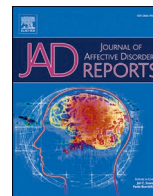




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Research Paper

An analysis of antidepressant prescribing trends in England 2015–2019.

Hasnain M. Lalji, Anita McGrogan, Sarah J. Bailey*

Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK



ARTICLE INFO

Keywords:

Antidepressant
Depression
General Practice
Mental health
Cardiovascular prescribing

ABSTRACT

Background Growing concerns about the impact of coronavirus disease 2019 (COVID-19) will likely lead to increased mental health diagnoses and treatment. To provide a pre-COVID-19 baseline, we have examined antidepressant prescribing trends for 5 years preceding COVID-19.

Methods A retrospective analysis of anonymised data on medicines prescribed by GPs in England from the Open-Prescribing Database (January 2015 to December 2019) identified the 10 most prescribed antidepressants and, for comparison, cardiovascular medicines.

Results Prescription items for the 10 most prescribed antidepressants rose 25% from 58 million (2015) to 72 million (2019). Citalopram was the most prescribed antidepressant; prescriptions for sertraline rose fastest at 2 million items year on year. Over the same period, costs for antidepressant prescribing fell 27.8%. Across all Clinical Commissioning Groups (CCGs) in England, antidepressant prescribing levels, adjusted for population were positively correlated with the index of multiple deprivation (IMD) score. In comparison, prescribing for the top 10 most prescribed cardiovascular medicines increased by 2.75% from 207 million (2015) to 213 million (2019) items.

Limitations Anonymised data in the Open-Prescribing Database means no patient diagnoses or treatment plans are linked to this data.

Conclusion Antidepressant prescribing, particularly sertraline, is increasing. Prescribing is higher in more deprived regions, but costs are falling to < 2% of all items prescribed. Absolute numbers of prescriptions for cardiovascular medicines are higher, likely reflecting the greater prevalence of cardiovascular disease, and are rising more slowly. This study will enable future work to look at the impact of COVID-19 on prescribing for mental health.

1. Introduction

According to the World Health Organization (WHO), depression affects more than 264 million people and is a leading cause of disability worldwide (WHO, 2020). In 2014, the Adult Psychiatric Morbidity Survey showed an increase in the prevalence of depression in England to 3.8 from 2.8% in 2000, alongside an increase in other mental health conditions such as anxiety which increased from 4.7 to 6.6% (McManus et al., 2016). In the UK, GP data on antidepressant prescribing showed a 2-fold increase in the number of antidepressant prescriptions from 1975 to 1998 (Middleton et al., 2001). A descriptive study using the general practice research database (GPRD) reported that most antidepressant prescriptions were issued to patients receiving long-term treatment for depression or intermittent treatment (Moore et al., 2009). Public Health England recently reviewed National Health Service (NHS) community

prescriptions in England reported to the NHS Business Services Authority (NHSBSA) and showed that the proportion of adult residents in England receiving a prescription for antidepressants increased in the period 2015–2018 (Taylor et al., 2019). Interestingly, incidence of antidepressant use varies across countries and indication. Antidepressant use in older adults has been reported to vary 24-fold by country, with the UK being among the lowest (Tamblyn et al. 2019). Tamblyn et al. (2019) reported that chronic pain was the most common potential treatment indication, with tricyclic antidepressants used most frequently in the UK. Concerns are expressed that rising prescribing represents over-diagnosis of depression and over-use of antidepressants (Middleton and Moncrieff, 2011; Spence, 2016). On the other hand, increasing prescriptions can be viewed as an increase in the number of patients on long term antidepressant treatment to reduce relapse rates (Moore et al., 2009).

Abbreviations: CCG, Clinical Commissioning Group; COVID-19, coronavirus disease 2019; IMD, index of multiple deprivation; NHS, National Health Service; NHSBSA, NHS Business Services Authority; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

* Corresponding author.

<https://doi.org/10.1016/j.jadr.2021.100205>

Received 17 March 2021; Received in revised form 29 July 2021; Accepted 29 July 2021

Available online 4 August 2021

2666-9153/© 2021 The Authors.

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

There are growing concerns about the impact of coronavirus disease 2019 (COVID-19) on mental health. This relates not only to the potential direct effect on mental health and the neurotropic potential of SARS-CoV-2 but also the associated psychosocial impacts of restrictions placed on large populations (Pfefferbaum and North, 2020; Vindegaard and Benros, 2020; Xiong et al. 2020). Set against a background where antidepressant prescribing is reportedly rising amid concerns expressed that this represents over-diagnosis of depression and over-use of antidepressants; it will be necessary to determine whether COVID-19 impacts on diagnoses and treatment of mental health conditions. To enable future research into treatment and interventions for mental health, it is essential to understand what the baseline was pre-COVID-19. Therefore, we have investigated antidepressant prescribing practice for 5 years immediately preceding COVID-19 from January 2015–December 2019 in England. Using the Open Prescribing database (OpenPrescribing.net, EBM DataLab, University of Oxford, 2021), we have performed a retrospective analysis of anonymised data on medicines prescribed by GPs. We have examined the most prescribed antidepressants, identified whether this reflects prescribing guidelines by clinical commissioning group (CCGs) and variations in local formularies. CCGs commission most of the hospital and community National Health Service (NHS) services in the local areas for which they are responsible. To provide a context for the antidepressant prescribing trends, we also considered prescribing levels for cardiovascular medicines, as a comparison with prevalent physical health condition prescribing.

2. Methods

The Open Prescribing database (OpenPrescribing.net, EBM DataLab, University of Oxford, 2021) was used to gather prescribing information in England across five years preceding COVID-19 from January 2015 to December 2019. The database contains anonymised data about medicines prescribed as prescription items (a single supply of a medicine prescribed on a prescription form), quantity and cost incurred. The data includes prescriptions written by GPs and other non-medical prescribers (such as nurses, pharmacists, optometrists, chiropractors and potentially radiographers) who are attached to practices. The data does not cover private prescriptions. Where prescribing cannot be linked to a practice the data is excluded and amounts to approximately 0.2% of dispensed items. No information is provided on the duration of treatment, patient diagnosis or quantity of medicine prescribed (NHS Digital, 2018). Prescribing data is from the monthly files published by NHS Business Services Authority (NHSBSA), used under the terms of the Open Government Licence.

