Trends in antipsychotic prescribing to children and adolescents in England: cohort study using 2000–19 primary care data

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Summary

Background The prescription of antipsychotics to children and adolescents has been increasing worldwide. We described up-to-date trends in antipsychotic prescribing and identified likely indications in a contemporary English cohort.

Methods We used a large primary care database, the Clinical Practice Research Datalink (CPRD) Aurum database, and we included all children and adolescents aged 3–18 years in the database and registered in England between Jan 1, 2000, and Dec 31, 2019, excluding those whose gender was recorded as indeterminate. Participants were followed up until the earliest of Dec 31, 2019, June 30 of the year they turned 18 years, their death, when they transferred from the primary care practice, or when the practice left the database. Data were not collected on ethnicity. We recorded antipsychotic prescriptions using the date a prescription was issued. As CPRD prescriptions are not linked to indications, we developed an algorithm to ascertain the most likely indication associated with participants' first antipsychotic prescription using clinical codes. We reported prescribing trends as annual period prevalence and the rate of first antipsychotic prescription, and we used joinpoint regression analysis to identify changes in the outcome trend. We stratified prevalence estimates by age group, gender, and Index of Multiple Deprivation quintiles, we reported frequencies of likely indications associated with incident prescriptions, and we explored clinical preference for typical versus atypical antipsychotics within deprivation quintiles.

Findings Between Jan 1, 2000, and Dec 31, 2019, we included 7 216 791 children and adolescents, of whom 3 480 730 (48·2%) were girls and 3 736 061 (51·8%) were boys, with a mean age at the start of follow-up of 7·3 years (SD 4·9; range 3–18). Median follow-up was 4·1 years (IQR 1·5–8·5). 19 496 (0·3%) individuals received 243 529 antipsychotic prescriptions over follow-up, including 225 710 (92·7%) atypical and 17 819 (7·3%) typical antipsychotic prescriptions. The annual period prevalence of antipsychotic prescriptions rose from 0·057% (95% CI 0·052–0·063%) in 2000 to 0·105% (0·100–0·111%) in 2019. From joinpoint analyses, the period prevalence of all antipsychotic prescriptions increased by an average of 3·3% per year (2·2–4·9%) and the rate of first prescriptions increased by 2·2% per year (1·7–2·7%). The most likely indications of the first identified antipsychotic prescriptions were for autism spectrum disorder (2477 [12·7%]), non-affective psychosis (1669 [8·6%]), anxiety disorders (1466 [7·5%]), ADHD (1391 [7·1%]), depression (1256 [6·4%]), and conduct disorders (1181 [6·1%]).

Interpretation The observed increase in antipsychotic prescriptions over 20 years results from the accumulation of repeated prescriptions to the same individuals combined with an increase in new prescriptions. These findings highlight the need for continued monitoring of trends in antipsychotic use and, although this was not examined in this paper, the findings highlights the need for better information about long-term antipsychotic safety.

Funding None.

Lancet Psychiatry 2023

Published Online
January 10, 2023
https://doi.org/10.1016/S2215-0366(22)00404-7

See Online/Comments
https://doi.org/10.1016/S2215-0366(23)00003-2

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Introduction

Studies across the globe have raised concerns that antipsychotics are increasingly prescribed to children and adolescents.[1–4] Although this trend might be appropriate with changing clinical needs, most antipsychotics are not licensed for use in children and adolescents because of incomplete safety profiles, particularly for long-term use. The safety concerns relate to interactions with children and adolescents' physical and psychological development, leading to possible lasting consequences such as the accumulation of cardiometabolic risk.[5,6] In the UK, the National Institute for Health and Care Excellence (NICE) approved three drugs for those younger than 18 years: aripiprazole in 2011 for schizophrenia and in 2013 for bipolar disorder; clozapine in 2013 for treatment-resistant schizophrenia in adolescents;[7–9] and risperidone in 2013 for severely aggressive behaviour in conduct disorders in children older than 5 years.[10]

Trends in antipsychotic prescribing to children and adolescents in the UK have been examined up to

Research in context

Evidence before this study

Evidence for trends in antipsychotic prescribing among children and adolescents was collated by searching MEDLINE and Embase for records in any language, published anytime from the date records began up to the date of the search (Aug 18, 2022) using the following search terms: ("child" OR "children" OR "adolescent*" OR "teen*" OR "teenager*" OR "youth*") AND ("antipsychotic*" OR "major tranquillizing" OR "major tranquillizers" OR "neuroleptic*") AND ("prescribing" OR "prevalence" OR "incidence" OR "person-time") AND ("cohort study" OR "trend" OR "population-based") AND ("United Kingdom" OR "the UK" OR "England"). Articles were included if they used population-based samples, distinct samples of children and adolescents, and focused on antipsychotics, excluding co-prescribing. Three studies met these criteria, using data from the General Practice Research Database or The Health Improvement Network primary care databases covering the period from Jan 1, 1992, to Dec 31, 2012. These studies reported an increasing trend in antipsychotic use in children and adolescents, especially in those aged 15–19 years. They also identified higher rates of prescription of atypical antipsychotics than typical antipsychotics, and that the prescribing rates in the UK were between those of other European countries and the USA. In the UK, between 2011 and 2013, the National Institute for Health and Care Excellence approved three drugs for patients younger than 18 years: aripiprazole for schizophrenia and bipolar disorder; clozapine for treatment-resistant schizophrenia; and risperidone for severely aggressive behaviour in conduct disorder. There is a need to update the information on how many children were prescribed antipsychotics after these guidelines were introduced.

Added value of this study

Using a cohort of children and adolescents (age 3–18 years) assembled from a large English primary care database, we observed a doubling in the proportion of prescribed antipsychotics between 2000 and 2019. This finding was partly explained by an increase in the rate of new prescriptions, and partly by a trend towards more repeat prescriptions. Although prescribing trends were similar between different areas of deprivation, typical antipsychotic prescribing was more frequent for children in more deprived areas. We also found multiple clinical indications for antipsychotics beyond their initial approvals, most commonly for anxiety and depression.

