Pharmaco-epidemiology of antidepressant exposure in a UK cohort record-linkage study

Journal of
Psychopharmacology

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Journal:	*Journal of Psychopharmacology*
Manuscript ID	JOP-2018-3504.R2
Manuscript Type:	Original Paper
Date Submitted by the Author:	n/a
Complete List of Authors:	Hafferty, Jonathan; University of Edinburgh, Division of Psychiatry Wigmore, Eleanor; University of Edinburgh, Division of Psychiatry Howard, David; University of Edinburgh, Division of Psychiatry Adams, Mark; University of Edinburgh, Division of Psychiatry Clarke, Toni-Kim; University of Edinburgh, Division of Psychiatry Campbell, Archie; University of Edinburgh, Centre for Genomic and Experimental Medicine MacIntyre, Donald; University of Edinburgh, Psychiatry Nicodemus, Kristin; University of Edinburgh, Centre for Genomic and Experimental Medicine Lawrie, Stephen ; University of Edinburgh, Psychiatry Porteous, David; University of Edinburgh, Centre for Genomic and Experimental Medicine McIntosh, Andrew; University of Edinburgh, Department of Psychiatry
Please list at least 3 keywords which relate to your manuscript::	antidepressants, prevalence, record-linkage, pharmacoepidemiology, adherence
Abstract:	Objective Antidepressants are the most commonly prescribed psychiatric medication but concern has been raised about significant increases in their usage in high income countries. We aimed to quantify antidepressant prevalence, incidence, adherence and predictors of use in the adult population. Method The study record-linked administrative prescribing and morbidity data to the Generation Scotland cohort(GS:SFHS, N=11052), between 2009-16. Prevalence and incidence of any antidepressant use was determined. Antidepressant adherence was measured using Proportion of Days Covered and Medication Possession Ratio. Time-to-event analysis for antidepressant use, within 5 years, for antidepressant naïve GS:SFHS participants was performed to reveal patient-level predictors of use. Results Almost one third (28.0%, 95%CI 26.7-29.1) of the adults in our sample were prescribed at least one antidepressant in the five-year period 2012-16. There was a 30.7% increase in annual prevalence between 2010-2016. Incidence was 2.4(2.3-2.6)% per year. The majority of antidepressant episodes (56.5%) were greater than 9 months and

	adherence was generally high (66.8% with Proportion of Days Covered >80%). Only 11.6(10.2-13.0)% of antidepressant episodes were evidently reviewed by outpatient psychiatry. Predictors of new antidepressant use included history of affective disorder, being female, physical comorbidities, higher neuroticism scores, and lower cognitive function scores. Conclusions Antidepressant prevalence is greater than previously reported but incidence remains relatively stable. We found the majority of antidepressant episodes to be of relatively long duration with good estimated adherence. Increased long-term use among existing (and returning) users, along with wider ranges of indications for antidepressants, has significantly increased the prevalence of these medications.

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Jonathan D Hafferty(MD)[1*], Eleanor M Wigmore(PhD)[1], David M Howard(PhD) [1], Mark J Adams(PhD)[1], Toni-Kim Clarke(PhD)[1], Archie I Campbell(MA)[2], Donald J MacIntyre(MD)[1], Kristin K Nicodemus(PhD)[2,3], Stephen M Lawrie(MD) [1], David J Porteous(PhD) [2,3], Andrew M McIntosh(MD) [1,3]

1. Division of Psychiatry, Royal Edinburgh Hospital, University of Edinburgh, Edinburgh, UK, EH10 5HF
2. Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, Western General Hospital, University of Edinburgh, Edinburgh, UK
3. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

*Corresponding author

JDH, EMW, AIC, DJM, KKN, SML, DJP and AMM were involved in the conception and design of the study. JDH, EMW, DMH, MJA, TKC, AIC were involved in the analysis and interpretation of the data.

Drafting of the article, critical revisions, and final approval of the version to be published was performed by JDH, EMW, DMH, MJA, TKC, AIC, DJM, KKN, SML, DJP and AMM.

Declaration of Conflict of Interest.

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of the article.

Funding.

JDH gratefully acknowledges receipt of an MRC/MRF PsySTAR PhD fellowship. Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates [CZD/16/6] and the Scottish Funding Council [HR03006]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "STratifying Resilience and Depression Longitudinally" (STRADL) Reference 104036/Z/14/Z).

Ethical Approval.

All components of STRADL received formal, national ethical approval from the NHS Tayside committee on research ethics (reference 14/SS/0039).

Article Word Count : 5111

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

Abstract (241 words)

Objective

Antidepressants are the most commonly prescribed psychiatric medication but concern has been raised about significant increases in their usage in high income countries. We aimed to quantify antidepressant prevalence, incidence, adherence and predictors of use in the adult population.

Method

The study record-linked administrative prescribing and morbidity data to the Generation Scotland cohort(N=11052), between 2009-16. Prevalence and incidence of any antidepressant use was determined. Antidepressant adherence was measured using Proportion of Days Covered and Medication Possession Ratio. Time-to-event analysis for incident antidepressant use within 5 years of GS:SFHS recruitment was performed to reveal patient-level predictors of use.

Results

Almost one third (28.0%, 95%CI 26.9-29.1) of the adults in our sample were prescribed at least one antidepressant in the five-year period 2012-16. There was a 36.2% increase in annual prevalence between 2010 and 2016. Incidence was 2.4(2.1-2.7)% per year. The majority of antidepressant episodes (57.6%) were greater than 9 months duration and adherence was generally high (69.0% with Proportion of Days Covered >80%). Predictors of new antidepressant use included history of affective disorder, being female, physical comorbidities, higher neuroticism scores, and lower cognitive function scores.

Conclusions

Antidepressant prevalence is greater than previously reported but incidence remains relatively stable. We found the majority of antidepressant episodes to be of relatively long duration with good estimated adherence. Our study supports the hypothesis that increased long-term use among existing (and returning) users, along with wider ranges of indications for antidepressants, has significantly increased the prevalence of these medications.

Introduction

Antidepressants are the most commonly prescribed psychiatric medication and one of the most commonly prescribed medicines(Raymond et al., 2007; Olfson and Marcus, 2009). In the last 30 years, there has been a significant increase in antidepressant usage in high income countries(Ilyas and Moncrieff, 2012; Kendrick et al., 2015; Moore et al., 2009; Meijer et al., 2004; Huijbregts et al., 2017; Lockhart and Guthrie, 2011; Munoz-Arroyo et al., 2006; Petty et al., 2006; Raymond et al., 2007; Exeter et al., 2009; Mojtabai and Olfson, 2014; Olfson and Marcus, 2009; Gonzalez-Lopez et al., 2015; Mars et al., 2017). Antidepressant consumption has reportedly increased 400% in the USA between 1998-2008(Pratt et al., 2011), while antidepressant prescriptions in the UK increased twofold between 1995-2011(Spence et al., 2014). Comparison of electronic prescribing records in five European countries suggests that antidepressant prescribing is comparatively high in the UK for adults aged 20-60, especially among females(Abbing-Karahagopian Huerta et al., 2014). In the USA, annual antidepressant prevalence for 2011 was estimated at 14.4%(Zhong et al., 2014) compared to an annual prevalence of depression in 2015 of 6.7%(National Institute of Mental Health, 2017b) and 2.7% for generalized anxiety disorder(National Institute of Mental Health, 2017a).

The extent to which this rising tide of antidepressant prescribing is appropriate to clinical need is an area of ongoing controversy(Cruickshank et al., 2008; Lockhart and Guthrie, 2011; Reid I, 2013; Spence D, 2013). Antidepressant use has risen to a significantly greater degree than any rise in the prevalence of depression(Munoz-Arroyo et al., 2006) or of anxiety disorders(Bandelow and Michaelis, 2015). There is some evidence that illnesses treated by these medications, such as depression and anxiety, are now better recognised and treated at the primary care level(Kessler et al., 2005) and that GPs and patients are more willing to utilise antidepressant treatment for a wider range of indications(Trifiro et al., 2007; Kessler et al., 2005; Mojtabai and Olfson, 2014). It has also been argued that a greater antidepressant prescription rate does not correspond to an upsurge in incident cases, but rather represents a significant lengthening in the treatment period for existing users(Moore et al., 2009; Raymond et al., 2007; Mojtabai and Olfson, 2014; Mars et al., 2017; Reid I, 2013). Advisory bodies such as NICE and the WHO now recommend a minimum of six to nine months antidepressant treatment for moderate major depressive disorder (MDD) and two years or more treatment for chronic or relapsing illness(Petty et al., 2006; Reid I, 2013; Mars et al.,

2017). This can serve to increase prescribing prevalence rates without necessarily increasing incidence.

Nevertheless, concerns have been raised about a medicalisation of ordinary distress with antidepressants(Hollinghurst et al., 2005), and there are ongoing debates about the efficacy of antidepressants in mild-moderate depressive illness(Olfson and Marcus, 2009; Kirsch et al., 2008; Cipriani et al., 2018). There has been increased attention to potential adverse effects of antidepressants(Bet et al., 2013), including discontinuation syndromes(Petty et al., 2006; Bosman et al., 2016), adverse physical outcomes in older adults(Coupland et al., 2011), risk of epilepsy(Hill et al., 2015), increased risk of suicidal thoughts in teens and young adults(Zhong et al., 2014) and increased rates of attempted suicide in the first 28 days after starting and stopping antidepressant treatment (Coupland et al., 2015). There are concerns that antidepressants are insufficiently reviewed by clinicians, leading to unnecessarily long treatment durations(Bosman et al., 2016; Johnson et al., 2012).

Estimating the true prevalence and incidence of antidepressant usage is difficult and there have been few large population-based studies of antidepressant pharmaco-epidemiology. Many research studies of antidepressant use have relatively short follow-up periods(Huijbregts et al., 2017). A number of studies have used survey data(Lewer et al., 2015; Mojtabai and Olfson, 2014; Olfson and Marcus, 2009), although such data is potentially susceptible to recall biases. Other studies have concentrated on use of antidepressants in depressive illness(Kendrick et al., 2015; Moore et al., 2009), which can underestimate the true population prevalence due to the wide range of indications for antidepressants. Record-linking existing population-based cohorts to routinely collected administrative health data presents an opportunity to improve pharmaco-epidemiological estimates of antidepressant use.

Understanding patterns of antidepressant use is important in ensuring appropriate allocation of healthcare resources for patients and in maintaining effective monitoring systems for prescribing and adverse effects. In this study we have used a subset(N=11,052) of Generation Scotland, a large population- and family-based cohort of Scottish adults, with record-linkage to national prescribing data for the period 2009-2016. We aimed to provide a contemporaneous and population-scale quantification of patterns of antidepressant use, in

terms of prevalence, incidence, duration of prescribing episodes, adherence to medication, and patient-level predictors of use.

Method

Study Sample

We used the Generation Scotland: Scottish Family Health Study (GS:SFHS) population- and family-based cohort (N=21,474) of adult volunteers across Scotland, recruited February 2006-March 2011, which has been described elsewhere (Smith et al., 2006; Smith et al., 2013)(for overview, see Supplementary Materials). Recruitment to GS:SFHS began in 2006, but prescribing data was available only from 2009 onwards. We therefore restricted our analysis to those individuals in GS:SFHS recruited from September 2009 to March 2011 (N=11052, 6518 females and 4534 males, see Figure 1 and Supplementary Table S1). This ensured that all individuals had at least six months of prescribing data prior to their enrolment in GS:SFHS, with which to ascertain their pre-enrolment medication usage, and at least five years' worth of prescribing data following their enrolment. Of these, 96.5% had medication records available in the prescribing data (the remainder were presumably not using prescribed medication), which compared with 95.6% for the whole GS:SFHS cohort.

Like GS:SFHS as a whole, the study sample had a higher proportion of females (59%) and was of older age (mean 49 males SD 15.3, 49 females SD 15.2) compared to the Scottish general population (mean 37 males, 39 females, 2001 census)(Smith et al., 2013). The study sample was typically healthier and more affluent that the general Scottish population, nevertheless 32.9% of individuals lived in areas with socio-economic deprivation worse than the average(median), as measured by the Scottish Index of Multiple Deprivation(Smith et al., 2013). 99% of the study sample was of white ethnicity (Scottish population 98%).

Phenotyping in Generation Scotland

Sociodemographic information recorded in GS:SFHS included sex, age, smoking status and relationship status, collected by pre-clinic questionnaire at recruitment (see Table S1, Supplementary Materials). Lifetime history of affective disorder (major depressive disorder(MDD) and bipolar disorder) was obtained using the Structured Clinical Interview for DSM-IV disorders(SCID)(Smith et al., 2013). This was operationalised in the pre-clinic questionnaire using two screening questions, with those who answered affirmatively going on be interviewed with the mood sections of the SCID. The screening questions were : "Have you ever seen anyone for emotional or psychiatric problems?" and "Was there ever a time

when you, or someone else, thought you should see someone because of the way you were feeling or acting?".

Cognitive tests included the digit symbol substitution test from the Wechsler Adult Intelligence Scale III (Wechsler D, 1998b), logical memory from the Wechsler Memory Scale III (Wechsler D, 1998a), and verbal fluency(Lezak, 1995). From these tests, we derived a measure of cognitive ability (*g*) as the first unrotated principal component, explaining 44% of the variance in scores(Marioni et al., 2014).

Psychological distress was measured using the General Health Questionnaire (GHQ-28, Likert scoring)(Goldberg and Hillier, 1979). An overall score of 24 or greater has been used to identify cases of potential psychiatric disorder(Swallow, 2003). Neuroticism was measured using the Eysenck Personality Questionnaire Short Form Revised (EPQ-SF)(Eysenck and Eysenck, 1964). The EPQ-SF is a self-report questionnaire consisting of twelve Yes/No questions which are used to assess neuroticism (on a scale 0-12, with higher scores representing greater neuroticism). The EPQ-SF has been validated with other quantitative measures of neuroticism(Gow et al., 2005) with high reliability(Eysenck et al., 1985). Schizotypal traits were elicited using the Schizotypy Personality Questionnaire (SPQ)(Raine, 1991). Socioeconomic deprivation was determined using the Scottish Index of Multiple Deprivation 2009 (SIMD)(Scottish Government, 2009).

Prescribing Data and Linkage

All Scottish citizens registered with a General Practitioner are assigned a unique identifier, the Community Health Index(CHI). This was used to deterministically record-link GS:SFHS participants to the national Prescribing Information System (PIS) administered by NHS Services Scotland Information Services Division(ISD)(Alvarez-Madrazo et al., 2016). PIS is a database of all Scottish NHS medications prescribed by GPs, nurses, dentists, pharmacists, and hospitals, where the medication was dispensed in the community. There is no prescription charge in Scotland since 2011. Hospital-dispensed prescriptions and over-the-counter medications are not included. We obtained PIS prescribing data for April 2009 (the earliest date available) to December 2016.

We additionally linked to the Scottish Morbidity Records (SMR00, SMR01 and SMR04) to obtain information about appointments with outpatient or inpatient secondary mental health

services during the period of study. The SMR records Scotland-wide outpatient, daycase and inpatient hospital (including psychiatric hospital) attendances per annum since 1981. We also linked to ISD data on mortality to determine which participants of GS:SFHS had died during the period of follow up and excluded these from our estimates where relevant.

Identification of Psychiatric Medication Usage

The PIS data allows medication to be identified by approved drug name and/or associated British National Formulary(BNF)(Joint Formulary Committee, 2012) paragraph code. Medication indication is not recorded in PIS. PIS records medication type, dose, dosage instructions and number of defined daily doses (DDDs) for each medication. DDDs are a measure for standardising drug doses(WHO, 2011). For a small part of the dataset (4.9%) the dosage instructions were missing, and these were imputed (as described in the Supplementary Materials).

We defined antidepressants (drugs for depression) as any drug included in BNF Chapter 4.3, entitled "Antidepressant Drugs". Selective Serotonin Reuptake Inhibitors (SSRIs) were identified via BNF Section 4.3.3, Tricyclic Antidepressants (TCAs) via Section 4.3.1 and Selective Serotonin and Noradrenaline Reuptake Inhibitors(SNRIs) were identified from Section 4.3.4 (venlafaxine and duloxetine). We defined 'other antidepressants' as including Monoamine Oxidase Inhibitors (MAOIs), identified via Section 4.3.2, and the remaining drugs within Section 4.3.4. To comply with Neuroscience-based Nomenclature(Worley, 2017), a glossary of the mechanisms of action of each of the medications included in our study is provided in Table S5 of the Supplementary Material.

We recorded antidepressant medication use as any dispensed prescription during the period analysed(which was the defined 5 year period 2012-2016 in some analyses and 1-5 years following individual GS:SFHS recruitment in others, as specified). We also applied additional thresholds : in the majority of our analyses, and unless otherwise stated, we repeated our analyses excluding low dose (<75mg) amitriptyline prescriptions, as this medication and dosage is most commonly prescribed for non-psychiatric purposes (such as neuropathic pain, migraine and tension headache) and frequently for very short periods(Mars et al., 2017). With regard to antidepressant dosage, we produced estimates for antidepressants of all dosages, and separate estimates for antidepressants prescriptions which met at least minimum BNF dose recommendations for MDD (for adult or older adults as appropriate).

