ORIGINAL RESEARCH

Antidepressants, Depression, and Venous Thromboembolism Risk: Large Prospective Study of UK Women

Lianne Parkin, MB ChB, PhD; Angela Balkwill, MSc; Siân Sweetland, DPhil; Gillian K. Reeves, PhD; Jane Green, MB ChB, DPhil; Valerie Beral, MD, FRS; for the Million Women Study Collaborators*

Background—Some investigators have reported an excess risk of venous thromboembolism (VTE) associated with depression and with use of antidepressant drugs. We explored these associations in a large prospective study of UK women.

Methods and Results—The Million Women Study recruited 1.3 million women through the National Health Service Breast Screening Programme in England and Scotland. Three years after recruitment, women were sent a second questionnaire that enquired about depression and regular use of medications in the previous 4 weeks. The present analysis included those who responded and did not have prior VTE, cancer, or recent surgery. Follow-up for VTE was through linkage to routinely collected National Health Service statistics. Cox regression analyses yielded adjusted hazard ratios and 95% CIs. A total of 734 092 women (mean age 59.9 years) were included in the analysis; 6.9% reported use of antidepressants, 2.7% reported use of other psychotropic drugs, and 1.8% reported being treated for depression or anxiety but not use of psychotropic drugs. During follow-up for an average of 7.3 years, 3922 women were hospitalized for and/or died from VTE. Women who reported antidepressant use had a significantly higher risk of VTE than women who reported neither depression nor use of psychotropic drugs (hazard ratio, 1.39; 95% CI, 1.23–1.56). VTE risk was not significantly increased in women who reported being treated for depression or anxiety but no use of antidepressants or other psychotropic drugs (hazard ratio, 1.19; 95% CI, 0.95–1.49).

Conclusions—Use of antidepressants is common in UK women and is associated with an increased risk of VTE. **(*J Am Heart Assoc*. 2017;6:e005316. DOI: 10.1161/JAHA.116.005316.)**

Key Words: antidepressants • cohort study • deep vein thrombosis • depression • pulmonary embolism

Venous thromboembolism (VTE; deep vein thrombosis and/or pulmonary embolism) is an important cause of potentially preventable morbidity and death in many countries, including the United Kingdom and the United States.[1] Depression is a common disorder. In England, the point prevalence of major depression in the 2007 National Psychiatric Morbidity Survey was 3.7% in women and 2.5% in men aged 16 to 78 years,[2] while the proportion of participants in the World Health Organization Mental Health Survey Initiative who had experienced a major depressive episode in the previous 12 months ranged from 2.2% (Japan) to 8.3% (United States).[3] Antidepressant drugs are one therapeutic option for the treatment of depression and anxiety, and some of these drugs are also prescribed for neuropathic pain, irritable bowel syndrome, and migraine prophylaxis.[4] The prevalence of antidepressant use in some populations is high; for example, the 2013 Health Survey of England found that antidepressants had been used in the previous week by 11% of women and 6% of men aged 16 years and older,[5] while the 2005–2008 National Health and Nutrition Examination Surveys in the United States reported figures of 15% and 6% for females and males, respectively, aged 12 years and older.[6] A few studies have found a significant relationship between antidepressant use and VTE,[7–9] whereas others have not.[10–13] In addition, 2 studies reported an association between depression and VTE risk, although only one investigated antidepressant use.[14,15] It is therefore unclear whether a relationship exists between antidepressant use and VTE, and, if it does, whether it is due to the drugs or to the underlying conditions for which they are used.

To explore the relationships between antidepressants, depression, and VTE we linked questionnaire data about

From the Cancer Epidemiology Unit, University of Oxford, United Kingdom (L.P., A.B., S.S., G.K.R., J.G., V.B.); Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand (L.P.).

*A complete list of the Million Women Study Collaborators can be found in the Appendix.

Correspondence to: Lianne Parkin, MB ChB, PhD, Department of Preventive and Social Medicine, University of Otago, 18 Frederick Street, PO Box 56, Dunedin 9054, New Zealand. E-mail: lianne.parkin@otago.ac.nz

Received February 2, 2017; accepted March 21, 2017.

depression and regular use of antidepressants with hospital admissions and deaths attributed to VTE in a large UK prospective study, the Million Women Study.