All antidepressants were identified in the Open Prescribing database using the British National Formulary (BNF) (Joint Formulary Committee, 2020) (Supplementary Table 2). For each antidepressant, monthly information was categorised as: name of clinical commissioning group (CCG), month of prescribing, total items prescribed, total quantity of tablets and total cost incurred by CCG and compiled in a spreadsheet which was then exported to Microsoft Access 365 for analysis. The top 10 most prescribed antidepressants, in terms of total numbers of items prescribed, were identified by summing the number of items prescribed for each antidepressant across the whole study period 2015 to 2019 and ranking them. Similar prescribing data were also extracted on the top 10 most prescribed cardiovascular medicines.

Due to merging and/or creation of new CCGs in 2020, the number of CCGs went from 191 (2015–2018) to 135 (in 2019) in the Open-Prescribing database to accommodate this change. Therefore, where we have analyzed prescribing trends by CCG, we have only examined the 118 CCGs that remained unchanged throughout the analysis period (2015–2019). To examine variations in prescribing across CCGs in England, and to identify CCGs for further analysis, the number of prescription items for the top 5 most prescribed antidepressants (citalopram, amitriptyline, sertraline, mirtazapine and fluoxetine) was summed for each CCG. Population estimates for each CCG were obtained

from the Office for National Statistics and the mid-2018 values used to adjust data for population size (Office for National Statistics, 2019). The top 10 and the lowest 10 antidepressant prescribing CCGs, in terms of total items prescribed/population of CCG, were identified. Local CCG formularies for each of these 20 CCGs, obtained from the relevant CCG's or the equivalent netFormulary platform, were used to identify any differences in antidepressant prescribing guidance across the CCGs.

To identify whether socioeconomic factors might contribute to differences in prescribing practice, the 2019 index of multiple deprivation (IMD) average scores were obtained for each CCG (Oxford Consultants for Social Inclusion, 2019). The IMD score is a relative measure of deprivation incorporating education, income, employment, health and crime facets.

2.1. Statistical analysis

InVivo Stat 3.7.0.0 software was used to summarise and analyse the data (Clark et al., 2012). A linear regression analysis was used to investigate the relationship between IMD score and items prescribed/population with Pearson's correlation coefficient used as a measure of the strength of the association. Linear regressions were also used to evaluate the change in items prescribed over time and by region of England.

3. Results

We found a 25% increase in the annual number of the 10 most prescribed antidepressant items in England, from 58 to 72 million 2015–2019 (Table 1, Fig. 1). All of these are generic medicines and account for 96% of all antidepressant prescribing. The selective serotonin reuptake inhibitor (SSRI) citalopram was the most popular antidepressant prescribed with over 71 million items in 5 years (Table 1, Fig. 1). The number of prescriptions for the SSRI sertraline increased every year, from 9.3 to 16.7 million in 2019. Over the same period,

Table 1

The 10 most prescribed antidepressant and cardiovascular medicines in England 2015–2019.

Antidepressant	Drug Class	Total items prescribed	Total cost (£)
Citalopram	SSRI	71,177,723	88,775,221
Amitriptyline	TCA	65,908,492	122,208,111
Sertraline	SSRI	64,619,046	92,896,634
Mirtazapine	Other	40,722,592	68,983,897
Fluoxetine	SSRI	32,928,229	63,428,155
Venlafaxine	SNRI	20,513,043	181,241,748
Duloxetine	SNRI	10,281,654	91,508,884
Paroxetine	SSRI	6,929,370	25,822,303
Trazodone	Other	5,588,382	107,441,782
Escitalopram	SSRI	5,219,690	12,928,482
Atorvastatin	Lipid regulating drug	184,496,120	269,222,364
Ramipril	ACE inhibitor	140,035,650	210,994,193
Amlodipine	Calcium channel blocker	139,431,269	184,955,330
Simvastatin	Lipid regulating drug	138,347,044	154,214,122
Aspirin	Antiplatelet (COX 1 inhibitor)	124,613,771	102,131,695
Bisoprolol fumarate	β blocker	111,419,052	107,395,429
Furosemide	Loop diuretic	60,773,842	72,411,390
Bendroflumethiazide	Thiazide diuretic	55,706,038	47,572,919
Losartan potassium	Angiotensin receptor blocker	47,220,853	118,916,648
Warfarin sodium	Anticoagulant	47,213,118	73,855,343

Antidepressants are listed in the top half and cardiovascular medicines in the bottom half of the table. All medicines are ranked in descending order according to the number of items prescribed. The drug class was obtained from the summary of product characteristics for the relevant medicine. ACE (angiotensin converting enzyme), COX-1 (cyclooxygenase 1), SSRI (Selective serotonin reuptake inhibitor), SNRI (serotonin noradrenaline reuptake inhibitor), TCA (Tricyclic antidepressant).