Implications of all the available evidence

The evidence to date suggests an increasing tendency towards managing the mental health of young people by prescribing antipsychotics for a longer period of time, for a wider range of reasons, and to a broader group of children and adolescents. This tendency is of concern, given that the last National Institute for Health and Care Excellence guidance that focused on the use of antipsychotics in children and adolescents with psychosis was in 2013, updated in 2016. We recommend reviews be conducted into the short-term and long-term safety of atypical and typical antipsychotics in children and adolescents, and that new recommendations should be issued urgently. We also advocate a national audit of existing prescribing practices to ensure clinicians are adhering to current recommendations and identify potential gaps between guidance and implementation that might cause harm to young people in the UK.

Dec 31, 2012, but the effects of these newer approvals have not been observed. Three studies used primary care databases to examine the prescription of antipsychotics to children and adolescents from Jan 1, 1992, to Dec 31, 2012.[11–13] The authors reported an increase in prescriptions over time, especially for atypical antipsychotics, with the highest frequency among adolescents and a decreasing boy-to-girl prescription ratio.[11,12] One UK study suggested adults were more likely to receive an antipsychotic if they lived in more deprived areas.[14] However, two French studies in young people reported no evidence for this potential health inequality,[15,16] and no UK studies in children and adolescents have examined this question. Furthermore, little evidence exists on indications for, and doses of, antipsychotic prescribing in children and adolescents.[11]

We aimed to provide contemporary evidence about trends in antipsychotic prescribing for children and adolescents in England, using the largest, most accurate primary health-care database, the Clinical Practice Research Datalink (CPRD). Primary care is a gatekeeper to specialist mental health services and plays an essential role in medication prescribing.[11] We studied prescribing trends from Jan 1, 2000, to Dec 31, 2019, to examine the possible influences of the 2011 and 2013 approvals. We investigated prescribing trends overall and by antipsychotic type, as well as by the young person's age, gender, and level of deprivation. Notably, we examined indications associated with prescriptions and more detailed prescribing patterns, including the most prescribed medications, doses, and prescription duration per indication.

Methods

Study design and participants

This cohort study used the CPRD Aurum database, comprising routinely collected electronic health records from participating primary care practices in England.[17,18] This database contains anonymised patient information on demographics, diagnoses, symptoms, prescriptions, laboratory tests, and referrals to secondary and tertiary care. Prescriptions in this database are derived from general practitioners and are either general

practitioner-initiated or specialist-initiated, but not prescriptions issued solely in secondary care. In the UK, general practitioners do not initiate antipsychotic medications in patients younger than 18 years. The CPRD Aurum database includes 46·7 million patients from 1565 general practices; its latest data collection had 15·7 million active participants, covering 28% of the English population with a median follow-up of 8·96 years, as of October, 2022.[19]

Our sample included children and adolescents aged 3–18 years with available CPRD Aurum database records between Jan 1, 2000, and Dec 31, 2019 (appendix p 2). Children were included at the latest of the following dates: Jan 1, 2000; when they turned 3 years; the date they were registered with a participating general practice; or when the practice started reporting data. The participants were followed up until the earliest of the following: Dec 31, 2019; June 30 of the year they turned 18 years; their death; when they transferred from the practice; or when their practice left the CPRD Aurum database. Children with their gender recorded as indeterminate were excluded.

CPRD has ethical approval to support public health research using anonymised patient data (Multiple Research Ethics Committee reference 05/MRE04/87). Patients provided data to general practices as part of their care and support, and general practices consented to the CPRD collecting all deidentified patient records. All CPRD studies require scientific approval from the UK Medicines and Healthcare products Regulatory Agency Independent Scientific Advisory Committee; this study (protocol number 18_073) received Independent Scientific Advisory Committee approval on April 17, 2018.

Antipsychotic use

We defined antipsychotic use (with antipsychotic defined as Anatomical Therapeutic Chemical [ATC] class N05A) as any prescription (one or more) in the study sample over the course of the follow-up. We included typical (first generation) and atypical (second generation) antipsychotics listed in the British National Formulary.[20] The timing of each prescription was established by the date it was issued. The Martindale Complete Drug Reference was searched for discontinued antipsychotics in the UK.[21] We excluded the mood stabiliser lithium (ATC code N05AN01) and prochlorperazine (ATC code N05AB04), which is primarily an antiemetic.[11,12]

CPRD prescriptions are not linked to indications, so we developed an algorithm to ascertain the most likely indication associated with participants' first recorded antipsychotic prescription, using clinical codes related to diagnoses and symptoms. We identified potential indications from records occurring within 6 months before and after the incident prescription.[11] Two psychiatrists (ES and KMA) independently categorised the indications before and after each antipsychotic prescription, then met together to discuss these and develop the following order of ranking priority for which indication to assign in each case: non-affective psychosis; affective psychosis; autism spectrum disorder (ASD); conduct disorders; obsessive-compulsive disorders; tic disorders; eating disorders; anxiety disorders including post-traumatic stress disorder; depression; ADHD; nausea; other mental illnesses; and other indications. When no indication was given on the day of prescription, but multiple indications were present (12·6% of prescriptions), the higher ranked category in this list was given priority and was assigned as the most likely diagnosis (appendix p 3).

See Online for appendix

Other variables

We used participant age, sex, general practice region of England, and Index of Multiple Deprivation (IMD) for descriptive purposes and stratification. Age was categorised according to developmental stages: early (3–5 years, ie, from third to sixth birthday), childhood (6–11 years, ie, until 12th birthday), early adolescence (12–14 years, ie, until 15th birthday), and adolescence (15–18 years, ie, maximum possible calculated age 18·5 years).[22] We identified these groups each year, allowing individuals to transition between age groups over follow-up. For regression models, age was included as a continuous variable. CPRD contains a self-reported gender variable.[17] For descriptive purposes only, we used participant birth year and general practice region of England. General practices were linked to area-level deprivation from postcodes using 2015 IMD measurements. Areas were then categorised using quintiles of the IMD distribution, where the fifth quintile represented the most deprived areas in England.