Methods

Study Population

The Million Women Study is a prospective cohort study that recruited 1.3 million women between 1996 and 2001 through the National Health Service (NHS) Breast Screening Programme in England and Scotland.[16] At recruitment, women completed a questionnaire that collected information about medical and reproductive history, hormone use, weight, height, lifestyle, and sociodemographic factors. Women were sent a second study questionnaire, the 3-year re-survey, an average of 3.3 (SD, 1) years after recruitment, which enquired about conditions they were currently being treated for (including a question about depression or anxiety) and about medications used during most of the last 4 weeks. They were asked to indicate, using tick boxes, which of several listed medications (including "amitriptyline" and "Prozac") they had taken and to provide the names of any other medications they had used. Women were classified as antidepressant users if they ticked the amitriptyline or Prozac boxes, or if they recorded the names of other antidepressants. Antidepressant users were further classified as users of a tricyclic, a selective serotonin reuptake inhibitor (SSRI), or other antidepressants according to British National Formulary groupings.[4] Compound preparations containing a tricyclic or monoamine oxidase inhibitor antidepressant were included in the "other" group. Nonusers of antidepressants who reported taking antipsychotics, lithium and other drugs used to treat bipolar disorder, anxiolytics, or hypnotics (as categorized in the British National Formulary[4]) were classified as users of other psychotropic drugs. Women were sent an 8-year re-survey questionnaire 4.3 (SD, 2) years, on average, after the 3-year re-survey and identical questions on amitriptyline and Prozac were asked. Reports of use of these drugs at the 3- and 8-year re-surveys were compared, to assess the persistence of use over time (study questionnaires can be viewed at www.millionwomenstudy.org/questionnaires/). The present analysis is based on the women who completed the 3-year re-survey questionnaire.

Follow-up of all women in the cohort for deaths, cancer registrations, and emigration was achieved through linkage to the NHS Central Registers. In addition, admissions (as a day or inpatient) to NHS hospitals were identified by linkage to the English Hospital Episodes Statistics[17] and the Scottish Morbidity Records.[18] The data relating to each hospital admission included the dates of admission and discharge, main and secondary diagnoses (coded to the *International Classifications of Diseases, 10th Revision*),[19] and any procedures undertaken (coded to the *Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, Fourth Revision*).[20] VTE during follow-up was identified using *International Classifications of Diseases, 10th Revision,* codes I26 (pulmonary embolism), I80 (phlebitis and thrombophlebitis), I81 (portal vein thrombosis), and I82 (other venous embolism and thrombosis). To permit comparisons with previous studies, cerebral sinovenous thrombosis was not included.

Statistical Analysis

We excluded from the analyses women who reported a history of blood clots or treatment for blood clots in the recruitment or 3-year re-survey questionnaires, those who reported use of oral anticoagulants or low-molecular-weight heparin for any reason in the 3-year re-survey questionnaire, and those who had a hospital admission for VTE or a previous cancer registration (excluding nonmelanoma skin cancer) at any time before completion of the 3-year re-survey questionnaire, or if they had surgery in the 12 weeks before that date.

Women were followed from the date they completed the 3-year re-survey questionnaire (referred to as "baseline" hereafter) until the earliest of the following: any (day or inpatient) surgery; a registered diagnosis of cancer; emigration, death, or other loss to follow-up in the NHS Central Registers; or the end of hospital and death record follow-up (December 31, 2014, in both England and Scotland). VTE events which resulted in hospital admission and/or death during follow-up were identified using the same approach as in our previous VTE analyses.[21–24]

Hazard ratios (HRs) of VTE, according to reported use of antidepressants and current treatment for depression or anxiety, were estimated using Cox regression models. Attained age, measured in days and incremented during follow-up, was the underlying time variable. The proportional hazards assumption was assessed using tests based on Schoenfeld residuals. There was a violation of the assumption for use of hormone therapy; however, when we repeated the analyses and stratified by hormone therapy use, the HRs were unchanged. All analyses were stratified by recruitment region and adjusted for body mass index (<25, 25–29, 30–34, ≥35 kg/m^2), smoking (never; past; current <5, 5–9, 10–14, 15–19, ≥20 cigarettes per day), alcohol consumption (none, <7, 7–13, ≥14 drinks per week), frequency of strenuous physical activity (rarely/never, ≤once, ≥once a week), hormone therapy (never, past, current), diabetes mellitus (yes, no), high blood pressure (yes, no), and deprivation (quintiles of Townsend deprivation index[25]). An "unknown" category was created for the adjustment variables to deal with missing values (data missing for <3% of women per

covariate, except body mass index and alcohol consumption, for which the proportions of women with missing values were 8% and 13%, respectively). The values of all covariates were obtained from the 3-year re-survey questionnaire, with the exception of height (to calculate body mass index) and frequency of strenuous physical activity, which were both taken from the recruitment questionnaire.

The risk of VTE was explored in 4 exposure categories: reported use of antidepressants; reported use of other psychotropic drugs; reported treatment for depression or anxiety, but no reported use of antidepressants or other psychotropic drugs; and no reported treatment for depression or anxiety and no reported use of any psychotropic drugs (the reference group). The primary analysis focused on the use of any antidepressant, while a secondary analysis explored the association between VTE and 3 separate antidepressant groups (tricyclic, SSRI, other). These analyses were also repeated in the subset of the cohort who were never smokers. Finally, a sensitivity analysis was undertaken to explore the risk of VTE in 2 groups of antidepressant users: those who reported concurrent use of other psychotropic drugs and those who did not.