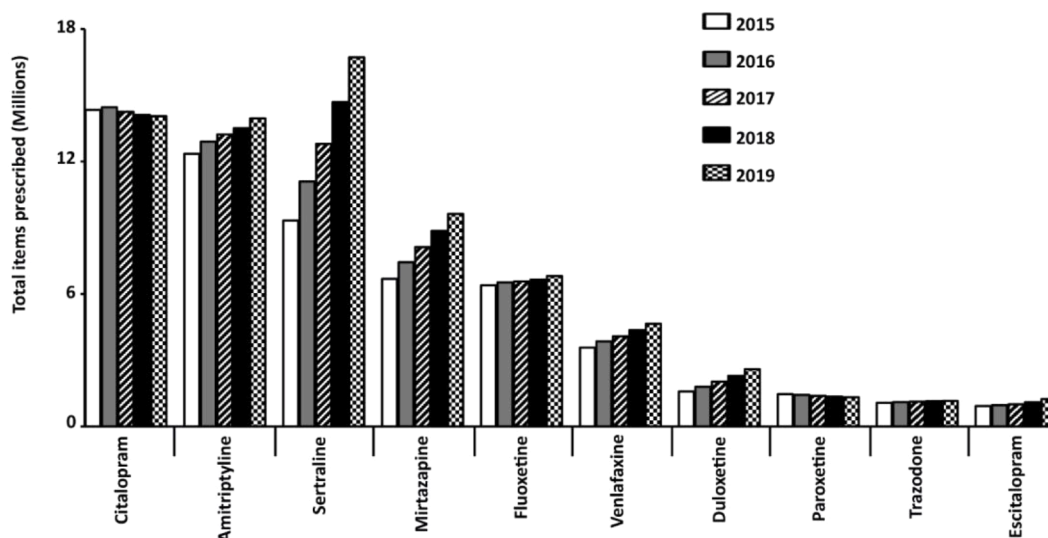


Fig. 1. Annual number of prescription items for the 10 most prescribed antidepressants in England 2015–2019. Antidepressants are ranked from left to right according to the greatest number of items prescribed in each calendar year.

prescriptions for mirtazapine (an atypical antidepressant acting as presynaptic α_2 adrenergic receptor antagonist, also known as a noradrenergic and specific serotonergic antidepressant (NaSSA)) increased from 6.7 to 9.6 million. The annual increase in prescriptions of sertraline was at a quicker rate than mirtazapine; the number of sertraline items prescribed increased by on average 2 million year on year, 2.7 times higher than the mirtazapine annual rise (increasing by 0.7 million items per year) (Fig. 1). Other antidepressants were prescribed at almost constant levels year on year.

Despite an increase in antidepressant items prescribed, we found an overall 27.8% decrease in the cost incurred for prescribing these 10 antidepressants from £202 million (2015) to £146 million (2019). The total cost incurred data does not account for how drug costs in primary care may have fluctuated for any item and therefore the overall trend may mask differing trends for individual drugs. Fig. 2 shows the total cost and the number of items prescribed for each of the top 10 antidepressants, cumulatively 2015–2019. Citalopram is one of the cheapest antidepressants (£89 million) and has the highest number of items

prescribed over 5 years (71 million). On the other hand, venlafaxine is the most expensive antidepressant in terms of costs incurred (£181 million) but has one of the lowest total number of items prescribed over 5 years (21 million) (Fig. 2, Table 1).

We investigated whether there were variations in antidepressant prescribing across CCGs. The number of items for the 5 most prescribed antidepressants (accounting for 82% of total antidepressant items prescribed) was adjusted to account for the population of each CCG and then ranked. On this basis, the top 10 (high antidepressant prescribing) and the bottom 10 (low antidepressant prescribing) CCG's were selected for further analysis. The mean (+/- SD) increase in antidepressant prescribing was 27.3% +/- 6.4% for the top 10 antidepressant prescribing CCGs, compared to 24.6% +/- 6.5% for the bottom 10 CCGs over the full 5-year study period (2015–2019) (Table 2). Citalopram, amitriptyline and sertraline were the most prescribed antidepressants in each of the CCGs. The only exception was Brent CCG where amitriptyline was the most prescribed antidepressant during the study period 2015–2018 but this was overtaken by sertraline in 2019. For both the highest 10 and

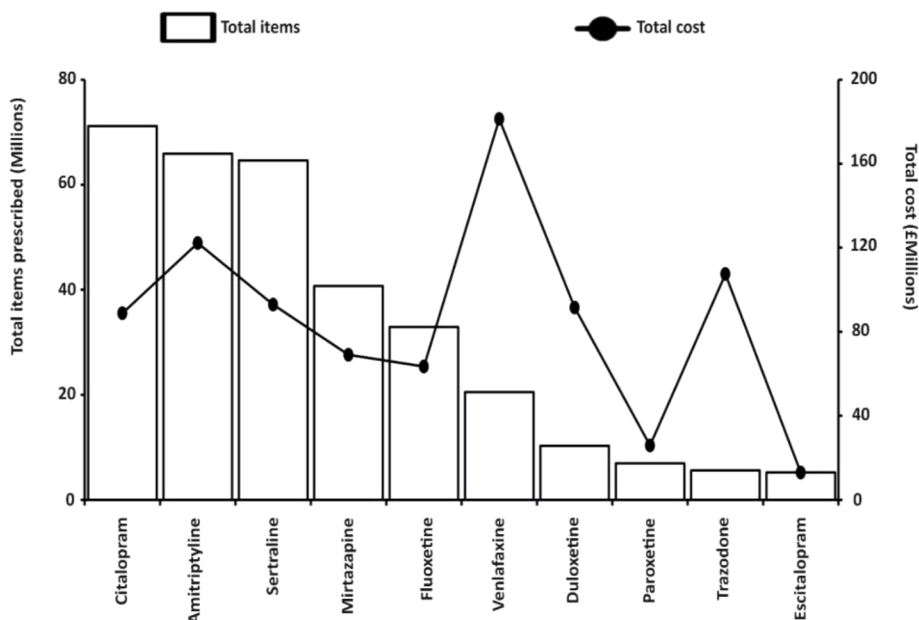


Fig. 2. Total cost (line graph) and total items prescribed (columns) for the 10 most prescribed antidepressants in England 2015–2019.

Table 2

Characteristics of clinical commissioning groups (CCGs) with highest (top 10) and lowest (bottom 10) numbers, cumulatively, of the 5 most prescribed antidepressant items/ population of CCG in England 2015–2019.

