General Practitioner Prescribing Trends among Pediatric Patients in the United Kingdom: 1998-2018

Running title: Prescribing Trends in Children

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ABSTRACT

Purpose: To describe the prescribing trends of 17 therapeutic drug categories and the specific drug classes of systemic antibiotics, analgesics, and antidepressants in children and adolescents in the United Kingdom between 1998 and 2018.

Methods: A population-based retrospective cohort study including children and adolescents aged 0 to 18 years. Overall and annual prescription rates per 10,000 person-years and corresponding 95% confidence intervals (CIs) were calculated. Rate ratios and 95% CIs were calculated to assess changes in prescription rates during the study period using Poisson regression.

Results: Among 4,075,527 children and adolescents during the study period from 1998 to 2018, the prescribing rates increased by 15% for attention deficit hyperactivity disorder (ADHD) drugs (rate ratio: 1.15, 95% CI: 1.12 to 1.18), 14% for anxiolytics and hypnotics (rate ratio: 1.14, 95% CI: 1.13 to 1.16), and 8% for drugs for gastro-esophageal reflux disease (GERD) (rate ratio: 1.08, 95% CI: 1.07 to 1.09). Prescribing rates decreased by 6% for cough preparations (rate ratio: 0.94, 95% CI: 0.92 to 0.95) and by 3% for analgesics (rate ratio: 0.97, 95% CI: 0.96 to 0.99). No meaningful changes were observed for systemic antibiotics (rate ratio: 1.02, 95% CI: 0.99 to 1.04). Among specific drug classes, prescribing rates decreased for broad-spectrum penicillins and cephalosporins, and they increased for selective serotonin reuptake inhibitors, opioids, and drugs for migraine.

Conclusions: Between 1998 and 2018, the prescribing of centrally-acting drugs and drugs for GERD increased among pediatric patients, whereas prescribing of cough preparations and analgesics declined in this population.

Keywords: utilization, prescription drugs, children, cohort, trends

KEYPOINTS

- Licensed and unlicensed drugs of different therapeutic categories are increasingly prescribed among pediatric patients in the UK.
- Longitudinal assessments of national drug utilization patterns that can inform research and clinical practice are limited in the pediatric population.
- General practitioner prescribing of drugs among children and adolescents increased in the UK between 1998 and 2018.
- Substantial increases were observed in the prescription of centrally-acting and gastrointestinal drugs, while decreased prescribing was observed for cough preparations and analgesics.
- This study identified important changes in prescribing patterns in this vulnerable and understudied population, including potential areas for future real-world safety and effectiveness studies.

PURPOSE

Monitoring prescribing patterns at the population level can inform research and clinical practice.[1] The study of prescribing trends in children and adolescents is particularly important due to the changes in their health needs and updates to clinical practice guidelines that target this population, which may shift prescribing patterns over time.[2-4] Furthermore, childhood is a critical time of development and growth, and prescription drug use in this population often falls outside the specified indication, approved age group, dosage, or route of administration (i.e., "off-label").[2-7] In addition, drugs may have substantially different safety profiles in children than in adults, and increased vigilance in this population is therefore paramount.[6]

There has been increased prescribing of certain drugs among pediatric patients over the last decades for several reasons, including the discovery of new drugs, increased survival following pediatric surgery, and changes in the burden of disease among children and adolescents.[2,3,8] Furthermore, the prevalence of childhood diseases, such as gastrointestinal diseases, neurodevelopmental disorders, and obesity, has increased during this time.[9-12] Given these underlying trends, understanding drug utilization patterns among pediatric patients is an important component in the post-marketing surveillance of prescription drugs. In addition to providing key information on the frequency and patterns of use according to therapeutic areas and patient characteristics, such surveillance allows for the identification of patterns of "off-label" prescribing, providing insight where potential safety and effectiveness studies might be needed.[13,14] It may also assist in targeting risk management and informing clinical decision making.

