Association between mirtazapine use and serious self-harm in people with depression: an active comparator cohort study using UK electronic health records

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ABSTRACT

Background Studies report an increased risk of self-harm or suicide in people prescribed mirtazapine compared with other antidepressants.

Objectives To compare the risk of serious self-harm in people prescribed mirtazapine versus other antidepressants as second-line treatments.

Design and setting Cohort study using anonymised English primary care electronic health records, hospital admission data and mortality data with study window 1 January 2005 to 30 November 2018.

Participants 24516 people diagnosed with depression, aged 18–99 years, initially prescribed a selective serotonin reuptake inhibitor (SSRI) and then prescribed mirtazapine, a different SSRI, amitriptyline or venlafaxine.

Main outcome measures Hospitalisation or death due to deliberate self-harm. Age–sex standardised rates were calculated and survival analyses were performed using inverse probability of treatment weighting to account for baseline covariates.

Results Standardised rates of serious self-harm ranged from 3.8/1000 person-years (amitriptyline) to 14.1/1000 person-years (mirtazapine). After weighting, the risk of serious self-harm did not differ significantly between the mirtazapine group and the SSRI or venlafaxine groups (HRs (95% CI) 1.18 (0.84 to 1.65) and 0.85 (0.51 to 1.41) respectively). The risk was significantly higher in the mirtazapine than the amitriptyline group (3.04 (1.36 to 6.79)) but was attenuated after adjusting for dose.

Conclusions There was no evidence for a difference in risk between mirtazapine and SSRIs or venlafaxine after accounting for baseline characteristics. The higher risk in the mirtazapine versus the amitriptyline group might reflect residual confounding if amitriptyline is avoided in people considered at risk of self-harm.

Clinical implications Addressing baseline risk factors and careful monitoring might improve outcomes for people at risk of serious self-harm.

INTRODUCTION

Mirtazapine is licensed in the UK to treat depression in adults. Although mirtazapine has similar efficacy and tolerability to other antidepressants, observational studies have suggested an increased risk of self-harm or suicide among people prescribed mirtazapine compared with other antidepressants. Wu et al reported a 47% increased risk of hospitalisation for self-harm among people prescribed mirtazapine compared with selective serotonin reuptake inhibitors (SSRIs). Coupland et al reported an increased risk of self-harm for adults prescribed mirtazapine compared with citalopram, and an increased risk of suicide for
Deliberate self-harm and suicidal behaviour are complex health problems associated with a range of risk factors. Prior self-harm is a strong predictor of future self-harm or suicide, and people with other physical and mental health conditions also have an increased risk. Some characteristics associated with self-harm or suicide may also influence the choice of antidepressant prescribed, confounding the relationship between individual antidepressants (eg, mirtazapine) and self-harm. Treating underlying mental health conditions, including alcohol and drug use disorders, depression, psychosis and schizophrenia, borderline personality disorder and bipolar disorder, is one of the recommendations of the UK’s National Institute for Health and Care Excellence (NICE) for the long-term management of self-harm, and antidepressant treatment has been associated with reduced suicide risk in adults with depression.

In the UK, mirtazapine is not recommended as a first-line treatment for depression. NICE recommend that if adults with depression initiate antidepressant treatment, they should be prescribed an SSRI in the first instance, unless contraindicated. The guidelines recommend switching to a different SSRI or an antidepressant from a different class if symptoms have not adequately responded to initial pharmacological interventions. In practice, therefore, people prescribed mirtazapine will often have switched from a different antidepressant.

**Study aim**

This study aimed to compare the risk of serious self-harm (suicide or hospital admission due to deliberate self-harm) in people with depression prescribed mirtazapine, an SSRI, amitriptyline or venlafaxine as a second-line antidepressant, accounting for differences in baseline characteristics.

**METHODS**

The study protocol, code lists (https://clinicalcodes.rss.mhs.man.ac.uk) and statistical code used to prepare and analyse the data (https://doi.org/10.5281/zenodo.4779024) are available online. The study used anonymised data provided under licence by the Clinical Practice Research Datalink (CPRD). The protocol was reviewed and approved by CPRD’s Independent Scientific Advisory Committee (reference 19_241).