CCG name	Total items prescribed cumulatively for top 5 antidepressants ¹	% increase in AD prescribing ²	Population ³	IMD average score ⁴	Rank of IMD average score ⁵	Items/ population of CCG ⁶
Blackpool	1,428,981	20.7	139,305	45.04	2	10.26
Sunderland	2,484,968	40.1	277,417	30.59	30	8.96
Barnsley	2,039,857	30.2	245,199	29.93	32	8.32
South Tyneside	1,177,825	27.7	150,265	31.51	24	7.84
North Tyneside	1,579,118	24.9	205,985	22.28	85	7.67
Knowsley	1,137,808	22.5	149,571	43.01	3	7.61
St Helens	1,328,490	27.5	180,049	31.52	23	7.38
Newcastle Gateshead	3,698,904	27.9	502,704	29.15	39	7.36
Salford	1,844,764	18.0	254,408	34.21	12	7.25
Hull	1,844,619	33.1	260,645	40.56	5	7.08
Hillingdon	845,994	18.8	304,824	18.22	120	2.78
Hounslow	749,529	26.0	270,782	21.49	94	2.77
Newham	932,844	32.3	352,005	29.58	34	2.65
Ealing	905,920	37.4	341,982	22.71	78	2.65
Waltham Forest	659,944	21.5	276,700	25.21	64	2.39
West London	535,363	19.1	226,099	22.35	84	2.37
City and Hackney	669,171	24.4	288,371	32.09	21	2.32
Brent	725,697	21.7	330,795	25.56	62	2.19
Harrow	547,811	16.8	250,149	15.03	151	2.19
Redbridge	626,867	28.4	303,858	17.20	131	2.06

¹ The 5 most prescribed antidepressants are citalopram, amitriptyline, sertraline, mirtazapine and fluoxetine. ² Antidepressant (AD) prescribing in 2019 as a % of 2015 values. ³ Mid-2018 population estimates for CCGs in England from the Office for National Statistics. ⁴ The Index of Multiple Deprivation (IMD) average scores for 2019 for each CCG. ⁵ Ranking of IMD average score across all CCGs out of 191. The higher the IMD average score (e.g. 45.04), the lower the rank of average score (e.g. 2), and the more deprived a particular CCG area is. ⁶ Calculated by the formula: total items cumulatively for 5 most prescribed antidepressants per CCG divided by CCG population.

lowest 10 antidepressant prescribing CCGs, sertraline prescriptions are rising reflecting the national picture (Fig. 1). For example, in Knowsley (top 10) and Hounslow (bottom 10), citalopram was the most prescribed antidepressant in 2015/2016 but it was overtaken by sertraline in 2018/2019. Across these 20 CCGs, local formularies providing guidance on antidepressant prescribing were found to be broadly similar. Sertraline, fluoxetine and citalopram are the first line treatments of choice in a patient with depression. Mirtazapine is a second-line treatment in patients not responding to, or that cannot tolerate, the SSRI treatments. Exceptions to this general agreement amongst the CCGs are shown in

Supplementary Table 1.

We used the IMD score to rank 118 CCGs to look at the influence of socioeconomic factors on antidepressant prescribing. The higher the IMD score, the more deprived the area is (e.g. Blackpool CCG IMD score = 45.04), and the higher the rank (close to 1) of the CCG (e.g. Blackpool is ranked 2). Table 2 shows the IMD score for CCGs with the highest and lowest levels of antidepressant prescribing. When the number of antidepressant items for only the 5 most prescribed antidepressants is considered, adjusted to account for population, there are 5 times as many antidepressant prescriptions in Blackpool than in Redbridge

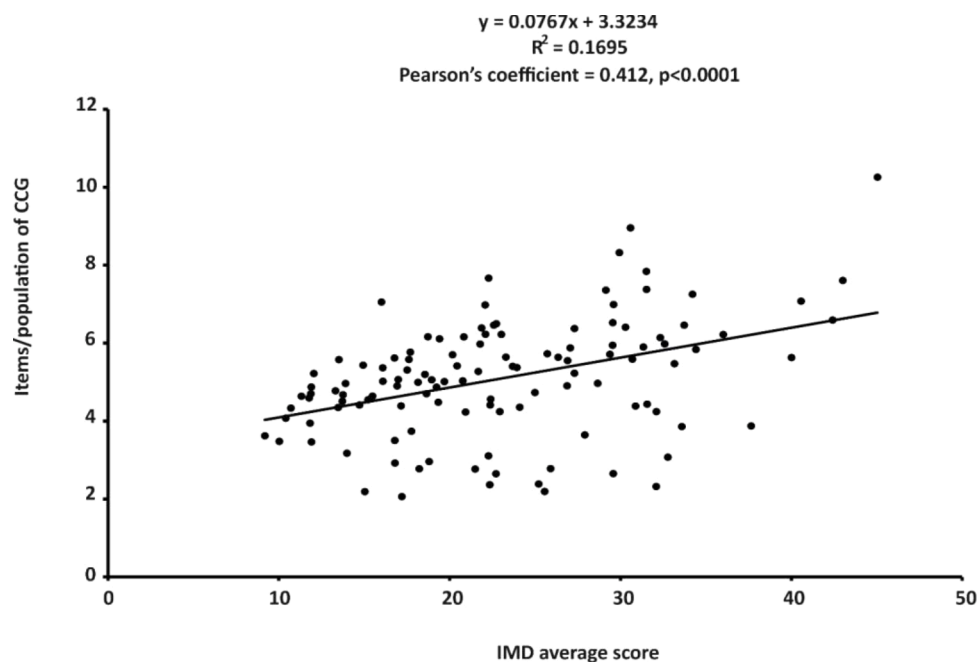


Fig. 3. Correlation between total items prescribed (2015–2019) cumulatively for the 5 most prescribed antidepressants/population of CCG and CCG IMD average score in 118 CCGs in England. The line of best fit indicating the correlation is shown. IMD (Index of Multiple Deprivation), CCGs (clinical commissioning groups).

(Table 2). Looking across all 118 CCGs (Fig. 3), the IMD score is positively correlated with the cumulative number of antidepressant prescription items (Pearson's coefficient = 0.412, $P < 0.0001$). For every one-point increase in the IMD score, the number of antidepressant items prescribed per population of CCG increases by 0.08.

