

# BMJ Open

## Prescribing of antipsychotics in United Kingdom primary care. Cohort study in United Kingdom primary care

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006135
Article Type:	Research
Date Submitted by the Author:	16-Jul-2014
Complete List of Authors:	Marston, Louise; University College London, Primary Care and Population Health Nazareth, Irwin; UCL, Primary Care and Population Health Petersen, Irene; University College London Medical School, Department of Primary Care and Population health Walters, Kate; University College London, Primary Care and Population Health Osborn, David; UCL, Division of Psychiatry
<b>Primary Subject Heading</b>:	General practice / Family practice
Secondary Subject Heading:	Epidemiology, Mental health
Keywords:	MENTAL HEALTH, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3 **Prescribing of antipsychotics in United Kingdom primary care. Cohort study in United Kingdom**  
4  
5 **primary care**  
6  
7  
8

9 Louise Marston<sup>1\*</sup>

10  
11 Irwin Nazareth<sup>1</sup>

12  
13 Irene Petersen<sup>1</sup>

14  
15 Kate Walters<sup>1</sup>

16  
17 David PJ Osborn<sup>2,3</sup>

18  
19  
20 1. Research Department of Primary Care and Population Health, UCL, London UK.

21  
22 2. UCL Division of Psychiatry, UCL, London UK.

23  
24 3. Camden and Islington NHS Foundation Trust, London UK.  
25  
26  
27

28  
29 **\*Corresponding author-**

30  
31 Dr Louise Marston

32  
33 Research Department of Primary Care and Population Health

34  
35 UCL

36  
37 London

38  
39 NW3 2PF

40  
41  
42  
43  
44 Email: [l.marston@ucl.ac.uk](mailto:l.marston@ucl.ac.uk)

45  
46 Telephone: +44 (0) 20 7794 0500 (36768)  
47  
48

49  
50 Keywords: antipsychotic, primary care, schizophrenia, dementia, depression  
51  
52

53  
54  
55 Word Count:  
56  
57  
58  
59  
60

**Abstract****Objective**

To examine the recorded indication for antipsychotic prescriptions in primary care.

**Design**

Cohort study

**Setting**

Primary Care.

**Participants**

Individuals prescribed antipsychotics between 2007 and 2011.

**Measures**

The proportion of individuals prescribed antipsychotics with a diagnostic record for 1) psychosis and bipolar disorder 2) Other diagnoses including depression, anxiety and dementia and 3) None of these diagnoses.

**Results**

We identified 47,724 individuals prescribed antipsychotic agents. 13,941 received first generation agents and 27,966 received second generation agents. Rates of prescribing were higher in females (incidence rate ratio 1.092 (95% CI 1.088 to 1.095), older people (80+ versus 40–49 IRR 2.234 (2.222, 2.246) and in those from the most deprived areas (most deprived versus least deprived IRR 3.487 (3.567, 3.606). Of those receiving first generation antipsychotics less than 50% had a recorded diagnosis of psychosis/ bipolar disorder. For second generation agents, the numbers ranged from 4824 (36%) for quetiapine to 7094 (62%) for olanzapine. In patients without psychosis/ bipolar records, common diagnoses included anxiety, depression, dementia, sleep and personality disorders. For example in risperidone users, 14% had an anxiety code, 22% depression, 12% dementia, 11% sleep disorder and 4% personality disorder. Median daily doses and duration of treatment were greater in those with schizophrenia (eg risperidone median daily dose 4mg; IQR 2, 6: median duration 1.2 years), compared to those with non-psychotic/ bipolar disorders such as depression or

1  
2  
3 anxiety (eg risperidone 1mg; IQR 1, 2: 0.6 years). A relatively large proportion (between 6 and 17%)  
4  
5 of people receiving individual antipsychotics had none of the records above.  
6

## 7 **Conclusions**

8  
9 In UK primary care, a large proportion of people prescribed antipsychotics have no record of a  
10  
11 psychotic or bipolar disorder. They are often older people, with conditions including dementia, non-  
12  
13 psychotic depression, anxiety and sleep disorders.  
14

## 15 **Article summary**

### 16 **Strengths and limitations of this study**

17  
18 We determined the recorded indication for antipsychotic prescriptions in a large, representative  
19  
20 sample of people in UK primary care. The data source contained accurate prescribing information  
21  
22 although prescriptions issued in secondary care will not have been captured. Diagnoses of severe  
23  
24 mental illnesses have been validated in primary care. The nature of the data did not allow us to  
25  
26 determine the clinicians' rationale for prescribing antipsychotics to people without psychoses or  
27  
28 bipolar disorder diagnoses.  
29  
30  
31  
32  
33  
34  
35  
36  
37

- 38 • Less than half of people prescribed the most common first generation antipsychotics in UK  
39  
40 primary care have a recorded diagnosis of a psychosis or bipolar disorder.
- 41  
42 • Findings were similar for second generation agents, although 62% of people receiving  
43  
44 olanzapine did have a record of psychosis or bipolar disorder
- 45  
46 • These agents are more commonly prescribed to older people, despite the propensity of this  
47  
48 age group to develop side effects.
- 49  
50 • Antipsychotics are still commonly prescribed to people with a diagnosis of dementia,  
51  
52 contrary to clinical guidance, and this need further attention in UK primary care.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- Other commonly recorded diagnoses included depression, anxiety disorders, personality disorders and ADHD, while up to 17% of people receiving antipsychotics had none of the diagnoses we explored.

For peer review only

**BACKGROUND**

Antipsychotic medications are the first line pharmacological intervention for severe mental illnesses (SMI) such as schizophrenia and other psychoses. However, they are also increasingly prescribed for treatment of bipolar affective disorder. They are not routinely recommended for other mental health conditions such as depression, sleep disorders or Obsessive Compulsive Disorder (OCD). There is concern about rates of antipsychotic prescribing in dementia since they may be associated with increased rates of strokes and all-cause mortality.[1, 2] Prescription of antipsychotics requires caution given their association with a range of serious adverse effects including extra-pyramidal side effects with the first generation agents, weight gain and lipid/glucose dysregulation with second generation agents. International guidelines stress the importance of regular monitoring of BMI, glucose and lipids in people receiving repeat prescriptions of these agents, given their propensity to affect these parameters.

National guidelines do recommend antipsychotics for the relatively rare condition of psychotic depression and as a possible intervention for treatment resistant cases of severe depression[3] and OCD[4] and in clinical practice these agents may be prescribed “off-label” for patients who do not have a record of SMI in their clinical notes. They are sometimes used to augment antidepressants in complex or treatment resistant cases of OCD, anxiety and personality disorders. Although antipsychotics may be used in sleep disorders, treatment guidelines do not recommend using such agents on account of their side effect profiles.[5] Guidelines for borderline personality disorder recommend that short term treatment with antipsychotics (up to a week) may be beneficial in crisis or when comorbid psychotic symptoms occur.[6]

Our aim was to examine the recorded indication for antipsychotic prescriptions in United Kingdom primary care. Further we sought to describe the prescribing pattern by diagnostic group.

## Objectives

1. To examine the recorded indication for antipsychotic prescribing in UK primary care.
2. To describe prescribing patterns (duration of treatment and average dose) in three broad groups of people who may receive antipsychotics in primary care:
  - i) Those with diagnoses of an SMI (psychosis or bipolar disorder)
  - ii) Those without a record of SMI but with a mental health diagnosis such as depression, personality disorder or dementia
  - iii) Individuals with no record of these conditions in their general practice notes.

## METHOD

### Study design

Cohort study

### Setting

Primary care in the UK

### Data source

We used data from The Health Improvement Network (THIN),[7] a UK primary care database which is based on data from routine clinical care and administration. THIN data are from practices using Vision software and are available anonymously for research.[8] The database includes demographics and Townsend deprivation quintile. The latter is a validated measure of social deprivation, attributed to the patient's geographical postcode, covering a small area of approximately 150 households.[9] Data such as diagnoses and symptoms are entered as Read codes, a hierarchical classification system.[10] The database also includes records of all prescriptions issued and these are linked to the British National Formulary (BNF).[11] Prescribing is well recorded in THIN because all prescriptions are generated via the computerised system. This

1  
2  
3 information produces a longitudinal record for each individual in the database. THIN is  
4  
5 representative of the general UK population in terms of their demographic characteristics[12] and  
6  
7 practices are geographically spread across the UK. At the time of this study the full database  
8  
9 included almost 10 million patients. For quality purposes data were only extracted after the date at  
10  
11 which there was evidence that general practices were using their computer system fully (acceptable  
12  
13 computer use (ACU) dates[13]) and mortality were adequately recorded (Acceptable Mortality Rate  
14  
15 (AMR)[14]).  
16  
17  
18  
19

### 20 **Participants**

21  
22 We initially included all people who received at least one prescription for any antipsychotic  
23  
24 medication after 01/01/2007 or after the date at which practice met quality standards. Follow-up  
25  
26 ended at the earliest of date of 1) death, 2) transferring out of the practice, 3) last data collection  
27  
28 from the practice, 4) reaching the age of 100 years or 5) 31/12/2011. The start of follow up for each  
29  
30 individual was the date of the first antipsychotic prescription during these periods. We excluded  
31  
32 individuals with less than 6 months of follow-up data.  
33  
34  
35  
36  
37

### 38 **Antipsychotic data**

39  
40 First we determined overall rates of prescribing of all first generation and second generation  
41  
42 antipsychotics in UK primary care. Subsequently we focussed on the three most commonly  
43  
44 prescribed first generation (Haloperidol, Chlorpromazine and Trifluoperazine) and second generation  
45  
46 agents (Olanzapine, Quetiapine and Risperidone). We determined the average daily dose prescribed  
47  
48 for each antipsychotic during the follow-up period, as well as the length of time for which  
49  
50 antipsychotics were prescribed. We excluded total daily doses which were implausibly high for  
51  
52 community prescribing of antipsychotics, since these were likely to represent erroneous entries. We  
53  
54 defined this upper threshold at twice the maximum recommended daily dose in the BNF,[11] namely  
55  
56 over 60mg for haloperidol, over 2000mg for chlorpromazine, over 120mg for trifluoperazine, over  
57  
58  
59  
60



1  
2  
3 40mg for olanzapine, over 1500 for quetiapine and over 32 mg for risperidone. Relatively few (221)  
4  
5 prescriptions were excluded for this reason.  
6  
7

### 8 9 **Mental health conditions**

10  
11 We defined severe mental illness as schizophrenia-like disorders, bipolar affective disorders and  
12  
13 other non-organic psychosis such as delusional disorder, “psychoses not otherwise specified” and  
14  
15 severe depression with psychoses (Appendix I). We identified an additional category for people who  
16  
17 were included on the practice’s SMI register without having a Read code for the SMI diagnoses  
18  
19 above (a GP SMI register is required as part of the GP contract in the UK since 2004).  
20  
21

22  
23  
24 Next we identified common mental health conditions for which antipsychotics might be prescribed  
25  
26 off-label, using diagnostic Read code lists compiled by two clinical academics - a GP and a  
27  
28 psychiatrist.[15] These non-SMI conditions comprised depression, anxiety disorders, sleep disorders  
29  
30 (insomnia, non-specific sleep disorders, apnoea, hypersomnia), dementia, attention deficit and  
31  
32 hyperactivity disorder, personality disorders, post-traumatic stress disorder and obsessive  
33  
34 compulsive disorder.  
35  
36

37  
38  
39 We created a diagnostic hierarchy for people with more than one mental health diagnosis in their  
40  
41 clinical notes. Hence, if a patient ever had a record of SMI we considered this as the indication for  
42  
43 antipsychotics. However, if there were no record of SMI, then all non-SMI diagnoses were extracted  
44  
45 and included in this study. In other words the non-SMI diagnoses were not mutually exclusive so a  
46  
47 person could count as both a case of anxiety and a case of obsessive compulsive disorder.  
48  
49

### 50 51 52 **Ethical approval**

53  
54  
55 THIN has overall ethical approval from the South East Multicentre Research Ethics Committee  
56  
57 (reference number: 07/H1102/103) and further study specific approval for this study was gained as  
58  
59

1  
2  
3 part of an additional MREC approval from the London Research Ethics Committee. Reference  
4  
5 number: 09/H0718/11.  
6  
7

### 8 9 **Statistical analysis**

10  
11 We calculated rates of prescribing any antipsychotics, per 100,000 person years at risk. We then  
12  
13 calculated rates of any first or second generation antipsychotics then we determined rates of  
14  
15 prescribing individual agents for the three most commonly prescribed first and second generation  
16  
17 antipsychotic agents. Multivariable Poisson regression was used to determine associations between  
18  
19 sex, age group, Townsend deprivation quintile, calendar year and 1) overall antipsychotic  
20  
21 prescribing, 2) All first and second generation antipsychotic agents and 3) The six most commonly  
22  
23 prescribed individual antipsychotics. For these analyses, we defined the population at risk as the  
24  
25 total population registered with the general practices in the period 2007-2011.  
26  
27

28  
29  
30  
31 We calculated frequencies (%) for each recorded indication (diagnosis) for each of the six most  
32  
33 commonly prescribed antipsychotics. We also calculated the median (interquartile range) daily dose  
34  
35 in milligrams and length of time prescribed a given antipsychotic within three groups: The SMI  
36  
37 (psychosis/bipolar) subgroup, the group with non-SMI diagnoses and the group with no record of  
38  
39 any of these diagnoses.  
40  
41

42  
43  
44 Analyses were carried out using Stata version 13.[16]  
45  
46  
47

### 48 **RESULTS**

49  
50 We identified 47,724 eligible individuals who were prescribed antipsychotic medications. Of these  
51  
52 13,941 were solely prescribed first generation antipsychotics, 27,966 solely second generation  
53  
54 antipsychotics and 5817 received both classes of agent during their follow-up period (Figure 1). The  
55  
56 median length of follow-up for people receiving any antipsychotic was 2.4 years (IQR 1.3, 4.1). The  
57  
58  
59  
60

1  
2  
3 length of follow-up was slightly longer for those receiving both first and second generation  
4  
5 antipsychotic (3.0 years; IQR 1.7, 4.7).  
6  
7

8  
9 [Figure 1 here]  
10  
11

### 12 13 14 **Rates of antipsychotic prescribing by socio-demographic characteristics and over time**

15  
16 Overall 1% of individuals received an antipsychotic at some time over the study period. For women  
17  
18 the rate of prescribing any antipsychotic was 699 per 100,000 PYAR (95% CI 693, 705) compared to  
19  
20 612 per 100,000 PYAR (95% CI 607, 617) for men. Individuals aged above 80 years were more likely  
21  
22 to receive antipsychotics (Incidence rate ratio (IRR) 2.234; 95% CI 2.222, 2.246 compared with those  
23  
24 aged 40-49 years). In contrast, those under the age of 18 and those aged 18-29 were much less  
25  
26 likely to receive antipsychotics (Table 1). Those living in the most deprived areas were more than  
27  
28 three times as likely to receive antipsychotics compared to those in the least deprived areas (IRR  
29  
30 3.587 (95% CI 3.587, 3.606) (Table 1). These patterns were also observed when the subgroups  
31  
32 prescribed first generation and second generation of antipsychotic were examined separately (Table  
33  
34  
35 1).  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1: Rates of antipsychotic prescribing by class of antipsychotic, age gender and social deprivation

	Any antipsychotic				Any first generation antipsychotic				Any second generation antipsychotic				First and second generation antipsychotics			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	612	(607, 617)	1.000		197	(194, 200)	1.000		458	(454, 462)	1.000		43	(41, 44)	1.000	
Female	699	(693, 705)	1.092	(1.088, 1.095)	256	(253, 259)	1.204	(1.196, 1.211)	489	(484, 493)	1.050	(1.046, 1.054)	46	(44, 47)	1.010	(1.096, 1.103)
Under 18	63	(61, 66)	0.044	(0.044, 0.045)	5	(4, 5)	0.009	(0.008, 0.009)	59	(57, 62)	0.058	(0.057, 0.059)	0.6	(0.4, 0.9)	0.026	(0.026, 0.027)
18-29	459	(451, 467)	0.351	(0.349, 0.353)	111	(107, 115)	0.223	(0.220, 0.227)	376	(369, 383)	0.401	(0.398, 0.404)	28	(26, 30)	0.348	(0.346, 0.351)
30-39	817	(806, 828)	0.804	(0.799, 0.808)	238	(232, 244)	0.643	(0.636, 0.650)	638	(628, 648)	0.867	(0.861, 0.872)	58	(56, 62)	0.803	(0.799, 0.807)
40-49	852	(842, 863)	1.000		289	(283, 295)	1.000		628	(619, 637)	1.000		64	(62, 67)	1.000	
50-59	712	(701, 723)	0.872	(0.867, 0.877)	283	(276, 290)	1.045	(1.035, 1.056)	483	(474, 492)	0.804	(0.799, 0.809)	54	(51, 57)	0.872	(0.867, 0.877)
60-69	642	(631, 653)	0.824	(0.819, 0.829)	281	(274, 289)	1.039	(1.029, 1.050)	406	(398, 415)	0.740	(0.735, 0.745)	46	(43, 49)	0.824	(0.819, 0.829)
70-79	842	(827, 857)	0.973	(0.967, 0.980)	350	(341, 360)	1.192	(1.179, 1.205)	546	(534, 559)	0.888	(0.881, 0.894)	54	(51, 58)	0.971	(0.965, 0.977)
80+	2,201	(2,170, 2,231)	2.234	(2.222, 2.246)	793	(775, 811)	2.358	(2.334, 2.382)	1,529	(1,504, 1,555)	2.185	(2.171, 2.199)	121	(114, 129)	2.221	(2.209, 2.234)
Townsend																
Least deprived	403	(398, 409)	1.000		138	(135, 142)	1.000		291	(286, 296)	1.000		26	(24, 27)	1.000	
2	499	(492, 506)	1.211	(1.203, 1.218)	180	(176, 184)	1.251	(1.237, 1.265)	351	(345, 357)	1.194	(1.186, 1.203)	33	(31, 35)	1.214	(1.207, 1.222)
3	645	(637, 653)	1.707	(1.697, 1.716)	223	(218, 228)	1.764	(1.745, 1.782)	465	(458, 472)	1.683	(1.672, 1.695)	43	(41, 45)	1.714	(1.705, 1.724)
4	844	(834, 854)	2.457	(2.443, 2.470)	295	(290, 301)	2.516	(2.491, 2.542)	608	(600, 616)	2.432	(2.416, 2.448)	59	(57, 62)	2.476	(2.463, 2.489)
Most deprived	1,158	(1,145, 1,172)	3.587	(3.567, 3.606)	386	(378, 394)	3.649	(3.612, 3.686)	853	(841, 865)	3.560	(3.537, 3.583)	80	(76, 84)	3.613	(3.593, 3.633)
Missing	806	(781, 830)	2.282	(2.259, 2.305)	270	(256, 284)	2.360	(2.315, 2.406)	586	(566, 608)	2.250	(2.223, 2.277)	51	(45, 57)	2.187	(2.165, 2.210)
Year																
2007	591	(584, 599)	1.000		236	(231, 241)	1.000		399	(393, 405)	1.000		44	(42, 46)	1.000	
2008	654	(646, 663)	1.075	(1.069, 1.080)	243	(238, 248)	0.990	(0.981, 1.000)	456	(449, 463)	1.118	(1.111, 1.125)	45	(43, 47)	1.075	(1.070, 1.081)
2009	679	(670, 687)	1.110	(1.104, 1.115)	237	(232, 242)	0.946	(0.938, 0.955)	487	(480, 494)	1.194	(1.186, 1.201)	45	(43, 47)	1.108	(1.102, 1.114)
2010	718	(710, 727)	1.151	(1.145, 1.157)	227	(222, 232)	0.880	(0.872, 0.888)	536	(529, 543)	1.290	(1.282, 1.298)	44	(42, 47)	1.147	(1.141, 1.153)
2011	637	(629, 646)	1.065	(1.059, 1.071)	189	(184, 193)	0.745	(0.737, 0.752)	492	(484, 499)	1.230	(1.222, 1.238)	43	(41, 45)	1.055	(1.050, 1.061)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

1  
2  
3 The three most commonly prescribed first generation antipsychotics were haloperidol,  
4 chlorpromazine and trifluoperazine; while olanzapine, risperidone and quetiapine were the most  
5 commonly issued second generation agents (Tables 2a and 2b). Rates of prescribing these individual  
6 agents followed similar patterns to the aggregate results in terms of their distributions by age and  
7 deprivation. Haloperidol and trifluoperazine were more commonly prescribed to women, as was  
8 quetiapine, while rates of risperidone and olanzapine prescribing were lower in women. Few under-  
9 18s received antipsychotics, but compared to other agents, risperidone was prescribed far more  
10 commonly to this young age group (Table 2b). Over the five years of the study (2007-2011), rates of  
11 prescribing for each first generation agent decreased while quetiapine prescription rates increased  
12 the most over time. For example, IRR for trifluoperazine in 2011 (reference category is 2007) 0.665  
13 (95% CI 0.645, 0.685) and IRR for quetiapine in 2011 (reference category is 2007) 1.480 (95% CI  
14 1.463, 1.497). There was a smaller increase in rates of prescribing for both risperidone and  
15 olanzapine (Table 2b).  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Table 2a: Rates of antipsychotic prescribing for the three most commonly prescribed first generation antipsychotics

Characteristic	Haloperidol				Chlorpromazine				Trifluoperazine			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	42	(41, 44)	1.000		51	(50, 53)	1.000		22	(21, 23)	1.000	
Female	55	(54, 57)	1.123	(1.107, 1.138)	52	(50, 53)	1.121	(1.107, 1.135)	36	(35, 38)	1.577	(1.547, 1.607)
Under 18	1	(1, 2)	0.017	(0.015, 0.019)	0.6	(0.4, 0.9)	0.004	(0.003, 0.004)	0.6	(0.4, 0.9)	0.006	(0.005, 0.008)
18-29	16	(15, 18)	0.204	(0.196, 0.213)	33	(31, 35)	0.231	(0.225, 0.237)	13	(12, 15)	0.195	(0.186, 0.205)
30-39	35	(33, 38)	0.659	(0.641, 0.678)	72	(68, 75)	0.640	(0.628, 0.653)	30	(28, 32)	0.634	(0.613, 0.655)
40-49	42	(40, 44)	1.000		85	(82, 89)	1.000		37	(35, 40)	1.000	
50-59	44	(42, 47)	1.085	(1.058, 1.112)	77	(74, 81)	0.992	(0.974, 1.010)	38	(35, 40)	1.046	(1.015, 1.078)
60-69	51	(48, 54)	1.175	(1.145, 1.205)	63	(60, 67)	0.822	(0.806, 0.839)	46	(43, 49)	1.378	(1.339, 1.419)
70-79	98	(93, 104)	2.123	(2.073, 2.175)	54	(50, 58)	0.613	(0.598, 0.629)	54	(50, 58)	1.739	(1.687, 1.792)
80+	330	(319, 342)	5.833	(5.710, 5.958)	58	(53, 63)	0.595	(0.578, 0.614)	72	(67, 78)	1.868	(1.808, 1.931)
Townsend												
Least deprived	32	(30, 33)	1.000		24	(22, 25)	1.000		19	(18, 21)	1.000	
2	48	(46, 50)	1.499	(1.464, 1.534)	33	(32, 35)	1.225	(1.194, 1.257)	22	(20, 23)	1.185	(1.146, 1.225)
3	53	(51, 56)	1.914	(1.871, 1.957)	46	(44, 48)	2.117	(2.068, 2.167)	28	(27, 30)	1.809	(1.754, 1.867)
4	60	(58, 63)	2.360	(2.307, 2.413)	68	(65, 71)	3.131	(3.062, 3.202)	39	(37, 41)	2.839	(2.756, 2.925)
Most deprived	62	(58, 65)	2.666	(2.603, 2.731)	116	(112, 120)	5.743	(5.619, 5.870)	50	(47, 53)	3.703	(3.591, 3.818)
Missing	49	(43, 56)	2.315	(2.217, 2.417)	95	(86, 103)	4.103	(3.961, 4.250)	30	(26, 35)	2.113	(1.987, 2.246)
Year												
2007	51	(49, 54)	1.000		58	(55, 60)	1.000		33	(31, 35)	1.000	
2008	54	(52, 56)	1.019	(0.998, 1.039)	56	(54, 59)	0.973	(0.955, 0.992)	31	(29, 32)	0.941	(0.916, 0.967)
2009	52	(50, 54)	0.955	(0.936, 0.974)	53	(51, 56)	0.899	(0.882, 0.916)	29	(27, 31)	0.899	(0.874, 0.924)
2010	48	(46, 50)	0.822	(0.805, 0.840)	47	(45, 49)	0.824	(0.807, 0.840)	30	(28, 32)	0.901	(0.876, 0.926)
2011	39	(37, 41)	0.684	(0.669, 0.700)	44	(41, 46)	0.751	(0.736, 0.766)	24	(22, 26)	0.665	(0.645, 0.685)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

