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Prevalence, incidence, indication and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in UK Clinical Practice Research Datalink

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Keywords:	Antidepressant, Chronic kidney disease, Prevalence, Incidence, Depression
Abstract:	Purpose: People with chronic kidney disease (CKD) have an increased prevalence of depression, anxiety, and neuropathic pain. We examined prevalence, incidence, indication for, and choice of antidepressants among patients with and without CKD. Methods: Using the UK Clinical Practice Research Datalink, we identified patients with CKD (two measurements of estimated glomerular filtration rate <60 mL/min/1.73m2 for ≥3 months) between April 2004 and March 2014. We compared those with CKD to a general population cohort without CKD (matched on age, sex, general practice, and calendar time [index date]). We identified any antidepressant prescribing in the six months prior to index date (prevalence), the first prescription after index date among non-prevalent users (incidence), and recorded diagnoses (indication). We compared antidepressant choice between patients with and without CKD among patients with a diagnosis of depression. Results: There were 242,349 matched patients (median age 76

	[interquartile range 70-82], male 39.3%) with and without CKD. Prevalence of antidepressant prescribing was 16.3% and 11.9%, and incidence was 57.2 and 42.4/1000 person-years, in patients with and without CKD respectively. After adjusting for confounders, CKD remained associated with higher prevalence and incidence of antidepressant prescription. Regardless of CKD status, selective serotonin reuptake inhibitors were predominantly prescribed for depression or anxiety, while tricyclic antidepressants were prescribed for neuropathic pain or other reasons. Antidepressant choice was similar in depressed patients with and without CKD. Conclusions: The rate of antidepressant prescribing was nearly one and a half times higher among people with CKD than in the general population.

Prevalence, incidence, indication and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in UK Clinical Practice Research Datalink

Running head: Antidepressants in patients with chronic kidney disease

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Keywords: Antidepressants; Chronic kidney disease; Prevalence; Incidence; Depression

Key points:

- This study examined details of antidepressant prescribing in patients with chronic kidney disease using a large, contemporary UK database of routine medical record data. We defined chronic kidney disease using serum creatinine measurements and compared people with and without chronic kidney disease matched for age, sex, general practice, and calendar time.
- Patients with chronic kidney disease were exposed to antidepressants more frequently; with higher prevalence and incidence of antidepressant prescribing than the general population. The positive association between chronic kidney disease and increased frequency of antidepressant prescribing remained after adjusting for measured confounders such as diabetes and cardiovascular disease.
- Among patients starting antidepressants, indication for antidepressant prescription (recorded diagnoses of depression, anxiety, or neuropathic pain) was similar between patients with and without chronic kidney disease. Antidepressant choice was also similar between depressed patients with and without chronic kidney disease.

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Abstract

Purpose: People with chronic kidney disease (CKD) have an increased prevalence of depression, anxiety, and neuropathic pain. We examined prevalence, incidence, indication for, and choice of antidepressants among patients with and without CKD.

Methods: Using the UK Clinical Practice Research Datalink, we identified patients with CKD (two measurements of estimated glomerular filtration rate <60 mL/min/1.73m^2 for ≥3 months) between April 2004 and March 2014. We compared those with CKD to a general population cohort without CKD (matched on age, sex, general practice, and calendar time [index date]). We identified any antidepressant prescribing in the six months prior to index date (prevalence), the first prescription after index date among non-prevalent users (incidence), and recorded diagnoses (indication). We compared antidepressant choice between patients with and without CKD among patients with a diagnosis of depression.

Results: There were 242,349 matched patients (median age 76 [interquartile range 70-82], male 39.3%) with and without CKD. Prevalence of antidepressant prescribing was 16.3% and 11.9%, and incidence was 57.2 and 42.4/1000 person-years, in patients with and without CKD respectively. After adjusting for confounders, CKD remained associated with higher prevalence and incidence of antidepressant prescription. Regardless of CKD status, selective serotonin reuptake inhibitors were predominantly prescribed for depression or anxiety, while tricyclic antidepressants were prescribed for neuropathic pain or other reasons.

Antidepressant choice was similar in depressed patients with and without CKD.

Conclusions: The rate of antidepressant prescribing was nearly one and a half times higher among people with CKD than in the general population.

Introduction

Antidepressants are among the most commonly prescribed classes of medication in industrialized countries, including the US[1] and UK.[2] The recent increase in the prescription of antidepressants is dramatic, with an average 10% increase per year from 1998 to 2010.[3] Antidepressants can be prescribed not only for depressive symptoms but also for other conditions such as anxiety and neuropathic pain.[4] In addition, off-label use of antidepressants is common for chronic pain, including non-neuropathic pain, and conditions where non-specific sedation is required.[5-7]

Chronic kidney disease (CKD), an impairment of kidney structure or function, is now recognized as a major public health problem.[8] CKD is associated with a range of comorbidities including obesity, hypertension, diabetes, and cardiovascular disease.[9,10] Level of kidney function, expressed as estimated glomerular filtration rate (eGFR), is closely associated with increased risk of death, cardiovascular events, and hospitalization.[11]

CKD is also associated with a range of mental health problems including anxiety[12] and depression[13]; almost one quarter of adults with pre-dialysis CKD are depressed. These conditions may be due to co-existing chronic diseases such as diabetes and heart failure, which are also associated with depression and anxiety symptoms,[14,15] or directly related to CKD. In addition, other indications for antidepressants such as chronic pain and insomnia are more common among patients with CKD.[16,17]

Patients with CKD are frequently excluded from clinical trials,[18,19] and concerns have been recently raised about the lack of knowledge regarding how kidney function is related to adverse effects of antidepressants.[20,21] Despite this, there has been no systematic research investigating frequency and patterns of antidepressant prescribing among patients with CKD. Understanding how antidepressants are actually prescribed in patients with CKD, compared to those without CKD, is important groundwork for the planning of future studies on the safety of antidepressants in this population. Therefore, we aimed to compare the frequency (prevalence and incidence), indications for, and choice of antidepressant prescription between patients with and without CKD, in the UK general population.

Methods

Data sources

The Clinical Practice Research Datalink (CPRD) is a database of routinely-recorded primary care electronic health record data from 7% of the UK population.[22] The database includes the following data: patient demographics; diagnoses; prescriptions; laboratory test results; and referrals made by general practitioners (GPs). Diseases can be identified using diagnostic codes (Read codes) recorded in routine data. We used CPRD linked to additional data sources: the inpatient Hospital Episodes Statistics (HES) database to provide data on ethnicity (to improve data completeness)[23]; Office for National Statistics (ONS) data for mortality; and Index of Multiple Deprivation (IMD) data for deprivation indices. We obtained study approval from the institutional review board of the London School of Hygiene and Tropical Medicine (reference: 9196), as well as the Independent Scientific Advisory Committee, which oversees research involving CPRD data (Protocol 15_219R). Informed consent from individual patients was waived because the data are anonymous.

Study population and matched cohort

All adults (age 18 or older) alive and contributing to HES-linked CPRD anytime from 1st April 2004 to 31st March 2014 were potentially eligible for inclusion. Patients were eligible for inclusion at the latest of: one year after practice registration,[24] the date that the practice

reached CPRD quality control standards, or 1st April 2004. Patients were no longer eligible for follow-up at the first of: renal replacement therapy (RRT) initiation, death, change of practice, last data collection from the practice, or 31st March 2014. We excluded patients already receiving RRT (hemodialysis, peritoneal dialysis, and kidney transplantation) prior to cohort entry.

First, we identified patients with CKD based on two consecutive measurements of eGFR <60ml/min/1.73m^2 more than three months apart.[25] Estimated GFR was calculated from serum creatinine values recorded in CPRD, using the Chronic Kidney Disease Epidemiology Collaboration equation.[26] Patients, including those who had CKD before April 2004, were included in the cohort on the date when they first satisfied the CKD definition (i.e. second eGFR <60ml/min/1.73m^2) during eligible follow-up (index date).