Several drug utilization studies have been previously conducted among pediatric outpatients. Two of these studies were conducted using insurance based claims data from the United States (US).[13,14] While the first study assessed the top 20 prescription drugs dispensed in children per year, the latter examined the prevalence of prescription use according to parental and

self-report.[13,14] Three multi-database cohort studies assessed prescribing rates of antipsychotics, non-steroidal anti-inflammatory drugs, and antibiotics in Europe.[15-17] Another multi-database cohort study in Europe assessed general prescribing rates among children, however this study was conducted in 2005.[18] Other population-based studies in the United Kingdom (UK) have assessed prescribing patterns of specific drugs such as metformin or attention deficit hyperactivity disorder (ADHD) drugs in children and adolescents using the Clinical Practice Research Datalink (CPRD).[19-23] However, little up to date information is available regarding overall prescribing among pediatric patients in the UK. Given this knowledge gap and the underlying changes in disease burden among children and adolescents, we conducted a population-based cohort study to describe prescribing trends of 17 therapeutic drug categories among children and adolescents in the UK between 1998 and 2018.

METHODS

Data Source

We conducted a population-based retrospective cohort study using data from the CPRD Gold. The CPRD, which contains data on over 17 million patients enrolled with more than 700 general practitioner practices in the UK, is one of the world's largest electronic databases of anonymized primary care medical records.[24,25] The geographic distribution of the practices, as well as the age and sex distributions of patients, broadly reflects that of the UK population. The CPRD contains information such as demographic data, medical diagnosis (recorded using the Read coding system), lifestyle information (e.g., smoking, alcohol use), procedures that are documented by general practitioners, laboratory data results, clinical measures (e.g., blood pressure), and prescriptions written by the general practitioner (not medications purchased over-the-counter). These prescriptions are automatically recorded into the computerized patient file and are classified according to the British National Formulary (BNF). Data quality and completeness, as well as consistency with medical files, are regularly monitored, and CPRD data have been shown to be valid.[26-28]

Study Population

We constructed a cohort of individuals aged less than 18 years in the CPRD between November 21st, 1998 and June 30th, 2018. Cohort entry was defined by the date of registration with the CPRD practice, the date the CPRD practice became *up-to-standard* (a CPRD measure of data quality), or November 21st, 1998, whichever occurred last. Patients were followed until censoring due to death, departure from the CPRD practice, reaching an age of 19 years, or end of

153 the study period (June 30th, 2018), whichever occurred first. We excluded patients with missing
154 age, sex, and practice region data.
155
156 **Drug Prescriptions**
157 We identified prescriptions written by general practitioners during follow-up and classified
158 them into 17 therapeutic categories based on the chapters and corresponding headers listed in the
159 BNF. The following therapeutic categories were chosen based on previous utilization studies
160 among children[13,14,18] and in consultation with a paediatrician. These therapeutic categories are
161 more likely to be encountered in daily clinical practice among pediatric patients and focus on drugs
162 that are administered systemically. These categories were based on BNF chapters and relevant
163 headers within each chapter. In each header, we included all relevant BNF codes to identify
164 prescriptions. The 17 categories were: systemic antibiotics, bronchodilators (including inhaled
165 corticosteroids), systemic steroids, analgesics, antihistamines and allergy drugs, cough
166 preparations, ADHD drugs, antidepressants, drugs used in psychosis and related disorders,
167 antiepileptics, hypnotics and anxiolytics, drugs for gastro-esophageal reflux disease (GERD),
168 diuretics, drugs for hypertension and heart failure (including beta blockers), anticoagulants,
169 antiplatelets, and drugs used in diabetes and hypoglycemia. All drugs and BNF codes included in
170 the study are available in Appendix 1.
171
172 **Statistical Analysis**
173 We estimated prescription rates for each therapeutic category by dividing the total number
174 of prescriptions in each therapeutic category by the total number of person-years (PYs) of follow-
175 up contributed by cohort members. Prescription rates and their corresponding 95% confidence