**Data sources**

CPRD contains anonymised UK primary care electronic health records, linked to the English Hospital Episode Statistics (HES) data sets and the Office for National Statistics (ONS) mortality data set. The primary care data include coded information about diagnoses, lifestyle characteristics, prescriptions, test results and referrals to secondary care. The November 2019 release of the CPRD GOLD data set was used.

This study used linked hospital admissions and mortality data (set 17, containing records up to 30 November 2018). Linkage to HES data sets and the ONS mortality data set is performed for CPRD by a trusted third party based on National Health Service number, sex, date of birth and postcode. The HES admission data include all diagnoses recorded during an inpatient stay in hospital. The ONS mortality data set includes the date and underlying cause of death.

**Study cohort**

People in the cohort had at least 1 year of ‘up-to-standard’ (a data quality indicator) follow-up within CPRD before their first antidepressant prescription and were registered at general practices in England linked to the HES and ONS data sets. The study window was 1 January 2005 to 30 November 2018. People were included if their first recorded antidepressant was an SSRI and was prescribed during the study window, and if they were subsequently prescribed mirtazapine, a different SSRI, amitriptyline or venlafaxine as a second antidepressant at least 1 day after the initial SSRI prescription. The initial prescription date for this second antidepressant was the index date. The index date had to be during or less than 90 days after a period of exposure to the first antidepressant (see ‘Exposure’, below). The people included were aged 18–99 years at their index date and had a record of depression on or before the index date, but no more than 12 months before the first recorded antidepressant prescription. Diagnostic codes (Read v2 codes) for depression were based on existing published code lists (see the online supplemental file). People were excluded if they had a record of bipolar disorder or schizophrenia on or before their index date or had a hospital record of serious self-harm on or before their index date.

People were followed-up from the date of starting their second antidepressant until the earliest of: their first serious self-harm event, stopping the antidepressant (see below), death, leaving their general practice, last data collection date, 30 November 2018, or being prescribed a third antidepressant.

**Outcome**

Serious self-harm was defined as a record of ‘intentional self-harm’ (International Classification of Diseases (ICD)-10 codes X60-X84.9) in the hospital admission data, or intentional self-harm as the underlying cause of death in the mortality data. For hospital records, hospitalisation admission date was used as the event date. The earliest recorded event was used.

**Covariates**

Covariates were defined with respect to the index date and included age, sex, practice region, body mass index (BMI), smoking status, alcohol intake, socioeconomic status (SES, quintile of the Townsend score) and ethnicity. Comorbidities and health indicators that might influence choice of antidepressant were defined, including factors in the Charlson comorbidity index and the QMortality risk prediction algorithm and prescriptions for other medicines. Where possible code lists were sourced from the CALIBER phenotype resource, the ClinicalCodes repository or other published papers. Mental health indicators included depression severity, prior contact with mental health services and a prior primary care record for self-harm. A full list of covariates and further details about how they were defined are available in the online supplemental file.

**Exposure**

Primary care prescription records were used to estimate exposure to the antidepressants of interest. A published algorithm which uses information such as daily dose and quantity prescribed was used to estimate the length of each prescription. Further details are provided in the online supplemental file 1.

A risk carry-over window of 30 days was added to the end of each prescription for the study antidepressants. The exposure period ended after this window if there was no new prescription for the drug of interest within that time.

Antidepressant dose was estimated for each active prescription period based on the strength and daily dose of the drugs. Doses were converted to defined daily dose (DDD) using values from the WHO searchable index.

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Comorbidities and health indicators were classified as present/not present if recorded on or before index date. Prescribed medicine was classified as present/not present if there was a prescription on or in the 6 months prior to index date. Index year, current and most recent SSRI dose at index date and the length of time between starting the first and second antidepressants were also defined.

