# 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 |
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[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.

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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**

**Running head:** Antidepressants in patients with chronic kidney disease

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

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**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.

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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.

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**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]

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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.

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**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

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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

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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

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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.

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**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 $\chi^2$ 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.

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from 1$^{st}$ April–31$^{st}$ 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

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(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).

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**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 ≥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

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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%;

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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.

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**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

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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

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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

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(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

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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.

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**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.

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**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. .

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**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.

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**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.

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┌─────────────────────────────────────────────────────────────────────┐
│  All adults in HES-linked CPRD between 1st April 2004 and 31st March  │
│                              2014                                     │
│                         N = 4,073,639                                 │
└─────────────────────────────────────────────────────────────────────┘
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                                        ├──────────►  ┌────────────────────────────────┐
                                        │             │ Patients already on RRT : N = 2833 │
                                        │             └────────────────────────────────┘
                                        ▼
┌─────────────────────────────────────────────────────────────────────┐
│                        All adults without RRT                         │
│                         N = 4,070,806                                 │
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        │                          │           People with CKD         │
        │                          │           N = 264,628             │
        │                          └──────────────────────────────────┘
        ▼                                              ▼
┌──────────────────────┐       ┌──────────────────────────────────────────┐
│   Matched controls*  │       │ People with CKD and a matched control available │
│   N = 242,349        │       │            N = 242,349                     │
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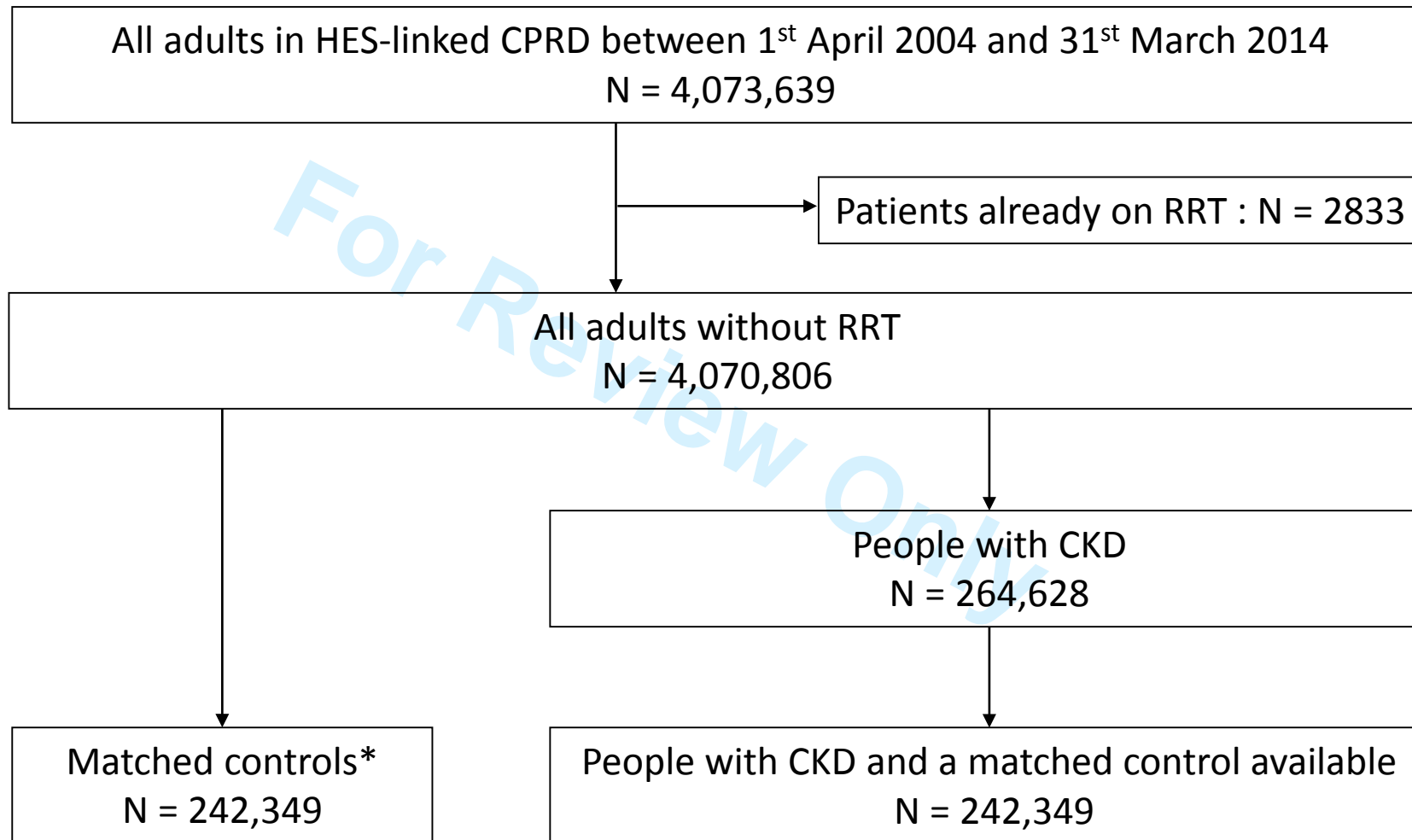
**Appendix 1.** List of diagnosis codes indicative of depression, anxiety, and neuropathic pain in Clinical Practice Research Datalink.

| 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 |

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|---|---|---|---|
| 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 | TCA | Others | SSRI | TCA | Others |
| | N = 2,984 | N = 3,591 | N = 501 | N = 9,940 | N = 14,081 | 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 | TCA | Others | SSRI | TCA | Others |
| | N = 17,124 | N = 23,286 | N = 3,000 | N = 868 | N = 976 | 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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## CONFLICT OF INTEREST DISCLOSURE

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8. Manuscript title (first six words are sufficient)

Prevalence, incidence, indication and choice of antidepressant

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

Masao Iwagami

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Laurie Alexandra Tomlinson

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Kathryn Elizabeth Mansfield

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Helen Isabel McDonald

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Liam Smeeth

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Dorothea Nitsch

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