Only

Table 2b: Rates of antipsychotic prescribing for the three most commonly prescribed second generation antipsychotics

Characteristic	Olanzapine				Quetiapine				Risperidone			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	168	(166, 171)	1.000		120	(117, 122)	1.000		137	(134, 139)	1.000	
Female	139	(136, 141)	0.835	(0.830, 0.841)	197	(194, 199)	1.542	(1.531, 1.553)	115	(113, 117)	0.854	(0.847, 0.)
Under 18	3	(2, 4)	0.008	(0.008, 0.009)	3	(3, 4)	0.012	(0.012, 0.013)	50	(47, 52)	0.196	(0.193, 0.200)
18-29	133	(129, 137)	0.349	(0.345, 0.354)	106	(102, 110)	0.418	(0.412, 0.424)	116	(112, 121)	0.484	(0.477, 0.491)
30-39	243	(237, 249)	0.822	(0.813, 0.830)	192	(186, 197)	0.941	(0.929, 0.952)	155	(150, 160)	0.810	(0.799, 0.820)
40-49	249	(243, 255)	1.000		175	(170, 180)	1.000		158	(154, 163)	1.000	
50-59	192	(187, 198)	0.868	(0.859, 0.877)	128	(124, 133)	0.730	(0.720, 0.740)	131	(127, 136)	0.845	(0.834, 0.857)
60-69	154	(149, 160)	0.781	(0.772, 0.790)	109	(105, 114)	0.670	(0.660, 0.679)	116	(111, 120)	0.819	(0.808, 0.831)
70-79	140	(134, 146)	0.673	(0.663, 0.683)	226	(219, 235)	1.263	(1.247, 1.280)	124	(118, 130)	0.772	(0.760, 0.785)
80+	195	(186, 204)	0.841	(0.829, 0.854)	891	(871, 910)	4.473	(4.427, 4.520)	289	(278, 300)	1.629	(1.606, 1.653)
Townsend												
Least deprived	81	(78, 84)	1.000		111	(108, 114)	1.000		79	(76, 81)	1.000	
2	101	(98, 104)	1.314	(1.296, 1.332)	130	(126, 134)	1.113	(1.100, 1.126)	93	(90, 96)	1.157	(1.141, 1.174)
3	140	(137, 144)	1.898	(1.873, 1.922)	164	(160, 168)	1.497	(1.480, 1.514)	121	(117, 124)	1.614	(1.593, 1.636)
4	211	(206, 216)	3.122	(3.084, 3.160)	192	(187, 196)	1.963	(1.941, 1.984)	163	(159, 168)	2.297	(2.267, 2.327)
Most deprived	320	(313, 328)	4.956	(4.897, 5.016)	239	(232, 245)	2.663	(2.633, 2.693)	227	(221, 233)	3.243	(3.201, 3.285)
Missing	200	(188, 212)	2.821	(2.761, 2.882)	196	(185, 209)	1.974	(1.933, 2.016)	148	(138, 159)	1.981	(1.933, 2.031)
Year												
2007	140	(137, 144)	1.000		117	(113, 120)	1.000		118	(114, 121)	1.000	
2008	153	(149, 157)	1.050	(1.039, 1.062)	144	(140, 148)	1.224	(1.209, 1.238)	124	(121, 128)	1.050	(1.037, 1.064)
2009	157	(153, 161)	1.088	(1.076, 1.100)	165	(161, 170)	1.360	(1.344, 1.376)	124	(120, 128)	1.053	(1.040, 1.066)
2010	166	(162, 170)	1.145	(1.133, 1.158)	190	(186, 195)	1.523	(1.506, 1.541)	138	(134, 142)	1.103	(1.089, 1.117)
2011	151	(147, 155)	1.077	(1.065, 1.089)	177	(173, 181)	1.480	(1.463, 1.497)	125	(121, 129)	1.040	(1.026, 1.053)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

### Records of mental health conditions in people prescribed antipsychotics

For people prescribed the three most common first generation antipsychotics, the proportion with a Read code for SMI (psychotic or bipolar disorders) varied between 27% (n=1331) for haloperidol and 35% (n=1545) for chlorpromazine (Table 3). The most common diagnosis recorded was schizophrenia and related conditions. For second generation antipsychotics, only 36% (n=4824) of those prescribed quetiapine had an SMI record, compared to 46% (n=4597) of those receiving risperidone and 62% (n=7094) of those receiving olanzapine (Table 3). More than half of people receiving first generation antipsychotics had no SMI diagnosis recorded in their notes, but did have a code for one of the non-SMI mental health conditions. The most common conditions were anxiety, depression and sleep disorders. Almost a third of people receiving haloperidol had a record of dementia. For second generation agents, the proportions with non-SMI diagnoses were similar, although the number of people with a record of dementia was highest for quetiapine (26% of prescriptions). Between 12 and 17% of people prescribed first generation agents had no record of SMI or of any non-SMI mental health diagnosis.



Table 3: Diagnosis by the three most commonly prescribed first and second generation antipsychotics 2007-2011

Diagnosis	Haloperidol (N=4913)		Chlorpromazine (N=4404)		Trifluoperazine (N=2633)		Olanzapine (N=11502)		Quetiapine (N=13326)		Risperidone (N=9956)	
	n	%	n	%	n	%	n	%	n	%	n	%
<b>SMI*</b>												
Any SMI diagnosis	1331	27	1545	35	783	30	7094	62	4824	36	4597	46
Schizophrenia	620	13	633	14	359	14	3060	27	1489	11	2143	22
Bipolar disorder	298	6	343	8	119	5	1655	14	1689	13	726	7
Other SMI	267	5	334	8	203	8	1898	17	1163	9	1291	13
On SMI register only	146	3	235	5	102	4	481	4	483	4	437	4
<b>Non-SMI*</b>												
Any non-SMI diagnosis	2762	56	2241	51	1529	58	3753	33	7623	57	4085	41
ADHD	36	0.7	33	0.7	10	0.4	75	0.7	77	0.6	538	5
Anxiety	783	16	1124	26	909	35	1779	15	2669	20	1391	14
Depression	1330	27	1748	40	1142	43	2964	26	4648	35	2204	22
Dementia	1521	31	183	4	157	6	466	4	3514	26	1211	12
OCD	40	0.8	93	2	47	2	216	2	250	2	221	2
PD	136	3	294	7	122	4	525	5	705	5	349	4
PTSD	37	0.8	97	2	29	1	197	2	210	2	94	0.9
Sleep disorders	761	15	815	19	511	19	1124	10	1926	14	1078	11
None of the above*	820	17	618	14	321	12	655	6	879	7	1274	13

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.

1  
2  
3  
4  
5 The median daily dose for antipsychotics was higher in those who did have a SMI diagnosis, and  
6  
7 highest amongst those with records of schizophrenia (Table 4). Within the non-SMI groups, median  
8  
9 daily doses were similar although the highest doses were observed in people with a record of a sleep  
10  
11 disorder or personality disorder. The longest durations of antipsychotic treatment were generally  
12  
13 observed for people with a diagnosis of schizophrenia or in those who were included on the SMI  
14  
15 register in general practice (Supplementary Table 4a). Within the non-SMI group, duration of  
16  
17 treatment showed little variation between diagnoses, although the median length of treatment  
18  
19 seemed longest in people with dementia or ADHD.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 4: Median (IQR) daily dose for the three most prescribed first and second generation antipsychotics by indication

Diagnosis	Haloperidol		Chlorpromazine		Trifluoperazine		Olanzapine		Quetiapine		Risperidone	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
<b>SMI*</b>												
Schizophrenia	7	(3, 14)	103	(55, 208)	10	(5, 18)	12	(9, 19)	326	(171, 546)	4	(2, 6)
Bipolar disorder	5	(2, 11)	93	(50, 174)	5	(2, 10)	10	(6, 15)	239	(100, 413)	2	(1, 4)
Other SMI	3	(1, 6)	88	(50, 171)	6	(2, 12)	10	(6, 15)	174	(70, 337)	2	(1, 4)
On SMI register only	4	(1, 8)	91	(51, 159)	4	(2, 8)	9	(5, 12)	119	(54, 254)	2	(1, 4)
<b>Non-SMI*</b>												
Any non-SMI diagnosis	2	(1, 3)	62	(38, 109)	3	(2, 5)	6	(4, 10)	66	(38, 132)	1	(1, 2)
ADHD	2	(1, 5)	82	(50, 184)	3	(2, 5)	7	(5, 11)	100	(50, 210)	1	(1, 2)
Anxiety	1	(1, 3)	61	(36, 108)	3	(2, 4)	6	(4, 10)	80	(46, 177)	1	(1, 3)
Depression	2	(1, 3)	58	(37, 102)	3	(2, 5)	6	(4, 10)	79	(43, 167)	1	(1, 2)
Dementia	1	(1, 3)	75	(39, 170)	3	(2, 7)	5	(3, 8)	52	(30, 89)	1	(1, 2)
OCD	2	(1, 5)	75	(42, 118)	3	(2, 5)	5	(4, 10)	95	(50, 205)	1	(1, 2)
PD	2	(1, 6)	82	(48, 150)	4	(2, 7)	8	(5, 12)	141	(58, 292)	2	(1, 3)
PTSD	2	(1, 3)	64	(38, 138)	2	(2, 5)	6	(4, 10)	100	(54, 232)	2	(1, 3)
Sleep disorders	3	(1, 8)	79	(49, 151)	4	(2, 11)	10	(6, 15)	155	(58, 340)	2	(1, 4)
None of the above*	2	(1, 4)	70	(38, 128)	2	(1, 5)	7	(4, 11)	56	(30, 119)	2	(1, 3)

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.

## CONCLUSION

In UK primary care, around half of prescriptions for first and second generation antipsychotics are issued to people who have no record of severe mental illness, defined as schizophrenia, bipolar affective disorder or other non-organic psychosis in their clinical notes. Furthermore, they are more likely to be prescribed to older people who may be more sensitive to adverse effects such as movement disorders and cardio-metabolic risk. When antipsychotics are prescribed to people without SMI, they tend to be given in lower doses and for slightly shorter periods, with the exception people with ADHD and dementia who receive these drugs for relatively long periods.

For first generation agents, the most common “non-SMI” mental health diagnoses we identified were anxiety, depression, sleep disorders, and dementia (especially for haloperidol). For second generation agents, the same mental health diagnoses were common including dementia, despite the fact that second generation antipsychotics are not recommended in people with dementia due to the risk of stroke and other-cause mortality.[1, 2] Reducing the potential harm associated with antipsychotics in dementia has been emphasised as a priority by organisations such as Department of Health in England and the US Food and Drug Administration.[17, 18] Our findings suggest that further effort is required to decrease primary care antipsychotic prescriptions in dementia.

Median daily doses and duration of treatment with antipsychotics tended to be slightly greater in people with SMI diagnoses (especially schizophrenia); however people with depression, anxiety, personality disorders and sleep disorders still received substantial doses of these agents, for relatively long periods of time. For instance the median daily dose of olanzapine prescribed to people with sleep disorders was 10mg per day; the same daily dose as people with a diagnosis of bipolar disorder and only slightly less than the average dose of 12mg per day prescribed to people with schizophrenia (Table 4). Within the non-SMI group, median doses of risperidone and

1  
2  
3 quetiapine were also highest in those with sleep disorders, post-traumatic stress disorder and  
4  
5 personality disorder.  
6  
7

8  
9  
10 There are a number of possible explanations for the high rates of antipsychotic prescribing to people  
11 without a record of psychosis. Firstly it may be that the clinician prescribes antipsychotics because  
12 the person does have psychotic symptoms, but the clinician does not assign a label of schizophrenia  
13 or other psychosis, either due to patient preference or to avoid the associated stigma with such  
14 labels. However this would suggest that there are large numbers of people with unrecorded  
15 psychosis and/or bipolar disorder in primary care. This is not consistent with other research in UK  
16 primary care databases which has shown that rates of schizophrenia and bipolar disorder recording  
17 in the database are similar to other epidemiological studies.[19] Therefore it seems unlikely that  
18 large numbers people in primary care have psychosis without a corresponding record.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

29  
30  
31 Secondly it is possible that in real life practice antipsychotics are prescribed quite commonly to  
32 people with problems related to depression, anxiety, sleep, dementia and other conditions, despite  
33 guidelines recommending caution and only suggesting this as a strategy in treatment unresponsive  
34 cases.[3, 6] It maybe that clinicians and/or mental health professionals quite frequently add  
35 antipsychotics to the treatment plan for people with non-psychotic disorders, either for agitation,  
36 poor sleep, anxiety or due to their general reputation as tranquilising medications. Since there were  
37 not major differences in the median doses and duration of treatment according to recorded  
38 diagnosis, these patterns of prescribing warrant some attention in terms of monitoring side effects  
39 particularly weight gain, extra-pyramidal side effects and metabolic impacts such as  
40 hyperprolactinaemia, glucose dysregulation and effects on lipid profiles. Current UK policy only  
41 recommends physical monitoring for people who the general practice includes on its SMI register. It  
42 may be that this recommendation should be extended to all people prescribed antipsychotics in  
43 primary care.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### Strengths and limitations

Primary care databases allow us to study large representative samples of patients in general practice across the UK. THIN has a good record of prescriptions issued and comparison with dispensing data suggests that the majority of THIN prescriptions issued are collected[20] but of course this may not mean patients have been actually taking the medication. Primary care diagnoses of SMI have been validated,[21] however this is not the case for some other conditions we explored such as ADHD and anxiety.

Research with routine clinical data has its limitations, for instance we could not perform more detailed assessment of patient characteristics and preferences which may influence treatment decisions. It would be useful to explore the reasons underpinning these high rates of prescription to groups not traditionally thought eligible for antipsychotic treatment. This might require primary research studies interviewing clinicians and reviewing individual patients. However further database work could explore symptoms associated with these antipsychotic prescriptions, and the treatment decisions pre-dating the choice of an antipsychotic agent. Also, the same databases could be used to assess how frequently cardiovascular risk factors are measured in this population, especially body mass index, cholesterol and HDL cholesterol as well as some indication of glucose regulation such as HBA1c, random or fasting glucose.

We need to know more about co-prescribing in the people without a diagnosis of psychosis or bipolar disorder. We also need to quantify the degree of benefit and harm that may be associated with using such treatments. To what degree do they cause physical and/ or mental health problems for the recipients, and to what extent do they lead to symptom remission? A meta-analysis of antipsychotics drugs in major depressive disorder found that although these agents may improve depression symptoms, they have no impact on functioning or quality of life.[22] The few existing

1  
2  
3 randomised controlled trials involving people with personality disorder have shown little benefit of  
4  
5 antipsychotics over placebo.[6, 23]  
6  
7

8  
9 Finally it is important to explore whether these agents are discontinued following amelioration of  
10  
11 any mental health problem for which they are chosen, and to assess the risks and benefits of  
12  
13 stopping such agents in different diagnostic groups.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure legend

Figure 1: Flow of individuals through the study

For peer review only



**Conflict of Interest**

The authors have no conflicts of interest to declare.

**Funding**

This work was funded by the NIHR School for Primary Care Research. Grant number 17321

**Authorship**

DPJO, KW, IP and IN had the original idea for the study. All authors developed the method, analysed and interpreted the results and wrote the manuscript. LM performed the analysis.

**Data sharing statement**

No data are available

I Dr Louise Marston the Corresponding Author of this article contained within the original manuscript which includes any diagrams & photographs, other illustrative material, video, film or any other material howsoever submitted by the Contributor(s) at any time and related to the Contribution ("the Contribution") have the right to grant on behalf of all authors and do grant on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licensees, to permit this Contribution (if accepted) to be published in BMJ Open and any other BMJ Group products and to exploit all subsidiary rights, as set out in the licence at:

[http://group.bmj.com/products/journals/instructions-for-authors/BMJOpen\\_licence.pdf](http://group.bmj.com/products/journals/instructions-for-authors/BMJOpen_licence.pdf)

## REFERENCES

- 1 Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934-43.
- 2 Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study (electronic article). *BMJ* 2008;
- 3 National Institute for Health and Care Excellence Depression: the treatment and management of depression in adults (update). CG90 2009a (<http://guidance.nice.org.uk/CG90>) (accessed May 2014)
- 4 Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology *J Psychopharmacol* 2005;19:567-96.
- 5 Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders *J Psychopharmacol* 2010;24:1577-1600.
- 6 National Institute for Health and Care Excellence Borderline personality disorder: Treatment and management. CG78 2009b (<http://www.nice.org.uk/CG78>) (accessed May 2014)
- 7 The Health Improvement Network The Health Improvement Network. London: The Health Improvement Network; 2014 (<http://csdmruk.cegedim.com/>) (Accessed May 2014).

1  
2  
3 8 Lis Y, Mann RD The VAMP Research multi-purpose database in the U.K. *J Clin Epidemiol*  
4  
5 1995;431-j 43  
6

7  
8  
9 9 Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North.  
10  
11 London: Croom Helm, 1988.  
12

13  
14  
15  
16 10 Booth N What are the Read Codes? *Health Libr Rev* 1994;177-82  
17

18  
19  
20 11 Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and  
21  
22 Pharmaceutical Press 2014 (<http://www.medicinescomplete.com>) (Accessed may 2014)  
23

24  
25  
26 12 Blak BT, Thompson M, Dattani H, et al Generalisability of The Health Improvement Network  
27  
28 (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*  
29  
30 2011;251-55  
31

32  
33  
34  
35 13 Horsfall L, Walters K, Petersen I. Identifying periods of acceptable computer usage in primary  
36  
37 care research databases. *Pharmacoepidemiol Drug Saf* 2013;64-9.  
38

39  
40  
41 14 Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality  
42  
43 reporting for research using automated data from primary care. *Pharmacoepidem Drug Saf* 2009;76-  
44  
45 83  
46  
47

48  
49  
50 15 Dave S, Petersen I. Creating medical and drug code lists to identify cases in primary care  
51  
52 databases. *Pharmacoepidem Drug Saf* 2009;18:704-7.  
53  
54

1  
2  
3 16 Stata Corporation. *Stata Statistical Software: Release 13*. College Station, TX: Stata  
4 Corporation; 2013  
5  
6  
7

8  
9 17 Department of Health The use of antipsychotic medication for people with dementia: time  
10 for action. Department of Health. London 2009  
11  
12

13  
14  
15 18 U.S. Food and Drug Administration Public Health Advisory: Deaths with Antipsychotics in  
16 Elderly Patients with Behavioral Disturbances 2005  
17  
18

19  
20 ([http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/  
21 DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm))  
22  
23

24 (accessed May 2014)  
25  
26

27  
28  
29 19 Haroon S, Hayes JF, Blackburn R et al. Recording of severe mental illness in United Kingdom  
30 primary care, 2000-2010. *PLoS One* 2013;12;8(12):e82365.  
31  
32

33  
34  
35 20 The NHS Information Centre PaPCS. Prescribing compliance: a review of the proportion of  
36 prescriptions dispensed. 2011 (<http://www.hscic.gov.uk/pubs/presccompliance>) (accessed May  
37 2014)  
38  
39

40  
41  
42  
43 21 Nazareth I, King M, Haines A et al. Accuracy of diagnosis of psychosis on general practice  
44 computer system *BMJ* 1993;307(6895):32-4  
45  
46

47  
48  
49  
50 22 Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive Atypical Antipsychotic Treatment  
51 for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes  
52 *PLoS Med* 2013;10(3):e1001403  
53  
54  
55

1  
2  
3 23 Inghoven T, Lafay P, Rinne T, et al. Effectiveness of pharmacotherapy for severe  
4  
5 personality disorders: metaanalyses of randomized controlled trials. *J Clin Psychiatry*. 2010;71:14–  
6  
7 25.  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	7, 8
Study size	10	Explain how the study size was arrived at	7-9+figure
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
<b>Results</b>			

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9+figure
		(b) Give reasons for non-participation at each stage	figure
		(c) Consider use of a flow diagram	figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15, Table 3
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9, 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10, 12, Tables 1, 2a, 2b
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 12, Tables 1, 2a, 2b
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 12, Tables 1, 2a, 2b
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	19
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

## Appendix: Read code list for severe mental illness (SMI)

Description	Read code
H/O: schizophrenia	1464.00
H/O: manic depressive disorder	146D.00
H/O: psychosis	146H.00
On national service framework mental health	9H6..00
On severe mental illness register	9H8..00
Non-organic psychoses	E1...00
Schizophrenic disorders	E10..00
Simple schizophrenia	E100.00
Schizophrenia simplex	E100.11
Unspecified schizophrenia	E100000
Subchronic schizophrenia	E100100
Chronic schizophrenic	E100200
Acute exacerbation of subchronic schizophrenia	E100300
Acute exacerbation of chronic schizophrenia	E100400
Schizophrenia in remission	E100500
Simple schizophrenia NOS	E100z00
Hebephrenic schizophrenia	E101.00
Unspecified hebephrenic schizophrenia	E101000
Subchronic hebephrenic schizophrenia	E101100
Chronic hebephrenic schizophrenia	E101200
Acute exacerbation of subchronic hebephrenic schizophrenia	E101300
Acute exacerbation of chronic hebephrenic schizophrenia	E101400
Hebephrenic schizophrenia in remission	E101500
Hebephrenic schizophrenia NOS	E101z00
Catatonic schizophrenia	E102.00
Unspecified catatonic schizophrenia	E102000
Subchronic catatonic schizophrenia	E102100
Chronic catatonic schizophrenia	E102200
Acute exacerbation of subchronic catatonic schizophrenia	E102300
Acute exacerbation of chronic catatonic schizophrenia	E102400
Catatonic schizophrenia in remission	E102500
Catatonic schizophrenia NOS	E102z00
Paranoid schizophrenia	E103.00
Unspecified paranoid schizophrenia	E103000
Subchronic paranoid schizophrenia	E103100
Chronic paranoid schizophrenia	E103200
Acute exacerbation of subchronic paranoid schizophrenia	E103300
Acute exacerbation of chronic paranoid schizophrenia	E103400
Paranoid schizophrenia in remission	E103500
Paranoid schizophrenia NOS	E103z00
Acute schizophrenic episode	E104.00
Oneirophrenia	E104.11
Latent schizophrenia	E105.00
Unspecified latent schizophrenia	E105000
Subchronic latent schizophrenia	E105100
Chronic latent schizophrenia	E105200
Acute exacerbation of subchronic latent schizophrenia	E105300
Acute exacerbation of chronic latent schizophrenia	E105400
Latent schizophrenia in remission	E105500
Latent schizophrenia NOS	E105z00
Residual schizophrenia	E106.00
Restzustand - schizophrenia	E106.11