Next, as a control group, we selected at random patients without CKD from the general population. Because (i) CKD status largely depends on age and sex, and (ii) pattern of antidepressant prescription is expected to depend on general practice and calendar time, we matched controls to patients with CKD by age (same year of birth), sex, general practice, and calendar time. Each control entered the cohort on the same index date as their CKD counterpart. Individuals selected as controls (i.e. non-CKD patients) may be found to have CKD later; in this situation they were censored as a control at the time of satisfying CKD definition and contributed separately as an incident patient with CKD from that time point

forward (with their own matched control).

Prevalence and incidence of antidepressant prescription

We estimated the prevalence of existing users of antidepressants, defined as receiving an antidepressant prescription within six months prior to the index date. Incidence of antidepressant prescription was based on the first antidepressant prescription after index date, after exclusion of existing users.[27]

Covariates

In order to examine the independent association between CKD status and antidepressant prescription, we considered baseline characteristics of patients: age and sex; ethnicity; socio-economic status (SES); smoking status; body mass index (BMI); and common chronic physical illnesses that are considered to be associated with mental health conditions (diabetes mellitus, congestive heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease, rheumatoid arthritis, cancer, Parkinson's disease, and epilepsy).[28,29] Based on previous studies using UK primary care data,[30,31] we classified patients with no record of ethnicity as white. SES was assigned by quintile at an individual level, using 2010 ONS estimates of the IMD (a composite area-level marker of deprivation).[32] For patients with missing individual-level SES, we used the SES for the patient's general practice. Smoking

status and BMI were assigned using the data recorded closest to the index date. We defined each chronic physical illnesse as present if a relevant diagnosis code of that illness was recorded at least once before a patient's index date.

Indication

We identified morbidity codes for three common diagnoses suggesting indications for antidepressant prescription[4]: depression, anxiety, and neuropathic pain (included in **Appendix 1**). We included symptom codes as well as diagnostic codes because GPs in the UK commonly use symptom codes (e.g. "depressive symptoms", "anxiousness") rather than definitive diagnostic codes (e.g. "major depression", "general anxiety disorder").[33-35] We included codes recorded by GPs any time prior to the first antidepressant prescription until three months later, to account for possible time lag in recording diagnosis codes in electronic health records.[36,37] We categorized type of antidepressant, according to British National Formulary headings, into the following categories:[4] Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), or other antidepressants. Monoamine oxidase inhibitors were grouped into other antidepressants because of a small number of prescriptions. For each type of antidepressant, we identified the proportion of patients with each indication as well as those with none of the three indications.

Choice of antidepressants and initial prescription dose

There are 26 antidepressants currently available in the UK, only a few are indicated for anxiety and neuropathic pain, whilst all 26 are indicated for depressive conditions.[4] Therefore, we restricted this analysis to patients with a recorded diagnosis of depression. We compared the pattern of antidepressant choice (the proportion of patients prescribed each antidepressant as their first incident prescription) between depressed patients with and without CKD. We also compared the initial dose prescribed in those with and without CKD to examine whether antidepressants were started at a lower dose in patients with CKD than those without.

Statistical analyses

We compared the baseline characteristics of patients with and without CKD using χ^2 tests. We calculated crude prevalence and incidence rates for antidepressant prescribing. We then conducted a conditional logistic regression analysis (to account for matching) to investigate the association between CKD status and *prevalence* of antidepressant prescription. After excluding existing users of antidepressants (meaning matching was no longer maintained), we conducted an unconditional Poisson regression analysis to investigate the association between CKD status and *incidence* of new antidepressant prescription, adjusting for age, sex and financial year, and taking account clustering by general practice using robust standard errors. We adjusted for financial year (by including financial year as a categorical variable, i.e.

from 1st April–31st March for each year) because the frequency of antidepressant prescribing has been increasing year by year.[3] We further adjusted for ethnicity, SES, smoking status, and BMI, and, then, in a fully adjusted model, also included chronic physical illnesses. In models including smoking status and BMI, we included an additional absent category for those with no recorded smoking status or BMI. In a subsequent sensitivity analysis we dropped all those with missing smoking or BMI status. All the data management and statistical analyses were conducted using STATA version 14 (Stata Corp, Texas).

Renal function subgroup analyses

To examine the association between severity of kidney function and antidepressant prescribing, we classified patients with CKD according to the level of kidney function on the index date into two categories: eGFR 30-59 (CKD stage 3), and <30 mL/min/1.73 m^2 (CKD stage 4 and 5).[25] In patients without CKD, we differentiated patients with and without serum creatinine results recorded in CPRD prior to index date, because these subgroups are expected to be systematically different due to testing incentives for those at risk of CKD in the UK Quality and Outcomes Framework.[38] To compare the prevalence of existing users of antidepressants between subgroups of renal function, we used an unconditional logistic regression analysis, adjusting for age, sex and financial year, and taking account of clustering by general practice using robust standard errors. We also repeated all other principal analyses

(described under 'Statistical analyses' subheading) using renal function subgroups.

Additional analyses

Any difference in the duration of follow-up lengths between patients with and without CKD may affect the likelihood of starting antidepressants. Therefore, as a post hoc analysis, we compared the proportion of patients starting antidepressants within the first six months of follow-up in those with and without CKD.

We undertook a further analysis to investigate whether patients with CKD were more likely to start antidepressants for the first episode of depression in their life, or for a recurrent episode of depression. In CPRD, GPs routinely record a patient's past medical history shortly after registration with a new practice and, therefore, a previous episode of depression would be recorded between CPRD registration and index date of the study (as index dates need to be at least one year after CPRD registration by our definition). Therefore, in patients starting antidepressants with a recorded diagnosis of depression, we compared the proportion of those with and without CKD who had: (1) their first depression diagnosis in CPRD recorded between CPRD registration and index date (more likely to suggest a recurrence); and (2) their first depression diagnosis recorded in CPRD after index date (more likely to suggest the first ever depression diagnosis).

Results

Among 4,070,806 eligible patients (median age 39 [IQR 27-56], male 48.8%), we identified 264,628 patients with CKD (median age 77 [IQR 71-83], male 38.7%) (**Figure 1**). Of those with CKD, 242,349 (91.6%) (median age 76 [IQR 70-82], male 39.3%) were matched with a control patient without CKD who had the same age, sex, and general practice on the index date of their CKD counterpart. Unmatched patients with CKD (n = 22,279) were older and more likely to be female (median age 88 [IQR 84-92], male 31.5%). Of the 242,349 matched control patients without CKD, 41,151 (17.0%) were subsequently found to have CKD.

Compared to patients without CKD, patients with CKD were more likely to be deprived, ex-smokers and overweight (BMI $\geq$25 kg/m^2) (**Table 1**). Chronic physical illnesses, except for Parkinson's disease and epilepsy, were more common among patients with CKD.

Prevalence of existing use of antidepressants at index date was 16.3% and 11.9% in patients with and without CKD, respectively (**Table 2**). The incidence rate of new antidepressant prescription was 57.2 and 42.4/1000 person-years in patients with and without CKD, respectively (**Table 3**). After adjusting for confounding, CKD remained positively associated with increased prevalence and incidence of antidepressant prescribing (**Tables 2** and **3**). Our results were similar to those in the main analysis after excluding patients with missing smoking status and BMI (data not shown).

The pattern of recorded diagnoses was broadly similar between patients with and

without CKD (**Table 4**). Regardless of CKD status, the majority of patients prescribed SSRIs had recorded diagnoses of depression or anxiety, while TCAs were prescribed for neuropathic pain or other reasons. Among patients with a recorded diagnosis of depression, the choice of antidepressant was similar between patients with and without CKD (**Table 5**). Irrespective of CKD status, the most commonly prescribed antidepressant was citalopram, followed by amitriptyline, fluoxetine, sertraline, and mirtazapine. There was no clear evidence that antidepressants were started at a reduced dose in patients with CKD, compared to those without CKD.

