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

Louise Marston[1*]

Irwin Nazareth[1]

Irene Petersen[1]

Kate Walters[1]

David PJ Osborn[2,3]

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

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

3. Camden and Islington NHS Foundation Trust, London UK.

***Corresponding author-**

Dr Louise Marston

Research Department of Primary Care and Population Health

UCL

London

NW3 2PF

Email: l.marston@ucl.ac.uk

Telephone: +44 (0) 20 7794 0500 (36768)

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**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

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 records 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 recorded 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 recorded diagnosis of a psychosis or bipolar disorder.
- Findings were similar for second generation agents, although 62% of people receiving olanzapine did have a record 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.

- 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.

**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

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

**Participants**

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

**Antipsychotic data**

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

40mg for olanzapine, over 1500 for quetiapine and over 32 mg for risperidone. Relatively few (221) prescriptions were excluded for this reason.

**Mental health conditions**

We defined severe mental illness as schizophrenia-like disorders, bipolar affective disorders and other non-organic psychosis such as delusional disorder, "psychoses not otherwise specified" and severe depression with psychoses (Appendix I). We identified an additional category for people who were included on the practice's SMI register without having a Read code for the SMI diagnoses above (a GP SMI register is required as part of the GP contract in the UK since 2004).

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

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

**Ethical approval**

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

part of an additional MREC approval from the London Research Ethics Committee. Reference number: 09/H0718/11.

**Statistical analysis**

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

We calculated frequencies (%) for each recorded indication (diagnosis) for each of the six most commonly prescribed antipsychotics. We also calculated the median (interquartile range) daily dose in milligrams and length of time prescribed a given antipsychotic within three groups: The SMI (psychosis/bipolar) subgroup, the group with non-SMI diagnoses and the group with no record of any of these diagnoses.

Analyses were carried out using Stata version 13.[16]

**RESULTS**

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

length of follow-up was slightly longer for those receiving both first and second generation antipsychotic (3.0 years; IQR 1.7, 4.7).

[Figure 1 here]

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

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

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.

The three most commonly prescribed first generation antipsychotics were haloperidol, chlorpromazine and trifluoperazine; while olanzapine, risperidone and quetiapine were the most commonly issued second generation agents (Tables 2a and 2b). Rates of prescribing these individual agents followed similar patterns to the aggregate results in terms of their distributions by age and deprivation. Haloperidol and trifluoperazine were more commonly prescribed to women, as was quetiapine, while rates of risperidone and olanzapine prescribing were lower in women. Few under-18s received antipsychotics, but compared to other agents, risperidone was prescribed far more commonly to this young age group (Table 2b). Over the five years of the study (2007-2011), rates of prescribing for each first generation agent decreased while quetiapine prescription rates increased the most over time. For example, IRR for trifluoperazine in 2011 (reference category is 2007) 0.665 (95% CI 0.645, 0.685) and IRR for quetiapine in 2011 (reference category is 2007) 1.480 (95% CI 1.463, 1.497). There was a smaller increase in rates of prescribing for both risperidone and olanzapine (Table 2b).

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 | % |
| **SMI*** | | | | | | | | | | | | |
| 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 |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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.

The median daily dose for antipsychotics was higher in those who did have a SMI diagnosis, and highest amongst those with records of schizophrenia (Table 4). Within the non-SMI groups, median daily doses were similar although the highest doses were observed in people with a record of a sleep disorder or personality disorder. The longest durations of antipsychotic treatment were generally observed for people with a diagnosis of schizophrenia or in those who were included on the SMI register in general practice (Supplementary Table 4a). Within the non-SMI group, duration of treatment showed little variation between diagnoses, although the median length of treatment seemed longest in people with dementia or ADHD.

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 |
| **SMI*** | | | | | | | | | | | | |
| 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) |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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

quetiapine were also highest in those with sleep disorders, post-traumatic stress disorder and personality disorder.

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

Secondly it is possible that in real life practice antipsychotics are prescribed quite commonly to people with problems related to depression, anxiety, sleep, dementia and other conditions, despite guidelines recommending caution and only suggesting this as a strategy in treatment unresponsive cases.[3, 6] It maybe that clinicians and/or mental health professionals quite frequently add antipsychotics to the treatment plan for people with non-psychotic disorders, either for agitation, poor sleep, anxiety or due to their general reputation as tranquilising medications. Since there were not major differences in the median doses and duration of treatment according to recorded diagnosis, these patterns of prescribing warrant some attention in terms of monitoring side effects particularly weight gain, extra-pyramidal side effects and metabolic impacts such as hyperprolactinaemia, glucose dysregulation and effects on lipid profiles. Current UK policy only recommends physical monitoring for people who the general practice includes on its SMI register. It may be that this recommendation should be extended to all people prescribed antipsychotics in primary care.

**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

randomised controlled trials involving people with personality disorder have shown little benefit of antipsychotics over placebo.[6, 23]

Finally it is important to explore whether these agents are discontinued following amelioration of any mental health problem for which they are chosen, and to assess the risks and benefits of stopping such agents in different diagnostic groups.

Figure legend

Figure 1: Flow of individuals through the study

**Conflict of Interest**

The authors have no conflicts of interest to declare.

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**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

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**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 |
| **Introduction** | | | |
| 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 |
| **Methods** | | | |
| 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 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| 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 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 19 |
| **Limitations** | | | |
| 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 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 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.