Schizo-affective schizophrenia	E107.00
Cyclic schizophrenia	E107.11
Unspecified schizo-affective schizophrenia	E107000
Subchronic schizo-affective schizophrenia	E107100
Chronic schizo-affective schizophrenia	E107200
Acute exacerbation subchronic schizo-affective schizophrenia	E107300
Acute exacerbation of chronic schizo-affective schizophrenia	E107400
Schizo-affective schizophrenia in remission	E107500
Schizo-affective schizophrenia NOS	E107z00
Other schizophrenia	E10y.00
Cenesthopathic schizophrenia	E10y.11
Atypical schizophrenia	E10y000
Coenesthopathic schizophrenia	E10y100
Other schizophrenia NOS	E10yz00
Schizophrenia NOS	E10z.00
Affective psychoses	E11..00
Bipolar psychoses	E11..11
Depressive psychoses	E11..12
Manic psychoses	E11..13
Manic disorder, single episode	E110.00
Hypomanic psychoses	E110.11
Single manic episode, unspecified	E110000
Single manic episode, mild	E110100
Single manic episode, moderate	E110200
Single manic episode, severe without mention of psychosis	E110300
Single manic episode, severe, with psychosis	E110400
Single manic episode in partial or unspecified remission	E110500
Single manic episode in full remission	E110600
Manic disorder, single episode NOS	E110z00
Recurrent manic episodes	E111.00
Recurrent manic episodes, unspecified	E111000
Recurrent manic episodes, mild	E111100
Recurrent manic episodes, moderate	E111200
Recurrent manic episodes, severe without mention psychosis	E111300
Recurrent manic episodes, severe, with psychosis	E111400
Recurrent manic episodes, partial or unspecified remission	E111500
Recurrent manic episodes, in full remission	E111600
Recurrent manic episode NOS	E111z00
Single major depressive episode, severe, with psychosis	E112400
Recurrent major depressive episodes, severe, with psychosis	E113400
Bipolar affective disorder, currently manic	E114.00
Manic-depressive - now manic	E114.11
Bipolar affective disorder, currently manic, unspecified	E114000
Bipolar affective disorder, currently manic, mild	E114100
Bipolar affective disorder, currently manic, moderate	E114200
Bipolar affect disord, currently manic, severe, no psychosis	E114300
Bipolar affect disord, currently manic,severe with psychosis	E114400
Bipolar affect disord,currently manic, part/unspec remission	E114500
Bipolar affective disorder, currently manic, full remission	E114600
Bipolar affective disorder, currently manic, NOS	E114z00
Bipolar affective disorder, currently depressed	E115.00
Manic-depressive - now depressed	E115.11
Bipolar affective disorder, currently depressed, unspecified	E115000
Bipolar affective disorder, currently depressed, mild	E115100

1		
2		
3	Bipolar affective disorder, currently depressed, moderate	E115200
4	Bipolar affect disord, now depressed, severe, no psychosis	E115300
5	Bipolar affect disord, now depressed, severe with psychosis	E115400
6	Bipolar affect disord, now depressed, part/unspec remission	E115500
7	Bipolar affective disorder, now depressed, in full remission	E115600
8	Bipolar affective disorder, currently depressed, NOS	E115z00
9	Mixed bipolar affective disorder	E116.00
10	Mixed bipolar affective disorder, unspecified	E116000
11	Mixed bipolar affective disorder, mild	E116100
12	Mixed bipolar affective disorder, moderate	E116200
13	Mixed bipolar affective disorder, severe, without psychosis	E116300
14	Mixed bipolar affective disorder, severe, with psychosis	E116400
15	Mixed bipolar affective disorder, partial/unspec remission	E116500
16	Mixed bipolar affective disorder, in full remission	E116600
17	Mixed bipolar affective disorder, NOS	E116z00
18	Unspecified bipolar affective disorder	E117.00
19	Unspecified bipolar affective disorder, unspecified	E117000
20	Unspecified bipolar affective disorder, mild	E117100
21	Unspecified bipolar affective disorder, moderate	E117200
22	Unspecified bipolar affective disorder, severe, no psychosis	E117300
23	Unspecified bipolar affective disorder, severe with psychosis	E117400
24	Unspecified bipolar affect disord, partial/unspec remission	E117500
25	Unspecified bipolar affective disorder, in full remission	E117600
26	Unspecified bipolar affective disorder, NOS	E117z00
27	Other and unspecified manic-depressive psychoses	E11y.00
28	Unspecified manic-depressive psychoses	E11y000
29	Atypical manic disorder	E11y100
30	Other mixed manic-depressive psychoses	E11y300
31	Other and unspecified manic-depressive psychoses NOS	E11yz00
32	Other and unspecified affective psychoses	E11z.00
33	Unspecified affective psychoses NOS	E11z000
34	Other affective psychosis NOS	E11zz00
35	Paranoid states	E12..00
36	Simple paranoid state	E120.00
37	Chronic paranoid psychosis	E121.00
38	Sander's disease	E121.11
39	Paraphrenia	E122.00
40	Shared paranoid disorder	E123.00
41	Folie a deux	E123.11
42	Other paranoid states	E12y.00
43	Paranoia querulans	E12y000
44	Other paranoid states NOS	E12yz00
45	Paranoid psychosis NOS	E12z.00
46	Other nonorganic psychoses	E13..00
47	Reactive psychoses	E13..11
48	Reactive depressive psychosis	E130.00
49	Psychotic reactive depression	E130.11
50	Acute hysterical psychosis	E131.00
51	Acute paranoid reaction	E133.00
52	Bouffee delirante	E133.11
53	Psychogenic paranoid psychosis	E134.00
54	Other reactive psychoses	E13y.00
55	Psychogenic stupor	E13y000
56	Brief reactive psychosis	E13y100
57		
58		
59		
60		

1		
2		
3	Other reactive psychoses NOS	E13yz00
4	Nonorganic psychosis NOS	E13z.00
5	Psychotic episode NOS	E13z.11
6	Other specified non-organic psychoses	E1y..00
7	Non-organic psychosis NOS	E1z..00
8	Schizotypal personality	E212200
9	[X]Schizophrenia, schizotypal and delusional disorders	Eu2..00
10	[X]Schizophrenia	Eu20.00
11	[X]Paranoid schizophrenia	Eu20000
12	[X]Paraphrenic schizophrenia	Eu20011
13	[X]Hebephrenic schizophrenia	Eu20100
14	[X]Disorganised schizophrenia	Eu20111
15	[X]Catatonic schizophrenia	Eu20200
16	[X]Catatonic stupor	Eu20211
17	[X]Schizophrenic catalepsy	Eu20212
18	[X]Schizophrenic catatonia	Eu20213
19	[X]Schizophrenic flexibilatis cerea	Eu20214
20	[X]Undifferentiated schizophrenia	Eu20300
21	[X]Atypical schizophrenia	Eu20311
22	[X]Post-schizophrenic depression	Eu20400
23	[X]Residual schizophrenia	Eu20500
24	[X]Chronic undifferentiated schizophrenia	Eu20511
25	[X]Restzustand schizophrenic	Eu20512
26	[X]Simple schizophrenia	Eu20600
27	[X]Other schizophrenia	Eu20y00
28	[X]Cenesthopathic schizophrenia	Eu20y11
29	[X]Schizophreniform disord NOS	Eu20y12
30	[X]Schizophrenifrm psychos NOS	Eu20y13
31	[X]Schizophrenia, unspecified	Eu20z00
32	[X]Schizotypal disorder	Eu21.00
33	[X]Latent schizophrenic reaction	Eu21.11
34	[X]Borderline schizophrenia	Eu21.12
35	[X]Latent schizophrenia	Eu21.13
36	[X]Prepsychotic schizophrenia	Eu21.14
37	[X]Prodromal schizophrenia	Eu21.15
38	[X]Pseudoneurotic schizophrenia	Eu21.16
39	[X]Pseudopsychopathic schizophrenia	Eu21.17
40	[X]Schizotypal personality disorder	Eu21.18
41	[X]Persistent delusional disorders	Eu22.00
42	[X]Delusional disorder	Eu22000
43	[X]Paranoid psychosis	Eu22011
44	[X]Paranoid state	Eu22012
45	[X]Paraphrenia - late	Eu22013
46	[X>Sensitiver Beziehungswahn	Eu22014
47	[X]Paranoia	Eu22015
48	[X]Delusional misidentification syndrome	Eu22100
49	[X]Capgras syndrome	Eu22111
50	[X]Cotard syndrome	Eu22200
51	[X]Other persistent delusional disorders	Eu22y00
52	[X]Delusional dysmorphophobia	Eu22y11
53	[X]Involutional paranoid state	Eu22y12
54	[X]Paranoia querulans	Eu22y13
55	[X]Persistent delusional disorder, unspecified	Eu22z00
56	[X]Acute and transient psychotic disorders	Eu23.00
57		
58		
59		
60		

1		
2		
3	[X]Acute polymorphic psychot disord without symp of schizop	Eu23000
4	[X]Bouffee delirante	Eu23011
5	[X]Cycloid psychosis	Eu23012
6	[X]Acute polymorphic psychot disord with symp of schizopren	Eu23100
7	[X]Bouffee delirante with symptoms of schizophrenia	Eu23111
8	[X]Cycloid psychosis with symptoms of schizophrenia	Eu23112
9	[X]Acute schizophrenia-like psychotic disorder	Eu23200
10	[X]Brief schizophreniform disorder	Eu23211
11	[X]Brief schizophrenifrm psych	Eu23212
12	[X]Oneirophrenia	Eu23213
13	[X]Schizophrenic reaction	Eu23214
14	[X]Other acute predominantly delusional psychotic disorders	Eu23300
15	[X]Psychogenic paranoid psychosis	Eu23312
16	[X]Other acute and transient psychotic disorders	Eu23y00
17	[X]Acute and transient psychotic disorder, unspecified	Eu23z00
18	[X]Brief reactive psychosis NOS	Eu23z11
19	[X]Reactive psychosis	Eu23z12
20	[X]Induced delusional disorder	Eu24.00
21	[X]Folie a deux	Eu24.11
22	[X]Induced paranoid disorder	Eu24.12
23	[X]Induced psychotic disorder	Eu24.13
24	[X]Schizoaffective disorders	Eu25.00
25	[X]Schizoaffective disorder, manic type	Eu25000
26	[X]Schizoaffective psychosis, manic type	Eu25011
27	[X]Schizophreniform psychosis, manic type	Eu25012
28	[X]Schizoaffective disorder, depressive type	Eu25100
29	[X]Schizoaffective psychosis, depressive type	Eu25111
30	[X]Schizophreniform psychosis, depressive type	Eu25112
31	[X]Schizoaffective disorder, mixed type	Eu25200
32	[X]Cyclic schizophrenia	Eu25211
33	[X]Mixed schizophrenic and affective psychosis	Eu25212
34	[X]Other schizoaffective disorders	Eu25y00
35	[X]Schizoaffective disorder, unspecified	Eu25z00
36	[X]Schizoaffective psychosis NOS	Eu25z11
37	[X]Other nonorganic psychotic disorders	Eu2y.00
38	[X]Chronic hallucinatory psychosis	Eu2y.11
39	[X]Unspecified nonorganic psychosis	Eu2z.00
40	[X]Psychosis NOS	Eu2z.11
41	[X]Manic episode	Eu30.00
42	[X]Bipolar disorder, single manic episode	Eu30.11
43	[X]Hypomania	Eu30000
44	[X]Mania without psychotic symptoms	Eu30100
45	[X]Mania with psychotic symptoms	Eu30200
46	[X]Mania with mood-congruent psychotic symptoms	Eu30211
47	[X]Mania with mood-incongruent psychotic symptoms	Eu30212
48	[X]Manic stupor	Eu30213
49	[X]Other manic episodes	Eu30y00
50	[X]Manic episode, unspecified	Eu30z00
51	[X]Mania NOS	Eu30z11
52	[X]Bipolar affective disorder	Eu31.00
53	[X]Manic-depressive illness	Eu31.11
54	[X]Manic-depressive psychosis	Eu31.12
55	[X]Mainc-depressive reaction	Eu31.13
56	[X]Bipolar affective disorder, current episode hypomanic	Eu31000
57		
58		
59		
60		

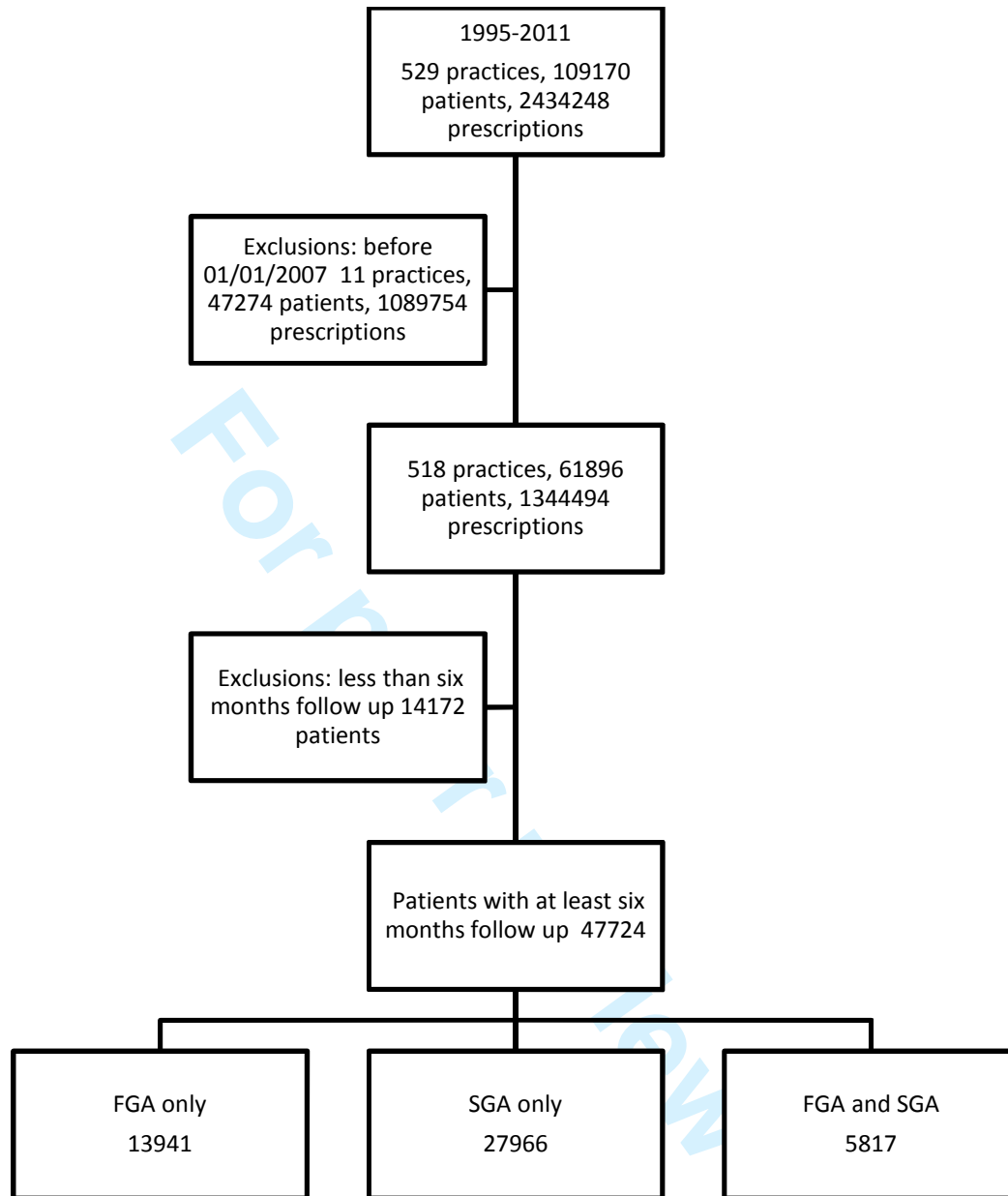
1		
2		
3	[X]Bipolar affect disorder cur epi manic wout psychotic symp	Eu31100
4	[X]Bipolar affect disorder cur epi manic with psychotic symp	Eu31200
5	[X]Bipolar affect disorder cur epi mild or moderate depressn	Eu31300
6	[X]Bipol aff disord, curr epis sev depress, no psychot symp	Eu31400
7	[X]Bipolar affect dis cur epi severe depres with psyc symp	Eu31500
8	[X]Bipolar affective disorder, current episode mixed	Eu31600
9	[X]Bipolar affective disorder, currently in remission	Eu31700
10	[X]Other bipolar affective disorders	Eu31y00
11	[X]Bipolar II disorder	Eu31y11
12	[X]Recurrent manic episodes	Eu31y12
13	[X]Bipolar affective disorder, unspecified	Eu31z00
14	[X]Severe depressive episode with psychotic symptoms	Eu32300
15	[X]Single episode of major depression and psychotic symptoms	Eu32311
16	[X]Single episode of psychogenic depressive psychosis	Eu32312
17	[X]Single episode of psychotic depression	Eu32313
18	[X]Single episode of reactive depressive psychosis	Eu32314
19	[X]Major depression, severe with psychotic symptoms	Eu32800
20	[X]Manic-depress psychosis,depressd,no psychotic symptoms	Eu33213
21	[X]Recurrent depress disorder cur epi severe with psyc symp	Eu33300
22	[X]Endogenous depression with psychotic symptoms	Eu33311
23	[X]Manic-depress psychosis,depressed type+psychotic symptoms	Eu33312
24	[X]Recurr severe episodes/major depression+psychotic symptom	Eu33313
25	[X]Recurr severe episodes/psychogenic depressive psychosis	Eu33314
26	[X]Recurrent severe episodes of psychotic depression	Eu33315
27	[X]Recurrent severe episodes/reactive depressive psychosis	Eu33316
28	[X]Affective psychosis NOS	Eu3z.11
29	[X]Hysterical psychosis	Eu44.14
30	[X]Symbiotic psychosis	Eu84314
31	Profile of mood states, bipolar	ZRby100
32	Schizophrenic language	ZS7C611
33	[V]Personal history of schizophrenia	ZV11000
34	[V]Personal history of manic-depressive psy	ZV11111
35	[V]Personal history of manic-depressive psy	ZV11112
36		
37		
38		
39		
40		
41		
42		
43		
44		
45		
46		
47		
48		
49		
50		
51		
52		
53		
54		
55		
56		
57		
58		
59		
60		

Supplementary Table 4a: Median (IQR) time (years) for which antipsychotics are prescribed by the three most commonly prescribed first and second generation antipsychotics by indication

Diagnosis	Haloperidol		Chlorpromazine		Trifluoperazine		Olanzapine		Quetiapine		Risperidone	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
<b>SMI*</b>												
Schizophrenia	0.62	(0.13, 2.25)	0.89	(0.19, 2.85)	1.19	(0.28, 3.80)	1.62	(0.56, 3.82)	0.93	(0.30, 2.46)	1.15	(0.33, 2.97)
Bipolar disorder	0.41	(0.08, 1.51)	0.57	(0.08, 2.17)	0.46	(0.09, 1.63)	1.00	(0.30, 2.55)	0.93	(0.30, 2.04)	0.76	(0.19, 2.16)
Other SMI	0.30	(0.08, 1.13)	0.64	(0.10, 2.50)	0.80	(0.13, 2.60)	1.14	(0.36, 2.78)	0.90	(0.32, 2.11)	0.77	(0.22, 2.18)
On SMI register only	0.64	(0.15, 2.65)	1.72	(0.40, 4.38)	1.07	(0.16, 3.53)	1.92	(0.61, 4.31)	1.45	(0.45, 3.49)	1.84	(0.43, 4.61)
<b>Non-SMI*</b>												
Any non-SMI diagnosis	0.32	(0.08, 0.98)	0.31	(0.08, 1.37)	0.18	(0.08, 0.97)	0.67	(0.19, 1.81)	0.96	(0.33, 1.96)	0.77	(0.23, 1.93)
ADHD	0.77	(0.20, 1.47)	0.69	(0.15, 1.49)	0.16	(0.08, 1.30)	0.48	(0.13, 0.94)	0.52	(0.15, 1.33)	0.90	(0.38, 1.88)
Anxiety	0.18	(0.08, 0.78)	0.31	(0.08, 1.25)	0.19	(0.08, 1.01)	0.63	(0.18, 1.64)	0.87	(0.27, 1.83)	0.59	(0.14, 1.72)
Depression	0.27	(0.08, 0.90)	0.32	(0.08, 1.33)	0.21	(0.08, 1.04)	0.66	(0.19, 1.73)	0.90	(0.29, 1.86)	0.61	(0.16, 1.65)
Dementia	0.47	(0.11, 1.12)	0.44	(0.08, 1.27)	0.46	(0.08, 1.31)	1.10	(0.33, 2.44)	1.30	(0.57, 2.41)	0.71	(0.27, 1.49)
OCD	0.33	(0.08, 0.90)	0.48	(0.08, 2.24)	0.31	(0.08, 1.05)	0.59	(0.15, 1.72)	0.77	(0.25, 1.73)	0.59	(0.20, 2.09)
PD	0.26	(0.08, 1.22)	0.62	(0.16, 1.65)	0.21	(0.08, 1.13)	0.58	(0.22, 1.61)	0.82	(0.30, 1.72)	0.59	(0.18, 1.70)
PTSD	0.09	(0.06, 0.34)	0.36	(0.08, 1.21)	0.08	(0.08, 0.58)	0.67	(0.19, 2.01)	0.92	(0.34, 1.86)	0.63	(0.21, 1.95)
Sleep disorders	0.21	(0.08, 0.77)	0.25	(0.08, 1.21)	0.17	(0.08, 0.89)	0.63	(0.16, 1.67)	0.91	(0.27, 1.84)	0.64	(0.17, 1.67)
None of the above*	0.29	(0.08, 0.93)	0.24	(0.08, 1.86)	0.10	(0.08, 0.71)	0.66	(0.16, 2.15)	0.73	(0.25, 1.68)	1.14	(0.38, 2.82)

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.



# BMJ Open

## Prescribing of antipsychotics in United Kingdom primary care. Cohort study in United Kingdom primary care

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006135.R1
Article Type:	Research
Date Submitted by the Author:	15-Oct-2014
Complete List of Authors:	Marston, Louise; University College London, Primary Care and Population Health Nazareth, Irwin; UCL, Primary Care and Population Health Petersen, Irene; University College London Medical School, Department of Primary Care and Population health Walters, Kate; University College London, Primary Care and Population Health Osborn, David; UCL, Division of Psychiatry
<b>Primary Subject Heading</b>:	General practice / Family practice
Secondary Subject Heading:	Epidemiology, Mental health
Keywords:	MENTAL HEALTH, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts



1  
2  
3 **Prescribing of antipsychotics in United Kingdom primary care. Cohort study in United Kingdom**  
4  
5 **primary care**  
6  
7  
8

9 Louise Marston<sup>1\*</sup>

10  
11 Irwin Nazareth<sup>1</sup>

12  
13 Irene Petersen<sup>1</sup>

14  
15 Kate Walters<sup>1</sup>

16  
17 David PJ Osborn<sup>2,3</sup>

18  
19  
20 1. Research Department of Primary Care and Population Health, UCL, London UK.

21  
22 2. UCL Division of Psychiatry, UCL, London UK.

23  
24 3. Camden and Islington NHS Foundation Trust, London UK.  
25  
26  
27

28  
29 **\*Corresponding author-**

30  
31 Dr Louise Marston

32  
33 Research Department of Primary Care and Population Health

34  
35 UCL

36  
37 London

38  
39 NW3 2PF

40  
41  
42  
43  
44 Email: [l.marston@ucl.ac.uk](mailto:l.marston@ucl.ac.uk)

45  
46 Telephone: +44 (0) 20 7794 0500 (36768)  
47  
48

49  
50 Keywords: antipsychotic, primary care, schizophrenia, dementia, depression  
51  
52

53  
54  
55 Word Count: 3326  
56  
57  
58  
59  
60

**Abstract****Objective**

To examine the recorded indication for antipsychotic prescriptions in primary care.

**Design**

Cohort study

**Setting**

Primary Care.

**Participants**

Individuals prescribed antipsychotics between 2007 and 2011.

**Measures**

The proportion of individuals prescribed antipsychotics with a diagnosis of 1) psychosis and bipolar disorder 2) Other diagnoses including depression, anxiety and dementia and 3) None of these diagnoses.

