PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prescribing of antipsychotics in United Kingdom primary care. Cohort study in United Kingdom primary care
AUTHORS	Marston, Louise; Nazareth, Irwin; Petersen, Irene; Walters, Kate; Osborn, David

VERSION 1 - REVIEW

REVIEWER	Ian Douglas London School of Hygiene & Tropical Medicine United Kigdom
REVIEW RETURNED	30-Jul-2014

GENERAL COMMENTS	This is a very well written paper on an important topic - assessing the likely indication for the prescribing of antipsychotics in UK primary care. Given concerns over recent years about the inapproriate use of these drugs, particularly in indications for which the balance of risks and benefits is likely to be negative, it is very helpful to have evidence of current usage patterns. The authors have included a very helpful discussion of their findings and possible implications for the future, e.g. the suggestion that all patients prescribed antipsychotics should be monitored, not just those with SMIs. My main comment is around the temporal considerations for matching possible indications with prescribing. It isn't clear from the methods whether clinical diagnoses were considered as possible indications for a prescription regardless of when they were recorded in the study period, or whether a time window was placed around the prescription, during which clinical records were considered as possible indications. If the former, there could be substantial misclassification of possible indication e.g. a diagnosis in 2011 may not have any connection with a prescription issued in 2007. It would be good to clarify and justify the methodology for this aspect of the study. Related to this, I think it could be considered slightly misleading to refer to the likely indication as "recorded indication". The indication as identified in this study is inferred rather than recorded - and this is the best that can be done given the structure of the software used by the GPs. One of the most important findings is the very high usage of haloperidol and quetiapine in people with dementia and the authors rightly focus on this as deserving further attention. What would be nice is to see whether this pattern is constant throughout their observation period or whether usage has decreased over that time.

REVIEWER	Hélène VERDOUX University of Bordeaux, France
REVIEW RETURNED	22-Sep-2014

GENERAL COMMENTS	Considering the increasing rates of persons from the general population exposed to antipsychotic drugs in most developed countries, it is of interest to further explore the characteristics associated with antipsychotic prescribing. The present study has several strengths such as its large sample size and availability of information on psychiatric diagnoses. However, the authors should further address the following points or limitations. 1. Readers outside the UK are not familiar with the THIN network. How are recruited practitioners participating in this network? Is this network overlapping with the CPRD? 2. More information should be given on the diagnostic method, as the present study is focused on this issue. Read codes used for diagnoses and symptoms are little known. Have these codes been validated for psychiatric diagnoses, particularly what is their concordance with diagnoses made using international classification such as ICD-10? 3. The full list of drugs classified as second-generation antipsychotic has to be given, as the list of marketed second-generation antipsychotics is different from one country to another. 4. More information has to be given on the method used to calculate average daily dose and duration of antipsychotic treatment. The authors have to explain which exact information on drug prescription was available in the database, as such information may widely vary from one database to another. If assumptions had to be made to estimate average daily dose or duration of treatment, these assumptions have to be detailed. 5. Incident (or new) as well as prevalent prescriptions of antipsychotics were apparently considered in the present study, since no exclusion criteria is mentioned regarding the period before the index prescription recorded in the database (i.e. 3 or 6 months without antipsychotic prescription. This methodological choice is problematic as duration of treatment is calculated using left censored data. Only “new” prescriptions should be considered to calculate duration of treatment. 6. The fact that patients were excluded if they had less than 6 months of follow-up data after the index prescription may have favoured a selection bias if patients shortly admitted to psychiatric hospital after the onset of antipsychotic treatment were not considered. It is hence necessary to further explain how was calculated the duration of follow-up. More generally, it is necessary to explain how psychiatric admission was taken into account. 7. The definition of the population at risk deserves further explanations. Is the total population registered with the general practices equivalent to the population living in the catchment areas of the general practices? If not, what is the approximate percentage of persons from the general population not registered in the general practices? For example, in some European countries, a large percentage of persons with severe mental illness are not registered in general practices, and only psychiatrists are prescribing