When we repeated our analyses in subgroups of renal function (**Appendix 2 Tables 1-5**), as the level of kidney function decreased patients tended to be older and sicker. Among patients without CKD, those with serum creatinine results recorded in CPRD were sicker than those without. Prevalence and incidence of antidepressant prescribing increased among people with more severe kidney function: prevalence was 16.1% and 18.3%, and incidence was 56.9 and 62.3/1000 person-years in patients with eGFR 30-59 and <30 mL/min/1.73m^2, respectively. This trend remained after adjusting for confounders. Patterns of indication for and choice of antidepressant, as well as initial prescription dose, were broadly similar for patients with different levels of kidney function.

In additional analyses with follow-up restricted to the first six months, the percentage of patients starting antidepressants was higher amongst patients with CKD (3.5%;

7,155/202,921) than amongst those without it (2.5%; 5,233/213,611) (P < 0.001).

The proportion of patients starting antidepressants with their first depression diagnosis recorded between CPRD registration and index date was larger among patients with CKD (5.8%; 11,781/202,921) than those without CKD (4.0%; 8,476/213,611) (P < 0.001). Similarly, the proportion of patients starting antidepressants with their first depression diagnosis recorded in CPRD after index date was larger among patients with CKD (3.6%; 7,295/202,921) than those without CKD (2.4%; 5,112/213,611) (P < 0.001). These results suggest that patients with CKD are more likely than those without CKD to start antidepressants both for recurrent episodes of depression, and for their first ever episode of depression.

Discussion

Main findings

In this large study, we found that patients with CKD were more likely than patients without CKD to be receiving an antidepressant, or among non-users, to start one during follow-up. The increase in prevalence and incidence was graded according to severity of kidney function and the association remained after adjusting for baseline characteristics including chronic physical illnesses. The pattern of indication for and choice of antidepressants, as well as initial prescription dose, were broadly similar between patients with and without CKD.

Strengths and limitations

We used a detailed source of routinely collected data that is representative of UK population demographics.[22] In the UK, GPs manage the vast majority of non-refractory cases of mental health disorders,[39,40] and even when patients see psychiatrists in secondary care, prescriptions are usually administered by primary care.[41] Therefore, we expect that most antidepressant prescriptions are captured in CPRD. To better understand the characteristics of patients with CKD, we used a comparison group of patients without CKD matched on age, sex, general practice, and calendar time. Although previous studies suggested that the proportion of patients with CKD receiving antidepressants may be high as an absolute value,[42,43] we are not aware of any study that has directly compared frequency and patterns of antidepressant

prescribing between patients with and without CKD. We defined CKD using eGFR calculated from serum creatinine measurement. This method is more accurate than using recorded diagnosis of CKD, which has low sensitivity for detecting people with CKD in UK primary care databases.[44]

We must acknowledge several limitations of our study. Firstly, serum creatinine testing in primary care is not universal – currently it is only recommended and incentivized for people who are considered to be at risk for CKD.[9,38] We may have misclassified patients with unmeasured CKD to the matched control cohort, which could dilute the true association between CKD and antidepressant prescription. However, a recent study showed that the prevalence of CKD identified in CPRD is similar to that estimated in a nationally-representative survey (Health Survey for England), suggesting that most CKD patients are captured in CPRD.[45] Secondly, although we adjusted for important confounders that may be associated with mental health conditions,[28,29] the observed association between CKD status and the prevalence/incidence of antidepressant prescribing could be influenced by residual confounding due to un-coded poor health status or access to talking therapies. Thirdly, we examined three common diagnoses associated with antidepressant use (depression, anxiety, and neuropathic pain). However, for patients with two or more different diagnoses (e.g. depression and neuropathic pain), it was not possible to determine the most likely indication for antidepressant prescription because diagnosis and prescription records

are separate in CPRD. Also, patients may have received antidepressants for other reasons, such as non-neuropathic pain and insomnia, but reliable identification of these conditions has not been established in CPRD. Finally, we demonstrated that the initial dose of antidepressant prescribed was similar in depressed patients with and without CKD. However, this does not ensure that the subsequent dose was also similar between those with and without CKD (as doctors may increase or decrease antidepressant dose after initial prescription, according to perceived effectiveness or side effects).

Comparison with other studies

Two studies conducted in the US have examined antidepressant use in patients with CKD.[42,43] The Chronic Renal Insufficiency Cohort study investigated the proportion of patients with CKD receiving an antidepressant at recruitment.[43] Of 3,853 participants, 700 (18.2%) were taking antidepressants. This number is close to the prevalence of existing users of antidepressants in patients with CKD (16.3%) found in our study. Another US cohort study showed that around 30% of patients with CKD (with or without diagnosis of depression) were receiving antidepressants at any time during a two-year period between 2004 and 2006.[42] These antidepressant users appeared to include both existing and new users of antidepressants. Our study demonstrated the incident rate of antidepressant prescription at 57.2/1000 person-years in patient with CKD. Together with the prevalence of existing users

(16.3%), the cumulative effect of this was consistent with over 30% of CKD patients exposed to antidepressants during follow-up. Neither US study included a comparison group of patients without CKD in order to compare prescribing in CKD patients to that in the general population. Indication and choice of antidepressants were also not examined.

Explanation of findings and implication for future studies

Patients with mild CKD generally do not have related physical symptoms. However, a previous study has suggested that negative perception of CKD is associated with depression and lower quality of life, even in the early stages of CKD.[46] Patients with more advanced CKD (eGFR <30 mL/min/1.73m^2) tend to have symptoms including fatigue, nausea, sleep disturbances, itching, and peripheral neuropathy, any of which could influence quality of life and mental health. This is in line with our finding that patients with advanced CKD were more likely to be prescribed antidepressants, even without a specifically coded diagnosis of depression and anxiety.

While most SSRIs were associated with a coded diagnosis of depression or anxiety, more than half of patients starting TCAs (mostly amitriptyline) did not have any recorded diagnoses of depression, anxiety or neuropathic pain. Amitriptyline may have been predominantly prescribed as an off-label indication for non-psychiatric conditions such as chronic pain and insomnia.[5-7] When restricted to patients with a coded diagnosis of

depression, SSRIs accounted for the majority of antidepressant prescribing, which is in keeping with current guidelines for management of depression.[39] Patterns of antidepressant choice did not differ substantially according to CKD status or level of kidney function. This is probably because to date there is no evidence of greater efficacy or safety concerns for specific antidepressants among patients with CKD.[20,21]

Increased adverse events as renal function declines is an important concern. For example, amitriptyline clearance is reduced in patients with decreased kidney function.[47] As a result, amitriptyline may accumulate, causing serious adverse outcomes through neurotoxicity[48] and cardiotoxicity.[49] Another example is the potential amplification of bleeding risk both with use of SSRIs and with decreased kidney function itself.[50] Finally, the results of our analyses stratified by severity of renal function demonstrate that many patients are prescribed antidepressants at levels of renal function below those where cessation is recommended by manufacturers (e.g. eGFR <30 mL/min/1.73m^2). According to the British National Formulary,[4] escitalopram, paroxetine, sertraline, imipramine, lofepramine, trazodone, duloxetine, mirtazapine, and venlafaxine should be used with caution or avoided in those with reduced renal function, but our real-world data suggest that these drugs are prescribed similarly in patients with moderately or severely decreased kidney function, compared to those with normal kidney function. Better evidence regarding the potential adverse effects of these drugs for patients with decreased kidney function is needed.

Conclusions

This study using a large UK database suggests that patients with CKD are more likely to be prescribed antidepressants than the general population, whilst prescribing patterns did not appear to be influenced by kidney function. These real-world data emphasize the need for research investigating the potential adverse effects of antidepressant therapy in people with decreased kidney function.

Author contributions

MI planned the study, carried out the data extraction, processing and analysis, and drafted the manuscript. DN and LT contributed substantially to the study design, interpretation of the results, and writing of the manuscript. KM and HM supported the data processing and writing of the manuscript. LS was involved in discussions of the analytical approach to this study and made comments on the results. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Flow chart for the selection of matched patients with and without chronic kidney disease

CKD = chronic kidney disease, CPRD = clinical practice research datalink, HES = hospital episode statistics, RRT = renal replacement therapy.

*Matched cohort: randomly selected individuals without chronic kidney disease matched for age, sex, general practice, and calendar time.