**Results**

We identified 47,724 individuals prescribed antipsychotic agents. 13,941 received first generation agents and 27,966 received second generation agents. Rates of prescribing were higher in females (incidence rate ratio 1.092 (95% CI 1.088 to 1.095), older people (80+ versus 40–49 IRR 2.234 (2.222, 2.246) and in those from the most deprived areas (most deprived versus least deprived IRR 3.487 (3.567, 3.606). Of those receiving first generation antipsychotics less than 50% had a diagnosis of psychosis/ bipolar disorder. For second generation agents, the numbers ranged from 4824 (36%) for quetiapine to 7094 (62%) for olanzapine. In patients without psychosis/ bipolar, common diagnoses included anxiety, depression, dementia, sleep and personality disorders. For example in risperidone users, 14% had an anxiety code, 22% depression, 12% dementia, 11% sleep disorder and 4% personality disorder. Median daily doses and duration of treatment were greater in those with schizophrenia (eg risperidone median daily dose 4mg; IQR 2, 6: median duration 1.2 years), compared to those with non-psychotic/ bipolar disorders such as depression or anxiety (eg

risperidone 1mg; IQR 1, 2: 0.6 years). A relatively large proportion (between 6 and 17%) of people receiving individual antipsychotics had none of the diagnoses above.

## Conclusions

In UK primary care, a large proportion of people prescribed antipsychotics have no record of a psychotic or bipolar disorder. They are often older people, with conditions including dementia, non-psychotic depression, anxiety and sleep disorders.

## Article summary

### Strengths and limitations of this study

We determined the likely indication for antipsychotic prescriptions in a large, representative sample of people in UK primary care. The data source contained accurate prescribing information although prescriptions issued in secondary care will not have been captured. Diagnoses of severe mental illnesses have been validated in primary care. The nature of the data did not allow us to determine the clinicians' rationale for prescribing antipsychotics to people without psychoses or bipolar disorder diagnoses.

- Less than half of people prescribed the most common first generation antipsychotics in UK primary care have a diagnosis of a psychosis or bipolar disorder.
- Findings were similar for second generation agents, although 62% of people receiving olanzapine did have a diagnosis of psychosis or bipolar disorder
- These agents are more commonly prescribed to older people, despite the propensity of this age group to develop side effects.
- Antipsychotics are still commonly prescribed to people with a diagnosis of dementia, contrary to clinical guidance, and this need further attention in UK primary care.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- Other common diagnoses included depression, anxiety disorders, personality disorders and ADHD, while up to 17% of people receiving antipsychotics had none of the diagnoses we explored.

For peer review only

**BACKGROUND**

Antipsychotic medications are the first line pharmacological intervention for severe mental illnesses (SMI) such as schizophrenia and other psychoses. However, they are also increasingly prescribed for treatment of bipolar affective disorder. They are not routinely recommended for other mental health conditions such as depression, sleep disorders or Obsessive Compulsive Disorder (OCD). There is concern about rates of antipsychotic prescribing in dementia since they may be associated with increased rates of strokes and all-cause mortality.[1, 2] Prescription of antipsychotics requires caution given their association with a range of serious adverse effects including extra-pyramidal side effects with the first generation agents, weight gain and lipid/glucose dysregulation with second generation agents. International guidelines stress the importance of regular monitoring of BMI, glucose and lipids in people receiving repeat prescriptions of these agents, given their propensity to affect these parameters.

National guidelines do recommend antipsychotics for the relatively rare condition of psychotic depression and as a possible intervention for treatment resistant cases of severe depression[3] and OCD[4] and in clinical practice these agents may be prescribed “off-label” for patients who do not have a diagnosis of SMI in their clinical notes. They are sometimes used to augment antidepressants in complex or treatment resistant cases of OCD, anxiety and personality disorders. Although antipsychotics may be used in sleep disorders, treatment guidelines do not recommend using such agents on account of their side effect profiles.[5] Guidelines for borderline personality disorder recommend that short term treatment with antipsychotics (up to a week) may be beneficial in crisis or when comorbid psychotic symptoms occur.[6]

Our aim was to examine the recorded indication for antipsychotic prescriptions in United Kingdom primary care. Further we sought to describe the prescribing pattern by diagnostic group.

## Objectives

1. To examine the likely indication for antipsychotic prescribing in UK primary care.
2. To describe prescribing patterns (duration of treatment and average dose) in three broad groups of people who may receive antipsychotics in primary care:
  - i) Those with diagnoses of an SMI (psychosis or bipolar disorder)
  - ii) Those without a diagnosis of SMI but with a mental health diagnosis such as depression, personality disorder or dementia
  - iii) Individuals with none of these conditions in their general practice notes.

## METHOD

### Study design

Cohort study

### Setting

Primary care in the UK

### Data source

We used data from The Health Improvement Network (THIN),[7] a UK primary care database like CPRD[8] which is based on data from routine clinical care and administration. THIN data like CPRD are derived from practices using Vision software and are available anonymously for research.[9] The database includes demographics and Townsend deprivation quintile. The latter is a validated measure of social deprivation, attributed to the patient's geographical postcode, covering a small area of approximately 150 households.[10] Data such as diagnoses and symptoms are entered as Read codes, a hierarchical classification system.[11] The database also includes records of all prescriptions issued and these are linked to the British National Formulary (BNF).[12] The exception to this is Clozapine, which is almost exclusively prescribed and monitored in hospital outpatient

1  
2  
3 clinics. Prescribing is well recorded in THIN because all prescriptions from general practice are  
4 generated via the computerised system. This information produces a longitudinal record for each  
5 individual in the database. Ninety eight percent of the UK population is registered with a general  
6 practice;<sup>[9]</sup> THIN is representative of the general UK population in terms of their demographic  
7 characteristics<sup>[13]</sup> and practices are geographically spread across the UK. At the time of this study  
8 the full database included almost 10 million patients. For quality purposes data were only extracted  
9 after the date at which there was evidence that general practices were using their computer system  
10 fully (acceptable computer use (ACU) dates<sup>[14]</sup>) and mortality were adequately recorded  
11 (Acceptable Mortality Rate (AMR)<sup>[15]</sup>).

### 22 23 24 **Participants**

25 We initially included all people who received at least one prescription for any antipsychotic  
26 medication after 01/01/2007 or after the date at which practice met quality standards. Follow-up  
27 ended at the earliest of date of 1) death, 2) transferring out of the practice, 3) last data collection  
28 from the practice, 4) reaching the age of 100 years or 5) 31/12/2011. The start of follow up for each  
29 individual was the date of the first antipsychotic prescription during these periods. We excluded  
30 individuals with less than 6 months of follow-up data.

### 31 32 33 **Antipsychotic data**

34 First we determined overall rates of prescribing of all first generation and second generation  
35 antipsychotics in UK primary care (see Appendix 2 for the full list of first and second generation  
36 antipsychotics). Subsequently we focussed on the three most commonly prescribed first generation  
37 (Haloperidol, Chlorpromazine and Trifluoperazine) and second generation agents (Olanzapine,  
38 Quetiapine and Risperidone). We determined the average daily dose prescribed for each  
39 antipsychotic during the follow-up period, as well as the length of time for which antipsychotics  
40 were prescribed. We did this by using data on the strength of the antipsychotics prescribed, the  
41

1  
2  
3 total amount prescribed and the dose per day. From this information it was possible to calculate the  
4  
5 total possible mg per prescription. These were cumulated for all prescriptions of a given  
6  
7 antipsychotic. The amount of time on a given antipsychotic was calculated using the first and last  
8  
9 prescription dates, adding on the number of days the final prescription was expected to last if it was  
10  
11 taken as directed. We excluded total daily doses which were implausibly high for community  
12  
13 prescribing of antipsychotics, since these were likely to represent erroneous entries. We defined  
14  
15 this upper threshold at twice the maximum recommended daily dose in the BNF,[12] namely over  
16  
17 60mg for haloperidol, over 2000mg for chlorpromazine, over 120mg for trifluoperazine, over 40mg  
18  
19 for olanzapine, over 1500 for quetiapine and over 32 mg for risperidone. Relatively few (221)  
20  
21 prescriptions were excluded for this reason.  
22  
23

### 24 25 26 **Mental health conditions**

27  
28 We defined severe mental illness as schizophrenia-like disorders, bipolar affective disorders and  
29  
30 other non-organic psychosis such as delusional disorder, “psychoses not otherwise specified” and  
31  
32 severe depression with psychoses (Appendix 1). Read codes for SMI diagnoses have been previously  
33  
34 been validated.[16] We identified an additional category for people who were included on the  
35  
36 practice’s SMI register without having a Read code for the SMI diagnoses above (a GP SMI register is  
37  
38 required as part of the GP contract in the UK since 2004). Hardoon et al[17] determined that the  
39  
40 prevalence of SMI in THIN is similar to that of epidemiological studies.  
41  
42  
43  
44  
45

46  
47 Next we identified common mental health conditions for which antipsychotics might be prescribed  
48  
49 off-label, using diagnostic Read code lists compiled by two clinical academics - a GP and a  
50  
51 psychiatrist.[18] These non-SMI conditions comprised depression, anxiety disorders, sleep disorders  
52  
53 (insomnia, non-specific sleep disorders, apnoea, hypersomnia), dementia, attention deficit and  
54  
55 hyperactivity disorder, personality disorders, post-traumatic stress disorder and obsessive  
56  
57  
58  
59  
60



1  
2  
3 compulsive disorder. These have not been validated; however, we have reported on trends in  
4  
5 anxiety and depression symptom and diagnosis recording in THIN.[19, 20]  
6  
7

8  
9 We created a diagnostic hierarchy for people with more than one mental health diagnosis in their  
10  
11 clinical notes. Hence, if a patient ever had an SMI diagnosis we considered this as the indication for  
12  
13 antipsychotics. However, if there were no SMI diagnosis, then all non-SMI diagnoses were extracted  
14  
15 and included in this study. In other words the non-SMI diagnoses were not mutually exclusive so a  
16  
17 person could count as both a case of anxiety and a case of obsessive compulsive disorder.  
18  
19

### 20 21 22 **Ethical approval**

23  
24 THIN has overall ethical approval from the South East Multicentre Research Ethics Committee  
25  
26 (reference number: 07/H1102/103) and further study specific approval for this study was gained as  
27  
28 part of an additional MREC approval from the London Research Ethics Committee. Reference  
29  
30 number: 09/H0718/11.  
31  
32

### 33 34 35 **Statistical analysis**

36  
37 We calculated rates of prescribing any antipsychotics, per 100,000 person years at risk (PYAR). We  
38  
39 then calculated rates of any first or second generation antipsychotics then we determined rates of  
40  
41 prescribing individual agents for the three most commonly prescribed first and second generation  
42  
43 antipsychotic agents. Multivariable Poisson regression was used to determine associations between  
44  
45 sex, age group, Townsend deprivation quintile, calendar year and 1) overall antipsychotic  
46  
47 prescribing, 2) All first and second generation antipsychotic agents and 3) The six most commonly  
48  
49 prescribed individual antipsychotics. For these analyses, we defined the population at risk as the  
50  
51 total population registered with the general practices in the period 2007-2011.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 We calculated frequencies (%) for each indication (diagnosis) for each of the six most commonly  
4 prescribed antipsychotics. We also calculated the median (interquartile range (IQR)) daily dose in  
5 milligrams and length of time prescribed a given antipsychotic within three groups: The SMI  
6 (psychosis/bipolar) subgroup, the group with non-SMI diagnoses and the group with no record of  
7 these diagnoses.  
8  
9  
10  
11  
12

13  
14  
15  
16 Analyses were carried out using Stata version 13.[21]  
17  
18  
19

## 20 RESULTS

21  
22 We identified 47,724 eligible individuals who were prescribed antipsychotic medications. Of these  
23 13,941 were solely prescribed first generation antipsychotics, 27,966 solely second generation  
24 antipsychotics and 5817 received both classes of agent during their follow-up period (Figure 1). The  
25 median length of follow-up for people receiving any antipsychotic was 2.4 years (IQR 1.3, 4.1). The  
26 length of follow-up was slightly longer for those receiving both first and second generation  
27 antipsychotic (3.0 years; IQR 1.7, 4.7).  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

[Figure 1 here]

### 42 Rates of antipsychotic prescribing by socio-demographic characteristics and over time

43  
44 Overall 1% of individuals received an antipsychotic at some time over the study period. For women  
45 the rate of prescribing any antipsychotic was 699 per 100,000 PYAR (95% CI 693, 705) compared to  
46 612 per 100,000 PYAR (95% CI 607, 617) for men. Individuals aged above 80 years were more likely  
47 to receive antipsychotics (Incidence rate ratio (IRR) 2.234; 95% CI 2.222, 2.246 compared with those  
48 aged 40-49 years). In contrast, those under the age of 18 and those aged 18-29 were much less  
49 likely to receive antipsychotics (Table 1). Those living in the most deprived areas were more than  
50 three times as likely to receive antipsychotics compared to those in the least deprived areas (IRR  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

3.587 (95% CI 3.587, 3.606) (Table 1). These patterns were also observed when the subgroups prescribed first generation and second generation of antipsychotic were examined separately (Table 1).

For peer review only

Table 1: Rates of antipsychotic prescribing by class of antipsychotic, age gender and social deprivation

	Any antipsychotic				Any first generation antipsychotic				Any second generation antipsychotic				First and second generation antipsychotics			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	612	(607, 617)	1.000		197	(194, 200)	1.000		458	(454, 462)	1.000		43	(41, 44)	1.000	
Female	699	(693, 705)	1.092	(1.088, 1.095)	256	(253, 259)	1.204	(1.196, 1.211)	489	(484, 493)	1.050	(1.046, 1.054)	46	(44, 47)	1.010	(1.096, 1.103)
Under 18	63	(61, 66)	0.044	(0.044, 0.045)	5	(4, 5)	0.009	(0.008, 0.009)	59	(57, 62)	0.058	(0.057, 0.059)	0.6	(0.4, 0.9)	0.026	(0.026, 0.027)
18-29	459	(451, 467)	0.351	(0.349, 0.353)	111	(107, 115)	0.223	(0.220, 0.227)	376	(369, 383)	0.401	(0.398, 0.404)	28	(26, 30)	0.348	(0.346, 0.351)
30-39	817	(806, 828)	0.804	(0.799, 0.808)	238	(232, 244)	0.643	(0.636, 0.650)	638	(628, 648)	0.867	(0.861, 0.872)	58	(56, 62)	0.803	(0.799, 0.807)
40-49	852	(842, 863)	1.000		289	(283, 295)	1.000		628	(619, 637)	1.000		64	(62, 67)	1.000	
50-59	712	(701, 723)	0.872	(0.867, 0.877)	283	(276, 290)	1.045	(1.035, 1.056)	483	(474, 492)	0.804	(0.799, 0.809)	54	(51, 57)	0.872	(0.867, 0.877)
60-69	642	(631, 653)	0.824	(0.819, 0.829)	281	(274, 289)	1.039	(1.029, 1.050)	406	(398, 415)	0.740	(0.735, 0.745)	46	(43, 49)	0.824	(0.819, 0.829)
70-79	842	(827, 857)	0.973	(0.967, 0.980)	350	(341, 360)	1.192	(1.179, 1.205)	546	(534, 559)	0.888	(0.881, 0.894)	54	(51, 58)	0.971	(0.965, 0.977)
80+	2,201	(2,170, 2,231)	2.234	(2.222, 2.246)	793	(775, 811)	2.358	(2.334, 2.382)	1,529	(1,504, 1,555)	2.185	(2.171, 2.199)	121	(114, 129)	2.221	(2.209, 2.234)
Townsend																
Least deprived	403	(398, 409)	1.000		138	(135, 142)	1.000		291	(286, 296)	1.000		26	(24, 27)	1.000	
2	499	(492, 506)	1.211	(1.203, 1.218)	180	(176, 184)	1.251	(1.237, 1.265)	351	(345, 357)	1.194	(1.186, 1.203)	33	(31, 35)	1.214	(1.207, 1.222)
3	645	(637, 653)	1.707	(1.697, 1.716)	223	(218, 228)	1.764	(1.745, 1.782)	465	(458, 472)	1.683	(1.672, 1.695)	43	(41, 45)	1.714	(1.705, 1.724)
4	844	(834, 854)	2.457	(2.443, 2.470)	295	(290, 301)	2.516	(2.491, 2.542)	608	(600, 616)	2.432	(2.416, 2.448)	59	(57, 62)	2.476	(2.463, 2.489)
Most deprived	1,158	(1,145, 1,172)	3.587	(3.567, 3.606)	386	(378, 394)	3.649	(3.612, 3.686)	853	(841, 865)	3.560	(3.537, 3.583)	80	(76, 84)	3.613	(3.593, 3.633)
Missing	806	(781, 830)	2.282	(2.259, 2.305)	270	(256, 284)	2.360	(2.315, 2.406)	586	(566, 608)	2.250	(2.223, 2.277)	51	(45, 57)	2.187	(2.165, 2.210)
Year																
2007	591	(584, 599)	1.000		236	(231, 241)	1.000		399	(393, 405)	1.000		44	(42, 46)	1.000	
2008	654	(646, 663)	1.075	(1.069, 1.080)	243	(238, 248)	0.990	(0.981, 1.000)	456	(449, 463)	1.118	(1.111, 1.125)	45	(43, 47)	1.075	(1.070, 1.081)
2009	679	(670, 687)	1.110	(1.104, 1.115)	237	(232, 242)	0.946	(0.938, 0.955)	487	(480, 494)	1.194	(1.186, 1.201)	45	(43, 47)	1.108	(1.102, 1.114)
2010	718	(710, 727)	1.151	(1.145, 1.157)	227	(222, 232)	0.880	(0.872, 0.888)	536	(529, 543)	1.290	(1.282, 1.298)	44	(42, 47)	1.147	(1.141, 1.153)
2011	637	(629, 646)	1.065	(1.059, 1.071)	189	(184, 193)	0.745	(0.737, 0.752)	492	(484, 499)	1.230	(1.222, 1.238)	43	(41, 45)	1.055	(1.050, 1.061)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

1  
2  
3 The three most commonly prescribed first generation antipsychotics were haloperidol,  
4 chlorpromazine and trifluoperazine; while olanzapine, risperidone and quetiapine were the most  
5 commonly issued second generation agents (Tables 2a and 2b). Rates of prescribing these individual  
6 agents followed similar patterns to the aggregate results in terms of their distributions by age and  
7 deprivation. Haloperidol and trifluoperazine were more commonly prescribed to women, as was  
8 quetiapine, while rates of risperidone and olanzapine prescribing were lower in women. Few under-  
9 18s received antipsychotics, but compared to other agents, risperidone was prescribed far more  
10 commonly to this young age group (Table 2b). Over the five years of the study (2007-2011), rates of  
11 prescribing for each first generation agent decreased while quetiapine prescription rates increased  
12 the most over time. For example, IRR for trifluoperazine in 2011 (reference category is 2007) 0.665  
13 (95% CI 0.645, 0.685) and IRR for quetiapine in 2011 (reference category is 2007) 1.480 (95% CI  
14 1.463, 1.497). There was a smaller increase in rates of prescribing for both risperidone and  
15 olanzapine (Table 2b).  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 2a: Rates of antipsychotic prescribing for the three most commonly prescribed first generation antipsychotics

Characteristic	Haloperidol				Chlorpromazine				Trifluoperazine			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	42	(41, 44)	1.000		51	(50, 53)	1.000		22	(21, 23)	1.000	
Female	55	(54, 57)	1.123	(1.107, 1.138)	52	(50, 53)	1.121	(1.107, 1.135)	36	(35, 38)	1.577	(1.547, 1.607)
Under 18	1	(1, 2)	0.017	(0.015, 0.019)	0.6	(0.4, 0.9)	0.004	(0.003, 0.004)	0.6	(0.4, 0.9)	0.006	(0.005, 0.008)
18-29	16	(15, 18)	0.204	(0.196, 0.213)	33	(31, 35)	0.231	(0.225, 0.237)	13	(12, 15)	0.195	(0.186, 0.205)
30-39	35	(33, 38)	0.659	(0.641, 0.678)	72	(68, 75)	0.640	(0.628, 0.653)	30	(28, 32)	0.634	(0.613, 0.655)
40-49	42	(40, 44)	1.000		85	(82, 89)	1.000		37	(35, 40)	1.000	
50-59	44	(42, 47)	1.085	(1.058, 1.112)	77	(74, 81)	0.992	(0.974, 1.010)	38	(35, 40)	1.046	(1.015, 1.078)
60-69	51	(48, 54)	1.175	(1.145, 1.205)	63	(60, 67)	0.822	(0.806, 0.839)	46	(43, 49)	1.378	(1.339, 1.419)
70-79	98	(93, 104)	2.123	(2.073, 2.175)	54	(50, 58)	0.613	(0.598, 0.629)	54	(50, 58)	1.739	(1.687, 1.792)
80+	330	(319, 342)	5.833	(5.710, 5.958)	58	(53, 63)	0.595	(0.578, 0.614)	72	(67, 78)	1.868	(1.808, 1.931)
Townsend												
Least deprived	32	(30, 33)	1.000		24	(22, 25)	1.000		19	(18, 21)	1.000	
2	48	(46, 50)	1.499	(1.464, 1.534)	33	(32, 35)	1.225	(1.194, 1.257)	22	(20, 23)	1.185	(1.146, 1.225)
3	53	(51, 56)	1.914	(1.871, 1.957)	46	(44, 48)	2.117	(2.068, 2.167)	28	(27, 30)	1.809	(1.754, 1.867)
4	60	(58, 63)	2.360	(2.307, 2.413)	68	(65, 71)	3.131	(3.062, 3.202)	39	(37, 41)	2.839	(2.756, 2.925)
Most deprived	62	(58, 65)	2.666	(2.603, 2.731)	116	(112, 120)	5.743	(5.619, 5.870)	50	(47, 53)	3.703	(3.591, 3.818)
Missing	49	(43, 56)	2.315	(2.217, 2.417)	95	(86, 103)	4.103	(3.961, 4.250)	30	(26, 35)	2.113	(1.987, 2.246)
Year												
2007	51	(49, 54)	1.000		58	(55, 60)	1.000		33	(31, 35)	1.000	
2008	54	(52, 56)	1.019	(0.998, 1.039)	56	(54, 59)	0.973	(0.955, 0.992)	31	(29, 32)	0.941	(0.916, 0.967)
2009	52	(50, 54)	0.955	(0.936, 0.974)	53	(51, 56)	0.899	(0.882, 0.916)	29	(27, 31)	0.899	(0.874, 0.924)
2010	48	(46, 50)	0.822	(0.805, 0.840)	47	(45, 49)	0.824	(0.807, 0.840)	30	(28, 32)	0.901	(0.876, 0.926)
2011	39	(37, 41)	0.684	(0.669, 0.700)	44	(41, 46)	0.751	(0.736, 0.766)	24	(22, 26)	0.665	(0.645, 0.685)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

Table 2b: Rates of antipsychotic prescribing for the three most commonly prescribed second generation antipsychotics