For more on **the Independent Scientific Advisory Committee approval for this study** see https://cprd.com/protocol/trends-antipsychotic-prescribing-children-uk-primary-care

Statistical analysis

Antipsychotics were described by the number of identified prescriptions over follow-up, the number of participants receiving these prescriptions, and the prescription rate per 10 000 person-years. We reported the 20-year prescribing trends of all, typical, and atypical antipsychotics as annual period prevalence, calculated for each year as the number of individuals with antipsychotic prescriptions within a calendar year divided by the total number of individuals in the cohort that year, stratified by age, gender, and IMD. Direct standardisation was used to standardise prevalence estimates using the age-stratified, gender-stratified, and region-stratified population estimates for England in 2019.[23] The incidence rate was estimated as the number of individuals with a new antipsychotic prescription (all, typical, or atypical) in a particular year divided by the total person-years in that year.

We reported frequencies (percentages) of the most likely indications associated with incident antipsychotic prescriptions tabulated by age, gender, and IMD groups. Finally, we provided antipsychotic prescription details per indication. These details included the five most prescribed oral medications, each medication's number of prescriptions, prescribed doses, and prescription

duration. We reported dose consumption as the mean (minimum to maximum) daily dose, the total prescribed defined daily dose (DDD; ie, the average maintenance dose for the drug's main indication in adults[24,25]), and prescribed DDD per individual allowing between-medication comparisons. Each prescription duration, not including the duration of repeat prescriptions, was defined as the quantity of medication divided by daily dose, reported as median (IQR).

We undertook three additional analyses. First, we examined factors associated with the likelihood of receiving typical versus atypical antipsychotics using multivariable binary logistic regression with age, gender, IMD, and indication as predicting factors, controlled for the prescription year and using multiple imputation, with ten imputed datasets, to account for missing data. Second, we identified changes in annual period prevalence and incidence using joinpoint analysis to identify changes in the (log) outcome trend, by fitting multi-segmented regression, with the number of segments (joins) established using the Monte Carlo permutation method. Joinpoint models estimated the years when changes to the trend occurred, as well as the average yearly change over a period. Third, we examined the frequency of follow-up prescriptions. For this analysis, a sub-cohort of children and adolescents was chosen (appendix p 2) and examined for 1·5 years of follow-up from their first prescription, to ascertain whether another antipsychotic prescription was issued 0 to <6 months, 6 to <12 months, or 12 to 18 months after the first prescription.

Finally, we conducted a sensitivity analysis to examine whether changes to the window of time used to capture indications influenced the indications captured by our algorithm. We changed the window from 6 months to 3 months, and then to 1 month, and we compared the distribution of indications. We used Stata 16 for data management and statistical analyses, and Joinpoint Regression Program (version 4.5.0) and R version 4.1.3 for data visualisation.

	Study sample (n=7 216 791)	Individuals with antipsychotic prescription (n=19 496)
Year of birth		
1984–87	730 121 (10·1%)	2173 (11·2%)
1988–93	1 093 900 (15·1%)	4065 (20·8%)
1994–99	1 392 947 (19·3%)	5998 (30·8%)
2000–05	1 537 645 (21·3%)	5845 (30·0%)
2006–12	1 490 748 (20·7%)	1332 (6·8%)
2013–16	971 430 (13·5%)	83 (0·4%)
Gender		
Girls	3 480 730 (48·2%)	7168 (36·8%)
Boys	3 736 061 (51·8%)	12 328 (63·2%)
Region of England*		
North East	206 174 (2·9%)	587 (3·0%)
North West	1 238 852 (17·2%)	3192 (16·4%)
Yorkshire and the Humber	235 900 (3·3%)	391 (2·0%)
East Midlands	157 085 (2·2%)	395 (2·0%)
West Midlands	1 157 252 (16·0%)	4642 (23·9%)
East of England	297 865 (4·1%)	838 (4·3%)
Southwest	790 977 (11·0%)	2109 (10·8%)
South central	860 411 (11·9%)	2584 (13·3%)
London	1 649 548 (22·9%)	2772 (14·2%)
Southeast coast	612 031 (8·5%)	1957 (10·1%)
Quintiles of multiple deprivation†		
1st (least deprived)	1 007 362 (15·8%)	2499 (14·6%)
2nd	1 091 693 (17·1%)	3101 (18·1%)
3rd	1 165 592 (18·3%)	3175 (18·6%)
4th	1 477 915 (23·2%)	4150 (24·3%)
5th (most deprived)	1 639 789 (25·7%)	4175 (24·4%)

Data shown as n (%). *There were 10 696 missing values in the study sample, of which 29 were among individuals with antipsychotic prescriptions, because of the absence of the postal addresses of the general practices. †There were 834 440 missing values in the study sample, of which 2396 were among individuals with antipsychotic prescriptions, because the general practices did not consent to deprivation index linkage.

Table 1: **Descriptive statistics of the study sample**

Role of the funding source

There was no funding source for this study.

Results

The study sample included 7 217 098 children and adolescents registered at a participating practice between Jan 1, 2000, and Dec 31, 2019. 307 children with their gender recorded as indeterminate were excluded. The mean age at the start of follow-up was 7·3 years (SD 4·9; range 3–18), and 3 480 730 (48·2%) were girls and 3 736 061 (51·8%) were boys (table 1). Data on ethnicity were not captured. Median follow-up was 4·1 years (IQR 1·5–8·5). Within the study sample, 19 496 (0·3%) individuals received antipsychotic prescriptions over follow-up. Over 20 years, we identified 243 529 prescriptions of 26 different antipsychotics to 3–18-year-olds: 225 710 (92·7%) were atypical and 17 819 (7·3%) were typical (table 2). The most prescribed antipsychotics were risperidone (149 562 [61·4%] of all prescriptions), aripiprazole (33 385 [13·7%]), quetiapine (24 287 [10·0%]), and olanzapine (16 928 [7·0%]).