Table 1. Baseline characteristics of matched patients with and without chronic kidney disease.

	Patients without CKD N = 242,349 n (%)	Patients with CKD N = 242,349 n (%)	P value
Age (years):			1.000
<55	6,845 (2.8)	6,845 (2.8)	
55-64	23,556 (9.7)	23,556 (9.7)	
65-74	71,112 (29.3)	71,112 (29.3)	
75-84	102,594 (42.3)	102,594 (42.3)	
≥85	38,242 (15.8)	38,242 (15.8)	
Sex (male):	95,318 (39.3)	95,318 (39.3)	1.000
Ethnicity:			
White/not-recorded*	238,533 (98.4)	238,138 (98.3)	<0.001
South Asian	1,796 (0.7)	2,317 (1.0)	
Black	1,156 (0.5)	1,060 (0.4)	
Other ethnicity	864 (0.4)	834 (0.3)	
Socio-economic status**:			
1 (least deprived)	56,800 (23.4)	53,034 (21.9)	<0.001
2	61,647 (25.4)	60,501 (25.0)	
3	50,466 (20.8)	50,709 (20.9)	
4	42,221 (17.4)	44,692 (18.4)	
5 (most deprived)	31,215 (12.9)	33,413 (13.8)	
Smoking status:			<0.001
Non-smoker	92,363 (38.1)	80,721 (33.3)	
Ex-smoker	107,737 (44.5)	131,510 (54.3)	
Current-smoker	36,338 (15.0)	29,243 (12.1)	
Missing	5,911 (2.4)	875 (0.4)	
Body mass index (kg/m^2):			<0.001
<18.5	6,638 (2.7)	4,562 (1.9)	
18.5 - 25	85,473 (35.3)	70,102 (28.9)	
≥25	80,458 (33.2)	88,083 (36.4)	
≥30	40,326 (16.6)	63,183 (26.1)	
Missing	29,454 (12.2)	16,419 (6.8)	
Chronic physical illnesses:			
Diabetes mellitus	24,292 (10.0)	52,802 (21.8)	<0.001
Congestive heart failure	7,581 (3.1)	23,774 (9.8)	<0.001
Myocardial infarction	11,459 (4.7)	25,746 (10.6)	<0.001
Stroke	12,243 (5.1)	19,982 (8.3)	<0.001

Chronic obstructive pulmonary disease	14,996 (6.2)	18,229 (7.5)	<0.001
Rheumatoid arthritis	4,270 (1.8)	6,031 (2.5)	<0.001
Cancer	47,431 (19.6)	54,450 (22.5)	<0.001
Parkinson's disease	2,691 (1.1)	2,293 (1.0)	<0.001
Epilepsy	3,972 (1.6)	3,682 (1.5)	0.001

CKD = chronic kidney disease.

* White/not-recorded: 136,119 (56.2%) and 140,784 (58.1%) patients with and without CKD respectively, had no recorded ethnicity.

** Socio-economic status: 259 (0.1%) and 272 (0.1%) patients with and without CKD respectively, did not have individual-level data, we therefore used the socio-economic status of their general practice. .

Table 2. Prevalence of antidepressant prescription by chronic kidney disease status.

	No. of patients receiving antidepressants in the past 6 months	Prevalence % (95% CI)	Adjusted odds ratio (95% CI)		
			Model 1*	Model 2**	Model 3***
Patients without CKD (N = 242,349)	28,738	11.9 (11.7 – 12.0)	1 (Reference)	1 (Reference)	1 (Reference)
Patients with CKD (N = 242,349)	39,428	16.3 (16.1 – 16.4)	1.46 (1.43 – 1.48)	1.43 (1.41 – 1.46)	1.35 (1.32 – 1.37)

CI = confidence interval, CKD = chronic kidney disease.

*Model 1: Accounted for the matched nature of the groups (age, sex, general practice, and calendar time) in conditional logistic regression analysis.

**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status, and body mass index.

***Model 3: Model 2 + adjusted by chronic physical illnesses.

Table 3. Incidence of new antidepressant prescription by chronic kidney disease status.

	Total follow-up length (person-years)	No. of patients starting antidepressants	Incidence rate (/1000 person-years) (95%CI)	Adjusted rate ratio (95%CI)		
				Model 1*	Model 2**	Model 3***
Patients without CKD (N = 213,611)	774,660	32,846	42.4 (41.9 – 42.9)	1 (Reference)	1 (Reference)	1 (Reference)
Patients with CKD (N = 202,921)	794,150	45,394	57.2 (56.6 – 57.7)	1.35 (1.33 – 1.37)	1.30 (1.28 – 1.32)	1.25 (1.23 – 1.26)

CI = confidence interval, CKD = chronic kidney disease, IQR = interquartile range.

*Model 1: Adjusted by age, sex and financial year, and taking account of clustering by general practice with robust standard errors using unconditional Poisson regression analysis.

**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status and body mass index.

***Model 3: Model 2 + adjusted by chronic physical illnesses.

Table 4. Recorded diagnoses for patients prescribed antidepressants stratified by chronic kidney disease status and type of antidepressant.

	Patients without CKD (N = 32,846)			Patients with CKD (N = 45,394)		
	SSRI	TCA	Others	SSRI	TCA	Others
	N = 12,924	N = 17,672	N = 2,250	N = 17,992	N = 24,262	N = 3,140
Depression, n (%)*	8,123 (62.9)	4,430 (25.1)	1,035 (46.0)	11,363 (63.2)	6,257 (25.8)	1,456 (46.4)
Anxiety, n (%)*	4,843 (37.5)	3,902 (22.1)	708 (31.5)	6,131 (34.1)	5,055 (20.8)	935 (29.8)
Neuropathic pain, n (%)*	625 (4.8)	2,536 (14.4)	152 (6.8)	997 (5.5)	3,491 (14.4)	209 (6.7)
None of the above, n (%)	3,188 (24.7)	9,699 (54.9)	894 (39.7)	4,683 (26.0)	13,259 (54.7)	1,256 (40.0)

CKD = chronic kidney disease, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants.

*Percentages are column percentages. Each patient may have one or more recorded diagnosis.

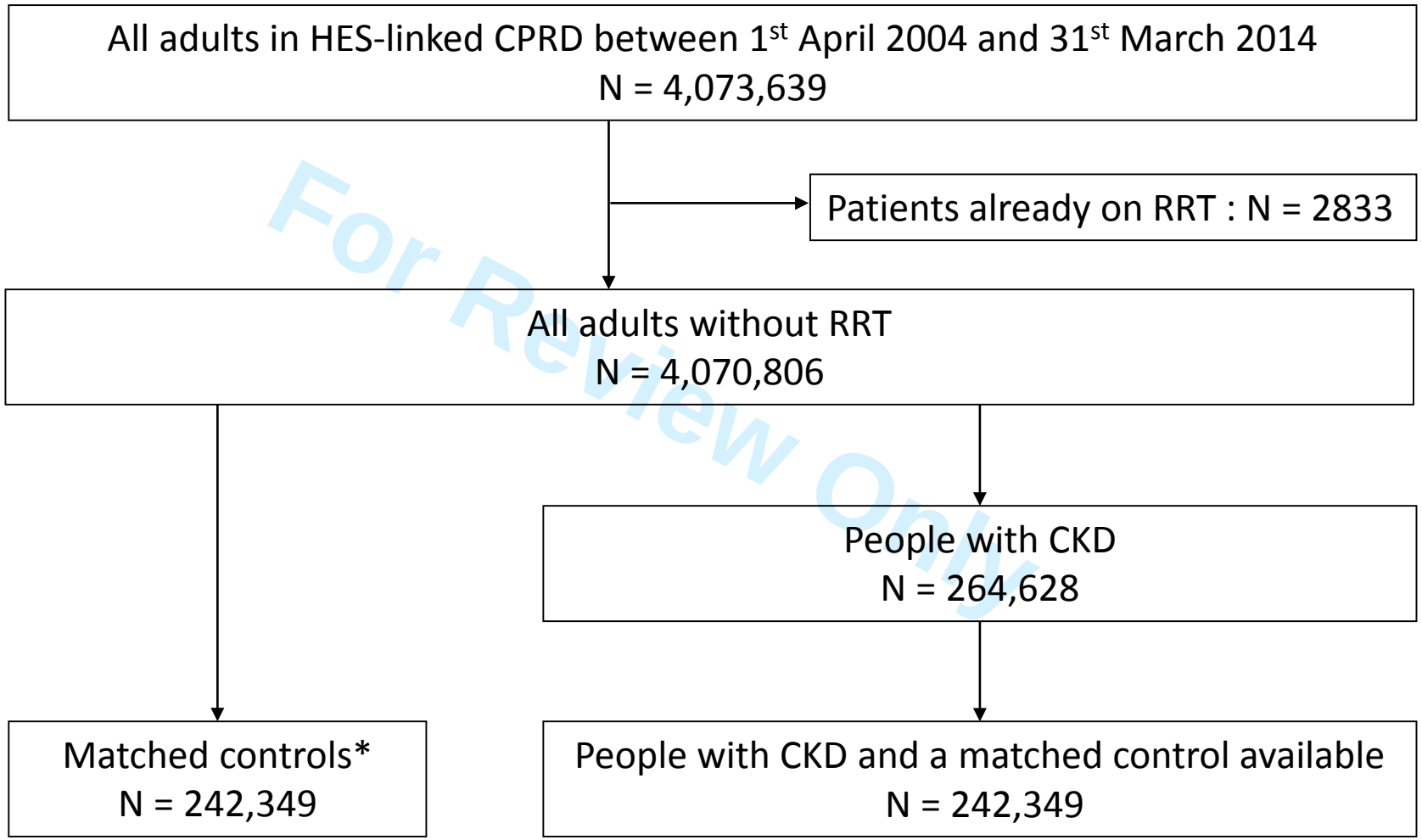
Table 5. Choice of antidepressants and initial prescription dose for patients with diagnosed depression by chronic kidney disease status.

