cessation therapy.

Possible confounding factors

We investigated the possible confounding effect of sex; age (five age groups of 18-30, 31-40, 41-50, 51-60, >60 years); previous psychiatric consultation; alcohol misuse; current (at the time of starting smoking cessation product) or previous use of psychotropic medication (hypnotics, antipsychotics, or antidepressants (*British National Formulary* classes 4.1, 4.2, and 4.3 respectively)); previous self harm or suicidal thoughts; previous prescriptions for smoking cessation products; number of GP visits per year (to control for propensity to consult and so report symptoms; four categories of ≤1.8, >1.8-3.1, >3.1-5.2, and >5.2 average consultations/year); whether initial exposure occurred before or after January 2008, when there was considerable

publicity concerning possible suicide related side effects with varenicline; index of multiple deprivation (an ecological measure of socioeconomic position including area levels of income, employment, education, and a range of other factors (five levels))[10]; region of the UK (England, Northern Ireland, Scotland, or Wales); and whether other smoking cessation products were prescribed after the index prescription. There were no missing data for these possible confounders.

Analysis

We used Cox proportional hazards regression models in Stata, release 9.2 (StataCorp, College Station, TX, USA) for all analyses. We used calendar time since starting the product as the time axis and linked this to prescription duration to identify "current exposure." Follow-up began on the date of the first prescription of a smoking cessation product after 1 September 2006 and ended three months after the date of the last prescription or with a primary end point (fatal or non-fatal self harm). Patients who died from causes other than suicide, who left their practice, or who started another smoking cessation product during the exposure period were censored on the relevant dates. The last date that the practice contributed data to the GPRD was also incorporated into the censoring. In our initial models we controlled for age and sex, we then assessed the effect of controlling for all the confounding factors listed above, fitted as categorical variables to the models.

We conducted separate analyses in relation to the other study end points (suicidal thoughts and depression). In these analyses subjects who died or left the practice were censored on their dates of death or departure. We used nicotine replacement therapy as the baseline (reference) category for our risk estimates as most patients were prescribed these products and most episodes of self harm occurred in this group.

By fitting appropriate interaction terms to the models, we investigated whether any associations differed by sex; age (five categories); calendar year of prescription (in view of changes in the Summary of Product Characteristics and *British National Formulary* warnings concerning varenicline and publication of the Drug Safety Update influencing prescribing patterns and reporting in 2007-8); and past psychiatric history or treatment with psychotropic drugs.

We investigated the proportional hazards assumption graphically. For some confounders where there was some graphical evidence that the proportionality assumptions were violated, we fitted models with these variables as strata. The effects on the model estimates for the smoking cessation therapies were minimal and in the final analysis no stratification was used.

RESULTS

Altogether 80 660 patients were prescribed a new course of a smoking cessation product over the study period: the first treatment prescribed was a nicotine replacement product (n=63 265), bupropion (n=6422), or varenicline (n=10 973). Total exposure time was 24 055.6 person years: 18 879.2 person years for nicotine replacement therapies (mean 15.5 weeks per person); 1690.8 person years for bupropion (mean 13.7 weeks per person), and 3485.6 person years for varenicline (mean 16.5 weeks per person).

The characteristics of patients prescribed varenicline were similar to those prescribed bupropion (table 1). Compared with patients prescribed nicotine replacement products, patients prescribed bupropion and varenicline were more often male and less likely to have a history of psychiatric consultation, alcohol misuse, use of psychotropic medication, or self harm or suicidal thoughts. People prescribed bupropion were younger than those prescribed the other products, but the differences were slight. Altogether, 9.5% of patients prescribed varenicline had previously harmed themselves or experienced suicidal thoughts. Almost half of all patients had previously been prescribed a smoking cessation product.

