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Clinical Correlates of Antidepressant Use in a Secondary Mental Health Care Setting

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Abstract

Objective: To investigate the association between clinical correlates and antidepressant use in a psychiatric healthcare setting using a retrospective cohort study design.

Setting: Data was extracted from an interactive database sourced from a secondary psychiatric electronic register based in South East London. Relative risk ratio estimates were obtained from multinomial logistic regression analysis to ascertain the probability of receiving common antidepressant treatments relative to Sertraline.

Participants: Patients were included if they received active care (defined as at least one face-to-face contact with the service) and a clinical diagnoses of depression with antidepressant treatment between 1st March 2015 and 31st August 2015. Patients were excluded if they did not receive any antidepressants or received a combination of three of more antidepressants.

Results: Age was associated with increased use of all antidepressants, except for Fluoxetine (RRR 0.98; 95% CI 0.96 – 0.98) and a combination of two SSRIs (0.98; 0.96 – 0.99). Male gender was associated with increased use of mirtazapine compared to female patients (2.57; 1.85 – 3.57). Past antidepressant use, past antipsychotic and mood stabiliser use were associated with newer antidepressant use (i.e. SNRIs, mirtazapine or a combination of both). Affective symptoms were associated with reduced use of citalopram (0.58; 0.27 – 0.83) and fluoxetine (0.42; 0.22 – 0.72) and somatic symptoms were associated with increased use of mirtazapine (1.60; 1.00 – 2.75) relative to sertraline. Furthermore, in adults, past benzodiazepine use was associated with a combination of SSRIs (2.97; 1.32 – 6.68), mirtazapine (1.94; 1.20 – 3.16) and venlafaxine (1.87; 1.04 – 3.34), whilst past suicide attempts were associated with increased use of fluoxetine (2.06; 1.10 – 3.87) relative to sertraline.

Conclusion: There were some associations of patient and clinical correlates with antidepressant treatment use, which contributes towards understanding the association of antidepressants with suicidality.

Keywords: antidepressant use; depressive disorders; secondary care; psychiatric service; clinical factors; antidepressant prescription

Strengths and Limitations of this study

- This is the first study profiling antidepressant use in a cohort of treatment resistant patients receiving treatment in a secondary mental health care setting in the UK.
- The data included hard to measure variables such as depressive symptoms owing to the use of text mining algorithms.
- Using antidepressant data in a 6-month window limited sample sizes included in analysis hence while trends were detected in univariate analysis (past medication use, past symptom experience) they disappeared in the fully adjusted analysis.
- The study is cross-sectional and any significant results do not indicate any direct causal relationship.
- The duration of the antidepressant treatment during the observation period was not known and this could hinder interpretation of the results given some patients were new users of the antidepressants, while others could be using the antidepressants for longer periods of time.

Introduction

There are standard national guidelines directing antidepressant prescription in secondary care [1]; however in practice a range of patient and clinician characteristics may influence this [1,2] because those seen by secondary services are a select group, skewed towards patients with treatment-resistant moderate to severe disorders [3]. Studies profiling antidepressant prescription in secondary care can highlight factors that play a key role in managing treatment-resistant depression and individuals with exacerbated symptom profiles. British guidelines for the management of depression in secondary care specify that care plans should involve, among other things, the development of a crisis plan that identifies and details management of potential triggers for a depressive episode or a worsening of existing symptoms [1]. Knowledge of factors involved in antidepressant prescription can provide a pragmatic idea of how antidepressants are being prescribed, how this reflects existing guidelines and can help inform policy and practice.

Studies to date profiling antidepressant prescriptions have established that patient-clinician relationships, past experiences and patient symptoms can influence antidepressant prescription; however, these have been set in primary care [4–7] and there are few studies investigating factors associated with antidepressant use in a secondary mental healthcare setting [8,9]. To the best of our knowledge there has not been a study profiling antidepressant prescription in the UK, outside of primary care [10,11]. The objective of our study was to investigate which clinical symptoms (including previous suicide attempts), past treatment and demographic factors are associated with different antidepressant treatment schedules in a mental healthcare setting.

Methods

The Dataset

The Clinical Record Interactive Search (CRIS) system provides de-identified case note information from the South London and Maudsley (SLaM) NHS Trust, a large mental healthcare provider serving a geographic catchment of approximately 1.3 million residents in four south London boroughs (Lambeth, Southwark, Lewisham, and Croydon). Electronic health records (EHRs) have been used comprehensively across all SLaM services since 2006. CRIS was established in 2008 to allow searching and retrieval of de-identified [12] clinical information for research purposes within a robust, patient-led governance framework, and currently houses records on over 250,000 cases [13,14]. The system allows for retrieval of information from de-identified structured and free-text fields, and the use of CRIS for research was approved by the Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5). Patient consent was not required due to research data being pseudonymised.

Observation Window and Inclusion Criteria

A 6-month interval from 1st March to 31st August 2015 was selected as the observation period where type of antidepressant use, defined as single antidepressant use and antidepressants users on two antidepressants (referred to here as binary antidepressant use) represented the main dependent variable. All antidepressant use groups were mutually exclusive as described in the next section. Independent variables (demographic and clinical variables) were extracted 12 months prior to the observation window and their associations with antidepressant use within the observation window were analysed.

Patients were included if they received active SLaM care between 1st March 2015 and 31st August 2015, and had received any of the following clinical diagnoses according to 10th Revision of the International Classification of Diseases (ICD-10) codes on or before the 31st of August 2015: Depressive episode (F32), Recurrent depressive disorder (F33), Dysthymia (F34.1), and/or Mixed Anxiety and Depression (F41.2). Individuals were excluded if they had received any F01 – F09 (Dementia and Alzheimer's), F20 – F29 (Schizophrenia and Schizoaffective disorders) or F31 (bipolar disorders) diagnoses on or before the 31st of August 2015. Active care was defined as at least one face-to-face contact with SLaM service within the observation window. Patients were excluded if they did not receive any antidepressants during the window or if they received a combination of three of more antidepressants during this window.

Antidepressant Use

Antidepressant use data was ascertained using text mining software, GATE and TextHunter, [15] designed to extract data specifically on any medication recorded in free-text fields (e.g. case notes, correspondence). Details of the development of this algorithm have previously been published [14,16]. For each patient in the final cohort, any antidepressant use (regardless of the stage of antidepressant use) during the observation window was extracted as a binary variable. The antidepressants for which data were collected comprised the following: i) tricyclic and tricyclic related - amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, mianserin and trazodone; ii) mono-amine oxidase inhibitors (MAOIs) - isocarboxazid, phenelzine, tranylcypromaine and moclobemide; iii) Selective Serotonin Re-uptake Inhibitors (SSRIs) - sertraline, fluoxetine, citalopram, escitalopram, fluvoxamine and paroxetine; iv) Selective Norepinephrine Reuptake Inhibitors (SNRIs) - venlafaxine, reboxetine and duloxetine; and v) Other classes - agomelatine, bupropion, and mirtazapine.

The final cohort comprised 1,561 patients. The most common mutually exclusive monotherapy antidepressant used within the 6-month window was sertraline (360 patients), followed by mirtazapine (305), citalopram (213), fluoxetine (200), venlafaxine (143), escitalopram (52). The most common mutually exclusive double antidepressant combinations were any one SSRI with mirtazapine (110), any one SNRI with mirtazapine (89) and a combination of any two SSRIs (89). Groups with less than 50 patients or with more than two antidepressants being used in combination were excluded from the analysis to avoid low sample sizes and inaccurate representation of antidepressant use. All antidepressant groups were mutually exclusive.

Clinical Determinants included in the Study

Apart from demographic variables, all other covariate data was extracted from data recorded in the 12 months prior to the observation window. Demographic variables were recorded in structured fields, but all other data variables (listed below) were individually extracted using GATE and TextHunter, two text mining software tools which can be programmed to extract data from free-text notes via rules-based and machine learning techniques, respectively. All clinical symptom data variables were extracted using TextHunter. Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the same period.

Demographic variables: Ethnicity, age, gender, marital status and area-level deprivation score; latest diagnostic code (this served as a proxy indicator of severity of depression)**; Past medication/therapy use:** Non-antidepressant medication data: antipsychotic, benzodiazepine, mood stabilizer and antidepressant use in the past 12 months; **Patient Referral data:** Length of current referral and having been an inpatient in the past 12 months; **Non-medication therapies:** Psychotherapy in the past 12 months and referral to IAPT services**. Clinical symptom data collected were Past psychotic symptoms:** Hallucinations and delusions; **Patients' past depressive symptoms**: 14 symptoms of depression were extracted from TextHunter. To avoid small patient groups for analysis, depressive symptoms were clustered together. Deciding which symptoms to cluster together was based on results from a study using confirmatory factor analysis on the Beck Depressive Inventory-II (Beck et al, 1996) using an at risk (clinical) psychiatric population[17]. There is evidence for grouping the Beck Inventory items into three factors: Somatic, Affective and Cognitive. Studies have supported these findings[18,19] or generated two different factors in older populations[20]. Hence the groupings are as follows: ***Cognitive symptoms***: helplessness, worthlessness and hopelessness; ***Affective symptoms***: anhedonia, poor motivation, apathy and low mood; ***Somatic symptoms***: poor concentration, agitation, irritability, low energy, insomnia, poor appetite and anergia. **Suicidal behaviour:** suicidal ideation, suicide attempt in the past 12 months.

Statistical Analysis

Group differences were analysed using Chi-squared tests for categorical variables and t-tests or one-way ANOVAs for normally distributed continuous variables, or the Kruskal-Wallis test for non-normally distributed continuous data. Multinomial logistic regression analyses were used to answer the research question. The probability of receiving any of the common antidepressant treatments relative to sertraline (the referent antidepressant class, since it consisted of the most patient users) was estimated using exponentiated regression coefficients from the multinomial regression which represents Relative Risk Ratios (RRR). In order to build a representative model of which correlates predict antidepressant use in secondary care, decisions to include variables in the final model were guided by the contribution of each variable in an initial model including age and gender as covariates. Variables that did not have any significant associations in age- and gender- adjusted analysis were not included in the final model. For initial selection based on age- and gender- adjusted analysis, the significance was set at $p \leq 0.25$ [21]. This was to help minimise i) exclusion of potentially key covariates and ii) inclusion of $p < 0.05$ significant estimates occurring by chance. The selected variables were then

simultaneously entered in a full model. In the fully adjusted model significance level was set at $p < 0.05$ for retaining variables. The correlates retained in the final multinomial regression model were age, gender, past inpatient status, past benzodiazepine use, past antipsychotic use, past mood stabiliser use, past antidepressant use, past psychotherapy and IAPT referrals, past experience of psychotic, somatic, affective and cognitive symptoms; and past experience of suicidal ideation and past suicide attempts. In addition, separate analysis was conducted in the adult group only (i.e. 26 years or older) because most of the patient cohort consisted of adults (See Cohort demographics in Table 1) and different factors may need to be taken into consideration when considering prescriptions of antidepressants to children, adolescents and young people relative to adults [1,22].

Results

Table 1 compares each antidepressant or antidepressant combination by demographics, referral data, past medication use and past psychological therapy referral. The demographic and clinical differences between the antidepressant groups are statistically significant apart from ethnicity, area deprivation and having had a past referral for psychotherapy. Notably, a majority of young patients receive fluoxetine, whilst the older patients are on a combination of newer antidepressants such as mirtazapine and a SNRI; there are more males receiving mirtazapine than females; most of the antidepressant users are single, and only a minority have had non-antidepressant treatment or psychotherapy in the past. Table 2 indicates that the majority of patients have a moderate to severe diagnosis of depression, a large majority of whom have not experienced suicidal ideation or attempted suicide. Apart from severity and past psychotic symptoms, for all other past depressive symptoms and past suicidal ideation and attempts, the analysis indicated significant heterogeneity across the antidepressant user groups. Tables 3 and 4 show the Relative Risk Ratio (RRR), estimating the probability of patients being on any antidepressant relative to sertraline (the most common antidepressant received in our cohort), derived from the fully adjusted multinomial logistic regression models in the entire cohort and the adult-only cohort respectively.

Table 3 shows that relative to females, males are more likely to be on mirtazapine relative to sertraline. It also indicates that patients on newer antidepressants are more likely to have used non-antidepressant medication or been on antidepressants in the past. Those on citalopram or fluoxetine are less likely to have experienced affective symptoms (such as low mood and poor motivation) in the past compared to those on sertraline, whilst those who have experienced somatic symptoms (such as insomnia and agitation) in the past are more likely to be on mirtazapine relative to sertraline.