All analyses were performed using STATA version 14.1 (StataCorp, College Station, TX).

Ethical Approval

The Million Women Study has approval from the Health Research Authority Cambridge South Research Ethics Committee (formerly Oxford and Anglia Multi-Centre Research Ethics Committee) and is sponsored by the University of Oxford. Access and linkage to medical records is provided by NHS Digital in England and the Information and Statistics Division of the NHS in Scotland. All participants gave written consent for inclusion and follow-up.

Data Access

Data and access policies for the Million Women Study are available on the study website, www.millionwomenstudy.org.

Results

A total of 734 092 women (mean age 59.9 years; SD, 4.9) were included in the present analysis after the exclusion of 117 313 women who responded to the baseline (3-year re-survey) questionnaire, but had a history of blood clots, hospital admission for VTE, current use of an oral anticoagulant or low-molecular-weight heparin, a cancer registration, or surgery in the 12 weeks before baseline. Overall, 50 354 (6.9%) women reported at baseline that they used an antidepressant for most of the last 4 weeks, of whom 29 901 (59.4%) also reported that they were currently being treated for depression or anxiety. In addition, 19 468 (2.7%) women reported use of other psychotropic drugs for most of the last 4 weeks, and a further 13 563 (1.8%) reported they were being treated for depression or anxiety, without use of any psychotropic drug (hereafter referred to as the "treatment/no drugs" group). The remaining 650 707 (88.6%) women reported neither treatment for depression or anxiety nor use of any psychotropic drug (hereafter referred to as the "no treatment/no drugs" group).

This baseline information on use of psychotropic drugs was collected between 1999 and 2005 (mean, 2002), at the 3-year re-survey. We assessed changes in use of 2 specific psychotropic drugs in the 569 744 women who answered identical questions about amitriptyline and Prozac at the 8-year re-survey, 4.4 (SD, 1.3) years, on average, after baseline. Among the 13 678 women who reported use of amitriptyline at baseline, 58.5% (7996) reported still using it 4 years later, whereas only 1.8% (10 239 of 556 066) of those who did not report use of amitriptyline at baseline reported using it 4 years later. Likewise, 43.4% (2914 of 6170) of women who reported using Prozac at baseline reported still using it 4 years later, compared with 1.2% (6655 of 563 034) of women who reported no use at baseline.

Table 1 shows the characteristics of women at baseline, overall, and in relation to exposure status. The mean age was similar among the 4 groups. Women in the no treatment/no drugs group were less likely to come from the lowest socioeconomic tertile and were generally healthier than women in the other 3 groups, with the lowest proportions reporting that they were being treated for diabetes mellitus or hypertension; they were also less likely to be smokers, be inactive, or use hormone therapy. These differences were all statistically significant ($P<0.0001$). Overall, 3922 women had a hospital admission for and/or died from VTE during 5.2 million woman-years of follow-up (an average of 7.3 years of follow-up per woman; SD, 4.7).

The results of the primary analysis of VTE risk associated with depression and use of psychotropic drugs are shown in Table 2. Women who reported use of antidepressants had a significantly higher risk of VTE than those in the no treatment/no drugs group (adjusted HR, 1.39; 95% CI, 1.23–1.56 [$P<0.0001$]). Significantly elevated risks were found separately for VTE with and without pulmonary embolism (HR, 1.49; 95% CI, 1.27–1.75 [$P<0.0001$]) and HR, 1.28; 95% CI, 1.07–1.52 [$P=0.006$], respectively). Reported use of other psychotropic drugs was also associated with a significantly higher risk of VTE (HR, 1.41; 95% CI, 1.19–1.67 [$P<0.0001$]), whereas VTE risk was not significantly increased in the treatment/no drugs group (HR, 1.19; 95% CI, 0.95–1.49 [$P=0.13$]). Repeating the analysis restricted to never smokers produced similar results. Both users of

Table 1. Characteristics at Baseline and Follow-Up, All Women and By Self-Reported Treatment for Depression or Anxiety and Self-Reported Use of Antidepressants and Other Psychotropic Drugs