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 |

| | |
|---|---|
| Bipolar affective disorder, currently depressed, moderate | E115200 |
| Bipolar affect disord, now depressed, severe, no psychosis | E115300 |
| Bipolar affect disord, now depressed, severe with psychosis | E115400 |
| Bipolar affect disord, now depressed, part/unspec remission | E115500 |
| Bipolar affective disorder, now depressed, in full remission | E115600 |
| Bipolar affective disorder, currently depressed, NOS | E115z00 |
| Mixed bipolar affective disorder | E116.00 |
| Mixed bipolar affective disorder, unspecified | E116000 |
| Mixed bipolar affective disorder, mild | E116100 |
| Mixed bipolar affective disorder, moderate | E116200 |
| Mixed bipolar affective disorder, severe, without psychosis | E116300 |
| Mixed bipolar affective disorder, severe, with psychosis | E116400 |
| Mixed bipolar affective disorder, partial/unspec remission | E116500 |
| Mixed bipolar affective disorder, in full remission | E116600 |
| Mixed bipolar affective disorder, NOS | E116z00 |
| Unspecified bipolar affective disorder | E117.00 |
| Unspecified bipolar affective disorder, unspecified | E117000 |
| Unspecified bipolar affective disorder, mild | E117100 |
| Unspecified bipolar affective disorder, moderate | E117200 |
| Unspecified bipolar affective disorder, severe, no psychosis | E117300 |
| Unspecified bipolar affective disorder,severe with psychosis | E117400 |
| Unspecified bipolar affect disord, partial/unspec remission | E117500 |
| Unspecified bipolar affective disorder, in full remission | E117600 |
| Unspecified bipolar affective disorder, NOS | E117z00 |
| Other and unspecified manic-depressive psychoses | E11y.00 |
| Unspecified manic-depressive psychoses | E11y000 |
| Atypical manic disorder | E11y100 |
| Other mixed manic-depressive psychoses | E11y300 |
| Other and unspecified manic-depressive psychoses NOS | E11yz00 |
| Other and unspecified affective psychoses | E11z.00 |
| Unspecified affective psychoses NOS | E11z000 |
| Other affective psychosis NOS | E11zz00 |
| Paranoid states | E12..00 |
| Simple paranoid state | E120.00 |
| Chronic paranoid psychosis | E121.00 |
| Sander's disease | E121.11 |
| Paraphrenia | E122.00 |
| Shared paranoid disorder | E123.00 |
| Folie a deux | E123.11 |
| Other paranoid states | E12y.00 |
| Paranoia querulans | E12y000 |
| Other paranoid states NOS | E12yz00 |
| Paranoid psychosis NOS | E12z.00 |
| Other nonorganic psychoses | E13..00 |
| Reactive psychoses | E13..11 |
| Reactive depressive psychosis | E130.00 |
| Psychotic reactive depression | E130.11 |
| Acute hysterical psychosis | E131.00 |
| Acute paranoid reaction | E133.00 |
| Bouffee delirante | E133.11 |
| Psychogenic paranoid psychosis | E134.00 |
| Other reactive psychoses | E13y.00 |
| Psychogenic stupor | E13y000 |
| Brief reactive psychosis | E13y100 |

| | |
|---|---|
| Other reactive psychoses NOS | E13yz00 |
| Nonorganic psychosis NOS | E13z.00 |
| Psychotic episode NOS | E13z.11 |
| Other specified non-organic psychoses | E1y..00 |
| Non-organic psychosis NOS | E1z..00 |
| Schizotypal personality | E212200 |
| [X]Schizophrenia, schizotypal and delusional disorders | Eu2..00 |
| [X]Schizophrenia | Eu20.00 |
| [X]Paranoid schizophrenia | Eu20000 |
| [X]Paraphrenic schizophrenia | Eu20011 |
| [X]Hebephrenic schizophrenia | Eu20100 |
| [X]Disorganised schizophrenia | Eu20111 |
| [X]Catatonic schizophrenia | Eu20200 |
| [X]Catatonic stupor | Eu20211 |
| [X]Schizophrenic catalepsy | Eu20212 |
| [X]Schizophrenic catatonia | Eu20213 |
| [X]Schizophrenic flexibilatis cerea | Eu20214 |
| [X]Undifferentiated schizophrenia | Eu20300 |
| [X]Atypical schizophrenia | Eu20311 |
| [X]Post-schizophrenic depression | Eu20400 |
| [X]Residual schizophrenia | Eu20500 |
| [X]Chronic undifferentiated schizophrenia | Eu20511 |
| [X]Restzustand schizophrenic | Eu20512 |
| [X]Simple schizophrenia | Eu20600 |
| [X]Other schizophrenia | Eu20y00 |
| [X]Cenesthopathic schizophrenia | Eu20y11 |
| [X]Schizophreniform disord NOS | Eu20y12 |
| [X]Schizophrenifrm psychos NOS | Eu20y13 |
| [X]Schizophrenia, unspecified | Eu20z00 |
| [X]Schizotypal disorder | Eu21.00 |
| [X]Latent schizophrenic reaction | Eu21.11 |
| [X]Borderline schizophrenia | Eu21.12 |
| [X]Latent schizophrenia | Eu21.13 |
| [X]Prepsychotic schizophrenia | Eu21.14 |
| [X]Prodromal schizophrenia | Eu21.15 |
| [X]Pseudoneurotic schizophrenia | Eu21.16 |
| [X]Pseudopsychopathic schizophrenia | Eu21.17 |
| [X]Schizotypal personality disorder | Eu21.18 |
| [X]Persistent delusional disorders | Eu22.00 |
| [X]Delusional disorder | Eu22000 |
| [X]Paranoid psychosis | Eu22011 |
| [X]Paranoid state | Eu22012 |
| [X]Paraphrenia - late | Eu22013 |
| [X]Sensitiver Beziehungswahn | Eu22014 |
| [X]Paranoia | Eu22015 |
| [X]Delusional misidentification syndrome | Eu22100 |
| [X]Capgras syndrome | Eu22111 |
| [X]Cotard syndrome | Eu22200 |
| [X]Other persistent delusional disorders | Eu22y00 |
| [X]Delusional dysmorphophobia | Eu22y11 |
| [X]Involutional paranoid state | Eu22y12 |
| [X]Paranoia querulans | Eu22y13 |
| [X]Persistent delusional disorder, unspecified | Eu22z00 |
| [X]Acute and transient psychotic disorders | Eu23.00 |