	Patients without CKD N = 13,588		Patients with CKD N = 19,076	
	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]
Selective serotonin reuptake inhibitors				
Citalopram	4,934 (36.3)	10 [10 – 20]	7,070 (37.1)	10 [10 – 20]
Escitalopram	353 (2.6)	5 [5 – 10]	429 (2.3)	5 [5 – 10]
Fluoxetine	1,651 (12.2)	20 [20 – 20]	2,270 (11.9)	20 [20 – 20]
Fluvoxamine	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Paroxetine	132 (1.0)	20 [20 – 20]	144 (0.8)	20 [20 – 20]
Sertraline	1,053 (7.8)	50 [50 – 50]	1,449 (7.6)	50 [50 – 50]
Tricyclic and related antidepressants				
Amitriptyline	3,506 (25.8)	10 [10 – 20]	5,024 (26.3)	10 [10 – 15]
Clomipramine	26 (0.2)	25 [10 – 37.5]	27 (0.1)	20 [10 – 37.5]
Dosulepin	407 (3.0)	37.5 [25 – 75]	512 (2.7)	37.5 [25 – 75]
Doxepin	19 (0.1)	25 [25 – 37.5]	24 (0.1)	25 [20 – 30]
Imipramine	30 (0.2)	25 [10 – 30]	45 (0.2)	25 [10 – 30]
Lofepramine	113 (0.8)	70 [70 – 140]	186 (1.0)	70 [70 – 140]
Nortriptyline	94 (0.7)	15 [10 – 15]	158 (0.8)	10 [10 – 15]
Trimipramine	15 (0.1)	25 [10 – 37.5]	26 (0.1)	25 [20 – 50]
Mianserin	7 (0.1)	30 [30 – 30]	5 (<0.1)	30 [30 – 30]
Trazodone	213 (1.6)	50 [50 – 100]	250 (1.3)	50 [50 – 75]
Monoamine oxidase inhibitors**	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Other antidepressants:				
Agomelatine	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Duloxetine	98 (0.7)	40 [30 – 60]	169 (0.9)	40 [30 – 60]
Flupentixol	63 (0.5)	1 [0.5 – 1]	88 (0.5)	1 [0.5 – 1]
Mirtazapine	758 (5.6)	15 [15 – 15]	1,045 (5.5)	15 [15 – 15]
Reboxetine	<5 (<0.1)	n/a	<5 (<0.1)	n/a
Venlafaxine	85 (0.6)	75 [75 – 75]	97 (0.5)	75 [75 – 75]
Two or more different antidepressants	27 (0.2)	n/a	53 (0.3)	n/a

CKD = chronic kidney disease, IQR = interquartile range.

*Cell counts less than five have been suppressed to preserve patient privacy.

**Phenelzine, isocarboxazid, tranylcypromine, and moclobemide are combined due to small sample sizes.



Appendix 1. List of diagnosis codes indicative of depression, anxiety, and neuropathic pain in Clinical Practice Research Datalink.

Read code	Medcode*	Read term
Depression:		
E2B..00	324	Depressive disorder NEC
Eu32z11	543	[X]Depression NOS
E112.14	595	Endogenous depression
E200300	655	Anxiety with depression
E135.00	1055	Agitated depression
E204.00	1131	Neurotic depression reactive type
Eu31.11	1531	[X]Manic-depressive illness
E290.00	1533	Brief depressive reaction
2257.00	1908	O/E - depressed
1B17.00	1996	Depressed
1B1N.00	2147	Poor self esteem
E11..12	2560	Depressive psychoses
E204.11	2639	Postnatal depression
1465.00	2716	H/O: depression
62T1.00	2923	Puerperal depression
1B17.12	2930	C/O - feeling unhappy
Eu32z00	2970	[X]Depressive episode, unspecified
E2B0.00	2972	Postviral depression
Eu32z12	3291	[X]Depressive disorder NOS
Eu33.00	3292	[X]Recurrent depressive disorder
E2B1.00	4323	Chronic depression
Eu32.00	4639	[X]Depressive episode
E115.00	4677	Bipolar affective disorder, currently depressed
Eu31500	4732	[X]Bipolar affect dis cur epi severe depres with psyc symp
1B17.11	4824	C/O - feeling depressed
Eu53012	4979	[X]Postpartum depression NOS
E112.11	5879	Agitated depression
Eu32z14	5987	[X] Reactive depression NOS
E113700	6482	Recurrent depression
E112.12	6546	Endogenous depression first episode
Eu32y00	6854	[X]Other depressive episodes
E113.11	6932	Endogenous depression - recurrent
E112.13	6950	Endogenous depression first episode
E112z00	7011	Single major depressive episode NOS

1BJ..00	7412	Loss of confidence
Eu32.13	7604	[X]Single episode of reactive depression
Eu34113	7737	[X]Neurotic depression
Eu41211	7749	[X]Mild anxiety depression
Eu34100	7953	[X]Dysthymia
E130.00	8478	Reactive depressive psychosis
Eu34111	8584	[X]Depressive neurosis
Eu33.15	8826	[X]SAD - Seasonal affective disorder
Eu33.11	8851	[X]Recurrent episodes of depressive reaction
Eu33.13	8902	[X]Recurrent episodes of reactive depression
1BT..11	8928	Low mood
Eu32.11	9055	[X]Single episode of depressive reaction
E11z200	9183	Masked depression
Eu32100	9211	[X]Moderate depressive episode
Eu32200	9667	[X]Severe depressive episode without psychotic symptoms
1B1U.00	9796	Symptoms of depression
1BT..00	10015	Depressed mood
Eu34112	10290	[X]Depressive personality disorder
1B1U.11	10438	Depressive symptoms
E211200	10455	Depressive personality disorder
E112.00	10610	Single major depressive episode
Eu32400	10667	[X]Mild depression
Eu32y11	10720	[X]Atypical depression
E118.00	10825	Seasonal affective disorder
Eu33212	11252	[X]Major depression, recurrent without psychotic symptoms
Eu33211	11329	[X]Endogenous depression without psychotic symptoms
E11y000	11596	Unspecified manic-depressive psychoses
Eu32000	11717	[X]Mild depressive episode
Eu41200	11913	[X]Mixed anxiety and depressive disorder
Eu32300	12099	[X]Severe depressive episode with psychotic symptoms
E115.11	12831	Manic-depressive - now depressed
Eu53011	13307	[X]Postnatal depression NOS
E113200	14709	Recurrent major depressive episodes, moderate
E113.00	15099	Recurrent major depressive episode
E112200	15155	Single major depressive episode, moderate
E112300	15219	Single major depressive episode, severe, without psychosis
Eu34114	15220	[X]Persistant anxiety depression
E115000	15923	Bipolar affective disorder, currently depressed, unspecified