The results from the adult-only analysis (Table 4) again show increased likelihood of males being on mirtazapine compared to females. They also show that relative to sertraline, patients on citalopram or fluoxetine are less like to have experienced severe affective symptoms. Patients on mirtazapine are more likely to have experienced somatic symptoms relative to sertraline compared to those who experienced milder symptoms. Of note, in the adult-only analysis patients on fluoxetine were more likely to have made at least one suicide attempt in the past 12 months relative to those on sertraline.

Discussion

The aim of this study was to ascertain patient demographic and clinical characteristics that correlate with antidepressant use in patients actively receiving secondary health care for clinical depression. While there were no notable trends that suggested definite demographics, medication or depressive clinical symptoms may be associated with antidepressant use, our results suggest that in adults age, gender, past medication use and having made suicide attempts in the past 12 months are some of the factors that could contribute to antidepressant use in secondary care.

We found that with every unit increase in age, patients are less likely to be using fluoxetine or a combination of two SSRIs relative to sertraline. Comparable to our study, a large scale study using a cohort of war veterans with a diagnosis of depression (Veterans' Affairs [VA] dataset; N = 507,179)[9] to investigate whether patient and clinical variables were predictors of newly initiated antidepressant use, found that relative to younger patients, older patients were less likely (RRR 0.70; 95% CI: 0.67- 0.73) to have started on fluoxetine than sertraline. We also found that men, compared to women, are more likely to use mirtazapine relative to sertraline. Mirtazapine has been shown to have lower incidence of sexual dysfunction side-effects [23] and may be more likely to be prescribed to men.

Our results also suggest that, in adults, past suicide attempts were associated with increased likelihood of using fluoxetine relative to sertraline, which may reflect the evidence collated from meta-analyses of randomized controlled trials and observation studies where fluoxetine has been shown to carry reduced risk of suicidal behaviour in adults compared to children and adolescents[24–26]. There are indications in our analysis that patients on past non-antidepressant and antidepressant medication are more likely to be on newer antidepressants such as mirtazapine and venlafaxine or a combination of low toxicity antidepressants. As this cohort may predominantly consistent of individuals' with some resistance to first line antidepressant treatment, it may follow that these individuals were on other medication in the past and have now been switched to newer antidepressants.

The lack of notable trend of covariates associated with antidepressant use potentially suggests that antidepressants may be prescribed based on individual experiences after patient-clinician communication, which supports the advice set by the British guidelines emphasising patient-clinician communication. However, the current study only provides speculative indication and further qualitative studies may be able to confirm this.

The results have to be interpreted with study limitations in mind. Firstly, using antidepressant data in a 6-month window limited sample sizes included in analysis. So while trends were detected in univariate analysis

(past medication use, past symptom experience) they disappeared in the fully adjusted analysis. Secondly, the study is cross-sectional and any significant results do not indicate any direct causal relationship. Thirdly, the duration of the antidepressant treatment during the observation period was not known and this could hinder interpretation of the results given some patients were new users of the antidepressants, while others could be using the antidepressants for longer periods of time. The results of the study may not be generalizable to patients in other secondary psychiatric healthcare settings due to the potential ethnic diversity found in south east London where this study is based. Finally, we could only investigate factors that were available to us in the current dataset. The literature reports various clinical covariates[8], patient demographics[9], medication use[27], clinician characteristics[28] and clinical location[8,9] as factors involved for antidepressant prescription in secondary mental healthcare settings. We could not account for all these factors in our analysis.

Limitations notwithstanding there are key strengths to this paper. To our knowledge this is the first study profiling antidepressant use in a cohort of treatment resistant patients receiving treatment in a secondary mental health care setting in the UK. In addition, the data included hard to measure variables such as depressive symptoms owing to the use of text mining algorithms which allows for capture of data recorded in free-text and circumvented the need to use data from structured fields.

The individual significant findings could inform clinical practice within this clinical setting. Knowledge of factors involved in antidepressant prescription could be used to audit clinical practices and inform whether the clinical practices are benefitting patient treatment outcomes[29]. Further qualitative work could highlight main themes involved in selecting antidepressant treatment. Continual monitoring of treatment choices in this cohort may contribute to providing optimal care for secondary care patients.

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Contributors: RS, RD and AF conceived of the study and were responsible for the design and search strategy. AF, HS and DC were responsible for data extraction. AF was responsible for conducting the analysis and producing the tables. The analysis was guided by MD initially and then MK. The initial draft of the manuscript was prepared by AF then circulated among all authors for revision. All authors helped to evolve analysis plans, interpret data and critically revise successive drafts of the manuscript.

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Statement on manuscript: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1: Demographics, Patient Referral data, Past Medication use and Past Psychological Therapy characteristics by Common Antidepressant User Groups

	Any one SNRI and Mirtazapine (89)	Any one SSRI and Mirtazapine (110)	Any two SSRIs (89)	Citalopram (213)	Escitalopram (52)	Fluoxetine (200)	Mirtazapine (305)	Sertraline (360)	Venlafaxine (143)	Total 1561	Test statistic; p-value [c, d]
DEMOGRAPHICS											
Mean Age in years [SD]	52.9 [16.6]	48.6 [18.6]	34.1 [16.2]	42.7 [15.5]	44.1 [16.3]	33.3 [16.0]	49.2 [18.8]	39.3 [16.8]	48.8 [18.1]	1561	25.38; <0.001
Gender: Female	60 (67.4%)	65 (59.6)	64 (71.9)	147 (69)	35 (67.3)	139 (69.5)	138 (45.2)	251 (69.7)	91 (63.6)	990	60.07;
Male	29 (32.6%)	44 (40.4)	25 (28.1)	66 (31)	17 (32.70)	61 (30.5)	167 (54.8)	109 (30.3)	52 (36.4)	571	<0.001
Ethnicity: White	61 (68.5%)	69 (62.7)	49 (55.1)	135 (63.4)	39 (75)	127 (63.5)	176 (57.7)	213 (59.2)	101 (70.6)	970	15.70;
Other	28 (31.5%)	41 (37.3)	40 (44.9)	78 (36.6)	13 (25)	73 (36.5)	129 (42.3)	147 (40.8)	42 (29.4)	591	0.05
Marital Status: Single	34 (38.2%)	61 (55.5)	47 (52.8)	127 (59.6)	25 (48.1)	133 (66.5)	169 (55.4)	216 (60)	79 (55.2)	891	df = 16;
Married	31 (34.8%)	26 (23.6)	24 (27.0)	40 (18.8)	18 (34.6)	23 (11.5)	72 (23.6)	80 (22.2)	35 (24.5)	349	37.40;
Other	24 (27%)	23 (20.9)	18 (20.2)	46 (21.6)	9 (17.3)	44 (22)	64 (21)	64 (17.8)	29 (20.3)	321	0.002
[a]1st Tertile (2.25 – 22.3)	29 (32.6%)	27 (25.5)	31 (34.8)	62 (29.5)	20 (38.5)	64 (32.3)	82 (27.2)	122 (34.5)	60 (42.9)	497	df = 16;
2nd Tertile	50 (56.2%)	67 (63.2)	44 (49.4)	131 (62.4)	26 (50)	120 (60.6)	184 (60.9)	205 (57.9)	71 (50.7)	898	26.33;
3rd Tertile (42.3 – 62.3)	10 (11.2%)	12 (11.3)	14 (15.7)	17 (8.1)	6 (11.5)	14 (7.1)	36 (11.9)	27 (7.6)	9 (6.4)	145	0.05
REFERRAL DATA											
Length of Spell: Mean years (SD)	0.91 [2.45]	0.94 [1.94]	0.51 [0.77]	0.80 [2.80]	1.04 [1.50]	0.81 [1.16]	0.90 [1.64]	0.73 [1.27]	1.40 [3.00]		2.00; 0.043
Past[b] Inpatient at SLaM: Yes	16 (18%)	24 (21.8)	16 (18)	18 (8.5)	3 (5.8)	13 (6.5)	32 (10.5)	47 (13.1)	16 (11.2)	185	27.64
No	73 (82%)	86 (78.2)	73 (82)	195 (91.5)	49 (94.2)	187 (93.5)	273 ()89.5	313 (86.9)	127 (88.8)	1376	<0.001
PAST[b] MEDICATION USE											
Benzodiazepine Use: Yes	26 (29.2%)	25 (22.7)	19 (21.4)	35 (16.4)	11 (21.2)	21 (10.5)	71 (23.3)	55 (15.3)	36 (25.2)	299	28.01
No	63 (70.8%)	85 (77.3)	70 (78.6)	178 (83.6)	41 (78.8)	179 (89.5)	234 (76.7)	305 (84.7)	107 (74.8)	1262	<0.001
Antipsychotic Use: Yes	39 (43.8%)	35 (31.8)	22 (24.7)	46 (21.6)	18 (34.6)	41 (20.5)	97 (31.8)	92 (25.6)	53 (37.1)	443	32.07;
No	50 (56.2%)	75 (68.2)	67 (75.3)	167 (78.4)	34 (65.4)	159 (79.5)	208 (68.2)	268 (74.4)	90 (62.9)	1118	<0.001
Mood Stabiliser Use: Yes	13 (14.6%)	7 (6.4)	5 (5.6)	8 (3.8)	6 (11.5)	10 (5)	19 (6.2)	15 (4.2)	21 (14.7)	104	33.48
No	76 (85.4%)	103 (93.6)	84 (94.4)	205 (96.2)	46 (88.4)	190 (95)	286 (93.8)	345 (95.8)	122 (85.3)	1457	<0.001
Antidepressant Use: Yes	82 (92.1%)	86 (78.2)	61 (68.5)	132 (62)	41 (78.8)	150 (75)	233 (76.4)	273 (75.8)	114 (79.7)	1172	38.43;
No	7 (7.9%)	24 (21.8)	28 (31.5)	81 (38)	11 (21.2)	50 (25)	72 (23.6)	87 (24.2)	29 (20.3)	389	<0.001
PAST[b] PSYCHOLOGICAL THERAPY REFERRAL											
Psychotherapy Referral: Yes	13 (14.6%)	18 (16.4)	11 (12.4)	14 (6.6)	7 (13.5)	22 (11)	29 (9.5)	46 (12.8)	19 (13.3)	179	11.03
No	76 (85.4%)	92 (83.6)	78 (87.6)	199 (93.4)	45 (86.5)	178 (89)	276 (90.5)	314 (87.2)	124 (86.7)	1382	0.200
IAPT Referral: Yes	51 (57.3%)	50 (45.5)	40 (44.9)	108 (50.7)	27 (51.9)	77 (38.5)	131 (42.9)	181 (50.3)	58 (40.6)	723	17.21
No	38 (42.7%)	60 (54.5)	49 (55.1)	105 (49.3)	25 (48.1)	123 (61.5)	174 (57.1)	179 (49.7)	85 (59.4)	838	0.028

a – Area-level Deprivation Tertiles (1st Tertile: Least Deprived; 3rd Tertile: Most Deprived); b – "Past" refers to the 12 months prior to the observation window. ; Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period; c –ANOVA, Chi-square test, t-tests or the Kruskal-Wallis tests were conducted to test differences between patient groups; d - degree of freedom (df) = 8, unless otherwise specified.