Prevalence and Incidence

For each one-year period, we calculated the number of patients receiving any antidepressant prescription. Annual prevalence was calculated as the number of living cohort members using at least one antidepressant prescription that year, as a proportion of the reference sample. We also calculated the period prevalence for 2012-16 and the period prevalence for antidepressant use in the five years following each individual's enrolment in GS:SFHS.

To calculate incidence, we defined antidepressant naïve individuals as those who (a) were not on any antidepressant at the time of enrolment to GS:SFHS, or the 6 months preceding, and (b) did not report antidepressant use on the medication self-report questionnaire included in GS:SFHS, and (c) did not have a history of MDD or bipolar disorder on the SCID (which would indicate likely, although not definite, previous antidepressant use) (d) did not have a previous diagnosis of affective or anxiety disorders in the Scottish Morbidity Record(SMR) prior to GS:SFHS recruitment. We calculated incidence on the basis of the number of new users from the antidepressant naïve group, divided by the number of cohort members without antidepressant use in the preceding year.

Identification of Antidepressant Episodes and Adherence

We defined a drug treatment "episode" as consecutively dispensed prescriptions with a maximum interval between prescribing events of 90 days after the expected end date of the previous prescription, based on the dosage instructions(Gardarsdottir et al., 2010). We used 90 days as the cut-off point as it is unusual in the UK to be given more than three months medication per prescribing event (for sensitivity analyses with alternative cut-off points see Table S6 in Supplementary Material). We did not include new episodes which began in the second half of 2016, as it was not possible to estimate their duration. We defined "long-term" antidepressant use as a consecutive antidepressant episode of at least 15 months (based on three months for acute treatment, nine months for continuation-phase treatment, and three months for discontinuation, following the approach of Keyloun (Keyloun et al., 2017)).

We calculated medication adherence using the Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) metrics(Keyloun et al., 2017). MPR is defined as the sum of the day's supply for all dispensed medication in the episode divided by the number of days

in the period, expressed as a percentage. PDC is defined as the number of days in a prescribing episode that are adequately "covered" by the preceding prescribing event, divided by the number of days in the episode, expressed as a percentage. Compared to MPR, PDC is generally regarded as a more conservative and preferred measure. Satisfactory adherence was defined as MPR or PDC >80% for the antidepressant episode(Keyloun et al., 2017).

Statistical Analysis

All analyses were carried out using R version 3.2.3. Prevalence and incidence rates were expressed as percentages, together with 95% confidence intervals. These estimates were reweighted by age and sex to reflect the Scottish population, using the 2011 Scottish census(Scottish Government, 2011). Age-sex reweighting was performed using the direct standardisation method using the R package "epitools".

As GS:SFHS is a family based cohort, which could lead to biases due to the hierarchical structure of the data, we used a mixed model implementation of Cox regression (with inter-relatedness controlled using pedigree as a random effect), using the R package "coxme". We controlled for potential confounding related to the recruitment area from which each participant was enrolled using a categorical variable in the model.

There was some (range 0.8-5.1%) missing data for some of the variables collected in Generation Scotland(see Supplementary Material including Table S2) and this missing data was imputed using the Multiple Imputation by Chained Equations method implemented in the R package "mice". The final estimates were the result of pooling n=100 imputed datasets, using Rubin's rules(van Buuren, 2012). Further details on the imputation, and the results of complete case analysis, are provided in the Supplementary Material. P values were corrected for multiple testing using the False Discovery Rate(FDR) method.

Results

Sample

The basic demographics of the sample compared to the Scottish population are available in the Supplementary Material(Table S1). An antidepressant was prescribed at least once to 3742 individuals (33.9(95%CI 33.0-34.8)%) of the 11,052 in our study between April 2009 and December 2016. There was a 36.2% increase in the annual prevalence of antidepressant

prescribing between 2010 (age-sex reweighted prevalence 12.7(95%CI 12.0-13.5)%) and 2016 (17.3(16.5-18.3)%). During the seven year period 2010-16, 79,857 antidepressant prescriptions were dispensed (22 for every antidepressant user in GS:SFHS).

Low dose amitriptyline prescriptions(<75mg) accounted for 18.3% of prescriptions and 943 individuals (25%) were only prescribed low dose amitriptyline. Discounting low dose amitriptyline, there were 2624 antidepressant users with a mean of 1.8 antidepressant episodes (range 1-9, S.D. 1.1) during the period 2010-16. Although we had no data on specific indication, 84.2% of these episodes reached a dosage equivalent to at least the required BNF minimum for the treatment of Major Depressive Disorder.

The most commonly prescribed class of antidepressants was Selective Serotonin Reuptake Inhibitors(SSRIs), accounting for 54% of prescriptions in 2010 and 52.7% in 2016 (65.6% and 64% respectively if low dose amitriptyline excluded). The proportion of Serotonin and Noradrenaline Reuptake Inhibitors(SNRIs) prescribed increased from 9.1% in 2010 to 10.9% in 2016, and the proportion of other antidepressants (such as mirtazapine) increased from 6.7% to 8.3% during the same period. The proportion of Tricyclic Antidepressants(TCAs) was 27.8% in 2016, or 12.3% if low dose amitriptyline excluded.

Period Prevalence 2012-16

The 5-year 2012-2016 age-sex reweighted period prevalence of antidepressant use was 28.0(95%CI 26.9-29.1)% for the cohort. With low dose amitriptyline excluded, the prevalence was 20.8 (19.9-21.8)% (see **Table 1**). The five-year prevalence was considerably higher among females, 34.9(33.3-36.6)%, than males, 20.4(19.0-22.0)%. There was a bimodal distribution of antidepressant use by age, with 2012-16 period prevalence highest in the 45-54 age group for all antidepressants(33.3(31.3-35.3%)) and a second peak in the 75+ age group(33.3(28.8-38.8)%) (**Figure 2**).

Prevalence of Antidepressant Prescribing in One to Five Years Follow-Up

In the first year following each individual's GS:SFHS enrolment, 11.2(95%CI 10.6-11.8)% of the cohort had at least one antidepressant prescription(excluding low dose amitriptyline, as does all analysis in this section), which increased to 20.8(20.0-21.6)% after five years.

Among those with history of recurrent MDD on recruitment, 52.4(48.5-56.2)% were prescribed at least one antidepressant within 1 year following GS recruitment and for bipolar disorder the proportion was 46.2(30.4-62.6)%. For those with no history of MDD on recruitment, 6.9(6.5-7.5)% were prescribed at least one antidepressant within one year – or 2.5(2.2-2.9)% if those already on antidepressants at recruitment were excluded.

Among those with a GHQ-28 Likert score of 24 or above at the time of GS:SFHS recruitment, 31.7(95% CI 29.4-34.1)% had at least one antidepressant prescription within 1 year. Among the antidepressant naïve subgroup at the time of GS:SFHS recruitment, 6.6(5.1-8.6)% of those with a Likert score of >=24 were prescribed antidepressants within 1 year and 9.2(4.1-18.6)% of those scoring over three standard deviations above the mean on the GHQ depression subscale (subscale D) were prescribed an antidepressant within 1 year.

Incidence of Antidepressant Prescribing 2012-16

The age-sex reweighted incidence of antidepressant prescribing was 2.4(2.1-2.7)% per year for all antidepressants and 1.6(1.4-1.9)% if low dose amitriptyline is excluded. Incidence was greater in females 2.7(2.4-3.2)% than males 2.0(1.6-2.5)%.

77.1% of incident antidepressant users were commenced on an SSRI, with 11.9% on a TCA (low dose amitriptyline excluded), 4.0% on a serotonin and noradrenaline reuptake inhibitor(SNRI) and 7.0% on other antidepressants(especially mirtazapine). The most common individual medication for new users was citalopram (39.9%), followed by fluoxetine (21.6%) and sertraline (14.2%). Less than 1% were commenced on paroxetine and none on reboxetine or MAOIs. The most common tricyclic antidepressant for new users was nortriptyline (3.9%) followed by higher dose amitriptyline(3.0%).

Antidepressant Episodes

In the five years period 2012-16, 2385 individuals used antidepressants and we defined 3595 antidepressant episodes(low dose amitriptyline excluded). Some 86.6% (n=3112) of episodes reached at least minimum dose required for treatment of MDD (although actual indication was not available). We allowed antidepressant switching or combination during episodes, with the majority of episodes(79.3%) having just one antidepressant, 13.6% having two and 7.1% having three or more(range 3-6).

Over half (57.6%) of antidepressant episodes were of 9 months or greater and 44.8% met our 15-month criteria for long term use, with the majority of antidepressant users (57.7%) having a least one episode of long term duration. Nevertheless, approximately one tenth (10.6%) of episodes were of less than 30 days duration and a further 12.6% were of 31-90 days, meaning that approximately one quarter of episodes were less than three months duration.

Adherence

For the 3595 antidepressant episodes between 2012-16(n=2385 individuals), the mean Medication Possession Ratio(MPR) per antidepressant episode was 96.0% (range 11-412) and the mean Proportion of Days Covered(PDC) was 84.9% (range 11-100). Using PDC >= 80% as defining adherence, 69.0% of antidepressant episodes were adherent, when using 90 days as the cut-off point between antidepressant episodes (for sensitivity analysis see Table S6 in Supplementary Materials). Mean PDC was similar across medication classes (SSRI 84.5%, TCA 84.3%, SNRI 83.2%, MAOI 77.3%, other 83.9%, see Table S6 in Supplementary Materials).

Polypharmacy

Other medications that were co-prescribed with antidepressants during an antidepressant episode were determined, with simultaneous use on at least three occasions being classed as "regular" use. Anxiolytics (medicines for anxiety) were co-prescribed to 34.1% of antidepressant users (16.4% regularly), including benzodiazepines 23.6% (10.7% regularly) and "Z-drugs"(the benzodiazepine-receptor agonists zopiclone, zolpidem and zaleplon) 18.9% (7.6% regularly). Pregabalin or gabapentin (alpha-2 delta calcium channel blockers often used to treat anxiety and neuropathic pain as well as epilepsy) were co-prescribed to 12.8% users (8.9% regularly). Antipsychotics (medicines to treat psychosis) were co-prescribed to 6.8% antidepressant users (5.1% regularly). Lithium compounds or sodium valproate, which are also used to treat mood disorders, were co-prescribed to 1.6% (1.4% regularly). Opiate-based analgesic (pain relieving) medications were co-prescribed to 22% of antidepressant users (13.3% regularly), compared to a general five-year prevalence of 15.6% (**Figure 3**). Opioid use was also higher in those with a history of bipolar disorder (33.3%,regular 18.5%) and recurrent MDD (27.8%, regular 17.3%) on GS:SFHS recruitment, compared to those with no affective disorder history (20.5%, regular 12.3%).

Use of psychiatric services

Using record linkage to hospital data, 10.0(8.9-11.2)% of antidepressant users in the five years following GS:SFHS enrolment, who were prescribed at least the minimum BNF recommended dosage for MDD, had a psychiatric outpatient appointment during at least one of their antidepressant treatment episodes. Some 1.8(1.4-2.5)% of antidepressant users were admitted to psychiatric hospital during at least one episode of antidepressant treatment.

Predictors of antidepressant use - time to event analysis

We performed time-to-antidepressant-use Cox regression analysis for the five years following individual GS:SFHS enrolment, excluding those individuals already on antidepressants (**Figure 4** and **Table 2**). Female gender was predictive of commencing antidepressants in the multivariable model (Hazard Ratio(HR)=1.74, 95% CI 1.53-1.98, p_{FDR}<0.0001). Lower SIMD deprivation status was associated with antidepressant use in univariate analysis (and in complete case analysis, see Supplementary Table S3) but was not significant in the multivariable model. Neuroticism (HR 1.12,1.09-1.14 per unit, p_{FDR}<0.0001), previous history of unemployment(HR=1.24, 1.06-1.45, p_{FDR}=0.02) and smoking status (current smokers HR 1.57(1.34-1.84, p_{FDR} <0.0001) were also positively associated with antidepressant use, whereas cognitive function (g) scores were negatively associated (HR 0.89, 0.85-0.93, p_{FDR} 0.001). Multiple physical comorbidities (3+) were positively associated with antidepressant use (HR 1.85,1.33-2.57, p_{FDR} 0.002). The most predictive factor for antidepressant use was previous history of affective disorder on GS:SFHS recruitment, with history of a single episode of MDD having a hazard ratio of 2.22 (1.85-2.67, p_{FDR}<0.0001).

Discussion

Summary of Main Results

In this study, we demonstrate an increase in antidepressant usage in this UK cohort, with an estimated 17.3% of the adult population using antidepressants in 2016, an increase of nearly one third(36.2%) on 2010(see Supplementary Table S4). We have found that, even if low dose amitriptyline use is discounted, one fifth of our sample (20.8%) has been prescribed an antidepressant at least once between 2012-16. The prescribing of antidepressants continues to be dominated by the SSRI class, but we observed a rise in the proportion of SNRIs, and other

antidepressants such as mirtazapine, prescribed. This is an interesting trend and may be further stimulated by future revisions of clinical guidance, which may recategorize mirtazapine as a first-line treatment in psychiatric disorders such as major depression, leading to further increases in prevalence of use and interest in the efficacy and safety profile of mirtazapine and other non-SSRI antidepressants(Coupland et al., 2015; Cipriani et al., 2018).

Our findings accord with recent UK data which has found that antidepressant prescribing is the highest ever at 64.7m prescriptions for England in 2016(NHS Digital, 2017). However, in this study we also found a reweighted incidence for new antidepressant users of just 2.4%, and a duration for antidepressant episodes of in excess of 15 months in nearly half of episodes identified. This supports the hypothesis of increased longer-term use by regular antidepressant users driving much of the increased prevalence of antidepressants we report. Our study also found that adherence to antidepressants was relatively high, meeting the more conservative PDC threshold adherence of 80% in 69.0% of cases.

We found that history of affective disorder, multiple physical comorbidities, and being female, were the most predictive of antidepressant use. We also report an interesting association between neuroticism and antidepressant use, with considerably greater incident antidepressant use in the upper tertile of EPQ-SF neuroticism scores(Figure 4). Neuroticism is a personality trait with significant clinical overlap with psychiatric disorder(Smith et al., 2016), which is relatively straightforward to measure prospectively, and our results suggest that it could be a useful predictor of future antidepressant usage. A recent study in older adults (Steffens et al., 2018)has found that neuroticism may be also associated with lower remission rates of antidepressant-treated depression. We also found that cognitive function had an inverse association with antidepressant use, in line with previous research indicating an association between cognitive impairment and MDD(Marazziti et al., 2010).

With this study methodology we cannot judge definitely whether the increasing antidepressant prevalence we found is appropriate to clinical indication. The prevalence of prescribing we report should be seen in the context of not only the prevalence of MDD, but the prevalence of anxiety disorders, eating disorders, sexual disorders, sleep disorders and other indications for antidepressant medication. Nevertheless, it has also been argued that current rates of antidepressant treatment may still not identify all those most likely to benefit (Kendrick et al., 2005). The National Health and Nutrition Examination Surveys 2005-

08(Pratt et al., 2011) found that only one third of those with severe depressive symptoms were on antidepressant therapy, and less than half of those taking multiple antidepressants had seen a mental health professional in the past year. In our study, we found that, among those antidepressant naïve individuals with the highest psychiatric 'caseness' according to GHQ scores in Generation Scotland, just 6.6% were prescribed an antidepressant within one year of follow-up, and less than 10% of those with the highest severe depression caseness (three standard deviations on the GHQ-28 D subscale) were prescribed an antidepressant within one year. This might indicate potential unmet clinical need for antidepressants, although such a conclusion should be approached with caution as GHQ is a measure of psychiatric distress at one timepoint, and higher GHQ scores do not necessarily indicate requirement for antidepressants.

It has also been previously argued that antidepressants are insufficiently reviewed by clinicians, leading to unnecessarily long treatment durations(Bosman et al., 2016; Johnson et al., 2012). The European Study of the Epidemiology of Mental Disorders (ESEMed) demonstrated that 63.5% of those with mood disorders had not consulted health services in the previous 12 months(Alonso J, 2004), with similar findings in the US National Comorbidity Survey Replication(Wang et al., 2005). We found that only a small minority of antidepressant users are being reviewed in outpatient psychiatry, suggesting that the majority of antidepressant monitoring takes place in primary care. The high prevalence of antidepressant use we report suggests that there may be scope for increasing the rate of medication reviews for long-term antidepressant users in primary (and secondary) care, with consideration of managed discontinuation of treatment. This can help manage the risks associated with prolonged antidepressant exposure when a sustained recovery from illness has been achieved.

Among medications frequently co-prescribed with antidepressants, the most common psychiatric class was anxiolytics, especially benzodiazepines and "Z-drugs". We found that the co-prescribing of analgesic and opiate medication was appreciably higher in antidepressant users, especially those with a history of recurrent depression and bipolar disorder. An association between depression and pain has been previously described(McIntosh et al., 2016) and could be related to altered pain sensitivity in depressed states and comorbidity of depression with painful conditions.