E112100	16506	Single major depressive episode, mild
Eu31300	16562	[X]Bipolar affect disorder cur epi mild or moderate depressn
E291.00	16632	Prolonged depressive reaction
Eu33315	16861	[X]Recurrent severe episodes of psychotic depression
E130.11	17770	Psychotic reactive depression
Eu32.12	18510	[X]Single episode of psychogenic depression
Eu3y111	19054	[X]Recurrent brief depressive episodes
Eu33.12	19696	[X]Recurrent episodes of psychogenic depression
Eu20400	20785	[X]Post-schizophrenic depression
E002100	21887	Senile dementia with depression
ZV11112	22080	[V]Personal history of manic-depressive psychosis
Eu33400	22116	[X]Recurrent depressive disorder, currently in remission
Eu32212	22806	[X]Single episode major depression w'out psychotic symptoms
Eu31400	23713	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Eu33311	23731	[X]Endogenous depression with psychotic symptoms
ZV11111	23963	[V]Personal history of manic-depressive psychosis
Eu32313	24112	[X]Single episode of psychotic depression
Eu32311	24117	[X]Single episode of major depression and psychotic symptoms
E113400	24171	Recurrent major depressive episodes, severe, with psychosis
1BQ..00	25435	Loss of capacity for enjoyment
E113z00	25563	Recurrent major depressive episode NOS
E113300	25697	Recurrent major depressive episodes, severe, no psychosis
1BT..12	26028	Sad mood
E11y200	27491	Atypical depressive disorder
E001300	27677	Presenile dementia with depression
Eu02z16	27759	[X] Senile dementia, depressed or paranoid type
E115200	27890	Bipolar affective disorder, currently depressed, moderate
Eu32z13	28248	[X]Prolonged single episode of reactive depression
Eu33312	28677	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33.14	28756	[X]Seasonal depressive disorder
Eu32314	28863	[X]Single episode of reactive depressive psychosis
E113100	29342	Recurrent major depressive episodes, mild
Eu33213	29451	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33100	29520	[X]Recurrent depressive disorder, current episode moderate
R007z13	29527	[D]Postoperative depression
Eu33000	29784	[X]Recurrent depressive disorder, current episode mild
Eu3y011	30688	[X]Mixed affective episode
1BP..00	30740	Loss of interest

Eu33314	31757	[X]Recurr severe episodes/psychogenic depressive psychosis
E112400	32159	Single major depressive episode, severe, with psychosis
Eu33313	32941	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33200	33469	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu31z00	33751	[X]Bipolar affective disorder, unspecified
E112000	34390	Single major depressive episode, unspecified
E115300	35607	Bipolar affect disord, now depressed, severe, no psychosis
E113000	35671	Recurrent major depressive episodes, unspecified
E115100	35734	Bipolar affective disorder, currently depressed, mild
E290z00	36246	Brief depressive reaction NOS
Eu33z11	36616	[X]Monopolar depression NOS
E115z00	37296	Bipolar affective disorder, currently depressed, NOS
Eu33316	37764	[X]Recurrent severe episodes/reactive depressive psychosis
E002z00	41089	Senile dementia with depressive or paranoid features NOS
Eu32211	41989	[X]Single episode agitated depressn w'out psychotic symptoms
E004300	43292	Arteriosclerotic dementia with depression
E112500	43324	Single major depressive episode, partial or unspec remission
Eu33z00	44300	[X]Recurrent depressive disorder, unspecified
E002.00	44674	Senile dementia with depressive or paranoid features
Eu31600	44693	[X]Bipolar affective disorder, current episode mixed
Eu33300	47009	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33y00	47731	[X]Other recurrent depressive disorders
Eu32312	52678	[X]Single episode of psychogenic depressive psychosis
1BU..00	53148	Loss of hope for the future
Eu31y00	53840	[X]Other bipolar affective disorders
E113600	55384	Recurrent major depressive episodes, in full remission
E113500	56273	Recurrent major depressive episodes,partial/unspec remission
Eu32y12	56609	[X]Single episode of masked depression NOS
E115600	57465	Bipolar affective disorder, now depressed, in full remission
Eu32213	59386	[X]Single episode vital depression w'out psychotic symptoms
1BP0.00	59869	Loss of interest in previously enjoyable activity
E11y.00	60178	Other and unspecified manic-depressive psychoses
E115400	63701	Bipolar affect disord, now depressed, severe with psychosis
E115500	72026	Bipolar affect disord, now depressed, part/unspec remission
Eu31y11	73924	[X]Bipolar II disorder
Eu33214	73991	[X]Vital depression, recurrent without psychotic symptoms
Eu32600	98252	[X]Major depression, moderately severe
Eu32500	98346	[X]Major depression, mild

Eu32700	98414	[X]Major depression, severe without psychotic symptoms
Eu32800	98417	[X]Major depression, severe with psychotic symptoms
Anxiety:		
1B13.00	131	Anxiousness
E200111	462	Panic attack
1B12.12	514	Tension - nervous
E200.00	636	Anxiety states
E200300	655	Anxiety with depression
E20z.11	791	Nervous breakdown
Eu41111	962	[X]Anxiety neurosis
E205.11	1582	Nervous exhaustion
E200400	1758	Chronic anxiety
R2y2.00	2509	[D]Nervousness
1BK..00	2524	Worried
E202100	3076	Agoraphobia with panic attacks
1B1..00	3328	General nervous symptoms
E200100	4069	Panic disorder
Eu41012	4081	[X]Panic state
E200z00	4534	Anxiety state NOS
E200500	4634	Recurrent anxiety
E200200	4659	Generalised anxiety disorder
Eu41.00	5385	[X]Other anxiety disorders
1B13.11	5902	Anxiousness - symptom
E292000	6221	Separation anxiety disorder
Eu41011	6408	[X]Panic attack
E200000	6939	Anxiety state unspecified
Eu41211	7749	[X]Mild anxiety depression
Z4L1.00	7999	Anxiety counselling
Eu41000	8205	[X]Panic disorder [episodic paroxysmal anxiety]
Eu60600	8424	[X]Anxious [avoidant] personality disorder
2259.00	8725	O/E - nervous
Eu41100	10344	[X]Generalized anxiety disorder
E202D00	10390	Fear of death
R2y2.12	10723	[D]Nervous tension
1B1V.00	11890	C/O - panic attack
Eu41200	11913	[X]Mixed anxiety and depressive disorder
E280.00	11940	Acute panic state due to acute stress reaction
E202200	12838	Agoraphobia without mention of panic attacks

2258.00	13124	O/E - anxious
Eu40012	14890	[X]Panic disorder with agoraphobia
Eu40011	16729	[X]Agoraphobia without history of panic disorder
Eu51511	17687	[X]Dream anxiety disorder
225J.00	19000	O/E - panic attack
1B1Z.00	20089	General nervous symptom NOS
1B1H.12	20163	Apprehension
Eu41z00	23838	[X]Anxiety disorder, unspecified
Eu41y00	24066	[X]Other specified anxiety disorders
Eu41z11	25638	[X]Anxiety NOS
225K.00	26331	O/E - fearful mood
Eu41y11	28167	[X]Anxiety hysteria
Z4I7200	28381	Alleviating anxiety
8HHp.00	28925	Referral for guided self-help for anxiety
1B12.00	29608	'Nerves' - nervousness
Eu40z00	34064	[X]Phobic anxiety disorder, unspecified
Eu41112	35825	[X]Anxiety reaction
2255.00	38155	O/E - afraid
1B1P000	40431	Cries easily
Eu41300	44321	[X]Other mixed anxiety disorders
Eu41113	50191	[X]Anxiety state
E292400	56924	Adjustment reaction with anxious mood
1B13.12	93401	Anxious
16ZB100	101422	Feeling low or worried

