

Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study

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ABSTRACT

Objective To compare the risk of suicide in adults using the antidepressant venlafaxine with the risk of suicide in adult using citalopram, fluoxetine, and dothiepin.

Design Retrospective cohort study.

Setting UK General Practice Research Database.

Participants 219 088 patients, aged 18-89 years, who were prescribed venlafaxine, citalopram, fluoxetine, or dothiepin from 1995 to 2005.

Main outcome measures Completed suicide and attempted suicide.

Results Venlafaxine users had a higher burden of risk factors for suicide, including previous suicide attempts and proxies for severe depression or depression that was difficult to treat. In the analysis for completed suicides, unadjusted and adjusted hazard ratios for venlafaxine compared with citalopram were 2.44 (95% confidence interval 1.12 to 5.31) and 1.70 (0.76 to 3.80), for venlafaxine compared with fluoxetine were 2.85 (1.37 to 5.94) and 1.63 (0.74 to 3.59), and for venlafaxine compared with dothiepin were 2.54 (1.07 to 6.02) and 1.31 (0.53 to 3.25). Compared with other study drugs, venlafaxine was also associated with an increased risk of attempted suicide, but adjustment for measured confounders substantially reduced the hazard ratios.

Conclusions Venlafaxine use was consistently associated with higher risk of suicide compared with citalopram, fluoxetine, and dothiepin. Venlafaxine users had a higher burden of suicide risk factors, however, and adjustment for measured confounders substantially reduced the excess risks. Since the secondary data used in this analysis allowed only indirect and partial measurements of potential confounders, it is possible that residual confounding explains much, if not all, of the observed excess risk.

INTRODUCTION

An observational study showed that users of the serotonin and noradrenaline reuptake inhibitor venlafaxine had a higher prevalence of risk factors for suicide than users of selective serotonin reuptake inhibitors.¹ We carried out a retrospective cohort study in the General Practice Research Database, which collects electronic medical records within UK primary care, to assess whether the risk of suicide in patients prescribed

venlafaxine differs from that in patients prescribed other antidepressants.^{2,3} We selected the selective serotonin reuptake inhibitor citalopram as a comparator. As citalopram and venlafaxine were introduced in the same year in the United Kingdom, we assumed that doctors would preferentially prescribe either drug to patients who were unresponsive to previous therapies⁴ and presumably had similar risks of suicide. Additional study comparators were fluoxetine and dothiepin.

METHODS

We selected patients with an incident prescription (first ever prescription recorded) for venlafaxine, citalopram, fluoxetine, or dothiepin during 1995 to 2005. Patients had to be aged 18 to 89 years at the time of incident prescription for any study drug, and have a record of depression or anxiety.

Patients were followed from their incident prescription date until the earliest of completed suicide or first attempted suicide, the end of the study period, or the end of their record. We censored follow-up time during periods of no use of any study drug.

Outcome measures and exposure to study drugs

Our end points were completed suicide (see definition on bmj.com) and the first attempted suicide during the study period, including completed suicides. For the completed suicide analysis we included patients who attempted suicide during the study period (see bmj.com).

We assumed that exposure to any study drug began on the day after the prescription date and extended to 14 days after the imputed end of the prescription, based on number of pills supplied and dosing instructions. If no gap existed between the imputed end of a first prescription plus 14 days and the date of the subsequent prescription for the same drug, we concatenated the exposure periods. We concatenated subsequent prescriptions similarly. Participants could experience multiple episodes of treatment for one or more study drugs.

When records indicated concomitant use of multiple antidepressants, we assumed there was a switch in therapy. We accounted for such a switch in analyses. We also examined the effect of assuming exposure for

seven rather than 14 days after the imputed end of a prescription.

Analysis covariates

The confounders considered were age, sex, diagnosis (depression or anxiety), suicide attempts, life events, lifestyle factors, family history of psychiatric morbidity, psychotropic comedications, and psychiatric comorbidities. We also evaluated chronic and disabling non-psychiatric morbidities associated with depression. We estimated severity of depression and treatment resistant depression using proxies such as history of antidepressants. We also used an initial prescription of 14 days or less as a proxy for clinician perceived risk of suicide. Because the first 30 days of treatment with antidepressants have been associated with a higher risk of suicide,⁵ we coded this period separately.

At the start of each treatment episode we reassessed confounders that could change throughout follow-up. We derived confounders for any time and for one month, one year, and ever before a treatment episode, as appropriate.

Statistical analysis

For each drug group we calculated the incidence rate (95% confidence intervals) for completed suicide and first attempted suicide. We evaluated the potential confounding effect of each covariate by comparing unadjusted and adjusted incidence rate ratios using Mantel-Haenszel methods.