Characteristics and Follow-Up	All Women (N=734 092)	Exposure Category*			
		Reported Neither Treatment for Depression or Anxiety Nor Use of Any Psychotropic Drugs (n=650 707)	Reported Treatment for Depression or Anxiety, But No Use of Antidepressants or Other Psychotropic Drugs (n=13 563)	Reported Use of Antidepressants† (n=50 354)	Reported Use of Other Psychotropic Drugs‡ (n=19 468)
Characteristics					
Age, mean (SD), y	59.9 (4.9)	59.9 (4.9)	59.5 (4.8)	59.6 (4.8)	61.0 (5.3)
Lowest socioeconomic tertile, %	29.3	28.4	39.7	35.6	36.0
Body mass index, mean (SD), kg/m^2	26.1 (4.5)	26.0 (4.4)	27.0 (5.2)	27.1 (5.1)	26.1 (4.8)
Current smoker, %	12.3	11.5	17.6	18.6	18.9
Alcohol consumption, mean (SD), drinks per wk	4.5 (5.8)	4.5 (5.8)	3.9 (5.8)	3.8 (6.0)	4.1 (6.1)
Strenuous physical activity > never or rarely, %§	55.9	57.1	49.5	45.8	46.6
Current hormone therapy use, %	34.6	33.4	41.2	47.0	39.4
Self-reported history of diabetes mellitus, %	3.6	3.4	5.4	5.6	5.0
Self-reported history of hypertension, %	31.7	30.9	39.9	38.6	37.1
Follow-up					
Person-years of follow-up‖	5 254 000	4 765 000	83 000	289 000	117 000
No. of venous thromboembolism cases	3922	3393	79	313	137

*Based on responses to 2 separate questions about: (1) "any medication use for most of the last 4 weeks," and (2) which conditions "you are now being treated for."
†Includes women who did (n=29 901) and did not (n=20 453) report being treated for depression or anxiety and women who did (n=8011) and did not (n=42 343) report taking other psychotropic drugs.
‡Antipsychotics, lithium and other drugs used to treat bipolar disorder, anxiolytics, and hypnotics.
§At recruitment.
‖Censored at first surgery or first cancer registration after baseline.

antidepressants and users of other psychotropic drugs had significantly higher risks of VTE, while women in the treatment/no drugs group did not (HR, 1.42; 95% CI, 1.19–1.69 [P<0.0001]; HR, 1.59, 95% CI, 1.24–2.04 [P=0.0002]; and HR, 1.09; 95% CI, 0.77–1.54 [P=0.63], respectively).

Table 3 shows the results of the analysis that explored the risk of VTE by class of antidepressant. Users of antidepressants from more than one class are excluded from this analysis. Most women who reported antidepressant use were taking tricyclic or SSRI products. All 3 groups of antidepressant users had significantly higher risks of VTE than women in the no treatment/no drugs group. The adjusted HRs for tricyclic, SSRI, and other antidepressants, respectively, were 1.32 (95% CI, 1.12–1.55; P=0.001), 1.40 (95% CI, 1.17–1.68; P<0.0001), and 1.61 (95% CI, 1.04–2.47; P=0.03). An analysis restricted to never smokers yielded comparable results.

Finally, a significantly increased risk of VTE was observed for both antidepressant users who did and did not report concomitant use of other psychotropic drugs. Compared with women in the no treatment/no drugs group, the HR for women who reported using antidepressants only was 1.30 (95% CI, 1.14–1.48; P<0.0001), whereas the HR for women who reported concurrent use of antidepressants and other psychotropic drugs was 1.86 (95% CI, 1.46–2.37; P<0.0001).

Discussion

In this large prospective study of UK women of an average age of 59.9 years, 6.9% reported that during most of the previous 4 weeks they had used antidepressants and 2.7% reported use of other psychotropic drugs during the 4-week period. Women who reported taking antidepressants had a 40%

Table 2. Adjusted HRs of Hospital Admission for and/or Death From Venous Thromboembolism (and Separately for Pulmonary Embolism and for Venous Thrombosis Without Pulmonary Embolism) by Self-Reported Treatment for Depression or Anxiety and Self-Reported Use of Antidepressants and Other Psychotropic Drugs

Exposure Category*	No. at Risk (n=734 092)	Venous Thromboembolism†		Venous Thrombosis With Pulmonary Embolism‡		Venous Thrombosis Without Pulmonary Embolism	
		No. of Cases (n=3922)	Adjusted HRs (95% CI)§	No. of Cases (n=2029)	Adjusted HRs (95% CI)§	No. of Cases (n=1893)	Adjusted HRs (95% CI)§
Reported neither treatment for depression or anxiety nor use of any psychotropic drugs	650 707	3393	1.00 (reference)	1739	1.00 (reference)	1654	1.00 (reference)
Reported treatment for depression or anxiety, but no use of antidepressants or other psychotropic drugs	13 563	79	1.19 (0.95–1.49)	39	1.16 (0.84–1.60)	40	1.22 (0.89–1.67)
Reported use of antidepressants‖	50 354	313	1.39 (1.23–1.56)	171	1.49 (1.27–1.75)	142	1.28 (1.07–1.52)
Reported use of other psychotropic drugs¶	19 468	137	1.41 (1.19–1.67)	80	1.58 (1.26–1.98)	57	1.22 (0.94–1.59)