Neuropathic pain:

F262500	321	Periodic migrainous neuralgia
F301.00	1541	Other specified trigeminal neuralgia
A531.11	1598	Post-herpetic neuralgia
N242000	2284	Neuralgia unspecified
F301z00	6581	Trigeminal neuralgia NOS
F356100	6884	Morton's neuralgia
F300.00	7584	Post-herpetic trigeminal neuralgia
A531511	10223	Postherpetic neuralgia
A531200	11498	Postherpetic trigeminal neuralgia
N242300	11544	Neuropathic pain
1475.00	16481	H/O: trigeminal neuralgia
F321.00	16932	Glossopharyngeal neuralgia
A531500	17180	Postzoster neuralgia

N242z00	23839	Neuralgia, neuritis or radiculitis NOS
F262100	33362	Horton's (histamine) neuralgia
F372100	35785	Chronic painful diabetic neuropathy
F372000	48078	Acute painful diabetic neuropathy
N242.00	54992	Neuralgia, neuritis and radiculitis unspecified

*There is a one-to-one correspondence between Medcode and Read code in Clinical Practice Research Datalink.

Appendix 2. Subgroup analyses according to level of kidney function (among patients with CKD) and creatinine measurement (among patients without CKD).

Table 1. Baseline characteristics.

	Patients without CKD (N = 242,349)		Patients with CKD (N = 242,349)		
	without creatinine measurement in CPRD N = 62,971 n (%)	with creatinine measurement in CPRD N = 179,378 n (%)	with eGFR 30-59 mL/min/1.73m^2 at baseline N = 228,055 n (%)	with eGFR <30 mL/min/1.73m^2 at baseline N = 14,294 n (%)	P value
Age (years):					<0.001
<55	3,279 (5.2)	3,566 (2.0)	6,022 (2.6)	823 (5.8)	
55-64	7,693 (12.2)	15,863 (8.8)	22,531 (9.9)	1,025 (7.2)	
65-74	17,450 (27.7)	53,662 (29.9)	68,494 (30.0)	2,618 (18.3)	
75-84	23,536 (37.4)	79,058 (44.1)	96,868 (42.5)	5,726 (40.1)	
≥85	11,013 (17.5)	27,229 (15.2)	34,140 (15.0)	4,102 (28.7)	
Sex (male):	23,015 (36.6)	72,303 (40.3)	89,289 (39.2)	6,029 (42.2)	<0.001
Ethnicity:					<0.001
White/not-recorded	62,319 (99.0)	176,214 (98.2)	224,211 (98.3)	13,927 (97.3)	
South Asian	302 (0.5)	1,494 (0.8)	2,141 (0.9)	176 (1.2)	
Black	146 (0.2)	1,010 (0.6)	932 (0.4)	128 (0.9)	
Other ethnicity	204 (0.3)	660 (0.4)	771 (0.3)	63 (0.4)	
Socio-economic status:					<0.001
1 (least deprived)	14,724 (23.4)	42,076 (23.5)	50,295 (22.1)	2,739 (19.2)	
2	15,603 (24.8)	46,044 (25.7)	57,190 (25.1)	3,311 (23.2)	
3	12,950 (20.6)	37,516 (20.9)	47,616 (20.9)	3,093 (21.6)	
4	11,222 (17.8)	30,999 (17.3)	41,829 (18.3)	2,863 (20.0)	

5 (most deprived)	8,472 (13.5)	22,743 (12.7)	31,125 (13.7)	2,288 (16.0)	
Smoking status:					<0.001
Non-smoker	27,736 (44.1)	64,627 (36.0)	75,701 (33.2)	5,020 (35.1)	
Ex-smoker	18,549 (29.5)	89,188 (49.7)	124,290 (54.5)	7,220 (50.5)	
Current-smoker	11,791 (18.7)	24,547 (13.7)	27,374 (12.0)	1,869 (13.1)	
Missing	4,895 (7.8)	1,016 (0.6)	690 (0.3)	185 (1.3)	
Body mass index:					<0.001
<18.5	1,628 (2.6)	5,010 (2.8)	4,189 (1.8)	373 (2.6)	
18.5 - 25	21,981 (34.9)	63,492 (35.4)	65,841 (28.9)	4,261 (29.8)	
≥25	17,526 (27.8)	62,932 (35.1)	83,733 (36.7)	4,350 (30.4)	
≥30	6,829 (10.8)	33,497 (18.7)	59,910 (26.3)	3,273 (22.9)	
Missing	15,007 (23.8)	14,447 (8.1)	14,382 (6.3)	2,037 (14.3)	
Chronic physical illnesses:					
Diabetes mellitus	669 (1.1)	23,623 (13.2)	49,017 (21.5)	3,785 (26.5)	<0.001
Congestive heart failure	824 (1.3)	6,757 (3.8)	20,723 (9.1)	3,051 (21.3)	<0.001
Myocardial infarction	783 (1.2)	10,676 (6.0)	23,664 (10.4)	2,082 (14.6)	<0.001
Stroke	1,507 (2.4)	10,736 (6.0)	18,330 (8.0)	1,652 (11.6)	<0.001
Chronic obstructive pulmonary disease	2,312 (3.7)	12,684 (7.1)	17,006 (7.5)	1,223 (8.6)	<0.001
Rheumatoid arthritis	527 (0.8)	3,743 (2.1)	5,674 (2.5)	357 (2.5)	<0.001
Cancer	8,593 (13.7)	38,838 (21.7)	50,799 (22.3)	3,651 (25.5)	<0.001
Parkinson's disease	500 (0.8)	2,191 (1.2)	2,143 (0.9)	150 (1.1)	<0.001
Epilepsy	670 (1.1)	3,302 (1.8)	3,450 (1.5)	232 (1.6)	<0.001

CKD = chronic kidney function, eGFR = estimated glomerular filtration rate.

Table 2. Prevalence of antidepressant prescription.

	No. of patients receiving antidepressants in the past 6 months	Prevalence, % (95% CI)	Adjusted odds ratio (95% CI)		
			Model 1*	Model 2**	Model 3***
Non-CKD patients without creatinine measurement in CPRD (N = 62,971)	4,515	7.2 (7.0 – 7.4)	0.49 (0.47 – 0.51)	0.48 (0.46 – 0.50)	0.52 (0.49 – 0.54)
Non-CKD patients with creatinine measurement in CPRD (N = 179,378)	24,223	13.5 (13.3 – 13.7)	1 (Reference)	1 (Reference)	1 (Reference)
CKD patients with eGFR 30-59 mL/min/1.73m^2 at baseline (N = 228,055)	36,815	16.1 (16.0 – 16.3)	1.24 (1.22 – 1.27)	1.23 (1.21 – 1.26)	1.19 (1.16 – 1.21)
CKD patients with eGFR <30 mL/min/1.73m^2 at baseline (N = 14,294)	2,613	18.3 (17.6 – 18.9)	1.35 (1.26 – 1.44)	1.31 (1.23 – 1.41)	1.20 (1.12 – 1.29)

CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate.

*Model 1: Adjusted by age, sex and financial year, and taking account of clustering by general practices with robust standard errors using unconditional logistic regression analysis.

**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status and body mass index.

***Model 3: Model 2 + adjusted by chronic physical illnesses.

Table 3. Incidence of new antidepressant prescription.