intervals (CIs) were estimated overall and by fiscal year as prescriptions per 10,000 PYs. Two Poisson regression models were used to examine changes in prescribing trends during the study period. In the first, we estimated rate ratios (RRs) for each therapeutic category comparing the prescription rates in the last versus first year of the study period for each therapeutic category. In the second, we considered fiscal year as a continuous variable and estimated rate ratios of one-year increase in fiscal year to estimate overall changes in time trends during the study period. An overdispersion parameter was included in the models to account for extra-Poisson variation. In addition, we explored prescription rates of three specific drug classes: systemic antibiotics, analgesics, and antidepressants. We selected systemic antibiotics and analgesics as they were the most prescribed therapeutic categories and antidepressants due to safety concerns surrounding their use among pediatric patients.[29] Annual prescription rates were also stratified by sex and by age (<2 years, 2 to 4.9 years, 5 to 12.9 years, and 13 to 18 years). Data management and analyses were performed using the Aetion platform, R programming environment Version 3.6.3 (ggplot2 package),[30,31] and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Aetion has previously been validated by accurately repeating a range of previously published studies and by replicating or predicting clinical trial findings.[30,32,33]

RESULTS

Patient Characteristics

The study cohort included 4,075,527 children and adolescents who were followed for a total of 22,539,843 PYs. Demographic characteristics at cohort entry are reported in **Table 1**. The median age was 5.0 (interquartile range: 0 to 12.0), and 50.8% were boys. Between 1998 and 2018, 27,447,824 prescriptions across the 17 therapeutic categories of interest were issued to the cohort members.

Prescription Rates

Overall prescription rates for the 17 therapeutic categories between 1998 and 2018, rate ratios for a one-year change in fiscal year, and rate ratios comparing the last and first year prescription rates are reported in **Table 2**. The overall prescription rate between 1998 and 2018 for all 17 therapeutic categories was 12,128 prescriptions per 10,000 PYs (95% CI: 12,095 to 12,162). The therapeutic categories that had the highest increase in the prescribing rates during the entire study period were ADHD drugs (RR: 1.15, 95% CI: 1.12 to 1.18), anxiolytics and hypnotics (RR: 1.14, 95% CI: 1.13 to 1.16), drugs for GERD (RR: 1.08, 95% CI: 1.07 to 1.09), drugs for hypertension and heart failure with (RR: 1.08, 95% CI: 1.07 to 1.09), and antidepressants (RR: 1.07, 95% CI: 1.05 to 1.09). We observed a 6% decrease in the prescribing of cough preparations (RR: 0.94, 95% CI: 0.92 to 0.95), and analgesics (RR: 0.97, 95% CI: 0.96 to 0.99). The prescribing rates of systemic antibiotics remained relatively stable during the study period (RR: 1.02, 95% CI: 0.99 to 1.04). When examining rate differences between the first and the last year of the study, drugs for ADHD, and hypnotics and anxiolytics had a ~10-fold increase in the

prescribing rates, drugs for hypertension and heart failure, and antidepressants a 4-fold increase, and 85% and 50% percent decreases for cough preparations and analgesics, respectively.