Self harm and suicidal thoughts

Over the follow-up period there were 166 episodes of non-fatal self harm (154 (93%) being cases of self poisoning), two suicides (both in patients prescribed nicotine replacement products, one by means of hanging, the other with a firearm), and 37 episodes of suicidal thoughts. The incidence of self harm, standardised for age and sex, was 533.1 (95% confidence interval 277.0 to 789.2) per 100 000 person years in patients prescribed varenicline, 498.7 (169.1 to 828.2) for bupropion, and 751.7 (627.4 to 876.0) for nicotine replacement products.

The age and sex adjusted hazard ratio for self harm associated with prescribed varenicline was similar to that for bupropion, and the hazard ratios suggest a lower risk of self harm than that associated with nicotine replacement products, although the confidence intervals were wide and included 1.00 (table 2). After controlling for possible confounding factors, we found very weak evidence of an increased risk in relation to both varenicline (hazard ratio 1.12 (0.67 to 1.88)) and bupropion (hazard ratio 1.17 (0.59 to 2.32)). The confounding factors that most strongly contributed to the change in direction of the association with varenicline were past and current use of antidepressants. There was no statistical evidence that associations of smoking cessation products with self harm differed by sex (P(interaction)=0.74), age (P(interaction)=0.70), the timing of the prescribing (before or after media publicity around January 2008) (P(interaction)=0.32), or past psychiatric problems (P(interaction)=0.96).

In fully adjusted models varenicline was associated with a 43% (95% confidence interval −47% to 285%) increased risk of suicidal thoughts compared with nicotine replacement products. However, the wide confidence intervals were consistent with a large protective effect, no effect, or a large adverse effect.

Table 1 | Comparison of baseline characteristics of people prescribed different smoking cessation therapies. Values are numbers (percentages) of patients unless stated otherwise

Variable	Nicotine replacement (n=63 265)	Bupropion (n=6422)	Varenicline (n=10 973)	Total (n=80 660)
Male sex	27 780 (43.9)	3109 (48.4)	5109 (46.6)	35 998 (44.6)
Median age (years)	45.80	43.29	45.91	45.52
Previous mental health consultation	2563 (4.1)	156 (2.4)	279 (2.5)	2998 (3.7)
Alcohol misuse	6702 (10.6)	468 (7.3)	909 (8.3)	8079 (10.0)
Hypnotics use:				
None	38 682 (61.1)	4205 (65.5)	6824 (62.2)	49 711 (61.6)
Previous	15 604 (24.7)	1561 (24.3)	3043 (27.7)	20 208 (25.1)
Current	8979 (14.2)	656 (10.2)	1106 (10.1)	10 741 (13.3)
Antipsychotic use:				
None	49 592 (78.4)	5491 (85.5)	9038 (82.4)	64 121 (79.5)
Previous	9837 (15.6)	775 (12.1)	1660 (15.1)	12 272 (15.2)
Current	3836 (6.1)	156 (2.4)	275 (2.5)	4267 (5.3)
Antidepressant use:				
None	31 174 (49.3)	3610 (56.2)	5648 (51.5)	40 432 (50.1)
Previous	16 107 (25.5)	1819 (28.3)	3344 (30.5)	21 270 (26.4)
Current	15 984 (25.3)	993 (15.5)	1981 (18.1)	18 958 (23.5)
Previous suicide related event	6985 (11.0)	563 (8.8)	1041 (9.5)	8589 (10.7)
Previous smoking cessation therapy	30 640 (48.4)	3518 (54.8)	5725 (52.2)	39 883 (49.4)
Median No of clinical visits per year	3.18	2.71	2.83	3.09
Exposed to treatment before January 2008	52 953 (83.7)	5720 (89.1)	6378 (58.1)	65 051 (80.7)
Index of multiple deprivation score:				
0	10 289 (16.3)	1110 (17.3)	1566 (14.3)	12 965 (16.1)
1	10 230 (16.2)	1249 (19.4)	1968 (17.9)	13 447 (16.7)
2	12 512 (19.8)	1262 (19.7)	1877 (17.1)	15 651 (19.4)
3	13 536 (21.4)	1364 (21.2)	1980 (18.1)	16 880 (20.9)
4	16 698 (26.4)	1437 (22.4)	3582 (32.6)	21 717 (26.9)
UK region:				
England	49 521 (78.3)	5523 (86.0)	8409 (76.6)	63 453 (78.6)
Northern Ireland	2822 (4.5)	109 (1.7)	602 (5.5)	3533 (4.4)
Scotland	4460 (7.0)	425 (6.6)	1306 (11.9)	6191 (7.7)
Wales	6462 (10.2)	365 (5.7)	656 (6.0)	7483 (9.3)
No of smoking cessation drugs used*:				
1	59 109 (93.4)	5023 (78.2)	10 207(93.0)	74 339 (92.2)
2	4023 (6.4)	1272 (19.8)	749 (6.8)	6044 (7.5)
3	133 (0.2)	127 (2.0)	17 (0.2)	277 (0.3)

