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# Drug prescriptions to outpatient children: a review of the literature

Antonio Clavenna · Maurizio Bonati

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## Abstract

**Purpose** To evaluate the drug prescription pattern in outpatient children.

**Methods** A systematic literature search was performed in MEDLINE and EMBASE to identify studies published between 1994 and 2008 evaluating drug prescriptions to outpatient children.

**Results** A total of 128 drug utilisation studies were identified, 107 of which were focused on a specific drug class, in particular psychotropic drugs (49 studies) and antibiotics (32 studies). The 21 studies that evaluated all drug prescriptions involved 21 countries, mainly from Europe (13 studies). Large differences were found between studies concerning data source, sample size and age range. A prevalence ranging from 51% in Denmark to 70% in Greenland and a prescription rate (number of drugs per children) ranging from 0.8 in Norway to 3.2 in the United States were reported in the 11 studies that monitored the overall paediatric population. The prevalence rate was higher in preschoolers, with a peak between 72 and 90%, and decreased in children >6 years. Antibiotics were the most prescribed drugs (20–33% of the prescriptions) followed by antiasthmatics (10–25%). According to the results of four studies comparable in terms of data source and children's age, the overall prevalence estimate was 60%.

**Conclusion** A large heterogeneity was found between studies, making a comparative evaluation often difficult or incomplete. The epidemiological evaluation of drug use in children should therefore be improved, in particular in terms of methodological quality of studies, and prospective

multinational collaborative studies aimed at collecting valid and comparable data should be performed to improve the rational use of drugs.

**Keywords** Drug utilisation · Child · Adolescents · Outpatients · Review

## Introduction

Despite the many initiatives planned at the international level to guarantee safe and effective therapies for children, a lack of information on safety and efficacy of drugs in childhood still exists [1–4].

Many aspects can contribute to the fact that children do not often participate in clinical trials, in particular ethical and financial reasons, resources and research capabilities, and regulatory guidelines and constraints [3, 5]. More efforts are thus needed to guarantee that children receive medications that are appropriate (safe and effective) to their clinical conditions, in doses and formulations suitable to their personal requirements, for adequate periods of time, and at the lowest cost to their families and communities, i.e. a rational drug use. In such a context, pharmacoepidemiology is a useful tool that, with the appropriate methodologies, can improve the effectiveness and efficiency of health-care interventions [6].

In this regard, a review of drug utilisation studies published between 1988 and 1993 found eight studies that evaluated drug prescriptions in outpatient children. Differences in prescribing patterns among countries were found, with an average number of drugs per child ranging from 0.7 to 3.0 [7]. Quantitative and qualitative differences were also observed in subsequent reviews concerning antibiotic and psychotropic drug prescriptions [8, 9].

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A search of the literature was, therefore, performed to update the drug utilisation profile in outpatient children and adolescents.

## Materials and methods

A literature search was performed in MEDLINE and EMBASE for studies published from January 1994 to December 2008. The MeSH terms used in the search strategy were drug utilisation/prescription/pharmacoepidemiology; infant/child/adolescent/paediatrics. The search was limited to papers in English. Letters, comments and editorials were excluded.

Titles and abstracts were screened by the authors to assess the relevance of the studies. Studies involving the adult population, inpatient children, or children attending the emergency department, or those evaluating adverse drug reactions, costs, or health-care resource utilisation were excluded.

The references retrieved were collected and analysed using the software program Reference Manager, version 11 (Institute for Scientific Information, Berkeley, California). For each study, data concerning the type of study, data source, country, sample size, age of children and drugs monitored were collected, and a descriptive analysis was performed.

An in-depth analysis was performed taking into account studies that analysed all drug prescriptions. For these studies, prevalence rate (number of youths who received at least one prescription per 100 individuals in the population) and prescription rate (average number of prescription per person) were used as indicators.

The meta-analytic weighted average and 95% CIs of the prevalence rate of drug prescription were estimated using a random effect model to take into account the heterogeneity of the various studies [10].