Table 2: Depression Severity and Past Clinical Symptoms Groups by Common Antidepressant User Groups

	Any one SNRI and Mirtazapine (89)	Any one SSRI and Mirtazapine (110)	Any two SSRIs (89)	Citalopram (213)	Escitalopram (52)	Fluoxetine (200)	Mirtazapine (305)	Sertraline (360)	Venlafaxine (143)	Total (1561)	Test statistic; p-value[c, d]
DEPRESSION SEVERITY											
Depression Severity: Mild	16 (18)	22 (20)	19 (21.4)	33 (15.5)	14 (26.9)	41 (20.5)	57 (18.7)	79 (21.9)	22 (15.4)	303	df = 16;
Moderate to Severe	49 (55)	50 (45.5)	37 (41.6)	91 (42.7)	18 (34.6)	84 (42)	185 (60.7)	165 (45.8)	60 (42)	739	17.44
Other	13 (14.6)	13 (11.8)	15 (16.9)	45 (21.1)	9 (17.3)	29 (14.5)	52 (17.1)	59 (16.4)	34 (23.8)	269	0.358
PAST SYMPTOMS[b]											
Past Psychotic Symptoms:											
Zero to One mention	68 (76.4)	77 (70)	70 (78.7)	176 (82.6)	46 (88.5)	168 (84)	238 (78.1)	293 (81.4)	112 (78.3)	1248	14.33;
>= 2 mentions	21 (23.6)	33 (30)	19 (21.3)	37 (17.4)	6 (11.5)	32 (16)	67 (21.9)	67 (18.6)	31 (21.7)	313	0.073
Past Cognitive Symptoms:											
Zero to One mention	62 (69.7)	78 (70.9)	68 (76.4)	186 (87.3)	45 (86.5)	179 (89.5)	254 (83.3)	293 (81.4)	111 (77.6)	1276	34.50;
>= 2 mentions	27 (30.3)	32 (29.1)	21 (23.6)	27 (12.6)	7 (13.5)	21 (10.5)	51 (16.7)	67 (18.6)	32 (22.4)	285	<0.001
Past Affective Symptoms:											
Zero to One mention	29 (32.6)	40 (36.4)	33 (37.1)	119 (55.9)	24 (46.2)	110 (55)	113 (37.1)	131 (36.4)	52 (36.4)	651	46.24
>= 2 mentions	60 (67.4)	70 (63.6)	56 (62.9)	94 (44.1)	28 (53.8)	90 (45)	192 (62.9)	229 (63.6)	91 (63.6)	910	<0.001
Past Somatic Symptoms:											
Zero to One mention	39 (43.8)	57 (51.2)	49 (55.1)	154 (72.3)	34 (65.4)	134 (67)	155 (50.8)	203 (56.4)	85 (59.4)	900	42.07;
>= 2 mentions	50 (56.2)	53 (48.1)	40 (44.9)	59 (27.7)	18 (34.6)	66 (33)	150 (49.2)	157 (43.6)	58 (40.6)	651	<0.001
PAST SUICIDALITY											
Past Suicide Ideation: Yes	33 (37.1)	38 (34.5)	30 (33.7)	40 (18.8)	10 (19.2)	44 (22)	78 (25.6)	101 (28.1)	35 (24.5)	409	22.12;
No	56 (62.9)	72 (65.5)	59 (66.3)	173 (81.2)	42 (80.8)	156 (78)	227 (74.4)	259 (71.9)	108 (75.5)	1152	<0.05
Past Suicide Attempt: Yes	20 (22.4)	34 (30.9)	30 (33.7)	39 (18.3)	6 (11.5)	48 (24)	65 (21.3)	77 (21.4)	32 (22.4)	351	17.37;
No	69 (77.5)	76 (69.1)	59 (66.3)	174 (81.7)	46 (88.5)	152 (76)	240 (76.7)	283 (78.6)	111 (77.6)	1210	<0.05

b – "Past" refers to the 12 months prior to the observation window; Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period

c –ANOVA, Chi-square test, t-tests or the Kruskal-Wallis tests were conducted to test differences between patient groups;

d - degree of freedom (df) = 8, unless otherwise specified.

Table 3: Fully adjusted Relative Risk Ratio estimates from Multinomial Logistic Regression models with sertraline as the Referent Group in the Entire Cohort (N = 1561)

	Any one SNRI and Mirtazapine	Any one SSRI and Mirtazapine	Any two SSRIs	Citalopram	Escitalopram	Fluoxetine	Mirtazapine	Venlafaxine
Age	**1.05 (1.03 – 1.04)‡**	**1.03 (1.02 – 1.04)‡**	**0.98 (0.96 – 0.99)‡‡**	**1.01 (1.00 – 1.02)‡‡**	1.01 (0.99 – 1.03)	**0.98(0.96 – 0.98)‡**	**1.03 (1.02 – 1.04)‡**	**1.03 (1.02 – 1.03)‡**
Gender (a)	0.97 (0.57 – 1.76)	1.33 (0.84 – 2.09)	0.95 (0.56 – 1.61)	0.95 (0.65 – 1.39)	1.07 (0.56 – 2.01)	1.08 (0.73 – 1.60)	**2.57 (1.85 – 3.57)‡**	1.16 (0.76 – 1.76)
Past Inpatient: Yes (b)	1.09 (0.47 – 1.54)	1.26 (0.59 – 2.70)	0.97 (0.42 – 2.27)	0.80 (0.43 – 1.88)	0.60 (0.14 – 2.60)	0.48 (0.21 – 1.07)	0.68 (0.37 – 1.27)	0.70 (0.32 – 1.54)
Past Benzodiazepine Use: Yes (b)	1.30 (0.70 – 2.81)	1.03 (0.55 – 1.90)	1.63 (0.82 – 3.25)	1.60 (0.94 – 2.73)	1.77 (0.78 – 4.01)	0.97 (0.53 -1.77)	1.58 (1.00 – 2.50)	1.63 (0.94 – 2.81)
Past Antipsychotic Use: Yes (b)	**1.78 (1.03 – 2.36)‡‡**	1.17 (0.69 – 1.99)	0.91 (0.49 – 1.70)	0.99 (0.63 – 1.60)	1.53 (0.77 – 3.07)	0.74 (0.46 – 1.17)	1.19 (0.80 – 1.75)	1.47 (0.91 – 2.36)
Past Mood Stabiliser Use: Yes (b)	**2.38 (1.04 – 6.34)‡‡**	1.23 (0.47 – 3.20)	1.50 (0.50 – 4.36)	0.99 (0.40 – 2.42)	2.60 (0.93 – 7.27)	1.65 (0.71 - 3.86)	1.23 (0.60 – 2.55)	**2.96 (1.44 – 6.08)‡‡**
Past Antidepressant Use: Yes (b)	**3.06 (1.34 – 7.85)‡‡**	0.95 (0.50 – 1.78)	0.59 (0.31 – 1.10)	0.76 (0.48 – 1.20)	1.27 (0.55 – 2.94)	1.42 (0.88 – 2.30)	0.98 (0.63 – 1.53)	1.10 (0.62 – 1.96)
Has had Psychotherapy treatment before: Yes (b)	0.67 (0.31 – 1.51)	0.91 (0.45 – 1.75)	0.88 (0.42 – 1.86)	**0.51 (0.27 – 0.98)‡‡**	1.17 (0.48 – 2.89)	0.91 (0.51 – 1.64)	**0.55 (0.32 – 0.94)‡‡**	0.81 (0.43 – 1.52)
Has been referred to IAPT services: Yes (b)	**1.90 (1.15 – 1.91)‡‡**	1.02 (0.65 – 1.60)	0.81 (0.50 – 1.33)	0.96 (0.68 – 1.37)	1.18 (0.64 – 2.17)	**0.62 (0.43 - 0.91)‡**	0.88 (0.63 – 1.22)	0.79 (0.53 – 1.20)
Psychotic Symptom:>2 mentions (c)	0.82 (0.38 – 1.89)	1.54 (0.72 – 2.71)	1.00 (0.58 – 2.12)	1.53 (0.95 – 3.00)	0.67 (0.26 – 2.26)	1.42 (0.79 – 2.51)	1.16 (0.64 – 1.73)	1.17 (0.54 – 1.90)
Cognitive Symptom:>2 mentions (c)	1.37 (0.67 – 2.67)	1.40 (0.72 – 2.76)	1.18 (0.56 – 2.47)	0.94 (0.54 – 1.87)	0.96 (0.30 – 2.17)	0.77 (0.39 – 1.44)	0.72 (0.49 – 1.38)	1.32 (0.76 – 2.67)
Affective Symptom: >2 mentions (c)	0.53 (0.28 – 1.31)	0.60 (0.24 – 1.13)	0.93 (0.33 – 1.66)	**0.58 (0.27 – 0.83)‡‡**	0.72 (0.31 – 1.87)	**0.42 (0.22 – 0.72)‡**	0.79 (0.41 – 1.18)	0.92 (0.36 – 1.32)
Somatic Symptom: >2 mentions (c)	1.40 (0.63 – 1.78)	1.02 (0.65 – 2.84)	0.92 (0.47 – 2.33)	0.65 (0.36 – 1.16)	0.84 (0.39 – 2.40)	1.10 (0.62 – 1.97)	**1.60 (1.00 – 2.75)‡‡**	0.70 (0.50 – 1.80)
Past Suicide Ideation: Yes (b)	1.34 (0.76 – 1.33)	1.07 (0.62 – 1.86)	1.04 (0.57 – 1.90)	0.80 (0.50 – 1.29)	0.75 (0.34 – 1.68)	0.88 (0.55 – 1.42)	0.90 (0.60 – 1.36)	0.79 (0.47 – 1.33)
Past Suicide Attempt: Yes (b)	1.01 (0.51 – 2.05)	1.49 (0.82 – 2.68)	1.74 (0.95 – 3.19)	1.23 (0.74 – 2.05)	0.66 (0.25 – 1.74)	1.57 (0.97 – 2.54)	1.13 (0.72 – 1.77)	1.18 (0.67 – 2.06)

p-value: ‡ <0.05; ‡‡ < 0.001
a – Reference: Female
b – Reference: No
c – Reference: 0 or 1 mention of the symptom. Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period.

Table 4: Fully adjusted Relative Risk Ratio estimates from Multinomial Logistic Regression models with sertraline as the Referent Group in the adult-only sample (N = 1248)

	Any one SNRI and Mirtazapine	Any one SSRI and Mirtazapine	Any two SSRIs	Citalopram	Escitalopram	Fluoxetine	Mirtazapine	Venlafaxine
Age	**1.04 (1.02 – 1.05)‡**	**1.03 (1.01 – 1.04)‡**	0.99 (0.97 – 1.01)	1.00 (0.99 – 1.02)	1.00 (0.98 – 1.03)	0.99 (0.98 – 1.01)	**1.03 (1.02 – 1.04)‡**	**1.02 (1.01 – 1.04)‡**
Gender (a)	0.87 (0.51 – 1.50)	1.29 (0.79 – 2.11)	0.89 (0.47 – 1.69)	0.89 (0.59 – 1.35)	1.04 (0.52 – 2.07)	1.25 (0.78 – 2.00)	**2.36 (1.64 – 3.37)‡**	1.10 (0.70 – 1.73)
Past Inpatient: Yes (b)	1.10 (0.45 – 2.69)	0.96 (0.40 – 2.24)	0.30 (0.07 – 1.26)	0.83 (0.36 – 1.95)	0.50 (0.09 – 3.23)	0.50 (0.18 – 1.37)	0.62 (0.31 – 1.24)	0.61 (0.25 – 1.47)
Past Benzodiazepine Use: Yes (b)	1.46 (0.76 – 2.78)	1.25 (0.65 – 2.41)	**2.97 (1.32 – 6.68)‡‡**	1.61 (0.89 – 2.90)	1.90 (0.80 – 4.49)	1.13 (0.57 – 2.24)	**1.94 (1.20 – 3.16)‡‡**	**1.87 (1.04 – 3.34)‡‡**
Past Antipsychotic Use: Yes (b)	**2.02 (1.14 – 3.58)‡‡**	1.30 (0.73 – 2.32)	1.02 (0.46 – 2.26)	1.08 (0.66 – 1.80)	1.55 (0.73 – 3.30)	1.02 (0.57 – 1.80)	1.16 (0.76 – 1.78)	1.53 (0.92 – 2.57)
Past Mood Stabiliser Use: Yes (b)	2.26 (0.97 – 5.30)	1.03 (0.37 – 2.90)	1.17 (0.31 – 4.44)	0.78 (0.30 – 2.14)	2.67 (0.91 – 7.76)	1.75 (0.68 – 4.47)	1.27 (0.60 – 2.71)	**2.76 (1.28 – 5.97)‡‡**
Past Antidepressant Use: Yes (b)	**2.70 (1.07 – 6.86)‡‡**	0.81 (0.41 – 1.61)	**0.44 (0.20 – 0.95)‡‡**	0.72 (0.43 – 1.21)	2.07 (0.43 – 5.54)	1.07 (0.20 – 1.96)	0.83 (0.50 – 1.36)	1.09 (0.60 – 2.05)
Has had Psychotherapy treatment before: Yes (b)	0.80 (0.36 – 1.76)	1.30 (0.64 – 2.63)	0.95 (0.33 – 2.71)	0.52 (0.24 – 1.15)	1.75 (0.66 – 4.57)	1.12 (0.51 – 2.44)	0.68 (0.38 – 1.23)	0.86 (0.43 – 1.73)
Has been referred to IAPT services: Yes (b)	**2.04 (1.20 – 3.48)‡‡**	0.99 (0.60 – 1.62)	0.93 (0.50 – 1.73)	1.00 (0.67 – 1.50)	1.36 (0.70 – 2.66)	0.98 (0.61 – 1.68)	0.93 (0.64 -1.34)	0.83 (0.53 – 1.31)
Psychotic Symptom:>2 mentions (c)	0.81 (0.39 – 1.69)	1.67 (0.85 – 3.26)	0.88 (0.36 – 2.22)	1.70 (0.94 – 3.09)	0.70 (0.23 – 2.13)	1.45 (0.75 – 2.81)	1.24 (0.75 -2.06)	1.19 (0.63 – 2.23)
Cognitive Symptom:>2 mentions (c)	1.16 (0.58 – 2.34)	1.26 (0.63 – 2.53)	0.88 (0.35 – 2.26)	0.86 (0.44 – 1.66)	0.98 (0.33 – 2.88)	0.77 (0.37 – 1.64)	0.61 (0.36 -1.05)	1.12 (0.58 – 2.13)
Affective Symptom: >2 mentions (c)	0.51 (0.25 – 1.03)	0.57 (0.29 -1.12)	0.93 (0.41 – 2.10)	**0.51 (0.30 – 0.86)‡‡**	0.48 (0.21 – 1.10)	**0.35 (0.19–0.66)‡‡**	0.82 (0.50 – 1.32)	0.95 (0.53 – 1.68)
Somatic Symptom: >2 mentions (c)	1.39 (0.71 – 2.74)	1.01 (0.52 – 1.96)	1.11 (0.49 – 2.48)	0.66 (0.38 – 1.14)	1.02 (0.47 – 2.42)	1.18 (0.63 – 2.19)	**1.61 (1.01 – 2.56)‡‡**	0.70 (0.39 – 1.22)
Past Suicide Ideation: Yes (b)	1.37 (0.75 – 2.50)	1.03 (0.57 – 1.89)	0.89 (0.40 – 1.98)	0.80 (0.47 – 1.37)	0.50 (0.19 – 1.34)	0.92 (0.51 – 1.67)	0.93 (0.59 – 1.46)	0.84 (0.48 – 1.48)
Past Suicide Attempt: Yes (b)	1.04 (0.51 – 2.11)	1.51 (0.78 -2.91)	1.74 (0.76 – 4.00)	1.35 (0.75 – 2.41)	0.44 (0.12 – 1.64)	**2.06 (1.10–3.87)‡‡**	1.18 (0.71 – 1.95)	1.19 (0.63 – 2.20)

p-value: ‡ <0.05; ‡‡ < 0.001
a – Reference: Female
b – Reference: No
c – Reference: 0 or 1 mention of the symptom. Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 2		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5, 6 and 7		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	Page 5	RECORD 6.1: The methods of study population selection (such as codes or	Page 5 - 8