Antidepressants, Antibiotics, and Analgesics

Table 3 reports overall prescription rates and rate ratios for the specific drug classes of antidepressants, systemic antibiotics, and antidepressants. Prescribing rates of selective serotonin reuptake inhibitors (SSRIs) and other antidepressants (serotonin norepinephrine reuptake inhibitors [SNRIs], mirtazapine, and tryptophan) increased substantially during the study period (RR: 5.72, 95% CI: 5.53 to 5.91) and (RR: 4.94, 95% CI: 4.39 to 5.57), respectively. Among the 10 most prescribed systemic antibiotics, there were decreases in the prescribing of broad-spectrum penicillins that include amoxicillin, amoxicillin/clavulanate, and ampicillin (RR: 0.81, 95% CI: 0.80 to 0.82) and in the prescribing of cephalosporins (RR: 0.17, 95% CI: 0.16 to 0.18). The prescribing rates of penicillinase-resistant penicillins that include cloxacillin, flucloxacillin, temocillin, and flucloxacillin/ampicillin increased by approximately 50% (RR: 1.47, 95% CI: 1.44 to 1.50). Prescribing rates of codeine-containing analgesics (RR: 0.60 95% CI: 0.57 to 0.62) and non-opioid compound analgesics (RR: 0.31 95% CI: 0.30 to 0.32) decreased during the study period, while the prescribing rates of migraine medications (RR: 1.58 95% CI: 1.52 to 1.65) and opioids excluding codeine (RR: 1.97 95% CI: 1.75 to 2.20) increased during this period.

Calendar Time Trends

Prescription rates by year are described in **Figures 1 to 7.** During the study period, prescription rates increased for all centrally-acting drugs (**Figure 1)**. Prescription rates increased for cardiovascular drugs (excluding diuretics) during the study period (**Figure 2**). Increases were

also observed for drugs used for GERD (**Figure 3**) and for drugs for diabetes and hypoglycaemia representing an overall 6% increase during the study period (**Figure 4**). In contrast, prescription rates for analgesics and cough preparations decreased over time (**Figures 5 and 6)**. No meaningful changes were present in the prescription rates for systemic antibiotics, bronchodilators, systemic steroids, and diuretics during the study period (**Figures 2, 6, and 7**).

Stratified Analyses

Figure 8 and **e-Table 1** report prescription rates stratified by sex. Higher prescription rates were observed among boys for antiepileptics, antihistamine and allergy drugs, bronchodilators, ADHD drugs, and hypnotics and anxiolytic drugs. For ADHD drugs, the rate among boys (571 prescriptions per 10,000 PYs, 95% CI: 559 to 584) was 4.5 times higher than that among girls (122 prescriptions per 10,000 PYs, 95% CI: 117 to 128). Higher prescription rates were observed among girls for analgesics, antibiotics, hypertension and heart failure drugs, and antidepressants. For antidepressants, the rate among girls (281 prescriptions per 10,000 PYs, 95% CI: 277 to 285) was more than twice that of boys (126 prescriptions per 10,000 PYs, 95% CI 123 to 129). **e-Table 2** reports prescription rates stratified by age group.

DISCUSSION

Our study was designed to examine the longitudinal prescribing trends of commonly prescribed drugs in children and adolescents in the UK between 1998 and 2018. We found that prescription rates increased over time for many therapeutic categories, with the largest increases observed for centrally-acting drugs, drugs for GERD, drugs for hypertension and heart failure, and antidepressants. In contrast, prescription rates decreased for analgesics and for cough preparations. Among antidepressant drug classes, the prescribing of SSRIs and SNRIs increased during the study period despite known safety concerns. Although some fluctuations were present, the overall prescribing of antibiotics did not change meaningfully during the study period. However, among drug classes of antibiotics, the prescribing of broad-spectrum penicillins (amoxicillin, amoxicillin/clavulanate, ampicillin) and cephalosporins decreased, while the prescribing of penicillinase-resistant penicillins (cloxacillin, flucloxacillin, temocillin, and flucloxacillin/ampicillin) increased. Lastly, there was an increase in the prescribing of opioids and migraine medications, while the prescribing of codeine-containing analgesics decreased. We generally observed higher prescribing rates among boys, especially for ADHD drugs, while girls had higher prescribing rates for antidepressants. These population-based prescribing trends provide crucial information for public health. They provide real-world data that may help assess disease burden and the impact of adopting treatment guidelines and regulatory decisions. They can also help direct resources to real-world safety and effectiveness studies of prescription drugs in this vulnerable population. These data may also help identify "off-label" prescribing in certain age groups such as that observed for drug prescriptions for GERD, antipsychotics, and cardiovascular drugs in the present study.[5,34]