## Results

### Search results

A total of 980 articles were retrieved from the literature databases: 464 from EMBASE and 422 from Medline, and 94 from both. In all, 734 papers were excluded because they were not pertinent.

Moreover, 99 of the 246 remaining studies involved children with particular conditions, mainly respiratory-tract infections (37%), mental disorders (22%) and asthma (20%) and were therefore not taken into account in the analysis. The same was true for 10 studies evaluating off-label/ unlicensed drug use and for 9 studies analysing the prescriptions of a single drug.

### Characteristics of the drug utilisation studies

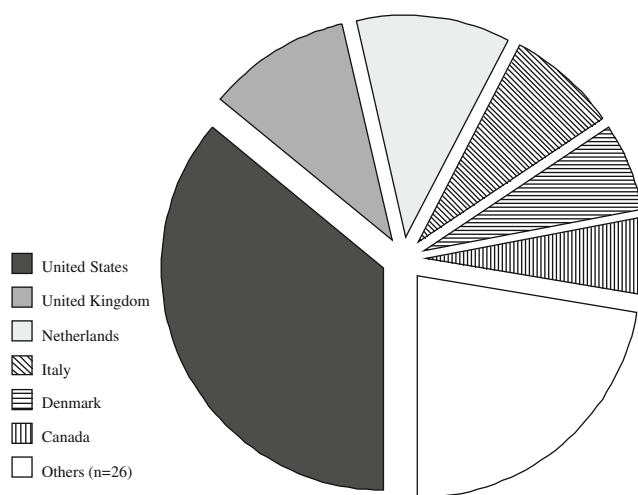
A total of 128 drug utilisation studies were therefore analysed. These studies were published in 59 journals, 23 of which published more than one article. The first 10 journals in order of number of papers covered 46% of the retrieved articles. The *European Journal Clinical Pharmacology* was the first journal in order of published papers (10), followed by *Acta Paediatrica*, *Pharmacoepidemiology and Drug Safety* and *Psychiatric Services* (7 papers each).

The distribution of papers per year of publication ranged from 1 in 1994 to 18 in 2006 and 2007 (mean: 8.5). Only 19 studies (17%) were published before 2000, while 74 studies were published in the 2004–2008 period.

The 128 articles were published by 459 authors, 83 (18%) of whom appeared in at least two papers. In all, 14 authors published four or more papers. These authors belong to a few groups particularly involved in the field of paediatric pharmacoepidemiology based in Baltimore, MD (USA), Milan (Italy), Groningen (The Netherlands), London, and Aberdeen (UK), and accounted for 28 studies (22% of the total).

The 128 studies involved 32 countries, 14 of which were involved in more than 1 study. In all, 57 out of 128 studies (44%) were performed in Europe and 51 (40%) in North America. Only eight studies involved developing countries. Thirty-five percent of the studies involved the United States, followed by the Netherlands (11%), the United Kingdom (10%), Italy (8%) and Denmark (6%) (Fig. 1). In all, six studies were multinational.

The data sources were mainly national or regional prescription databases (28% of the studies), general practitioner (GP) or paediatrician practices (19%), national surveys (e.g. National Ambulatory Medical Care Survey, Medical Expenditure Panel Survey) (14%), health maintenance organisations (HMO) and Medicaid/national health



**Fig. 1** Distribution of the drug utilisation studies by country

insurance (12% each) and questionnaires administered to patients or parents (10%).

A total of 107 studies was focused on a specific drug class. In particular, 49 studies (46%) concerned psychotropic drug prescriptions, 32 (30%) antibiotics, 9 (8%) antiasthmatics, 5 (5%) over the counter drugs and 4 (4%) anticonvulsants. (Fig. 2).