Comparison With Previous Studies

A previous prescribing database study of the Tayside population of Scotland (n=325,000)(Lockhart and Guthrie, 2011) found an increase in prevalence from 8.0% in 1995/96 to 13.4% in 2006/07. The standardised rate for 2006-07 antidepressants was 13.1% (SSRIs 7.9%, TCAs 5.2%, other antidepressants 1.9%) compared to the reweighted 2016 rates of 17.3% (10.5%, 5.8%, 3.2%) found in our study. Analysis of the UK Clinical Practice Research Datalink (CPRD, N=1,524,201) found that 23% of individuals were prescribed at least one antidepressant between 1995 and 2001(Mars et al., 2017).

Results from the US National Health and Nutrition Examination Survey (NHANES) found a 2009-10 annual prevalence of 10.4%(Mojtabai and Olfson, 2014), with 67.4% reporting use for 24 months or longer, and 17.1% for <6 months. Incidence was estimated at 2.55% (per 100 individuals per year) in comparison with our estimated incidence of 2.4%. In this US study, 32.5% of antidepressant users had visited a mental health professional in the previous year, compared with 10.0% in our UK-based study.

A prescription database study in British Columbia conducted in 2004(Raymond et al., 2007) found a prevalence of 7.2% and found that lower socioeconomic groupings and lowest income groupings had higher prevalences of antidepressant use. In our time-to-event analysis we found the lowest SIMD quintiles were associated with antidepressant use in univariate analysis but not in the multivariable model.

A recent study of routine general practice care data in a cohort based in Amsterdam (n=156,620) found 43.7% of antidepressant users were long-term users(Huijbregts et al., 2017), which is similar to our own finding of 44.8%.

Strengths and Limitations

This study benefitted from the relatively large population-based GS:SFHS cohort and the availability of structured clinical interview data alongside quantitative measures of non-specific psychiatric morbidity and numerous demographic, socio-economic and psychological variables. The national prescribing and morbidity data to which it was linked was of high fidelity (with a capture rate in excess of 95%) and, being nationally based, reduced the chance of individuals being lost to follow up during the study period due to, for

example, moving their GP practice. We were also able to record the date of dispensing as well as prescribing, and whether the medication was collected. By applying a longitudinal retrospective design rather than a cross-sectional approach, this study increased the potential for accurate measurement of the pharmaco-epidemiological variables.

However, by using a cohort study as its basis, this analysis is also susceptible to selection and confounding biases. Another significant limitation is the lack of details of the indication of medication use in the PIS prescribing data(as with many other prescribing databases based on routinely collected administrative data). In GS:SFHS, previous history of affective disorder was collected via screening using the SCID, but we were not able to determine ongoing and subsequent psychiatric diagnoses in the period studied following GS:SFHS recruitment. It is likely that a proportion of those individuals with no previous history of affective disorder were subsequently diagnosed with such, or that other psychiatric disorders such as anxiety disorders were the indication for later antidepressant treatment. GS:SFHS did not provide data on baseline history of anxiety disorders to complement the SCID-derived history of affective disorders. We were also not able to determine the extent to which severity of psychiatric symptoms or level of functional impairment determines antidepressant usage.

Prescribing data is also an imperfect proxy for medication use, given that the medication may not be taken (primary noncompliance) or may not be used as directed (secondary noncompliance). Noncompliance to antidepressant medication has been previously estimated at 50%(Haynes et al., 2008). The PIS prescribing data only covered prescriptions issued in the community, and therefore may underestimate true prevalence and treatment duration, although it would be expected that most antidepressant users commenced in hospital would continue medication in the community. A further limitation of our study being based on routinely collected administrative prescribing data is that it is also not possible to determine the extent to which the antidepressant prescribing we recorded was appropriate to clinical need or consistent with treatment guidelines.

Although we attempted to apply stringent criteria for incident use of antidepressants - using prescription data, linked morbidity data, self-report and objectively measured history of affective disorder to screen antidepressant naïve cohort members - we may still have falsely identified some previous antidepressant users as incident cases, particularly as we did not have data preceding April 2009.

Our Cox regression analysis of predictors of antidepressant use within 5 years was necessarily restricted by the variables available to us in GS:SFHS. We were able to derive effect sizes for numerous variables previously associated with antidepressant use, such as history of affective disorder, medical comorbidities and female gender. However, due to the limited diagnostic information available in GS:SFHS we were not able to quantify the association between non-affective psychiatric disorders such as anxiety disorders (which are likely to be significantly predictive) and antidepressant use. The conclusions of our time-to-event analysis need to be placed in the context of the variables available in our model.

The cohort was also for adults only, thereby not including antidepressant use among the under 18s, and the overall population prevalence and incidence would be expected to be lower than our figures since children are prescribed antidepressants less frequently.

Future Directions and Clinical Implications

We found that antidepressant prevalence was higher than previously reported for the UK, but that incidence remains relatively stable. This suggests that increased antidepressant prevalence is driven by longer treatment durations and good levels of adherence, and previous users returning to medication for a wider range of indications, rather than an upsurge in incident cases. Our study also demonstrates the utility of record-linking administrative health data to population-based cohorts to provide enhanced pharmaco-epidemiological estimates of prevalence, incidence and adherence. We also found significant relationships between neuroticism and cognitive function for antidepressant use, even when affective disorder was controlled for. These tests are relatively easy to administer and could provide useful to clinicians in constructing predictive models of clinical risk.

More research is required to investigate the clinical appropriateness of antidepressant prescribing. Our research suggests that the vast majority of antidepressant prescribing and medication review takes place in the primary care setting in the UK. Primary care will necessarily therefore remain the focal point for future efforts to improve antidepressant prescribing practices, monitoring of adherence and adverse effects, and managed discontinuation of treatment when clinically appropriate.

Declaration of Conflict of Interest.

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of the article.

Funding.

JDH gratefully acknowledges receipt of an MRC/MRF PsySTAR PhD fellowship. Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates [CZD/16/6] and the Scottish Funding Council [HR03006]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "STratifying Resilience and Depression Longitudinally" (STRADL) Reference 104036/Z/14/Z).

Ethical Approval.

All components of STRADL received formal, national ethical approval from the NHS Tayside committee on research ethics (reference 14/SS/0039).

Article Word Count : 5111

References

Abbing-Karahagopian Huerta C, Souverein P, de Abajo F, et al. (2014) Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *Eur J Clin Pharmacol* 70: 849-857.

Alonso J AM, Bernert S, et al. . (2004) Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 420: 21-27.

Alvarez-Madrazo S, McTaggart S, Nangle C, et al. (2016) Data Resource Profile: The Scottish National Prescribing Information System (PIS). *Int J Epidemiol*.

Bandelow B and Michaelis S. (2015) Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci* 17(3): 327-335.

Bet PM, Hugtenburg JG, Penninx BW, et al. (2013) Side effects of antidepressants during long-term use in a naturalistic setting. *Eur Neuropsychopharmacol* 23(11): 1443-1451.

Bosman RC, Huijbregts KM, Verhaak PF, et al. (2016) Long-term antidepressant use: a qualitative study on perspectives of patients and GPs in primary care. *Br J Gen Pract* 66(651): e708-719.

Cipriani A, Furukawa TA, Salanti G, et al. (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*.

Coupland C, Dhiman P, Morriss R, et al. (2011) Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 343(d4551).

Coupland C, Hill T, Morriss R, et al. (2015) Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ* 350: h517.

Cruickshank G, Macgillivray S, Bruce D, et al. (2008) Cross-sectional survey of patients in receipt of long-term repeat prescriptions for antidepressant drugs in primary care. *Ment Health Fam Med* 5(2): 105-109.

Exeter D, Robinson E and Wheeler A. (2009) Antidepressant dispensing trends in New Zealand between 2004 and 2007. *Aust N Z J Psychiatry* 43(12): 1131-1140.

Eysenck SB and Eysenck HJ. (1964) An Improved Short Questionnaire for the Measurement of Extraversion and Neuroticism. *Life Sci (1962)* 3: 1103-1109.

Eysenck SB, Eysenck HJ and Barrett P. (1985) A revised version of the psychoticism scale. *Personality and Individual Differences* 61(1): 21-29.

Gardarsdottir H, Souverein PC, Egberts TC, et al. (2010) Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *J Clin Epidemiol* 63(4): 422-427.

Goldberg DP and Hillier VF. (1979) A scaled version of the General Health Questionnaire. *Psychol Med* 9(1): 139-145.

Gonzalez-Lopez MC, Rodriguez-Lopez CM, Parron-Carreno T, et al. (2015) Trends in the dispensation of antidepressant drugs over the past decade (2000-2010) in Andalusia, Spain. *Soc Psychiatry Psychiatr Epidemiol* 50(5): 705-712.

Gow A, Whiteman M, Pattie A, et al. (2005) Goldberg's IPIP'Big-Five factor markers: Internal consistency and concurrent validation in Scotland. *Personality and Individual Differences* 39(2): 317-329.

Haynes RB, Ackloo E, Sahota N, et al. (2008) Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* (2).

Hill T, Coupland C, Morriss R, et al. (2015) Antidepressant use and risk of epilepsy and seizures in people aged 20 to 64 years: cohort study using a primary care database. *BMC Psychiatry* 15: 315.

Hollinghurst S, Kessler D, Peters TJ, et al. (2005) Opportunity cost of antidepressant prescribing in England: analysis of routine data. *BMJ* 330(7498): 999-1000.

Huijbregts KM, Hoogendoorn A, Slottje P, et al. (2017) Long-Term and Short-Term Antidepressant Use in General Practice: Data from a Large Cohort in the Netherlands. *Psychother Psychosom* 86(6): 362-369.

Ilyas S and Moncrieff J. (2012) Trends in prescriptions and costs of drugs for mental disorders
in England, 1998 –2010. *BJPsych* 200: 393-398.

Johnson CF, Macdonald HJ, Atkinson P, et al. (2012) Reviewing long-term antidepressants can reduce drug burden: a prospective observational cohort study. *Br J Gen Pract* 62(604): e773-779.

Joint Formulary Committee. (2012) *British National Formulary*: Pharmaceutical Press.

Kendrick T, King F, Albertella L, et al. (2005) GP treatment decisions for patients with depression: an observational study. *British Journal of General Practice* 55(513): 280-286.

Kendrick T, Stuart B, Newell C, et al. (2015) Did NICE guidelines and the Quality Outcomes Framework change GP antidepressant prescribing in England? Observational study with time trend analyses 2003-2013. *J Affect Disord* 186: 171-177.

Kessler D, Sharp D and Lewis G. (2005) Screening for depression in primary care. *Br J Gen Pract* 55(518): 659-660.

Keyloun KR, Hansen RN, Hepp Z, et al. (2017) Adherence and Persistence Across Antidepressant Therapeutic Classes: A Retrospective Claims Analysis Among Insured US Patients with Major Depressive Disorder (MDD). *CNS Drugs* 31(5): 421-432.

Kirsch I, Deacon BJ, Huedo-Medina TB, et al. (2008) Initial severity and antidepressant benefits: A meta-analysis of data submitted to the food and drug administration. *Plos Medicine* 5(2): 260-268.

Lewer D, O'Reilly C, Mojtabai R, et al. (2015) Antidepressant use in 27 European countries: associations with sociodemographic, cultural
and economic factors. *The British Journal of Psychiatry* 207: 221-206.

Lezak M. (1995) *Neuropsychological Testing,* Oxford: Oxford University Press.

Lockhart P and Guthrie B. (2011) Trends in primary care antidepressant prescribing 1995-2007: a longitudinal population database analysis. *Br J Gen Pract* 61(590): e565-572.

Marazziti D, Consoli G, Picchetti M, et al. (2010) Cognitive impairment in major depression. *Eur J Pharmacol* 626(1): 83-86.

Marioni RE, Batty GD, Hayward C, et al. (2014) Common genetic variants explain the majority of the correlation between height and intelligence: the generation Scotland study. *Behav Genet* 44(2): 91-96.

Mars B, Heron J, Kessler D, et al. (2017) Influences on antidepressant prescribing trends in the UK: 1995-2011. *Soc Psychiatry Psychiatr Epidemiol* 52(2): 193-200.

McIntosh AM, Hall LS, Zeng Y, et al. (2016) Genetic and Environmental Risk for Chronic Pain and the Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-Model Analysis. *Plos Medicine* 13(8): e1002090.

Meijer WE, Heerdink ER, Leufkens HG, et al. (2004) Incidence and determinants of long-term use of antidepressants. *Eur J Clin Pharmacol* 60(1): 57-61.

Mojtabai R and Olfson M. (2014) National trends in long-term use of antidepressant medications: results from the US National Health and Nutrition Examination Survey. *J Clin Psychiatry.* 75(2): 169-177.

Moore M, Yuen HM and Dunn N. (2009) Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. . *BMJ* 339(2): b3999.

Munoz-Arroyo R, Sutton M and Morrison J. (2006) Exploring potential explanations for the increase in antidepressant prescribing in Scotland using secondary analyses of routine data. *Br J Gen Pract* 56(527): 423-428.

National Institute of Mental Health. (2017a) *Generalized Anxiety Disorder*. Available at: https://www.nimh.nih.gov/health/statistics/generalized-anxiety-disorder.shtml.

National Institute of Mental Health. (2017b) *Major Depression*. Available at: https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml

NHS Digital. (2017) *http://content.digital.nhs.uk/article/7756/Antidepressants-were-the-area-with-largest-increase-in-prescription-items-in-2016*.

Olfson M and Marcus SC. (2009) National patterns in antidepressant medication treatment. *Arch Gen Psychiatry* 66(8): 848-856.

Petty DR, House A, Knapp P, et al. (2006) Prevalence, duration and indications for prescribing of antidepressants in primary care. *Age Ageing* 35(5): 523-526.

Pratt LA, Brody DJ and Gu Q. (2011) Antidepressant use in persons aged 12 and over: United States, 2005-2008. *NCHS Data Brief* (76): 1-8.

Raine A. (1991) The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull* 17(4): 555-564.

Raymond CB, Morgan SG and Caetano PA. (2007) Antidepressant utilization in British Columbia from 1996 to 2004: increasing prevalence but not incidence. *Psychiatr Serv* 58(1): 79-84.

Reid I. (2013) Are antidepressants overprescribed? No. *BMJ* 346: f190.

Scottish Government. (2009) *Scottish Index of Multiple Deprivation 2009 General Report,* Edinburgh: Office of the Chief Statistician.

Scottish Government. (2011) *Scotland Census 2011*.

Smith BH, Campbell A, Linksted P, et al. (2013) Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. *Int J Epidemiol* 42(3): 689-700.

Smith BH, Campbell H, Blackwood D, et al. (2006) Generation Scotland: the Scottish Family Health Study; a new resource for researching genes and heritability. *BMC Med Genet* 7: 74.

Smith DJ, Escott-Price V, Davies G, et al. (2016) Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Mol Psychiatry* 21(11): 1644.

Spence D. (2013) Are antidepressants overprescribed? Yes. *BMJ* 346(3): f191.

Spence R, Roberts A, Ariti C, et al. (2014) Focus On:Antidepressantprescribing. *The Health Foundation*.

Steffens DC, Wu R, Grady JJ, et al. (2018) Presence of neuroticism and antidepressant remission rates in late-life depression: results from the Neurobiology of Late-Life Depression (NBOLD) study. *Int Psychogeriatr* 30(7): 1069-1074.

Swallow BL, S.W.;Masson,E.;Hay,D.M. (2003) The use of the General Health Questionnaire (GHQ-28) to estimate prevalence of psychiatric disorder in early pregnancy. *Psychology, Health and Medicine* 8(2): 213-217.

Trifiro G, Barbui C, Spina E, et al. (2007) Antidepressant drugs: prevalence, incidence and indication of use in general practice of Southern Italy during the years 2003-2004. *Pharmacoepidemiol Drug Saf* 16(5): 552-559.

van Buuren S. (2012) *Flexible Imputation of Missing Data* Chapman and Hall.

Wang PS, Lane M, Olfson M, et al. (2005) Twelve-month use of Mental Health Services in the United States - Results from the National Comorbidity Survey Replication. *Archives of General Psychiatry* 62(6): 629-640.

Wechsler D. (1998a) *Wechsler Adult Intelligence Scale III,* London: Psychological Corporation.

Wechsler D. (1998b) *Wechsler Memory Scale III, ,* London: Psychological Corporation.

WHO. (2011) *World Health Organisation Collaborating Centre for Drug Statistics ATC/DDD Index 2011,* Oslo: World Health Organisation /Norwegian Institute of Public Health.

Worley L. (2017) Neuroscience-based nomenclature (NbN). *Lancet Psychiatry* 4(4): 272-273.

Zhong WJ, Kremers HM, Yawn BP, et al. (2014) Time trends of antidepressant drug prescriptions in men versus women in a geographically defined US population. *Archives of Womens Mental Health* 17(6): 485-492.

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

Abstract (241 words)

Objective

Antidepressants are the most commonly prescribed psychiatric medication but concern has been raised about significant increases in their usage in high income countries. We aimed to quantify antidepressant prevalence, incidence, adherence and predictors of use in the adult population.