To provide context for the antidepressant data, Table 1 also shows the 10 most prescribed cardiovascular medicines in the same study period. The total items prescribed cumulatively for the 10 most prescribed cardiovascular medicines account for 65% of all cardiovascular prescribing and increased by 2.75% from 207 million (2015) to 213 million (2019). At the same time, the total cost incurred dropped by 3.8% from £295 million (2015) to £284 million (2019) (Table 1). Results from linear regression analyses (Supplementary Table 3) show that eight of the 10 antidepressants included had a mean increase in items prescribed over time whereas only five of the cardiovascular drugs showed increases. Comparing prescribing between regions of England indicated that almost all antidepressants in all regions of England were prescribed more than in London (Supplementary Table 4a). For cardiovascular medicines the picture was more mixed with some areas prescribing more of one medication than the London region while others prescribed at a lower frequency (Supplementary Table 4b).

Overall, there were 5.522 billion items dispensed in the community in England 2015–19, at a total cost of £45.5 billion (Table 3). The 10 most prescribed antidepressant items represent 5.87% of the total items dispensed, at a cost of £0.9 billion or 1.88% of the total cost (Table 3). NHSBSA (2020) data showed that citalopram (#15,#16), amitriptyline (#18,#17), and more recently sertraline (#17–#14 in 2017–2019) have been in the top 20 most prescribed items for all medicines in England from 2015–2019. For the 10 most prescribed cardiovascular medicines, over the study period, there were 3.2 times more cardiovascular prescription items than the number of antidepressant items, accounting for 19% of the total items dispensed. NHSBSA data also showed that simvastatin (#1) was the most prescribed medicine in 2015, overtaken by atorvastatin in 2016–2019 with 45.8 million prescription items in 2019 alone. This is expected given that in England 14% of adults aged 16 and over reported having had any doctor-diagnosed cardiovascular disease in 2017 (Scholes and Mindell, 2018), unchanged since 2011, whereas depression prevalence is 3.8% of the population (McManus et al., 2016).

4. Discussion

We found that antidepressant prescribing for the 10 most prescribed antidepressants in England has risen 25% from 58 million in 2015 to 72

million in 2019. These 10 antidepressants account for 96% of all antidepressant prescribing. Of the top 10 most prescribed antidepressants, the SSRI citalopram was the number one item prescribed and between 2015–2019 was among the top 20 most prescribed medicines in England across all prescription items. The rise in antidepressant prescribing is likely accounted for by rising year on year prescriptions for sertraline and mirtazapine. Most other antidepressants were prescribed at comparable levels year on year. Over the same period the cost of antidepressant prescribing has fallen 27.8%. This fall in prescription costs may be due to a competitive generics market facilitating the supply of lower cost generic medicines to the NHS (Andalo, 2019).

Strengths and limitations

Presenting antidepressant prescribing data in isolation may create the unwarranted impression that antidepressant prescribing outstrips all other medications. A strength of this study is that we have reported antidepressant prescribing trends alongside physical health prescribing. This reduces the risk of stigmatizing antidepressant use which is a significant deterrent to patients seeking help and treatment (Castaldelli-Maia et al., 2011; Nutt et al., 2014; Arnaez et al., 2020). Between 2006 and 2016, the number of cardiovascular prescriptions grew by 36.2% to around 320 million items, while the number for the central nervous system increased by 60.1% to about 207 million (Ewbank et al., 2018). We have shown that prescribing for the 10 most prescribed cardiovascular medicines accounts for 19%, while the 10 most prescribed antidepressants accounts for 5.9%, of all prescription items in England 2015–2019. The total cost incurred for the 10 most prescribed cardiovascular medicines is 2.95% and for the 10 most prescribed antidepressants is 1.88% of the total prescription costs. This is an underestimate of prescribing for cardiovascular medicine as the top 10 cardiovascular medicines represents only 65% of all cardiovascular medicines while the top 10 antidepressants represent 96% of all antidepressant prescribing.

A limitation of using the Open Prescribing database is that prescribing information is not linked to patients. So, while it is useful for identifying prescribing trends, on a group level, we cannot identify patient numbers nor characteristics nor indication the medicine is prescribed for, nor the duration or quantity of the medicine prescribed. Antidepressants are used in other disorders, for example neuropathic pain (amitriptyline), urinary incontinence (duloxetine) and high levels of amitriptyline prescribing may reflect a high incidence of neuropathic pain, rather than any change in antidepressant prescribing per se. Using

Table 3

Comparison of antidepressant and cardiovascular prescribing as a proportion of the total number of items and cost for prescriptions in England 2015–2019.

Year	Total items dispensed in England (Millions) ¹	Total cost (£Millions) ¹	Total AD items dispensed (Millions) ²	Total cost AD items (£Millions) ³	% of total items dispensed (AD) ⁴	% of total cost (AD) ⁵	Total CV items dispensed (Millions) ⁶	Total cost CV items (£Millions) ⁷	% of total items dispensed (CV) ⁸	% of total cost (CV) ⁹
2015	1,084	9,267	58	202	5.32	2.18	207	295	19.11	3.19
2016	1,104	9,205	62	185	5.57	2.01	209	257	18.92	2.79
2017	1,106	9,167	65	171	5.84	1.87	210	268	18.95	2.92
2018	1,109	8,831	68	152	6.14	1.72	211	237	19.01	2.69
2019	1,120	9,079	72	146	6.44	1.6	213	284	19.01	3.13
Total	5,522	45,548	324	855	5.87	1.88	1,049	1,342	19	2.95

¹ Values obtained from the prescription cost analysis for England 2019 data from the NHS Business Services Authority – the additional analysis tables Table A1 (Total items, cost, number of items and cost per capita, 2014 to 2019). Values are rounded to the nearest million for ease of display. Available from; <https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis/prescription-cost-analysis-england-2019>

² Total items dispensed per calendar year for the top 10 antidepressants (AD) (Table 1) from the Open Prescribing Database.

³ Total cost incurred for the top 10 antidepressants (AD) per calendar year from the Open Prescribing Database.

⁴ Antidepressant (AD) prescribing (top 10 items prescribed) expressed as a percentage of the total items dispensed per calendar year.

⁵ Cost of AD prescribing (top 10 items prescribed) per calendar year, expressed as a percentage of the total cost of prescribing in England.