Characteristic	Olanzapine				Quetiapine				Risperidone			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	168	(166, 171)	1.000		120	(117, 122)	1.000		137	(134, 139)	1.000	
Female	139	(136, 141)	0.835	(0.830, 0.841)	197	(194, 199)	1.542	(1.531, 1.553)	115	(113, 117)	0.854	(0.847, 0.)
Under 18	3	(2, 4)	0.008	(0.008, 0.009)	3	(3, 4)	0.012	(0.012, 0.013)	50	(47, 52)	0.196	(0.193, 0.200)
18-29	133	(129, 137)	0.349	(0.345, 0.354)	106	(102, 110)	0.418	(0.412, 0.424)	116	(112, 121)	0.484	(0.477, 0.491)
30-39	243	(237, 249)	0.822	(0.813, 0.830)	192	(186, 197)	0.941	(0.929, 0.952)	155	(150, 160)	0.810	(0.799, 0.820)
40-49	249	(243, 255)	1.000		175	(170, 180)	1.000		158	(154, 163)	1.000	
50-59	192	(187, 198)	0.868	(0.859, 0.877)	128	(124, 133)	0.730	(0.720, 0.740)	131	(127, 136)	0.845	(0.834, 0.857)
60-69	154	(149, 160)	0.781	(0.772, 0.790)	109	(105, 114)	0.670	(0.660, 0.679)	116	(111, 120)	0.819	(0.808, 0.831)
70-79	140	(134, 146)	0.673	(0.663, 0.683)	226	(219, 235)	1.263	(1.247, 1.280)	124	(118, 130)	0.772	(0.760, 0.785)
80+	195	(186, 204)	0.841	(0.829, 0.854)	891	(871, 910)	4.473	(4.427, 4.520)	289	(278, 300)	1.629	(1.606, 1.653)
Townsend												
Least deprived	81	(78, 84)	1.000		111	(108, 114)	1.000		79	(76, 81)	1.000	
2	101	(98, 104)	1.314	(1.296, 1.332)	130	(126, 134)	1.113	(1.100, 1.126)	93	(90, 96)	1.157	(1.141, 1.174)
3	140	(137, 144)	1.898	(1.873, 1.922)	164	(160, 168)	1.497	(1.480, 1.514)	121	(117, 124)	1.614	(1.593, 1.636)
4	211	(206, 216)	3.122	(3.084, 3.160)	192	(187, 196)	1.963	(1.941, 1.984)	163	(159, 168)	2.297	(2.267, 2.327)
Most deprived	320	(313, 328)	4.956	(4.897, 5.016)	239	(232, 245)	2.663	(2.633, 2.693)	227	(221, 233)	3.243	(3.201, 3.285)
Missing	200	(188, 212)	2.821	(2.761, 2.882)	196	(185, 209)	1.974	(1.933, 2.016)	148	(138, 159)	1.981	(1.933, 2.031)
Year												
2007	140	(137, 144)	1.000		117	(113, 120)	1.000		118	(114, 121)	1.000	
2008	153	(149, 157)	1.050	(1.039, 1.062)	144	(140, 148)	1.224	(1.209, 1.238)	124	(121, 128)	1.050	(1.037, 1.064)
2009	157	(153, 161)	1.088	(1.076, 1.100)	165	(161, 170)	1.360	(1.344, 1.376)	124	(120, 128)	1.053	(1.040, 1.066)
2010	166	(162, 170)	1.145	(1.133, 1.158)	190	(186, 195)	1.523	(1.506, 1.541)	138	(134, 142)	1.103	(1.089, 1.117)
2011	151	(147, 155)	1.077	(1.065, 1.089)	177	(173, 181)	1.480	(1.463, 1.497)	125	(121, 129)	1.040	(1.026, 1.053)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

### Records of mental health conditions in people prescribed antipsychotics

For people prescribed the three most common first generation antipsychotics, the proportion with a Read code for SMI (psychotic or bipolar disorders) varied between 27% (n=1331) for haloperidol and 35% (n=1545) for chlorpromazine (Table 3). The most common diagnosis was schizophrenia and related conditions. For second generation antipsychotics, only 36% (n=4824) of those prescribed quetiapine had an SMI record, compared to 46% (n=4597) of those receiving risperidone and 62% (n=7094) of those receiving olanzapine (Table 3). More than half of people receiving first generation antipsychotics had no SMI diagnosis recorded in their notes, but did have a code for one of the non-SMI mental health conditions. The most common conditions were anxiety, depression and sleep disorders. Almost a third of people receiving haloperidol had a record of dementia. For second generation agents, the proportions with non-SMI diagnoses were similar, although the number of people with a record of dementia was highest for quetiapine (26% of prescriptions). Between 12 and 17% of people prescribed first generation agents had no record of SMI or of any non-SMI mental health diagnosis.



Table 3: Diagnosis by the three most commonly prescribed first and second generation antipsychotics 2007-2011

Diagnosis	Haloperidol (N=4913)		Chlorpromazine (N=4404)		Trifluoperazine (N=2633)		Olanzapine (N=11502)		Quetiapine (N=13326)		Risperidone (N=9956)	
	n	%	n	%	n	%	n	%	n	%	n	%
<b>SMI*</b>												
Any SMI diagnosis	1331	27	1545	35	783	30	7094	62	4824	36	4597	46
Schizophrenia	620	13	633	14	359	14	3060	27	1489	11	2143	22
Bipolar disorder	298	6	343	8	119	5	1655	14	1689	13	726	7
Other SMI	267	5	334	8	203	8	1898	17	1163	9	1291	13
On SMI register only	146	3	235	5	102	4	481	4	483	4	437	4
<b>Non-SMI*</b>												
Any non-SMI diagnosis	2762	56	2241	51	1529	58	3753	33	7623	57	4085	41
ADHD	36	0.7	33	0.7	10	0.4	75	0.7	77	0.6	538	5
Anxiety	783	16	1124	26	909	35	1779	15	2669	20	1391	14
Depression	1330	27	1748	40	1142	43	2964	26	4648	35	2204	22
Dementia	1521	31	183	4	157	6	466	4	3514	26	1211	12
OCD	40	0.8	93	2	47	2	216	2	250	2	221	2
PD	136	3	294	7	122	4	525	5	705	5	349	4
PTSD	37	0.8	97	2	29	1	197	2	210	2	94	0.9
Sleep disorders	761	15	815	19	511	19	1124	10	1926	14	1078	11
None of the above*	820	17	618	14	321	12	655	6	879	7	1274	13

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.

1  
2  
3  
4  
5 The median daily dose for antipsychotics was higher in those who did have a SMI diagnosis, and  
6 highest amongst those with records of schizophrenia (Table 4). Within the non-SMI groups, median  
7 daily doses were similar although the highest doses were observed in people with a record of a sleep  
8 disorder or personality disorder. The longest durations of antipsychotic treatment were generally  
9 observed for people with a diagnosis of schizophrenia or in those who were included on the SMI  
10 register in general practice (Supplementary Table 1). Within the non-SMI group, duration of  
11 treatment showed little variation between diagnoses, although the median length of treatment  
12 seemed longest in people with dementia or ADHD.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 4: Median (IQR) daily dose for the three most prescribed first and second generation antipsychotics by indication

Diagnosis	Haloperidol		Chlorpromazine		Trifluoperazine		Olanzapine		Quetiapine		Risperidone	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
<b>SMI*</b>												
Schizophrenia	7	(3, 14)	103	(55, 208)	10	(5, 18)	12	(9, 19)	326	(171, 546)	4	(2, 6)
Bipolar disorder	5	(2, 11)	93	(50, 174)	5	(2, 10)	10	(6, 15)	239	(100, 413)	2	(1, 4)
Other SMI	3	(1, 6)	88	(50, 171)	6	(2, 12)	10	(6, 15)	174	(70, 337)	2	(1, 4)
On SMI register only	4	(1, 8)	91	(51, 159)	4	(2, 8)	9	(5, 12)	119	(54, 254)	2	(1, 4)
<b>Non-SMI*</b>												
Any non-SMI diagnosis	2	(1, 3)	62	(38, 109)	3	(2, 5)	6	(4, 10)	66	(38, 132)	1	(1, 2)
ADHD	2	(1, 5)	82	(50, 184)	3	(2, 5)	7	(5, 11)	100	(50, 210)	1	(1, 2)
Anxiety	1	(1, 3)	61	(36, 108)	3	(2, 4)	6	(4, 10)	80	(46, 177)	1	(1, 3)
Depression	2	(1, 3)	58	(37, 102)	3	(2, 5)	6	(4, 10)	79	(43, 167)	1	(1, 2)
Dementia	1	(1, 3)	75	(39, 170)	3	(2, 7)	5	(3, 8)	52	(30, 89)	1	(1, 2)
OCD	2	(1, 5)	75	(42, 118)	3	(2, 5)	5	(4, 10)	95	(50, 205)	1	(1, 2)
PD	2	(1, 6)	82	(48, 150)	4	(2, 7)	8	(5, 12)	141	(58, 292)	2	(1, 3)
PTSD	2	(1, 3)	64	(38, 138)	2	(2, 5)	6	(4, 10)	100	(54, 232)	2	(1, 3)
Sleep disorders	3	(1, 8)	79	(49, 151)	4	(2, 11)	10	(6, 15)	155	(58, 340)	2	(1, 4)
None of the above*	2	(1, 4)	70	(38, 128)	2	(1, 5)	7	(4, 11)	56	(30, 119)	2	(1, 3)

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.

## DISCUSSION

In this study of antipsychotic prescribing in a large primary care database representative of the UK, around half of prescriptions for first and second generation antipsychotics are issued to people who have no record of severe mental illness, defined as schizophrenia, bipolar affective disorder or other non-organic psychosis in their clinical notes. Furthermore, they are more likely to be prescribed to older people who may be more sensitive to adverse effects such as movement disorders and cardio-metabolic risk. When antipsychotics are prescribed to people without SMI, they tend to be given in lower doses and for slightly shorter periods, with the exception people with ADHD and dementia who receive these drugs for relatively long periods.

Other studies on antipsychotic prescribing relate to an earlier time period prior to the introduction of antipsychotic guidelines in the UK.[22, 23] The pattern of prescribing since then has changed over time[24], with approximately two thirds of prescriptions in the current study being for second generation antipsychotics.

For first generation agents, the most common “non-SMI” mental health diagnoses we identified were anxiety, depression, sleep disorders, and dementia (especially for haloperidol). For second generation agents, the same mental health diagnoses were common including dementia, despite the fact that second generation antipsychotics are not recommended in people with dementia due to the risk of stroke and other-cause mortality.[1, 2] Reducing the potential harm associated with antipsychotics in dementia has been emphasised as a priority by organisations such as Department of Health in England and the US Food and Drug Administration.[25, 26] Our findings suggest that further effort is required to decrease primary care antipsychotic prescriptions in dementia and assessing time trends in antipsychotic prescribing in this group is an important area for future research.

1  
2  
3 Median daily doses and duration of treatment with antipsychotics tended to be slightly greater in  
4  
5 people with SMI diagnoses (especially schizophrenia); however people with depression, anxiety,  
6  
7 personality disorders and sleep disorders still received substantial doses of these agents, for  
8  
9 relatively long periods of time. For instance the median daily dose of olanzapine prescribed to  
10  
11 people with sleep disorders was 10mg per day; the same daily dose as people with a diagnosis of  
12  
13 bipolar disorder and only slightly less than the average dose of 12mg per day prescribed to people  
14  
15 with schizophrenia (Table 4). Within the non-SMI group, median doses of risperidone and  
16  
17 quetiapine were also highest in those with sleep disorders, post-traumatic stress disorder and  
18  
19 personality disorder. Whilst median dose is a crude method of quantifying the amount prescribed  
20  
21 for each indication explored in this paper, it does allow us to make comparisons between these  
22  
23 diagnoses.  
24  
25  
26  
27  
28

29 There are a number of possible explanations for the high rates of antipsychotic prescribing to people  
30  
31 without a psychosis diagnosis. Firstly, it may be that the clinician prescribes antipsychotics because  
32  
33 the person does have psychotic symptoms, but the clinician does not assign a label of schizophrenia  
34  
35 or other psychosis, either due to patient preference or to avoid the associated stigma with such  
36  
37 labels. However, this would suggest that there are large numbers of people with unrecorded  
38  
39 psychosis and/ or bipolar disorder in primary care. This is not consistent with other research in UK  
40  
41 primary care databases which has shown that rates of schizophrenia and bipolar disorder recording  
42  
43 in the database are similar to other epidemiological studies.[17] Therefore it seems unlikely that  
44  
45 large numbers of people in primary care have psychosis without a corresponding record.  
46  
47  
48  
49

50 Secondly, it is possible that in real life practice antipsychotics are prescribed quite commonly to  
51  
52 people with problems related to depression, anxiety, sleep, dementia and other conditions, despite  
53  
54 guidelines recommending caution and only suggesting this as a strategy in treatment unresponsive  
55  
56 cases.[3, 6] It maybe that clinicians and/or mental health professionals quite frequently add  
57  
58  
59  
60

1  
2  
3 antipsychotics to the treatment plan for people with non-psychotic disorders, either for agitation,  
4  
5 poor sleep, anxiety or due to their general reputation as tranquilising medications. Since there were  
6  
7 not major differences in the median doses and duration of treatment according to likely indication,  
8  
9 these patterns of prescribing warrant some attention in terms of monitoring side effects particularly  
10  
11 weight gain, extra-pyramidal side effects and metabolic impacts such as hyperprolactinaemia,  
12  
13 glucose dysregulation and effects on lipid profiles. Current UK policy only recommends physical  
14  
15 monitoring for people who the general practice includes on its SMI register. It may be that this  
16  
17 recommendation should be extended to all people prescribed antipsychotics in primary care.  
18  
19

### 20 21 22 **Strengths and limitations**

23  
24 Primary care databases allow us to study large representative samples of patients in general practice  
25  
26 across the UK. THIN has a good record of prescriptions issued and comparison with dispensing data  
27  
28 suggests that the majority of THIN prescriptions issued are collected[27] but of course this may not  
29  
30 mean patients have been actually taking the medication. Primary care diagnoses of SMI have been  
31  
32 validated,[16] however this is not the case for some other conditions we explored such as ADHD and  
33  
34 OCD.  
35  
36

37  
38  
39 Research with routine clinical data has its limitations, for instance we could not perform more  
40  
41 detailed assessment of patient characteristics and preferences which may influence treatment  
42  
43 decisions. For non-SMI diagnoses such as depression and anxiety, we extracted all diagnoses which  
44  
45 had been entered at any time. We did this because GPs do not routinely re-enter diagnoses at each  
46  
47 subsequent appointments and we wanted to capture all relevant information regarding possible  
48  
49 indication. A limitation of this method, and of the database, is that we cannot be certain that the  
50  
51 decision to prescribe was temporally related to the mental health condition entered at another time.  
52  
53 However, this method does give an indication of the long term clinical presentation of people  
54  
55 without an SMI Read code who are prescribed antipsychotics. It would be useful to explore the  
56  
57  
58  
59  
60

1  
2  
3 reasons underpinning these high rates of prescribing to groups not traditionally thought eligible for  
4  
5 antipsychotic treatment. This might require primary research studies interviewing clinicians and  
6  
7 reviewing individual patients. However further database work could explore symptoms associated  
8  
9 with these antipsychotic prescriptions, and the treatment decisions pre-dating the choice of an  
10  
11 antipsychotic agent. Also, the same databases could be used to assess how frequently  
12  
13 cardiovascular risk factors are measured in this population, especially body mass index, cholesterol  
14  
15 and HDL cholesterol as well as some indication of glucose regulation such as HBA1c, random or  
16  
17 fasting glucose.  
18  
19

20  
21  
22 We need to know more about co-prescribing in the people without a diagnosis of psychosis or  
23  
24 bipolar disorder for instance benzodiazepines and mood stabilisers. We also need to quantify the  
25  
26 degree of benefit and harm that may be associated with using such treatments. To what degree do  
27  
28 they cause physical and/ or mental health problems for the recipients, and to what extent do they  
29  
30 lead to symptom remission? A meta-analysis of antipsychotics drugs in major depressive disorder  
31  
32 found that although these agents may improve depression symptoms, they have no impact on  
33  
34 functioning or quality of life.[28] The few existing randomised controlled trials involving people with  
35  
36 personality disorder have shown little benefit of antipsychotics over placebo.[6, 29]  
37  
38  
39

40  
41  
42 Finally it is important to explore whether these agents are discontinued following amelioration of  
43  
44 any mental health problem for which they are chosen, and to assess the risks and benefits of  
45  
46 stopping such agents in different diagnostic groups.  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Figure legend  
4

5 Figure 1: Flow of individuals through the study  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



**Conflict of Interest**

The authors have no conflicts of interest to declare.

**Funding**

This work was funded by the NIHR School for Primary Care Research. Grant number 17321

**Authorship**

DPJO, KW, IP and IN had the original idea for the study. All authors developed the method, analysed and interpreted the results and wrote the manuscript. LM performed the analysis.

**Data sharing statement**

No additional data are available

I Dr Louise Marston the Corresponding Author of this article contained within the original manuscript which includes any diagrams & photographs, other illustrative material, video, film or any other material howsoever submitted by the Contributor(s) at any time and related to the Contribution ("the Contribution") have the right to grant on behalf of all authors and do grant on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licensees, to permit this Contribution (if accepted) to be published in BMJ Open and any other BMJ Group products and to exploit all subsidiary rights, as set out in the licence at:

[http://group.bmj.com/products/journals/instructions-for-authors/BMJOpen\\_licence.pdf](http://group.bmj.com/products/journals/instructions-for-authors/BMJOpen_licence.pdf)

## REFERENCES

- 1 Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934–43.
- 2 Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study (electronic article). *BMJ* 2008;
- 3 National Institute for Health and Care Excellence Depression: the treatment and management of depression in adults (update). CG90 2009a (<http://guidance.nice.org.uk/CG90>) (accessed May 2014)
- 4 Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology *J Psychopharmacol* 2005;19:567-96.
- 5 Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders *J Psychopharmacol* 2010;24:1577-1600.
- 6 National Institute for Health and Care Excellence Borderline personality disorder: Treatment and management. CG78 2009b (<http://www.nice.org.uk/CG78>) (accessed May 2014)
- 7 The Health Improvement Network The Health Improvement Network. London: The Health Improvement Network; 2014 (<http://csdmruk.cegedim.com/>) (Accessed May 2014).

1  
2  
3 8 CPRD Clinical Practice Research Datalink (CPRD) website. Crown Copyright 2014.  
4  
5 (<http://www.cprd.com/intro.asp>) (accessed October 2014)  
6  
7

8  
9 9 Lis Y, Mann RD The VAMP Research multi-purpose database in the U.K. *J Clin Epidemiol*  
10  
11 1995;431-j 43  
12

13  
14  
15  
16 10 Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North.  
17  
18 London: Croom Helm, 1988.  
19

20  
21  
22 11 Booth N What are the Read Codes? *Health Libr Rev* 1994;177-82  
23

24  
25  
26 12 Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and  
27  
28 Pharmaceutical Press 2014 (<http://www.medicinescomplete.com>) (Accessed may 2014)  
29

30  
31  
32 13 Blak BT, Thompson M, Dattani H, et al Generalisability of The Health Improvement Network  
33  
34 (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*  
35  
36 2011;251-55  
37  
38

39  
40  
41 14 Horsfall L, Walters K, Petersen I. Identifying periods of acceptable computer usage in primary  
42  
43 care research databases. *Pharmacoepidemiol Drug Saf* 2013;64-9.  
44  
45

46  
47  
48 15 Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality  
49  
50 reporting for research using automated data from primary care. *Pharmacoepidem Drug Saf* 2009;76-  
51  
52 83  
53  
54

- 1  
2  
3 16 Nazareth I, King M, Haines A et al. Accuracy of diagnosis of psychosis on general practice  
4 computer system *BMJ* 1993;307(6895):32-4  
5  
6  
7  
8  
9  
10 17 Haroon S, Hayes JF, Blackburn R et al. Recording of severe mental illness in United Kingdom  
11 primary care, 2000-2010. *PLoS One* 2013;12;8(12):e82365.  
12  
13  
14  
15  
16 18 Dave S, Petersen I. Creating medical and drug code lists to identify cases in primary care  
17 databases. *Pharmacoepidem Drug Saf* 2009;18:704-7.  
18  
19  
20  
21  
22 19 Walters K, Rait G, Griffin M et al. Recent Trends in the Incidence of Anxiety Diagnoses and  
23 Symptoms in Primary Care. *PLoS One* 2012;7(8):e4167  
24  
25  
26  
27  
28  
29 20 Rait G, Walters K, Griffin M et al Recent trends in the incidence of recorded depression and  
30 depressive symptoms in primary care. *Brit J Psychiat* 2009;195:520-524  
31  
32  
33  
34  
35 21 Stata Corporation. *Stata Statistical Software: Release 13*. College Station, TX: Stata  
36 Corporation; 2013  
37  
38  
39  
40  
41  
42 22 Verdoux H, Tournier M, Bégau B. Antipsychotic prescribing trends: a review of pharmaco-  
43 epidemiological studies. *Acta Psychiatr Scand* 2010;121:4–10.  
44  
45  
46  
47  
48 23 Kaye JA, Bradbury BD, Jick H. Changes in antipsychotic drug prescribing by general  
49 practitioners in the United Kingdom from 1991 to 2000: a population-based observational study. *Br J*  
50 *Clin Pharmacol* 2003;56:569–575.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 24 Prah P, Petersen I, Nazareth I, et al National changes in oral antipsychotic treatment for  
4  
5 people with schizophrenia in primary care between 1998 and 2007 in the United Kingdom. .  
6  
7 *Pharmacoepidem Drug Saf* 2012;21:161–169  
8  
9

10  
11 25 Department of Health The use of antipsychotic medication for people with dementia: time  
12  
13 for action. Department of Health. London 2009  
14

15  
16  
17 26 U.S. Food and Drug Administration Public Health Advisory: Deaths with Antipsychotics in  
18  
19 Elderly Patients with Behavioral Disturbances 2005  
20  
21  
22 ([http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm)  
23  
24 [DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm))  
25  
26 (accessed May 2014)  
27  
28  
29

30  
31 27 The NHS Information Centre PaPCS. Prescribing compliance: a review of the proportion of  
32  
33 prescriptions dispensed. 2011 (<http://www.hscic.gov.uk/pubs/presccompliance>) (accessed May  
34  
35 2014)  
36  
37  
38

39  
40 28 Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive Atypical Antipsychotic Treatment  
41  
42 for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes  
43  
44 *PLoS Med* 2013;10(3):e1001403  
45  
46  
47

48  
49 29 Ingenhoven T, Lafay P, Rinne T, et al. Effectiveness of pharmacotherapy for severe  
50  
51 personality disorders: metaanalyses of randomized controlled trials. *J Clin Psychiatry*. 2010;71:14–  
52  
53 25.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Prescribing of antipsychotics in United Kingdom primary care. Cohort study in United Kingdom**  
4  
5 **primary care**  
6  
7  
8

9 Louise Marston<sup>1\*</sup>

10 Irwin Nazareth<sup>1</sup>

11 Irene Petersen<sup>1</sup>

12 Kate Walters<sup>1</sup>

13 David PJ Osborn<sup>2,3</sup>

14  
15  
16  
17  
18 1. Research Department of Primary Care and Population Health, UCL, London UK.

19  
20  
21  
22 2. UCL Division of Psychiatry, UCL, London UK.

23  
24  
25 3. Camden and Islington NHS Foundation Trust, London UK.  
26  
27

28  
29 **\*Corresponding author-**

30 Dr Louise Marston

31 Research Department of Primary Care and Population Health

32 UCL

33 London

34 NW3 2PF

35  
36  
37  
38  
39  
40  
41  
42  
43  
44 Email: [l.marston@ucl.ac.uk](mailto:l.marston@ucl.ac.uk)

45  
46 Telephone: +44 (0) 20 7794 0500 (36768)  
47  
48

49  
50  
51 Keywords: antipsychotic, primary care, schizophrenia, dementia, depression  
52  
53

54  
55 | Word Count: [3326](#)  
56  
57  
58  
59  
60

**Abstract****Objective**

To examine the recorded indication for antipsychotic prescriptions in primary care.

**Design**

Cohort study

**Setting**

Primary Care.

**Participants**

Individuals prescribed antipsychotics between 2007 and 2011.

**Measures**

The proportion of individuals prescribed antipsychotics with a ~~diagnostic record for~~ diagnosis of 1) psychosis and bipolar disorder 2) Other diagnoses including depression, anxiety and dementia and 3) None of these diagnoses.