Analysis
Differences in baseline characteristics between the four antidepressant exposure groups were compared using χ² and Kruskal-Wallis tests. Age-sex standardised incidence rates of serious self-harm were calculated using direct standardisation and the age-sex structure of the whole study population. Rate differences between the mirtazapine and other treatment groups were calculated. Survival analysis using Fine-Gray regression was performed to account for non-suicide death as a competing risk was performed to compare the risk of serious self-harm between the mirtazapine group and the other treatment groups. The proportional hazards assumption was tested by examining log-log plots of survival and comparing observed and predicted Kaplan Meier survival plots. A separate analysis was performed to assess the impact of current antidepressant dose, including current dose of mirtazapine, SSRIs, amitriptyline and venlafaxine as time-varying variables.

Stabilised inverse probability of treatment weighting was used to account for differences in baseline characteristics between the treatment groups. Propensity scores were estimated using multinomial logistic regression. From these, inverse weights were calculated, then stabilised by multiplying by the unadjusted propensity scores. Further sensitivity analyses using multiple imputation by chained equations was used to estimate missing values of BMI, ethnicity, smoking status, alcohol intake and SES. The imputation models included all variables used to estimate the propensity scores, the study outcome and follow-up time. Twenty imputed data sets were generated. The regression analyses were performed on each imputed data set and then the results were combined using Rubin’s rules.

In line with the protocol, we reported statistical significance at the 0.05 level. Results are presented with 95% CIs. Data analyses were performed using Stata MP/V.16.1.

Sensitivity analyses
Rates were recalculated after excluding people with baseline primary care records of self-harm, and including people with baseline schizophrenia or bipolar disorder. Regression analyses were repeated: using multivariable Fine-Gray regression, using Cox regression, and using all defined covariates to estimate propensity scores. Further sensitivity analyses using multivariable Cox regression were excluding people with primary care records of self-harm at baseline; stratifying by age group (18–64 years, 65–99 years), changing the risk carry-over window (0 days, 6 months and the end of follow-up); censoring follow-up after 1 year or 5 years and restricting the first or second SSRI to citalopram, the most commonly prescribed SSRI (see online supplemental table S2). Finally, we included primary care records for self-harm in the definition of the outcome, excluding people with a baseline primary care record of self-harm.

RESULTS
Figure 1 shows the selection of the study cohort. Of the 358 911 people for whom linked data were requested, 24 516 people from 380 general practices met the inclusion criteria: 4777 (19.5%) people in the mirtazapine group, 14428 (58.8%) in the SSRI group, 3801 (15.5%) in the amitriptyline group and 1510 (6.2%) in the venlafaxine group.

Baseline characteristics are summarised in table 1, with additional results in online supplemental table S2. The median age of the study population was 41 years (IQR, 29–54 years). A higher proportion of the mirtazapine group was men (51.4%, compared with 41.6% for the whole study population). The mirtazapine group had the lowest median BMI (25.6) and the highest proportion of current smokers (34.9%) and heavy drinkers (6.1%).

The median length of follow-up ranged from 2.2 (IQR 1.9–5.2) months (amitriptyline group) to 5.6 (IQR 2.0–21.3) months (venlafaxine group) (online supplemental table S3). Overall, there were 235 serious self-harm events (including 13 deaths) over 26 679 person-years of follow-up, giving a crude incidence rate of 8.8 (95% CI 7.8 to 10.0) events/1000 person-years. Age-sex standardised rates are summarised in table 2. The mirtazapine group had the highest standardised rate of serious self-harm (14.1 events/1000 person-years, 95% CI 10.4 to 18.7), with 6.1 additional events/1000 person-years compared with the SSRI group and 10.3 additional events/1000 person-years compared with the amitriptyline group.

Table 3 shows the results of survival analyses using Fine-Gray regression. The proportional hazards assumption was met, although the majority of events happened early in follow-up (67% in the first 6 months). In the propensity score weighted analysis, the risk of serious self-harm in the mirtazapine group was not significantly different to the SSRI group (subdistribution HR (SHR) 1.18, 95% CI 0.84 to 1.65) or the venlafaxine group (SHR 0.85, 95% CI 0.51 to 1.41). The risk of serious self-harm was significantly higher in the mirtazapine group compared with the amitriptyline group (SHR 3.04, 95% CI 1.36 to 6.79).