*Based on responses to 2 separate questions about: (1) "any medication use for most of the last 4 weeks," and (2) which conditions "you are now being treated for."
†Diagnosis of deep vein thrombosis and/or pulmonary embolism.
‡Pulmonary embolism with or without a recorded diagnosis of concurrent deep vein thrombosis.
§Hazard ratios (HRs) are adjusted for age, body mass index, smoking, alcohol consumption, frequency of strenuous physical activity, hormone therapy, diabetes mellitus, high blood pressure, and socioeconomic status, and stratified by recruitment region.
‖Includes women who did (n=29 901) and did not (n=20 453) report being treated for depression or anxiety and women who did (n=8011) and did not (n=42 343) report taking other psychotropic drugs.
¶Antipsychotics, lithium and other drugs used to treat bipolar disorder, anxiolytics, and hypnotics.

higher risk of subsequently being admitted to the hospital for and/or dying from VTE than women in the no treatment/no drugs group. The increased risk of VTE was of similar magnitude for users of tricyclics, SSRIs, and other antidepressants, as well as for those using other psychotropic drugs. No significant increase in risk was found for the 1.8% of women in the treatment/no drugs group, although the power was low.

Our results suggest that the women classified here as using psychotropic drugs are likely to be long-duration users, and that there is relatively little contamination by those starting use after baseline. Approximately 43% to 60% of the women who were asked specifically about use of amitriptyline and of Prozac 4 years after baseline reported still using the identical drug 4.4 years later, whereas fewer than 2% who were not taking these drugs at baseline reported taking them 4 years later.

Findings in Relation to Previous Studies

Although the 6.9% of women who reported at baseline, on average in 2002, having taken antidepressant drugs during most of the previous 4 weeks is lower than the 16% point prevalence for women aged 55 to 64 years reported for 2013 by the Health Survey of England,[5] the difference is likely to reflect, at least in part, the different questions that were asked. Our question about drug use during most of the previous 4 weeks would not include short-duration users, but this exclusion is an advantage for studying of the effects of psychotropic drugs on VTE risk. That a sizeable proportion of women who reported taking an antidepressant did not report being treated for anxiety or depression, and similarly that not all women who reported they were being treated for depression or anxiety reported use of antidepressants, is consistent with previous US and UK research.[26–28]

Many previous studies reported findings consistent with ours, although the CIs in some studies were wide. Of 5 studies with prospectively collected exposure information,[7–11] a significant relationship between antidepressant use and VTE was reported in 3 (which was largely confined to users of tricyclic products),[7–9] and the findings from one other was consistent with our findings, with wide CIs.[11] The fifth study found no association,[10] but the comparison group included patients taking thyroid replacement hormones, patients with a history of VTE or cancer were only excluded if diagnosed in the 36 months before cohort entry, follow-up was not censored at cancer diagnosis or surgery, and no adjustment for body mass index, smoking, or physical activity was performed. Of 2 studies with retrospectively collected exposure data,[12,13] the results of one were consistent with our findings,[12] while the other found no association,[13] but controls were drawn from the same hospital wards as the cases and participants were classified as users of antidepressants only if they had taken them in the week before

Table 3. Adjusted HRs of Hospital Admission For and/or Death From Venous Thromboembolism by Self-Reported Use of Tricyclics, Selective Serotonin Reuptake Inhibitors, and Other Antidepressants

Exposure Category*	No. at Risk (n=699 758)†	Venous Thromboembolism	
		No. of Cases (n=3695)	Adjusted HRs (95% CI)‡
Reported neither treatment for depression or anxiety nor use of any psychotropic drugs	650 707	3393	1.00 (reference)
Reported use of tricyclic antidepressants	26 158	158	1.32 (1.12–1.55)
Reported use of selective serotonin reuptake inhibitor antidepressants	19 890	123	1.40 (1.17–1.68)
Reported use of other antidepressants	3003	21	1.61 (1.04–2.47)

*Based on responses to 2 separate questions about: (1) "any medication use for most of the last 4 weeks," and (2) which conditions "you are now being treated for."
†Women who reported use of antidepressants from more than one class are excluded from this analysis.
‡Hazard ratios (HRs) are adjusted for age, body mass index, smoking, alcohol consumption, frequency of strenuous physical activity, hormone therapy, diabetes mellitus, high blood pressure, and socioeconomic status, and stratified by recruitment region.

admission—both of which might have resulted in an underestimation of risk.