Method

The study record-linked administrative prescribing and morbidity data to the Generation Scotland cohort(N=11052), between 2009-16. Prevalence and incidence of any antidepressant use was determined. Antidepressant adherence was measured using Proportion of Days Covered and Medication Possession Ratio. Time-to-event analysis for incident antidepressant use within 5 years of GS:SFHS recruitment was performed to reveal patient-level predictors of use.

Results

Almost one third (28.0%, 95%CI 26.9-29.1) of the adults in our sample were prescribed at least one antidepressant in the five-year period 2012-16. There was a 36.2% increase in annual prevalence between 2010 and 2016. Incidence was 2.4(2.1-2.7)% per year. The majority of antidepressant episodes (57.6%) were greater than 9 months duration and adherence was generally high (69.0% with Proportion of Days Covered >80%). Predictors of new antidepressant use included history of affective disorder, being female, physical comorbidities, higher neuroticism scores, and lower cognitive function scores.

Conclusions

Antidepressant prevalence is greater than previously reported but incidence remains relatively stable. We found the majority of antidepressant episodes to be of relatively long duration with good estimated adherence. Our study supports the hypothesis that increased long-term use among existing (and returning) users, along with wider ranges of indications for antidepressants, has significantly increased the prevalence of these medications.

Introduction

Antidepressants are the most commonly prescribed psychiatric medication and one of the most commonly prescribed medicines(Raymond et al., 2007; Olfson and Marcus, 2009). In the last 30 years, there has been a significant increase in antidepressant usage in high income countries(Ilyas and Moncrieff, 2012; Kendrick et al., 2015; Moore et al., 2009; Meijer et al., 2004; Huijbregts et al., 2017; Lockhart and Guthrie, 2011; Munoz-Arroyo et al., 2006; Petty et al., 2006; Raymond et al., 2007; Exeter et al., 2009; Mojtabai and Olfson, 2014; Olfson and Marcus, 2009; Gonzalez-Lopez et al., 2015; Mars et al., 2017). Antidepressant consumption has reportedly increased 400% in the USA between 1998-2008(Pratt et al., 2011), while antidepressant prescriptions in the UK increased twofold between 1995-2011(Spence et al., 2014). Comparison of electronic prescribing records in five European countries suggests that antidepressant prescribing is comparatively high in the UK for adults aged 20-60, especially among females(Abbing-Karahagopian Huerta et al., 2014). In the USA, annual antidepressant prevalence for 2011 was estimated at 14.4%(Zhong et al., 2014) compared to an annual prevalence of depression in 2015 of 6.7%(National Institute of Mental Health, 2017b) and 2.7% for generalized anxiety disorder(National Institute of Mental Health, 2017a).

The extent to which this rising tide of antidepressant prescribing is appropriate to clinical need is an area of ongoing controversy(Cruickshank et al., 2008; Lockhart and Guthrie, 2011; Reid I, 2013; Spence D, 2013). Antidepressant use has risen to a significantly greater degree than any rise in the prevalence of depression(Munoz-Arroyo et al., 2006) or of anxiety disorders(Bandelow and Michaelis, 2015). There is some evidence that illnesses treated by these medications, such as depression and anxiety, are now better recognised and treated at the primary care level(Kessler et al., 2005) and that GPs and patients are more willing to utilise antidepressant treatment for a wider range of indications(Trifiro et al., 2007; Kessler et al., 2005; Mojtabai and Olfson, 2014). It has also been argued that a greater antidepressant prescription rate does not correspond to an upsurge in incident cases, but rather represents a significant lengthening in the treatment period for existing users(Moore et al., 2009; Raymond et al., 2007; Mojtabai and Olfson, 2014; Mars et al., 2017; Reid I, 2013). Advisory bodies such as NICE and the WHO now recommend a minimum of six to nine months antidepressant treatment for moderate major depressive disorder (MDD) and two years or more treatment for chronic or relapsing illness(Petty et al., 2006; Reid I, 2013; Mars et al.,

2017). This can serve to increase prescribing prevalence rates without necessarily increasing incidence.

Nevertheless, concerns have been raised about a medicalisation of ordinary distress with antidepressants(Hollinghurst et al., 2005), and there are ongoing debates about the efficacy of antidepressants in mild-moderate depressive illness(Olfson and Marcus, 2009; Kirsch et al., 2008; Cipriani et al., 2018). There has been increased attention to potential adverse effects of antidepressants(Bet et al., 2013), including discontinuation syndromes(Petty et al., 2006; Bosman et al., 2016), adverse physical outcomes in older adults(Coupland et al., 2011), risk of epilepsy(Hill et al., 2015), increased risk of suicidal thoughts in teens and young adults(Zhong et al., 2014) and increased rates of attempted suicide in the first 28 days after starting and stopping antidepressant treatment (Coupland et al., 2015). There are concerns that antidepressants are insufficiently reviewed by clinicians, leading to unnecessarily long treatment durations(Bosman et al., 2016; Johnson et al., 2012).

Estimating the true prevalence and incidence of antidepressant usage is difficult and there have been few large population-based studies of antidepressant pharmaco-epidemiology. Many research studies of antidepressant use have relatively short follow-up periods(Huijbregts et al., 2017). A number of studies have used survey data(Lewer et al., 2015; Mojtabai and Olfson, 2014; Olfson and Marcus, 2009), although such data is potentially susceptible to recall biases. Other studies have concentrated on use of antidepressants in depressive illness(Kendrick et al., 2015; Moore et al., 2009), which can underestimate the true population prevalence due to the wide range of indications for antidepressants. Record-linking existing population-based cohorts to routinely collected administrative health data presents an opportunity to improve pharmaco-epidemiological estimates of antidepressant use.

Understanding patterns of antidepressant use is important in ensuring appropriate allocation of healthcare resources for patients and in maintaining effective monitoring systems for prescribing and adverse effects. In this study we have used a subset(N=11,052) of Generation Scotland, a large population- and family-based cohort of Scottish adults, with record-linkage to national prescribing data for the period 2009-2016. We aimed to provide a contemporaneous and population-scale quantification of patterns of antidepressant use, in

terms of prevalence, incidence, duration of prescribing episodes, adherence to medication, and patient-level predictors of use.

Method

Study Sample

We used the Generation Scotland: Scottish Family Health Study (GS:SFHS) population- and family-based cohort (N=21,474) of adult volunteers across Scotland, recruited February 2006-March 2011, which has been described elsewhere (Smith et al., 2006; Smith et al., 2013)(for overview, see Supplementary Materials). Recruitment to GS:SFHS began in 2006, but prescribing data was available only from 2009 onwards. We therefore restricted our analysis to those individuals in GS:SFHS recruited from September 2009 to March 2011 (N=11052, 6518 females and 4534 males, see Figure 1 and Supplementary Table S1). This ensured that all individuals had at least six months of prescribing data prior to their enrolment in GS:SFHS, with which to ascertain their pre-enrolment medication usage, and at least five years' worth of prescribing data following their enrolment. Of these, 96.5% had medication records available in the prescribing data (the remainder were presumably not using prescribed medication), which compared with 95.6% for the whole GS:SFHS cohort.

Like GS:SFHS as a whole, the study sample had a higher proportion of females (59%) and was of older age (mean 49 males SD 15.3, 49 females SD 15.2) compared to the Scottish general population (mean 37 males, 39 females, 2001 census)(Smith et al., 2013). The study sample was typically healthier and more affluent that the general Scottish population, nevertheless 32.9% of individuals lived in areas with socio-economic deprivation worse than the average(median), as measured by the Scottish Index of Multiple Deprivation(Smith et al., 2013). 99% of the study sample was of white ethnicity (Scottish population 98%).

Phenotyping in Generation Scotland

Sociodemographic information recorded in GS:SFHS included sex, age, smoking status and relationship status, collected by pre-clinic questionnaire at recruitment (see Table S1, Supplementary Materials). Lifetime history of affective disorder (major depressive disorder(MDD) and bipolar disorder) was obtained using the Structured Clinical Interview for DSM-IV disorders(SCID)(Smith et al., 2013). This was operationalised in the pre-clinic questionnaire using two screening questions, with those who answered affirmatively going on be interviewed with the mood sections of the SCID. ~~given the Structured Clinical Interview for DSM-IV disorders(Smith et al., 2013).~~ The screening questions were : "Have you ever seen anyone for emotional or psychiatric problems?" and "Was there ever a time when you,

or someone else, thought you should see someone because of the way you were feeling or acting?".

Cognitive tests included the digit symbol substitution test from the Wechsler Adult Intelligence Scale III (Wechsler D, 1998b), logical memory from the Wechsler Memory Scale III (Wechsler D, 1998a), and verbal fluency(Lezak, 1995). From these tests, we derived a measure of cognitive ability (*g*) as the first unrotated principal component, explaining 44% of the variance in scores(Marioni et al., 2014).

Psychological distress was measured using the General Health Questionnaire (GHQ-28, Likert scoring)(Goldberg and Hillier, 1979). An overall score of 24 or greater has been used to identify cases of potential psychiatric disorder(Swallow, 2003). Neuroticism was measured using the Eysenck Personality Questionnaire Short Form Revised (EPQ-SF)(Eysenck and Eysenck, 1964). The EPQ-SF is a self-report questionnaire consisting of twelve Yes/No questions which are used to assess neuroticism (on a scale 0-12, with higher scores representing greater neuroticism). The EPQ-SF has been validated with other quantitative measures of neuroticism(Gow et al., 2005) with high reliability(Eysenck et al., 1985). Schizotypal traits were elicited using the Schizotypy Personality Questionnaire (SPQ)(Raine, 1991). Socioeconomic deprivation was determined using the Scottish Index of Multiple Deprivation 2009 (SIMD)(Scottish Government, 2009).

Prescribing Data and Linkage

All Scottish citizens registered with a General Practitioner are assigned a unique identifier, the Community Health Index(CHI). This was used to deterministically record-link GS:SFHS participants to the national Prescribing Information System (PIS) administered by NHS Services Scotland Information Services Division(ISD)(Alvarez-Madrazo et al., 2016). PIS is a database of all Scottish NHS medications prescribed by GPs, nurses, dentists, pharmacists, and hospitals, where the medication was dispensed in the community. There is no prescription charge in Scotland since 2011. Hospital-dispensed prescriptions and over-the-counter medications are not included. We obtained PIS prescribing data for April 2009 (the earliest date available) to December 2016.

We additionally linked to the Scottish Morbidity Records (SMR00, SMR01 and SMR04) to obtain information about appointments with outpatient or inpatient secondary mental health

services during the period of study. The SMR records Scotland-wide outpatient, daycase and inpatient hospital (including psychiatric hospital) attendances per annum since 1981. We also linked to ISD data on mortality to determine which participants of GS:SFHS had died during the period of follow up and excluded these from our estimates where relevant.

Identification of Psychiatric Medication Usage

The PIS data allows medication to be identified by approved drug name and/or associated British National Formulary(BNF)(Joint Formulary Committee, 2012) paragraph code. Medication indication is not recorded in PIS. PIS records medication type, dose, dosage instructions and number of defined daily doses (DDDs) for each medication. DDDs are a measure for standardising drug doses(WHO, 2011). For a small part of the dataset (4.9%) the dosage instructions were missing, and these were imputed (as described in the Supplementary Materials).

We defined antidepressants (drugs for depression) as any drug included in BNF Chapter 4.3, entitled "Antidepressant Drugs". Selective Serotonin Reuptake Inhibitors (SSRIs) were identified via BNF Section 4.3.3, Tricyclic Antidepressants (TCAs) via Section 4.3.1 and, Selective Serotonin and Noradrenaline Reuptake Inhibitors(SNRIs) were identified from Section 4.3.4 (venlafaxine and duloxetine). We defined , and 'other antidepressants' as including Monoamine Oxidase Inhibitors (MAOIs), identified via Section 4.3.2, and (monoamine oxidase inhibitors, MAOIs) and the remaining drugs within Section 4.3.4 (other antidepressants). To comply with Neuroscience-based Nomenclature(Worley, 2017), a glossary of the mechanisms of action of each of the medications included in our study is provided in Table S5 of the Supplementary Material.

We recorded antidepressant medication use as any dispensed prescription during the period analysed(which was the defined 5 year period 2012-2016 in some analyses and 1-5 years following individual GS:SFHS recruitment in others, as specified). We also applied additional thresholds : in the majority of our analyses, and unless otherwise stated, we repeated our analyses excluding low dose (<75mg) amitriptyline prescriptions, as this medication and dosage is most commonly prescribed for non-psychiatric purposes (such as neuropathic pain, migraine and tension headache) and frequently for very short periods(Mars et al., 2017). With regard to antidepressant dosage, we produced estimates for antidepressants

of all dosages, and separate estimates for antidepressants prescriptions which met at least minimum BNF dose recommendations for MDD (for adult or older adults as appropriate).

Prevalence and Incidence

For each one-year period, we calculated the number of patients receiving any antidepressant prescription. Annual prevalence was calculated as the number of living cohort members using at least one antidepressant prescription that year, as a proportion of the reference sample. We also calculated the period prevalence for 2012-16 and the period prevalence for antidepressant use in the five years following each individual's enrolment in GS:SFHS.

To calculate incidence, we defined antidepressant naïve individuals as those who (a) were not on any antidepressant at the time of enrolment to GS:SFHS, or the 6 months preceding, and (b) did not report antidepressant use on the medication self-report questionnaire included in GS:SFHS, and (c) did not have a history of MDD or bipolar disorder on the SCID (which would indicate likely, although not definite, previous antidepressant use) (d) did not have a previous diagnosis of affective or anxiety disorders in the Scottish Morbidity Record(SMR) prior to GS:SFHS recruitment. We calculated incidence on the basis of the number of new users from the antidepressant naïve group, divided by the number of cohort members without antidepressant use in the preceding year.

Identification of Antidepressant Episodes and Adherence

We defined a drug treatment "episode" as consecutively dispensed prescriptions with a maximum interval between prescribing events of 90 days after the expected end date of the previous prescription, based on the dosage instructions(Gardarsdottir et al., 2010). We used 90 days as the cut-off point as it is unusual in the UK to be given more than three months medication per prescribing event (for sensitivity analyses with alternative cut-off points see Table S6 in Supplementary Material). We did not include new episodes which began in the second half of 2016, as it was not possible to estimate their duration. We defined "long-term" antidepressant use as a consecutive antidepressant episode of at least 15 months (based on three months for acute treatment, nine months for continuation-phase treatment, and three months for discontinuation, following the approach of Keyloun (Keyloun et al., 2017)).

We calculated medication adherence using the Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) metrics(Keyloun et al., 2017). MPR is defined as the sum of the day's supply for all dispensed medication in the episode divided by the number of days in the period, expressed as a percentage. PDC is defined as the number of days in a prescribing episode that are adequately "covered" by the preceding prescribing event, divided by the number of days in the episode, expressed as a percentage. Compared to MPR, PDC is generally regarded as a more conservative and preferred measure. Satisfactory adherence was defined as MPR or PDC >80% for the antidepressant episode(Keyloun et al., 2017).

Statistical Analysis

All analyses were carried out using R version 3.2.3. Prevalence and incidence rates were expressed as percentages, together with 95% confidence intervals. These estimates were reweighted by age and sex to reflect the Scottish population, using the 2011 Scottish census(Scottish Government, 2011). Age-sex reweighting was performed using the direct standardisation method using the R package "epitools".

As GS:SFHS is a family based cohort, which could lead to biases due to the hierarchical structure of the data, we used a mixed model implementation of Cox regression (with inter-relatedness controlled using pedigree as a random effect), using the R package "coxme". We controlled for potential confounding related to the recruitment area from which each participant was enrolled using a categorical variable in the model.

There was some (range 0.8-5.1%) missing data for some of the variables collected in Generation Scotland(see Supplementary Material including Table S2) and this missing data was imputed using the Multiple Imputation by Chained Equations method implemented in the R package "mice". The final estimates were the result of pooling n=100 imputed datasets, using Rubin's rules(van Buuren, 2012). Further details on the imputation, and the results of complete case analysis, are provided in the Supplementary Material. P values were corrected for multiple testing using the False Discovery Rate(FDR) method.

Results

Sample

The basic demographics of the sample compared to the Scottish population are available in the Supplementary Material(Table S1). An antidepressant was prescribed at least once to 3742 individuals (33.9(95%CI 33.0-34.8)%) of the 11,052 in our study between April 2009 and December 2016. There was a 36.2% increase in the annual prevalence of antidepressant prescribing between 2010 (age-sex reweighted prevalence 12.7(95%CI 12.0-13.5)%) and 2016 (17.3(16.5-18.3)%). During the seven year period 2010-16, 79,857 antidepressant prescriptions were dispensed (22 for every antidepressant user in GS:SFHS).

Low dose amitriptyline prescriptions(<75mg) accounted for 18.3% of prescriptions and 943 individuals (25%) were only prescribed low dose amitriptyline. Discounting low dose amitriptyline, there were 2624 antidepressant users with a mean of 1.8 antidepressant episodes (range 1-9, S.D. 1.1) during the period 2010-16. Although we had no data on specific indication, 84.2% of these episodes reached a dosage equivalent to at least the required BNF minimum for the treatment of Major Depressive Disorder.