#### Characteristics of studies evaluating all drug prescriptions

A total of 21 studies evaluated all the drugs prescribed (Table 1) [11–31]. These studies involved 21 countries: 5 studies were performed in Denmark (3 of them in Greenland), 3 studies in Italy and 2 studies each in the Netherlands and the UK. Two studies were multinational: one compared data collected in five different countries [29], and one in three European countries [30]. The sources of data were represented by paediatricians/general practitioners (9 studies), national and regional prescription databases (7), questionnaires (3), HMO and health-facilities databases (1 each).

The studies involved from 56 to 923,353 children.

Eleven studies evaluated drug prescriptions in the entire paediatric population, with an upper age limit ranging from 13 to 19 years [21–31], while 10 studies were focused only on a specific age group: 3 involved only infants [11–13], 5 only preschoolers [14–18] and 2 only adolescents [19, 20].

The observation periods ranged from 1988 to 2006. Only seven studies (33%) evaluated data collected after 2000 [11, 17–19, 21, 23, 30].

#### Infants

Only one out of three studies involving infants reported the drug prescription prevalence: 96% of infants aged less than 6 months were given at least one drug, and the drug most

commonly used was paracetamol (84% of the infants), followed by teething gel (54%) [12]. Another study analysed 2,282 prescriptions dispensed to infants by 20 health-care centres in Bahrain. Paracetamol was the most prescribed drug and accounted for 58% of prescriptions, followed by saline nasal drops (32% of prescriptions) [11].

A study performed in Alexandria, Egypt, evaluated the use of non-prescribed medications. During a 1-month observation period, 24.6% of the mothers administered non-prescribed medications to their children, in particular antispasmodics (47%), antipyretics (13%) and cough and cold medications (8%).

#### Preschoolers

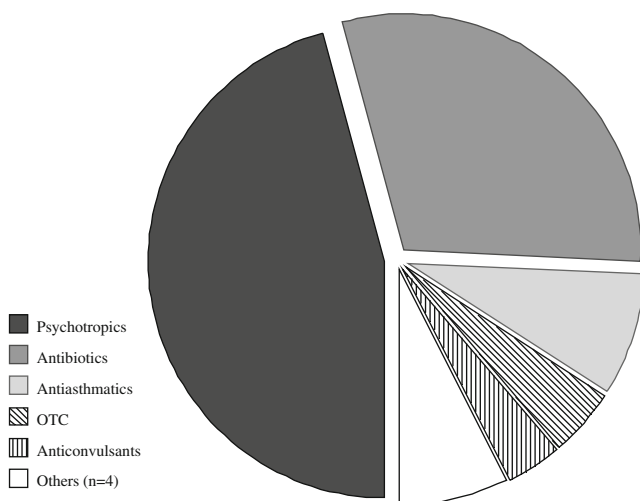
Studies involving only preschoolers were performed almost exclusively in developing countries (four out of five papers), and three were performed in Africa. None of these studies reported the prevalence of drug prescriptions and only two reported the average number of drugs per patient but in a non-comparable manner [14, 16].

Antimalarials, antibiotics and analgesics/antipyretics were the most used drugs in the three studies performed in African countries [14, 17, 18]. Antimalarials accounted for 24% of drugs purchased at pharmacies or drug stores in the Kibaha district, Tanzania [18], while a study performed in Nigeria reported that these drugs were prescribed to 65% of children <5 years old attending an outpatient clinic [17]. In these two studies, antibiotics covered 31% of purchased drugs and 54% of patients. Chloroquine was prescribed in 70% of sick-patient visits in health facilities in Kenya, penicillin in 61%, and antipyretics in 59% [14].

A quite different prescribing profile was observed in the two studies performed outside Africa. Antibiotics were prescribed in 49% and paracetamol in 25% of encounters in a study performed in Pakistan [15]. Antibiotics were also the most prescribed drugs in preschool-aged children in Greenland (50% of prescriptions), followed by respiratory drugs (21%) and dermatologicals (20%) [16].