*Including initial study treatment.

Depression

Of the 64 296 patients not taking antidepressants at baseline, 2244 (3.5%) were treated for depression over the follow-up period. Among these patients there was no evidence in either age and sex adjusted or fully adjusted models that varenicline was associated with an increased risk of developing treated depression compared with nicotine replacement products, and major increases in risk can be ruled out (hazard ratio 0.88 (0.77 to 1.00), table 2).

Sensitivity analyses and all-cause mortality

The risk of self harm and depression with varenicline and bupropion compared with nicotine replacement products were essentially unchanged in (*a*) models restricted to people who took only one smoking cessation product after 1 September 2006, with adjusted hazard ratios for self harm in relation to varenicline 1.12 (95% confidence interval 0.67 to 1.88) and in relation to bupropion 1.29 (0.63 to 2.66); and (*b*) models censoring follow-up to 10 weeks after treatment started for all subjects (adjusted hazard ratios for self harm in relation to varenicline 0.93 (0.49 to 1.76) and bupropion (1.10 (0.50 to 2.38)).

Overall 208 participants died over the follow-up period. In age and sex adjusted models we found no evidence that either varenicline or bupropion were associated with an increased risk of all cause mortality risk compared with nicotine replacement therapy (hazard ratios 0.26 (0.13 to 0.53) and 0.56 (0.26 to 1.19) respectively).

Table 2 | Relative risks of fatal and non-fatal self harm, suicidal thoughts, and depression in people prescribed different smoking cessation products*

Smoking cessation product	No of events/No of people prescribed the product	Hazard ratio (95% CI)	
		Adjusted for age and sex	Fully adjusted†
Fatal and non-fatal self harm			
Nicotine replacement	141/63 265	1.0	1.0
Bupropion	9/6422	0.66 (0.33 to 1.29)	1.17 (0.59 to 2.32)
Varenicline	18/10 973	0.71 (0.43 to 1.16)	1.12 (0.67 to 1.88)
Suicidal thoughts			
Nicotine replacement	30/63 265	1.0	1.0
Bupropion	2/6422	0.69 (0.16 to 2.90)	1.20 (0.28 to 5.12)
Varenicline	5/10 973	0.94 (0.36 to 2.42)	1.43 (0.53 to 3.85)
Start of antidepressant therapy‡			
Nicotine replacement	1792/49 415	1.0	1.0
Bupropion	160/5719	0.86 (0.73 to 1.01)	0.91 (0.77 to 1.07)
Varenicline	292/9162	0.82 (0.72 to 0.93)	0.88 (0.77 to 1.00)

*Risks calculated from Cox proportional hazards regression model.
†Adjusted for age; sex; use of hypnotics, antipsychotics, and antidepressants; alcohol misuse; previous suicide related event; previous smoking cessation therapy; psychiatric consultation; date of initial exposure to product, number of general practice visits per year, index of multiple deprivation, UK region.
‡Restricted to those with no antidepressants in the six months before smoking cessation therapy.