Our study has several strengths. The CPRD is a large and high-quality database that includes prescribing information provided by general practitioners working in primary care. Its data are nationally representative of the UK population, which ensures representation of utilization trends across the country. Furthermore, we present a thorough evaluation of prescribing trends for a wide range of drugs. In addition, because prescriptions are automatically recorded in the CPRD at the time they are issued by general practitioners, the present study provides a more robust measure of prescribing practices relative to previous studies in this area that relied on self-report.[14,35]

Our study also has limitations. First, we did not capture dispensing information, indications, dosages, or data on the use of over-the-counter drugs. While these data may have provided additional information on why these drugs were prescribed and how they were used, we were interested in assessing general prescribing trends in the last 20 years among the paediatric population in the UK. Furthermore, we may have missed initial prescriptions issued by specialists, however, subsequent prescriptions are usually provided by general practitioners, the gatekeepers of the UK healthcare system. Second, we used broad therapeutic categories to identify prescriptions and did not assess prescribing patterns of individual drugs. The use of broad therapeutic definitions and the lack of information on indications may have prevented us from fully interpreting some of the observed changes in prescribing trends observed in our study. Furthermore, some drugs appear under more than one BNF category. Finally, our data were restricted to outpatient prescriptions and do not reflect prescribing patterns for pediatric inpatients, who may have different characteristics.

The results from our study are not entirely consistent with those of previous drug utilization studies conducted among pediatric populations. A population-based study in the US conducted

using the IMS Vector One claims database examined dispensing trends among children aged 0-17 years and found that overall dispensing decreased by 7% between 2002 to 2010.[13] This study also found decreased dispensing of antibiotics, allergy drugs, analgesics, antidepressants, and cough and cold drugs and increased dispensing of asthma and ADHD drugs during this period.[13] Sturkenboom et al., assessed prescribing trends of drugs among children aged up to 18 years in three European countries between 2000 and 2005 and reported that antibiotics, asthma drugs, and dermatological preparations were frequently prescribed while cardiovascular drugs were not.[18] An Italian population-based study examined drug utilization patterns in pediatric outpatients aged 0-18 years between 2010 and 2015 and reported an overall 3.2% reduction in prescribing during this period.[36] This study found that, for antibiotics, respiratory drugs, and hormones, prescribing was greater among boys than among girls.[36] There are several factors that may have contributed to the observed changes in prescribing during the study period. These factors include the implementation and uptake of revised treatment guidelines, the publication of safety warnings and expert reviews by regulatory agencies such as the Medicines and Healthcare products Regulatory Agency (MHRA), and underlying shifts in disease burden among children and adolescents.[2,37-41]

For example, changes in antidepressant prescribing, which decreased after 2004 and gradually increased after 2008, may be explained by regulatory warnings issued during the study period. In 2002, the U.S. Food and Drug Administration issued a black box warning alerting health care providers about an increased risk of suicidality in children and adolescents taking antidepressants.[40] Despite this warning, the prescribing of SSRIs and other antidepressants including SNRIs substantially increased during the study period. Furthermore, although some fluctuations were present, the prescribing rates of systemic antibiotics did not change meaningfully during the study period. However, when examining prescribing rates of specific classes of systemic