After accounting for current antidepressant dose, the difference in risk between the mirtazapine and amitriptyline groups was attenuated, and no longer statistically significant in the weighted model (SHR 1.70, 95% CI 0.59 to 4.85) (online supplemental table S4). The risk of serious self-harm increased with increasing current dose of mirtazapine (not statistically significant in the multivariable adjusted model), SSRIs and venlafaxine.

Sensitivity analyses
After excluding 863 people with a primary care record of self-harm at baseline, the rate difference between the mirtazapine and the SSRI and amitriptyline groups was reduced. Including people with baseline schizophrenia or bipolar disorder made no difference to the event rates (online supplemental table S5).

Overall, changes to the regression analyses did not have a large impact on the results (online supplemental tables S6 and S7). For the comparison between mirtazapine and amitriptyline, excluding people with baseline primary care self-harm records

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Acceptable patients* with first SSRI recorded when aged 18+ years, in the period 01 Jan 2005-30 Nov 2018, after 1+ years of up-to-standard* follow-up (n=835,654)

- Excluded, not eligible for linkage (n=476,753)
- Eligible for linkage (n=358,911)

- Excluded, first antidepressant was not an SSRI (n=87,403)
- First antidepressant was an SSRI (n=271,868)

- Excluded (n=188,597)
  - No second antidepressant (n=179,978)
  - Second antidepressant was not mirtazapine, a different SSRI, amitriptyline, or venlafaxine (n=8,619)

- Second antidepressant was mirtazapine, a different SSRI, amitriptyline, or venlafaxine (n=83,271)

- Excluded (n=38,490)
  - Second antidepressant prescribed on same day as first ever antidepressant (n=508)
  - Second antidepressant prescribed >90 days after period of exposure to the first antidepressant (n=37,982)

- Second antidepressant recorded within specified window (n=44,781)

- Excluded (n=18,961)
  - No depression record on or before starting second antidepressant (n=17,231)
  - The only depression record(s) were 12+ months before the first antidepressant (n=1,730)

- Depression record within specified window (n=25,820)

- Excluded (n=1304)
  - Start third antidepressant on same day as second antidepressant (n=85)
  - Aged 100+ years, record of bipolar disorder, or record of schizophrenia on or before starting second antidepressant (n=137)
  - Hospital record of intentional self harm on or before starting second antidepressant (n=1,082)

- Included in study (n=24,518)

**Figure 1** Flow diagram showing the definition of the study cohort. SSRI, selective serotonin reuptake inhibitor. *Markers of data quality in the Clinical Practice Research Datalink.

attenuated the risk difference (HR 2.26, 95%CI 1.04 to 4.88), as did restricting to those aged 18–64 years (HR 2.84, 95%CI 1.33 to 6.06) and including primary care records when defining the self-harm outcome (HR 1.96, 95%CI 1.15 to 3.33). Lengthening the carry-over period after stopping the antidepressant led to a smaller difference in risk (HR 2.08, 95%CI 1.31 to 3.31 when the carry-over window continued to the end of follow-up). For the comparison between mirtazapine and venlafaxine, excluding people with baseline primary care self-harm records increased the risk difference (HR 0.60, 95%CI 0.36 to 1.01). Overall, there were few events in the 65–99 years age group. Restricting to a specific SSRI (citalopram) led to some changes in the magnitudes of the effects, but the sample size was reduced for these comparisons.

**DISCUSSION**

Adults with depression who were prescribed mirtazapine as a second-line antidepressant had higher age–sex standardised rates of serious self-harm than people prescribed amitriptyline or an SSRI. However, when baseline covariates were accounted for the risk of serious self-harm in people prescribed mirtazapine was not statistically significantly different to the risk in people prescribed an SSRI or venlafaxine. The risk of serious self-harm remained significantly higher in the mirtazapine group compared with the amitriptyline group, although the difference was attenuated after current antidepressant dose was accounted for.