DISCUSSION

Main findings

We found no clear evidence of an increased risk of self harm associated with varenicline compared with other smoking cessation products, although the limited study power means we cannot rule out either a halving or a twofold increase in risk. Analysis of those patients prescribed varenicline suggested that they were likely to be at lower risk of self harm than those prescribed nicotine replacement products—they had lower levels of past psychiatric consultation and previous self harm. Nevertheless, controlling for these factors in multivariable models did not alter our conclusions. We found no evidence that varenicline increased the incidence of suicidal thoughts. However, associations with suicidal thoughts should be treated with caution as they are under-recorded in the General Practice Research Database (GPRD). Varenicline was associated with a reduced risk of treated depression, as indexed by initiation of antidepressant therapy.

Strengths and limitations of study

The GPRD contains detailed records of prescribing and health related events for a large number of people registered with general practitioners in the United Kingdom and so can provide timely information concerning emerging drug safety concerns. Detailed data on patient sociodemographics and medical history enable assessment of possible confounding.

There are several limitations to this analysis. Firstly, study power was limited: despite the large coverage of the GPRD, we identified only 10 973 people prescribed varenicline over the study period, and only 18 episodes of self harm were recorded in this group.

Secondly, our analysis is restricted to products prescribed in primary care. Patients receiving smoking cessation products in NHS smoking cessation clinics or buying over the counter products from pharmacies will be excluded. People who visit their general practitioner for prescriptions of smoking cessation products may differ from those attending specific smoking cessation clinics, meaning findings may not be generalisable to the wider population of people taking smoking cessation aids.

Thirdly, people taking varenicline and bupropion may be more likely to have already tried (and failed) to stop smoking with nicotine replacement therapy and so differ in underlying characteristics or level of addiction (and possibly suicide risk) compared with those prescribed nicotine replacement products. Such a possibility is supported by our observation that those prescribed varenicline or bupropion had slightly higher levels of previous use of smoking cessation products (52% and 55% respectively) than those prescribed nicotine replacement products (49%).

Fourthly, bupropion is licensed for the treatment of depression in some countries (but not the UK). It is possible (though unlikely) that some bupropion prescribing is off-label use for depression. Such an effect would exaggerate any increased suicide risk associated with bupropion.

Fifthly, this is an observational study, and the small differences (or lack of differences) between products could be due to uncontrolled confounding. We found some evidence of this in our fully adjusted models, where the lower risks of self harm associated with varenicline in our age and sex adjusted models were reversed.

Lastly, full death certificates were not obtained for study members who died, possibly leading to an underestimation of suicide deaths. The ratio of episodes of non-fatal self harm to suicide in the general population (and in our previous GPRD study[9]) is around 20-30:1, but it is 80:1 in our current study, indicating that we may have failed to identify some cases of suicide. Such an effect is unlikely to bias our results, as cause of death certification should be non-differential with respect to smoking cessation product. Furthermore, as there are 20-30 episodes of non-fatal self harm for every suicide death, any under-numeration will have little impact on the precision of our effect estimates. Similarly, the relatively low number of cases of suicidal thoughts (n=37) suggests these were under-recorded: in the general population the incidence of suicidal thoughts is considerably higher than that for fatal and non-fatal self harm.[11]

Relevant research literature

Many prospective studies have found that smokers are at two to three times greater risk of suicide than non-smokers.[5,6] Possible explanations for this increase in risk[2] include (*a*) smoking may be used as "self medication" by people with mental illness, and such people are at increased risk of suicide; (*b*) confounding by factors such as low socioeconomic position, alcohol misuse, and psychiatric illness, all of which are associated with increased smoking prevalence and suicide

WHAT IS ALREADY KNOWN ON THIS TOPIC

Varenicline is an effective smoking cessation product, but there are concerns that it may increase the risk of suicidal behaviour and suicide

Smokers are at an increased risk of suicide

WHAT THIS STUDY ADDS

We found no clear evidence of an increased risk of self harm or depression associated with varenicline

risk[12 13]; and (*c*) smoking may cause psychological illness and physical health problems, both of which are associated with suicide risk. In studies that have controlled for a wide range of social and mental health related risk factors for suicide, associations of smoking with suicidal behaviour are abolished.[5 14] Nevertheless, these studies indicate that people who smoke (and who give up smoking) are a high risk group.