| | |
|---|---|
| [X]Acute polymorphic psychot disord without symp of schizoph | Eu23000 |
| [X]Bouffee delirante | Eu23011 |
| [X]Cycloid psychosis | Eu23012 |
| [X]Acute polymorphic psychot disord with symp of schizophren | Eu23100 |
| [X]Bouffee delirante with symptoms of schizophrenia | Eu23111 |
| [X]Cycloid psychosis with symptoms of schizophrenia | Eu23112 |
| [X]Acute schizophrenia-like psychotic disorder | Eu23200 |
| [X]Brief schizophreniform disorder | Eu23211 |
| [X]Brief schizophrenifrm psych | Eu23212 |
| [X]Oneirophrenia | Eu23213 |
| [X]Schizophrenic reaction | Eu23214 |
| [X]Other acute predominantly delusional psychotic disorders | Eu23300 |
| [X]Psychogenic paranoid psychosis | Eu23312 |
| [X]Other acute and transient psychotic disorders | Eu23y00 |
| [X]Acute and transient psychotic disorder, unspecified | Eu23z00 |
| [X]Brief reactive psychosis NOS | Eu23z11 |
| [X]Reactive psychosis | Eu23z12 |
| [X]Induced delusional disorder | Eu24.00 |
| [X]Folie a deux | Eu24.11 |
| [X]Induced paranoid disorder | Eu24.12 |
| [X]Induced psychotic disorder | Eu24.13 |
| [X]Schizoaffective disorders | Eu25.00 |
| [X]Schizoaffective disorder, manic type | Eu25000 |
| [X]Schizoaffective psychosis, manic type | Eu25011 |
| [X]Schizophreniform psychosis, manic type | Eu25012 |
| [X]Schizoaffective disorder, depressive type | Eu25100 |
| [X]Schizoaffective psychosis, depressive type | Eu25111 |
| [X]Schizophreniform psychosis, depressive type | Eu25112 |
| [X]Schizoaffective disorder, mixed type | Eu25200 |
| [X]Cyclic schizophrenia | Eu25211 |
| [X]Mixed schizophrenic and affective psychosis | Eu25212 |
| [X]Other schizoaffective disorders | Eu25y00 |
| [X]Schizoaffective disorder, unspecified | Eu25z00 |
| [X]Schizoaffective psychosis NOS | Eu25z11 |
| [X]Other nonorganic psychotic disorders | Eu2y.00 |
| [X]Chronic hallucinatory psychosis | Eu2y.11 |
| [X]Unspecified nonorganic psychosis | Eu2z.00 |
| [X]Psychosis NOS | Eu2z.11 |
| [X]Manic episode | Eu30.00 |
| [X]Bipolar disorder, single manic episode | Eu30.11 |
| [X]Hypomania | Eu30000 |
| [X]Mania without psychotic symptoms | Eu30100 |
| [X]Mania with psychotic symptoms | Eu30200 |
| [X]Mania with mood-congruent psychotic symptoms | Eu30211 |
| [X]Mania with mood-incongruent psychotic symptoms | Eu30212 |
| [X]Manic stupor | Eu30213 |
| [X]Other manic episodes | Eu30y00 |
| [X]Manic episode, unspecified | Eu30z00 |
| [X]Mania NOS | Eu30z11 |
| [X]Bipolar affective disorder | Eu31.00 |
| [X]Manic-depressive illness | Eu31.11 |
| [X]Manic-depressive psychosis | Eu31.12 |
| [X]Mainc-depressive reaction | Eu31.13 |
| [X]Bipolar affective disorder, current episode hypomanic | Eu31000 |

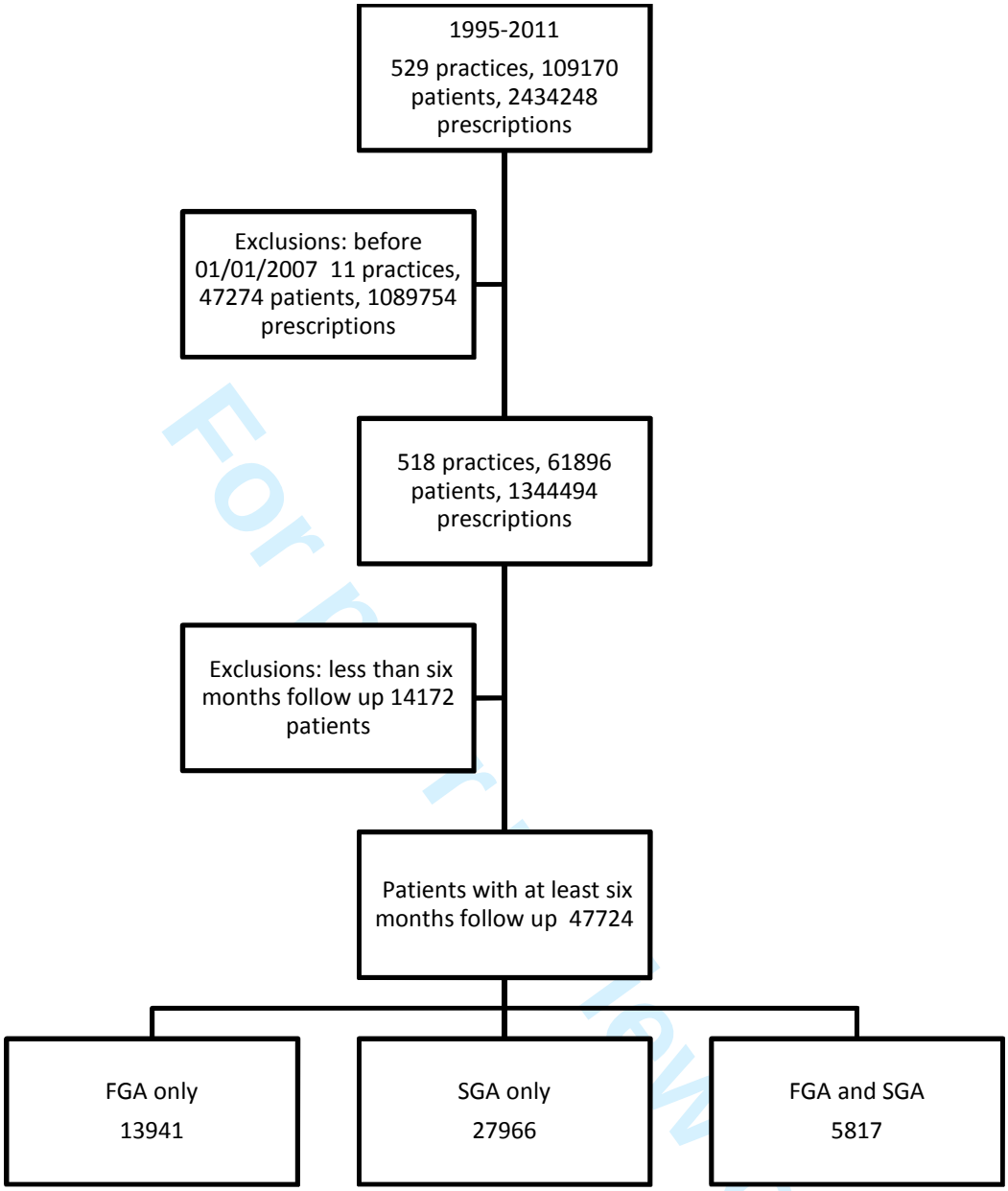
| | |
|---|---|
| [X]Bipolar affect disorder cur epi manic wout psychotic symp | Eu31100 |
| [X]Bipolar affect disorder cur epi manic with psychotic symp | Eu31200 |
| [X]Bipolar affect disorder cur epi mild or moderate depressn | Eu31300 |
| [X]Bipol aff disord, curr epis sev depress, no psychot symp | Eu31400 |
| [X]Bipolar affect dis cur epi severe depres with psyc symp | Eu31500 |
| [X]Bipolar affective disorder, current episode mixed | Eu31600 |
| [X]Bipolar affective disorder, currently in remission | Eu31700 |
| [X]Other bipolar affective disorders | Eu31y00 |
| [X]Bipolar II disorder | Eu31y11 |
| [X]Recurrent manic episodes | Eu31y12 |
| [X]Bipolar affective disorder, unspecified | Eu31z00 |
| [X]Severe depressive episode with psychotic symptoms | Eu32300 |
| [X]Single episode of major depression and psychotic symptoms | Eu32311 |
| [X]Single episode of psychogenic depressive psychosis | Eu32312 |
| [X]Single episode of psychotic depression | Eu32313 |
| [X]Single episode of reactive depressive psychosis | Eu32314 |
| [X]Major depression, severe with psychotic symptoms | Eu32800 |
| [X]Manic-depress psychosis,depressd,no psychotic symptoms | Eu33213 |
| [X]Recurrent depress disorder cur epi severe with psyc symp | Eu33300 |
| [X]Endogenous depression with psychotic symptoms | Eu33311 |
| [X]Manic-depress psychosis,depressed type+psychotic symptoms | Eu33312 |
| [X]Recurr severe episodes/major depression+psychotic symptom | Eu33313 |
| [X]Recurr severe episodes/psychogenic depressive psychosis | Eu33314 |
| [X]Recurrent severe episodes of psychotic depression | Eu33315 |
| [X]Recurrent severe episodes/reactive depressive psychosis | Eu33316 |
| [X]Affective psychosis NOS | Eu3z.11 |
| [X]Hysterical psychosis | Eu44.14 |
| [X]Symbiotic psychosis | Eu84314 |
| Profile of mood states, bipolar | ZRby100 |
| Schizophrenic language | ZS7C611 |
| [V]Personal history of schizophrenia | ZV11000 |
| [V]Personal history of manic-depressive psy | ZV11111 |
| [V]Personal history of manic-depressive psy | ZV11112 |