The difference in risk between the mirtazapine and SSRI group was smaller than that reported in the previous studies and, like Valenstein et al, was not statistically significant. In the sensitivity analysis excluding people with baseline primary care self-harm records the direction of the risk difference was reversed, possibly indicating a higher baseline risk for the mirtazapine group that was not fully accounted for in the main analysis. This study looked at second-line antidepressants, whereas Wu et al grouped people according to their first recorded antidepressant and Coupland et al allowed the antidepressant exposure groups...
to vary over time. These differences may account for the

difference in results. The ‘new user’ design used in the current study
aims to reduce the level of residual or unmeasured confounding by
comparing people at a similar point in their disease and treatment
history.13 We designed the study around new users of the
second-line antidepressants to mirror the UK treatment guide-
lines.14 Coupland et al15 included primary care records when
defining their study outcome. We performed a sensitivity anal-
ysis in which we included primary care self-harm records in our
outcome definition. In this sensitivity analysis, the risk difference

Table 1 Characteristics of people in the study cohort, determined at index date

| Count | All | Mirtazapine | SSRI | Amitriptyline | Venlafaxine | Statistic |
|-------|-----|-------------|------|---------------|-------------|-----------|
| Age, median (IQR) | 24516 | 4777 | 14428 | 3801 | 1510 |
| Sex, n (%) | 41 (29–54) | 44 (31–59) | 39 (27–51) | 48 (37–61) | 41 (30–51) |
| Male | 10190 (41.6) | 2456 (51.4) | 5731 (39.7) | 1303 (34.3) | 700 (46.4) |
| Female | 14326 (58.4) | 2321 (48.6) | 8697 (60.3) | 2498 (65.7) | 810 (53.6) |
| Ethnicity, n (%)* | | | | | |
| Asian | 447 (2.5) | 105 (2.9) | 237 (2.3) | 83 (2.8) | 22 (2.1) |
| Black | 259 (1.5) | 37 (1.0) | 150 (1.5) | 56 (1.9) | 16 (1.5) |
| Mixed | 159 (0.9) | 35 (1.0) | 96 (0.9) | 18 (0.6) | 10 (1.0) |
| Other | 214 (1.2) | 34 (1.0) | 136 (1.3) | 32 (1.1) | 12 (1.1) |
| White | 16728 (93.9) | 3350 (94.1) | 9614 (94.0) | 2773 (93.6) | 991 (94.3) |
| Missing ethnicity, n (%) | 6709 (27.4) | 1216 (25.5) | 4195 (29.1) | 839 (22.1) | 459 (30.4) |
| Townsend Score quintile, n (%)* | | | | | |
| 1 (least deprived) | 4830 (19.7) | 861 (18.0) | 2853 (19.8) | 795 (20.9) | 321 (21.3) |
| 2 | 4962 (20.3) | 941 (19.7) | 2898 (20.1) | 763 (20.1) | 360 (23.9) |
| 3 | 5290 (21.6) | 1004 (21.0) | 3118 (21.6) | 843 (22.2) | 325 (21.5) |
| 4 | 5305 (21.7) | 1049 (22.0) | 3186 (22.1) | 807 (21.2) | 263 (17.4) |
| 5 (most deprived) | 4111 (16.8) | 918 (19.2) | 2360 (16.4) | 593 (15.6) | 240 (15.9) |
| Missing Townsend score, n (%) | 30 (0.1%)† | <5 | 13 (0.1%) | <5 | <5 |
| BMI, median (IQR)* | 6954 (28.4) | 1809 (29.5) | 4316 (29.9) | 794 (20.9) | 435 (28.8) |
| Smoking status, n (%)* | | | | | |
| Never | 9635 (40.5) | 1774 (38.3) | 5725 (41.0) | 1503 (40.1) | 633 (43.4) |
| Former | 6565 (27.6) | 1243 (26.8) | 3747 (26.8) | 1173 (31.3) | 402 (27.6) |