The annual period prevalence of all antipsychotic prescriptions increased over the study period (figure 1A), from 0·057% (95% CI 0·052 to 0·063%) in 2000 up to 0·105% (0·100 to 0·111%) in 2019, reaching its maximum in 2017 (0·119%; 0·113 to 0·125%). Joinpoint analysis identified four periods with distinct trends (appendix p 7): 2000–05 (average percentage change 3·14%; 95% CI 0·2 to 6·2%); 2005–10 (7·8%; 4·5 to 11·3%), 2010–17 (3·7%; 2·3 to 5·2%), and 2017–19 (6·1%; –12·8 to 1·1%). Over the whole period from 2000 to 2019, the period prevalence increased by an average of 3·3% per year (95% CI 2·2 to 4·9%; appendix p 9). The rate of first

antipsychotic prescription increased from 3·83 (95% CI 3·53 to 4·15) in 2000 to a maximum of 5·55 (5·25 to 5·87) in 2016, decreasing to 4·84 (4·56 to 5·13) prescriptions per 10 000 person-years in 2019 (figure 1B). There was no significant change in the trend of the rate of first prescriptions, and the average increase was 2·2% per year (1·7 to 2·7%).

Typical antipsychotics were dominant in 2000 but decreased 11·5 times by 2019, whereas the annual period prevalence of atypical antipsychotic prescriptions increased 6·6 times over the same period. Twice as many boys received antipsychotic prescriptions as girls for almost every year (figure 2A); between 2000 and 2019, prescription prevalence increased similarly in girls and boys, by an average of 4·1% (95% CI 2·5–5·6%) per year in girls and 3·7% (2·5–4·8%) per year in boys (appendix p 7–9). However, the increases began at different times, with notable increases in 2000–11 for boys and in 2009–16 for girls.

We found a higher annual period prevalence in the prescription of any antipsychotics in older groups (figure 2B). The annual period prevalence of prescriptions of antipsychotics in children aged 3–5 years was between 0·002% and 0·007% (appendix p 5), and there was an estimated decrease of 3·1% (95% CI 1·1–5·0%; appendix p 9) per year. Young adolescents (aged 12–14 years) had the greatest relative increase in prescription annual period prevalence (average annual increase 5·0%; 95% CI 4·0–6·1%). Overall, the period prevalence of prescriptions for those aged 15–18 years was double that in those aged 12–14 years, and six times higher than in those aged 6–11-years. There was no obvious difference in trend according to IMD quintile (figure 2C).

We were able to establish the most likely indication for 13 185 (67·6%) of 19 496 prescriptions. The most likely indications in the first identified antipsychotic prescriptions were for ASD (2477 [12·7%]), non-affective psychosis (1669 [8·6%]), anxiety disorders (1466 [7·5%]), ADHD (1391 [7·1%]), depression (1256 [6·4%]), and conduct disorders (1181 [6·1%]; table 3). Non-specific mental health codes (eg, listed as mixed behaviour and emotional disorder or as seen in child psychology clinic) accounted for 2189 (11·2%) of first prescriptions, whereas 1179 (6·0%) had mental illness codes that did not fit other categories (eg, listed as persistent or suspected drug misuse, or as suicidal). 3868 (19·8%) were identified as other codes that did not relate to a diagnostic category, including laboratory tests (eg, listed as serum lipids) or clinical descriptions (eg, listed as monitoring metabolic variables). No codes were provided in 254 (1·3%) of prescriptions.

The indications with the highest proportion of girls were eating disorders (380 [88·2%] of 442), depression (810 [64·5%] of 1256), and anxiety disorders (870 [59·3%] of 1466). The indications with the highest proportion of boys were ADHD (1171 [84·2%] of 1391), tic disorders (474 [81·2%] of 584), ASD (1917 [77·4%] of 2477), conduct disorders (887 [75·1%] of 1181), and learning difficulties (348 [72·2%] of 482; table 3). Antipsychotics for ASD, conduct disorders, non-specific mental illnesses, and other codes were prescribed equally to any age group. For tic disorders and ADHD, prescriptions were more common in children; and for depression, non-affective and affective psychosis, other mental illnesses, anxiety disorders, eating disorders, and obsessive-compulsive disorder, prescriptions were more common in adolescents (aged 15-18 years). Obsessive-compulsive disorder was the most likely indication for antipsychotics in least deprived areas and learning difficulties were the most likely in most deprived areas (appendix p 10).

Risperidone was the most prescribed antipsychotic for all indications apart from depression, for which the most prescribed antipsychotic was quetiapine, and eating

	Number of prescriptions* (n=243 529)	Number of individuals with a prescription*† (n=19 496)	Rate of prescription per 10 000 person-years (n=1224·5)
Atypical antipsychotics	225 710 (92·7%)	16 801 (86·2%)	1135·0
Risperidone	149 562 (61·4%)	10 642 (54·6%)	752·1
Aripiprazole	33 385 (13·7%)	3427 (17·6%)	167·9
Quetiapine	24 287 (10·0%)	2683 (13·8%)	122·1
Olanzapine	16 928 (7·0%)	2212 (11·3%)	85·1
Amisulpride	1316 (0·5%)	145 (0·7%)	6·6
Lurasidone	165 (0·1%)	10 (0·1%)	0·8
Clozapine	46 (<0·1%)	28 (0·1%)	0·2
Paliperidone	10 (<0·1%)	<10 (<0·1%)	..
Zotepine	10 (<0·1%)	<10 (<0·1%)	..
Asenapine	<10 (<0·1%)	<10 (<0·1%)	..
Typical antipsychotics	17 819 (7·3%)	3345 (17·2%)	89·6
Haloperidol	5683 (2·3%)	713 (3·7%)	28·6
Chlorpromazine	2927 (1·2%)	653 (3·3%)	14·7
Sulpiride	2344 (1·0%)	225 (1·2%)	11·8
Thioridazine	1861 (0·8%)	369 (1·9%)	9·4
Levomepromazine	1487 (0·6%)	352 (1·8%)	7·5
Flupentixol	948 (0·4%)	463 (2·4%)	4·8
Trifluoperazine	865 (0·4%)	337 (1·7%)	4·4
Promazine	671 (0·3%)	264 (1·4%)	3·4
Periciazine	384 (0·2%)	48 (0·2%)	1·9
Zuclopenthixol	208 (0·1%)	26 (0·1%)	1·1
Pimozide	182 (0·1%)	23 (0·1%)	0·9
Fluphenazine	90 (<0·1%)	43 (0·2%)	0·5
Perphenazine	76 (<0·1%)	33 (0·2%)	0·4
Benperidol	51 (<0·1%)	<10 (<0·1%)	..
Pipotiazine	29 (<0·1%)	<10 (<0·1%)	..
Droperidol	13 (<0·1%)	<10 (<0·1%)	..