**Results**

We identified 47,724 individuals prescribed antipsychotic agents. 13,941 received first generation agents and 27,966 received second generation agents. Rates of prescribing were higher in females (incidence rate ratio 1.092 (95% CI 1.088 to 1.095), older people (80+ versus 40–49 IRR 2.234 (2.222, 2.246) and in those from the most deprived areas (most deprived versus least deprived IRR 3.487 (3.567, 3.606). Of those receiving first generation antipsychotics less than 50% had a ~~recorded~~ diagnosis of psychosis/ bipolar disorder. For second generation agents, the numbers ranged from 4824 (36%) for quetiapine to 7094 (62%) for olanzapine. In patients without psychosis/ bipolar ~~records~~, common diagnoses included anxiety, depression, dementia, sleep and personality disorders. For example in risperidone users, 14% had an anxiety code, 22% depression, 12% dementia, 11% sleep disorder and 4% personality disorder. Median daily doses and duration of treatment were greater in those with schizophrenia (eg risperidone median daily dose 4mg; IQR 2, 6: median duration 1.2 years), compared to those with non-psychotic/ bipolar disorders such as depression or

1  
2  
3 anxiety (eg risperidone 1mg; IQR 1, 2: 0.6 years). A relatively large proportion (between 6 and 17%)  
4  
5 of people receiving individual antipsychotics had none of the ~~records~~diagnoses above.  
6

## 7 **Conclusions**

8  
9 In UK primary care, a large proportion of people prescribed antipsychotics have no record of a  
10  
11 psychotic or bipolar disorder. They are often older people, with conditions including dementia, non-  
12  
13 psychotic depression, anxiety and sleep disorders.  
14

## 15 **Article summary**

### 16 **Strengths and limitations of this study**

17  
18 We determined the ~~recorded~~likely indication for antipsychotic prescriptions in a large,  
19  
20 representative sample of people in UK primary care. The data source contained accurate prescribing  
21  
22 information although prescriptions issued in secondary care will not have been captured. Diagnoses  
23  
24 of severe mental illnesses have been validated in primary care. The nature of the data did not allow  
25  
26 us to determine the clinicians' rationale for prescribing antipsychotics to people without psychoses  
27  
28 or bipolar disorder diagnoses.  
29  
30  
31  
32  
33  
34  
35  
36  
37

- 38 • Less than half of people prescribed the most common first generation antipsychotics in UK  
39  
40 primary care have a ~~recorded~~ diagnosis of a psychosis or bipolar disorder.
- 41  
42 • Findings were similar for second generation agents, although 62% of people receiving  
43  
44 olanzapine did have a ~~record~~diagnosis of psychosis or bipolar disorder
- 45  
46 • These agents are more commonly prescribed to older people, despite the propensity of this  
47  
48 age group to develop side effects.
- 49  
50 • Antipsychotics are still commonly prescribed to people with a diagnosis of dementia,  
51  
52 contrary to clinical guidance, and this need further attention in UK primary care.  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- Other commonly ~~recorded~~ diagnoses included depression, anxiety disorders, personality disorders and ADHD, while up to 17% of people receiving antipsychotics had none of the diagnoses we explored.

For peer review only

## BACKGROUND

Antipsychotic medications are the first line pharmacological intervention for severe mental illnesses (SMI) such as schizophrenia and other psychoses. However, they are also increasingly prescribed for treatment of bipolar affective disorder. They are not routinely recommended for other mental health conditions such as depression, sleep disorders or Obsessive Compulsive Disorder (OCD). There is concern about rates of antipsychotic prescribing in dementia since they may be associated with increased rates of strokes and all-cause mortality.[1, 2] Prescription of antipsychotics requires caution given their association with a range of serious adverse effects including extra-pyramidal side effects with the first generation agents, weight gain and lipid/glucose dysregulation with second generation agents. International guidelines stress the importance of regular monitoring of BMI, glucose and lipids in people receiving repeat prescriptions of these agents, given their propensity to affect these parameters.

National guidelines do recommend antipsychotics for the relatively rare condition of psychotic depression and as a possible intervention for treatment resistant cases of severe depression[3] and OCD[4] and in clinical practice these agents may be prescribed “off-label” for patients who do not have a ~~record-diagnosis~~ of SMI in their clinical notes. They are sometimes used to augment antidepressants in complex or treatment resistant cases of OCD, anxiety and personality disorders. Although antipsychotics may be used in sleep disorders, treatment guidelines do not recommend using such agents on account of their side effect profiles.[5] Guidelines for borderline personality disorder recommend that short term treatment with antipsychotics (up to a week) may be beneficial in crisis or when comorbid psychotic symptoms occur.[6]

Our aim was to examine the recorded indication for antipsychotic prescriptions in United Kingdom primary care. Further we sought to describe the prescribing pattern by diagnostic group.

## Objectives

1. To examine the ~~recorded~~likely indication for antipsychotic prescribing in UK primary care.
2. To describe prescribing patterns (duration of treatment and average dose) in three broad groups of people who may receive antipsychotics in primary care:
  - i) Those with diagnoses of an SMI (psychosis or bipolar disorder)
  - ii) Those without a ~~record~~diagnosis of SMI but with a mental health diagnosis such as depression, personality disorder or dementia
  - iii) Individuals with ~~no~~ne record of these conditions in their general practice notes.

## METHOD

### Study design

Cohort study

### Setting

Primary care in the UK

### Data source

We used data from The Health Improvement Network (THIN),<sup>[7]</sup> a UK primary care database [like CPRD<sup>\[8\]</sup>](#) which is based on data from routine clinical care and administration. THIN data [like CPRD](#) are [derived](#) from practices using Vision software and are available anonymously for research.<sup>[89]</sup>

The database includes demographics and Townsend deprivation quintile. The latter is a validated measure of social deprivation, attributed to the patient's geographical postcode, covering a small area of approximately 150 households.<sup>[910]</sup> Data such as diagnoses and symptoms are entered as Read codes, a hierarchical classification system.<sup>[1011]</sup> The database also includes records of all prescriptions issued and these are linked to the British National Formulary (BNF).<sup>[1112]</sup> The exception to this is Clozapine, which is almost exclusively prescribed and monitored in hospital

1  
2  
3 [outpatient clinics](#). Prescribing is well recorded in THIN because all prescriptions [from general](#)  
4 [practice](#) are generated via the computerised system. This information produces a longitudinal  
5 record for each individual in the database. [Ninety eight percent of the UK population is registered](#)  
6 [with a general practice](#);<sup>[9]</sup> THIN is representative of the general UK population in terms of their  
7 demographic characteristics<sup>[1213]</sup> and practices are geographically spread across the UK. At the  
8 time of this study the full database included almost 10 million patients. For quality purposes data  
9 were only extracted after the date at which there was evidence that general practices were using  
10 their computer system fully (acceptable computer use (ACU) dates<sup>[1314]</sup>) and mortality were  
11 adequately recorded (Acceptable Mortality Rate (AMR)<sup>[1415]</sup>).  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

### 25 **Participants**

26 We initially included all people who received at least one prescription for any antipsychotic  
27 medication after 01/01/2007 or after the date at which practice met quality standards. Follow-up  
28 ended at the earliest of date of 1) death, 2) transferring out of the practice, 3) last data collection  
29 from the practice, 4) reaching the age of 100 years or 5) 31/12/2011. The start of follow up for each  
30 individual was the date of the first antipsychotic prescription during these periods. We excluded  
31 individuals with less than 6 months of follow-up data.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

### 42 **Antipsychotic data**

43 First we determined overall rates of prescribing of all first generation and second generation  
44 antipsychotics in UK primary care [\(see Appendix 2 for the full list of first and second generation](#)  
45 [antipsychotics\)](#). Subsequently we focussed on the three most commonly prescribed first generation  
46 (Haloperidol, Chlorpromazine and Trifluoperazine) and second generation agents (Olanzapine,  
47 Quetiapine and Risperidone). We determined the average daily dose prescribed for each  
48 antipsychotic during the follow-up period, as well as the length of time for which antipsychotics  
49 were prescribed. [We did this by using data on the strength of the antipsychotics prescribed, the](#)  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 total amount prescribed and the dose per day. From this information it was possible to calculate the  
4  
5 total possible mg per prescription. These were cumulated for all prescriptions of a given  
6  
7 antipsychotic. The amount of time on a given antipsychotic was calculated using the first and last  
8  
9 prescription dates, adding on the number of days the final prescription was expected to last if it was  
10  
11 taken as directed. We excluded total daily doses which were implausibly high for community  
12  
13 prescribing of antipsychotics, since these were likely to represent erroneous entries. We defined  
14  
15 this upper threshold at twice the maximum recommended daily dose in the BNF,<sup>[11,12]</sup> namely over  
16  
17 60mg for haloperidol, over 2000mg for chlorpromazine, over 120mg for trifluoperazine, over 40mg  
18  
19 for olanzapine, over 1500 for quetiapine and over 32 mg for risperidone. Relatively few (221)  
20  
21 prescriptions were excluded for this reason.  
22  
23

### 24 25 26 27 **Mental health conditions**

28  
29 We defined severe mental illness as schizophrenia-like disorders, bipolar affective disorders and  
30  
31 other non-organic psychosis such as delusional disorder, “psychoses not otherwise specified” and  
32  
33 severe depression with psychoses (Appendix 1). Read codes for SMI diagnoses have been  
34  
35 previously been validated.[16] We identified an additional category for people who were included  
36  
37 on the practice’s SMI register without having a Read code for the SMI diagnoses above (a GP SMI  
38  
39 register is required as part of the GP contract in the UK since 2004). Hardoon et al[17] determined  
40  
41 that the prevalence of SMI in THIN is similar to that of epidemiological studies.  
42  
43  
44  
45

46  
47 Next we identified common mental health conditions for which antipsychotics might be prescribed  
48  
49 off-label, using diagnostic Read code lists compiled by two clinical academics - a GP and a  
50  
51 psychiatrist.<sup>[15,18]</sup> These non-SMI conditions comprised depression, anxiety disorders, sleep  
52  
53 disorders (insomnia, non-specific sleep disorders, apnoea, hypersomnia), dementia, attention deficit  
54  
55 and hyperactivity disorder, personality disorders, post-traumatic stress disorder and obsessive  
56  
57  
58  
59  
60

1  
2  
3 compulsive disorder. These have not been validated; however, we have reported on trends in  
4  
5 anxiety and depression symptom and diagnosis recording in THIN.[19, 20]  
6  
7

8  
9 We created a diagnostic hierarchy for people with more than one mental health diagnosis in their  
10 clinical notes. Hence, if a patient ever had an record of SMI diagnosis we considered this as the  
11 indication for antipsychotics. However, if there were no record of SMI diagnosis, then all non-SMI  
12 diagnoses were extracted and included in this study. In other words the non-SMI diagnoses were  
13 not mutually exclusive so a person could count as both a case of anxiety and a case of obsessive  
14 compulsive disorder.  
15  
16  
17  
18  
19  
20  
21  
22  
23

#### 24 **Ethical approval**

25  
26 THIN has overall ethical approval from the South East Multicentre Research Ethics Committee  
27 (reference number: 07/H1102/103) and further study specific approval for this study was gained as  
28 part of an additional MREC approval from the London Research Ethics Committee. Reference  
29 number: 09/H0718/11.  
30  
31  
32  
33  
34  
35  
36  
37

#### 38 **Statistical analysis**

39  
40 We calculated rates of prescribing any antipsychotics, per 100,000 person years at risk (PYAR). We  
41 then calculated rates of any first or second generation antipsychotics then we determined rates of  
42 prescribing individual agents for the three most commonly prescribed first and second generation  
43 antipsychotic agents. Multivariable Poisson regression was used to determine associations between  
44 sex, age group, Townsend deprivation quintile, calendar year and 1) overall antipsychotic  
45 prescribing, 2) All first and second generation antipsychotic agents and 3) The six most commonly  
46 prescribed individual antipsychotics. For these analyses, we defined the population at risk as the  
47 total population registered with the general practices in the period 2007-2011.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 We calculated frequencies (%) for each ~~recorded~~ indication (diagnosis) for each of the six most  
4 commonly prescribed antipsychotics. We also calculated the median (interquartile range (IQR)) daily  
5 dose in milligrams and length of time prescribed a given antipsychotic within three groups: The SMI  
6 (psychosis/bipolar) subgroup, the group with non-SMI diagnoses and the group with no record of  
7  
8  
9  
10  
11  
12 ~~any of~~ these diagnoses.

13  
14  
15  
16 Analyses were carried out using Stata version 13.~~[1621]~~

## 20 RESULTS

21  
22 We identified 47,724 eligible individuals who were prescribed antipsychotic medications. Of these  
23 13,941 were solely prescribed first generation antipsychotics, 27,966 solely second generation  
24 antipsychotics and 5817 received both classes of agent during their follow-up period (Figure 1). The  
25 median length of follow-up for people receiving any antipsychotic was 2.4 years (IQR 1.3, 4.1). The  
26 length of follow-up was slightly longer for those receiving both first and second generation  
27 antipsychotic (3.0 years; IQR 1.7, 4.7).  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

[Figure 1 here]

### 42 Rates of antipsychotic prescribing by socio-demographic characteristics and over time

43  
44 Overall 1% of individuals received an antipsychotic at some time over the study period. For women  
45 the rate of prescribing any antipsychotic was 699 per 100,000 PYAR (95% CI 693, 705) compared to  
46 612 per 100,000 PYAR (95% CI 607, 617) for men. Individuals aged above 80 years were more likely  
47 to receive antipsychotics (Incidence rate ratio (IRR) 2.234; 95% CI 2.222, 2.246 compared with those  
48 aged 40-49 years). In contrast, those under the age of 18 and those aged 18-29 were much less  
49 likely to receive antipsychotics (Table 1). Those living in the most deprived areas were more than  
50 three times as likely to receive antipsychotics compared to those in the least deprived areas (IRR  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 3.587 (95% CI 3.587, 3.606) (Table 1). These patterns were also observed when the subgroups  
4  
5 prescribed first generation and second generation of antipsychotic were examined separately (Table  
6  
7 1).  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



Table 1: Rates of antipsychotic prescribing by class of antipsychotic, age gender and social deprivation

	Any antipsychotic				Any first generation antipsychotic				Any second generation antipsychotic				First and second generation antipsychotics			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	612	(607, 617)	1.000		197	(194, 200)	1.000		458	(454, 462)	1.000		43	(41, 44)	1.000	
Female	699	(693, 705)	1.092	(1.088, 1.095)	256	(253, 259)	1.204	(1.196, 1.211)	489	(484, 493)	1.050	(1.046, 1.054)	46	(44, 47)	1.010	(1.096, 1.103)
Under 18	63	(61, 66)	0.044	(0.044, 0.045)	5	(4, 5)	0.009	(0.008, 0.009)	59	(57, 62)	0.058	(0.057, 0.059)	0.6	(0.4, 0.9)	0.026	(0.026, 0.027)
18-29	459	(451, 467)	0.351	(0.349, 0.353)	111	(107, 115)	0.223	(0.220, 0.227)	376	(369, 383)	0.401	(0.398, 0.404)	28	(26, 30)	0.348	(0.346, 0.351)
30-39	817	(806, 828)	0.804	(0.799, 0.808)	238	(232, 244)	0.643	(0.636, 0.650)	638	(628, 648)	0.867	(0.861, 0.872)	58	(56, 62)	0.803	(0.799, 0.807)
40-49	852	(842, 863)	1.000		289	(283, 295)	1.000		628	(619, 637)	1.000		64	(62, 67)	1.000	
50-59	712	(701, 723)	0.872	(0.867, 0.877)	283	(276, 290)	1.045	(1.035, 1.056)	483	(474, 492)	0.804	(0.799, 0.809)	54	(51, 57)	0.872	(0.867, 0.877)
60-69	642	(631, 653)	0.824	(0.819, 0.829)	281	(274, 289)	1.039	(1.029, 1.050)	406	(398, 415)	0.740	(0.735, 0.745)	46	(43, 49)	0.824	(0.819, 0.829)
70-79	842	(827, 857)	0.973	(0.967, 0.980)	350	(341, 360)	1.192	(1.179, 1.205)	546	(534, 559)	0.888	(0.881, 0.894)	54	(51, 58)	0.971	(0.965, 0.977)
80+	2,201	(2,170, 2,231)	2.234	(2.222, 2.246)	793	(775, 811)	2.358	(2.334, 2.382)	1,529	(1,504, 1,555)	2.185	(2.171, 2.199)	121	(114, 129)	2.221	(2.209, 2.234)
Townsend																
Least deprived	403	(398, 409)	1.000		138	(135, 142)	1.000		291	(286, 296)	1.000		26	(24, 27)	1.000	
2	499	(492, 506)	1.211	(1.203, 1.218)	180	(176, 184)	1.251	(1.237, 1.265)	351	(345, 357)	1.194	(1.186, 1.203)	33	(31, 35)	1.214	(1.207, 1.222)
3	645	(637, 653)	1.707	(1.697, 1.716)	223	(218, 228)	1.764	(1.745, 1.782)	465	(458, 472)	1.683	(1.672, 1.695)	43	(41, 45)	1.714	(1.705, 1.724)
4	844	(834, 854)	2.457	(2.443, 2.470)	295	(290, 301)	2.516	(2.491, 2.542)	608	(600, 616)	2.432	(2.416, 2.448)	59	(57, 62)	2.476	(2.463, 2.489)
Most deprived	1,158	(1,145, 1,172)	3.587	(3.567, 3.606)	386	(378, 394)	3.649	(3.612, 3.686)	853	(841, 865)	3.560	(3.537, 3.583)	80	(76, 84)	3.613	(3.593, 3.633)
Missing	806	(781, 830)	2.282	(2.259, 2.305)	270	(256, 284)	2.360	(2.315, 2.406)	586	(566, 608)	2.250	(2.223, 2.277)	51	(45, 57)	2.187	(2.165, 2.210)
Year																
2007	591	(584, 599)	1.000		236	(231, 241)	1.000		399	(393, 405)	1.000		44	(42, 46)	1.000	
2008	654	(646, 663)	1.075	(1.069, 1.080)	243	(238, 248)	0.990	(0.981, 1.000)	456	(449, 463)	1.118	(1.111, 1.125)	45	(43, 47)	1.075	(1.070, 1.081)
2009	679	(670, 687)	1.110	(1.104, 1.115)	237	(232, 242)	0.946	(0.938, 0.955)	487	(480, 494)	1.194	(1.186, 1.201)	45	(43, 47)	1.108	(1.102, 1.114)
2010	718	(710, 727)	1.151	(1.145, 1.157)	227	(222, 232)	0.880	(0.872, 0.888)	536	(529, 543)	1.290	(1.282, 1.298)	44	(42, 47)	1.147	(1.141, 1.153)
2011	637	(629, 646)	1.065	(1.059, 1.071)	189	(184, 193)	0.745	(0.737, 0.752)	492	(484, 499)	1.230	(1.222, 1.238)	43	(41, 45)	1.055	(1.050, 1.061)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

1  
2  
3 The three most commonly prescribed first generation antipsychotics were haloperidol,  
4 chlorpromazine and trifluoperazine; while olanzapine, risperidone and quetiapine were the most  
5 commonly issued second generation agents (Tables 2a and 2b). Rates of prescribing these individual  
6 agents followed similar patterns to the aggregate results in terms of their distributions by age and  
7 deprivation. Haloperidol and trifluoperazine were more commonly prescribed to women, as was  
8 quetiapine, while rates of risperidone and olanzapine prescribing were lower in women. Few under-  
9 18s received antipsychotics, but compared to other agents, risperidone was prescribed far more  
10 commonly to this young age group (Table 2b). Over the five years of the study (2007-2011), rates of  
11 prescribing for each first generation agent decreased while quetiapine prescription rates increased  
12 the most over time. For example, IRR for trifluoperazine in 2011 (reference category is 2007) 0.665  
13 (95% CI 0.645, 0.685) and IRR for quetiapine in 2011 (reference category is 2007) 1.480 (95% CI  
14 1.463, 1.497). There was a smaller increase in rates of prescribing for both risperidone and  
15 olanzapine (Table 2b).  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 2a: Rates of antipsychotic prescribing for the three most commonly prescribed first generation antipsychotics

Characteristic	Haloperidol				Chlorpromazine				Trifluoperazine			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	42	(41, 44)	1.000		51	(50, 53)	1.000		22	(21, 23)	1.000	
Female	55	(54, 57)	1.123	(1.107, 1.138)	52	(50, 53)	1.121	(1.107, 1.135)	36	(35, 38)	1.577	(1.547, 1.607)
Under 18	1	(1, 2)	0.017	(0.015, 0.019)	0.6	(0.4, 0.9)	0.004	(0.003, 0.004)	0.6	(0.4, 0.9)	0.006	(0.005, 0.008)
18-29	16	(15, 18)	0.204	(0.196, 0.213)	33	(31, 35)	0.231	(0.225, 0.237)	13	(12, 15)	0.195	(0.186, 0.205)
30-39	35	(33, 38)	0.659	(0.641, 0.678)	72	(68, 75)	0.640	(0.628, 0.653)	30	(28, 32)	0.634	(0.613, 0.655)
40-49	42	(40, 44)	1.000		85	(82, 89)	1.000		37	(35, 40)	1.000	
50-59	44	(42, 47)	1.085	(1.058, 1.112)	77	(74, 81)	0.992	(0.974, 1.010)	38	(35, 40)	1.046	(1.015, 1.078)
60-69	51	(48, 54)	1.175	(1.145, 1.205)	63	(60, 67)	0.822	(0.806, 0.839)	46	(43, 49)	1.378	(1.339, 1.419)
70-79	98	(93, 104)	2.123	(2.073, 2.175)	54	(50, 58)	0.613	(0.598, 0.629)	54	(50, 58)	1.739	(1.687, 1.792)
80+	330	(319, 342)	5.833	(5.710, 5.958)	58	(53, 63)	0.595	(0.578, 0.614)	72	(67, 78)	1.868	(1.808, 1.931)
Townsend												
Least deprived	32	(30, 33)	1.000		24	(22, 25)	1.000		19	(18, 21)	1.000	
2	48	(46, 50)	1.499	(1.464, 1.534)	33	(32, 35)	1.225	(1.194, 1.257)	22	(20, 23)	1.185	(1.146, 1.225)
3	53	(51, 56)	1.914	(1.871, 1.957)	46	(44, 48)	2.117	(2.068, 2.167)	28	(27, 30)	1.809	(1.754, 1.867)
4	60	(58, 63)	2.360	(2.307, 2.413)	68	(65, 71)	3.131	(3.062, 3.202)	39	(37, 41)	2.839	(2.756, 2.925)
Most deprived	62	(58, 65)	2.666	(2.603, 2.731)	116	(112, 120)	5.743	(5.619, 5.870)	50	(47, 53)	3.703	(3.591, 3.818)
Missing	49	(43, 56)	2.315	(2.217, 2.417)	95	(86, 103)	4.103	(3.961, 4.250)	30	(26, 35)	2.113	(1.987, 2.246)
Year												
2007	51	(49, 54)	1.000		58	(55, 60)	1.000		33	(31, 35)	1.000	
2008	54	(52, 56)	1.019	(0.998, 1.039)	56	(54, 59)	0.973	(0.955, 0.992)	31	(29, 32)	0.941	(0.916, 0.967)
2009	52	(50, 54)	0.955	(0.936, 0.974)	53	(51, 56)	0.899	(0.882, 0.916)	29	(27, 31)	0.899	(0.874, 0.924)
2010	48	(46, 50)	0.822	(0.805, 0.840)	47	(45, 49)	0.824	(0.807, 0.840)	30	(28, 32)	0.901	(0.876, 0.926)
2011	39	(37, 41)	0.684	(0.669, 0.700)	44	(41, 46)	0.751	(0.736, 0.766)	24	(22, 26)	0.665	(0.645, 0.685)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

Table 2b: Rates of antipsychotic prescribing for the three most commonly prescribed second generation antipsychotics