For each outcome we built a time dependent Cox hazards regression model. Follow-up time was linked to calendar time (zero was 1 January 1995). Patients could contribute exposure time to more than one drug. To avoid saturation in the completed suicide analysis we limited the covariates to age, sex, age-sex interaction, overlap with other antidepressants, and the 10 confounders associated with the largest changes of the adjusted incidence rate ratio of venlafaxine with each comparator (see *bmj.com*). The larger number of outcomes in the attempted suicide analysis allowed us to include all the variables that modified the adjusted

incidence rate ratios. We estimated hazard ratios (95% confidence intervals) for each comparison and for each potential confounder.

RESULTS

Overall, 219088 adults (18-89 years) who were prescribed venlafaxine, citalopram, fluoxetine, or dothiepin from 1995 to 2005 were identified from the General Practice Research Database. Demographic characteristics across drug groups and covariates were similar. Data only from the completed suicide analysis are on *bmj.com*.

Most patients (90.5%, n=198231) had depression. About 25% of patients had depression and anxiety, and this proportion was higher among venlafaxine users (35.4%, n=7725) than among users of fluoxetine (22.0%, n=20893), citalopram (27.3%, n=16073), or dothiepin (23.9%, n=10387). Venlafaxine users also showed signs of more severe or difficult to treat depression (see *bmj.com*). Furthermore, proxies of depression severity were more common among venlafaxine users than among those using comparator drugs (see *bmj.com*). Previous attempted suicide was twice as common among venlafaxine users as among citalopram or fluoxetine users. Other suicide risk factors were also more common among venlafaxine users (see *bmj.com*). Distribution of chronic or incapacitating morbidities known to be associated with depression, of bereavement, and of marital problems did not differ across drug groups (see *bmj.com*).

Incidence rate and hazard ratio

The completed suicide analysis encompassed 54 events over 173452 person years of exposure to any study drug, and the first attempted suicide analysis encompassed 3060 events over 169735 person years at risk. The incidence rate of both completed and first attempted suicide was higher for venlafaxine treatment than for each comparator (table 1).

Adjustment for the higher risk of suicide during the first 30 days of treatment consistently increased the incidence rate ratio for both completed and attempted suicide analyses in each comparison (data not shown). For most confounders, however, adjustment was associated with a reduced incidence rate ratio. History of antidepressants and previous suicide attempts had the strongest confounding effect on the association between venlafaxine and completed or attempted suicide.

The unadjusted risk of completed suicide was more than twice as high for venlafaxine users as for other study drugs. Adjustment for the measured confounders in the completed suicide models, however, reduced the excess risk by at least 50% in each comparison (table 2, see also *bmj.com*). The unadjusted risk of attempted suicide was also higher during venlafaxine treatment than during citalopram, fluoxetine, and dothiepin treatments. The hazard ratio was substantially reduced after adjustment for measured confounders (table 2, see also *bmj.com*).

When the extended time at risk was reduced to seven days after the imputed end of a prescription,

Table 1 | Unadjusted incidence rate (95% confidence interval) of completed and first attempted suicides in adults according to antidepressant

Event and antidepressant	No of patients*	Person years at risk	No of events	Incidence rate (95% CI) per 1000 person years
Completed suicide:				
Venlafaxine	37 857	28 087	18	0.64 (0.40 to 1.02)
Citalopram	75 749	45 639	12	0.26 (0.15 to 0.46)
Fluoxetine	108 934	66 636	15	0.23 (0.14 to 0.37)
Dothiepin	54 035	33 090	9	0.27 (0.14 to 0.52)
First attempted suicide:				
Venlafaxine	37 132	26 854	715	26.6 (24.7 to 28.7)
Citalopram	75 103	44 788	781	17.4 (16.3 to 18.7)
Fluoxetine	108 474	65 416	1138	17.4 (16.4 to 18.4)
Dothiepin	53 818	32 677	426	13.0 (11.9 to 14.3)

*Patients could contribute person years at risk to more than one antidepressant.