antibiotics, notable changes occurred during the study. We observed decreased prescribing of broad-spectrum penicillins (amoxicillin, amoxicillin/clavulanate, ampicillin), cephalosporines, and metronidazole, and increased prescribing of penicillinase-resistant penicillins (cloxacillin, flucloxacillin, temocillin, and flucloxacillin/ampicillin), macrolides, and urinary tract infections drugs. These findings are not fully consistent with the findings of other studies conducted in the UK, where the overall prescribing of broad-spectrum antibiotics decreased among pediatric patients but the prescribing of amoxicillin, a broad-spectrum penicillin, remained unchanged.[37,42-44] Our findings highlight the need for future research to examine prescribing patterns of antibiotics among the pediatric population. Furthermore, the prescription of analgesics decreased during the study period, with decreased prescribing of codeine-containing analgesics and non-opioid compound analgesics and increased prescribing of opioids (excluding codeine) and migraine medications. In 2015, the MHRA published a statement restricting the use of codeine in children aged less than 12 years due to the risk of serious adverse effects such as respiratory depression and death.[38] In the last two decades, there have been major advances in the treatment of congenital heart defects and more children that survive these procedures may suffer from residual heart conditions that require drug therapy.[45-47] The increased rates of drugs for hypertension and heart failure may also be attributed to prescribing of hypertension drugs in children and adolescents with obesity. Finally, the increased rates may also be attributed to the use of clonidine and guanfacine, centrally-acting hypertension medications that are approved for the treatment of ADHD.[48] Future studies of pediatric drug utilization should examine potential regulatory and guideline changes that may have contributed to the observed changes in practice during this period.

CONCLUSIONS

The present study describes population-based prescribing patterns in a nationally representative sample of pediatric patients in the UK between 1998 and 2018. Prescribing rates in this population increased during the study period, with marked increases in the prescribing of centrally-acting drugs and drugs for GERD. Notable decreases were observed for analgesics and cough preparations. Post-marketing surveillance of prescription drug utilization in the pediatric population is crucial for identifying potential real-world safety and effectiveness studies in this understudied and vulnerable population.

Ethics statement: This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (ISAC Protocol Number 19_141A, which was made available to journal reviewers) and the research ethics board of the Jewish General Hospital in Montreal, Canada (REB # 2020-1877). The need for informed consent was waived given the deidentified nature of the study data.

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Conflicts of interest: Dr. Platt has consulted for and received speaking fees from Amgen, Biogen, Eli Lilly, Merck, and Pfizer, and Bayer, unrelated to the current work. All authors have completed the Pharmacoepidemiology and Drug Safety conflict of interest form and declare that none of the authors have conflicts of interest to disclose.

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523 **Table 1.** Demographic characteristics at cohort entry among pediatric patients in the United Kingdom
524 between 1998 and 2018.

Characteristic	Number (%)
Total number of patients	4,075,527
Age, y (median, IQR)	5.0 (0, 12)
Age Categories	
<2 years	1,306,164 (32.0)
2 to 4.9 years	565,420 (12.9)
5 to 12.9 years	1,254,794 (28.6)
13 to 18 years	949,149 (23.3)
Sex	
Male	2,069,837 (50.8)
Female	2,005,690 (49.2)
Practice Region	
North East	58,821 (1.4)
North West	396,031 (9.7)
Yorkshire & The Humber	132,623 (3.3)
East Midlands	127,664 (3.1)
West Midlands	350,523 (8.6)
East of England	341,528 (8.4)
South West	374,547 (9.2)
South Central	440,631 (10.8)
London	522,595 (12.8)
South East Coast	394,546 (9.7)
Northern Ireland	118,434 (2.9)
Scotland	399,672 (9.8)
Wales	417,912 (10.3)

525 Data are expressed as n (%), mean (standard deviation) or median (interquartile range).

Table 2. General practitioner prescription rates and rate ratios in 17 therapeutic areas among 4,075,527 pediatric patients in the United Kingdom between 1998 and 2018.