⁶ Total items dispensed per calendar year for top 10 prescribed cardiovascular (CV) medicines (Table 1) from the Open Prescribing Database.

⁷ Total cost incurred per calendar year for top 10 prescribed cardiovascular (CV) medicines from the Open Prescribing Database.

⁸ Cardiovascular (CV) prescribing (top 10 items prescribed) expressed as a percentage of the total items dispensed per calendar year.

⁹ Cost of cardiovascular prescribing (CV) (top 10 items prescribed), per calendar year, expressed as a percentage of the total cost of prescribing in England.

a different database, the Clinical Practice Research Datalink (CPRD), where patient diagnoses are linked with prescriptions, an analysis of antidepressant prescribing has shown that 63% of antidepressant prescribing was for depression, 38% for anxiety and 5% for neuropathic pain (Iwagami et al. 2017). The Open Prescribing database does not provide information on dosing. As low dose amitriptyline is likely used for pain rather than depression (Moore et al. 2015), dosing information may allow inferences to be made as to the indication for which amitriptyline was prescribed.

This study has focused on group level analysis and interpretation of data and therefore there is no risk of committing ecological fallacy. We are not able to draw any conclusions about individual patients and any prescriptions they receive for antidepressants or cardiovascular disease medications or individual socioeconomic status. We have reported the CCG-level of antidepressant prescribing in this study and not prescribing at an individual patient or GP practice level. While this gives a good overview of prescribing of antidepressants in English CCGs, we emphasise that this is not at a GP practice or patient level data. Future studies will look at antidepressant prescribing in individual patients to understand more about how patients switch between different treatments and length of treatment. Also, the IMD average score for 2019 (most recent) has been used as a measure to assess deprivation and to explain variation in prescribing across different CCGs. IMD scores are released by the office of national statistics every 4 to 5 years so any variation of deprivation levels in the CCGs over the study period cannot be accounted for with this measure.

Comparison with existing literature

Our data are in line with previous reports showing increasing antidepressant prescribing in England for at least the last 10 years (Balinskaite, 2019) and a similar pattern is seen globally (for example, Gualano et al. 2014; Soleymani et al. 2018). One reason accounting for rising prescribing might be better treatment of patients, perhaps influenced by prescribing guidance. In terms of the specific antidepressants being prescribed, our findings likely reflect adherence to key evidence-based prescribing guidelines which are incorporated into CCG formularies. Our analysis of a sample of CCG local formularies showed little difference between the highest and lowest antidepressant prescribing CCGs. Sertraline prescriptions rose fastest of all the antidepressants and has been reported to have slightly higher efficacy than other SSRIs. NICE and British Association for Psychopharmacology (BAP) guidelines recommend the use of sertraline for patients with a co-morbid chronic physical health condition because of lesser chances of drug-drug interactions (NICE, 2009a; NICE, 2009b; Cleare et al., 2015). A study by Hoehn-Saric et al. (2000) showed that sertraline is more effective in patients with co-morbid depression and obsessive-compulsive-disorder. A meta-analysis of 59 studies by Cipriani et al. (2010) showed that sertraline has higher efficacy than fluoxetine and was tolerated better than mirtazapine, paroxetine and amitriptyline during acute phase of depression treatment. Furthermore, sertraline has proved effective in managing seasonal depression (Moscovitch et al., 2004). Prescriptions for mirtazapine are also rising year on year. An open multicentre study including 4771 patients with major depressive episode found that mirtazapine showed a significant and quicker reduction of suicidal thoughts than SSRIs (Lavergne et al., 2005). This suggests that mirtazapine may be safer to use in depressed patients who are more prone to suicidal thoughts, such as adolescents (Strandheim et al., 2014).

The level of antidepressant prescribing was influenced by the relative socio-economic deprivation in different regions, in line with previous reports on mental health treatments (Taylor et al., 2019; Von Soest et al., 2012; Delphin-Rittmon et al., 2015; Giebel et al., 2020). Across 118 CCGs in England, antidepressant prescribing levels, adjusted for population, were positively correlated with the IMD average score. The degree of scatter in the data point to additional factors influencing the

volume of antidepressant prescribing. Additional socio-economic factors that have been linked to antidepressant prescribing include employment status, educational achievement, perceived social class, patient age and sex (Butterworth et al., 2013; Lewer et al., 2015; Halonen et al., 2018). Our analysis identified that high antidepressant prescribing CCGs are geographically located in the North West and North East of England, whereas the low prescribing CCGs are in the greater London area, similar to other studies (Balinskaite, 2019). Antidepressant prescribing has also been identified to be higher in urban locations than in rural areas (Grigorioglou et al., 2020; Morrison et al., 2009). These factors have a complex interplay affecting antidepressant prescribing.

Implications for research and/or practice

Antidepressant prescribing is increasing in England, specifically sertraline and mirtazapine, in line with clinical guidelines. While relative socio-economic deprivation is a contributing factor, it is not clear what is driving this increase. Whether the rise in antidepressant prescribing seen here reflects changes in the recognition and treatment of depression in primary care or a higher prevalence of depression, or a combination of these factors, remains to be determined. Additionally, the risk of significant withdrawal effects on stopping antidepressant treatment remains a concern and a potential contributory factor to increasing levels of prescribing (Davies and Read, 2019; Taylor et al. 2019). Reflecting these concerns, the National Institute for Health and Care Excellence has updated its guidance to recognize the severity and length of antidepressant withdrawal (NICE, 2009a).

In conclusion, given the potential concerns of the impact of COVID-19 on mental health, this pre-COVID-19 analysis provides a baseline against which to assess antidepressant prescribing in the future. Recent reports suggest that the number of antidepressant prescriptions made in general practice in the 6 months from April 1st 2020 was 3.9% higher than the corresponding period in 2019 (Armitage, 2021). However, whether this increase reflects changes during the pandemic or whether it reflects the year on year increase in antidepressant prescribing remains to be determined (Walker et al. 2021).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Hasnain M. Lalji: Data curation, Formal analysis, Writing – original draft. **Anita McGrogan:** Data curation, Writing – review & editing, Writing – original draft. **Sarah J. Bailey:** Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

None

Acknowledgment

Anneka Mitchell for initial help with the open prescribing database. Sarah Jones for comments on an early draft of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jadr.2021.100205](https://doi.org/10.1016/j.jadr.2021.100205).