Data shown as n (%). *Clinical Practice Research Datalink data protection rules mean frequencies with numbers of less than 10 are not presented. The number of individuals with all antipsychotic prescriptions reported here is larger than the number of individuals with any antipsychotic prescription because it includes individuals with more than one type of antipsychotic prescription. †Categories are not mutually exclusive.

Table 2: **Descriptive statistics of antipsychotic prescribing to children and adolescents in England (2000–19)**

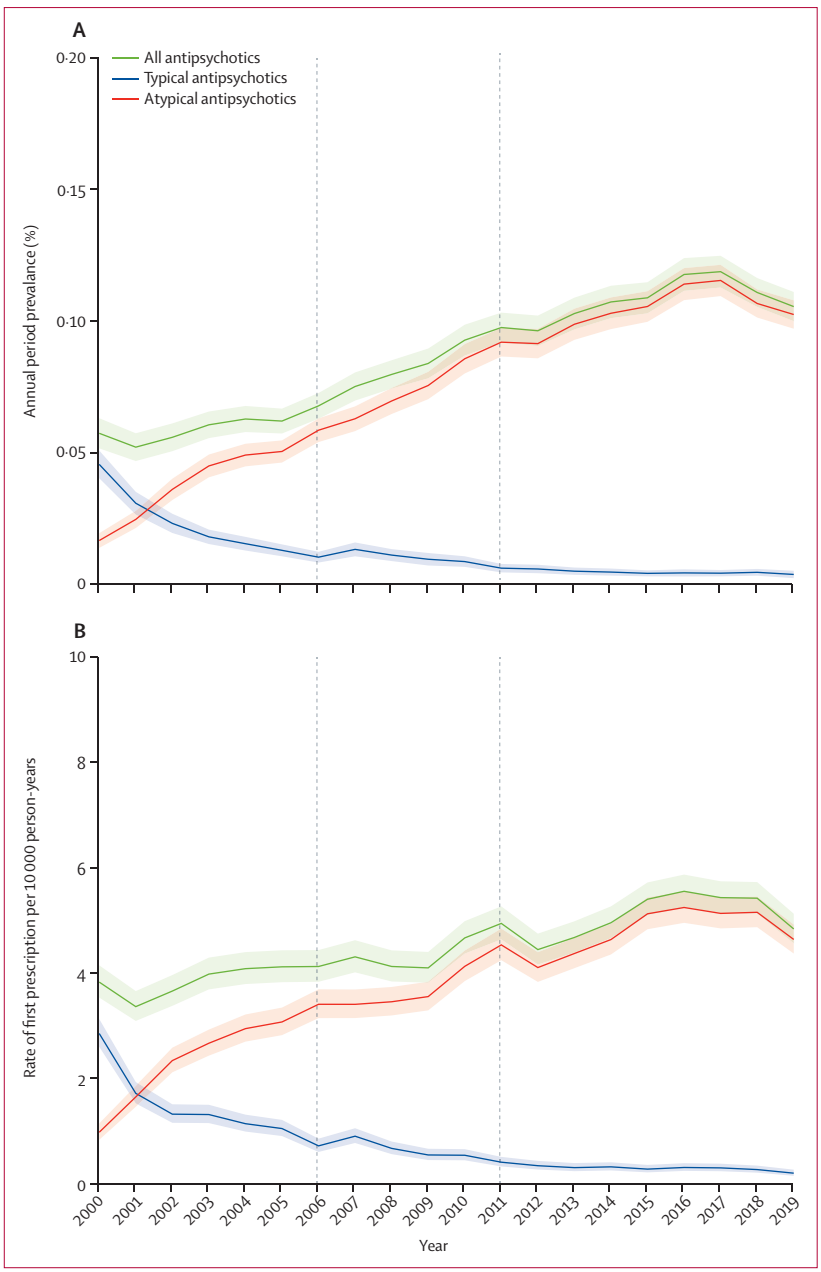

Figure 1: **Trends in antipsychotic prescribing to children and adolescents in England in 2000–19**
(A) Annual period prevalence. (B) The rate of first antipsychotic prescription per 10 000 person-years. The shaded areas beside the solid lines represent 95% CIs. The vertical dashed lines indicate the years of the first antipsychotic approvals in children and adolescents: in 2006, risperidone was approved in the USA, and in 2011, aripiprazole was approved in the UK. Additionally, for children and adolescents, the following antipsychotics were approved: in the USA, aripiprazole in 2007, olanzapine and quetiapine in 2009, paliperidone in 2011, and asenapine in 2015; and in the UK, risperidone and clozapine in 2013. The underlying data are available in the appendix (p 4).

disorders, for which it was olanzapine (appendix pp 11–13). Risperidone accounted for more than 70% of prescriptions for ASD, ADHD, conduct disorders, and learning difficulties. Prescribed doses were mostly within therapeutic ranges and were occasionally lower, most notably for haloperidol. There were a few cases when olanzapine (for non-affective psychosis and ADHD) was prescribed at more than the maximal daily dose. Drug consumption (total DDDs and DDD per individual) was highest for aripiprazole for almost all indications. The consumption of this antipsychotic ranged from 33·2 DDD per individual for non-affective psychosis to 69·2 DDD per individual for learning difficulties, in contrast with risperidone, the consumption of which varied from 7·5 DDD per individual for eating disorders to 15·1 DDD per individual for non-affective psychosis. For most medications, the median duration of each prescription was approximately 1 month.