Two other studies with prospectively recorded exposure data reported an apparent relationship between depression and VTE.[14,15] A Norwegian study found a 1.6-fold risk of subsequent VTE in participants who reported they had often felt depressed in the previous 2 weeks, compared with those who had not; however, antidepressant use was not included in the analyses.[14] A record linkage study in Taiwan found that participants with depression had a significant 1.4-fold risk of subsequent VTE compared with those without depression, and that there was no significant difference in risk by antidepressant user status, although the researchers were unable to adjust for several important risk factors for VTE.[15]

The focus of the present analysis was on antidepressants, but we also found a significantly increased risk of VTE associated with use of other psychotropic drugs, which is consistent with findings from the previous reports that examined this association.[7,11–13,29,30]

Strengths and Limitations

A key strength of this study is that we had information both on depression and on regular use of antidepressants. This, along with the large number of participants and incident cases of VTE, meant that we could examine reliably the risk of VTE in women who reported antidepressant use and, separately, in women who reported being treated for depression or anxiety but did not report the use of any psychotropic drugs. The linkage of questionnaire data with hospital admission, cancer registration, and death and emigration records allowed us to exclude women with a history of VTE, cancer, recent surgery, or treatment with anticoagulants at baseline; provided information on important potential confounders; and enabled virtually complete follow-up for hospital admissions and deaths. A high degree of accuracy in the linkage between NHS data sets has been reported,[18] as has the identification of Million Women Study participants and the reliability of VTE diagnoses within those data sets.[31] Furthermore, cause of death information was available for 99.9% of women who died during follow-up.

There are several features of the study that require further discussion. Antidepressant exposure was that recorded at baseline. If, as was suggested by one investigation,[9] the risk of VTE is highest in new users during the first few months of use, the present study may have underestimated the risk in women who reported taking antidepressants if a large proportion were likely to be long-term users. Similarly, misclassification of exposure status during follow-up might have resulted in some underestimation of long-term risk, given that 43% to 60% of women who reported using amitriptyline or Prozac at baseline were still using these drugs 4 years later and, conversely, fewer than 2% of women who were not using these drugs at baseline were doing so 4 years later. We were unable to distinguish between women being treated for depression and those being treated for anxiety; however, these conditions often coexist and antidepressants are prescribed for both disorders.[4,28]

Although uncomplicated deep vein thrombosis was increasingly treated in community and outpatient settings during the study period,[32,33] an earlier validation study found that only a small proportion of VTE events among participants in the Million Women Study were treated solely in general practice.[31] Hence, it is likely that we identified virtually all of the serious cases of deep vein thrombosis and pulmonary embolism.

It is unclear whether the increased risk of VTE we observed in women taking antidepressants reflects a pharmacological effect or some other factor associated with depression or anxiety, as an excess risk was observed for chemically diverse

classes of antidepressants including SSRIs which have been reported to inhibit platelet function.[34] We were able to explore potential confounding by a number of major risk factors for VTE, including comorbidities such as inflammatory bowel disease, although we did not have information about factors such as thrombophilia and family history. However, antidepressant use was not a confirmed risk factor for VTE during the study period so it seems unlikely that prescribing would have been influenced by the presence of these risk factors. We cannot rule out some residual confounding by immobility; we censored follow-up at first surgery (and, therefore, all major trauma that required surgical treatment) and adjusted for frequency of strenuous physical activity at recruitment, but we did not include additional information about immobility subsequently. However, if depression-related immobility was driving an increased risk of VTE, we might have expected to find a similarly elevated risk in women who reported being treated for depression or anxiety and did not report use of antidepressants or other psychotropic drugs.

Conclusions

Depressive disorders were an important cause of years lived with disability in the 2010 Global Burden of Disease Study.[35] Antidepressants are used to treat depression, anxiety, and various pain-related conditions, and the utilization of these drugs has been increasing in the United Kingdom, United States, and elsewhere.[27,36,37] National quality standards in the United Kingdom, which recommend that people who may have depression are assessed to determine the severity of the condition and identify appropriate treatments,[38] and a national objective to increase the proportion of US adults with major depressive disorders who receive treatment,[39] may lead to further increases in antidepressant use.

Appendix

The Million Women Study Collaborators

The Million Women Study coordinating center staff are as follows: Hayley Abbiss, Simon Abbott, Rupert Alison, Miranda Armstrong, Krys Baker, Angela Balkwill, Isobel Barnes, Valerie Beral, Judith Black, Roger Blanks, Kathryn Bradbury, Anna Brown, Benjamin Cairns, Dexter Canoy, Andrew Chadwick, Dave Ewart, Sarah Ewart, Lee Fletcher, Sarah Floud, Toral Gathani, Laura Gerrard, Adrian Goodill, Jane Green, Lynden Guiver, Alicia Heath, Darren Hogg, Michal Hozak, Isobel Lingard, Sau Wan Kan, Nicky Langston, Kath Moser, Kirstin Pirie, Alison Price, Gillian Reeves, Keith Shaw, Emma Sherman, Rachel Simpson, Helena Strange, Sian Sweetland, Sarah Tipper, Ruth Travis, Lyndsey Trickett, Anthony Webster, Clare Wotton, Lucy Wright, Owen Yang, and Heather Young.

The Advisory Committee are: Emily Banks, Valerie Beral, Lucy Carpenter, Carol Dezateux, Jane Green, Julietta Patnick, Richard Peto, and Cathie Sudlow.