References

- Andalo, D., 2019. Cost of prescriptions dispensed in community falls for third year running. *Pharm. J.* 302 <https://doi.org/10.1211/PJ.2019.20206358> online |.
- Armitage, R., 2021. Antidepressants, primary care, and adult mental health services in England during COVID-19. *Lancet Psych.* 8 (2), e3.
- Arnaez, J.M., Krendl, A.C., McCormick, B.P., Chen, Z., Chomistek, A.K., 2020. The association of depression stigma with barriers to seeking mental health care: a cross-sectional analysis. *J. Ment. Health* 29, 182–190.
- Balinskaite, V., 2019. Trends and geographical variation in antidepressant prescribing in primary care in England: a descriptive analysis. *Lancet* 394, S21.
- Butterworth, P., Olesen, S.C., Leach, L.S., 2013. Socioeconomic differences in antidepressant use in the PATH through life study: evidence of health inequalities, prescribing bias, or an effective social safety net? *J. Affect. Disord.* 149, 75–83.
- Castaldelli-Maia, J.M., Scomparini, L.B., Andrade, A.G.D., Bhugra, D., De Toledo Ferraz Alves, T.C., D'Elia, G., 2011. Perceptions of and attitudes toward antidepressants: stigma attached to their use—a review. *J. Nerv. Ment. Dis.* 199, 866–871.
- Cipriani, A., La Ferla, T., Furukawa, T.A., Signoretti, A., Nakagawa, A., Churchill, R., McGuire, H., Barbui, C., 2010. Sertraline versus other antidepressive agents for depression. *Cochrane Database Syst. Rev.* 4 <https://doi.org/10.1002/14651858.CD006117.pub4>. CD006117-CD006117.
- Clark, R.A., Shoaib, M., Hewitt, K.N., Stanford, S.C., Bate, S.T., 2012. A comparison of InVivoStat with other statistical software packages for analysis of data generated from animal experiments. *J. Psychopharmacol.* 26, 1136–1142.
- Cleare, A., Pariante, C.M., Young, A.H., Anderson, I.M., Christmas, D., Cowen, P.J., Dickens, C., Ferrier, I.N., Geddes, J., Gilbody, S., Haddad, P.M., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R.H., Ramchandani, P., Scott, J., Taylor, D., Uher, R., 2015. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British association for psychopharmacology guidelines. *J. Psychopharmacol.* 29, 459–525.
- Davies, J., Read, J., 2019. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: are guidelines evidence-based? *Addict. Behav.* 97, 111–121.
- Delphin-Rittmon, M.E., Flanagan, E.H., Andres-Hyman, R., Ortiz, J., Amer, M.M., Davidson, L., 2015. Racial-ethnic differences in access, diagnosis, and outcomes in public-sector inpatient mental health treatment. *Psychol. Serv.* 12, 158–166.
- L. Ewbank, D. Omojomolou, K. Sullivan, H. McKenna, 2018. The rising cost of medicines to the NHS what's the story? <https://www.kingsfund.org.uk/sites/default/files/2018-04/Rising-cost-of-medicines.pdf> (accessed 30 June 2020).
- Giebel, C., Corcoran, R., Goodall, M., Campbell, N., Gabbay, M., Daras, K., Barr, B., Wilson, T., Kullu, C., 2020. Do people living in disadvantaged circumstances receive different mental health treatments than those from less disadvantaged backgrounds? *BMC Public Health* 20, 651.
- Grigoroglou, C., Munford, L., Webb, R.T., Kapur, N., Ashcroft, D.M., Kontopantelis, E., 2020. Prevalence of mental illness in primary care and its association with deprivation and social fragmentation at the small-area level in England. *Psychol. Med.* 50, 293–302.
- Gualano, M.R., Bert, F., Mannocci, A., La Torre, G., Zeppego, P., Siliquini, R., 2014. Consumption of antidepressants in Italy: recent trends and their significance for public health. *Psychiatr. Serv.* 65, 1226–1231.
- Halonen, J.I., Koskinen, A., Kouvonen, A., Varje, P., Pirkola, S., Väänänen, A., 2018. Distinctive use of newer and older antidepressants in major geographical areas: a nationally representative register-based study. *J. Affect. Disord.* 229, 358–363.
- Hoehn-Saric, R., Ninan, P., Black, D.W., Stahl, S., Greist, J.H., Lydiard, B., McElroy, S., Zajecka, J., Chapman, D., Clary, C., Harrison, W., 2000. Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Arch. Gen. Psychiatry* 57, 76–82.
- Iwagami, M., Tomlinson, L.A., Mansfield, K.E., McDonald, H.I., Smeeth, L., Nitsch, D., 2017. Prevalence, incidence, indication, and choice of antidepressants in patients with and without chronic kidney disease: a matched cohort study in UK clinical practice research datalink. *Pharmacoepidemiol. Drug Saf.* 26 (7), 792–801.
- Joint Formulary Committee, 2020. British National Formulary (online). BMJ Group and Pharmaceutical Press, London. <http://www.medicinescomplete.com>. accessed 25 February 2020.
- Lavergne, F., Berlin, I., Gamma, A., Stassen, H., Angst, J., 2005. Onset of improvement and response to mirtazapine in depression: a multicenter naturalistic study of 4771 patients. *Neuropsychiatr. Dis. Treat.* 1, 59–68.
- Lewer, D., O'Reilly, C., Mojtatabi, R., Evans-Lacko, S., 2015. Antidepressant use in 27 European countries: associations with sociodemographic, cultural and economic factors. *Br. J. Psychiatry* 207, 221–226.
- McManus, S., Bebbington, P., Jenkins, R., Brugha, T., 2016. Mental Health and Wellbeing in England: Adult Psychiatric Morbidity Survey 2014, eds. NHS Digital, Leeds.
- Middleton, H., Moncrieff, J., 2011. They won't do any harm and might do some good: time to think again on the use of antidepressants? *Br. J. Gen. Pract.* 61, 47–49.