Smoking is common among people with psychiatric illness,[13] and it is possible that it has a beneficial effect on psychiatric symptoms, such as anxiety, that may be lost with smoking cessation. Furthermore, as smoking is addictive, smoking cessation leads to unpleasant withdrawal symptoms. Thus, reported associations of psychiatric symptoms and self harm with varenicline and bupropion may be confounded by the effects of smoking cessation or influenced by the fact that smokers are a high risk group. Nevertheless, it is noteworthy that in a review of adverse outcomes associated with smoking cessation in three randomised trials of interventions that achieved more than a 10% reduction in smoking in the intervention arm compared with controls, those in the intervention arm had a reduced risk of suicide at follow-up (odds ratio 0.56 (95% confidence interval 0.26 to 1.21)).[15] These trials involved lifestyle interventions to reduce cardiovascular risk as well as smoking cessation advice or treatment and all preceded the introduction of varenicline and bupropion.

Clinical trials show that the most commonly reported adverse effect of varenicline is nausea—reported by about a quarter of patients.[1] Possible adverse effects of varenicline on mood and suicidal thoughts do not seem to have been systematically assessed in the larger placebo controlled trials of this product.[16 17] However, these trials find no evidence of a greater adverse effect of varenicline on sleep or irritability compared with placebo, though there is evidence that varenicline increases the incidence of vivid dreams and increased frequency of dreams. In our analysis, those receiving varenicline were less likely to initiate antidepressant therapy over the follow-up period than those prescribed nicotine replacement products (fully adjusted hazard ratio 0.88 (0.77 to 1.00)). There are several possible explanations for this finding. Firstly, it may be due to chance. Secondly, general practitioners may be less willing to prescribe antidepressants to patients already prescribed varenicline or bupropion than to those prescribed a nicotine replacement product. Thirdly, in view of the warnings on the risk of suicide, general practitioners were encouraged to be cautious about prescribing varenicline to patients with a history of depression—so this perceived protective effect may be due to confounding by indication. Fourthly, it may be due to confounding by factors we did not control for in our analysis—the presence of such factors is suggested by the lower all cause mortality in people prescribed varenicline compared with those prescribed nicotine replacement products. Lastly, it could reflect a possible beneficial impact of varenicline on mood.[18]

Conclusion

We found no clear evidence of an increased risk of self harm, suicidal thoughts, or depression in people prescribed varenicline compared with those prescribed other smoking cessation products. In view of increasing concerns about the possible increased risk of suicide associated with these drugs and their increasing popularity, further investigation of their effect on suicide risk is required in other databases and through secondary analysis of all adverse event reporting in relevant clinical trials. Any such risk must be balanced against the likely long term health benefits of smoking cessation and the robust evidence of the effectiveness of varenicline as an aid to smoking cessation.

Contributors: All authors contributed to the study proposal, design of the analysis, and interpretation of the findings. DI was responsible for data extraction. DI undertook the analysis with input from DG, LW, and RMM. DG wrote the first draft of the paper, which was revised by all authors. DG and DI will act as guarantors.
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Competing interests: DG is a member of the Pharmacovigilance Expert Advisory Group of the MHRA. DI, LW, and CD are employees of the MHRA. RMM is a member of Independent Scientific Advisory Committee for MHRA database research (ISAC).
Ethical approval: Approval was given by the General Practice Research Database's Independent Scientific Advisory Committee. The GPRD Group has obtained ethical approval from a multicentre research ethics committee for all purely observational research using GPRD data.

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