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 5- 8	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 5 - 8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5 – 8		
Bias	9	Describe any efforts to address potential sources of bias	Page 5		
Study size	10	Explain how the study size was	Page 5		

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 7		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page 5
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	Page 5

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 8	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 5
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page 8, 16 - 21		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Page 16 - 21		
Main results	16	(a) Give unadjusted estimates	Page 16 - 21		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page 8		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 10		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 10	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 12		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Not Applicable

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Demographic and clinical factors associated with different antidepressant treatments: a retrospective cohort study design in a UK psychiatric healthcare setting

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Demographic and clinical factors associated with different antidepressant treatments: a retrospective cohort study design in a UK psychiatric healthcare setting

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Abstract

Objective: To investigate the demographic and clinical factors associated with antidepressant use for depressive disorder in a psychiatric healthcare setting using a retrospective cohort study design.

Setting: Data were extracted from a de-identified data resource sourced from the electronic health records of a London mental health service. Relative risk ratios were obtained from multinomial logistic regression analysis to ascertain the probability of receiving common antidepressant treatments relative to sertraline.

Participants: Patients were included if they received mental health care and a diagnosis of depression with antidepressant treatment between March and August 2015 and exposures were measured over the preceding 12 months.

Results: Older age was associated with increased use of all antidepressants compared to sertraline, except for negative associations with fluoxetine (Relative Risk Ratio [RRR] 0.98; 95%CI 0.96-0.98) and a combination of two SSRIs (0.98; 0.96-0.99), and no significant association with escitalopram. Male gender was associated with increased use of mirtazapine compared to sertraline (2.57; 1.85-3.57). Previous antidepressant, antipsychotic and mood stabiliser use were associated with newer antidepressant use (i.e. SNRIs, mirtazapine or a combination of both), while affective symptoms were associated with reduced use of citalopram (0.58; 0.27-0.83) and fluoxetine (0.42; 0.22-0.72) and somatic symptoms were associated with increased use of mirtazapine (1.60; 1.00-2.75) relative to sertraline. In patients older than 25 years, past benzodiazepine use was associated with a combination of SSRIs (2.97; 1.32-6.68), mirtazapine (1.94; 1.20-3.16) and venlafaxine (1.87; 1.04-3.34), whilst past suicide attempts were associated with increased use of fluoxetine (2.06; 1.10-3.87) relative to sertraline.

Conclusion: There were several factors associated with different antidepressant receipt in psychiatric healthcare. In patients aged >25, those on fluoxetine were more likely to have past suicide attempt, while past use of antidepressant and non-antidepressant use was also associated with use of new generation antidepressants, potentially reflecting perceived treatment resistance.

Keywords: antidepressant use; depressive disorders; secondary care; psychiatric service; clinical factors; antidepressant prescription

Strengths and Limitations of this study

- To our knowledge, this is the first study profiling correlates of antidepressant use in a cohort of patients receiving treatment in a mental health service setting in the UK.
- The data included hard to measure variables such as depressive symptoms, derived using text mining algorithms.
- Focusing on antidepressant data in a 6-month window limited sample sizes for some analyses.
- The analysis is cross-sectional and causal relationships cannot be inferred from associations observed.
- The duration of the antidepressant treatment before and during the observation period was not known.

Introduction

There are standard national guidelines directing antidepressant prescription in secondary care [1] (secondary care refers to non-first-line treatment services provided by health professionals to patients who are usually referred by their primary care provider such as general practitioner). British guidelines for the management of depression in secondary care specify that care plans should involve, among other things, the development of a crisis plan that identifies and details management of potential triggers for a depressive episode or a worsening of existing symptoms[1]. However in practice a range of patient and clinician characteristics may influence antidepressant prescription [1,2]. For example, a community based study of data collected from 10 psychiatrists who offered antidepressant treatment to 1137 patients found that this was influenced by avoidance of side effects, the presence of comorbidities and the presence of specific depressive symptoms such as anxiety, insomnia, fatigue, irritability or increased appetite[3]. Supporting these results, studies profiling antidepressant prescriptions have established that patient-clinician relationships, past experiences with medication and patient symptoms can influence antidepressant prescription; however, to date these have been set in primary care [4–7].

There are few studies investigating factors associated with antidepressant use in a secondary mental healthcare setting[8,9], where antidepressant use is common, albeit more frequently in cases where first-line treatment has been ineffective or is complex for other reasons[10]. The limited availability of secondary mental health care (compared to primary care) data for research[11,12], has presented wider challenges for the identification of treatment receipt and response[13], compounded by the limited availability of data on important clinical parameters such as depressive symptoms[14] due to variation in clinical recording practices[15]. Limited data availability can be countered by novel approaches to information extraction applied to health records databases. For example, natural language processing techniques are being introduced in psychiatric research to help with data extraction on varying levels[16]. In a systematic review, Abbe et al[16] identified 38 studies using natural language processing techniques for psychiatry-related research, including analyses of patient perspectives on diagnosis and treatment, detecting diagnosis based on frequency of use of relevant terms, analyses of medical literature, and analyses of psychiatric clinical records. The review emphasized the potential value of text mining but also the unique challenges faced in this field, such as the mentions of emotions and subtle descriptions of personality or characteristics which may indicate symptomatology, the challenge of distinguishing of terms with multiple meanings, and the requirement for very large training corpora to achieve robust results.

To the best of our knowledge there has not been a study profiling antidepressant prescription in the UK, outside of primary care [17,18]. The objective of our study was to investigate whether clinical symptoms

(extracted with help of text mining techniques), past antidepressant or other psychotropic treatment or demographic factors are associated with different antidepressant treatment schedules used for depressive disorders in a secondary psychiatric healthcare setting.

Methods

The Dataset

The Clinical Record Interactive Search (CRIS) system provides de-identified case note information from the South London and Maudsley (SLaM) NHS Trust, a large mental healthcare provider serving a geographic catchment of approximately 1.3 million residents in four south London boroughs (Lambeth, Southwark, Lewisham, and Croydon). Electronic health records (EHRs) have been used comprehensively across all SLaM services since 2006. CRIS was established in 2008 to allow searching and retrieval of de-identified [19] clinical information for research purposes within a robust, patient-led governance framework, and currently houses records on over 270,000 cases [20,21]. The system allows for retrieval of information from de-identified structured and free-text fields, and the use of CRIS for research was approved by the Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5). Patient consent was not required due to research data being pseudonymised.

Observation Window and Inclusion Criteria

A 6-month interval from 1st March to 31st August 2015 was selected as the observation period where type of antidepressant use, defined as single antidepressant use and antidepressants users on two antidepressants (referred to here as binary antidepressant use) represented the main dependent variable. All antidepressant use groups were mutually exclusive as described in the next section. Independent variables (demographic and clinical variables) were extracted over the 12 months prior to the observation window and their associations with antidepressant use within the observation window were analysed.

Patients were included if they received active SLaM care within the 6-month observation interval, and if they had received any of the following clinical diagnoses according to 10th Revision of the International Classification of Diseases (ICD-10) codes on or before the 31st of August 2015: depressive episode (F32), recurrent depressive disorder (F33), dysthymia (F34.1), and/or mixed anxiety and depression (F41.2). Individuals were excluded if they had received any F01-F09 (organic disorders), F20-F29 (schizophrenia-like disorders) or F31 (bipolar disorder) diagnoses. Active care was defined as at least one face-to-face contact with SLaM service within the observation window.

Antidepressant Use

Antidepressant use was ascertained using an algorithm developed in General Architecture for Text Engineering (GATE) software, [22] designed to extract data specifically on any medication recorded in free-text fields (e.g. case notes, correspondence). Details of the development of this medication extraction algorithm have previously been published [14,21]. For each patient in the final cohort, any antidepressant use (regardless of the duration of use) during the observation window was extracted as a binary variable. The antidepressants for which data were collected comprised the following: i) tricyclic and tricyclic related - amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, mianserin and trazodone; ii) mono-amine oxidase inhibitors (MAOIs) - isocarboxazid, phenelzine, tranylcypromaine and moclobemide; iii) Selective Serotonin Re-uptake Inhibitors (SSRIs) - sertraline, fluoxetine, citalopram, escitalopram, fluvoxamine and paroxetine; iv) Selective Norepinephrine Reuptake Inhibitors (SNRIs) - venlafaxine, reboxetine and duloxetine; and v) Other classes - agomelatine, bupropion, and mirtazapine.

The final cohort comprised 1,561 patients. The most common mutually exclusive monotherapy antidepressant used within the 6-month window was sertraline (360 patients), followed by mirtazapine (305), citalopram (213), fluoxetine (200), venlafaxine (143), escitalopram (52). The most common mutually exclusive double antidepressant combinations were any one SSRI with mirtazapine (110), any one SNRI with mirtazapine (89) and a combination of any two SSRIs (89). Groups with no antidepressant use data (n = 1936) were excluded, as were groups with less than 50 patients (to avoid small cell sizes) and those where algorithms indicated use of three or more antidepressants (n = 494). All antidepressant groups were mutually exclusive.

Covariates

Apart from demographic variables, all other covariate data were extracted from data recorded within the 12 months prior to the observation window. Demographic variables were extracted from structured fields, but all other data variables (listed below) were individually extracted using GATE and TextHunter, two text mining software tools which can be programmed to extract data from free-text notes via rules-based and machine learning techniques, respectively. All clinical symptom data variables were extracted using TextHunter.

Demographic variables: Ethnic group, age, gender, marital status were extracted from structured fields in the source record. Area-level deprivation was measured from the Index of Multiple Deprivation (IMD) that is derived from 2011 national Census data for each individual address, aggregated to Lower Super Output Areas – geographic units with a mean of 1500 inhabitants. The widely-used IMD score combines Census-

derived data across multiple domains (income, employment, health, education, barriers to housing/ services, living environment, crime) and ranks each area at a national level[23].

Diagnosis-derived depression severity: Based on the latest-recorded diagnostic code, depression severity was estimated in three categories – Mild, Moderate/Severe and Unspecified. ***Mild severity*** included diagnoses of F32.0 Mild depressive episode, mild, F34.0 recurrent depressive episode, mild, F34.1 dysthymia and F41.2 mixed anxiety and depressive disorders. ***Moderate-to-Severe depressive severity*** included diagnoses of F32.1 moderate depressive episode, F32.3 severe depressive episode with psychotic episode, F32.2 severe depression without psychotic episode, F33.1 recurrent depressive episode, current episode moderate, F33.3 and F33.2 (respectively) recurrent depressive episode with and without psychotic episode, and F33.8 other recurrent depressive, unspecified. ***Unspecified severity*** was defined where there was no specified severity of depression within the ICD-code of depression, such as F32 – Depressive episode (unspecified severity), other depressive episodes, depressive episode, unspecified, F33- recurrent depressive disorder (unspecified severity), F33.4 recurrent depressive in remission (unspecified severity).