#### Adolescents

The prevalence of drug use in adolescents was 56% in a survey involving secondary-school students in Germany [20] and 70% in a study that analysed prescriptions made by general practitioners in New Zealand [19]. According to the first survey, the drugs most commonly used by the adolescents were antipyretics (35% of the adolescents), cough and cold medicines (23%) and sex hormones and urologicals (13%) [20]. In all, 28% of the prescriptions monitored in the second study were for respiratory system drugs, 23% for antinfectives and 10% for sex hormones and urologicals [19].



**Fig. 2** Distribution of the drug utilisation studies by drug class

**Table 1** Characteristics of the studies evaluating all drug prescriptions

Reference	Study type	Data source	Country	Year	Duration	Age (years)	Children ( <i>n</i> )
[11]	Prospective	Prescription DB	Bahrain	2004 (May)	2 weeks	1–12 months	–
[12]	Survey	Questionnaires	UK	1991		0–6 months	6,973
[13]	Survey	GP	Egypt	n.r.	1 month	<1	300
[14]	Retrospective	Health facility DB	Kenya	1995–1996	2 years	<5	14,267
[15]	Retrospective	GP	Pakistan	1992 (Apr–Dec)	9 months	<5	2,433
[16]	Cohort	GP	Greenland	1996–1998	2 years	<5	280
[17]	Prospective	GP	Nigeria	2004 (Jan–Apr)	4 months	<5	790
[18]	Survey	Questionnaires	Tanzania	2001(Aug–Sep)	2 months	<5	612
[19]	Prospective	GP	New Zealand	2000	1 year	13–19	20,216
[20]	Survey	Questionnaires	Germany	1997	2 weeks	15–17	56
[21]	Retrospective	Prescription DB	Italy	2006	1 year	<14	923,353
[22]	Cross-sectional	Prescription DB	Greenland	1991	1 year	<15	2,836
[23]	Retrospective	Prescription DB	Greenland	2001	1 year	<15	3,296
[24]	Cross-sectional	Prescription DB	Denmark	1997	1 year	<16	95,189
[25]	Cross-sectional	Prescription DB	Netherlands	1998	1 year	<17	25,020
[26]	Cross-sectional	Prescription DB	Denmark	1998	1 year	<19	104,897
[27]	Prospective	GP	Italy	1998 (April–June)	3 months	<12	9,917
[28]	Cross-sectional	GP	Norway	1988–1989	1 year	<13	7,299
[29]	Cross-sectional	GP	Multi	n.r.	4–7 months	<14	12,264
[30]	Prospective	GP	Multi	2000–2005	6 years	<19	675,868
[31]	Retrospective	HMO	US	1992–1993	1 year	<18	3,144

### Overall paediatric population

The prevalence rate was reported in 9 out of 11 studies that surveyed the entire paediatric population, and ranged from 51% in Denmark to 70% in Greenland, while the prescription rate (i.e. the average number of prescriptions per child in the population) ranged from 0.8 in Norway to 3.2 in the United States (Table 2).

No correlation was found between prevalence and prescription rates.

A total of seven studies reported the prevalence trend by age. In all these studies, the highest prevalence was observed in the preschoolers and decreased in children >6 years [21, 23–27, 31]. However, in Denmark, the Netherlands and the United States, the peak in prevalence was observed in children <2 years old, ranging from 75 to 90% [24–26, 31], while in Italy and Greenland the peak was reported in children 3–5 years old (72–80%) [21, 23, 27].

Antibiotics were the most frequently prescribed drugs, accounting for 20–33% of the prescriptions dispensed to children, followed by antiasthmatics (10–25% of the total prescriptions) and analgesics (10–16%). Four studies reported the most frequently prescribed drugs [21, 23, 27, 30], but only in two was the prevalence rate reported. Only paracetamol was among the 10 most prescribed drugs in all four studies, while salbutamol was reported in three out of four.