Compared with the first recorded antipsychotic of the participants over follow-up, the odds of receiving typical versus atypical antipsychotics decreased slightly with each year of age (adjusted odds ratio [aOR] 0·97; 95% CI 0·96–0·99), but they increased for girls (aOR 2·12; 1·90–2·37) and for individuals in the most deprived areas (aOR 1·53; 1·29–1·82; appendix p 14). Compared with the indication of non-affective psychosis, the likelihood of receiving typical over atypical antipsychotics was greatest for nausea (aOR 20·03; 13·55–29·60), tic disorders (aOR 13·08; 9·38–18·24), anxiety disorders (aOR 7·56; 5·64–10·14), and depression (aOR 4·83; 3·58–6·52).

In 2000, 185 (37·6%) of 492 children and adolescents with incident prescriptions had no follow-up prescription in the subsequent 18 months (appendix p 15). This proportion fell to 110 (15·7%) of 702 in 2012, before increasing to 140 (22·1%) of 635 in 2018. The proportion with a prescription 12–18 months after their incident prescription increased from 171 (34·8%) of 492 in 2000, to 303 (47·7%) of 635 in 2018. Sensitivity analyses showed that shortening the window of time used to capture indications from 6 months to 3 months or 1 month changed the proportion with a missing indication, but did not change the distribution of indications (appendix p 16).

Discussion

From 2000 to 2019, the prescriptions for antipsychotics for children and adolescents in England doubled from an annual period prevalence in 2000 of 0·057% (95% CI 0·052–0·063%) to 0·105% (0·100–0·111%) in 2019. The increase in prevalence results from an increase in new prescriptions (2·2% per year) and from more children and adolescents receiving longer term treatment (change in the proportion receiving antipsychotics at least 6 months after an initial prescription, 41·9% in 2000 to 62·8% in 2018; appendix p 16). From 2009 onwards, more than 90% of prescriptions were for atypical antipsychotics. Over time, risperidone dominated, with more than 60% of all prescriptions, followed by aripiprazole, quetiapine, olanzapine, and haloperidol as the most prescribed antipsychotics. Boys were more likely to receive antipsychotics overall. From 2012 onwards, we observed an increase in prescribing to girls and to adolescents (aged 15–18 years). We did not observe differences in 20-year prescribing trends by area-

level deprivation, but typical antipsychotics were prescribed more frequently in more deprived areas over time. The most recorded indications for prescribing were ASD, non-affective psychosis, anxiety disorders, ADHD, depression, and conduct disorders. Antipsychotics were mainly prescribed in therapeutic doses, occasionally in the lower range; aripiprazole had the highest consumption of DDDs.

This study has some limitations. First, follow-up in the CPRD Aurum database is restricted to the period when either patients or general practices were registered. This restriction means that first prescription in the database might not represent the first time a child received an antipsychotic or a diagnosis. Second, CPRD does not directly tie an indication to a prescription, and, despite using an algorithm including symptoms and a lead-in time for clinical assessment, we could not establish an indication for 32·6% of prescriptions. In addition, indications were based on an algorithm approach that inevitably contained some misclassification, although the distribution of indications was robust to the specification of the data capture window. Third, although the CPRD Aurum database is broadly representative of England socioeconomically and demographically,[17] the general practices that submitted data might not be fully representative of the English population. This factor was mitigated by standardising estimates. Fourth, the CPRD Aurum database does not include prescriptions issued solely in secondary care. Effectively, all antipsychotic prescribing to children is initiated in secondary care before continuation in primary care under specialist review. The absence of this information might underestimate the rate of prescribing. Fifth, we were unable to explore the relative effects of biological gender and self-described gender. Sixth, data on antipsychotic dosing regimens were complete for only a third of prescriptions. For incomplete prescriptions, reference was made to verbal instructions, specialist instructions, or previous use. Within complete prescriptions, there were no deviations from the official dosing recommendations. Thus, for missing regimens (daily frequency), we assumed recommended doses that could not affect minimum or maximum doses. Seventh, we did not investigate polypharmacy; in other words, whether indications were treated with several medications, and the mutual influence of prescribed medications on doses and durations or multiple diagnoses concurrently or over time. Lastly, we did not collect data on ethnicity because of its poor recording in general practice.

Compared with the 1990s, from 2000 to 2019, trends in antipsychotic prescribing to children and adolescents