- Middleton, N., Gunnell, D., Whitley, E., Dorling, D., Frankel, S., 2001. Secular trends in antidepressant prescribing in the UK, 1975–1998. *J. Public Health* 23, 262–267.
- Moore, M., Yuen, H.M., Dunn, N., Mullee, M.A., Maskell, J., Kendrick, T., 2009. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. *BMJ* 339, b3999.
- Moore, R.A., Derry, S., Aldington, D., Cole, P., Wiffen, P.J., 2015. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst. Rev.* 2015 <https://doi.org/10.1002/14651858.CD008242.pub3>. CD008242-CD008242.
- Morrison, J., Anderson, M.-J., Sutton, M., Munoz-Arroyo, R., McDonald, S., Maxwell, M., Power, A., Smith, M., Wilson, P., 2009. Factors influencing variation in prescribing of antidepressants by general practices in Scotland. *Br. J. Gen. Pract.* 59, e25–e31.
- Moscovitch, A., Blashko, C.A., Eagles, J.M., Darcourt, G., Thompson, C., Kasper, S., Lane, R.M., 2004. A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. *Psychopharmacology* 171, 390–397.
- National Institute for Health and Care Excellence (NICE), 2009a. Depression in Adults: Recognition and Management. NICE Guideline CG90. Updated 2020. <https://www.nice.org.uk/guidance/cg90/resources/depression-in-adults-recognition-and-management-pdf-975742636741> (accessed 02 July 2020).
- National Institute for Health and Care Excellence (NICE), 2009b. Depression in Adults with a Chronic Physical Health Problem: Recognition and Management. NICE Guideline CG91. <https://www.nice.org.uk/guidance/cg91/resources/depression-in-adults-with-a-chronic-physical-health-problem-recognition-and-management-pdf-975744316357>. accessed 02 July 2020.
- Scholes, S., Mindell, J.S. (2018) Health Survey for England 2017 Cardiovascular Diseases. <http://healthsurvey.hscic.gov.uk/media/78646/HSE17-CVD-rep.pdf> (accessed 10 June 2020).
- NHS Digital, 2018. Practice level prescribing-glossary of terms. a detailed description of the terms used in this data set. <https://digital.nhs.uk/data-and-information/areas-of-interest/prescribing/practice-level-prescribing-in-england-a-summary/practice-level-prescribing-glossary-of-terms#items> (accessed 15 June 2020).
- NHSBSA, 2020. Prescription cost analysis- England 2019, additional analysis data tables (Table A1). <https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis/prescription-cost-analysis-england-2019> (accessed 26 June 2020).
- Nutt, D.J., Goodwin, G.M., Bhugra, D., Fazel, S., Lawrie, S., 2014. Attacks on antidepressants: signs of deep-seated stigma? *Lancet Psychiat.* 1, 102–104.
- Office for National Statistics, 2019. Table SAPE21DT5: Mid-2018 population estimates for clinical commissioning groups (CCGs) in England by single year of age and sex-national statistics. <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/clinicalcommissioninggroupmidyearpopulationestimates> (accessed 25 February 2020).
- Oxford Consultants for Social Inclusion (OCSI) and Deprivation.org., 2019. English indices of deprivation 2019 (file 13- clinical commissioning group (CCG) summaries (IMD table)). <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019> (accessed 25 February 2020).
- Pfefferbaum, B., North, C.S., 2020. Mental Health and the COVID-19 pandemic. *N. Engl. J. Med.* 383 (6), 510–512.
- Soleymani, F., Taheri, F., Roughead, E., Nikfar, S., Abdollahi, M., 2018. Pattern of antidepressant utilization and cost in Iran from 2006 to 2013 in comparison with other countries. *J. Epidemiol. Glob. Health.* 8, 213–219.
- Spence, D., 2016. Bad medicine: the rise and rise of antidepressants. *Br. J. Gen. Pract.* 66, 573.
- Strandheim, A., Bjerkeset, O., Gunnell, D., Bjørnelv, S., Holmen, T.L., Bentzen, N., 2014. Risk factors for suicidal thoughts in adolescence—a prospective cohort study: the young-HUNT study. *BMJ Open* 4, e005867.
- Tamblyn, R., Bates, D.W., Buckeridge, D.L., et al., 2019. Multinational comparison of new antidepressant use in older adults: a cohort study. *BMJ Open* 9, e027663. <https://doi.org/10.1136/bmjopen-2018-027663>.
- Taylor, S., Annand, F., Burkinshaw, P., Greaves, F., Kelleher, M., Knight, J., Perkins, C., Tran, A., White, M., Marsden, J., 2019. Dependence and withdrawal associated with some prescribed medicines: an evidence review. *Public Health Engl.* https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829777/PHE_PM_report.pdf accessed 15 June 2020.
- Vindegaard, N., Benros, M.E., 2020. COVID-19 pandemic and mental health consequences: systematic review of the current evidence. *Brain Behav. Immun.* 89, 531–542.
- Von Soest, T., Bramness, J.G., Pedersen, W., Wichstrøm, L., 2012. The relationship between socio-economic status and antidepressant prescription: a longitudinal survey and register study of young adults. *Epidemiol. Psych. Sci.* 21, 87–95.
- Walker, A.J., Croker, R., Curtis, H.J., MacKenna, B., Goldacre, B., 2021. Trends in antidepressant prescribing in England. *Lancet Psych.* 8 (4), 278–279.
- World Health Organization (WHO), 2020. Depression. <https://www.who.int/news-room/fact-sheets/detail/depression> (accessed 10 June 2020).
- Xiong, J., Lipsitz, O., Nasri, F., Lui, L.M.W., Gill, H., Phan, L., Chen-Li, D., Iacobucci, M., Ho, R., Majeed, A., McIntyre, R.S., 2020. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. *J. Affect. Disord.* 277, 55–64.