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 |
| **SMI*** | | | | | | | | | | | | |
| 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) |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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.



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



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| | |

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

Louise Marston[1*]

Irwin Nazareth[1]

Irene Petersen[1]

Kate Walters[1]

David PJ Osborn[2,3]

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

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

3. Camden and Islington NHS Foundation Trust, London UK.

***Corresponding author-**

Dr Louise Marston

Research Department of Primary Care and Population Health

UCL

London

NW3 2PF

Email: l.marston@ucl.ac.uk

Telephone: +44 (0) 20 7794 0500 (36768)

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**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.

- 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.

**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

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

**Participants**

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

**Antipsychotic data**

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

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

**Mental health conditions**

We defined severe mental illness as schizophrenia-like disorders, bipolar affective disorders and other non-organic psychosis such as delusional disorder, "psychoses not otherwise specified" and severe depression with psychoses (Appendix 1). Read codes for SMI diagnoses have been previously been validated.[16] We identified an additional category for people who were included on the practice's SMI register without having a Read code for the SMI diagnoses above (a GP SMI register is required as part of the GP contract in the UK since 2004). Hardoon et al[17] determined that the prevalence of SMI in THIN is similar to that of epidemiological studies.

Next we identified common mental health conditions for which antipsychotics might be prescribed off-label, using diagnostic Read code lists compiled by two clinical academics - a GP and a psychiatrist.[18] These non-SMI conditions comprised depression, anxiety disorders, sleep disorders (insomnia, non-specific sleep disorders, apnoea, hypersomnia), dementia, attention deficit and hyperactivity disorder, personality disorders, post-traumatic stress disorder and obsessive

compulsive disorder. These have not been validated; however, we have reported on trends in anxiety and depression symptom and diagnosis recording in THIN.[19, 20]

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

**Ethical approval**

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

**Statistical analysis**

We calculated rates of prescribing any antipsychotics, per 100,000 person years at risk (PYAR). We then calculated rates of any first or second generation antipsychotics then we determined rates of prescribing individual agents for the three most commonly prescribed first and second generation antipsychotic agents. Multivariable Poisson regression was used to determine associations between sex, age group, Townsend deprivation quintile, calendar year and 1) overall antipsychotic prescribing, 2) All first and second generation antipsychotic agents and 3) The six most commonly prescribed individual antipsychotics. For these analyses, we defined the population at risk as the total population registered with the general practices in the period 2007-2011.

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

Analyses were carried out using Stata version 13.[21]

**RESULTS**

We identified 47,724 eligible individuals who were prescribed antipsychotic medications. Of these 13,941 were solely prescribed first generation antipsychotics, 27,966 solely second generation antipsychotics and 5817 received both classes of agent during their follow-up period (Figure 1). The median length of follow-up for people receiving any antipsychotic was 2.4 years (IQR 1.3, 4.1). The length of follow-up was slightly longer for those receiving both first and second generation antipsychotic (3.0 years; IQR 1.7, 4.7).

[Figure 1 here]

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

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

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).

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.