	antipsychotics to them. Is this possible in UK? 8. Full spelling of IQR and PYAR has to be given at first appearance in the text. 9. The authors distinguished three groups according to type of antipsychotic drugs used. However, as no information is available on the chronology of use of first or second generation antipsychotic (sequential or combined), such information is of limited interest. Hence, the group "first and second generation antipsychotic" should be suppressed. This would contribute to reduce the size of the tables, which are currently poorly presented. 10. It is also of limited interest to perform distinct analyses for the three most prescribed drugs of each group. Such analyses would be relevant to explore temporal trends, as pattern of prescription of a specific molecule is highly dependent on time-dependent issues such as date of market authorization or of generic authorization. This would also contribute to reduce the number of tables. The same comment applies to the section “records of mental health conditions” as this issue would be of interest to examine for all drugs, not only the most prescribed once. 11. As this information was available in the database, the authors should report the frequency of use of other psychotropic drugs in the persons with a prescription of antipsychotic. For example, how many persons with a diagnosis of bipolar disorder were co-prescribed a mood stabilizer? 12. Lastly, a large body of literature is now available on rates of antipsychotic use in general population samples (including samples recruited in primary care settings). The authors should at least briefly compare their findings to those obtained in previous studies. "The authors have adequately answered to the points raised in my review, and my recommendation is to accept the manuscript as is."

VERSION 1 – AUTHOR RESPONSE

Reviewer: Ian Douglas

This is a very well written paper on an important topic - assessing the likely indication for the prescribing of antipsychotics in UK primary care. Given concerns over recent years about the inappropriate use of these drugs, particularly in indications for which the balance of risks and benefits is likely to be negative, it is very helpful to have evidence of current usage patterns.

The authors have included a very helpful discussion of their findings and possible implications for the future, e.g. the suggestion that all patients prescribed antipsychotics should be monitored, not just those with SMIs.

My main comment is around the temporal considerations for matching possible indications with prescribing. It isn't clear from the methods whether clinical diagnoses were considered as possible indications for a prescription regardless of when they were recorded in the study period, or whether a time window was placed around the prescription, during which clinical records were considered as possible indications. If the former, there could be substantial misclassification of possible indication e.g. a diagnosis in 2011 may not have any connection with a prescription issued in 2007. It would be

good to clarify and justify the methodology for this aspect of the study.

We extracted diagnoses which were entered at any time. In our experience, mental health diagnoses are not routinely entered into primary care databases at the time of prescribing different medications. Once a diagnosis (for instance depression) has been established, the GP rarely re-enters this diagnosis on subsequent consultations or changes in treatment. Therefore new and repeat prescriptions may be issued without re-entering a diagnosis. Furthermore some diagnoses such as dementia might be entered at quite a late stage. We agree it might be that a given diagnosis was made some time before an antipsychotic is prescribed, and as the reviewer states, the time course could be the opposite. If a person had a severe mental health diagnosis (ie, schizophrenia, schizo affective disorder, bipolar disorder or being on the severe mental health register) then that was considered to be their main diagnosis. However for people without a Read code for SMI at any time, all of their diagnoses were considered and included in our analyses.

We accept that prescribing at a given point in the time course may not have been directly related to the non-SMI diagnoses we have identified, and this is a limitation. Therefore we have added the following text to the discussion acknowledging this.

“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.”

Related to this, I think it could be considered slightly misleading to refer to the likely indication as "recorded indication". The indication as identified in this study is inferred rather than recorded - and this is the best that can be done given the structure of the software used by the GPs.

We agree and have reworded where necessary.

One of the most important findings is the very high usage of haloperidol and quetiapine in people with dementia and the authors rightly focus on this as deserving further attention. What would be nice is to see whether this pattern is constant throughout their observation period or whether usage has decreased over that time.

We agree this would be interesting; however the exploration of time trends was not the aim of our paper. Furthermore, given we chose a relatively narrow time window it seems unlikely that the current manuscript would lend itself to explore time trends in dementia prescribing.
We have added a sentence to the discussion that “assessing time trends in antipsychotic prescribing in dementia is an important focus for future research in primary care”.

Reviewer: Hélène Verdoux

Considering the increasing rates of persons from the general population exposed to antipsychotic drugs in most developed countries, it is of interest to further explore the characteristics associated with antipsychotic prescribing. The present study has several strengths such as its large sample size and availability of information on psychiatric diagnoses. However, the authors should further address the following points or limitations.

1. Readers outside the UK are not familiar with the THIN network. How are recruited practitioners

participating in this network? Is this network overlapping with the CPRD?

THIN is equivalent to CPRD as both CPRD and THIN get their data from general practices across the UK that use Vision software. Some practices contribute to both primary care databases, while others contribute to one or the other.

We have clarified this in the paper by adding clarification to the first sentence to the Data Source section: "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]"

2. More information should be given on the diagnostic method, as the present study is focused on this issue. Read codes used for diagnoses and symptoms are little known. Have these codes been validated for psychiatric diagnoses, particularly what is their concordance with diagnoses made using international classification such as ICD-10?