Past medication/therapy use: Antipsychotic, benzodiazepine, mood stabilizer and antidepressant use in the preceding 12 months were ascertained, as were the duration of the current treatment episode, any inpatient in the past 12 months, psychotherapy in the past 12 months, and referral to Improving Access to Psychiatric Treatment (IAPT) services**.** IAPT services are a nationwide initiative introduced to increase access to psychological treatments for common mental disorders in primary care.

Clinical symptom data: As described, bespoke natural language processing algorithms were applied to ascertain symptoms mentioned as present in text fields from the source electronic records. Data on fourteen symptoms of depression were extracted on text fields from the preceding 12 months. To avoid small patient groups for analysis, depressive symptoms were categorised into sub-scales supported by previous results from confirmatory factor analysis on depression scale items (Beck Depressive Inventory-II) in a clinical psychiatric population[24] and subsequently supported by other findings[25,26] albeit with possible variation in factors at older ages[27]. Hence the groupings were as follows: ***Cognitive symptoms***: helplessness, worthlessness and hopelessness; ***Affective symptoms***: anhedonia, poor motivation, apathy and low mood; ***Somatic symptoms***: poor concentration, agitation, irritability, low energy, insomnia, poor appetite and anergia. In addition, the presence of ***psychotic symptoms*** over the previous 12 months were ascertained from algorithms for hallucinations and delusions. For these symptom groups, in order to minimise false positive occurrences, 2 or more mentions of

symptoms in that domain were classified as a positive instance. ***Suicidal behaviour*** was ascertained over the preceding 12 months using natural language processing algorithms for suicidal ideation and suicide attempt.

Patient and Public Involvement

Patients and public were not directly involved in this study, although all projects using the CRIS data resource are considered and approved by a patient-led Oversight Committee[19].

Statistical Analysis

Group differences were analysed using chi-squared tests for categorical variables, using t-tests or one-way ANOVAs for normally distributed continuous variables, and using the Kruskal-Wallis test for non-normally distributed continuous data. Multinomial logistic regression analyses were used to answer the research question. The probability of receiving any of the common antidepressant treatments relative to sertraline (the referent, most used, antidepressant category) was estimated using exponentiated regression coefficients from the multinomial regression which represents Relative Risk Ratios (RRR). To build a representative model of which correlates predict antidepressant use in secondary care, decisions to include variables in the final model were guided by the association of each variable in an initial model including age and gender as covariates. Variables that did not have any significant associations in age- and gender- adjusted analysis were not included in the final model. For initial selection based on age- and gender- adjusted analysis, the significance was set at $p \leq 0.25$ [28]. This was to help minimise i) exclusion of potentially key covariates and ii) inclusion of $p < 0.05$ significant estimates occurring by chance. The selected variables were then simultaneously entered in a full model. In the fully adjusted model significance level was set at $p < 0.05$ for retaining variables. The correlates retained in the final multinomial regression model were age, gender, past inpatient status, past benzodiazepine use, past antipsychotic use, past mood stabiliser use, past antidepressant use, past psychotherapy and IAPT referrals, past experience of psychotic, somatic, affective and cognitive symptoms; and past experience of suicidal ideation and past suicide attempts. In addition, separate analysis was conducted in those aged 26 and over, on the assumption that different factors may be taken into consideration when considering prescriptions of antidepressants to children, adolescents and young people relative to adults [1,29].

Any missing values were treated as null values in the analysis as they formed less than 5% of data. As part of sensitivity analysis, and to ensure important variables are not being excluded in the final model, a full multivariable model was analysed and any variables that were statistically and clinically non-significant were

then removed from the model. The results from the final models (from the entire cohort analysis and the adult-only cohort) are available in Appendix for comparison.

Results

Table 1 compares patient characteristics between patients using and not using antidepressants. Groups differed in age, ethnicity and deprivation with patients on antidepressants being older, less deprived and of white background. Table 2 compares each antidepressant or antidepressant combination group by demographics, referral data, past medication use and past psychological therapy referral. The demographic and clinical differences between the antidepressant groups are statistically significant apart from ethnicity, area-level deprivation and having had a past referral for psychotherapy. Notably, patients receiving fluoxetine were younger, whilst older patients were over-represented in those receiving a combination of newer antidepressants such as mirtazapine and a SNRI; there were more males receiving mirtazapine than females; most of the antidepressant users were single, and only a minority had recorded non-antidepressant psychotropic treatments or psychotherapy in the past. Table 3 indicates that the majority of patients had a moderate to severe diagnosis of depression, a large majority of whom were not recorded as having experienced suicidal ideation or attempted suicide in the preceding 12 months. Apart from diagnostic severity and past psychotic symptoms, for all other past depressive symptoms and past suicidal ideation and attempts, the analysis indicated significant heterogeneity across the antidepressant user groups.

Tables 4 and 5 show the Relative Risk Ratio (RRR), estimating the probability of patients being on any antidepressant relative to sertraline (the most common antidepressant received in our cohort), derived from the fully adjusted multinomial logistic regression models in the entire cohort and the adult-only cohort respectively. Table 4 shows that relative to females, males are more likely to be on mirtazapine relative to sertraline. It also indicates that patients on newer antidepressants are more likely to have used non-antidepressant psychotropic medication or been on antidepressants in the past. Those on citalopram or fluoxetine are less likely to have experienced affective symptoms (such as low mood and poor motivation) in the past compared to those on sertraline, whilst those who have experienced somatic symptoms (such as insomnia and agitation) in the past are more likely to be on mirtazapine relative to sertraline. In the entire cohort and in those aged >25, older age was associated with higher probability of being prescribed new generation antidepressants, namely – a combination of any one SNRI and mirtazapine, a combination of any one SSRI and mirtazapine, mirtazapine, and venlafaxine compared to sertraline. In the entire cohort older age was associated with a decreased probability of being prescribed any one SSRI (Table 4 and 5) compared to sertraline.

The results from the analysis in those aged >25 (Table 5) show increased likelihood of males being on mirtazapine compared to females. They also show that, relative to sertraline, patients on citalopram or fluoxetine

are less like to have recorded affective symptoms, patients on mirtazapine are more likely to have recorded somatic symptoms, and patients on fluoxetine were more likely to have a recorded suicide attempt in the past 12 months relative to those on sertraline. The sensitivity analyses did not give rise to any marked difference in findings (see Appendix).

Discussion

The aim of this study was to ascertain patient demographic and clinical factors that correlate with different antidepressant treatments in patients actively receiving secondary mental health care for clinical depression. While there were no strongly consistent trends across all comparison groups or exposures, our results suggest that age, past medication and/or psychotherapy receipt use and symptom profiles in the past 12 months have potentially some influence on antidepressant receipt in secondary mental healthcare.

We found that older patients were less likely to be using fluoxetine or a combination of two SSRIs relative to sertraline and were more likely to be on other combinations, citalopram, mirtazapine or venlafaxine. Comparable to our findings, a study of newly initiated antidepressant use in a cohort of over 500,000 war veterans with a diagnosis of depression [9] found that older patients were less likely (RRR 0.70) to have started on fluoxetine than sertraline. While we did not seek to collect data on the reasoning behind the choices, although this might reflect concerns around the longer half-life of fluoxetine in older age groups and the lower propensity of sertraline for cytochrome-related interactions with co-prescribed medications, the association was less strong in the sub-group aged >25, so might be more likely to reflect lower perceived risk of treatment-emergent suicidality associated with fluoxetine in adolescents and younger adults. Similarly, the association of older age with mirtazapine use, individually or in combination, may reflect perceived likelihood of sedation and weight gain – considered problematic in younger patients but potentially advantageous (when taken at night) in late life depression. On the other hand the higher use of mirtazapine (compared to sertraline) in men, compared to women, may reflect lower incidence of sexual dysfunction side-effects [30]. Of interest, we found no substantial variation in use by ethnicity, marital status or neighbourhood socioeconomic status, once age and gender had been accounted for, suggesting little evidence of socially determined variation in prescribing.

Considering past medication use, antipsychotic, mood stabiliser or antidepressant use in the previous 12 months was associated with a higher likelihood of the co-occurrence of SNRI with mirtazapine during the observation period, and mood stabiliser use was also predictive of venlafaxine compared to sertraline use. The SNRI-mirtazapine group were also more likely to have been referred for primary care based psychotherapy (the UK's IAPT service model). As this secondary care cohort is likely to have an over-representation of individuals with some resistance to first line antidepressant treatment, it may follow that these individuals were on other treatment regimes in the past and that newer antidepressant regimes were being prescribed in the context of higher levels of treatment resistance. However, it is hard to define, and therefore identify, patients who are resistant to antidepressant treatment especially from naturalistic clinical databases, so conclusions can only be

tentative.

Considering clinical features, suicidal ideation and past suicide attempts were not significantly associated with different antidepressant use overall; however, past suicide attempt was associated with an increased likelihood of fluoxetine compared to sertraline receipt in patients aged >25 which, as discussed above for age effects, may reflect the evidence collated from meta-analyses of randomized controlled trials and observation studies where fluoxetine has been shown to carry reduced risk of emergent suicidal behaviour in adults compared to children and adolescents[31–33]. Those with affective symptoms recorded were less likely to be on citalopram or fluoxetine than sertraline, while those with somatic symptoms were more likely to be on mirtazapine, associations which persisted in the cohort aged >25. Clinician prescribing preference may be influenced by perceived therapeutic actions or perceived risk of adverse drug events, or both. For example, the somatic symptoms of poor appetite and insomnia may increase the likelihood of a medication such as mirtazapine being prescribed because of recognised propensity to sedation and weight gain. There is some evidence to suggest citalopram may induce cardio toxicity in overdose[34]; however, apart from clinical guidelines on when to prescribe antidepressants studies are rarely conducted to assess the association singular drugs with depressive symptoms are being prescribed [35].

As mentioned, there has been very little previous research into factors associated with different antidepressant treatments for depression, particularly in secondary care. Improved knowledge in this area is important for several reasons. Firstly, it is helpful to understand factors potentially influencing prescribing behaviour to assess the impact of guidelines and to describe variations beyond guidelines. From our observations here, the relative lack of covariates consistently associated with antidepressant use suggests prescribing based on individual experiences after patient-clinician communication, consistent with national guidelines emphasising patient-clinician communication[35]. However, findings suggestive of prescribing motivations derived from observational data of this nature need further qualitative studies for confirmation. Secondly, while variations in prescribing may reflect potentially problematic non-evidence-based behaviour, it might also highlight novel patterns arising from clinical experience which need to be noted and assessed further to improve the evidence base. Early detection of adverse, or unexpectedly beneficial, effects is an example of this. indications of how antidepressants are being used for treatment in secondary care is more realistic than research from pharmaceutical trials. Our findings suggest that there are certain antidepressants that are avoided in certain clinical scenarios; for example, patients previously described as having symptoms in the 'affective' category were less likely to be receiving citalopram or fluoxetine compared to sertraline. There is a suggestion

from the results that newer generation antidepressants are used to treat more severe depression which may indicate greater clinician-perceived tolerability and/or lower toxicity and/or lower propensity to interact with other co-prescribed medication[35,29].

The results should be interpreted with study limitations in mind. First, using antidepressant data in a 6-month window limited sample sizes for analysis, and inaccurate measures of exposure status (for example, the use of area- rather than individual-level socioeconomic status) might have reduced the likelihood of identifying underlying associations. Second, the study is close to cross-sectional design, since there may have been co-occurrence of exposures and outcomes in the prior 12-month observation period; therefore direct causal relationships cannot be conclusively inferred. Third, the duration of the antidepressant treatment during the observation period was not known, so some patients will have been new users of antidepressants identified, while others may have been using the antidepressant(s) for much longer periods of time; similarly, where there was co-occurrence of two antidepressants during the time period evaluated, it was not possible to distinguish a switch from one agent to another from co-prescribing of the two agents. Fourth, the results of the study cannot assumed to be generalizable to all patients in secondary mental healthcare settings due to the social and ethnic diversity found in south east London from where this sample was drawn; in addition, the focus of the study was on antidepressant use in people with a depressive disorder diagnosis and being reviewed in secondary mental healthcare, so findings cannot assumed to generalise to antidepressant use in other circumstances or for other indications. Finally, we could only investigate factors that were available to us in the current dataset. The literature reports various clinical covariates[8], patient demographics[9], medication use[36], clinician characteristics[3] and clinical location[8,9] as factors involved for antidepressant prescription in secondary mental healthcare settings. We could not capture all these factors in our analysis.