The three most commonly prescribed first generation antipsychotics were haloperidol, chlorpromazine and trifluoperazine; while olanzapine, risperidone and quetiapine were the most commonly issued second generation agents (Tables 2a and 2b). Rates of prescribing these individual agents followed similar patterns to the aggregate results in terms of their distributions by age and deprivation. Haloperidol and trifluoperazine were more commonly prescribed to women, as was quetiapine, while rates of risperidone and olanzapine prescribing were lower in women. Few under-18s received antipsychotics, but compared to other agents, risperidone was prescribed far more commonly to this young age group (Table 2b). Over the five years of the study (2007-2011), rates of prescribing for each first generation agent decreased while quetiapine prescription rates increased the most over time. For example, IRR for trifluoperazine in 2011 (reference category is 2007) 0.665 (95% CI 0.645, 0.685) and IRR for quetiapine in 2011 (reference category is 2007) 1.480 (95% CI 1.463, 1.497). There was a smaller increase in rates of prescribing for both risperidone and olanzapine (Table 2b).

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 | % |
| **SMI*** | | | | | | | | | | | | |
| 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 |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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.

The median daily dose for antipsychotics was higher in those who did have a SMI diagnosis, and highest amongst those with records of schizophrenia (Table 4). Within the non-SMI groups, median daily doses were similar although the highest doses were observed in people with a record of a sleep disorder or personality disorder. The longest durations of antipsychotic treatment were generally observed for people with a diagnosis of schizophrenia or in those who were included on the SMI register in general practice (Supplementary Table 1). Within the non-SMI group, duration of treatment showed little variation between diagnoses, although the median length of treatment seemed longest in people with dementia or ADHD.

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 |
| **SMI*** | | | | | | | | | | | | |
| 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) |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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.

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 quetiapine were also highest in those with sleep disorders, post-traumatic stress disorder and personality disorder. Whilst median dose is a crude method of quantifying the amount prescribed for each indication explored in this paper, it does allow us to make comparisons between these diagnoses.

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

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

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

**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[27] but of course this may not mean patients have been actually taking the medication. Primary care diagnoses of SMI have been validated,[16] however this is not the case for some other conditions we explored such as ADHD and OCD.

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. For non-SMI diagnoses such as depression and anxiety, we extracted all diagnoses which had been entered at any time. We did this because GPs do not routinely re-enter diagnoses at each subsequent appointments and we wanted to capture all relevant information regarding possible indication. A limitation of this method, and of the database, is that we cannot be certain that the decision to prescribe was temporally related to the mental health condition entered at another time. However, this method does give an indication of the long term clinical presentation of people without an SMI Read code who are prescribed antipsychotics. It would be useful to explore the

reasons underpinning these high rates of prescribing 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 for instance benzodiazepines and mood stabilisers. 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.[28] The few existing randomised controlled trials involving people with personality disorder have shown little benefit of antipsychotics over placebo.[6, 29]

Finally it is important to explore whether these agents are discontinued following amelioration of any mental health problem for which they are chosen, and to assess the risks and benefits of stopping such agents in different diagnostic groups.

Figure legend

Figure 1: Flow of individuals through the study

**Conflict of Interest**

The authors have no conflicts of interest to declare.

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**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

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

Louise Marston[1*]

Irwin Nazareth[1]

Irene Petersen[1]

Kate Walters[1]

David PJ Osborn[2,3]

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

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

3. Camden and Islington NHS Foundation Trust, London UK.

***Corresponding author-**

Dr Louise Marston

Research Department of Primary Care and Population Health

UCL

London

NW3 2PF

Email: l.marston@ucl.ac.uk

Telephone: +44 (0) 20 7794 0500 (36768)

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**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

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 ~~records~~ 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 ~~recorded~~ 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 ~~recorded~~ diagnosis of a psychosis or bipolar disorder.
- Findings were similar for second generation agents, although 62% of people receiving olanzapine did have a ~~record~~ 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.

- Other common~~ly 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.

**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 none ~~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 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.[~~8~~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.[~~9~~10] Data such as diagnoses and symptoms are entered as Read codes, a hierarchical classification system.[~~10~~11] The database also includes records of all prescriptions issued and these are linked to the British National Formulary (BNF).[~~11~~12] The exception to this is Clozapine, which is almost exclusively prescribed and monitored in hospital

outpatient clinics. Prescribing is well recorded in THIN because all prescriptions from general practice are generated via the computerised system. This information produces a longitudinal record for each individual in the database. Ninety eight percent of the UK population is registered with a general practice;[9] THIN is representative of the general UK population in terms of their demographic characteristics[~~12~~13] and practices are geographically spread across the UK. At the time of this study the full database included almost 10 million patients. For quality purposes data were only extracted after the date at which there was evidence that general practices were using their computer system fully (acceptable computer use (ACU) dates[~~13~~14]) and mortality were adequately recorded (Acceptable Mortality Rate (AMR)[~~14~~15]).

**Participants**

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

**Antipsychotic data**

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

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

**Mental health conditions**

We defined severe mental illness as schizophrenia-like disorders, bipolar affective disorders and other non-organic psychosis such as delusional disorder, "psychoses not otherwise specified" and severe depression with psychoses (Appendix ~~1~~1). Read codes for SMI diagnoses have been previously been validated.[16] We identified an additional category for people who were included on the practice's SMI register without having a Read code for the SMI diagnoses above (a GP SMI register is required as part of the GP contract in the UK since 2004). Hardoon et al[17] determined that the prevalence of SMI in THIN is similar to that of epidemiological studies.

Next we identified common mental health conditions for which antipsychotics might be prescribed off-label, using diagnostic Read code lists compiled by two clinical academics - a GP and a psychiatrist.[~~15~~18] These non-SMI conditions comprised depression, anxiety disorders, sleep disorders (insomnia, non-specific sleep disorders, apnoea, hypersomnia), dementia, attention deficit and hyperactivity disorder, personality disorders, post-traumatic stress disorder and obsessive

compulsive disorder. These have not been validated; however, we have reported on trends in anxiety and depression symptom and diagnosis recording in THIN.[19, 20]

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

**Ethical approval**

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

**Statistical analysis**

We calculated rates of prescribing any antipsychotics, per 100,000 person years at risk (PYAR). We then calculated rates of any first or second generation antipsychotics then we determined rates of prescribing individual agents for the three most commonly prescribed first and second generation antipsychotic agents. Multivariable Poisson regression was used to determine associations between sex, age group, Townsend deprivation quintile, calendar year and 1) overall antipsychotic prescribing, 2) All first and second generation antipsychotic agents and 3) The six most commonly prescribed individual antipsychotics. For these analyses, we defined the population at risk as the total population registered with the general practices in the period 2007-2011.