Non-SMI diagnoses such as depression, anxiety and sleep disorders are likely to be predominantly made in primary care; however some, especially those for SMI will usually be made in secondary care, and the diagnoses in the form of Read codes are transferred from the psychiatrist's letter from secondary care to the primary care records.

Read codes for severe mental illness have been validated with Nazareth I, King M, Haines A et al. Accuracy of diagnosis of psychosis on general practice computer system BMJ 1993;307(6895):32-4 cited in this paper. Additionally, there are some Read codes that are used to identify those with severe mental illness for Quality Outcomes Framework (the system that contributes to general practice payments in the UK). Some of the other diagnoses have not been validated (for example, ADHD). However, these diagnoses were carefully extracted from a Read code dictionary by searching for keywords. These Read codes map onto ICD10 codes, and also include other codes, eg symptoms. Once Read codes for these were identified, neighbouring Read codes were also considered as these may also relate to the same diagnosis. When a list of possible Read codes for the diagnosis in question had been created, it was checked and modified by a General Practitioner and a Psychiatrist (KW, DO). Previous work from our group (Hardoon S, Hayes JF, Blackburn R et al. Recording of severe mental illness in United Kingdom primary care, 2000-2010. PLoS One 2013;12;8(12):e82365 reference 17) has shown that SMI prevalence in THIN is comparable with epidemiological surveys. We have added references to both these papers in the Mental Health Conditions section of the manuscript. Although the non-SMI diagnoses have not been validated, we have previously described trends in GP recording of depression and anxiety diagnosis and symptom codes. (See Rait et al Recent trends in the incidence of recorded depression and depressive symptoms in primary care. Br J Psych 2009; 195: 520-524 and Walters et al Incidence of anxiety diagnoses and symptoms recorded in primary care. PLoS One 2012, 7(8): e41670). We have added these references to the Mental health conditions section.

In Appendix 1, Read codes that are preceded with [X] are direct mappings to ICD10, but are mainly used for diagnoses made in secondary care.

3. The full list of drugs classified as second-generation antipsychotic has to be given, as the list of marketed second-generation antipsychotics is different from one country to another.

We have added Appendix 2 containing antipsychotics categorised as first and second generation in the UK. For the majority of the analyses in this paper, we included only the three most prescribed first and second generation antipsychotics during the time window. This was because prescribing of some

of the lesser used antipsychotics was sparse.

4. More information has to be given on the method used to calculate average daily dose and duration of antipsychotic treatment. The authors have to explain which exact information on drug prescription was available in the database, as such information may widely vary from one database to another. If assumptions had to be made to estimate average daily dose or duration of treatment, these assumptions have to be detailed.

We estimated average daily dose as follows: In the prescribing dataset, there is information regarding the drug given, its strength, the total amount prescribed (number of tablets, ml etc) and the dose per day. From this information, it is possible to calculate the total number of mg that were been prescribed in a given prescription. This is summed for all prescriptions of a given antipsychotic prescribed to an individual, so that it is known the total number of mg prescribed in a course of antipsychotics. Time elapsed between first and last prescription + the length of the last prescription can be calculated as using the dates of the first and last prescriptions plus the number of days the final prescription would have lasted if it was taken as prescribed.

We have further explained this in the Antipsychotic data section of the paper.

5. Incident (or new) as well as prevalent prescriptions of antipsychotics were apparently considered in the present study, since no exclusion criteria is mentioned regarding the period before the index prescription recorded in the database (i.e. 3 or 6 months without antipsychotic prescription. This methodological choice is problematic as duration of treatment is calculated using left censored data. Only “new” prescriptions should be considered to calculate duration of treatment.

This was a pragmatic study with the aim of identifying all people who were prescribed antipsychotics in primary care. We aimed to find out what is happening in the real world, so included incident and prevalent cases thus illustrating the burden and case mix of antipsychotic prescribing in the UK. If only incident case prescriptions were included we would lose many people, especially those between ages 40 and 60.

In THIN, people enter the database for various reasons, such as the practice joining the database, a patient moving and registering with a THIN practice, or a patient gaining a new prescription of antipsychotics. Those who transfer into a practice may not be incident as they may have had a diagnosis when they were with a previous practice. The length of treatment may be underestimated because for many people treatment started before the observation period started.

We have added a sentence in the discussion to acknowledge that median daily dose is a crude measure of the amount of a given antipsychotic prescribed; it does allow us to compare doses between diagnoses.

6. The fact that patients were excluded if they had less than 6 months of follow-up data after the index prescription may have favoured a selection bias if patients shortly admitted to psychiatric hospital after the onset of antipsychotic treatment were not considered. It is hence necessary to further explain how was calculated the duration of follow-up. More generally, it is necessary to explain how psychiatric admission was taken into account.