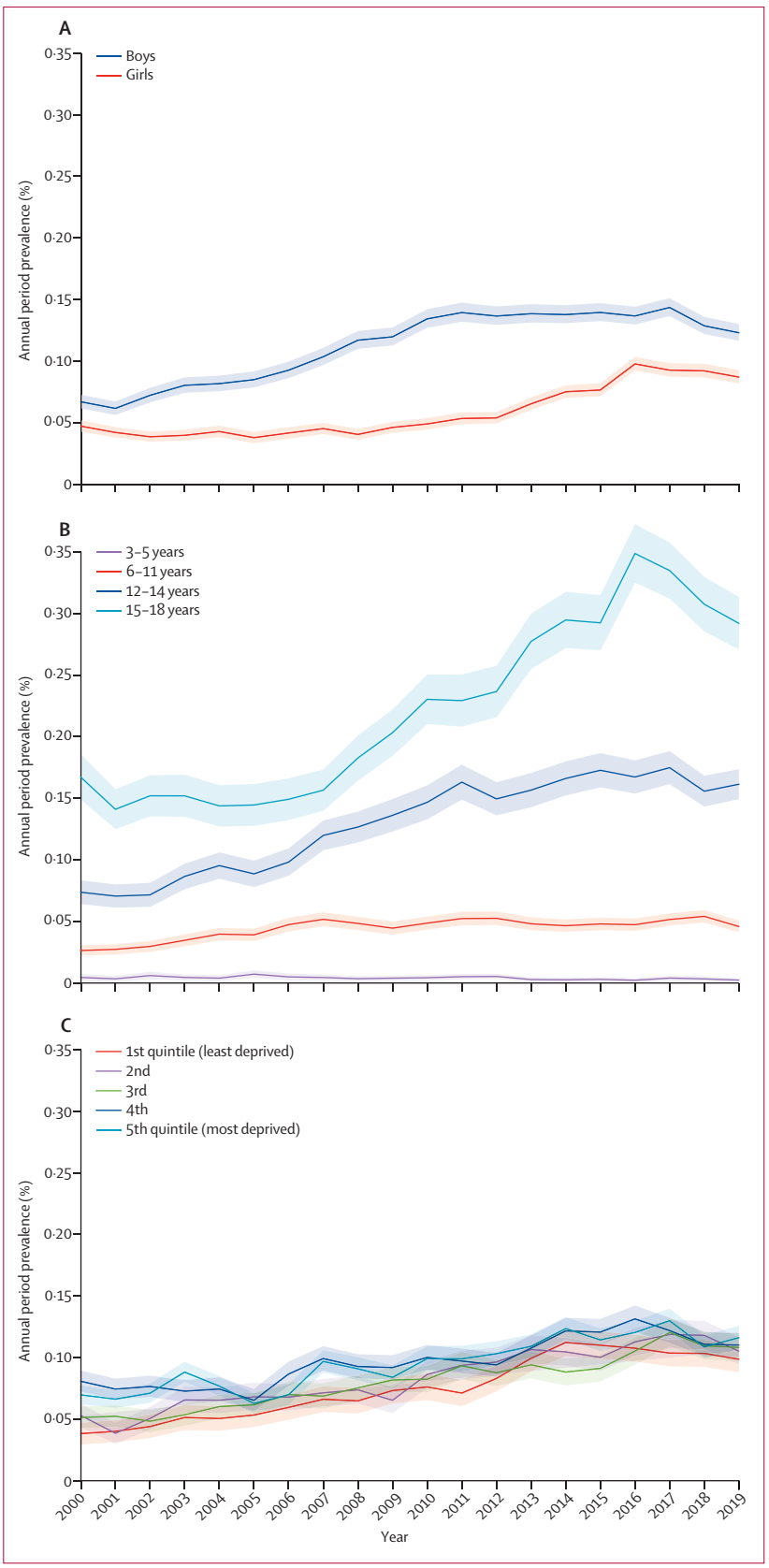

Figure 2: **Trends in antipsychotic prescriptions to children and adolescents in England in 2000–19 expressed as an annual period prevalence and stratified by categories of descriptive variables**

(A) Gender groups. (B) Age groups. (C) Quintiles of the Index of Multiple Deprivation. The shaded areas beside the solid lines represent 95% CIs. The underlying data are available in the appendix (pp 5–6).

	Total* (n=19 496)	Gender†		Age groups†		
		Girls	Boys	3–11 years‡	12–14 years	15–18 years
Autism spectrum disorder	2477 (12·7%)	560 (22·6%)	1917 (77·4%)	856 (34·6%)	734 (29·6%)	887 (35·8%)
Non-affective psychosis	1669 (8·6%)	705 (42·2%)	964 (57·8%)	25 (1·5%)	244 (14·6%)	1400 (83·9%)
Anxiety disorders	1466 (7·5%)	870 (59·3%)	596 (40·7%)	89 (6·1%)	244 (16·6%)	1133 (77·3%)
ADHD	1391 (7·1%)	220 (15·8%)	1171 (84·2%)	552 (39·7%)	436 (31·3%)	403 (29·0%)
Depression	1256 (6·4%)	810 (64·5%)	446 (35·5%)	20 (1·6%)	167 (13·3%)	1069 (85·1%)
Conduct disorders	1181 (6·1%)	294 (24·9%)	887 (75·1%)	369 (31·2%)	375 (31·8%)	437 (37·0%)
Tic disorders	584 (3·0%)	110 (18·8%)	474 (81·2%)	236 (40·4%)	199 (34·1%)	149 (25·5%)
Affective psychosis	546 (2·8%)	297 (54·4%)	249 (45·6%)	17 (3·1%)	90 (16·5%)	439 (80·4%)
Learning difficulties	482 (2·5%)	134 (27·8%)	348 (72·2%)	105 (21·8%)	134 (27·8%)	243 (50·4%)
Eating disorders	442 (2·3%)	390 (88·2%)	52 (11·8%)	24 (5·4%)	108 (24·4%)	310 (70·2%)
Obsessive-compulsive disorders	260 (1·3%)	106 (40·8%)	154 (59·2%)	27 (10·4%)	73 (28·1%)	160 (61·5%)
Nausea	252 (1·3%)	141 (56·0%)	111 (44·0%)	78 (31·0%)	63 (25·0%)	111 (44·0%)
Other mental illnesses	1179 (6·0%)	600 (50·9%)	579 (49·1%)	44 (3·7%)	204 (17·3%)	931 (79·0%)
Non-specific mental illnesses	2189 (11·2%)	689 (31·5%)	1500 (68·5%)	555 (25·4%)	649 (29·6%)	985 (45·0%)
Other codes	3868 (19·8%)	1187 (30·7%)	2681 (69·3%)	1259 (32·5%)	1101 (28·5%)	1508 (39·0%)
Missing codes	254 (1·3%)	55 (21·7%)	199 (78·3%)	67 (26·4%)	84 (33·1%)	103 (40·5%)

Data shown as n (%). *Percentages show the proportion of individuals with the indication among individuals with antipsychotic prescriptions. †Percentages show the proportion of individuals among gender and age groups who have the indication. ‡The age group 3–5 years was combined with the age group 6–11 years because of low frequencies.