	Total follow-up length (person-years)	No. of patients starting antidepressants	Incidence rate (/1000 person-years) (95%CI)	Adjusted rate ratio (95%CI)		
				Model 1**	Model 2***	Model 3***
Non-CKD patients without creatinine measurement in CPRD (N = 58,456)	258,474	7,076	27.4 (26.7 – 28.0)	0.55 (0.53 – 0.56)	0.58 (0.56 – 0.59)	0.60 (0.59 – 0.62)
Non-CKD patients with creatinine measurement in CPRD (N = 155,155)	516,186	25,770	49.9 (49.3 – 50.5)	1 (Reference)	1 (Reference)	1 (Reference)
CKD patients with eGFR 30-59 mL/min/1.73m^2 (N = 191,240)	762,310	43,410	56.9 (56.4 – 57.5)	1.14 (1.12 – 1.16)	1.13 (1.11 – 1.15)	1.10 (1.09 – 1.12)
CKD patients with eGFR <30 mL/min/1.73m^2 (N = 11,681)	31,839	1,984	62.3 (59.6 – 65.1)	1.24 (1.18 – 1.30)	1.23 (1.17 – 1.28)	1.16 (1.11 – 1.22)

CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range.

*Model 1: Adjusted by age, sex and financial year, and taking account of clustering by general practices with robust standard errors using unconditional Poisson regression analysis.

**Model 2: Model 1 + adjusted by ethnicity, socio-economic status, smoking status and body mass index.

***Model 3: Model 2 + adjusted by chronic physical illnesses.

Table 4. Recorded diagnoses for patients prescribed antidepressants stratified by type of antidepressant.

	Patients without CKD (N = 32,846)					
	without creatinine measurement in CPRD (N = 7,076)			with creatinine measurement in CPRD (N = 25,770)		
	SSRI N = 2,984	TCA N = 3,591	Others N = 501	SSRI N = 9,940	TCA N = 14,081	Others N = 1,749
Depression, n (%)*	1,741 (58.3)	759 (21.1)	197 (39.3)	6,382 (64.2)	3,671 (26.1)	838 (47.9)
Anxiety, n (%)*	1,030 (34.5)	646 (18.0)	133 (26.6)	3,813 (38.4)	3,256 (23.1)	575 (32.9)
Neuropathic pain, n (%)*	76 (2.6)	478 (13.3)	19 (3.8)	549 (5.5)	2,058 (14.6)	133 (7.6)
None of the above, n (%)	850 (28.5)	2,149 (59.8)	244 (48.7)	2,338 (23.5)	7,550 (53.6)	650 (37.2)

	Patients with CKD (N = 45,394)					
	eGFR 30-59 mL/min/1.73m^2 (N = 43,410)			eGFR <30 mL/min/1.73m^2 (N = 1,984)		
	SSRI N = 17,124	TCA N = 23,286	Others N = 3,000	SSRI N = 868	TCA N = 976	Others N = 140
Depression, n (%)*	10,871 (63.5)	6,017 (25.8)	1,390 (46.3)	492 (56.7)	240 (24.6)	66 (47.1)
Anxiety, n (%)*	5,904 (34.5)	4,874 (20.9)	897 (29.9)	227 (26.2)	181 (18.6)	38 (27.1)
Neuropathic pain, n (%)*	942 (5.5)	3,348 (14.4)	201 (6.7)	55 (6.3)	143 (14.7)	8 (5.7)
None of the above, n (%)	4,395 (25.7)	12,715 (54.6)	1,195 (39.8)	288 (33.2)	544 (55.7)	61 (43.6)

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants.

*Percentages are column percentages. Each patient may have one or more recorded diagnosis.

Table 5. Choice of antidepressants and initial prescription dose for patients with diagnosed depression.

	Patients without CKD (N = 13,588)				Patients with CKD (N = 19,076)			
	without creatinine measurement in CPRD N = 2,697		with creatinine measurement in CPRD N = 10,891		with eGFR 30-59 mL/min/1.73m^2 at baseline N = 18,278		with eGFR <30 mL/min/1.73m^2 at baseline N = 798	
	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]	n (%)*	Median initial dose (mg/day) [IQR]
Selective serotonin reuptake inhibitors								
Citalopram	1,051 (39.0)	10 [10 – 20]	3,883 (35.7)	10 [10 – 20]	6,760 (37.0)	10 [10 – 20]	310 (38.9)	10 [10 – 20]
Escitalopram	80 (3.0)	10 [5 – 10]	273 (2.5)	5 [5 – 10]	407 (2.2)	5 [5 – 10]	22 (2.8)	5 [5 – 10]
Fluoxetine	381 (14.3)	20 [20 – 20]	1,270 (11.7)	20 [20 – 20]	2,171 (11.9)	20 [20 – 20]	99 (12.4)	20 [20 – 20]
Fluvoxamine	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Paroxetine	35 (1.3)	20 [20 – 20]	97 (0.9)	20 [20 – 20]	133 (0.7)	20 [20 – 20]	11 (1.4)	20 [20 – 20]
Sertraline	194 (7.2)	50 [50 – 50]	859 (7.9)	50 [50 – 50]	1,399 (7.7)	50 [50 – 50]	50 (6.3)	50 [50 – 50]
Tricyclic and related antidepressants								
Amitriptyline	548 (20.3)	10 [10 – 15]	2,958 (27.2)	10 [10 – 20]	4,847 (26.5)	10 [10 – 15]	177 (22.2)	10 [10 – 15]
Clomipramine	<5 (<0.2)	n/a	22 (0.2)	20 [10 – 37.5]	27 (0.2)	20 [10 – 37.5]	<5 (<0.6)	n/a
Dosulepin	105 (3.9)	50 [25 – 75]	302 (2.8)	37.5 [25 – 75]	481 (2.6)	37.5 [25 – 50]	31 (3.9)	37.5 [25 – 75]
Doxepin	<5 (<0.2)	n/a	17 (0.2)	25 [25 – 37.5]	23 (0.1)	25 [20 – 25]	<5 (<0.6)	n/a
Imipramine	<5 (<0.2)	n/a	27 (0.3)	15 [10 – 25]	44 (0.2)	25 [10 – 30]	<5 (<0.6)	n/a
Lofepramine	26 (1.0)	70 [70 – 140]	87 (0.8)	70 [70 – 140]	179 (1.0)	70 [70 – 140]	7 (0.9)	70 [70 – 140]
Nortriptyline	10 (0.4)	15 [10 – 25]	84 (0.8)	15 [10 – 15]	155 (0.9)	10 [10 – 15]	<5 (<0.6)	n/a

Trimipramine	<5 (<0.2)	n/a	12 (0.1)	25 [15 – 37.5]	24 (0.1)	30 [15 – 50]	<5 (<0.6)	n/a
Mianserin	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Trazodone	55 (2.0)	50 [50 – 100]	158 (1.5)	50 [50 – 100]	233 (1.3)	50 [50 – 75]	17 (2.1)	50 [50 – 75]
Monoamine oxidase inhibitors**	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Other antidepressants:								
Agomelatine	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Duloxetine	15 (0.6)	60 [40 – 60]	83 (0.8)	40 [30 – 60]	164 (0.9)	40 [30 – 60]	5 (0.6)	60 [60 – 60]
Flupentixol	17 (0.6)	1 [0.5 – 1]	46 (0.4)	0.5 [0.5 – 1]	82 (0.5)	1 [0.5 – 1]	6 (0.8)	0.5 [0.5 – 0.5]
Mirtazapine	139 (5.2)	15 [15 – 15]	619 (5.7)	15 [15 – 15]	998 (5.5)	15 [15 – 15]	47 (5.9)	15 [15 – 15]
Reboxetine	<5 (<0.2)	n/a	<5 (<0.1)	n/a	<5 (<0.1)	n/a	<5 (<0.6)	n/a
Venlafaxine	19 (0.7)	75 [75 – 75]	66 (0.6)	75 [75 – 75]	94 (0.5)	75 [75 – 75]	<5 (<0.6)	n/a
Two or more different antidepressants	7 (0.3)	n/a	20 (0.2)	n/a	48 (0.3)	n/a	5 (0.6)	n/a

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range.

*Cell counts less than five have been suppressed to preserve patient privacy.

**Phenelzine, isocarboxazid, tranylcypromine and moclobemide are combined due to small sample sizes.

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- received research or educational support from a company with a vested interest in the product(s) being studied. No

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HM was funded by a Kidney Research UK studentship [ST2/2011].

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8. Manuscript title (first six words are sufficient)

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9. Author's full name (a separate form must be submitted for each author)

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