### Meta-analysis

Only four studies were comparable in terms of data source (prescription databases) and age and were thus selected for the meta-analysis [21, 23–25]. The estimated average prevalence, adjusted and weighted by sample size, was 60.4% (95% CI 54.0–66.8%). The estimated prevalence of antibiotics was 33.9% (95% CI 13.5–54.3%), while that of antiasthmatics was 14.5% (95% CI 4.5–24.2%). Wide differences were found concerning the prevalence rates of antibiotics and antiasthmatic drugs. The prevalence of antibiotics ranged from 21% in the Netherlands to 52% in Italy, while the prevalence of antiasthmatics ranged from 7% in the Netherlands to 26% in Italy.

### Discussion

This study updates a previous review that evaluated studies published between 1988 and 1993. The major strengths of this article are that the literature was searched systematically and that a 15-year period was monitored, even if only for papers in English, which may have caused some publications to be missed.

The increased attention towards the evaluation of drug use in children suggests that there may be recent interest in closing the gap in this area. However, most of the studies,

**Table 2** Prevalence and prescription rates reported in the 11 studies concerning the entire paediatric population

Reference	Data source	Country	Year	Age (years)	Children (n)	Prevalence		Prescription rate <sup>a</sup>	Population
						%	95% CI		
[27]	GP	Italy	1998	<12	9,917	64.7	63.8–65.6	0.9 (1.3)	Contacts
[28]	GP	Norway	1988–1989	<13	7,299	60.1	59.0–61.2	0.8 (1.4)	Contacts
[29]	GP	Spain	n.r.	<14	4,611	n.a.		1.5 (1.7)	Contacts
[29]	GP	France	n.r.	<14	1,990	n.a.		2.7 (2.8)	Contacts
[29]	GP	Russia	n.r.	<14	2,194	n.a.		2.9 (3.1)	Contacts
[29]	GP	Bulgaria	n.r.	<14	1,874	n.a.		2.6 (2.7)	Contacts
[29]	GP	Slovakia	n.r.	<14	1,495	n.a.		2.6 (2.7)	Contacts
[30]	GP	Italy	2000–2005	<15	406,156 <sup>b</sup>	n.r.	–	2.5	Contacts
[30]	GP	Netherlands	2000–2005	<19	282,869 <sup>b</sup>	n.r.	–	1.5	Contacts
[30]	GP	UK	2000–2005	<19	1,645,828 <sup>b</sup>	n.r.	–	2.5	Contacts
[31]	HMO	US	1992–1993	<18	3,144	59.1	57.2–60.9	3.2 (5.3)	Enrollees
[21]	Prescription DB	Italy	2006	<14	923,353	60.8	60.7–60.9	1.9 (3.2)	Inhabitants
[22]	Prescription DB	Greenland	1991	<15	2,836	60.0	58.3–61.9	2.2 (3.7)	Inhabitants
[23]	Prescription DB	Greenland	2001	<15	3,296	70.4	68.8–71.9	2.2 (3.4)	Inhabitants
[24]	Prescription DB	Denmark	1997	<16	95,189	50.6	50.2–50.8	1.6 (3.2)	Inhabitants
[25]	Prescription DB	Netherlands	1998	<17	25,020	60.0	59.4–60.6	n.r.	Inhabitants
[26]	Prescription DB	Denmark	1998	<19	104,897	52.6	52.4–53.0	1.7 (3.3)	All

<sup>a</sup> Between bracket is reported the average number of prescriptions in treated children

<sup>b</sup> Number of person years

especially those published since 2000, focused on one drug class only. In particular, nearly half of the studies concerned psychotropic drugs. This fact is likely due to the ongoing debate regarding the safety and efficacy of psychotropic drugs in the paediatric population and to the concerns associated with the increased use of these drugs [32, 33]. Moreover, 30% of the studies concerned antibiotics. In this case, the attention can be explained by the fact that these drugs are the most frequently prescribed drugs and are often given in a not-so-appropriate manner, increasing the risk of bacterial resistance [34]. On the contrary, some drug classes were not monitored. Only four studies considered anticonvulsant use, while gastrointestinal drugs, commonly used in infants, were taken into account only in one study.