Therapeutic Area	Patients That Were Issued a Prescription (%)	Prescription Rate Per 10,000 Person-years (95% CI)	Rate Ratio for 1 year change in fiscal year (95% CI)	Rate Ratio (95% CI) for 2018 vs. 1998
All therapeutic categories	4,840,113	12,128 (12,095, 12,162)	NA	NA
Anticoagulants	1,911 (<0.1)	13 (12, 15)	1.04 (1.03, 1.05)	2.32 (2.06, 2.62)
Antiplatelets	3,839 (<0.1)	15 (14, 16)	1.03 (1.02, 1.05)	2.60 (2.34, 2.88)
Diuretics	4,101 (<0.1)	17 (16, 18)	0.99 (0.98, 1.00)	0.95 (0.86, 1.04)
Diabetes and Hypoglycemia	10,895 (<0.1)	22 (223, 236)	1.06 (1.05, 1.07)	3.47 (3.37, 3.58)
Systemic Corticosteroids	8,384 (<0.1)	23 (21, 25)	0.99 (0.96, 1.02)	0.64 (0.60, 0.70)
Drugs for Psychosis and Related Disorders	39,700 (1.0)	44 (41, 46)	1.04 (1.03, 1.05)	2.37 (2.25, 2.50)
Hypertension and Heart Failure	34,346 (<1)	102 (99 to 105))	1.08 (1.07, 1.09)	4.12 (3.97, 4.28)
Cough Preparations	161,882 (4.0)	117 (116, 118)	0.94 (0.92, 0.95)	0.16 (0.15, 0.17)
Hypnotics and Anxiolytics	44,585 (1.1)	140 (137, 143)	1.14 (1.13, 1.16)	8.79 (8.48, 9.10)
Antidepressants	80,762 (2.0)	201 (198, 203)	1.07 (1.05, 1.09)	4.14 (4.00, 4.25)
Antiepileptics	18,133 (<0.1)	305 (297, 313)	1.03 (1.02, 1.04)	1.60 (1.57, 1.64)
ADHD Drugs	42,674 (1.0)	354 (347, 361)	1.15 (1.12, 1.18)	9.99 (9.68, 10.30)
Drugs for GERD	275,344 (6.8)	470 (466, 474)	1.08 (1.07, 1.09)	3.75 (3.68, 3.84)
Antihistamines and Allergy	753,083 (18.5)	1,523 (1,515, 1,531)	1.02 (1.01, 1.04)	1.54 (1.53, 1.56)
Analgesics	1,096,330 (27.0)	1,810 (1,803, 1,816)	0.97 (0.96, 0.99)	0.50 (0.49, 0.51)
Bronchodilators	676,674 (16.6)	2,890 (2,874, 2,904)	1.01 (1.00, 1.02)	1.13 (1.12, 1.14)
Systemic Antibiotics	1,957,229 (48.0)	3,902 (3,894, 3,911)	1.02 (0.99, 1.04)	0.98 (0.97, 0.99)

Abbreviations: ADHD: Attention Deficit and Hyperactivity Disorder; GERD: Gastro-Esophageal Reflux Disease and Dyspepsia

Table 3. General practitioner prescription rates for specific drug classes of antidepressants, antibiotics, and analgesics among 4,075,527 pediatric patients in the United Kingdom between 1998 and 2018.

	No. of prescriptions	Prescription Rate Per 10,000 Person-years (95% CI)	Rate Ratio (95% CI) for 2018 vs. 1998
Therapeutic Category			
***Antidepressants**			
Other Antidepressant Drugs	25,488	155 (153, 157)	4.94 (4.39, 5.57)
Tricyclic and Related Antidepressants	77,263	34 (33, 35)	1.09 (1.02, 1.16)
SSRIs	349,834	11 (10, 12)	5.72 (5.53, 5.91)
MAO-Is	167	<1	NA
****Systemic Antibiotics**			
Broad-Spectrum Penicillins	4,295,752	1,905 (1901, 1909)	0.81 (0.80, 0.82)
Benzylpenicillin and Phenoxymethylpenicillin	1,262,835	560 (558, 562)	1.28 (1.26, 1.30)
Macrolides	1,042,442	462 (460, 465)	1.05 (1.03, 1.07)
Penicillinase-Resistant Penicillins	802,377	356 (354, 358)	1.47 (1.44, 1.50)
Sulphonamides And Trimethoprim	573,395	254 (252, 256)	1.02 (1.00, 1.05)
Cephalosporins	367,643	163 (161, 165)	0.17 (0.16, 0.18)
Tetracyclines	267,514	119 (117, 120)	19.97 (18.55, 21.50)
Urinary Tract Infections Drugs	56,110	25 (24, 26)	7.14 (6.53, 7.80)
Metronidazole And Tinidazole	52,420	23 (22, 24)	0.77 (0.70, 0.85)
Quinolones	40,390	18 (17, 19)	0.82 (0.74, 0.82)
Other Antibiotics	34,338	<10	NA
***Analgesics**			
Non-Opioid Compound Analgesics	2,517,984	1,117 (1,112, 1,121)	0.31 (0.30, 0.32)
NSAIDs	1,333,721	592 (589, 594)	0.99 (0.97, 1.01)
Migraine Medications	189,021	84 (82, 85)	1.58 (1.52, 1.65)
Codeine-Containing Analgesics	243,227	108 (107, 109)	0.60 (0.57, 0.62)
Opioid Analgesics	29,744	13 (12, 14)	1.97 (1.75, 2.20)
Neuropathic Pain	2,248	<1	NA