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

Analyses were carried out using Stata version 13.[~~16~~21]

**RESULTS**

We identified 47,724 eligible individuals who were prescribed antipsychotic medications. Of these 13,941 were solely prescribed first generation antipsychotics, 27,966 solely second generation antipsychotics and 5817 received both classes of agent during their follow-up period (Figure 1). The median length of follow-up for people receiving any antipsychotic was 2.4 years (IQR 1.3, 4.1). The length of follow-up was slightly longer for those receiving both first and second generation antipsychotic (3.0 years; IQR 1.7, 4.7).

[Figure 1 here]

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

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

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).

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.

The three most commonly prescribed first generation antipsychotics were haloperidol, chlorpromazine and trifluoperazine; while olanzapine, risperidone and quetiapine were the most commonly issued second generation agents (Tables 2a and 2b). Rates of prescribing these individual agents followed similar patterns to the aggregate results in terms of their distributions by age and deprivation. Haloperidol and trifluoperazine were more commonly prescribed to women, as was quetiapine, while rates of risperidone and olanzapine prescribing were lower in women. Few under-18s received antipsychotics, but compared to other agents, risperidone was prescribed far more commonly to this young age group (Table 2b). Over the five years of the study (2007-2011), rates of prescribing for each first generation agent decreased while quetiapine prescription rates increased the most over time. For example, IRR for trifluoperazine in 2011 (reference category is 2007) 0.665 (95% CI 0.645, 0.685) and IRR for quetiapine in 2011 (reference category is 2007) 1.480 (95% CI 1.463, 1.497). There was a smaller increase in rates of prescribing for both risperidone and olanzapine (Table 2b).

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 | % |
| **SMI*** | | | | | | | | | | | | |
| 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 |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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.

The median daily dose for antipsychotics was higher in those who did have a SMI diagnosis, and highest amongst those with records of schizophrenia (Table 4). Within the non-SMI groups, median daily doses were similar although the highest doses were observed in people with a record of a sleep disorder or personality disorder. The longest durations of antipsychotic treatment were generally observed for people with a diagnosis of schizophrenia or in those who were included on the SMI register in general practice (Supplementary Table ~~4a~~1). Within the non-SMI group, duration of treatment showed little variation between diagnoses, although the median length of treatment seemed longest in people with dementia or ADHD.

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 |
| **SMI*** | | | | | | | | | | | | |
| 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) |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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~~DISCUSSION

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.[~~17~~25, ~~18~~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.

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 quetiapine were also highest in those with sleep disorders, post-traumatic stress disorder and personality disorder. Whilst median dose is a crude method of quantifying the amount prescribed for each indication explored in this paper, it does allow us to make comparisons between these diagnoses.

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

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

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

**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~~27] but of course this may not mean patients have been actually taking the medication. Primary care diagnoses of SMI have been validated,[~~21~~16] however this is not the case for some other conditions we explored such as ADHD and ~~anxiety~~OCD.

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. For non-SMI diagnoses such as depression and anxiety, we extracted all diagnoses which had been entered at any time. We did this because GPs do not routinely re-enter diagnoses at each subsequent appointments and we wanted to capture all relevant information regarding possible indication. A limitation of this method, and of the database, is that we cannot be certain that the decision to prescribe was temporally related to the mental health condition entered at another time.

However, this method does give an indication of the long term clinical presentation of people without an SMI Read code who are prescribed antipsychotics. It would be useful to explore the reasons underpinning these high rates of ~~prescription~~ prescribing 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 for instance benzodiazepines and mood stabilisers. 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~~28] The few existing randomised controlled trials involving people with personality disorder have shown little benefit of antipsychotics over placebo.[6, ~~23~~29]

Finally it is important to explore whether these agents are discontinued following amelioration of any mental health problem for which they are chosen, and to assess the risks and benefits of stopping such agents in different diagnostic groups.

Figure legend

Figure 1: Flow of individuals through the study

**Conflict of Interest**

The authors have no conflicts of interest to declare.

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**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

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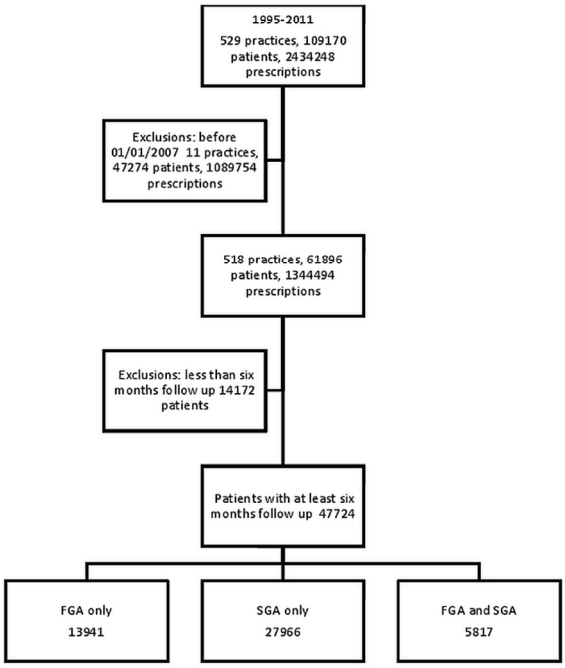


Flow of individuals through the study
90x127mm (300 x 300 DPI)

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 |
| **SMI*** | | | | | | | | | | | | |
| 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) |
| | | | | | | | | | | | | |
| **Non-SMI*** | | | | | | | | | | | | |
| 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 |