Table 3: **Results after attempting to find indications for 19 496 first antipsychotic prescriptions**

iand changed considerably as frequency, medication preferences, and indications expanded. A previous UK study (for 1992–2005) reported 21 089 antipsychotic prescriptions, with an atypical to typical ratio of 52:48.[11] Even when corrected for longer durations, in the CPRD Aurum database, we identified eight times more prescriptions and an atypical to typical ratio of 93:7. In European countries in 2012, this ratio was approximately 75:25;[12] in Japan, 78:22;[3] and in the USA, 98:2.[12] Previous UK reports found a steady incidence rate of 3·0–3·3 per 10 000 person-years;[11] we found 3·83–4·84 per 10 000 person-years. The doubling in the prevalence of prescriptions with a minor increase in new prescriptions indicates a trend towards lengthier treatments. These findings highlight the need for better information about long-term antipsychotic safety in developing individuals. We observed a decrease in the prevalence and incidence of antipsychotic prescribing in adolescents during the last 3 years of follow-up, which might imply prescribing optimisation.

We report 20 times more risperidone prescriptions than previously observed.[1] In 2006, the USA approved risperidone for children and adolescents with ASD, bipolar mania, and schizophrenia,[26] and the joinpoint model showed that this coincided with the steepest prescribing increase in England (appendix p 7). In 2011, NICE approved aripiprazole for adolescents; and in 2013, risperidone for conduct disorders.[7,10] Both US and European approvals are likely to influence antipsychotic prescribing in England. From 2007, atypical antipsychotic annual period prevalence exceeded the estimates for 2000 for all antipsychotics. From 2014, rates of first atypical prescription peaked, with more than 4·6 prescriptions per 10 000 person-years. Risperidone was the most prescribed antipsychotic for ASD and conduct disorders, ADHD, learning difficulties, non-specific mental illnesses, and other codes. Non-specific illnesses included referrals to specialists or descriptions of mixed symptoms, such as possibly early ASD or conduct disorders prescriptions before diagnosis was established. Other codes included the monitoring of metabolic factors and had higher odds of receiving (perhaps switching to) typical antipsychotics, such as possibly longer term atypical antipsychotic use for ASD and conduct disorders. Diagnoses might not have been captured because diagnosis was recorded only in secondary care before primary care took over repeat prescriptions. Aripiprazole on-label and off-label use was uncommon, but its consumption in DDDs was highest. Aripiprazole accounted for 13·7% of prescriptions, similar to Norway (13·6%), but less than in other European countries (24·8–28·3%).[1] Aripiprazole has been reported to cause fewer metabolic adverse effects and less weight gain in adults; therefore, clinicians might have considered it less likely to cause side-effects at higher doses in children and adolescents.[7]

Of note, the most common indications for antipsychotics were ASD, ADHD, anxiety, and depression. It could be the increasing prevalence of these disorders that causes higher prescribing rates. However, increasing ASD prevalence results primarily from patients with less severe ASD, who

are unlikely to receive antipsychotics.[27] NICE guidance for ADHD does not include antipsychotics and advises against co-prescribing atypical antipsychotics with stimulants for ADHD with co-existing aggression and irritability without tertiary services.[28] Since 2012, after the NICE approvals in 2011,[7,8] we observed increased prescriptions, especially for girls and adolescents; and anxiety and depression were the most common indications in these groups. Antipsychotics are known for their sedative effects (because they are major tranquilisers). However, they are not recommended for treating anxiety, and a meta-analysis in children and adolescents with ASD found no evidence of antipsychotic superiority over placebo for anxiety symptoms.[29]

Existing clinical trials of antipsychotics in children and adolescents are small and of short duration; meta-analyses consistently report adverse cardiometabolic events.[30] Atypical antipsychotics might have been preferred because of the perceived lower risk of extrapyramidal effects. However, their cardiometabolic and other risks also require weighing against efficacy in children and adolescents.[6] Undoubtedly, further research should examine antipsychotic safety; and the increasing duration of the prescriptions reported here means research should consider effects of long-term use. Possible health inequalities in medications provided to individuals from more deprived areas in England require further investigation, as does consideration of potential ethnic inequalities. Adherence to antipsychotic prescribing guidelines for children and adolescents in Europe was found to have notable gaps.[31] A national audit of how UK clinicians implement NICE recommendations is now necessary.

In conclusion, authorities in England should monitor and review the emerging trend we describe of broadening clinical indications for antipsychotic use in young people, as well as possible emerging health inequalities in their use. Efficacy and safety evidence should be reassessed and reflected in future guidelines considering the current clinical practices reported here.

Contributors

KMA conceived of the study. MP and ES wrote the protocol, and KMA and HH contributed to the protocol. MP and LT extracted the data. ES and KMA finalised antipsychotic terms and clinical indications. MP and LT had access to and verified the data, and did the analyses. MRR defined and contributed to medication analyses. MRR, MP, KMA, HH, ES, MS, and VPT contributed to data interpretation. MRR wrote the initial draft and created tables and figures. All authors contributed to the final manuscript and approved its submission for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The clinical codes, data management, and analysis code used in this study are available on request from the corresponding author. These data are fully anonymised and will be shared with any researchers on request. Access to data can be requested via application to the Clinical Practice Research Datalink. The criteria for applying for these data are available on the Clinical Practice Research Datalink website: https://cprd.com/.

Acknowledgments

MRR, HH, VPT, and KMA receive funding from the European Research Council (GA682741), and KMA received funding from the National Institute for Health Research (111905). MP is funded on a Henry Dale Fellowship by the Wellcome Trust and the Royal Society (224243/Z/21/Z). This study is based on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. We acknowledge all the data providers, patients, and general practices that made the anonymised data available for research. We acknowledge the funders, the European Research Council, the National Institute of Health Research, the Wellcome Trust, and the Royal Society. We thank Darren Ashcroft (University of Manchester) and Rosa Parisi (University of Manchester) for their help with the ethics application.

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