Characteristic	Olanzapine				Quetiapine				Risperidone			
	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI	Rate per 100,000 PYAR	95% CI	IRR*	95% CI
Male	168	(166, 171)	1.000		120	(117, 122)	1.000		137	(134, 139)	1.000	
Female	139	(136, 141)	0.835	(0.830, 0.841)	197	(194, 199)	1.542	(1.531, 1.553)	115	(113, 117)	0.854	(0.847, 0.)
Under 18	3	(2, 4)	0.008	(0.008, 0.009)	3	(3, 4)	0.012	(0.012, 0.013)	50	(47, 52)	0.196	(0.193, 0.200)
18-29	133	(129, 137)	0.349	(0.345, 0.354)	106	(102, 110)	0.418	(0.412, 0.424)	116	(112, 121)	0.484	(0.477, 0.491)
30-39	243	(237, 249)	0.822	(0.813, 0.830)	192	(186, 197)	0.941	(0.929, 0.952)	155	(150, 160)	0.810	(0.799, 0.820)
40-49	249	(243, 255)	1.000		175	(170, 180)	1.000		158	(154, 163)	1.000	
50-59	192	(187, 198)	0.868	(0.859, 0.877)	128	(124, 133)	0.730	(0.720, 0.740)	131	(127, 136)	0.845	(0.834, 0.857)
60-69	154	(149, 160)	0.781	(0.772, 0.790)	109	(105, 114)	0.670	(0.660, 0.679)	116	(111, 120)	0.819	(0.808, 0.831)
70-79	140	(134, 146)	0.673	(0.663, 0.683)	226	(219, 235)	1.263	(1.247, 1.280)	124	(118, 130)	0.772	(0.760, 0.785)
80+	195	(186, 204)	0.841	(0.829, 0.854)	891	(871, 910)	4.473	(4.427, 4.520)	289	(278, 300)	1.629	(1.606, 1.653)
Townsend												
Least deprived	81	(78, 84)	1.000		111	(108, 114)	1.000		79	(76, 81)	1.000	
2	101	(98, 104)	1.314	(1.296, 1.332)	130	(126, 134)	1.113	(1.100, 1.126)	93	(90, 96)	1.157	(1.141, 1.174)
3	140	(137, 144)	1.898	(1.873, 1.922)	164	(160, 168)	1.497	(1.480, 1.514)	121	(117, 124)	1.614	(1.593, 1.636)
4	211	(206, 216)	3.122	(3.084, 3.160)	192	(187, 196)	1.963	(1.941, 1.984)	163	(159, 168)	2.297	(2.267, 2.327)
Most deprived	320	(313, 328)	4.956	(4.897, 5.016)	239	(232, 245)	2.663	(2.633, 2.693)	227	(221, 233)	3.243	(3.201, 3.285)
Missing	200	(188, 212)	2.821	(2.761, 2.882)	196	(185, 209)	1.974	(1.933, 2.016)	148	(138, 159)	1.981	(1.933, 2.031)
Year												
2007	140	(137, 144)	1.000		117	(113, 120)	1.000		118	(114, 121)	1.000	
2008	153	(149, 157)	1.050	(1.039, 1.062)	144	(140, 148)	1.224	(1.209, 1.238)	124	(121, 128)	1.050	(1.037, 1.064)
2009	157	(153, 161)	1.088	(1.076, 1.100)	165	(161, 170)	1.360	(1.344, 1.376)	124	(120, 128)	1.053	(1.040, 1.066)
2010	166	(162, 170)	1.145	(1.133, 1.158)	190	(186, 195)	1.523	(1.506, 1.541)	138	(134, 142)	1.103	(1.089, 1.117)
2011	151	(147, 155)	1.077	(1.065, 1.089)	177	(173, 181)	1.480	(1.463, 1.497)	125	(121, 129)	1.040	(1.026, 1.053)

Abbreviations: IRR=Incident rate ratio, PYAR=person years at risk

\*All IRR are adjusted for the other characteristics in this table.

### Records of mental health conditions in people prescribed antipsychotics

For people prescribed the three most common first generation antipsychotics, the proportion with a Read code for SMI (psychotic or bipolar disorders) varied between 27% (n=1331) for haloperidol and 35% (n=1545) for chlorpromazine (Table 3). The most common diagnosis recorded was schizophrenia and related conditions. For second generation antipsychotics, only 36% (n=4824) of those prescribed quetiapine had an SMI record, compared to 46% (n=4597) of those receiving risperidone and 62% (n=7094) of those receiving olanzapine (Table 3). More than half of people receiving first generation antipsychotics had no SMI diagnosis recorded in their notes, but did have a code for one of the non-SMI mental health conditions. The most common conditions were anxiety, depression and sleep disorders. Almost a third of people receiving haloperidol had a record of dementia. For second generation agents, the proportions with non-SMI diagnoses were similar, although the number of people with a record of dementia was highest for quetiapine (26% of prescriptions). Between 12 and 17% of people prescribed first generation agents had no record of SMI or of any non-SMI mental health diagnosis.

Table 3: Diagnosis by the three most commonly prescribed first and second generation antipsychotics 2007-2011

Diagnosis	Haloperidol (N=4913)		Chlorpromazine (N=4404)		Trifluoperazine (N=2633)		Olanzapine (N=11502)		Quetiapine (N=13326)		Risperidone (N=9956)	
	n	%	n	%	n	%	n	%	n	%	n	%
<b>SMI*</b>												
Any SMI diagnosis	1331	27	1545	35	783	30	7094	62	4824	36	4597	46
Schizophrenia	620	13	633	14	359	14	3060	27	1489	11	2143	22
Bipolar disorder	298	6	343	8	119	5	1655	14	1689	13	726	7
Other SMI	267	5	334	8	203	8	1898	17	1163	9	1291	13
On SMI register only	146	3	235	5	102	4	481	4	483	4	437	4
<b>Non-SMI*</b>												
Any non-SMI diagnosis	2762	56	2241	51	1529	58	3753	33	7623	57	4085	41
ADHD	36	0.7	33	0.7	10	0.4	75	0.7	77	0.6	538	5
Anxiety	783	16	1124	26	909	35	1779	15	2669	20	1391	14
Depression	1330	27	1748	40	1142	43	2964	26	4648	35	2204	22
Dementia	1521	31	183	4	157	6	466	4	3514	26	1211	12
OCD	40	0.8	93	2	47	2	216	2	250	2	221	2
PD	136	3	294	7	122	4	525	5	705	5	349	4
PTSD	37	0.8	97	2	29	1	197	2	210	2	94	0.9
Sleep disorders	761	15	815	19	511	19	1124	10	1926	14	1078	11
None of the above*	820	17	618	14	321	12	655	6	879	7	1274	13

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.

1  
2  
3  
4  
5 The median daily dose for antipsychotics was higher in those who did have a SMI diagnosis, and  
6 highest amongst those with records of schizophrenia (Table 4). Within the non-SMI groups, median  
7 daily doses were similar although the highest doses were observed in people with a record of a sleep  
8 disorder or personality disorder. The longest durations of antipsychotic treatment were generally  
9 observed for people with a diagnosis of schizophrenia or in those who were included on the SMI  
10 register in general practice (Supplementary Table [4a1](#)). Within the non-SMI group, duration of  
11 treatment showed little variation between diagnoses, although the median length of treatment  
12 seemed longest in people with dementia or ADHD.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 4: Median (IQR) daily dose for the three most prescribed first and second generation antipsychotics by indication

Diagnosis	Haloperidol		Chlorpromazine		Trifluoperazine		Olanzapine		Quetiapine		Risperidone	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
<b>SMI*</b>												
Schizophrenia	7	(3, 14)	103	(55, 208)	10	(5, 18)	12	(9, 19)	326	(171, 546)	4	(2, 6)
Bipolar disorder	5	(2, 11)	93	(50, 174)	5	(2, 10)	10	(6, 15)	239	(100, 413)	2	(1, 4)
Other SMI	3	(1, 6)	88	(50, 171)	6	(2, 12)	10	(6, 15)	174	(70, 337)	2	(1, 4)
On SMI register only	4	(1, 8)	91	(51, 159)	4	(2, 8)	9	(5, 12)	119	(54, 254)	2	(1, 4)
<b>Non-SMI*</b>												
Any non-SMI diagnosis	2	(1, 3)	62	(38, 109)	3	(2, 5)	6	(4, 10)	66	(38, 132)	1	(1, 2)
ADHD	2	(1, 5)	82	(50, 184)	3	(2, 5)	7	(5, 11)	100	(50, 210)	1	(1, 2)
Anxiety	1	(1, 3)	61	(36, 108)	3	(2, 4)	6	(4, 10)	80	(46, 177)	1	(1, 3)
Depression	2	(1, 3)	58	(37, 102)	3	(2, 5)	6	(4, 10)	79	(43, 167)	1	(1, 2)
Dementia	1	(1, 3)	75	(39, 170)	3	(2, 7)	5	(3, 8)	52	(30, 89)	1	(1, 2)
OCD	2	(1, 5)	75	(42, 118)	3	(2, 5)	5	(4, 10)	95	(50, 205)	1	(1, 2)
PD	2	(1, 6)	82	(48, 150)	4	(2, 7)	8	(5, 12)	141	(58, 292)	2	(1, 3)
PTSD	2	(1, 3)	64	(38, 138)	2	(2, 5)	6	(4, 10)	100	(54, 232)	2	(1, 3)
Sleep disorders	3	(1, 8)	79	(49, 151)	4	(2, 11)	10	(6, 15)	155	(58, 340)	2	(1, 4)
None of the above*	2	(1, 4)	70	(38, 128)	2	(1, 5)	7	(4, 11)	56	(30, 119)	2	(1, 3)

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.



## CONCLUSIONDISCUSSION

In this study of antipsychotic prescribing in a large primary care database representative of the UK-

In UK primary care, around half of prescriptions for first and second generation antipsychotics are issued to people who have no record of severe mental illness, defined as schizophrenia, bipolar affective disorder or other non-organic psychosis in their clinical notes. Furthermore, they are more likely to be prescribed to older people who may be more sensitive to adverse effects such as movement disorders and cardio-metabolic risk. When antipsychotics are prescribed to people without SMI, they tend to be given in lower doses and for slightly shorter periods, with the exception people with ADHD and dementia who receive these drugs for relatively long periods.

Other studies on antipsychotic prescribing relate to an earlier time period prior to -the introduction of antipsychotic guidelines in the UK.[22, 23] The pattern of prescribing since then has changed over time[24], with approximately two thirds of prescriptions in the current study being for second generation antipsychotics.

For first generation agents, the most common “non-SMI” mental health diagnoses we identified were anxiety, depression, sleep disorders, and dementia (especially for haloperidol). For second generation agents, the same mental health diagnoses were common including dementia, despite the fact that second generation antipsychotics are not recommended in people with dementia due to the risk of stroke and other-cause mortality.[1, 2] Reducing the potential harm associated with antipsychotics in dementia has been emphasised as a priority by organisations such as Department of Health in England and the US Food and Drug Administration.[1725, 1826] Our findings suggest that further effort is required to decrease primary care antipsychotic prescriptions in dementia and assessing time trends in antipsychotic prescribing in this group is an important area for future research.

1  
2  
3 Median daily doses and duration of treatment with antipsychotics tended to be slightly greater in  
4  
5 people with SMI diagnoses (especially schizophrenia); however people with depression, anxiety,  
6  
7 personality disorders and sleep disorders still received substantial doses of these agents, for  
8  
9 relatively long periods of time. For instance the median daily dose of olanzapine prescribed to  
10  
11 people with sleep disorders was 10mg per day; the same daily dose as people with a diagnosis of  
12  
13 bipolar disorder and only slightly less than the average dose of 12mg per day prescribed to people  
14  
15 with schizophrenia (Table 4). Within the non-SMI group, median doses of risperidone and  
16  
17 quetiapine were also highest in those with sleep disorders, post-traumatic stress disorder and  
18  
19 personality disorder. Whilst median dose is a crude method of quantifying the amount prescribed  
20  
21 for each indication explored in this paper, it does allow us to make comparisons between these  
22  
23 diagnoses.  
24  
25  
26  
27  
28

29 There are a number of possible explanations for the high rates of antipsychotic prescribing to people  
30  
31 without a ~~record of~~ psychosis diagnosis. Firstly, it may be that the clinician prescribes antipsychotics  
32  
33 because the person does have psychotic symptoms, but the clinician does not assign a label of  
34  
35 schizophrenia or other psychosis, either due to patient preference or to avoid the associated stigma  
36  
37 with such labels. However, this would suggest that there are large numbers of people with  
38  
39 unrecorded psychosis and/ or bipolar disorder in primary care. This is not consistent with other  
40  
41 research in UK primary care databases which has shown that rates of schizophrenia and bipolar  
42  
43 disorder recording in the database are similar to other epidemiological studies.<sup>[49,17]</sup> Therefore it  
44  
45 seems unlikely that large numbers people in primary care have psychosis without a corresponding  
46  
47 record.  
48  
49  
50  
51  
52

53 Secondly, it is possible that in real life practice antipsychotics are prescribed quite commonly to  
54  
55 people with problems related to depression, anxiety, sleep, dementia and other conditions, despite  
56  
57 guidelines recommending caution and only suggesting this as a strategy in treatment unresponsive  
58  
59  
60

1  
2  
3 cases.[3, 6] It maybe that clinicians and/or mental health professionals quite frequently add  
4  
5 antipsychotics to the treatment plan for people with non-psychotic disorders, either for agitation,  
6  
7 poor sleep, anxiety or due to their general reputation as tranquilising medications. Since there were  
8  
9 not major differences in the median doses and duration of treatment according to ~~recorded~~  
10  
11 ~~diagnosis~~likely indication, these patterns of prescribing warrant some attention in terms of  
12  
13 monitoring side effects particularly weight gain, extra-pyramidal side effects and metabolic impacts  
14  
15 such as hyperprolactinaemia, glucose dysregulation and effects on lipid profiles. Current UK policy  
16  
17 only recommends physical monitoring for people who the general practice includes on its SMI  
18  
19 register. It may be that this recommendation should be extended to all people prescribed  
20  
21 antipsychotics in primary care.  
22  
23  
24  
25  
26

### 27 **Strengths and limitations**

28  
29 Primary care databases allow us to study large representative samples of patients in general practice  
30  
31 across the UK. THIN has a good record of prescriptions issued and comparison with dispensing data  
32  
33 suggests that the majority of THIN prescriptions issued are collected[2027] but of course this may  
34  
35 not mean patients have been actually taking the medication. Primary care diagnoses of SMI have  
36  
37 been validated,[2416] however this is not the case for some other conditions we explored such as  
38  
39 ADHD and ~~anxiety~~OCD.  
40  
41  
42  
43

44  
45 Research with routine clinical data has its limitations, for instance we could not perform more  
46  
47 detailed assessment of patient characteristics and preferences which may influence treatment  
48  
49 decisions. For non-SMI diagnoses such as depression and anxiety, we extracted all diagnoses which  
50  
51 had been entered at any time. We did this because GPs do not routinely re-enter diagnoses at each  
52  
53 subsequent appointments and we wanted to capture all relevant information regarding possible  
54  
55 indication. A limitation of this method, and of the database, is that we cannot be certain that the  
56  
57 decision to prescribe was temporally related to the mental health condition entered at another time.  
58  
59  
60

1  
2  
3 However, this method does give an indication of the long term clinical presentation of people  
4 without an SMI Read code who are prescribed antipsychotics. It would be useful to explore the  
5 reasons underpinning these high rates of prescription-prescribing to groups not traditionally thought  
6 eligible for antipsychotic treatment. This might require primary research studies interviewing  
7 clinicians and reviewing individual patients. However further database work could explore  
8 symptoms associated with these antipsychotic prescriptions, and the treatment decisions pre-dating  
9 the choice of an antipsychotic agent. Also, the same databases could be used to assess how  
10 frequently cardiovascular risk factors are measured in this population, especially body mass index,  
11 cholesterol and HDL cholesterol as well as some indication of glucose regulation such as HBA1c,  
12 random or fasting glucose.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

24  
25  
26  
27 We need to know more about co-prescribing in the people without a diagnosis of psychosis or  
28 bipolar disorder for instance benzodiazepines and mood stabilisers. We also need to quantify the  
29 degree of benefit and harm that may be associated with using such treatments. To what degree do  
30 they cause physical and/ or mental health problems for the recipients, and to what extent do they  
31 lead to symptom remission? A meta-analysis of antipsychotics drugs in major depressive disorder  
32 found that although these agents may improve depression symptoms, they have no impact on  
33 functioning or quality of life.[2228] The few existing randomised controlled trials involving people  
34 with personality disorder have shown little benefit of antipsychotics over placebo.[6, 2329]  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

45  
46 Finally it is important to explore whether these agents are discontinued following amelioration of  
47 any mental health problem for which they are chosen, and to assess the risks and benefits of  
48 stopping such agents in different diagnostic groups.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure legend

Figure 1: Flow of individuals through the study

For peer review only

**Conflict of Interest**

The authors have no conflicts of interest to declare.

**Funding**

This work was funded by the NIHR School for Primary Care Research. Grant number 17321

**Authorship**

DPJO, KW, IP and IN had the original idea for the study. All authors developed the method, analysed and interpreted the results and wrote the manuscript. LM performed the analysis.

**Data sharing statement**

No data are available

I Dr Louise Marston the Corresponding Author of this article contained within the original manuscript which includes any diagrams & photographs, other illustrative material, video, film or any other material howsoever submitted by the Contributor(s) at any time and related to the Contribution ("the Contribution") have the right to grant on behalf of all authors and do grant on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licensees, to permit this Contribution (if accepted) to be published in BMJ Open and any other BMJ Group products and to exploit all subsidiary rights, as set out in the licence at:

[http://group.bmj.com/products/journals/instructions-for-authors/BMJOpen\\_licence.pdf](http://group.bmj.com/products/journals/instructions-for-authors/BMJOpen_licence.pdf)

## REFERENCES

- 1 Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934–43.
- 2 Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study (electronic article). *BMJ* 2008;
- 3 National Institute for Health and Care Excellence Depression: the treatment and management of depression in adults (update). CG90 2009a (<http://guidance.nice.org.uk/CG90>) (accessed May 2014)
- 4 Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology *J Psychopharmacol* 2005;19:567-96.
- 5 Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders *J Psychopharmacol* 2010;24:1577-1600.
- 6 National Institute for Health and Care Excellence Borderline personality disorder: Treatment and management. CG78 2009b (<http://www.nice.org.uk/CG78>) (accessed May 2014)
- 7 The Health Improvement Network The Health Improvement Network. London: The Health Improvement Network; 2014 (<http://csdmruk.cegedim.com/>) (Accessed May 2014).

1  
2  
3 | [8](#) CPRD Clinical Practice Research Datalink (CPRD) website. Crown Copyright 2014.  
4  
5 | [\(<http://www.cprd.com/intro.asp>\)](http://www.cprd.com/intro.asp) (accessed October 2014)  
6  
7

8  
9 | [89](#) Lis Y, Mann RD The VAMP Research multi-purpose database in the U.K. *J Clin Epidemiol*  
10  
11 | 1995;431-j 43  
12

13  
14  
15  
16 | [910](#) Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North.  
17  
18 | London: Croom Helm, 1988.  
19

20  
21  
22 | [1011](#) Booth N What are the Read Codes? *Health Libr Rev* 1994;177-82  
23  
24

25  
26  
27 | [1112](#) Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and  
28  
29 | Pharmaceutical Press 2014 (<http://www.medicinescomplete.com>) (Accessed may 2014)  
30  
31

32  
33 | [1213](#) Blak BT, Thompson M, Dattani H, et al Generalisability of The Health Improvement Network  
34  
35 | (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*  
36  
37 | 2011;251-55  
38  
39

40  
41  
42 | [1314](#) Horsfall L, Walters K, Petersen I. Identifying periods of acceptable computer usage in primary  
43  
44 | care research databases. *Pharmacoepidemiol Drug Saf* 2013;64-9.  
45  
46

47  
48 | [1415](#) Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality  
49  
50 | reporting for research using automated data from primary care. *Pharmacoepidem Drug Saf* 2009;76-  
51  
52 | 83  
53  
54



1  
2  
3 [16 Nazareth I, King M, Haines A et al. Accuracy of diagnosis of psychosis on general practice](#)  
4 [computer system \*BMJ\* 1993;307\(6895\):32-4](#)

5  
6  
7  
8  
9 [17 Haroon S, Hayes JF, Blackburn R et al. Recording of severe mental illness in United Kingdom](#)  
10 [primary care, 2000-2010. \*PLoS One\* 2013;12;8\(12\):e82365.](#)

11  
12  
13  
14  
15  
16 [1518](#) Dave S, Petersen I. Creating medical and drug code lists to identify cases in primary care  
17 databases. *Pharmacoepidem Drug Saf* 2009;18:704-7.

18  
19  
20  
21  
22 [19 Walters K, Rait G, Griffin M et al. Recent Trends in the Incidence of Anxiety Diagnoses and](#)  
23 [Symptoms in Primary Care. \*PLoS One\* 2012;7\(8\):e4167](#)

24  
25  
26  
27  
28  
29 [20 Rait G, Walters K, Griffin M et al Recent trends in the incidence of recorded depression and](#)  
30 [depressive symptoms in primary care. \*Brit J Psychiat\* 2009;195:520-524](#)

31  
32  
33  
34  
35 [1621](#) Stata Corporation. *Stata Statistical Software: Release 13*. College Station, TX: Stata  
36 Corporation; 2013

37  
38  
39  
40  
41  
42 [22 Verdoux H, Tournier M, Bégau B. Antipsychotic prescribing trends: a review of pharmaco-](#)  
43 [epidemiological studies. \*Acta Psychiatr Scand\* 2010;121:4–10.](#)

44  
45  
46  
47  
48 [23 Kaye JA, Bradbury BD, Jick H. Changes in antipsychotic drug prescribing by general](#)  
49 [practitioners in the United Kingdom from 1991 to 2000: a population-based observational study. \*Br J\*](#)  
50 [Clin Pharmacol 2003;56:569–575.](#)

1  
2  
3 24 Prah P, Petersen I, Nazareth I, et al National changes in oral antipsychotic treatment for  
4 people with schizophrenia in primary care between 1998 and 2007 in the United Kingdom. .  
5  
6 *Pharmacoepidem Drug Saf* 2012;21:161–169  
7  
8  
9

10  
11 ~~1725~~ Department of Health The use of antipsychotic medication for people with dementia: time  
12 for action. Department of Health. London 2009  
13  
14

15  
16  
17  
18 ~~1826~~ U.S. Food and Drug Administration Public Health Advisory: Deaths with Antipsychotics in  
19 Elderly Patients with Behavioral Disturbances 2005  
20  
21 ([http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/  
22 DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm))  
23  
24  
25  
26 (accessed May 2014)  
27  
28  
29

30  
31 ~~19~~ ~~Hardoon S, Hayes JF, Blackburn R et al. Recording of severe mental illness in United Kingdom~~  
32 ~~primary care, 2000–2010. *PLoS One* 2013;12;8(12):e82365.~~  
33  
34  
35

36  
37  
38 ~~2027~~ The NHS Information Centre PaPCS. Prescribing compliance: a review of the proportion of  
39 prescriptions dispensed. 2011 (<http://www.hscic.gov.uk/pubs/presccompliance>) (accessed May  
40 2014)  
41  
42  
43  
44

45  
46 ~~21~~ ~~Nazareth I, King M, Haines A et al. Accuracy of diagnosis of psychosis on general practice~~  
47 ~~computer system *BMJ* 1993;307(6895):32–4~~  
48  
49  
50

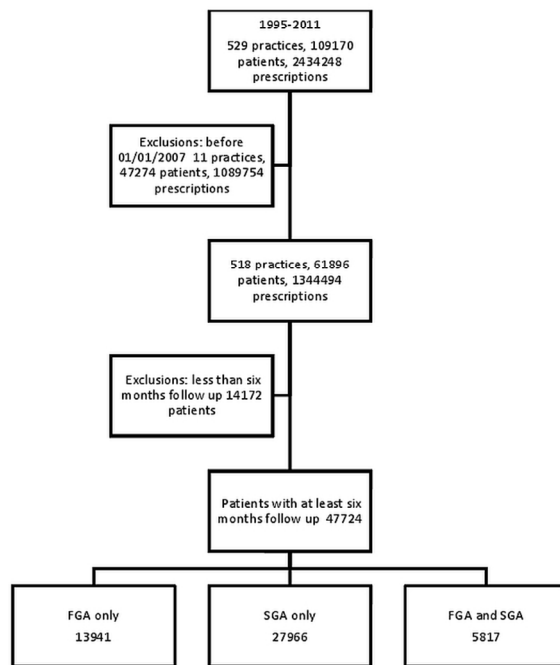
51  
52  
53 ~~2228~~ Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive Atypical Antipsychotic Treatment  
54 for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes  
55 *PLoS Med* 2013;10(3):e1001403  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

[2329](#) Ingenhoven T, Lafay P, Rinne T, et al. Effectiveness of pharmacotherapy for severe personality disorders: metaanalyses of randomized controlled trials. *J Clin Psychiatry*. 2010;71:14–25.