There was no account taken of psychiatric (or any other) admission in this study, as we do not have accurate information in the GP records of the date of admission and discharge. GPs frequently do not know that an individual has been admitted to hospital until the discharge letter is sent to the general practice. Even if the admission was planned, the GP may not know when a person was an inpatient until they receive a discharge letter. Those who were inpatient for part of the study period could have

their prescriptions issued in primary care issued throughout their time in the study “counted” in the study. Being an inpatient for psychiatric reasons may reduce the rates shown a little but it is unlikely to be by that much. Having an inpatient admission is not a criterion for exiting the cohort. Therefore, we may miss a small percentage of prescriptions during follow up, but they are unlikely to have a major impact on the results of this study.

The restriction on having less than six months’ follow up is most likely to affect those who register with a practice included in the study within six months of the end date of the study, which would apply to children as well as adults. This criterion would also affect those who deregister (transfer out of the practice) or die within six months of their entry into the cohort.

7. The definition of the population at risk deserves further explanations. Is the total population registered with the general practices equivalent to the population living in the catchment areas of the general practices? If not, what is the approximate percentage of persons from the general population not registered in the general practices? For example, in some European countries, a large percentage of persons with severe mental illness are not registered in general practices, and only psychiatrists are prescribing antipsychotics to them. Is this possible in UK?

The population at risk is the total population in THIN during the defined time window. The majority of people in the UK (98%) are registered with a general practice.

We have added this to the Data Source section: “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”

General practitioners prescribe the majority of medications, and in the majority of cases even if a medication regimen has been initiated in secondary care (for example, by a Psychiatrist), the GP will continue with the regimen, and the drug will be paid for from their prescribing budget. The exception to this is Clozapine prescribing which is prescribed and monitored in hospital outpatient clinics. These prescriptions will not usually be included the general practice records. Additionally, any medications prescribed while an individual is an inpatient will not be in the general practice records either. However, there are relatively few people prescribed Clozapine. Therefore, the “all antipsychotics” and “all second generation antipsychotics” rates may be a little lower than they should be if Clozapine prescribing data were included.

We have clarified that this refers to prescriptions from general practice in the Data source section of the methods and may miss the relatively small number of clozapine prescriptions issued in secondary care.

8. Full spelling of IQR and PYAR has to be given at first appearance in the text.

These have been added to the statistical analysis section.

9. The authors distinguished three groups according to type of antipsychotic drugs used. However, as no information is available on the chronology of use of first or second generation antipsychotic (sequential or combined), such information is of limited interest. Hence, the group "first and second generation antipsychotic" should be suppressed. This would contribute to reduce the size of the tables, which are currently poorly presented.

We feel this information should be maintained to give a fuller picture of antipsychotic prescribing.

10. It is also of limited interest to perform distinct analyses for the three most prescribed drugs of each

group. Such analyses would be relevant to explore temporal trends, as pattern of prescription of a specific molecule is highly dependent on time-dependent issues such as date of market authorization or of generic authorization. This would also contribute to reduce the number of tables. The same comment applies to the section “records of mental health conditions” as this issue would be of interest to examine for all drugs, not only the most prescribed once.

We believe that readers will be interested in the analysis of different individual agents since they have different side effect profiles (such as propensity to weight gain) and different individual agents have different indications and contraindications for instance in dementia. Reviewer 1 emphasises that this (prescribing in dementia) is an important component of the study.

11. As this information was available in the database, the authors should report the frequency of use of other psychotropic drugs in the persons with a prescription of antipsychotic. For example, how many persons with a diagnosis of bipolar disorder were co-prescribed a mood stabilizer?

We agree this would be interesting in future work, but this was not our original aim and it would lengthen the manuscript considerably. However we have added this recommendation to the discussion section.

12. Lastly, a large body of literature is now available on rates of antipsychotic use in general population samples (including samples recruited in primary care settings). The authors should at least briefly compare their findings to those obtained in previous studies.

We have changed the sentence at the beginning of the discussion to distinguish our study from other, including those in the reviewer’s 2009 systematic review. “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.”

We have also added a paragraph (second paragraph of the discussion) to acknowledge similar literature in the area, and have included a reference to the reviewer’s systematic review.

“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.”

VERSION 2 – REVIEW

REVIEWER	Hélène VERDOUX University of Bordeaux, France
REVIEW RETURNED	27-Oct-2014

GENERAL COMMENTS	"The authors have adequately answered to the points raised in my review, and my recommendation is to accept the manuscript as is.