| Current | 7600 (31.9) | 1614 (34.9) | 4496 (32.2) | 1066 (28.5) | 422 (29.0) |
| Missing smoking status, n (%) | 716 (2.9) | 146 (3.1) | 460 (3.2) | 57 (1.5) | 53 (3.5) |
| Alcohol intake, n (%)* | | | | | |
| Non-drinker | 3200 (33.4) | 615 (31.8) | 1875 (34.3) | 534 (32.3) | 176 (34.1) |
| Former drinker | 1367 (14.3) | 316 (16.3) | 725 (13.3) | 263 (15.9) | 63 (12.2) |
| Occasional drinker | 4092 (42.7) | 790 (40.8) | 2345 (42.9) | 733 (44.3) | 224 (43.4) |
| Moderate drinker | 450 (4.7) | 98 (5.1) | 256 (4.7) | 71 (4.3) | 25 (4.8) |
| Heavy drinker | 464 (4.8) | 118 (6.1) | 264 (4.8) | 54 (3.3) | 28 (5.4) |
| Missing alcohol intake, n (%) | 14943 (61.0) | 2840 (59.5) | 8963 (61.2) | 2146 (56.5) | 994 (65.8) |
| Mental health indicators | | | | | |
| Severe depression†, n (%) | 2303 (9.4) | 472 (9.9) | 1323 (9.2) | 327 (8.6) | 181 (12.0) |
| Recorded depression scale, n (%) | 15076 (61.5) | 2862 (59.9) | 8879 (61.5) | 2383 (62.7) | 952 (63.0) |
| Alcohol misuse, n (%) | 768 (3.1) | 220 (4.6) | 407 (2.8) | 99 (2.6) | 42 (2.8) |
| Anxiety, n (%) | 7319 (29.9) | 1458 (30.5) | 4292 (29.7) | 1090 (28.7) | 479 (31.7) |
| Contact with mental health services, n (%) | 5895 (24.0) | 1488 (31.1) | 3264 (22.6) | 684 (18.0) | 459 (30.4) |
| Eating disorder, n (%) | 94 (0.4) | 17 (0.4) | 61 (0.4) | 9 (0.2) | 7 (0.5) |
| Insomnia, n (%) | 2981 (12.2) | 769 (16.1) | 1411 (9.8) | 621 (16.3) | 180 (11.9) |
| Intellectual disability, n (%) | 80 (0.3) | 8 (0.2) | 58 (0.4) | 9 (0.2) | <5 |
| Personality disorder, n (%) | 101 (0.4) | 24 (0.5) | 52 (0.4) | 15 (0.4) | 10 (0.7) |
| Self-harm (primary care), n (%) | 863 (3.5) | 185 (3.9) | 507 (3.5) | 110 (2.9) | 61 (4.0) |
| Substance misuse disorder, n (%) | 577 (2.4) | 177 (3.7) | 303 (2.1) | 65 (1.7) | 32 (2.1) |

*: Counts and percentages do not include missing values.
†: Severe depression: Either a Read code for severe depression or depression with psychosis, scoring 15 or above on the Patient Health Questionnaire-9 scale, or scoring 16 or above on the Hospital Anxiety and Depression scale.
‡: Value rounded to mask small numbers.

BMI, body mass index; KW, Kruskal-Wallis test; n, number; SSRI, selective serotonin reuptake inhibitor.
The risk difference increased in some of the sensitivity analyses. This result was similar to Valenstein and colleagues, and the groups did not differ significantly in adjusted analyses. It has been argued that clinicians may avoid prescribing tricyclic antidepressants to people who are at a higher risk of suicide or overdose.3 4 27 These differences may not transfer to people prescribed one of the study drugs as their first antidepressant. Based on the basic data used to define the study population, applying only the follow-up date criteria and not considering other antidepressants not included in the study, approximately 19 000 people had mirtazapine as their first recorded antidepressant compared with approximately 18 000 people with mirtazapine as their second recorded antidepressant. Therefore, it is possible that our study findings based on second-line treatment apply to approximately half of mirtazapine users in the UK.