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Flow of individuals through the study  
90x127mm (300 x 300 DPI)

Supplementary Table 1: Median (IQR) time (years) for which antipsychotics are prescribed by the three most commonly prescribed first and second generation antipsychotics by indication

Diagnosis	Haloperidol		Chlorpromazine		Trifluoperazine		Olanzapine		Quetiapine		Risperidone	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
<b>SMI*</b>												
Schizophrenia	0.62	(0.13, 2.25)	0.89	(0.19, 2.85)	1.19	(0.28, 3.80)	1.62	(0.56, 3.82)	0.93	(0.30, 2.46)	1.15	(0.33, 2.97)
Bipolar disorder	0.41	(0.08, 1.51)	0.57	(0.08, 2.17)	0.46	(0.09, 1.63)	1.00	(0.30, 2.55)	0.93	(0.30, 2.04)	0.76	(0.19, 2.16)
Other SMI	0.30	(0.08, 1.13)	0.64	(0.10, 2.50)	0.80	(0.13, 2.60)	1.14	(0.36, 2.78)	0.90	(0.32, 2.11)	0.77	(0.22, 2.18)
On SMI register only	0.64	(0.15, 2.65)	1.72	(0.40, 4.38)	1.07	(0.16, 3.53)	1.92	(0.61, 4.31)	1.45	(0.45, 3.49)	1.84	(0.43, 4.61)
<b>Non-SMI*</b>												
Any non-SMI diagnosis	0.32	(0.08, 0.98)	0.31	(0.08, 1.37)	0.18	(0.08, 0.97)	0.67	(0.19, 1.81)	0.96	(0.33, 1.96)	0.77	(0.23, 1.93)
ADHD	0.77	(0.20, 1.47)	0.69	(0.15, 1.49)	0.16	(0.08, 1.30)	0.48	(0.13, 0.94)	0.52	(0.15, 1.33)	0.90	(0.38, 1.88)
Anxiety	0.18	(0.08, 0.78)	0.31	(0.08, 1.25)	0.19	(0.08, 1.01)	0.63	(0.18, 1.64)	0.87	(0.27, 1.83)	0.59	(0.14, 1.72)
Depression	0.27	(0.08, 0.90)	0.32	(0.08, 1.33)	0.21	(0.08, 1.04)	0.66	(0.19, 1.73)	0.90	(0.29, 1.86)	0.61	(0.16, 1.65)
Dementia	0.47	(0.11, 1.12)	0.44	(0.08, 1.27)	0.46	(0.08, 1.31)	1.10	(0.33, 2.44)	1.30	(0.57, 2.41)	0.71	(0.27, 1.49)
OCD	0.33	(0.08, 0.90)	0.48	(0.08, 2.24)	0.31	(0.08, 1.05)	0.59	(0.15, 1.72)	0.77	(0.25, 1.73)	0.59	(0.20, 2.09)
PD	0.26	(0.08, 1.22)	0.62	(0.16, 1.65)	0.21	(0.08, 1.13)	0.58	(0.22, 1.61)	0.82	(0.30, 1.72)	0.59	(0.18, 1.70)
PTSD	0.09	(0.06, 0.34)	0.36	(0.08, 1.21)	0.08	(0.08, 0.58)	0.67	(0.19, 2.01)	0.92	(0.34, 1.86)	0.63	(0.21, 1.95)
Sleep disorders	0.21	(0.08, 0.77)	0.25	(0.08, 1.21)	0.17	(0.08, 0.89)	0.63	(0.16, 1.67)	0.91	(0.27, 1.84)	0.64	(0.17, 1.67)
None of the above*	0.29	(0.08, 0.93)	0.24	(0.08, 1.86)	0.10	(0.08, 0.71)	0.66	(0.16, 2.15)	0.73	(0.25, 1.68)	1.14	(0.38, 2.82)

Abbreviations: SMI serious mental illness; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; PD personality disorder; PTSD post-traumatic stress disorder

\*If a person has an SMI diagnosis, any non-SMI diagnoses will not be included in the numbers below. For those who do not have an SMI diagnosis, all non-SMI diagnoses will be shown (ie, they are not mutually exclusive). "None of the above" means not having an SMI diagnosis or any of the non-SMI diagnoses in the table.

## Appendix 1: Read code list for severe mental illness (SMI)

Description	Read code
H/O: schizophrenia	1464.00
H/O: manic depressive disorder	146D.00
H/O: psychosis	146H.00
On national service framework mental health	9H6..00
On severe mental illness register	9H8..00
Non-organic psychoses	E1...00
Schizophrenic disorders	E10..00
Simple schizophrenia	E100.00
Schizophrenia simplex	E100.11
Unspecified schizophrenia	E100000
Subchronic schizophrenia	E100100
Chronic schizophrenic	E100200
Acute exacerbation of subchronic schizophrenia	E100300
Acute exacerbation of chronic schizophrenia	E100400
Schizophrenia in remission	E100500
Simple schizophrenia NOS	E100z00
Hebephrenic schizophrenia	E101.00
Unspecified hebephrenic schizophrenia	E101000
Subchronic hebephrenic schizophrenia	E101100
Chronic hebephrenic schizophrenia	E101200
Acute exacerbation of subchronic hebephrenic schizophrenia	E101300
Acute exacerbation of chronic hebephrenic schizophrenia	E101400
Hebephrenic schizophrenia in remission	E101500
Hebephrenic schizophrenia NOS	E101z00
Catatonic schizophrenia	E102.00
Unspecified catatonic schizophrenia	E102000
Subchronic catatonic schizophrenia	E102100
Chronic catatonic schizophrenia	E102200
Acute exacerbation of subchronic catatonic schizophrenia	E102300
Acute exacerbation of chronic catatonic schizophrenia	E102400
Catatonic schizophrenia in remission	E102500
Catatonic schizophrenia NOS	E102z00
Paranoid schizophrenia	E103.00
Unspecified paranoid schizophrenia	E103000
Subchronic paranoid schizophrenia	E103100
Chronic paranoid schizophrenia	E103200
Acute exacerbation of subchronic paranoid schizophrenia	E103300
Acute exacerbation of chronic paranoid schizophrenia	E103400
Paranoid schizophrenia in remission	E103500
Paranoid schizophrenia NOS	E103z00
Acute schizophrenic episode	E104.00
Oneirophrenia	E104.11
Latent schizophrenia	E105.00
Unspecified latent schizophrenia	E105000
Subchronic latent schizophrenia	E105100
Chronic latent schizophrenia	E105200
Acute exacerbation of subchronic latent schizophrenia	E105300
Acute exacerbation of chronic latent schizophrenia	E105400
Latent schizophrenia in remission	E105500
Latent schizophrenia NOS	E105z00
Residual schizophrenia	E106.00
Restzustand - schizophrenia	E106.11

1		
2		
3		
4	Schizo-affective schizophrenia	E107.00
5	Cyclic schizophrenia	E107.11
6	Unspecified schizo-affective schizophrenia	E107000
7	Subchronic schizo-affective schizophrenia	E107100
8	Chronic schizo-affective schizophrenia	E107200
9	Acute exacerbation subchronic schizo-affective schizophrenia	E107300
10	Acute exacerbation of chronic schizo-affective schizophrenia	E107400
11	Schizo-affective schizophrenia in remission	E107500
12	Schizo-affective schizophrenia NOS	E107z00
13	Other schizophrenia	E10y.00
14	Cenesthopathic schizophrenia	E10y.11
15	Atypical schizophrenia	E10y000
16	Coenesthopathic schizophrenia	E10y100
17	Other schizophrenia NOS	E10yz00
18	Schizophrenia NOS	E10z.00
19	Affective psychoses	E11..00
20	Bipolar psychoses	E11..11
21	Depressive psychoses	E11..12
22	Manic psychoses	E11..13
23	Manic disorder, single episode	E110.00
24	Hypomanic psychoses	E110.11
25	Single manic episode, unspecified	E110000
26	Single manic episode, mild	E110100
27	Single manic episode, moderate	E110200
28	Single manic episode, severe without mention of psychosis	E110300
29	Single manic episode, severe, with psychosis	E110400
30	Single manic episode in partial or unspecified remission	E110500
31	Single manic episode in full remission	E110600
32	Manic disorder, single episode NOS	E110z00
33	Recurrent manic episodes	E111.00
34	Recurrent manic episodes, unspecified	E111000
35	Recurrent manic episodes, mild	E111100
36	Recurrent manic episodes, moderate	E111200
37	Recurrent manic episodes, severe without mention psychosis	E111300
38	Recurrent manic episodes, severe, with psychosis	E111400
39	Recurrent manic episodes, partial or unspecified remission	E111500
40	Recurrent manic episodes, in full remission	E111600
41	Recurrent manic episode NOS	E111z00
42	Single major depressive episode, severe, with psychosis	E112400
43	Recurrent major depressive episodes, severe, with psychosis	E113400
44	Bipolar affective disorder, currently manic	E114.00
45	Manic-depressive - now manic	E114.11
46	Bipolar affective disorder, currently manic, unspecified	E114000
47	Bipolar affective disorder, currently manic, mild	E114100
48	Bipolar affective disorder, currently manic, moderate	E114200
49	Bipolar affect disord, currently manic, severe, no psychosis	E114300
50	Bipolar affect disord, currently manic,severe with psychosis	E114400
51	Bipolar affect disord,currently manic, part/unspec remission	E114500
52	Bipolar affective disorder, currently manic, full remission	E114600
53	Bipolar affective disorder, currently manic, NOS	E114z00
54	Bipolar affective disorder, currently depressed	E115.00
55	Manic-depressive - now depressed	E115.11
56	Bipolar affective disorder, currently depressed, unspecified	E115000
57	Bipolar affective disorder, currently depressed, mild	E115100
58		
59		
60		

1		
2		
3		
4	Bipolar affective disorder, currently depressed, moderate	E115200
5	Bipolar affect disord, now depressed, severe, no psychosis	E115300
6	Bipolar affect disord, now depressed, severe with psychosis	E115400
7	Bipolar affect disord, now depressed, part/unspec remission	E115500
8	Bipolar affective disorder, now depressed, in full remission	E115600
9	Bipolar affective disorder, currently depressed, NOS	E115z00
10	Mixed bipolar affective disorder	E116.00
11	Mixed bipolar affective disorder, unspecified	E116000
12	Mixed bipolar affective disorder, mild	E116100
13	Mixed bipolar affective disorder, moderate	E116200
14	Mixed bipolar affective disorder, severe, without psychosis	E116300
15	Mixed bipolar affective disorder, severe, with psychosis	E116400
16	Mixed bipolar affective disorder, partial/unspec remission	E116500
17	Mixed bipolar affective disorder, in full remission	E116600
18	Mixed bipolar affective disorder, NOS	E116z00
19	Unspecified bipolar affective disorder	E117.00
20	Unspecified bipolar affective disorder, unspecified	E117000
21	Unspecified bipolar affective disorder, mild	E117100
22	Unspecified bipolar affective disorder, moderate	E117200
23	Unspecified bipolar affective disorder, severe, no psychosis	E117300
24	Unspecified bipolar affective disorder, severe with psychosis	E117400
25	Unspecified bipolar affect disord, partial/unspec remission	E117500
26	Unspecified bipolar affective disorder, in full remission	E117600
27	Unspecified bipolar affective disorder, NOS	E117z00
28	Other and unspecified manic-depressive psychoses	E11y.00
29	Unspecified manic-depressive psychoses	E11y000
30	Atypical manic disorder	E11y100
31	Other mixed manic-depressive psychoses	E11y300
32	Other and unspecified manic-depressive psychoses NOS	E11yz00
33	Other and unspecified affective psychoses	E11z.00
34	Unspecified affective psychoses NOS	E11z000
35	Other affective psychosis NOS	E11zz00
36	Paranoid states	E12..00
37	Simple paranoid state	E120.00
38	Chronic paranoid psychosis	E121.00
39	Sander's disease	E121.11
40	Paraphrenia	E122.00
41	Shared paranoid disorder	E123.00
42	Folie a deux	E123.11
43	Other paranoid states	E12y.00
44	Paranoia querulans	E12y000
45	Other paranoid states NOS	E12yz00
46	Paranoid psychosis NOS	E12z.00
47	Other nonorganic psychoses	E13..00
48	Reactive psychoses	E13..11
49	Reactive depressive psychosis	E130.00
50	Psychotic reactive depression	E130.11
51	Acute hysterical psychosis	E131.00
52	Acute paranoid reaction	E133.00
53	Bouffee delirante	E133.11
54	Psychogenic paranoid psychosis	E134.00
55	Other reactive psychoses	E13y.00
56	Psychogenic stupor	E13y000
57	Brief reactive psychosis	E13y100
58		
59		
60		



1		
2		
3		
4	Other reactive psychoses NOS	E13yz00
5	Nonorganic psychosis NOS	E13z.00
6	Psychotic episode NOS	E13z.11
7	Other specified non-organic psychoses	E1y..00
8	Non-organic psychosis NOS	E1z..00
9	Schizotypal personality	E212200
10	[X]Schizophrenia, schizotypal and delusional disorders	Eu2..00
11	[X]Schizophrenia	Eu20.00
12	[X]Paranoid schizophrenia	Eu20000
13	[X]Paraphrenic schizophrenia	Eu20011
14	[X]Hebephrenic schizophrenia	Eu20100
15	[X]Disorganised schizophrenia	Eu20111
16	[X]Catatonic schizophrenia	Eu20200
17	[X]Catatonic stupor	Eu20211
18	[X]Schizophrenic catalepsy	Eu20212
19	[X]Schizophrenic catatonia	Eu20213
20	[X]Schizophrenic flexibilatis cerea	Eu20214
21	[X]Undifferentiated schizophrenia	Eu20300
22	[X]Atypical schizophrenia	Eu20311
23	[X]Post-schizophrenic depression	Eu20400
24	[X]Residual schizophrenia	Eu20500
25	[X]Chronic undifferentiated schizophrenia	Eu20511
26	[X]Restzustand schizophrenic	Eu20512
27	[X]Simple schizophrenia	Eu20600
28	[X]Other schizophrenia	Eu20y00
29	[X]Cenesthopathic schizophrenia	Eu20y11
30	[X]Schizophreniform disord NOS	Eu20y12
31	[X]Schizophrenifrm psychos NOS	Eu20y13
32	[X]Schizophrenia, unspecified	Eu20z00
33	[X]Schizotypal disorder	Eu21.00
34	[X]Latent schizophrenic reaction	Eu21.11
35	[X]Borderline schizophrenia	Eu21.12
36	[X]Latent schizophrenia	Eu21.13
37	[X]Prepsychotic schizophrenia	Eu21.14
38	[X]Prodromal schizophrenia	Eu21.15
39	[X]Pseudoneurotic schizophrenia	Eu21.16
40	[X]Pseudopsychopathic schizophrenia	Eu21.17
41	[X]Schizotypal personality disorder	Eu21.18
42	[X]Persistent delusional disorders	Eu22.00
43	[X]Delusional disorder	Eu22000
44	[X]Paranoid psychosis	Eu22011
45	[X]Paranoid state	Eu22012
46	[X]Paraphrenia - late	Eu22013
47	[X>Sensitiver Beziehungswahn	Eu22014
48	[X]Paranoia	Eu22015
49	[X]Delusional misidentification syndrome	Eu22100
50	[X]Capgras syndrome	Eu22111
51	[X]Cotard syndrome	Eu22200
52	[X]Other persistent delusional disorders	Eu22y00
53	[X]Delusional dysmorphophobia	Eu22y11
54	[X]Involutional paranoid state	Eu22y12
55	[X]Paranoia querulans	Eu22y13
56	[X]Persistent delusional disorder, unspecified	Eu22z00
57	[X]Acute and transient psychotic disorders	Eu23.00
58		
59		
60		

1	[X]Acute polymorphic psychot disord without symp of schizoph	Eu23000
2	[X]Bouffee delirante	Eu23011
3	[X]Cycloid psychosis	Eu23012
4	[X]Acute polymorphic psychot disord with symp of schizophren	Eu23100
5	[X]Bouffee delirante with symptoms of schizophrenia	Eu23111
6	[X]Cycloid psychosis with symptoms of schizophrenia	Eu23112
7	[X]Acute schizophrenia-like psychotic disorder	Eu23200
8	[X]Brief schizophreniform disorder	Eu23211
9	[X]Brief schizophrenifrm psych	Eu23212
10	[X]Oneirophrenia	Eu23213
11	[X]Schizophrenic reaction	Eu23214
12	[X]Other acute predominantly delusional psychotic disorders	Eu23300
13	[X]Psychogenic paranoid psychosis	Eu23312
14	[X]Other acute and transient psychotic disorders	Eu23y00
15	[X]Acute and transient psychotic disorder, unspecified	Eu23z00
16	[X]Brief reactive psychosis NOS	Eu23z11
17	[X]Reactive psychosis	Eu23z12
18	[X]Induced delusional disorder	Eu24.00
19	[X]Folie a deux	Eu24.11
20	[X]Induced paranoid disorder	Eu24.12
21	[X]Induced psychotic disorder	Eu24.13
22	[X]Schizoaffective disorders	Eu25.00
23	[X]Schizoaffective disorder, manic type	Eu25000
24	[X]Schizoaffective psychosis, manic type	Eu25011
25	[X]Schizophreniform psychosis, manic type	Eu25012
26	[X]Schizoaffective disorder, depressive type	Eu25100
27	[X]Schizoaffective psychosis, depressive type	Eu25111
28	[X]Schizophreniform psychosis, depressive type	Eu25112
29	[X]Schizoaffective disorder, mixed type	Eu25200
30	[X]Cyclic schizophrenia	Eu25211
31	[X]Mixed schizophrenic and affective psychosis	Eu25212
32	[X]Other schizoaffective disorders	Eu25y00
33	[X]Schizoaffective disorder, unspecified	Eu25z00
34	[X]Schizoaffective psychosis NOS	Eu25z11
35	[X]Other nonorganic psychotic disorders	Eu2y.00
36	[X]Chronic hallucinatory psychosis	Eu2y.11
37	[X]Unspecified nonorganic psychosis	Eu2z.00
38	[X]Psychosis NOS	Eu2z.11
39	[X]Manic episode	Eu30.00
40	[X]Bipolar disorder, single manic episode	Eu30.11
41	[X]Hypomania	Eu30000
42	[X]Mania without psychotic symptoms	Eu30100
43	[X]Mania with psychotic symptoms	Eu30200
44	[X]Mania with mood-congruent psychotic symptoms	Eu30211
45	[X]Mania with mood-incongruent psychotic symptoms	Eu30212
46	[X]Manic stupor	Eu30213
47	[X]Other manic episodes	Eu30y00
48	[X]Manic episode, unspecified	Eu30z00
49	[X]Mania NOS	Eu30z11
50	[X]Bipolar affective disorder	Eu31.00
51	[X]Manic-depressive illness	Eu31.11
52	[X]Manic-depressive psychosis	Eu31.12
53	[X]Mainc-depressive reaction	Eu31.13
54	[X]Bipolar affective disorder, current episode hypomanic	Eu31000

1		
2		
3		
4	[X]Bipolar affect disorder cur epi manic wout psychotic symp	Eu31100
5	[X]Bipolar affect disorder cur epi manic with psychotic symp	Eu31200
6	[X]Bipolar affect disorder cur epi mild or moderate depressn	Eu31300
7	[X]Bipol aff disord, curr epis sev depress, no psychot symp	Eu31400
8	[X]Bipolar affect dis cur epi severe depres with psyc symp	Eu31500
9	[X]Bipolar affective disorder, current episode mixed	Eu31600
10	[X]Bipolar affective disorder, currently in remission	Eu31700
11	[X]Other bipolar affective disorders	Eu31y00
12	[X]Bipolar II disorder	Eu31y11
13	[X]Recurrent manic episodes	Eu31y12
14	[X]Bipolar affective disorder, unspecified	Eu31z00
15	[X]Severe depressive episode with psychotic symptoms	Eu32300
16	[X]Single episode of major depression and psychotic symptoms	Eu32311
17	[X]Single episode of psychogenic depressive psychosis	Eu32312
18	[X]Single episode of psychotic depression	Eu32313
19	[X]Single episode of reactive depressive psychosis	Eu32314
20	[X]Major depression, severe with psychotic symptoms	Eu32800
21	[X]Manic-depress psychosis,depressed,no psychotic symptoms	Eu33213
22	[X]Recurrent depress disorder cur epi severe with psyc symp	Eu33300
23	[X]Endogenous depression with psychotic symptoms	Eu33311
24	[X]Manic-depress psychosis,depressed type+psychotic symptoms	Eu33312
25	[X]Recurr severe episodes/major depression+psychotic symptom	Eu33313
26	[X]Recurr severe episodes/psychogenic depressive psychosis	Eu33314
27	[X]Recurrent severe episodes of psychotic depression	Eu33315
28	[X]Recurrent severe episodes/reactive depressive psychosis	Eu33316
29	[X]Affective psychosis NOS	Eu3z.11
30	[X]Hysterical psychosis	Eu44.14
31	[X]Symbiotic psychosis	Eu84314
32	Profile of mood states, bipolar	ZRby100
33	Schizophrenic language	ZS7C611
34	[V]Personal history of schizophrenia	ZV11000
35	[V]Personal history of manic-depressive psy	ZV11111
36	[V]Personal history of manic-depressive psy	ZV11112
37		
38		
39		
40		
41		
42		
43		
44		
45		
46		
47		
48		
49		
50		
51		
52		
53		
54		
55		
56		
57		
58		
59		
60		

1  
2  
3 **Appendix 2**  
4

5 **First generation antipsychotics**

6 Benperidol  
7 Chlorpromazine  
8 Droperidol  
9 Flupenthix  
10 Flupentixol  
11 Fluphenaz  
12 Fluphenazine  
13 Fluspirilene  
14 Hadol  
15 Haloperidol  
16 Levomepromazine  
17 Loxapine  
18 Oxypertine  
19 Paliperidone  
20 Pericyazine  
21 Perphenazine  
22 Pimozide  
23 Pipotiazine  
24 Promazine  
25 Sulpiride  
26 Thioridazine  
27 Trifluoperazine  
28 Trifluoperidol  
29 Zuclopenthix  
30 Zuclopenthixol  
31  
32  
33

34 **Second generation antipsychotics**

35 Amisulpride  
36 Aripiprazole  
37 Clozapine  
38 Olanzapine  
39 Quetiapine  
40 Remoxipride  
41 Risperidone  
42 Sertindole  
43 Sertindone  
44 Zotepine  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7, 8
Study size	10	Explain how the study size was arrived at	7-9+figure
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	9-10
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9+figure
		(b) Give reasons for non-participation at each stage	figure
		(c) Consider use of a flow diagram	figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16, Table 3
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9, 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-11, 13, Tables 1, 2a, 2b
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11, 13, Tables 1, 2a, 2b
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11, 13, Tables 1, 2a, 2b
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	20
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).