Limitations notwithstanding there are key strengths to this paper. To our knowledge this is the first study profiling antidepressant use in a cohort of patients receiving treatment for depression in a secondary mental health care setting in the UK. Although from a single site, the use of health records data provides a more generalisable sample than would be possible through a conventional cohort design involving *de novo* interviews, let alone through the even more selected samples in clinical trials. In addition, the data included constructs such as depressive symptoms that are not usually available in administrative 'big' data, taking advantage of a suite of recently developed text mining algorithms to capture a greater depth of data from free-text fields, circumventing the usual restriction of analysed data to those recorded in structured fields. The findings have the potential to inform clinical practice within this clinical setting. Knowledge of factors involved in antidepressant prescription

could be used to audit clinical practices and inform whether the clinical practices are benefitting patient treatment outcomes[37]. However, further qualitative work is definitely indicated to identify and highlight processes involved in clinician-selection of antidepressant treatment. Continual monitoring of treatment choices in this cohort may contribute to providing optimal care for secondary care patients and there may be scope for further quantitative evaluation not only across a wider range of services, but also evaluating longer-term outcomes associated with different treatment decisions.

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Table 1: Comparing characteristics between patients receiving or not receiving antidepressants during the 6-month evaluation period (N = 3497).

Patient Characteristics	On single or dual therapy antidepressants N=1561	Not on antidepressants N=1936	
Gender			
Female	1229	1295	$\chi^2 = 0.07$, df = 1, p = 0.80
Male	706	759	
Mean age	44.3 years	40.1 years	t = -7.6, df = 3908, p < 0.001
Marital status			
Single	1091 (56.3%%)	1302 (63.4%)	$\chi^2 = 0.02$, df = 2, p = 0.999
Married	456 (23.5%)	319 (15.5%)	
Other	389 (20.0%)	434 (21.1%)	
Area-level deprivation score tertile			
2.25 – 22.3 (least deprived)	631 (33.0%)	580 (28.7%)	$\chi^2 = 9.1$, df = 2, p < 0.05
22.4 – 42.3	1099 (57.6%)	1224 (60.6%)	
42.4 – 62.3 (most deprived)	179 (9.4%)	215 (10.6%)	
Ethnicity			
White	1220 (63.9%)	864 (42.1%)	$\chi^2 = 10.5$, df = 1, p < 0.01
Other	716 (36.1%)	1191 (57.9%)	
Depression severity from diagnosis			
Mild	383 (24.5%)	460 (28.3%)	$\chi^2 = 0.007$, df = 2, p = 0.99
Moderate-Severe	845 (54.1%)	845 (48.4%)	
Unspecified	333 (21.3%)	379 (23.3%)	

Table 2: Comparison of demographic characteristics, past service use, and past psychotropic medication use by antidepressant category

	Any one SNRI and Mirtazapine N=89	Any one SSRI and Mirtazapine N=110	Any two SSRIs N=89	Citalopram N=213	Escitalopram N=52	Fluoxetine N=200	Mirtazapine N=305	Sertraline N=360	Venlafaxine N=143	Total N=1561 (%)	Test statistic; p-value [c, d]
DEMOGRAPHICS											
Mean Age in years [SD]	52.9 [16.6]	48.6 [18.6]	34.1 [16.2]	42.7 [15.5]	44.1 [16.3]	33.3 [16.0]	49.2 [18.8]	39.3 [16.8]	48.8 [18.1]	43.8 [18.2]	25.38;
Median Age in years	52	48	33	42	44	30	47	38	48	41	<0.001
Gender: Female	60 (67.4%)	65 (59.6)	64 (71.9)	147 (69)	35 (67.3)	139 (69.5)	138 (45.2)	251 (69.7)	91 (63.6)	990 (63.4)	60.07;
Male	29 (32.6%)	44 (40.4)	25 (28.1)	66 (31)	17 (32.70)	61 (30.5)	167 (54.8)	109 (30.3)	52 (36.4)	571 (36.6)	<0.001
Ethnicity: White	61 (68.5%)	69 (62.7)	49 (55.1)	135 (63.4)	39 (75)	127 (63.5)	176 (57.7)	213 (59.2)	101 (70.6)	970 (62.1)	15.70;
Other	28 (31.5%)	41 (37.3)	40 (44.9)	78 (36.6)	13 (25)	73 (36.5)	129 (42.3)	147 (40.8)	42 (29.4)	591 (37.9)	0.05
Marital Status: Single	34 (38.2%)	61 (55.5)	47 (52.8)	127 (59.6)	25 (48.1)	133 (66.5)	169 (55.4)	216 (60)	79 (55.2)	891 (57.1)	df = 16;
Married	31 (34.8%)	26 (23.6)	24 (27.0)	40 (18.8)	18 (34.6)	23 (11.5)	72 (23.6)	80 (22.2)	35 (24.5)	349 (22.3)	37.40;
Other	24 (27%)	23 (20.9)	18 (20.2)	46 (21.6)	9 (17.3)	44 (22)	64 (21)	64 (17.8)	29 (20.3)	321 (20.6)	0.002
Area-Level Deprivation Score											
[a]1st Tertile (2.25 – 22.3)	29 (32.6%)	27 (25.5)	31 (34.8)	62 (29.5)	20 (38.5)	64 (32.3)	82 (27.2)	122 (34.5)	60 (42.9)	497 (31.8)	df = 16;
2nd Tertile	50 (56.2%)	67 (63.2)	44 (49.4)	131 (62.4)	26 (50)	120 (60.6)	184 (60.9)	205 (57.9)	71 (50.7)	898 (57.5)	26.33;
3rd Tertile (42.3 – 62.3)	10 (11.2%)	12 (11.3)	14 (15.7)	17 (8.1)	6 (11.5)	14 (7.1)	36 (11.9)	27 (7.6)	9 (6.4)	145 (9.3)	0.05
REFERRAL DATA											
Length of Spell: Mean years	0.91	0.94	0.51	0.80	1.04	0.81	0.90	0.73	1.40	1561	2.00;
(SD)	[2.45]	[1.94]	[0.77]	[2.80]	[1.50]	[1.16]	[1.64]	[1.27]	[3.00]		0.043
Past[b] Inpatient at SLaM: Yes	16 (18%)	24 (21.8)	16 (18)	18 (8.5)	3 (5.8)	13 (6.5)	32 (10.5)	47 (13.1)	16 (11.2)	185 (11.9)	27.64
No	73 (82%)	86 (78.2)	73 (82)	195 (91.5)	49 (94.2)	187 (93.5)	273 (89.5)	313 (86.9)	127 (88.8)	1376 (88.2)	<0.001
PAST[b] MEDICATION USE											
Benzodiazepine Use: Yes	26 (29.2%)	25 (22.7)	19 (21.4)	35 (16.4)	11 (21.2)	21 (10.5)	71 (23.3)	55 (15.3)	36 (25.2)	299 (19.1)	28.01
No	63 (70.8%)	85 (77.3)	70 (78.6)	178 (83.6)	41 (78.8)	179 (89.5)	234 (76.7)	305 (84.7)	107 (74.8)	1262 (80.8)	<0.001
Antipsychotic Use: Yes	39 (43.8%)	35 (31.8)	22 (24.7)	46 (21.6)	18 (34.6)	41 (20.5)	97 (31.8)	92 (25.6)	53 (37.1)	443 (28.3)	32.07;
No	50 (56.2%)	75 (68.2)	67 (75.3)	167 (78.4)	34 (65.4)	159 (79.5)	208 (68.2)	268 (74.4)	90 (62.9)	1118 (71.6)	<0.001
Mood Stabiliser Use: Yes	13 (14.6%)	7 (6.4)	5 (5.6)	8 (3.8)	6 (11.5)	10 (5)	19 (6.2)	15 (4.2)	21 (14.7)	104 (6.7)	33.48
No	76 (85.4%)	103 (93.6)	84 (94.4)	205 (96.2)	46 (88.4)	190 (95)	286 (93.8)	345 (95.8)	122 (85.3)	1457 (93.3)	<0.001
Antidepressant Use: Yes	82 (92.1%)	86 (78.2)	61 (68.5)	132 (62)	41 (78.8)	150 (75)	233 (76.4)	273 (75.8)	114 (79.7)	1172 (75.1)	38.43;
No	7 (7.9%)	24 (21.8)	28 (31.5)	81 (38)	11 (21.2)	50 (25)	72 (23.6)	87 (24.2)	29 (20.3)	389 (24.9)	<0.001
PAST[b] PSYCHOLOGICAL THERAPY REFERRAL											
Psychotherapy Referral: Yes	13 (14.6%)	18 (16.4)	11 (12.4)	14 (6.6)	7 (13.5)	22 (11)	29 (9.5)	46 (12.8)	19 (13.3)	179 (11.5)	11.03
No	76 (85.4%)	92 (83.6)	78 (87.6)	199 (93.4)	45 (86.5)	178 (89)	276 (90.5)	314 (87.2)	124 (86.7)	1382 (88.5)	0.200
IAPT Referral: Yes	51 (57.3%)	50 (45.5)	40 (44.9)	108 (50.7)	27 (51.9)	77 (38.5)	131 (42.9)	181 (50.3)	58 (40.6)	723 (46.3)	17.21
No	38 (42.7%)	60 (54.5)	49 (55.1)	105 (49.3)	25 (48.1)	123 (61.5)	174 (57.1)	179 (49.7)	85 (59.4)	838 (53.7)	0.028

a – Area-level Deprivation Tertiles (1st Tertile: Least Deprived; 3rd Tertile: Most Deprived). b – "Past" refers to the 12 months prior to the observation window. c –ANOVA, Chi-square test, t-tests or the Kruskal-Wallis tests were conducted to test differences between patient groups; d - degree of freedom (df) = 8, unless otherwise specified.

Table 3: Comparison of depression diagnostic severity, symptomatology and suicidality by antidepressant category

	Any one SNRI and Mirtazapine N=89 (%)	Any one SSRI and Mirtazapine N=110 (%)	Any two SSRIs N=89 (%)	Citalopram N=213 (%)	Escitalopram N=52 (%)	Fluoxetine N=200 (%)	Mirtazapine N=305 (%)	Sertraline N=360 (%)	Venlafaxine N=143 (%)	Total N=1561 (%)	Test statistic; p-value[b, c]
DEPRESSION SEVERITY											
Depression Severity:											
Mild	16 (18)	22 (20)	19 (21.4)	33 (15.5)	14 (26.9)	41 (20.5)	57 (18.7)	79 (21.9)	22 (15.4)	303 (19.4)	df = 16;
Moderate to Severe	49 (55)	50 (45.5)	37 (41.6)	91 (42.7)	18 (34.6)	84 (42)	185 (60.7)	165 (45.8)	60 (42)	739 (47.3)	17.44
Unspecified Severity	13 (14.6)	13 (11.8)	15 (16.9)	45 (21.1)	9 (17.3)	29 (14.5)	52 (17.1)	59 (16.4)	34 (23.8)	269 (17.2)	0.358
PAST SYMPTOMS[a]											
Psychotic Symptoms:											
Zero to One mention	68 (76.4)	77 (70)	70 (78.7)	176 (82.6)	46 (88.5)	168 (84)	238 (78.1)	293 (81.4)	112 (78.3)	1248 (80)	14.33;
>= 2 mentions	21 (23.6)	33 (30)	19 (21.3)	37 (17.4)	6 (11.5)	32 (16)	67 (21.9)	67 (18.6)	31 (21.7)	313 (20)	0.073
Cognitive Symptoms:											
Zero to One mention	62 (69.7)	78 (70.9)	68 (76.4)	186 (87.3)	45 (86.5)	179 (89.5)	254 (83.3)	293 (81.4)	111 (77.6)	1276 (81.7)	34.50;
>= 2 mentions	27 (30.3)	32 (29.1)	21 (23.6)	27 (12.6)	7 (13.5)	21 (10.5)	51 (16.7)	67 (18.6)	32 (22.4)	285 (18.3)	<0.001
Affective Symptoms:											
Zero to One mention	29 (32.6)	40 (36.4)	33 (37.1)	119 (55.9)	24 (46.2)	110 (55)	113 (37.1)	131 (36.4)	52 (36.4)	651 (41.7)	46.24
>= 2 mentions	60 (67.4)	70 (63.6)	56 (62.9)	94 (44.1)	28 (53.8)	90 (45)	192 (62.9)	229 (63.6)	91 (63.6)	910 (58.3)	<0.001
Somatic Symptoms:											
Zero to One mention	39 (43.8)	57 (51.2)	49 (55.1)	154 (72.3)	34 (65.4)	134 (67)	155 (50.8)	203 (56.4)	85 (59.4)	900 (57.7)	42.07;
>= 2 mentions	50 (56.2)	53 (48.1)	40 (44.9)	59 (27.7)	18 (34.6)	66 (33)	150 (49.2)	157 (43.6)	58 (40.6)	651 (41.7)	<0.001
PAST SUICIDALITY											
Suicide Ideation: Yes	33 (37.1)	38 (34.5)	30 (33.7)	40 (18.8)	10 (19.2)	44 (22)	78 (25.6)	101 (28.1)	35 (24.5)	409 (26.2)	22.12;
No	56 (62.9)	72 (65.5)	59 (66.3)	173 (81.2)	42 (80.8)	156 (78)	227 (74.4)	259 (71.9)	108 (75.5)	1152 (73.8)	<0.05
Suicide Attempt: Yes	20 (22.4)	34 (30.9)	30 (33.7)	39 (18.3)	6 (11.5)	48 (24)	65 (21.3)	77 (21.4)	32 (22.4)	351 (22.5)	17.37;
No	69 (77.5)	76 (69.1)	59 (66.3)	174 (81.7)	46 (88.5)	152 (76)	240 (76.7)	283 (78.6)	111 (77.6)	1210 (77.5)	<0.05

– "Past" refers to the 12 months prior to the observation window; Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period

b –ANOVA, Chi-square test, t-tests or the Kruskal-Wallis tests were conducted to test differences between patient groups;

c - degree of freedom (df) = 8, unless otherwise specified.