Table 2 | Unadjusted and adjusted hazard ratios (95% CI) for completed and attempted suicides for venlafaxine treatment compared with citalopram, fluoxetine, and dothiepin treatment when time at risk included seven or 14 days after imputed end of prescription

Event and antidepressants	14 days		7 days	
	Unadjusted hazard ratio	Adjusted hazard ratio	Unadjusted hazard ratios	Adjusted hazard ratio
Completed suicide:				
Venlafaxine v citalopram	2.44 (1.12 to 5.31)	1.70 (0.76 to 3.80)	2.56 (1.14 to 5.77)	1.87 (0.81 to 4.29)
Venlafaxine v fluoxetine	2.85 (1.37 to 5.94)	1.63 (0.74 to 3.59)	3.19 (1.46 to 7.00)	1.87 (0.81 to 4.32)
Venlafaxine v dothiepin	2.54 (1.07 to 6.02)	1.31 (0.53 to 3.25)	2.37 (0.98 to 5.73)	1.27 (0.51 to 3.18)
Attempted suicide:				
Venlafaxine v citalopram	1.49 (1.34 to 1.66)	1.20 (1.07 to 1.34)	1.52 (1.36 to 1.69)	1.23 (1.10 to 1.37)
Venlafaxine v fluoxetine	1.68 (1.52 to 1.86)	1.28 (1.15 to 1.42)	1.68 (1.52 to 1.87)	1.28 (1.14 to 1.43)
Venlafaxine v dothiepin	2.41 (2.11 to 2.74)	1.47 (1.29 to 1.68)	2.38 (2.08 to 2.72)	1.45 (1.27 to 1.67)

the adjusted hazard ratio of venlafaxine compared with citalopram increased from 1.70 (95% confidence interval 0.76 to 3.80) to 1.87 (0.81 to 4.29) in the completed suicide analysis and from 1.20 (1.07 to 1.34) to 1.23 (1.10 to 1.37) in the attempted suicide analysis. This increase was inconsistent across comparisons (table 2).

DISCUSSION

The antidepressant venlafaxine was associated with a higher risk of suicide than citalopram, fluoxetine, and dothiepin. Venlafaxine users had a higher burden of risk factors for suicide, however, and adjustment for measured confounders reduced the excess risks. Although these data may reflect a causal association between venlafaxine use and suicide, given the substantial attenuation of this association after adjustment and the nature of the data, residual confounding could explain the remaining risk.

Venlafaxine use in this population of adults was associated with markers of severe and difficult to treat depression, psychiatric comorbidities, and treatment with psychotropic agents.¹ Admission to hospital for a psychiatric disorder and specialist care, family history of psychiatric morbidities, and previous suicide attempts were also more prevalent in venlafaxine users. Furthermore, venlafaxine users were twice as likely to have an overlap prescription for another antidepressant, suggesting that they had severe or treatment resistant depression.

In our study, suicide rates were consistently higher across drugs during the first 30 days of a treatment episode, confirming that starting antidepressants is associated with a higher risk of suicide.⁶ The study also confirmed that markers for severity of psychiatric morbidity were associated with an increased risk of suicide and suicide attempt in each drug group.

Confounding

Although randomised clinical trials can eliminate confounding by indication, such a design is not feasible to study suicide. The richness of records in the UK General Practice Research Database allowed adjustment for many factors associated with suicide risk and with selection of antidepressants, but our adjustment may have been incomplete. Controlling for confounding depends on the accurate measurement of potential con-

founders. Even when the sensitivity and specificity of confounders are 90%, more than 30% of confounding remains uncontrolled.⁷ Adjustment for misclassification of this magnitude would move the point estimate for the risk of completed suicide for venlafaxine compared with citalopram from 1.70 to 1.39, and for attempted suicide from 1.20 to 1.07. We anticipated that data for referrals to mental health care, admissions to hospital, and prescriptions were appropriate and comprehensive. Psychiatric disorders, however, may be undiagnosed or misclassified to a noticeable extent—severity of disease, a strong determinant of suicide risk, could only be measured indirectly. Furthermore, recognised risk factors for suicide, such as social isolation, are not routinely recorded in the database.

Adjustment for confounders substantially reduced the excess risk of suicide associated with venlafaxine. As the amount of residual confounding tends to reflect overall confounding,^{7,8} adjustment for measured confounding was unlikely to fully compensate for the potential bias of channelling more severely depressed patients towards venlafaxine. Correction for this bias could further change the effect estimates towards the null.

Study strengths and limitations

The major strengths of this study were the large study population and the completeness of records for drug use and risk factors. We confirmed many of the expected associations between factors and suicide risk. Limitations of the study included lack of direct measurement of disease severity and partial assessment of some variables that are likely to have been inconsistently recorded. The potential for some exposure and outcome misclassification should also be considered. We imputed drug use and time at risk from prescription records. Data on prescribing within secondary care might have been missing, however, leading to underestimation of drug use in more severely ill patients under psychiatric care. To impute duration of prescriptions, time at risk, and overall compliance with treatments we made assumptions. Reducing the exposure to study drug after the imputed end of prescriptions from 14 to seven days did not lead to a substantial difference in relative risk estimates.