### Strengths and limitations

The study was designed to reduce indication and channelling biases—everyone in the study had a diagnostic code for depression, a recent prescription for an SSRI and were new users of the drugs investigated. This improves the likelihood that the results are valid,26 but the additional inclusion and exclusion criteria are at the cost of power and generalisability. We may have excluded some people with depression if depression was not recorded or was recorded more than a year before starting antidepressants, or if only depression symptoms were recorded. Regarding generalisability, people in the study cohort were similar in terms of demographic characteristics to all those for whom we requested linked data, that is, people prescribed an SSRI within the study window (online supplemental table S10). As expected, the study cohort had slightly higher depression severity and a smaller proportion had a primary care record for self-harm at baseline. As the study compared second-line antidepressants, the results may not transfer to people prescribed one of the study drugs as their first antidepressant. Based on the basic data used to define the study population, applying only the follow-up date criteria and not considering other antidepressants not included in the study, approximately 19 000 people had mirtazapine as their first recorded antidepressant compared with approximately 18 000 people with mirtazapine as their second recorded antidepressant. Therefore, it is possible that our study findings based on second-line treatment apply to approximately half of mirtazapine users in the UK.

| Number of events | Person-years | Crude event rate (95% CI) | Standardised event rate (95% CI) | Rate difference (95% CI) |
|-----------------|--------------|---------------------------|----------------------------------|--------------------------|
| **Total**       |              |                           |                                  |                          |
| All             | 235          | 26 679                    | 8.8 (7.8 to 10.0)                | 8.8 (7.7 to 10.0)        | –                        |
| Mirtazapine     | 57           | 4 434                     | 12.9 (9.9 to 16.7)               | 14.1 (10.4 to 18.7)      | reference                |
| SSRI            | 143          | 17 006                    | 8.4 (7.1 to 9.9)                 | 8.0 (6.8 to 9.5)         | –6.1 (–7.9 to –4.3)      |
| Amitriptyline   | 8            | 3 045                     | 2.6 (1.3 to 5.3)                 | 3.8 (1.6 to 7.5)         | –10.3 (–11.9 to –8.7)    |
| Venlafaxine     | 27           | 2 194                     | 12.3 (8.4 to 17.9)               | 11.7 (7.6 to 18.0)       | –2.4 (–4.3 to –0.5)      |
| **Men**         |              |                           |                                  |                          |
| All             | 118          | 10 987                    | 10.7 (9.0 to 12.9)               | 11.1 (9.2 to 13.3)       | –                        |
| Mirtazapine     | –            | –                         | 15.0 (10.9 to 20.7)              | 15.3 (10.7 to 21.0)      | reference                |
| SSRI            | –            | –                         | 10.1 (7.9 to 12.8)               | 9.7 (7.5 to 12.4)        | –5.6 (–8.6 to –2.7)      |
| Amitriptyline   | –            | –                         | 3.9 (1.5 to 10.3)                | 5.4 (1.4 to 13.2)        | –9.9 (–12.6 to –7.2)     |
| Venlafaxine     | –            | –                         | 11.9 (6.6 to 21.5)               | 11.2 (5.5 to 22.2)       | –4.1 (–7.1 to –1.1)      |
| **Women**       |              |                           |                                  |                          |
| All             | 117          | 15 692                    | 7.5 (6.2 to 8.9)                 | 7.1 (5.9 to 8.5)         | –                        |
| Mirtazapine     | –            | –                         | 10.2 (6.6 to 15.8)               | 13.4 (8.1 to 20.4)       | reference                |
| SSRI            | –            | –                         | 7.4 (5.9 to 9.2)                 | 6.9 (5.4 to 8.6)         | –6.5 (–8.7 to –4.3)      |
| Amitriptyline   | –            | –                         | 2.0 (0.7 to 5.3)                 | 2.8 (0.7 to 7.1)         | –10.6 (–12.6 to –8.6)    |
| Venlafaxine     | –            | –                         | 12.6 (7.7 to 20.6)               | 12.1 (6.7 to 21.7)       | –1.3 (–3.8 to 1.2)       |

*Numbers in subgroups suppressed due to small numbers.