The following NHS breast screening centers took part in the recruitment and breast screening follow-up for the Million Women Study: Avon, Aylesbury, Barnsley, Basingstoke, Bedfordshire and Hertfordshire, Cambridge and Huntingdon, Chelmsford and Colchester, Chester, Cornwall, Crewe, Cumbria, Doncaster, Dorset, East Berkshire, East Cheshire, East Devon, East of Scotland, East Suffolk, East Sussex, Gateshead, Gloucestershire, Great Yarmouth, Hereford and Worcester, Kent, Kings Lynn, Leicestershire, Liverpool, Manchester, Milton Keynes, Newcastle, North Birmingham, North East Scotland, North Lancashire, North Middlesex, North Nottingham, North of Scotland, North Tees, North Yorkshire, Nottingham, Oxford, Portsmouth, Rotherham, Sheffield, Shropshire, Somerset, South Birmingham, South East Scotland, South East Staffordshire, South Derbyshire, South Essex, South Lancashire, South West Scotland, Surrey, Warrington Halton St Helens and Knowsley, Warwickshire Solihull and Coventry, West Berkshire, West Devon, West London, West Suffolk, West Sussex, Wiltshire, Winchester, Wirral, and Wycombe.

Author Contributions

Parkin, Sweetland, and Beral designed the study; Balkwill analyzed the data; Parkin drafted the first version of the manuscript; and all authors contributed to drafting revised versions of the manuscript and gave their final approval of the version to be published.

Acknowledgments

The authors thank the women who have participated in the Million Women Study as well as the staff from the participating NHS breast screening centers. We also thank NHS Digital in England and the Information Services Division in Scotland for linked follow-up data.

Sources of Funding

This study was funded by Cancer Research UK, the UK Medical Research Council, and Lifeblood. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosures

None.