Table 4: Fully adjusted relative risk ratio estimates from multinomial logistic regression models for associations of exposures with antidepressant categories (against sertraline as the referent group) in the total cohort (N = 1561)

	Any one SNRI and Mirtazapine	Any one SSRI and Mirtazapine	Any two SSRIs	Citalopram	Escitalopram	Fluoxetine	Mirtazapine	Venlafaxine
Age (year increment)	**1.05 (1.03 – 1.04)‡**	**1.03 (1.02 – 1.04)‡**	**0.98 (0.96 – 0.99)‡‡**	**1.01 (1.00 – 1.02)‡‡**	1.01 (0.99 – 1.03)	**0.98(0.96 – 0.98)‡**	**1.03 (1.02 – 1.04)‡**	**1.03 (1.02 – 1.03)‡**
Male gender (a)	0.97 (0.57 – 1.76)	1.33 (0.84 – 2.09)	0.95 (0.56 – 1.61)	0.95 (0.65 – 1.39)	1.07 (0.56 – 2.01)	1.08 (0.73 – 1.60)	**2.57 (1.85 – 3.57)‡**	1.16 (0.76 – 1.76)
Past Inpatient: Yes (b)	1.09 (0.47 – 1.54)	1.26 (0.59 – 2.70)	0.97 (0.42 – 2.27)	0.80 (0.43 – 1.88)	0.60 (0.14 – 2.60)	0.48 (0.21 – 1.07)	0.68 (0.37 – 1.27)	0.70 (0.32 – 1.54)
Past Benzodiazepine Use: Yes (b)	1.30 (0.70 – 2.81)	1.03 (0.55 – 1.90)	1.63 (0.82 – 3.25)	1.60 (0.94 – 2.73)	1.77 (0.78 – 4.01)	0.97 (0.53 -1.77)	1.58 (1.00 – 2.50)	1.63 (0.94 – 2.81)
Past Antipsychotic Use: Yes (b)	**1.78 (1.03 – 2.36)‡‡**	1.17 (0.69 – 1.99)	0.91 (0.49 – 1.70)	0.99 (0.63 – 1.60)	1.53 (0.77 – 3.07)	0.74 (0.46 – 1.17)	1.19 (0.80 – 1.75)	1.47 (0.91 – 2.36)
Past Mood Stabiliser Use: Yes (b)	**2.38 (1.04 – 6.34)‡‡**	1.23 (0.47 – 3.20)	1.50 (0.50 – 4.36)	0.99 (0.40 – 2.42)	2.60 (0.93 – 7.27)	1.65 (0.71 - 3.86)	1.23 (0.60 – 2.55)	**2.96 (1.44 – 6.08)‡‡**
Past Antidepressant Use: Yes (b)	**3.06 (1.34 – 7.85)‡‡**	0.95 (0.50 – 1.78)	0.59 (0.31 – 1.10)	0.76 (0.48 – 1.20)	1.27 (0.55 – 2.94)	1.42 (0.88 – 2.30)	0.98 (0.63 – 1.53)	1.10 (0.62 – 1.96)
Has had Psychotherapy treatment before: Yes (b)	0.67 (0.31 – 1.51)	0.91 (0.45 – 1.75)	0.88 (0.42 – 1.86)	**0.51 (0.27 – 0.98)‡‡**	1.17 (0.48 – 2.89)	0.91 (0.51 – 1.64)	**0.55 (0.32 – 0.94)‡‡**	0.81 (0.43 – 1.52)
Has been referred to IAPT services: Yes (b)	**1.90 (1.15 – 1.91)‡‡**	1.02 (0.65 – 1.60)	0.81 (0.50 – 1.33)	0.96 (0.68 – 1.37)	1.18 (0.64 – 2.17)	**0.62 (0.43 - 0.91)‡**	0.88 (0.63 – 1.22)	0.79 (0.53 – 1.20)
Psychotic Symptom:>=2 mentions (c)	0.82 (0.38 – 1.89)	1.54 (0.72 – 2.71)	1.00 (0.58 – 2.12)	1.53 (0.95 – 3.00)	0.67 (0.26 – 2.26)	1.42 (0.79 – 2.51)	1.16 (0.64 – 1.73)	1.17 (0.54 – 1.90)
Cognitive Symptom:>=2 mentions (c)	1.37 (0.67 – 2.67)	1.40 (0.72 – 2.76)	1.18 (0.56 – 2.47)	0.94 (0.54 – 1.87)	0.96 (0.30 – 2.17)	0.77 (0.39 – 1.44)	0.72 (0.49 – 1.38)	1.32 (0.76 – 2.67)
Affective Symptom: >=2 mentions (c)	0.53 (0.28 – 1.31)	0.60 (0.24 – 1.13)	0.93 (0.33 – 1.66)	**0.58 (0.27 – 0.83)‡‡**	0.72 (0.31 – 1.87)	**0.42 (0.22 – 0.72)‡**	0.79 (0.41 – 1.18)	0.92 (0.36 – 1.32)
Somatic Symptom: >=2 mentions (c)	1.40 (0.63 – 1.78)	1.02 (0.65 – 2.84)	0.92 (0.47 – 2.33)	0.65 (0.36 – 1.16)	0.84 (0.39 – 2.40)	1.10 (0.62 – 1.97)	**1.60 (1.00 – 2.75)‡‡**	0.70 (0.50 – 1.80)
Past Suicide Ideation: Yes (b)	1.34 (0.76 – 1.33)	1.07 (0.62 – 1.86)	1.04 (0.57 – 1.90)	0.80 (0.50 – 1.29)	0.75 (0.34 – 1.68)	0.88 (0.55 – 1.42)	0.90 (0.60 – 1.36)	0.79 (0.47 – 1.33)
Past Suicide Attempt: Yes (b)	1.01 (0.51 – 2.05)	1.49 (0.82 – 2.68)	1.74 (0.95 – 3.19)	1.23 (0.74 – 2.05)	0.66 (0.25 – 1.74)	1.57 (0.97 – 2.54)	1.13 (0.72 – 1.77)	1.18 (0.67 – 2.06)

p-value: ‡ <0.05; ‡‡ < 0.001
a – Reference: Female
b – Reference: No
c – Reference: 0 or 1 mention of the symptom. Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period.

Table 5: Fully adjusted relative risk ratio estimates from multinomial logistic regression models for associations of exposures with antidepressant categories (against sertraline as the referent group) in patients aged >25 years (N = 1248)

	Any one SNRI and Mirtazapine	Any one SSRI and Mirtazapine	Any two SSRIs	Citalopram	Escitalopram	Fluoxetine	Mirtazapine	Venlafaxine
Age (year increment)	**1.04 (1.02 – 1.05)‡**	**1.03 (1.01 – 1.04)‡**	0.99 (0.97 – 1.01)	1.00 (0.99 – 1.02)	1.00 (0.98 – 1.03)	0.99 (0.98 – 1.01)	**1.03 (1.02 – 1.04)‡**	**1.02 (1.01 – 1.04)‡**
Male gender (a)	0.87 (0.51 – 1.50)	1.29 (0.79 – 2.11)	0.89 (0.47 – 1.69)	0.89 (0.59 – 1.35)	1.04 (0.52 – 2.07)	1.25 (0.78 – 2.00)	**2.36 (1.64 – 3.37)‡**	1.10 (0.70 – 1.73)
Past Inpatient: Yes (b)	1.10 (0.45 – 2.69)	0.96 (0.40 – 2.24)	0.30 (0.07 – 1.26)	0.83 (0.36 – 1.95)	0.50 (0.09 – 3.23)	0.50 (0.18 – 1.37)	0.62 (0.31 – 1.24)	0.61 (0.25 – 1.47)
Past Benzodiazepine Use: Yes (b)	1.46 (0.76 – 2.78)	1.25 (0.65 – 2.41)	**2.97 (1.32 – 6.68)‡‡**	1.61 (0.89 – 2.90)	1.90 (0.80 – 4.49)	1.13 (0.57 – 2.24)	**1.94 (1.20 – 3.16)‡‡**	**1.87 (1.04 – 3.34)‡‡**
Past Antipsychotic Use: Yes (b)	**2.02 (1.14 – 3.58)‡‡**	1.30 (0.73 – 2.32)	1.02 (0.46 – 2.26)	1.08 (0.66 – 1.80)	1.55 (0.73 – 3.30)	1.02 (0.57 – 1.80)	1.16 (0.76 – 1.78)	1.53 (0.92 – 2.57)
Past Mood Stabiliser Use: Yes (b)	2.26 (0.97 – 5.30)	1.03 (0.37 – 2.90)	1.17 (0.31 – 4.44)	0.78 (0.30 – 2.14)	2.67 (0.91 – 7.76)	1.75 (0.68 – 4.47)	1.27 (0.60 – 2.71)	**2.76 (1.28 – 5.97)‡‡**
Past Antidepressant Use: Yes (b)	**2.70 (1.07 – 6.86)‡‡**	0.81 (0.41 – 1.61)	**0.44 (0.20 – 0.95)‡‡**	0.72 (0.43 – 1.21)	2.07 (0.43 – 5.54)	1.07 (0.20 – 1.96)	0.83 (0.50 – 1.36)	1.09 (0.60 – 2.05)
Has had Psychotherapy treatment before: Yes (b)	0.80 (0.36 – 1.76)	1.30 (0.64 – 2.63)	0.95 (0.33 – 2.71)	0.52 (0.24 – 1.15)	1.75 (0.66 – 4.57)	1.12 (0.51 – 2.44)	0.68 (0.38 – 1.23)	0.86 (0.43 – 1.73)
Has been referred to IAPT services: Yes (b)	**2.04 (1.20 – 3.48)‡‡**	0.99 (0.60 – 1.62)	0.93 (0.50 – 1.73)	1.00 (0.67 – 1.50)	1.36 (0.70 – 2.66)	0.98 (0.61 – 1.68)	0.93 (0.64 -1.34)	0.83 (0.53 – 1.31)
Psychotic Symptom:>2= mentions (c)	0.81 (0.39 – 1.69)	1.67 (0.85 – 3.26)	0.88 (0.36 – 2.22)	1.70 (0.94 – 3.09)	0.70 (0.23 – 2.13)	1.45 (0.75 – 2.81)	1.24 (0.75 -2.06)	1.19 (0.63 – 2.23)
Cognitive Symptom:>2= mentions (c)	1.16 (0.58 – 2.34)	1.26 (0.63 – 2.53)	0.88 (0.35 – 2.26)	0.86 (0.44 – 1.66)	0.98 (0.33 – 2.88)	0.77 (0.37 – 1.64)	0.61 (0.36 -1.05)	1.12 (0.58 – 2.13)
Affective Symptom: >2= mentions (c)	0.51 (0.25 – 1.03)	0.57 (0.29 -1.12)	0.93 (0.41 – 2.10)	**0.51 (0.30 – 0.86)‡‡**	0.48 (0.21 – 1.10)	**0.35 (0.19–0.66)‡‡**	0.82 (0.50 – 1.32)	0.95 (0.53 – 1.68)
Somatic Symptom: >2= mentions (c)	1.39 (0.71 – 2.74)	1.01 (0.52 – 1.96)	1.11 (0.49 – 2.48)	0.66 (0.38 – 1.14)	1.02 (0.47 – 2.42)	1.18 (0.63 – 2.19)	**1.61 (1.01 – 2.56)‡‡**	0.70 (0.39 – 1.22)
Past Suicide Ideation: Yes (b)	1.37 (0.75 – 2.50)	1.03 (0.57 – 1.89)	0.89 (0.40 – 1.98)	0.80 (0.47 – 1.37)	0.50 (0.19 – 1.34)	0.92 (0.51 – 1.67)	0.93 (0.59 – 1.46)	0.84 (0.48 – 1.48)
Past Suicide Attempt: Yes (b)	1.04 (0.51 – 2.11)	1.51 (0.78 -2.91)	1.74 (0.76 – 4.00)	1.35 (0.75 – 2.41)	0.44 (0.12 – 1.64)	**2.06 (1.10–3.87)‡‡**	1.18 (0.71 – 1.95)	1.19 (0.63 – 2.20)

p-value: ‡ <0.05; ‡‡ < 0.001
a – Reference: Female
b – Reference: No
c – Reference: 0 or 1 mention of the symptom. Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period.