One of the strengths of the General Practice Research Database is the high quality of information

WHAT IS ALREADY KNOWN ON THIS TOPIC

The risk of suicide during treatment with commonly prescribed selective serotonin reuptake inhibitors and tricyclic antidepressants is similar, but the risk with venlafaxine has not been evaluated in population based studies

WHAT THIS STUDY ADDS

Venlafaxine users were more likely to commit or attempt suicide than patients using citalopram, fluoxetine, or dothiepin

Venlafaxine users had a higher burden of suicide risk factors at start of treatment; adjustment for measured confounders reduced the excess risk

Because residual confounding was possible, the elevated risk of suicide associated with venlafaxine therapy should not be seen as causal

on mortality, including cause of death.^{3,9} None the less, in secondary data cause of death is associated with some misclassification, particularly as completed suicide is most often unwitnessed and loaded with stigma. We therefore cannot rule out potential misclassification and underascertainment, although we anticipate that misclassification of completed suicides is less likely among people with severe depression (venlafaxine users), who would be closely monitored. Attempted suicide is a less clearly defined outcome, and misclassification could occur.

Conclusions

We found a higher risk of suicide associated with venlafaxine compared with citalopram, fluoxetine, and dothiepin, which could reflect a causal association. However, because venlafaxine was channelled towards patients with more severe and treatment resistant depression, adjustment for measured risk factors could have left residual confounding that could explain some or all of the excess risk associated with venlafaxine.

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Competing interests: All other authors have no personal financial interest in the drug studies. RTI Health Solutions has received research funding from several companies, including Lilly, GlaxoSmithKline, and Pfizer, who market antidepressants and potentially gain or lose financially from the results of the study.

Ethical approval: This study was approved by the institutional review board at RTI International and the General Practice Research Database Scientific and Ethical Advisory Group.

- Mines D, Hill D, Yu H, Novelli L. Prevalence of risk factors for suicide in patients prescribed venlafaxine, fluoxetine, and citalopram. *Pharmacoepidemiol Drug Saf* 2005;14:367-72.
- Walley T, Mantgani A. The UK general practice research database. *Lancet* 1997;350:1097-9.
- García Rodríguez LA, Pérez Gutthann S. Use of the UK general practice research database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998;45:419-25.
- Egberts AC, Lenderink AW, de Koning FH, Leufkens HG. Channeling of three newly introduced antidepressants to patients not responding satisfactorily to previous treatment. *J Clin Psychopharmacol* 1997;17:149-55.
- Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004;292:338-43.
- Jick H, Ulcicka M, Dean A. Comparison of frequencies of suicidal tendencies among patients receiving fluoxetine, lofepramine, miansetin, or trazodone. *Pharmacotherapy* 1992;12:451-4.
- Savitz DA, Baron AE. Estimating and correcting for confounding misclassification. *Am J Epidemiol* 1989;129:1062-71.
- Rothman KJ, Wentworth III CE. Mortality of cystic fibrosis patients treated with tobramycin for inhalation. *Epidemiology* 2003;14:55-9.
- Martínez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ* 2005;330:389-93.

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IQ in childhood and vegetarianism in adulthood: 1970 British cohort study

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ABSTRACT

Objective To examine the relation between IQ in childhood and vegetarianism in adulthood.

Design Prospective cohort study in which IQ was assessed by tests of mental ability at age 10 years and vegetarianism by self-report at age 30 years.

Setting Great Britain.

Participants 8170 men and women aged 30 years participating in the 1970 British cohort study, a national birth cohort.

Main outcome measures Self-reported vegetarianism and type of diet followed.

Results 366 (4.5%) participants said they were vegetarian, although 123 (33.6%) admitted eating fish or chicken. Vegetarians were more likely to be female, to be of higher social class (both in childhood and currently),

and to have attained higher academic or vocational qualifications, although these socioeconomic advantages were not reflected in their income. Higher IQ at age 10 years was associated with an increased likelihood of being vegetarian at age 30 (odds ratio for one standard deviation increase in childhood IQ score 1.38, 95% confidence interval 1.24 to 1.53). IQ remained a statistically significant predictor of being vegetarian as an adult after adjustment for social class (both in childhood and currently), academic or vocational qualifications, and sex (1.20, 1.06 to 1.36). Exclusion of those who said they were vegetarian but ate fish or chicken had little effect on the strength of this association.

Conclusion Higher scores for IQ in childhood are associated with an increased likelihood of being a vegetarian as an adult.