*Other antidepressants: serotonin norepinephrine reuptake inhibitors, mirtazapine, and tryptophan.
**Broad-spectrum penicllins: amoxicillin, amoxicillin/clavulanate, ampicillin, ampicillin/cloxacillin, bacampicillin, ciclacillin, mecillinam, mezlocillin, pivampicillin, talampicillin.
Penicillinase-resistant penicillins: ampicillin sodium/flucloxacillin, cloxacillin, flucloxacillin, flucloxacillin/ampicillin, temocillin.
Urinary tract infections drugs: fosfomycin, methenamine, nitrofurantoin.
***Non-Opioid Compound Analgesics: caffeine in combination with aspirin paracetamol or other analgesics, nefopam, isometheptene, levomenthol, chlormezanone, benorilate, methylselicate all in combination with other analgesics.
Migraine medications: almotriptan, dihydroergotamine, eletriptan, ergotamine, frovatriptan, naratriptan, paracetamol/metoclopramide, rizatriptan, sumatriptan, tolfenamic acid, zolmitriptan, methysergide, pizotifen.
Neuropathic pain: gabapentin, pregabalin, duloxetine, ketamine, amitriptyline, imipramine, nortriptyline.

FIGURE LEGENDS

Figure 1. Prescription rates for centrally-acting drugs among pediatric patients in the United Kingdom between 1998 and 2018. Prescription rates are reported as prescriptions per 10,000 person-years.

Figure 2. Prescription rates for cardiovascular drugs among pediatric patients in the United Kingdom between 1998 and 2018. Prescription rates are reported as prescriptions per 10,000 person-years.

Figure 3. Prescription rates for gastro-esophageal reflux disease and dyspepsia drugs among pediatric patients in the United Kingdom between 1998 and 2018. Prescription rates are reported as prescriptions per 10,000 person-years.

Figure 4. Prescription rates for drugs for diabetes and hypoglycemia among pediatric outpatients in the United Kingdom between 1998 and 2018. Prescription rates are reported as prescriptions per 10,000 person-years.

Figure 5. Prescription rates for analgesics overall and by drug class among pediatric patients in the United Kingdom between 1998 and 2018. Prescription rates are reported as prescriptions per 10,000 person-years.

Figure 6. Prescription rates for cough preparations, bronchodilators, antihistamines and drugs for allergy, and systemic steroids among pediatric patients in the United Kingdom

between 1998 and 2018. Prescription rates are reported as prescriptions per 10,000 person-years.

Figure 7. Prescription rates for systemic antibiotics overall and for the 10 most prescribed systemic antibiotics among pediatric patients in the United Kingdom between 1998 and 2018. Prescription rates are reported as prescriptions per 10,000 person-years.

Figure 8. Prescription rates for drugs in 17 therapeutic categories among pediatric patients in the United Kingdom between 1998 and 2018, stratified by sex. Prescription rates are reported as prescriptions per 10,000 person-year.