SSRI, selective serotonin reuptake inhibitor.

### Table 3 Results of Fine-Gray (competing risks) regression comparing the risk of serious self-harm between study treatment groups

|                          | Unadjusted, SHR (95% CI) | Age-sex adjusted, SHR (95% CI) | Propensity score weighted, SHR (95% CI) |
|--------------------------|--------------------------|---------------------------------|----------------------------------------|
| Mirtazapine vs SSRI      | 1.35 (0.99 to 1.84)      | 1.51 (1.11 to 2.06)             | 1.18 (0.84 to 1.65)                     |
| Mirtazapine vs amitriptyline | 5.06 (2.42 to 10.59)   | 4.33 (2.05 to 9.11)             | 3.04 (1.36 to 6.79)                     |
| Mirtazapine vs venlafaxine | 0.84 (0.53 to 1.32)    | 0.94 (0.59 to 1.48)             | 0.85 (0.51 to 1.41)                     |

SHR, subdistribution hazard ratio; SSRI, selective serotonin reuptake inhibitor.
We accounted for baseline covariates using propensity score methods. However, as this was an observational study, there remains a risk of residual and unmeasured confounding. Some of the measures defined in the study may be incompletely captured in the medical record, other risk factors may not be recorded at all, and any differences in likelihood of seeking medical attention could lead to differential reporting of risk factors.

As prescriptions issued in UK general practices are automatically captured in the electronic record, the prescription data in CPRD are generally considered complete records of primary care prescribing.29 However, data about secondary care prescribing are not available in the data sets used for the study. Thus, there may be some underestimation of drug use, particularly in people with more severe illness. In addition, the prescription data do not guarantee that a prescription was filled or taken as prescribed. Differential adherence to the study drugs could introduce bias, particularly given the association between depression and self-harm or suicide.30

Serious self-harm is a rare outcome and CIs were wide, so we cannot rule out larger risk differences than those found in this study. The study outcome included only ‘intentional’ self-harm, thus may have excluded some true events that were classified as ‘undetermined intent’. The outcome included only the most severe events—those that led to a hospital admission or that were fatal—and so only represents this particular aspect of self-harm and suicidal behaviour.

This analysis differed from the original protocol13 in the following ways. First, a 30-day risk carry-over window was used instead of the planned 6 months (included as a sensitivity analysis). The original window was tailored to a different outcome (mortality), an analysis that will be reported separately. Based on the existing studies and the consideration that antidepressant-related self-harm events are thought to occur most frequently around the time of starting or stopping treatment,4 the shorter window was used to reduce the level of exposure misclassification. Second, we did not separate those who switched treatment from those who augmented treatment, due to the difficulty in defining this without using future exposure data. Thus, the study groups include some people who continued their original SSRI alongside the new treatment (summarised in online supplementary table S1).30

CONCLUSIONS

People with depression prescribed mirtazapine as a second-line antidepressant had a higher age–sex standardised rate of serious self-harm than people prescribed an SSRI, amitriptyline or venlafaxine. However, after accounting for additional baseline characteristics, people prescribed mirtazapine were not at a significantly increased risk of serious self-harm compared with people prescribed an SSRI or venlafaxine. Although we found an increased risk of self-harm for people prescribed mirtazapine compared with amitriptyline, the number of outcomes was low for this comparison, and other factors (eg, channeling bias) could have influenced this result. The higher rate of serious self-harm in people prescribed mirtazapine may reflect the higher prevalence of other risk factors in this group, for example, alcohol misuse. Thus, when prescribing antidepressants, discussion and additional support for such risk factors may improve outcomes for people at risk of serious self-harm.

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Contributors All authors contributed to the design of the work. RMJ performed the data analysis with support from RHJ and CC. All authors contributed to the interpretation of study results, and to drafting the work or revising it critically for important intellectual content. All authors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RMJ is guarantor for the work and as such accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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