| | |
|---|---|
| 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 |

| | |
|---|---|
| Bipolar affective disorder, currently depressed, moderate | E115200 |
| Bipolar affect disord, now depressed, severe, no psychosis | E115300 |
| Bipolar affect disord, now depressed, severe with psychosis | E115400 |
| Bipolar affect disord, now depressed, part/unspec remission | E115500 |
| Bipolar affective disorder, now depressed, in full remission | E115600 |
| Bipolar affective disorder, currently depressed, NOS | E115z00 |
| Mixed bipolar affective disorder | E116.00 |
| Mixed bipolar affective disorder, unspecified | E116000 |
| Mixed bipolar affective disorder, mild | E116100 |
| Mixed bipolar affective disorder, moderate | E116200 |
| Mixed bipolar affective disorder, severe, without psychosis | E116300 |
| Mixed bipolar affective disorder, severe, with psychosis | E116400 |
| Mixed bipolar affective disorder, partial/unspec remission | E116500 |
| Mixed bipolar affective disorder, in full remission | E116600 |
| Mixed bipolar affective disorder, NOS | E116z00 |
| Unspecified bipolar affective disorder | E117.00 |
| Unspecified bipolar affective disorder, unspecified | E117000 |
| Unspecified bipolar affective disorder, mild | E117100 |
| Unspecified bipolar affective disorder, moderate | E117200 |
| Unspecified bipolar affective disorder, severe, no psychosis | E117300 |
| Unspecified bipolar affective disorder,severe with psychosis | E117400 |
| Unspecified bipolar affect disord, partial/unspec remission | E117500 |
| Unspecified bipolar affective disorder, in full remission | E117600 |
| Unspecified bipolar affective disorder, NOS | E117z00 |
| Other and unspecified manic-depressive psychoses | E11y.00 |
| Unspecified manic-depressive psychoses | E11y000 |
| Atypical manic disorder | E11y100 |
| Other mixed manic-depressive psychoses | E11y300 |
| Other and unspecified manic-depressive psychoses NOS | E11yz00 |
| Other and unspecified affective psychoses | E11z.00 |
| Unspecified affective psychoses NOS | E11z000 |
| Other affective psychosis NOS | E11zz00 |
| Paranoid states | E12..00 |
| Simple paranoid state | E120.00 |
| Chronic paranoid psychosis | E121.00 |
| Sander's disease | E121.11 |
| Paraphrenia | E122.00 |
| Shared paranoid disorder | E123.00 |
| Folie a deux | E123.11 |
| Other paranoid states | E12y.00 |
| Paranoia querulans | E12y000 |
| Other paranoid states NOS | E12yz00 |
| Paranoid psychosis NOS | E12z.00 |
| Other nonorganic psychoses | E13..00 |
| Reactive psychoses | E13..11 |
| Reactive depressive psychosis | E130.00 |
| Psychotic reactive depression | E130.11 |
| Acute hysterical psychosis | E131.00 |
| Acute paranoid reaction | E133.00 |
| Bouffee delirante | E133.11 |
| Psychogenic paranoid psychosis | E134.00 |
| Other reactive psychoses | E13y.00 |
| Psychogenic stupor | E13y000 |
| Brief reactive psychosis | E13y100 |

| | |
|---|---|
| Other reactive psychoses NOS | E13yz00 |
| Nonorganic psychosis NOS | E13z.00 |
| Psychotic episode NOS | E13z.11 |
| Other specified non-organic psychoses | E1y..00 |
| Non-organic psychosis NOS | E1z..00 |
| Schizotypal personality | E212200 |
| [X]Schizophrenia, schizotypal and delusional disorders | Eu2..00 |
| [X]Schizophrenia | Eu20.00 |
| [X]Paranoid schizophrenia | Eu20000 |
| [X]Paraphrenic schizophrenia | Eu20011 |
| [X]Hebephrenic schizophrenia | Eu20100 |
| [X]Disorganised schizophrenia | Eu20111 |
| [X]Catatonic schizophrenia | Eu20200 |
| [X]Catatonic stupor | Eu20211 |
| [X]Schizophrenic catalepsy | Eu20212 |
| [X]Schizophrenic catatonia | Eu20213 |
| [X]Schizophrenic flexibilatis cerea | Eu20214 |
| [X]Undifferentiated schizophrenia | Eu20300 |
| [X]Atypical schizophrenia | Eu20311 |
| [X]Post-schizophrenic depression | Eu20400 |
| [X]Residual schizophrenia | Eu20500 |
| [X]Chronic undifferentiated schizophrenia | Eu20511 |
| [X]Restzustand schizophrenic | Eu20512 |
| [X]Simple schizophrenia | Eu20600 |
| [X]Other schizophrenia | Eu20y00 |
| [X]Cenesthopathic schizophrenia | Eu20y11 |
| [X]Schizophreniform disord NOS | Eu20y12 |
| [X]Schizophrenifrm psychos NOS | Eu20y13 |
| [X]Schizophrenia, unspecified | Eu20z00 |
| [X]Schizotypal disorder | Eu21.00 |
| [X]Latent schizophrenic reaction | Eu21.11 |
| [X]Borderline schizophrenia | Eu21.12 |
| [X]Latent schizophrenia | Eu21.13 |
| [X]Prepsychotic schizophrenia | Eu21.14 |
| [X]Prodromal schizophrenia | Eu21.15 |
| [X]Pseudoneurotic schizophrenia | Eu21.16 |
| [X]Pseudopsychopathic schizophrenia | Eu21.17 |
| [X]Schizotypal personality disorder | Eu21.18 |
| [X]Persistent delusional disorders | Eu22.00 |
| [X]Delusional disorder | Eu22000 |
| [X]Paranoid psychosis | Eu22011 |
| [X]Paranoid state | Eu22012 |
| [X]Paraphrenia - late | Eu22013 |
| [X]Sensitiver Beziehungswahn | Eu22014 |
| [X]Paranoia | Eu22015 |
| [X]Delusional misidentification syndrome | Eu22100 |
| [X]Capgras syndrome | Eu22111 |
| [X]Cotard syndrome | Eu22200 |
| [X]Other persistent delusional disorders | Eu22y00 |
| [X]Delusional dysmorphophobia | Eu22y11 |
| [X]Involutional paranoid state | Eu22y12 |
| [X]Paranoia querulans | Eu22y13 |
| [X]Persistent delusional disorder, unspecified | Eu22z00 |
| [X]Acute and transient psychotic disorders | Eu23.00 |