The most commonly prescribed class of antidepressants was Selective Serotonin Reuptake Inhibitors(SSRIs), accounting for 54% of prescriptions in 2010 and 52.7% in 2016 (65.6% and 64% respectively if low dose amitriptyline excluded). The proportion of Serotonin and Noradrenaline Reuptake Inhibitors(SNRIs) prescribed increased from 9.1% in 2010 to 10.9% in 2016, and the proportion of other antidepressants (such as mirtazapine) increased from 6.7% to 8.3% during the same period. The proportion of Tricyclic Antidepressants(TCAs) was 27.8% in 2016, or 12.3% if low dose amitriptyline excluded.

Period Prevalence 2012-16

The 5-year 2012-2016 age-sex reweighted period prevalence of antidepressant use was 28.0(95%CI 26.9-29.1)% for the cohort. With low dose amitriptyline excluded, the prevalence was 20.8 (19.9-21.8)% (see **Table 1**). The five-year prevalence was considerably higher among females, 34.9(33.3-36.6)%, than males, 20.4(19.0-22.0)%. There was a bimodal distribution of antidepressant use by age, with 2012-16 period prevalence highest in the 45-54 age group for all antidepressants(33.3(31.3-35.3%)) and a second peak in the 75+ age group(33.3(28.8-38.8)%) (**Figure 2**).

Prevalence of Antidepressant Prescribing in One to Five Years Follow-Up

In the first year following each individual's GS:SFHS enrolment, 11.2(95%CI 10.6-11.8)% of the cohort had at least one antidepressant prescription(excluding low dose amitriptyline, as does all analysis in this section), which increased to 20.8(20.0-21.6)% after five years.

Among those with history of recurrent MDD on recruitment, 52.4(48.5-56.2)% were prescribed at least one antidepressant within 1 year following GS recruitment and for bipolar disorder the proportion was 46.2(30.4-62.6)%. For those with no history of MDD on recruitment, 6.9(6.5-7.5)% were prescribed at least one antidepressant within one year – or 2.5(2.2-2.9)% if those already on antidepressants at recruitment were excluded.

Among those with a GHQ-28 Likert score of 24 or above at the time of GS:SFHS recruitment, 31.7(95% CI 29.4-34.1)% had at least one antidepressant prescription within 1 year. Among the antidepressant naïve subgroup at the time of GS:SFHS recruitment, 6.6(5.1-8.6)% of those with a Likert score of >=24 were prescribed antidepressants within 1 year and 9.2(4.1-18.6)% of those scoring over three standard deviations above the mean on the GHQ depression subscale (subscale D) were prescribed an antidepressant within 1 year.

Incidence of Antidepressant Prescribing 2012-16

The age-sex reweighted incidence of antidepressant prescribing was 2.4(2.1-2.7)% per year for all antidepressants and 1.6(1.4-1.9)% if low dose amitriptyline is excluded. Incidence was greater in females 2.7(2.4-3.2)% than males 2.0(1.6-2.5)%.

77.1% of incident antidepressant users were commenced on an SSRI, with 11.9% on a TCA (low dose amitriptyline excluded), 4.0% on a serotonin and noradrenaline reuptake inhibitor(SNRI) and 7.0% on other antidepressants(especially mirtazapine). The most common individual medication for new users was citalopram (39.9%), followed by fluoxetine (21.6%) and sertraline (14.2%). Less than 1% were commenced on paroxetine and none on reboxetine or MAOIs. The most common tricyclic antidepressant for new users was nortriptyline (3.9%) followed by higher dose amitriptyline(3.0%).

Antidepressant Episodes

In the five years period 2012-16, 2385 individuals used antidepressants and we defined 3595 antidepressant episodes(low dose amitriptyline excluded). Some 86.6% (n=3112) of episodes

reached at least minimum dose required for treatment of MDD (although actual indication was not available). We allowed antidepressant switching or combination during episodes, with the majority of episodes(79.3%) having just one antidepressant, 13.6% having two and 7.1% having three or more(range 3-6).

Over half (57.6%) of antidepressant episodes were of 9 months or greater and 44.8% met our 15-month criteria for long term use, with the majority of antidepressant users (57.7%) having a least one episode of long term duration. Nevertheless, approximately one tenth (10.6%) of episodes were of less than 30 days duration and a further 12.6% were of 31-90 days, meaning that approximately one quarter of episodes were less than three months duration.

Adherence

For the 3595 antidepressant episodes between 2012-16(n=2385 individuals), the mean Medication Possession Ratio(MPR) per antidepressant episode was 96.0% (range 11-412) and the mean Proportion of Days Covered(PDC) was 84.9% (range 11-100). Using PDC >= 80% as defining adherence, 69.0% of antidepressant episodes were adherent, when using 90 days as the cut-off point between antidepressant episodes (for sensitivity analysis see Table S6 in Supplementary Materials). Mean PDC was similar across medication classes (SSRI 84.5%, TCA 84.3%, SNRI 83.2%, MAOI 77.3%, other 83.9%, see Table S6 in Supplementary Materials).

Polypharmacy

Other medications that were co-prescribed with antidepressants during an antidepressant episode were determined, with simultaneous use on at least three occasions being classed as "regular" use. Anxiolytics (medicines for anxiety) were co-prescribed to 34.1% of antidepressant users (16.4% regularly), including benzodiazepines 23.6% (10.7% regularly) and "Z-drugs"(the benzodiazepine-receptor agonists zopiclone, zolpidem and zaleplon) 18.9% (7.6% regularly). Pregabalin or gabapentin (alpha-2 delta calcium channel blockers often used to treat anxiety and neuropathic pain as well as epilepsy) were co-prescribed to 12.8% users (8.9% regularly). Antipsychotics (medicines to treat psychosis) were co-prescribed to 6.8% antidepressant users (5.1% regularly). Lithium compounds or sodium valproate, which are also used to treat mood disorders, were co-prescribed to 1.6% (1.4% regularly). Opiate-based analgesic (pain relieving) medications were co-prescribed to 22% of

antidepressant users (13.3% regularly), compared to a general five-year prevalence of 15.6% (**Figure 3**). Opioid use was also higher in those with a history of bipolar disorder (33.3%,regular 18.5%) and recurrent MDD (27.8%, regular 17.3%) on GS:SFHS recruitment, compared to those with no affective disorder history (20.5%, regular 12.3%).

Use of psychiatric services

Using record linkage to hospital data, 10.0(8.9-11.2)% of antidepressant users in the five years following GS:SFHS enrolment, who were prescribed at least the minimum BNF recommended dosage for MDD, had a psychiatric outpatient appointment during at least one of their antidepressant treatment episodes. Some 1.8(1.4-2.5)% of antidepressant users were admitted to psychiatric hospital during at least one episode of antidepressant treatment.

Predictors of antidepressant use - time to event analysis

We performed time-to-antidepressant-use Cox regression analysis for the five years following individual GS:SFHS enrolment, excluding those individuals already on antidepressants (**Figure 4** and **Table 2**). Female gender was predictive of commencing antidepressants in the multivariable model (Hazard Ratio(HR)=1.74, 95% CI 1.53-1.98, p_{FDR}<0.0001). Lower SIMD deprivation status was associated with antidepressant use in univariate analysis (and in complete case analysis, see Supplementary Table S3) but was not significant in the multivariable model. Neuroticism (HR 1.12,1.09-1.14 per unit, p_{FDR}<0.0001), previous history of unemployment(HR=1.24, 1.06-1.45, p_{FDR}=0.02) and smoking status (current smokers HR 1.57(1.34-1.84, p_{FDR} <0.0001) were also positively associated with antidepressant use, whereas cognitive function (g) scores were negatively associated (HR 0.89, 0.85-0.93, p_{FDR} 0.001). Multiple physical comorbidities (3+) were positively associated with antidepressant use (HR 1.85,1.33-2.57, p_{FDR} 0.002). The most predictive factor for antidepressant use was previous history of affective disorder on GS:SFHS recruitment, with history of a single episode of MDD having a hazard ratio of 2.22 (1.85-2.67, p_{FDR}<0.0001).

Discussion

Summary of Main Results

In this study, we demonstrate an increase in antidepressant usage in this UK cohort, with an estimated 17.3% of the adult population using antidepressants in 2016, an increase of nearly

one third(36.2%) on 2010(see Supplementary Table S4). We have found that, even if low dose amitriptyline use is discounted, one fifth of our sample (20.8%) has been prescribed an antidepressant at least once between 2012-16. The prescribing of antidepressants continues to be dominated by the SSRI class, but we observed a rise in the proportion of SNRIs, and other antidepressants such as mirtazapine, prescribed. This is an interesting trend and may be further stimulated by future revisions of clinical guidance, which may recategorize mirtazapine as a first-line treatment in psychiatric disorders such as major depression, leading to further increases in prevalence of use and interest in the efficacy and safety profile of mirtazapine and other non-SSRI antidepressants(Coupland et al., 2015; Cipriani et al., 2018).

Our findings accord with recent UK data which has found that antidepressant prescribing is the highest ever at 64.7m prescriptions for England in 2016(NHS Digital, 2017). However, in this study we also found a reweighted incidence for new antidepressant users of just 2.4%, and a duration for antidepressant episodes of in excess of 15 months in nearly half of episodes identified. This supports the hypothesis of increased longer-term use by regular antidepressant users driving much of the increased prevalence of antidepressants we report. Our study also found that adherence to antidepressants was relatively high, meeting the more conservative PDC threshold adherence of 80% in 69.0% of cases.

We found that history of affective disorder, multiple physical comorbidities, and being female, were the most predictive of antidepressant use. We also report an interesting association between neuroticism and antidepressant use, with considerably greater incident antidepressant use in the upper tertile of EPQ-SF neuroticism scores(Figure 4). Neuroticism is a personality trait with significant clinical overlap with psychiatric disorder(Smith et al., 2016), which is relatively straightforward to measure prospectively, and our results suggest that it could be a useful predictor of future antidepressant usage. A recent study in older adults (Steffens et al., 2018)has found that neuroticism may be also associated with lower remission rates of antidepressant-treated depression. We also found that cognitive function had an inverse association with antidepressant use, in line with previous research indicating an association between cognitive impairment and MDD(Marazziti et al., 2010).

With this study methodology we cannot judge definitely whether the increasing antidepressant prevalence we found is appropriate to clinical indication. The prevalence of prescribing we report should be seen in the context of not only the prevalence of MDD, but

the prevalence of anxiety disorders, eating disorders, sexual disorders, sleep disorders and other indications for antidepressant medication. Nevertheless, it has also been argued that current rates of antidepressant treatment may still not identify all those most likely to benefit (Kendrick et al., 2005). The National Health and Nutrition Examination Surveys 2005-08(Pratt et al., 2011) found that only one third of those with severe depressive symptoms were on antidepressant therapy, and less than half of those taking multiple antidepressants had seen a mental health professional in the past year. In our study, we found that, among those antidepressant naïve individuals with the highest psychiatric 'caseness' according to GHQ scores in Generation Scotland, just 6.6% were prescribed an antidepressant within one year of follow-up, and less than 10% of those with the highest severe depression caseness (three standard deviations on the GHQ-28 D subscale) were prescribed an antidepressant within one year. This might indicate potential unmet clinical need for antidepressants, although such a conclusion should be approached with caution as GHQ is a measure of psychiatric distress at one timepoint, and higher GHQ scores do not necessarily indicate requirement for antidepressants.

It has also been previously argued that antidepressants are insufficiently reviewed by clinicians, leading to unnecessarily long treatment durations(Bosman et al., 2016; Johnson et al., 2012). The European Study of the Epidemiology of Mental Disorders (ESEMed) demonstrated that 63.5% of those with mood disorders had not consulted health services in the previous 12 months(Alonso J, 2004), with similar findings in the US National Comorbidity Survey Replication(Wang et al., 2005). We found that only a small minority of antidepressant users are being reviewed in outpatient psychiatry, suggesting that the majority of antidepressant monitoring takes place in primary care. The high prevalence of antidepressant use we report suggests that there may be scope for increasing the rate of medication reviews for long-term antidepressant users in primary (and secondary) care, with consideration of managed discontinuation of treatment. This can help manage the risks associated with prolonged antidepressant exposure when a sustained recovery from illness has been achieved.

Among medications frequently co-prescribed with antidepressants, the most common psychiatric class was anxiolytics, especially benzodiazepines and "Z-drugs". We found that the co-prescribing of analgesic and opiate medication was appreciably higher in antidepressant users, especially those with a history of recurrent depression and bipolar

disorder. An association between depression and pain has been previously described(McIntosh et al., 2016) and could be related to altered pain sensitivity in depressed states and comorbidity of depression with painful conditions.

Comparison With Previous Studies

A previous prescribing database study of the Tayside population of Scotland (n=325,000)(Lockhart and Guthrie, 2011) found an increase in prevalence from 8.0% in 1995/96 to 13.4% in 2006/07. The standardised rate for 2006-07 antidepressants was 13.1% (SSRIs 7.9%, TCAs 5.2%, other antidepressants 1.9%) compared to the reweighted 2016 rates of 17.3% (10.5%, 5.8%, 3.2%) found in our study. Analysis of the UK Clinical Practice Research Datalink (CPRD, N=1,524,201) found that 23% of individuals were prescribed at least one antidepressant between 1995 and 2001(Mars et al., 2017).

Results from the US National Health and Nutrition Examination Survey (NHANES) found a 2009-10 annual prevalence of 10.4%(Mojtabai and Olfson, 2014), with 67.4% reporting use for 24 months or longer, and 17.1% for <6 months. Incidence was estimated at 2.55% (per 100 individuals per year) in comparison with our estimated incidence of 2.4%. In this US study, 32.5% of antidepressant users had visited a mental health professional in the previous year, compared with 10.0% in our UK-based study.

A prescription database study in British Columbia conducted in 2004(Raymond et al., 2007) found a prevalence of 7.2% and found that lower socioeconomic groupings and lowest income groupings had higher prevalences of antidepressant use. In our time-to-event analysis we found the lowest SIMD quintiles were associated with antidepressant use in univariate analysis but not in the multivariable model.

A recent study of routine general practice care data in a cohort based in Amsterdam (n=156,620) found 43.7% of antidepressant users were long-term users(Huijbregts et al., 2017), which is similar to our own finding of 44.8%.

Strengths and Limitations

This study benefitted from the relatively large population-based GS:SFHS cohort and the availability of structured clinical interview data alongside quantitative measures of non-

specific psychiatric morbidity and numerous demographic, socio-economic and psychological variables. The national prescribing and morbidity data to which it was linked was of high fidelity (with a capture rate in excess of 95%) and, being nationally based, reduced the chance of individuals being lost to follow up during the study period due to, for example, moving their GP practice. We were also able to record the date of dispensing as well as prescribing, and whether the medication was collected. By applying a longitudinal retrospective design rather than a cross-sectional approach, this study increased the potential for accurate measurement of the pharmaco-epidemiological variables.

However, by using a cohort study as its basis, this analysis is also susceptible to selection and confounding biases. Another significant limitation is the lack of details of the indication of medication use in the PIS prescribing data(as with many other prescribing databases based on routinely collected administrative data). In GS:SFHS, previous history of affective disorder was collected via screening using the SCID, but we were not able to determine ongoing and subsequent psychiatric diagnoses in the period studied following GS:SFHS recruitment. It is likely that a proportion of those individuals with no previous history of affective disorder were subsequently diagnosed with such, or that other psychiatric disorders such as anxiety disorders were the indication for later antidepressant treatment. GS:SFHS did not provide data on baseline history of anxiety disorders to complement the SCID-derived history of affective disorders. We were also not able to determine the extent to which severity of psychiatric symptoms or level of functional impairment determines antidepressant usage.

Prescribing data is also an imperfect proxy for medication use, given that the medication may not be taken (primary noncompliance) or may not be used as directed (secondary noncompliance). Noncompliance to antidepressant medication has been previously estimated at 50%(Haynes et al., 2008). The PIS prescribing data only covered prescriptions issued in the community, and therefore may underestimate true prevalence and treatment duration, although it would be expected that most antidepressant users commenced in hospital would continue medication in the community. A further limitation of our study being based on routinely collected administrative prescribing data is that it is also not possible to determine the extent to which the antidepressant prescribing we recorded was appropriate to clinical need or consistent with treatment guidelines.

Although we attempted to apply stringent criteria for incident use of antidepressants - using prescription data, linked morbidity data, self-report and objectively measured history of affective disorder to screen antidepressant naïve cohort members - we may still have falsely identified some previous antidepressant users as incident cases, particularly as we did not have data preceding April 2009.

Our Cox regression analysis of predictors of antidepressant use within 5 years was necessarily restricted by the variables available to us in GS:SFHS. We were able to derive effect sizes for numerous variables previously associated with antidepressant use, such as history of affective disorder, medical comorbidities and female gender. However, due to the limited diagnostic information available in GS:SFHS we were not able to quantify the association between non-affective psychiatric disorders such as anxiety disorders (which are likely to be significantly predictive) and antidepressant use. The conclusions of our time-to-event analysis need to be placed in the context of the variables available in our model.