References

1. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. *J Thromb Haemost*. 2014;12:1580–1590.
2. Spiers N, Brugha TS, Bebbington P, McManus S, Jenkins R, Meltzer H. Age and birth cohort differences in depression in repeated cross-sectional surveys in England: the National Psychiatric Morbidity Surveys, 1993 to 2007. *Psychol Med*. 2012;42:2047–2055.
3. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health*. 2013;34:119–138.
4. BMJ Group, Royal Pharmaceutical Society of Great Britain. *British National Formulary*. London: BMJ Group, Pharmaceutical Press; 2015.
5. Scholes S, Faulding S, Mindell J. Chapter 5: use of prescribed medicines. In: *Health Survey for England 2013. Health, Social Care and Lifestyles*, ed. Joint Health Surveys Unit, NatCen, and Department of Epidemiology and Public Health, University College London. Leeds: The Health and Social Care Information Centre; 2014 Available at: http://content.digital.nhs.uk/catalogue/PUB16076/HSE2013-Ch5-pres-meds.pdf. Accessed December 8, 2015.
6. Pratt L, Brody D, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008. NCHS data brief, no 76: Hyattsville, MD: National Center for Health Statistics; 2011.
7. Parkin L, Skegg DC, Herbison GP, Paul C. Psychotropic drugs and fatal pulmonary embolism. *Pharmacoepidemiol Drug Saf*. 2003;12:647–652.
8. Jick SS, Li L. Antidepressant drug use and risk of venous thromboembolism. *Pharmacotherapy*. 2008;28:144–150.
9. Wu CS, Chang CM, Chen CY, Wu EC, Wu KY, Liang HY, Chao YL, Chung WS, Tsai HJ. Association between antidepressants and venous thromboembolism in Taiwan. *J Clin Psychopharmacol*. 2013;33:31–37.
10. Ray JG, Mamdani MM, Yeo EL. Antipsychotic and antidepressant drug use in the elderly and the risk of venous thromboembolism. *Thromb Haemost*. 2002;88:205–209.
11. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet*. 2000;356:1219–1223.
12. Thomassen R, Vandenbroucke JP, Rosendaal FR. Antipsychotic medication and venous thrombosis. *Br J Psychiatry*. 2001;179:63–66.
13. Lacut K, Le Gal G, Couturaud F, Cornily G, Leroyer C, Mottier D, Oger E. Association between antipsychotic drugs, antidepressant drugs and venous thromboembolism: results from the EDITH case-control study. *Fundam Clin Pharmacol*. 2007;21:643–650.
14. Enga KF, Braekkan SK, Hansen-Krone IJ, Hansen J-B. Emotional states and future risk of venous thromboembolism: the Tromso Study. *Thromb Haemost*. 2012;107:485–493.
15. Lee CWS, Liao CH, Lin CL, Liang JA, Sung FC, Kao CH. Depression and risk of venous thromboembolism: a population-based retrospective cohort study. *Psychosom Med*. 2015;77:591–598.
16. The Million Women Study Collaborative Group. The Million Women Study: design and characteristics of the study population. *Breast Cancer Res*. 1999;1:73–80.
17. Health & Social Care Information Centre. Hospital episode statistics. Available at: http://www.hscic.gov.uk/hes. Accessed October 27, 2015.
18. Kendrick S, Clark J. The Scottish record linkage system. *Health Bull*. 1993;51:72–79.
19. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems—Tenth Revision*. Vol. 1. Geneva: WHO; 1992.
20. Office of Population Censuses and Surveys. *Tabular List of the Classification of Surgical Operations and Procedures. 4th Revision*. London: Her Majesty's Stationery Office; 1990.
21. Sweetland S, Green J, Liu B, Berrington de Gonzalez A, Canonico M, Reeves G, Beral V; for the Million Women Study Collaborators. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *BMJ*. 2009;339:b4583.
22. Parkin L, Sweetland S, Balkwill A, Green J, Reeves G, Beral V; for the Million Women Study Collaborators. Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. *Circulation*. 2012;125:1897–1904.
23. Sweetland S, Beral V, Balkwill A, Liu B, Benson VS, Canonico M, Green J, Reeves GK; for the Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. *J Thromb Haemost*. 2012;10:2277–2286.
24. Sweetland S, Parkin L, Balkwill A, Green J, Reeves G, Beral V; for the Million Women Study Collaborators. Smoking, surgery, and venous thromboembolism risk in women: United Kingdom cohort study. *Circulation*. 2013;127:1276–1282.
25. Townsend P, Phillimore P, Beattie A. *Health and Deprivation: Inequality and the North*. London: Croom Helm; 1988.
26. Ornstein S, Stuart G, Jenkins R. Depression diagnoses and antidepressant use in primary care practices: a study from the Practice Partner Research Network (PPRNet). *J Fam Pract*. 2000;49:68–72.
27. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66:848–856.
28. McManus S, Meltzer H, Brugha T, Bebbington P, Jenkins R. *Adult Psychiatric Morbidity in England, 2007. Results of a Household Survey*. Leeds: The NHS Information Centre for Health and Social Care; 2009.
29. Jönsson AK, Spigset O, Hägg S. Venous thromboembolism in recipients of antipsychotics. Incidence, mechanisms, and management. *CNS Drugs*. 2012;26:649–662.
30. Conti V, Venegoni M, Cocci A, Fortino I, Lora A, Barbui C. Antipsychotic drug exposure and risk of pulmonary embolism: a population-based, nested case-control study. *BMC Psychiatry*. 2015;15:92.
31. Wright FL, Green J, Canoy D, Cairns BJ, Balkwill A, Beral V; for the Million Women Study Collaborators. Vascular disease in women: comparison of diagnoses in hospital episode statistics and general practice records in England. *BMC Med Res Methodol*. 2012;12:161.
32. Winter M, Keeling D, Sharpen F, Cohen H, Vallance P; on behalf of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. Procedures for the outpatient management of patients with deep venous thrombosis. *Clin Lab Haematol*. 2005;27:61–66.
33. Sampson FC, Goodacre S, Kelly AM, Kerr D. How is deep vein thrombosis diagnosed and managed in UK and Australian emergency departments? *Emerg Med J*. 2005;22:780–782.
34. Juurlink DN. Antidepressants, antiplatelets and bleeding: one more thing to worry about? *CMAJ*. 2011;183:1819–1820.
35. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: findings from the Global Burden of Disease Study 2010. *PLoS Med*. 2013;10:e1001547.
36. Ilyas S, Moncrieff J. Trends in prescriptions and costs of drugs for mental disorders in England, 1998–2010. *Br J Psychiatry*. 2012;200:393–398.
37. Spence R, Roberts A, Ariti C, Bardsley M. *Focus On: Antidepressant Prescribing. Trends in the Prescribing of Antidepressants in Primary Care*. London, England: The Health Foundation: The Nuffield Trust; 2014.
38. National Institute for Health and Clinical Excellence. Depression in adults. NICE quality standard [QS8]. 2011. Available at: https://www.nice.org.uk/guidance/qs8. Accessed December 8, 2015.
39. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Healthy People 2020 summary of objectives: mental health and mental disorders. 2010. Available at: http://www.healthypeople.gov/2020/topics-objectives/topic/mental-health-and-mental-disorders/objectives. Accessed December 8, 2015.

Antidepressants, Depression, and Venous Thromboembolism Risk: Large Prospective Study of UK Women

Lianne Parkin, Angela Balkwill, Siân Sweetland, Gillian K. Reeves, Jane Green, Valerie Beral and the Million Women Study Collaborators

J Am Heart Assoc. 2017;6:e005316; originally published May 17, 2017;
doi: 10.1161/JAHA.116.005316
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980