| | |
|---|---|
| [X]Acute polymorphic psychot disord without symp of schizoph | Eu23000 |
| [X]Bouffee delirante | Eu23011 |
| [X]Cycloid psychosis | Eu23012 |
| [X]Acute polymorphic psychot disord with symp of schizophren | Eu23100 |
| [X]Bouffee delirante with symptoms of schizophrenia | Eu23111 |
| [X]Cycloid psychosis with symptoms of schizophrenia | Eu23112 |
| [X]Acute schizophrenia-like psychotic disorder | Eu23200 |
| [X]Brief schizophreniform disorder | Eu23211 |
| [X]Brief schizophrenifrm psych | Eu23212 |
| [X]Oneirophrenia | Eu23213 |
| [X]Schizophrenic reaction | Eu23214 |
| [X]Other acute predominantly delusional psychotic disorders | Eu23300 |
| [X]Psychogenic paranoid psychosis | Eu23312 |
| [X]Other acute and transient psychotic disorders | Eu23y00 |
| [X]Acute and transient psychotic disorder, unspecified | Eu23z00 |
| [X]Brief reactive psychosis NOS | Eu23z11 |
| [X]Reactive psychosis | Eu23z12 |
| [X]Induced delusional disorder | Eu24.00 |
| [X]Folie a deux | Eu24.11 |
| [X]Induced paranoid disorder | Eu24.12 |
| [X]Induced psychotic disorder | Eu24.13 |
| [X]Schizoaffective disorders | Eu25.00 |
| [X]Schizoaffective disorder, manic type | Eu25000 |
| [X]Schizoaffective psychosis, manic type | Eu25011 |
| [X]Schizophreniform psychosis, manic type | Eu25012 |
| [X]Schizoaffective disorder, depressive type | Eu25100 |
| [X]Schizoaffective psychosis, depressive type | Eu25111 |
| [X]Schizophreniform psychosis, depressive type | Eu25112 |
| [X]Schizoaffective disorder, mixed type | Eu25200 |
| [X]Cyclic schizophrenia | Eu25211 |
| [X]Mixed schizophrenic and affective psychosis | Eu25212 |
| [X]Other schizoaffective disorders | Eu25y00 |
| [X]Schizoaffective disorder, unspecified | Eu25z00 |
| [X]Schizoaffective psychosis NOS | Eu25z11 |
| [X]Other nonorganic psychotic disorders | Eu2y.00 |
| [X]Chronic hallucinatory psychosis | Eu2y.11 |
| [X]Unspecified nonorganic psychosis | Eu2z.00 |
| [X]Psychosis NOS | Eu2z.11 |
| [X]Manic episode | Eu30.00 |
| [X]Bipolar disorder, single manic episode | Eu30.11 |
| [X]Hypomania | Eu30000 |
| [X]Mania without psychotic symptoms | Eu30100 |
| [X]Mania with psychotic symptoms | Eu30200 |
| [X]Mania with mood-congruent psychotic symptoms | Eu30211 |
| [X]Mania with mood-incongruent psychotic symptoms | Eu30212 |
| [X]Manic stupor | Eu30213 |
| [X]Other manic episodes | Eu30y00 |
| [X]Manic episode, unspecified | Eu30z00 |
| [X]Mania NOS | Eu30z11 |
| [X]Bipolar affective disorder | Eu31.00 |
| [X]Manic-depressive illness | Eu31.11 |
| [X]Manic-depressive psychosis | Eu31.12 |
| [X]Mainc-depressive reaction | Eu31.13 |
| [X]Bipolar affective disorder, current episode hypomanic | Eu31000 |

| | |
|---|---|
| [X]Bipolar affect disorder cur epi manic wout psychotic symp | Eu31100 |
| [X]Bipolar affect disorder cur epi manic with psychotic symp | Eu31200 |
| [X]Bipolar affect disorder cur epi mild or moderate depressn | Eu31300 |
| [X]Bipol aff disord, curr epis sev depress, no psychot symp | Eu31400 |
| [X]Bipolar affect dis cur epi severe depres with psyc symp | Eu31500 |
| [X]Bipolar affective disorder, current episode mixed | Eu31600 |
| [X]Bipolar affective disorder, currently in remission | Eu31700 |
| [X]Other bipolar affective disorders | Eu31y00 |
| [X]Bipolar II disorder | Eu31y11 |
| [X]Recurrent manic episodes | Eu31y12 |
| [X]Bipolar affective disorder, unspecified | Eu31z00 |
| [X]Severe depressive episode with psychotic symptoms | Eu32300 |
| [X]Single episode of major depression and psychotic symptoms | Eu32311 |
| [X]Single episode of psychogenic depressive psychosis | Eu32312 |
| [X]Single episode of psychotic depression | Eu32313 |
| [X]Single episode of reactive depressive psychosis | Eu32314 |
| [X]Major depression, severe with psychotic symptoms | Eu32800 |
| [X]Manic-depress psychosis,depressd,no psychotic symptoms | Eu33213 |
| [X]Recurrent depress disorder cur epi severe with psyc symp | Eu33300 |
| [X]Endogenous depression with psychotic symptoms | Eu33311 |
| [X]Manic-depress psychosis,depressed type+psychotic symptoms | Eu33312 |
| [X]Recurr severe episodes/major depression+psychotic symptom | Eu33313 |
| [X]Recurr severe episodes/psychogenic depressive psychosis | Eu33314 |
| [X]Recurrent severe episodes of psychotic depression | Eu33315 |
| [X]Recurrent severe episodes/reactive depressive psychosis | Eu33316 |
| [X]Affective psychosis NOS | Eu3z.11 |
| [X]Hysterical psychosis | Eu44.14 |
| [X]Symbiotic psychosis | Eu84314 |
| Profile of mood states, bipolar | ZRby100 |
| Schizophrenic language | ZS7C611 |
| [V]Personal history of schizophrenia | ZV11000 |
| [V]Personal history of manic-depressive psy | ZV11111 |
| [V]Personal history of manic-depressive psy | ZV11112 |

## Appendix 2

**First generation antipsychotics**

Benperidol
Chlorpromazine
Droperidol
Flupenthix
Flupentixol
Fluphenaz
Fluphenazine
Fluspirilene
Hadol
Haloperidol
Levomepromazine
Loxapine
Oxypertine
Paliperidone
Pericyazine
Perphenazine
Pimozide
Pipotiazine
Promazine
Sulpiride
Thioridazine
Trifluoperazine
Trifluperidol
Zuclopenthix
Zuclopenthixol

**Second generation antipsychotics**

Amisulpride
Aripiprazole
Clozapine
Olanzapine
Quetiapine
Remoxipride
Risperidone
Sertindole
Sertindone
Zotepine

**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 |
| **Introduction** | | | |
| 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 |
| **Methods** | | | |
| 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 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| 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 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 20 |
| **Limitations** | | | |
| 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 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 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.