The cohort was also for adults only, thereby not including antidepressant use among the under 18s, and the overall population prevalence and incidence would be expected to be lower than our figures since children are prescribed antidepressants less frequently.

Future Directions and Clinical Implications

We found that antidepressant prevalence was higher than previously reported for the UK, but that incidence remains relatively stable. This suggests that increased antidepressant prevalence is driven by longer treatment durations and good levels of adherence, and previous users returning to medication for a wider range of indications, rather than an upsurge in incident cases. Our study also demonstrates the utility of record-linking administrative health data to population-based cohorts to provide enhanced pharmaco-epidemiological estimates of prevalence, incidence and adherence. We also found significant relationships between neuroticism and cognitive function for antidepressant use, even when affective disorder was controlled for. These tests are relatively easy to administer and could provide useful to clinicians in constructing predictive models of clinical risk.

More research is required to investigate the clinical appropriateness of antidepressant prescribing. Our research suggests that the vast majority of antidepressant prescribing and

medication review takes place in the primary care setting in the UK. Primary care will necessarily therefore remain the focal point for future efforts to improve antidepressant prescribing practices, monitoring of adherence and adverse effects, and managed discontinuation of treatment when clinically appropriate.

Declaration of Conflict of Interest.

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of the article.

Funding.

JDH gratefully acknowledges receipt of an MRC/MRF PsySTAR PhD fellowship. Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates [CZD/16/6] and the Scottish Funding Council [HR03006]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "STratifying Resilience and Depression Longitudinally" (STRADL) Reference 104036/Z/14/Z).

Ethical Approval.

All components of STRADL received formal, national ethical approval from the NHS Tayside committee on research ethics (reference 14/SS/0039).

Article Word Count : 5111

References

Abbing-Karahagopian Huerta C, Souverein P, de Abajo F, et al. (2014) Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *Eur J Clin Pharmacol* 70: 849-857.

Alonso J AM, Bernert S, et al. . (2004) Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 420: 21-27.

Alvarez-Madrazo S, McTaggart S, Nangle C, et al. (2016) Data Resource Profile: The Scottish National Prescribing Information System (PIS). *Int J Epidemiol*.

Bandelow B and Michaelis S. (2015) Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci* 17(3): 327-335.

Bet PM, Hugtenburg JG, Penninx BW, et al. (2013) Side effects of antidepressants during long-term use in a naturalistic setting. *Eur Neuropsychopharmacol* 23(11): 1443-1451.

Bosman RC, Huijbregts KM, Verhaak PF, et al. (2016) Long-term antidepressant use: a qualitative study on perspectives of patients and GPs in primary care. *Br J Gen Pract* 66(651): e708-719.

Cipriani A, Furukawa TA, Salanti G, et al. (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*.

Coupland C, Dhiman P, Morriss R, et al. (2011) Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 343(d4551).

Coupland C, Hill T, Morriss R, et al. (2015) Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ* 350: h517.

Cruickshank G, Macgillivray S, Bruce D, et al. (2008) Cross-sectional survey of patients in receipt of long-term repeat prescriptions for antidepressant drugs in primary care. *Ment Health Fam Med* 5(2): 105-109.

Exeter D, Robinson E and Wheeler A. (2009) Antidepressant dispensing trends in New Zealand between 2004 and 2007. *Aust N Z J Psychiatry* 43(12): 1131-1140.

Eysenck SB and Eysenck HJ. (1964) An Improved Short Questionnaire for the Measurement of Extraversion and Neuroticism. *Life Sci (1962)* 3: 1103-1109.

Eysenck SB, Eysenck HJ and Barrett P. (1985) A revised version of the psychoticism scale. *Personality and Individual Differences* 61(1): 21-29.

Gardarsdottir H, Souverein PC, Egberts TC, et al. (2010) Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *J Clin Epidemiol* 63(4): 422-427.

Goldberg DP and Hillier VF. (1979) A scaled version of the General Health Questionnaire. *Psychol Med* 9(1): 139-145.

Gonzalez-Lopez MC, Rodriguez-Lopez CM, Parron-Carreno T, et al. (2015) Trends in the dispensation of antidepressant drugs over the past decade (2000-2010) in Andalusia, Spain. *Soc Psychiatry Psychiatr Epidemiol* 50(5): 705-712.

Gow A, Whiteman M, Pattie A, et al. (2005) Goldberg's IPIP'Big-Five factor markers: Internal consistency and concurrent validation in Scotland. *Personality and Individual Differences* 39(2): 317-329.

Haynes RB, Ackloo E, Sahota N, et al. (2008) Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* (2).

Hill T, Coupland C, Morriss R, et al. (2015) Antidepressant use and risk of epilepsy and seizures in people aged 20 to 64 years: cohort study using a primary care database. *BMC Psychiatry* 15: 315.

Hollinghurst S, Kessler D, Peters TJ, et al. (2005) Opportunity cost of antidepressant prescribing in England: analysis of routine data. *BMJ* 330(7498): 999-1000.

Huijbregts KM, Hoogendoorn A, Slottje P, et al. (2017) Long-Term and Short-Term Antidepressant Use in General Practice: Data from a Large Cohort in the Netherlands. *Psychother Psychosom* 86(6): 362-369.

Ilyas S and Moncrieff J. (2012) Trends in prescriptions and costs of drugs for mental disorders
in England, 1998 –2010. *BJPsych* 200: 393-398.

Johnson CF, Macdonald HJ, Atkinson P, et al. (2012) Reviewing long-term antidepressants can reduce drug burden: a prospective observational cohort study. *Br J Gen Pract* 62(604): e773-779.

Joint Formulary Committee. (2012) *British National Formulary*: Pharmaceutical Press.

Kendrick T, King F, Albertella L, et al. (2005) GP treatment decisions for patients with depression: an observational study. *British Journal of General Practice* 55(513): 280-286.

Kendrick T, Stuart B, Newell C, et al. (2015) Did NICE guidelines and the Quality Outcomes Framework change GP antidepressant prescribing in England? Observational study with time trend analyses 2003-2013. *J Affect Disord* 186: 171-177.

Kessler D, Sharp D and Lewis G. (2005) Screening for depression in primary care. *Br J Gen Pract* 55(518): 659-660.

Keyloun KR, Hansen RN, Hepp Z, et al. (2017) Adherence and Persistence Across Antidepressant Therapeutic Classes: A Retrospective Claims Analysis Among Insured US Patients with Major Depressive Disorder (MDD). *CNS Drugs* 31(5): 421-432.

Kirsch I, Deacon BJ, Huedo-Medina TB, et al. (2008) Initial severity and antidepressant benefits: A meta-analysis of data submitted to the food and drug administration. *Plos Medicine* 5(2): 260-268.

Lewer D, O'Reilly C, Mojtabai R, et al. (2015) Antidepressant use in 27 European countries: associations with sociodemographic, cultural
and economic factors. *The British Journal of Psychiatry* 207: 221-206.

Lezak M. (1995) *Neuropsychological Testing,* Oxford: Oxford University Press.

Lockhart P and Guthrie B. (2011) Trends in primary care antidepressant prescribing 1995-2007: a longitudinal population database analysis. *Br J Gen Pract* 61(590): e565-572.

Marazziti D, Consoli G, Picchetti M, et al. (2010) Cognitive impairment in major depression. *Eur J Pharmacol* 626(1): 83-86.

Marioni RE, Batty GD, Hayward C, et al. (2014) Common genetic variants explain the majority of the correlation between height and intelligence: the generation Scotland study. *Behav Genet* 44(2): 91-96.

Mars B, Heron J, Kessler D, et al. (2017) Influences on antidepressant prescribing trends in the UK: 1995-2011. *Soc Psychiatry Psychiatr Epidemiol* 52(2): 193-200.

McIntosh AM, Hall LS, Zeng Y, et al. (2016) Genetic and Environmental Risk for Chronic Pain and the Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-Model Analysis. *Plos Medicine* 13(8): e1002090.

Meijer WE, Heerdink ER, Leufkens HG, et al. (2004) Incidence and determinants of long-term use of antidepressants. *Eur J Clin Pharmacol* 60(1): 57-61.

Mojtabai R and Olfson M. (2014) National trends in long-term use of antidepressant medications: results from the US National Health and Nutrition Examination Survey. *J Clin Psychiatry.* 75(2): 169-177.

Moore M, Yuen HM and Dunn N. (2009) Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. . *BMJ* 339(2): b3999.

Munoz-Arroyo R, Sutton M and Morrison J. (2006) Exploring potential explanations for the increase in antidepressant prescribing in Scotland using secondary analyses of routine data. *Br J Gen Pract* 56(527): 423-428.

National Institute of Mental Health. (2017a) *Generalized Anxiety Disorder*. Available at: https://www.nimh.nih.gov/health/statistics/generalized-anxiety-disorder.shtml.

National Institute of Mental Health. (2017b) *Major Depression*. Available at: https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml

NHS Digital. (2017) *http://content.digital.nhs.uk/article/7756/Antidepressants-were-the-area-with-largest-increase-in-prescription-items-in-2016*.

Olfson M and Marcus SC. (2009) National patterns in antidepressant medication treatment. *Arch Gen Psychiatry* 66(8): 848-856.

Petty DR, House A, Knapp P, et al. (2006) Prevalence, duration and indications for prescribing of antidepressants in primary care. *Age Ageing* 35(5): 523-526.

Pratt LA, Brody DJ and Gu Q. (2011) Antidepressant use in persons aged 12 and over: United States, 2005-2008. *NCHS Data Brief* (76): 1-8.

Raine A. (1991) The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull* 17(4): 555-564.

Raymond CB, Morgan SG and Caetano PA. (2007) Antidepressant utilization in British Columbia from 1996 to 2004: increasing prevalence but not incidence. *Psychiatr Serv* 58(1): 79-84.

Reid I. (2013) Are antidepressants overprescribed? No. *BMJ* 346: f190.

Scottish Government. (2009) *Scottish Index of Multiple Deprivation 2009 General Report,* Edinburgh: Office of the Chief Statistician.

Scottish Government. (2011) *Scotland Census 2011*.

Smith BH, Campbell A, Linksted P, et al. (2013) Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. *Int J Epidemiol* 42(3): 689-700.

Smith BH, Campbell H, Blackwood D, et al. (2006) Generation Scotland: the Scottish Family Health Study; a new resource for researching genes and heritability. *BMC Med Genet* 7: 74.

Smith DJ, Escott-Price V, Davies G, et al. (2016) Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Mol Psychiatry* 21(11): 1644.

Spence D. (2013) Are antidepressants overprescribed? Yes. *BMJ* 346(3): f191.

Spence R, Roberts A, Ariti C, et al. (2014) Focus On:Antidepressantprescribing. *The Health Foundation*.

Steffens DC, Wu R, Grady JJ, et al. (2018) Presence of neuroticism and antidepressant remission rates in late-life depression: results from the Neurobiology of Late-Life Depression (NBOLD) study. *Int Psychogeriatr* 30(7): 1069-1074.

Swallow BL, S.W.;Masson,E.;Hay,D.M. (2003) The use of the General Health Questionnaire (GHQ-28) to estimate prevalence of psychiatric disorder in early pregnancy. *Psychology, Health and Medicine* 8(2): 213-217.

Trifiro G, Barbui C, Spina E, et al. (2007) Antidepressant drugs: prevalence, incidence and indication of use in general practice of Southern Italy during the years 2003-2004. *Pharmacoepidemiol Drug Saf* 16(5): 552-559.

van Buuren S. (2012) *Flexible Imputation of Missing Data* Chapman and Hall.

Wang PS, Lane M, Olfson M, et al. (2005) Twelve-month use of Mental Health Services in the United States - Results from the National Comorbidity Survey Replication. *Archives of General Psychiatry* 62(6): 629-640.

Wechsler D. (1998a) *Wechsler Adult Intelligence Scale III,* London: Psychological Corporation.

Wechsler D. (1998b) *Wechsler Memory Scale III, ,* London: Psychological Corporation.

WHO. (2011) *World Health Organisation Collaborating Centre for Drug Statistics ATC/DDD Index 2011,* Oslo: World Health Organisation /Norwegian Institute of Public Health.

Worley L. (2017) Neuroscience-based nomenclature (NbN). *Lancet Psychiatry* 4(4): 272-273.

Zhong WJ, Kremers HM, Yawn BP, et al. (2014) Time trends of antidepressant drug prescriptions in men versus women in a geographically defined US population. *Archives of Womens Mental Health* 17(6): 485-492.

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

Table 1 : Prevalence of Antidepressant Medications, by Class, 2012-2016

	All antidepressant		SSRI		TCA		Other antidepressants		Antidepressants excluding low dose amitriptyline	
	2012-16	n	2012-16	n	2012-16	n	2012-16	n	2012-16	n
Crude Rate	29.5(28.6-30.4)	3167	17.4(16.7-18.2)	1883	15.0(14.3-15.7)	1619	5.8(5.4-6.3)	630	21.9(21.1-22.7)	2366
Reweighted Rate	28.0(26.9-29.1)		16.5(15.7-17.4)		14.1(13.4-15.0)		5.6(5.1-6.2)		20.8(19.9-21.8)	
Sex -Male (crude)	20.4(19.2-21.7)	900	11.1(10.2-12.1)	489	10.0(9.1-11.0)	440	4.4(3.8-5.1)	195	14.7(13.7-15.8)	647
(RW)	20.4(19.0-22.0)		11.1(10.1-12.3)		9.9(8.7-11.1)		4.4(3.8-5.2)		14.7(13.5-16.1)	
Sex – Female (crude)	35.4(34.3-36.6)	2267	21.8(20.8-22.8)	1394	18.4(17.4-19.4)	1179	6.8(6.2-7.5)	435	26.9(25.8-28.0)	1719
(RW)	34.9 (33.3-36.6)		21.4(20.2-22.7)		18.1(16.9-19.3)		6.7(6.0-7.5)		26.4(25.0-27.9)	
Age - 18-24	22.6(19.8-25.7)	181	18.4(15.8-21.3)	147	6.6(5.0-8.6)	53	4.0(2.8-5.7)	32	19.5(16.8-22.4)	156
25-34	23.0(20.9-25.3)	335	17.5(15.6-19.5)	255	8.5(7.1-10.0)	123	4.7(3.7-6.0)	71	19.5(17.5-21.7)	284
35-44	32.9(30.7-35.1)	601	22.5(20.6-24.5)	411	14.1(12.5-15.8)	257	7.3(6.2-8.7)	134	26.6(24.6-28.7)	487
45-54	33.3(31.3-35.3)	739	20.6(19.0-22.4)	458	16.8(15.3-18.4)	373	6.1(5.1-7.2)	136	25.2(23.4-27.1)	560
55-64	29.1(27.4-30.7)	858	14.9(13.6-16.3)	440	17.0(15.7-18.4)	503	6.0(5.2-6.9)	177	20.6(19.1-22.1)	607
65-74	28.3(25.8-30.9)	346	10.6(9.0-12.5)	130	19.5(17.4-21.9)	239	4.6(3.5-5.9)	57	16.4(14.4-18.7)	201
75+	33.3(28.3-38.8)	107	13.1(9.7-17.4)	42	22.1(17.8-27.1)	71	7.2(4.7-10.7)	23	22.1(17.8-27.1)	71

Abbreviations : RW=age-sex reweighted. SSRI=Selective Serotonin Reuptake Inhibitors. TCA=Tricyclic Antidepressants. n = total number within grouping with prescription records of at least one antidepressant usage.