Appendix

Table A1: Results from sensitivity analysis. Fully-adjusted multinomial logistic regression analysis investigating the association between demographic and clinical factors with different antidepressant treatments.

	Any one SNRI and Mirtazapine	Any one SSRI and Mirtazapine	Any two SSRIs	Citalopram	Escitalopram	Fluoxetine	Mirtazapine	Venlafaxine
Age	**1.04 (1.03 – 1.06)**	**1.03 (1.02 – 1.04)**	**0.97 (0.96 – 0.99)**	**1.01 (1.00 – 1.02)**	1.01 (0.99 – 1.03)	**0.97 (0.95 – 0.98)**	**1.03 (1.02 – 1.04)**	**1.02 (1.01 – 1.04)**
Gender (a)	1.00 (0.60 – 1.67)	1.32 (0.83 – 2.08)	0.95 (0.56 – 1.61)	0.96 (0.66 – 1.40)	1.06 (0.58 – 2.00)	1.04 (0.71 – 1.54)	**2.62 (1.89 – 3.64)**	1.15 (0.76 – 1.75)
Race (White)	1.19 (0.71 – 2.01)	0.95 (0.60 – 1.51)	0.80 (0.50 – 1.30)	1.12 (0.78 – 1.61)	1.90 (0.98 – 3.74)	1.23 (0.88 – 1.78)	0.75 (0.54 – 1.04)	1.34 (0.87 – 2.06)
Past Inpatient: Yes (b)	1.13 (0.49 – 2.62)	1.24 (0.58 – 2.65)	0.97 (0.41 - 2.27)	0.90 (0.43 – 1.90)	0.60 (0.14 – 2.54)	0.47 (0.21 – 1.05)	0.71 (0.38 – 1.32)	0.70 (0.31 – 1.51)
Past Benzodiazepine Use: Yes (b)	1.39 (0.75 – 2.57)	1.04 (0.56 – 1.93)	1.63 (0.82 – 3.24)	1.57 (0.92 – 2.67)	1.78 (0.80 – 3.98)	0.88 (0.58 – 1.60)	**1.62 (1.04 – 2.55)**	1.68 (0.98 – 2.89)
Past Mood Stabiliser Use: Yes (b)	**2.61 (1.15 – 5.91)**	1.22 (0.47 – 3.17)	1.46 (0.50 – 4.30)	0.96 (0.39 – 2.35)	2.60 (0.93 – 7.21)	1.53 (0.77 – 3.60)	1.28 (0.62 – 2.63)	**3.08 (1.51 – 6.30)**
Past Antidepressant Use: Yes (b)	**3.70 (1.55 – 8.86)**	1.06 (0.59 – 1.93)	**0.54 (0.30 – 0.98)**	0.73 (0.48 – 1.12)	1.58 (0.72 – 3.46)	1.28 (0.77 – 2.02)	0.97 (0.63 – 1.48)	1.23 (0.72 – 2.12)
Has had Psychotherapy treatment before: Yes (b)	0.65 (0.31 – 1.37)	0.90 (0.47 – 1.71)	0.92 (0.44 – 1.94)	0.52 (0.28 – 1.01)	1.05 (0.43 – 2.57)	0.88 (0.50 – 1.58)	**0.56 (0.33 – 0.96)**	0.77 (0.41 – 1.42)
Has been referred to IAPT services: Yes (b)	**1.80 (1.09 – 2.98)**	0.98 (0.63 – 1.54)	0.81 (0.50 – 1.31)	0.95 (0.68 – 1.36)	1.10 (0.61 – 2.01)	**0.64 (0.45 – 0.93)**	0.87 (0.63 – 1.20)	0.75 (0.50 – 1.13)
Psychotic Symptom:>=2 mentions (c)	0.90 (0.45 – 1.81)	1.57 (0.85 – 2.91)	0.98 (0.49 – 1.96)	1.54 (0.90 – 2.65)	0.73 (0.27 – 2.02)	1.39 (0.80 – 2.40)	1.20 (0.75 – 1.87)	1.24 (0.70 – 2.22)
Cognitive Symptom:>=2 mentions (c)	1.35 (0.70 – 2.63)	1.38 (0.73 – 2.61)	1.17 (0.58 – 2.37)	0.95 (0.52 – 1.72)	0.95 (0.35 – 2.56)	0.80 (0.42 – 1.49)	0.71 (0.43 – 1.17)	1.32 (0.73 – 2.40)
Affective Symptom: >=2 mentions (c)	0.54 (0.28 – 1.04)	0.60 (0.32 – 1.12)	0.93 (0.47 – 1.83)	**0.58 (0.36 – 0.92)**	0.70 (0.33 – 1.51)	**0.42 (0.25 – 0.68)**	0.80 (0.51 – 1.25)	0.92 (0.54 – 1.56)
Somatic Symptom: >=2 mentions (c)	1.42 (0.74 – 2.71)	1.02 (0.55 – 1.90)	0.90 (0.47 – 1.75)	0.66 (0.40 – 1.09)	0.88 (0.40 – 1.96)	1.09 (0.66 – 1.81)	**1.60 (1.04 – 2.46)**	0.71 (0.42 – 1.22)
Past Suicide Ideation: Yes (b)	1.40 (0.79 – 2.47)	1.11 (0.64 – 1.91)	1.03 (0.57 – 1.86)	0.80 (0.50 – 1.29)	0.80 (0.36 – 1.79)	0.84 (0.52 – 1.35)	0.91 (0.61 – 1.37)	0.82 (0.49 – 1.38)
Past Suicide Attempt: Yes (b)	0.94 (0.49 – 1.83)	1.46 (0.81 – 2.61)	1.79 (0.97 – 3.29)	1.26 (0.76 – 2.08)	0.62 (0.23 – 1.64)	1.56 (0.97 – 2.52)	1.11 (0.71 – 1.74)	1.12 (0.65 – 1.95)

p-value: ‡ <0.05; ‡‡ < 0.001
a – Reference: Female
b – Reference: No
c – Reference: 0 or 1 mention of the symptom. Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period.

Table A2: Results from sensitivity analysis. Fully-adjusted multinomial logistic regression analysis investigating the association between demographic and clinical factors with different antidepressant treatments in the adult-only cohort (n = 1248).

	Any one SNRI and Mirtazapine	Any one SSRI and Mirtazapine	Any two SSRIs	Citalopram	Escitalopram	Fluoxetine	Mirtazapine	Venlafaxine
Age	**1.04 (1.02 – 1.05)**	**1.03 (1.01 – 1.05)**	0.99 (0.97 – 1.02)	1.00 (0.99 – 1.02)	1.00 (0.99 – 1.03)	0.99 (0.98 – 1.01)	**1.03 (1.01 – 1.04)**	**1.02 (1.01 – 1.04)**
Gender (a)	0.88 (0.51 – 1.50)	1.28 (0.79 – 2.08)	0.89 (0.47 – 1.70)	0.90 (0.50 – 1.36)	1.02 (0.52 – 2.01)	1.24 (0.82 – 2.00)	**2.33 (1.63 – 3.34)**	1.08 (0.69 – 1.70)
Past Inpatient: Yes (b)	1.08 (0.44 – 2.62)	0.96 (0.41 – 2.21)	0.30 (0.07 – 1.26)	0.79 (0.34 – 1.83)	0.58 (0.10 – 3.22)	0.51 (0.19 – 1.37)	0.60 (0.30 – 1.20)	0.59 (0.25 – 1.40)
Past Benzodiazepine Use: Yes (b)	1.44 (0.76 – 2.75)	1.26 (0.66 – 2.43)	**2.89 (1.30 – 6.43)**	1.56 (0.87 – 2.80)	1.85 (0.79 – 4.35)	1.14 (0.63 – 2.25)	**1.92 (1.18 – 3.12)**	**1.87 (1.04 – 3.33)**
Past Antipsychotic Use: Yes (b)	**2.01 (1.14 – 3.55)**	1.30 (0.73 – 2.27)	1.03 (0.47 – 2.27)	1.09 (0.66 – 1.81)	1.67 (0.80 – 3.52)	1.01 (0.57 – 1.80)	1.14 (0.74 – 1.75)	1.50 (0.90 – 2.50)
Past Mood Stabiliser Use: Yes (b)	2.25 (0.96 – 5.26)	1.02 (0.36 – 2.86)	1.11 (0.30 – 4.22)	0.77 (0.28 – 2.10)	2.52 (0.87 – 7.29)	1.71 (0.74 – 4.35)	1.24 (0.58 – 2.64)	**2.65 (1.23 – 5.70)**
Past Antidepressant Use: Yes (b)	**2.76 (1.12 – 6.81)**	0.92 (0.48 – 1.78)	**0.40 (0.19 – 0.85)**	0.70 (0.42 – 1.13)	2.19 (0.85 – 5.67)	1.04 (0.62 – 1.86)	0.80 (0.50 – 1.30)	1.08 (0.59 – 2.00)
Has been referred to IAPT services: Yes (b)	**2.04 (1.20 – 3.47)**	0.97 (0.60 – 1.59)	0.91 (0.50 – 1.69)	0.98 (0.66 – 0.47)	1.34 (0.68 – 2.60)	0.97 (0.61 – 1.53)	0.93 (0.64 – 1.34)	0.82 (0.52 – 1.28)
Psychotic Symptom:>=2 mentions (c)	0.80 (0.38 – 1.67)	1.70 (0.87 – 3.31)	0.89 (0.34 – 2.21)	1.67 (0.92 – 3.03)	0.72 (0.23 – 2.18)	1.45 (0.81 – 2.81)	1.22 (0.74 – 2.03)	1.18 (0.63 – 2.21)
Cognitive Symptom:>=2 mentions (c)	1.14 (0.57 – 2.30)	1.28 (0.65 – 2.56)	0.89 (0.35 – 2.25)	0.84 (0.43 – 1.62)	0.99 (0.34 – 2.88)	0.78 (0.47 – 1.64)	0.60 (0.35 – 1.02)	1.11 (0.58 – 2.11)
Affective Symptom: >=2 mentions (c)	0.51 (0.25 – 1.01)	0.59 (0.30 – 1.14)	0.92 (0.41 – 2.08)	**0.49 (0.29 – 0.82)**	0.51 (0.23 – 1.15)	**0.36 (0.20 – 0.67)**	0.79 (0.53 – 1.28)	0.93 (0.53 – 1.66)
Somatic Symptom: >=2 mentions (c)	1.40 (0.72 – 2.75)	0.99 (0.52 – 1.92)	1.11 (0.50 – 2.50)	0.66 (0.38 – 1.16)	1.00 (0.42 – 2.36)	1.17 (0.68 – 2.18)	**1.63 (1.02 – 2.59)**	0.69 (0.40 – 1.22)
Past Suicide Ideation: Yes (b)	1.37 (0.76 – 2.48)	1.08 (0.60 – 1.95)	0.89 (0.40 – 1.98)	0.79 (0.47 – 1.35)	0.53 (0.20 – 1.39)	0.92 (0.57 – 1.67)	0.92 (0.60 – 1.44)	0.84 (0.50 – 1.48)
Past Suicide Attempt: Yes (b)	1.03 (0.51 – 2.09)	1.44 (0.76 – 2.77)	1.75 (0.77 – 4.00)	1.45 (0.81 – 2.58)	0.44 (0.12 – 1.62)	**2.06 (1.11 – 3.84)**	1.18 (0.72 – 1.95)	1.17 (0.64 – 2.16)

p-value: ‡ <0.05; ‡‡ < 0.001
a – Reference: Female
b – Reference: No
c – Reference: 0 or 1 mention of the symptom. Individuals with zero or one mention of a symptom in the 12-month period prior to the observation frame were considered to be undergoing a milder experience of the symptom compared to individuals who had two or more mentions of the symptom in the 12-month period.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 2		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5, 6 and 7		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	Page 5	RECORD 6.1: The methods of study population selection (such as codes or	Page 5 - 8

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 5- 8	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 5 - 8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5 – 8		
Bias	9	Describe any efforts to address potential sources of bias	Page 5		
Study size	10	Explain how the study size was	Page 5		

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 7		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page 5
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	Page 5

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 8	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 5
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page 8, 16 - 21		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Page 16 - 21		
Main results	16	(a) Give unadjusted estimates	Page 16 - 21		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page 8		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 10		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 10	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 12		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Not Applicable

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.