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

Table 2 : Cox Regression of Time-To-Antidepressant-Use in GS:SFHS (Excluding those Already Using Antidepressants At Time Of Recruitment), N=9953 of whom n=1347 went on to use antidepressants within 5 years

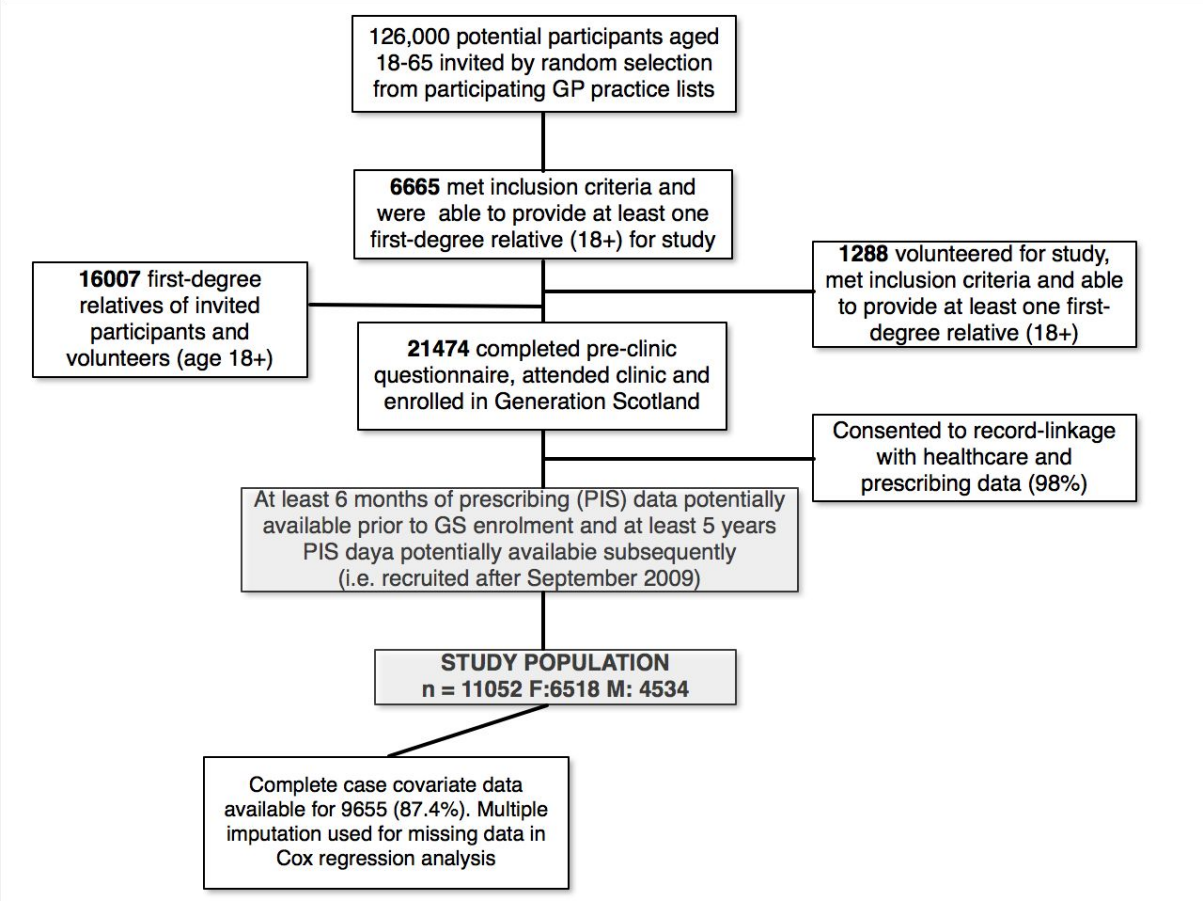
	Univariate		**Multivariable**		
	Hazard Ratio	p	Hazard Ratio	p(FDR)	Sig
Intercept					
Sex – male	Ref	Ref	Ref	Ref	
– female	1.94(1.72-2.19)	<0.0001	1.74(1.53-1.98)	<0.0001	***
Age :18-24	Ref	Ref	Ref	Ref	Ref
:25-34	0.81(0.64-1.03)	0.16	0.79(0.62-1.01)	0.119	
: 35-44	1.03(0.83-1.28)	0.92	0.95(0.75-1.21)	0.787	
: 45-54	0.99(0.80-1.22)	0.92	1.00(0.79-1.26)	0.993	
: 55-64	0.72(0.58-0.89)	0.007	0.72(0.57-0.92)	0.021	*
:65-74	0.49(0.37-0.64)	<0.0001	0.48(0.35-0.64)	<0.0001	***
:75+	0.93(0.67-1.29)	0.92	0.74(0.52-1.07)	0.193	
No MDD on Screening	Ref	Ref	Ref	Ref	Ref
MDD - Single Episode	3.17(2.69-3.76)	<0.0001	2.22(1.85-2.67)	<0.0001	***
MDD - Recurrent	4.33(3.54-5.30)	<0.0001	2.10(1.68-2.62)	<0.0001	***
MDD - Bipolar	4.84(2.38-9.85)	<0.0001	2.11(0.99-4.47)	0.109	
Never Smoked	Ref	Ref	Ref	Ref	Ref
Currently Smoke	2.05(1.78-2.37)	<0.0001	1.57(1.34-1.84)	<0.0001	***
Ex-Smoker	1.30(1.14-1.48)	<0.0001	1.33(1.15-1.53)	0.001	*
Neuroticism	1.20(1.18-1.22)	<0.0001	1.12(1.09-1.14)	<0.0001	***
SPQ	1.11(1.09-1.12)	<0.0001	1.03(1.01-1.05)	0.003	*
Cognitive function (g)	0.85(0.81-0.89)	<0.0001	0.89(0.85-0.93)	<0.0001	***
No physical health complaints	Ref	Ref	Ref	Ref	Ref
1-2 physical health complaints	1.22(1.08-1.38)	<0.0001	1.27(1.11-1.44)	0.003	*
3+ physical health complaints	1.79(1.34-2.41)	<0.0001	1.85(1.33-2.57)	0.002	*
Unemployment history			1.24(1.06-1.45)	0.021	*
SIMD – Most Deprived quintile	2.03(1.70-2.42)	<0.0001	1.23(1.01-1.49)	0.086	.
SIMD – 2nd quintile	1.47(1.23-1.76)	<0.001	1.07(0.88-1.29)	0.64	
SIMD – 3rd quintile	1.27(1.06-1.52)	0.013	1.06(0.88-1.28)	0.64	
SIMD – 4th quintile	1.02(0.87-1.21)	0.79	0.93(0.78-1.10)	0.54	
SIMD – Least Deprived quintile	Ref	Ref	Ref	Ref	Ref

N.B. The following covariates were in the model but not shown as not significant in multivariable analysis: Location of GS:SFHS enrolment(not significant in univariate or multivariable analyses), self-reported alcohol use, body mass index (bmi).
Abbreviations: Sig=significance level *p<0.05, **p=<0.001, ***p<0.0001 Ref=reference level g = cognitive function score. GHQ = General Health Questionnaire. MDD = Major Depressive Disorder. SIMD = Scottish Index of Multiple Deprivation. SPQ = Schizotypal Personality Questionnaire.

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

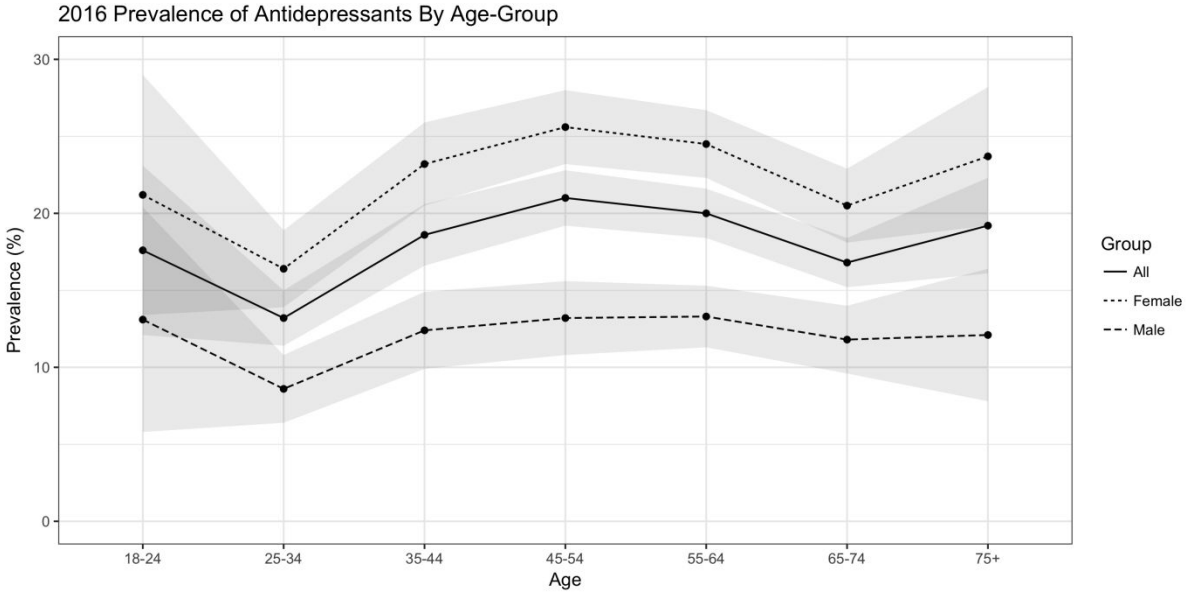
Figure 1 : Derivation of Study Population from Generation Scotland cohort



Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

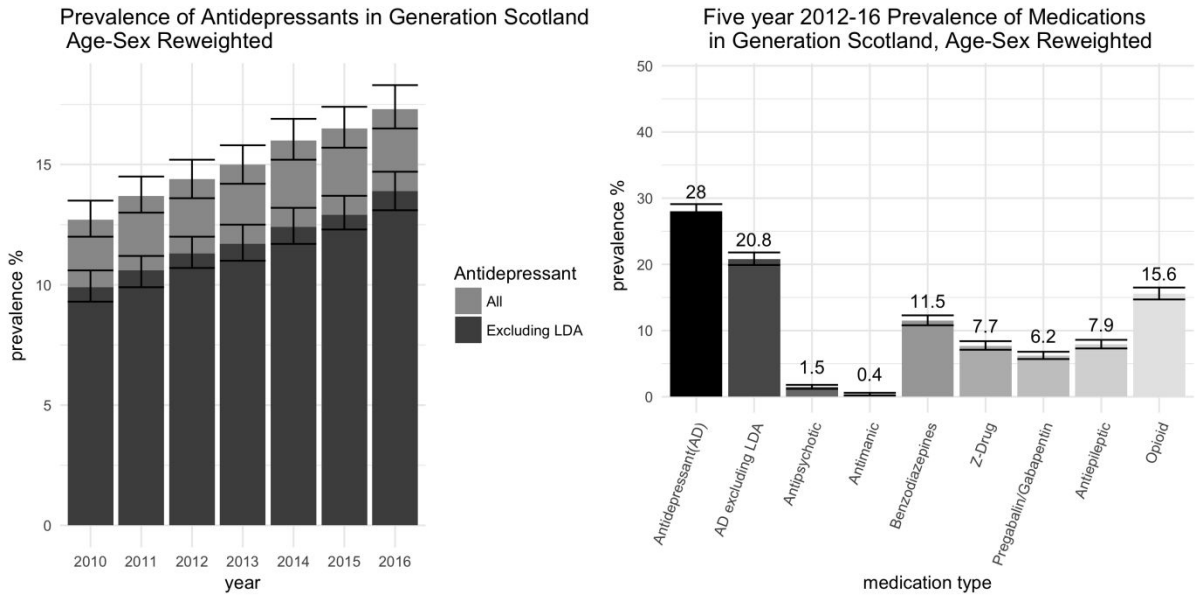
Figure 2 : 2016 Age and sex specific period prevalence of antidepressant for all antidepressant types and indications



Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

Figure 3 : Age-Sex Reweighted Prevalence of Antidepressants And Other Medications In GS:SFHS

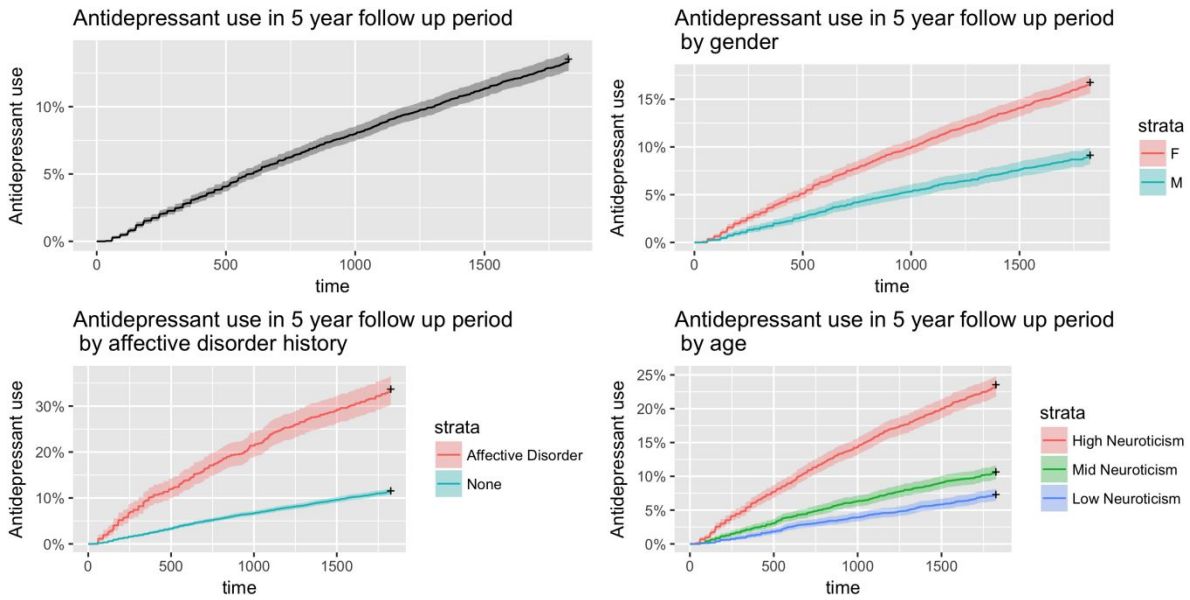


Abbreviations : LDA= low dose amitriptyline.

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

Figure 4 : Kaplan-Meier Time To Event Curves For Incident Antidepressant Prescriptions In 5 Years Following Recruitment To GS:SFHS



History of affective disorder is defined as previous history of single or recurrent episode MDD or bipolar disorder on the SCID interview. 'High' neuroticism is defined as a neuroticism score occurring in the upper tertile of Eysenck Personality Questionnaire-Short Form neuroticism scores, and 'low' is defined as occurring in the lower tertile. Abbreviations : "F" = Female. "M"=Male.

Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

Hafferty JD, Wigmore EM, Howard DM, Adams MJ, Clarke T-K, Campbell AI, MacIntyre DJ, Nicodemus KK, Lawrie SM, Porteous DJ, McIntosh AM

Supplementary Material

Generation Scotland : Scottish Family Health Study : Cohort Information

For full cohort profile, please refer to Smith et al. "Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness" *International Journal of Epidemiology* 2013: 42:689-700

Generation Scotland:Scottish Family Health Study(GS:SFHS) is a population- and family-based epidemiology study, with socio-demographic, clinical and genetic phenotyping. Potential participants were identified at random from lists provided by collaborating general medical practices across Scotland. In the UK, 96% of the population is registered with a GP and thus this recruitment method was favoured for recruiting a population-based sample. Invitations to participate were blinded to health status.

Potential participants were invited to the study and also to identify at least one first-degree relative (aged 18+) who would also participate. Nominated first-degree relatives could be from any location. The first recruitment phase (2006-10) involved potential participants aged 33-65 years and at least one nominated first-degree relative (aged 18+) from GP practices in Glasgow and Tayside areas of Scotland. In the second phase (2010-2011) the study was extended to include Aryshire, Arran and Northeastern Scotland, and the age of potential participants was broadened to 18-65 years (invited relatives remaining aged 18+).

In total, 126000 potential participants were invited and 12.3% volunteered and met study criteria. Not all participants were recruited, for logistical reasons or due to failure to recruit additional family members, leaving a total recruitment of 6665 (5.3% overall response rate). An additional 1288 individuals volunteered directly (age >18 years and at least one additional relative who

agreed to participate). A further 16007 family members associated with these invited participants and volunteers were also recruited, giving a total of 23960.

A total of 21474 individuals attended Generation Scotland research clinics in Glasgow, Dundee, Perth, Aberdeen or Kilmarnock. Prior to their appointment they completed a pre-clinic questionnaire. At the clinic appointment, a variety of measures were taken by trained clinic staff. This included screening for emotional and psychiatric problems using the structured clinical interview for DSM-IV disorders (SCID) (99.6% of cohort completed), mood sections of the SCID in the case of positive screening (18.8% completed), Eysenck personality questionnaire (99.4% completed), digit symbol test(98.8% completed), verbal fluency (98.7% completed), Mill Hill vocabulary scale (98.2% completed) and Wechsler memory test (99.3% completed). In total, 20,198 individuals completed all components of the phenotyping, including a two-hour face-to-face interview and sociodemographic and clinical questionnaires.

Written informed consent was also obtained for 98% of GS:SFHS for data linkage to routinely collected health records and only those individuals who provided consent were used in this study.

Subset of Generation Scotland Used In This Study

Recruitment to Generation Scotland began in February 2006 and ended in March 2011. However, the Prescribing Information System (PIS) data is only available from April 2009 onwards (data prior to that is not considered by Information Services Division Scotland to be complete and comprehensive enough for research purposes). We therefore restricted our analysis to those individuals in GS:SFHS recruited from September 2009 to March 2011 (N=11052, 6518 females and 4534 males). This ensured that all individuals had at least five years' worth of prescribing data following their enrolment in GS:SFHS, and also at least six months of prescribing data prior to their enrolment, with which to ascertain their pre-enrolment medication usage. Of these, 96.5% had medication records available in the prescribing data (the remainder were presumably not using prescribed medication), which compared with 95.6% for the whole GS:SFHS cohort (see **Figure 1**).

Table S1 : Demographics of Individuals Used In Current Study Compared to Entire Generation Scotland Cohort And To The Scottish Adult Population

	Individuals in the current study N(%)	GS:SFHS N(%)	Significance (p) of difference in proportion between study sample and GS:SFHS Effect size (Cohen d/h)	Scottish 18+ population N (%)
	(N=11052)	(N=20759) †		(N=4.3M)
Female	6518 (59.0%)	12246 (59.0%)	p=0.98	2.24M (52.1%)
Age 18-24 (Age in 2012)	801 (7.3%)	1194 (5.8%)	p=1.6x10^{-07} *h* = 0.06	501152 (11.7%)
Age 25-34	1460 (13.2%)	2810 (13.5%)	p=0.42	691908 (16.1%)
Age 35-44	1837 (16.6%)	3416 (16.5%)	p=0.70	688418 (16%)
Age 45-54	2246 (20.3%)	4422 (21.3%)	p=0.04 *h*=0.02	800265 (18.6%)
Age 55-64	3022 (27.3%)	5447 (26.2%)	p=0.03 *h*=0.03	663701 (15.5%)
Age 65-74	1295 (11.7%)	2649 (12.8%)	p=0.007 *h*=0.03	522236 (12.2%)
Age 75+	391 (3.5%)	821 (4.0%)	*p*=0.06	424626 (9.9%)
Affective Disorder History				
No MDD on screening	9624 (87.1%)	17998 (86.7%)	p=0.34	
SCID Single episode MDD	729 (6.6%)	1360 (6.6%)	p=0.88	
SCID Recurrent MDD	660 (6.0%)	1327 (6.4%)	p=0.14	
SCID Bipolar disorder	39 (0.4%)	74 (0.4%)	p=0.96	
Recruitment Location				
Aberdeen	1133 (10.3%)	1133 (5.5%)	p=<2.2x10^{-16} *h*=0.18	
Alyth	0 (0%)	14 (0.06%)		
Ayrshire	70 (0.6%)	70 (0.3%)	p=0.0002 *h*=0.04	
Glasgow (BHF)	2235 (20.2%)	4821 (23.2%)	p=8.5x10^{-10} *h*=0.07	
Dundee	3888 (35.2%)	6926 (33.4%)	p=0.001 *h*=0.04	
Perth	1106 10.1%)	3429 (16.5%)	p=<2.2x10^{-16} *h*=0.19	
Glasgow (Tennents)	2620 (23.7%)	4214 (20.3%)	p=1.9x10^{-12} *h*=0.08	
Dundee/Tayside	0 (0%)	152 (0.7%)		
Deprivation Index				
SIMD 1 - Most Deprived	1325(12.6%)*	2597 (13.3%)*	p=0.11	
SIMD 2nd quintile	1576 (15.0%)*	2761 (14.1%)*	p=0.04 *h*=0.03	
SIMD 3rd quintile	1693 (16.1%)*	3137 (16.0%)*	p=0.84	
SIMD 4th quintile	2604 (24.8%)*	5009 (25.6%)*	p=0.12	
SIMD 5 - Least Deprived	3293 (31.4%)*	6043 (30.9%)*	p=0.40	
Smoking History				
Never Smoked	5636 (52.8%)*	10604(52.8%)*	p=0.95	
Currently Smoke	1834 (17.2%)*	3565 (17.7%)*	p=0.22	
Ex- Smoker	3198 (30.0%)*	5918 (29.5%)*	p=0.34	
Other Variables				
GHQ (Likert)	15.8 (8.8)*	16.0 (8.7)*	p=0.09	
EPQ Neuroticism	3.7 (3.1)*	3.8 (3.1)*	p=0.0003 *d*=0.04	
Mill-Hill Vocabulary Test	30 (4.7) *	30 (4.8)*	p=0.55	

Wechsler Digit Symbol Substitution Task	72.0 (17.2)*	72.1 (17.3)*	p=0.02 *d*=0.03
Verbal Fluency Test	39.8 (11.7)*	39.7 (11.7)*	p=0.27
Body mass index	26.8 (5.2)*	26.7 (5.3) *	p=0.05

Abbreviations: MDD = Major Depressive Disorder. SCID = Structured Clinical Interview for DSM-IV Disorders. SIMD = Scottish Index of Multiple Deprivation. GHQ = General Health Questionnaire. EPQ = Eysenck Personality Questionnaire.

* Variable contained missing data which was imputed (see below)

An additional table with the other covariates used in the study is provided in Supplementary Materials

† Total GS:SFHS cohort 21474 but number who had consented to data linkage and where data linkage was possible was 20759

Imputation method for missing drug dosage data

There were 8048 records in the antidepressant data with missing prescription instructions (out of 134290 records in total, or 6.0% missing data). A five-step imputation strategy was employed for these missing records.

(1) If a missing data prescribing record could be matched to one with the same user (unique ID), the same antidepressant medication, at the same dose, and the same dispensed quantity, then these prescribing instructions were used to impute for that individual. This reduced the missing data from 8048 records to 814 records.

(2) If a prescribing record has the same user (unique ID), the same antidepressant, and the same strength as another prescription for the same users, then these prescribing instructions were used. This step did not reduce the count (did not improve upon the step above).

(3) If a missing data prescribing record could be matched to one with the same user (unique ID) and the same antidepressant, then these prescribing instructions were used to impute. This reduced missing data from 814 to 553 records.

(4) For the remaining 553 records (0.4% of the total dataset) the median dosage instructions for that specific antidepressant in the cohort were used.

Missing Data and Imputation of Generation Scotland phenotypic variables

As shown in Table 2, there was some missing data in the phenotypic variables used in the analyses of this study. The amount of missing data was <5% for every variable apart from SIMD quintile (5.1%) with the proportion of individuals with missing data in at least one field being 12.6%.

Imputation of these variables was performed using Multiple Imputation by Chained Equations in the R package "mice". An assumption of multiple imputation is that the missing data is not Not Missing At Random(NMAR) and can credibly be defined as Missing At Random(MAR) or Missing Completely At Random(MCAR).

As shown in Table 2, when stratified against the affective disorder status of GS:SFHS participants, there are no significant differences in the total missingness between those with a history of affective disorder and those without. We imputed the missing data on the basis of the hypothesis that the missingness was MAR type.

Complete case analysis (N=6855) for the time-to-event Cox regression is shown below in Table S3.

Table S2 : Missing Data in GS Variables

Variable name	**Missing records** (N=11052)	**% missing data (which was imputed)**	**% missingness in individuals with no history of affective disorder**	**% missingness in individuals with history of affective disorder (p= p value of two sample test for equality of proportions)**
Sex	0	-		
Age	0	-		
SCID affective disorder status	0	-		
SIMD Quintile	561	5.1%	5.0%	5.7%(p=0.3)
BMI	91	0.8%	0.8%	0.8% (p=0.9)
SPQ	261	2.4%	2.3%	2.7%(p=0.05)
Neuroticism	254	2.3%	2.4%	1.9%(=0.3)
Smoking	384	3.5%	3.5%	3.4%(p=0.9)
Alcohol	535	4.8%	4.7%	5.5% (p=0.2)
Physical Health	254	2.3%	2.3%	2.6%(p=0.05)
Appointment location	0	-		
Cognitive function (g)	203	1.8%	1.9%	0.9%(p=0.007)

Individuals with missing data in at least one field	1397	12.6%	12.7%	12.5%(p=0.9)

Table S3 : Complete Case Analysis Cox Regression of Time to Antidepressant Use in Generation Scotland Cohort (Excluding those Already Using Antidepressants At Time Of Recruitment), n=6855

	Multivariable		
	Hazard Ratio	p(FDR)	Sig
Intercept			
SexM	Ref	Ref	
SexF	1.83(1.59-2.10)	<0.001	***
Age_18-24	Ref	Ref	Ref
Age_25-34	0.77(0.59-1.01)	0.126	
Age_35-44	1.00(0.78-1.28)	1.00	
Age_45-54	1.02(0.80-1.31)	0.919	
Age_55-64	0.77(0.60-0.99)	0.093	.
Age_65-74	0.48(0.35-0.66)	<0.0001	***
Age_75+	0.77(0.51-1.15)	0.30	
No MDD on Screening	Ref	Ref	Ref
MDD - Single Episode	2.13(1.76-2.58)	<0.001	***
MDD - Recurrent	1.99(1.57-2.51)	<0.001	***
MDD - Bipolar	1.49(0.62-3.60)	0.491	
Never Smoked	Ref	Ref	Ref
Currently Smoke	1.54(1.31-1.82)	<0.0001	***
Ex Smoker	1.38(1.19-1.59)	<0.0001	***
SIMD – Most deprived quintile	1.30(1.06-1.60)	0.026	*
SIMD – 2nd quintile	1.15(0.95-1.40)	0.245	
SIMD – 3rd quintile	1.10(0.90-1.34)	0.458	
SIMD – 4th quintile	0.99(0.83-1.19)	0.951	
SIMD – Least deprived quintile	Ref	Ref	Ref
Neuroticism	1.12(1.10-1.15)	<0.0001	***
SPQ	1.03(1.01-1.05)	0.002	*
g	0.90(0.85-0.94)	<0.0001	***
No physical health complaints	Ref	Ref	Ref
1-2 physical health complaints	1.25(1.09-1.44)	0.004	*
3+ physical health complaints	2.05(1.45-2.89)	<0.0001	***

Table S4: Crude and Age-Sex Reweighted Prevalence of Antidepressants in Generation Scotland 2010-2016

Antidepressant Prevalence	2010	2011	2012	2013	2014	2015	2016
All antidepressants							
Crude	13.9(13.3-14.6)	14.8(14.2-15.5)	15.7(15.0-16.4)	16.3(15.6-17.0)	17.1(16.4-17.9)	17.8(17.1-18.5)	18.3(17.6-19.1)
Age-Sex Reweighted	12.7(12.0-13.5)	13.7(13.0-14.5)	14.4(13.6-15.2)	15.0(14.2-15.8)	16.0(15.2-16.9)	16.5(15.7-17.4)	17.3(16.5-18.3)
Exc. low dose amitriptyline							
Crude	11.0(10.5-11.6)	11.7(11.1-12.3(	12.5(11.8-13.1)	12.7(12.1-13.4)	13.4(12.8-14.1)	14.1(13.5-14.8)	14.7(14.0-15.4)
Age-Sex Reweighted	9.9(9.3-10.6)	10.6(9.9-11.2)	11.3(10.7-12.0)	11.7(11.0-12.5)	12.4(11.7-13.2)	12.9(12.3-13.7)	13.9(13.1-14.7)

Table S5 : Medications that previously antidepressant naïve (n=1250) antidepressant users in GS:SFHS were first commenced on during the entire period studied 2009-2016

	Mechanism of action*	Antidepressant class	Number of individuals	%
Amitriptyline	Reuptake inhibitor (SERT and NET), receptor antagonist (5-HT2)	TCA	37	3.0
Citalopram	Reuptake inhibitor (SERT)	SSRI	499	39.9
Duloxetine	Reuptake inhibitor (SERT and NET)	SNRI	31	2.5
Fluoxetine	Reuptake inhibitor (SERT)	SSRI	270	21.6
Mirtazapine	Receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)	Other	87	7.0
Nortriptyline	Reuptake inhibitor (NET)	TCA	49	3.9
Paroxetine	Reuptake inhibitor (SERT)	SSRI	5	0.4
Sertraline	Reuptake inhibitor (SERT)	SSRI	177	14.2
Tranylcypromine	Enzyme inhibitor (MAO-A and -B), releaser (DA, NE)	MAOI	0	0
Venlafaxine	Reuptake inhibitor (SERT and NET)	SNRI	19	1.5
Lofepramine	Reuptake inhibitor (NET and SERT)	TCA	9	0.7
Trazodone hydrochloride	Reuptake inhibitor (SERT), receptor agonist (5-HT1A), receptor antagonist (5-HT2)	Other	22	1.8
Agomelatine	Receptor agonist (Mel1,Mel2), receptor antagonist (5-HT2B, 5-HT2C)	Other	0	0
Clomipramine hydrochloride	Reuptake inhibitor (SERT, NET (metabolite))	TCA	4	0.3
Dosulepin hydrochloride	Reuptake inhibitor (SERT and NET)	TCA	11	0.9
Doxepin	Reuptake inhibitor (NET and SERT), receptor antagonist (5-HT2)	TCA	4	0.3
Escitalopram	Reuptake inhibitor (SERT)	SSRI	12	1.0
Flupentixol	Receptor antagonist (D2, 5-HT2)	Other	1	0.1
Fluvoxamine maleate	Reuptake inhibitor (SERT)	SSRI	0	0
Imipramine hydrochloride	Reuptake inhibitor (SERT and NET)	TCA	13	1.0
Mianserin hydrochloride	Receptor antagonist (alpha-2), reuptake inhibitor (NET)	TCA	0	0
Moclobemide	Reversible enzyme inhibitor (MAO-A)	MAOI	0	0
Phenelzine	Enzyme inhibitor (MAO-A and -B)	MAOI	0	0
Reboxetine	Reuptake inhibitor (NET)	Other	0	0
Trimipramine	Receptor antagonist (5-HT2 and D2)	TCA	0	0
Tryptophan	Essential amino acid, precursor to 5-HT and Me	Other	0	0

* = source : Neuroscience-Based nomenclature http://www.nbn2.org/ [Accessed 26-10-18]

Abbreviations : SERT = serotonin transporter. 5-HT = 5-hydroxytryptamine/serotonin. NE=noradrenaline. NET = noradrenaline transporter. DA/D=dopamine. Me=Melatonin. MAO=monoamine oxidase. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant. MAOI=monoamine reuptake inhibitor. SNRI=selective serotonin and noradrenaline reuptake inhibitor.

Table S6

Part A : Sensitivity Analysis of Medication Possession Ratio (MPR) per Antidepressant Episodes During 5 Year Period 2012-2016 With Cut-Off Point Between Episodes Varying Between 60 and 360 Days

Cut-Off Point Between Episodes	Individuals	Prescribing Episodes (2012-2016)	Mean Duration (days)	Median Duration (days)	Min MPR (%)	MPR 1Q (%)	MPR Median (%)	MPR Mean (%)	MPR 3Q (%)	Max MPR (%)
60	2385	4370	526	231	10.9	90.3	100	99.3	103.4	411.8
90	2385	3595	679	307	10.6	86.5	99.1	96.3	100.5	411.8
120	2385	3280	777	372	11.7	84.9	98.1	95	101.1	411.8
150	2385	3117	839	411	11.7	83.5	97.4	94	100.7	411.8
180	2385	3008	891	452	11.7	82.2	96.6	93.2	100.7	411.8
270	2385	2813	997	557	11.7	79.9	95.7	91.4	100.4	283.7
360	2385	2707	1064	654	11.7	77.8	94.7	90	100	283.7

Part B : Sensitivity Analysis of Proportion of Days Covered (PDC) per Antidepressant Episode During 5 Year Period 2012-2016 With Cut-Off Point Between Episodes Varying Between 60 and 360 Days

Cut-Off Point Between Episodes	Individuals	Prescribing Episodes (2012-16)	Mean Duration (days)	Median Duration (days)	Min PDC (%)	PDC 1Q (%)	PDC Median (%)	PDC Mean (%)	PDC 3Q (%)	PDC Max (%)	% Adherent PDC
60	2385	4370	526	231	10.7	80.3	88.9	87.4	100	100	76
90	2385	3595	679	307	10.6	77	86.3	84.9	99.3	100	69
120	2385	3280	777	372	5.8	74.4	85.1	82.7	96.9	100	64.6
150	2385	3117	839	411	3.1	72.3	84.5	81.4	96.3	100	61.7
180	2385	3008	891	452	3.1	70.4	83.6	80.1	95.5	100	59.3
270	2385	2813	997	557	3.1	65.9	82.2	77.6	94.5	100	55.5
360	2385	2707	1064	654	3.1	62.3	81.1	75.9	93.3	100	52.8

Part C : Comparison of Proportion of Days Covered for Antidepressant Episodes involving Different Medication Classes (SSRI, TCA, SNRI, MAOI, Other) and Different Previous Histories of Affective Disorder on GS:SFHS Recruitment

Group	Cut-Off Point Between Episodes	Individuals	Mean Duration (days)	Median Duration (days)	Min PDC (%)	PDC 1Q (%)	PDC Median (%)	PDC Mean (%)	PDC 3Q (%)	PDC Max (%)	% Adherent PDC (>= 80% PDC)
SSRI	90	1924	672	326	1	76.7	85.8	84.5	96.8	100	68.1
TCA*	90	422	937	488	1	76.8	85.5	84.3	100	100	67.8
SNRI	90	310	1120	931	25.7	76.3	84.2	83.2	90.8	100	67.3
MAOI	90	14	1251	1110	52.4	71	77.1	77.3	82.7	100	31.3
Other	90	414	908	522	28.5	76.8	85	83.9	94.1	100	65.9
MDD history:											
Bipolar disorder	90	29	813	568	62.9	72.9	81.8	83.5	94.2	100	56.3
Recurrent MDD	90	421	968	576	23.2	76.1	84.7	83.3	92.3	100	66.1

No MDD history	90	1611	578.9	265.5	10.6	77.7	87.4	85.5	100	100	70.3

*** = TCA - excluding low dose amitriptyline**

Abbreviations : MPR = Medication Possession Ratio. 1Q=1st quartile. 3Q=third quartile. MDD = major depressive disorder. MPR=medication possession ratio. PDC=proportion of days covered.