Moreover, few countries were involved and most of them were from Europe and North America. Only nine studies were performed in developing countries. This imbalance could be due to different reasons, in particular the fact that this review is focused only on outpatient drug prescriptions, a setting characteristic of developed health systems. In addition, the difficulty in collecting reliable data and in publishing papers should be considered. However, despite the imbalanced quantitative figures observed, qualitative drug utilisation profiles underline different therapeutic needs (e.g. antimalarials versus respiratory drugs) and suggest that different priorities exist between children living in the south and the north of the world.

Another limit is that only data published in international scientific journals were considered. Thus prescription data routinely collected by national or local health authorities for administrative purposes are missed.

#### Methodological issues

A wide heterogeneity of studies was found, with large differences in study types (design and methods), populations (in terms of sample size and age groups) and data collected, making a comparative evaluation often difficult or incomplete.

Use of different data sources contributes to this heterogeneity. Every source has strengths and limitations that should be taken into account in planning and evaluating drug utilisation studies.

Prescription databases have the advantage of monitoring the prescriptions dispensed by all the physicians to an entire population in a specific region or nation. The main limits are that over-the-counter drugs and drugs not reimbursed by the national health service are not included, that the therapeutic indication is often lacking, and that it is not possible to know if the patient actually took the drug.

On the other hand, the advantages with data collected by general practitioners and paediatricians are that drugs that are not reimbursed can also be monitored and that, in many cases, details about the disease for which a drug was

prescribed can be collected. The limits with this type of data collection are that the number of physicians involved is often limited and that it is possible to collect only information about children visiting physicians. It is not therefore possible to estimate the drug prescription prevalence in the population and to know if the patient filled the prescription and took the drug.

Surveys using questionnaires administered to patients or parents can monitor the actual use of drugs. However, only a sample of the population can be surveyed and only for a short period of time (usually a few weeks). Recall bias is possible and reliability of information is scarce. Thus, the overall accuracy of these data sources can affect the estimates.

However, the heterogeneity of the studies is not explained only by the different data sources. If only studies that analysed all drug prescriptions are considered, nearly half are found to concern specific age groups. Moreover, the 11 studies that covered the entire paediatric population used different age ranges, leaving four studies comparable on the basis of data source and children's age. Only six studies reported the prevalence trend by age, while the most frequently prescribed drugs were reported in only four studies (and in two cases without reporting the prevalence). An improvement in the methodology of drug utilisation studies is therefore needed in order to collect data that can be compared across regional or national settings. In this regard, it is interesting to note that differences in data sources and children's ages were found also in a multinational cohort study that compared prescribing profiles in the Netherlands, UK and Italy [30].

Moreover, time trends may be an additional factor explaining heterogeneity among studies, even if differences in design and population also exist in the more recent studies.

#### Differences in drug prescribing to children and adolescents

Despite some limitations, quantitative and qualitative differences in prescribing patterns to children were found. Prevalence rates in developed countries ranged between 51 and 70%, and each child treated received, on average, between 1.3 and 5.3 prescriptions. On the basis of the results of the meta-analysis, it can be estimated that 60% of children receive an average of three drug prescriptions in a 1-year period. In particular, 33% receive antibiotics and 15% receive antiasthmatics.

However, while for the majority of the studies the prevalence rate was nearly 60%, some differences were found when evaluating the prevalence of the most prescribed drug classes. It was interesting to note, for example, that Italian children have a 2.5-fold greater chance of receiving an antibiotic compared with Dutch children and a 3.6-fold higher chance of receiving an antiasthmatic drug prescription, even though the overall prevalence rates in the

two countries are the same. These findings are consistent with the results of a review of studies evaluating antibiotic drug prescriptions [9].

Moreover, despite the fact that few studies reported the most prescribed drugs, it was interesting to note that a common attitude among countries was evident for only paracetamol and salbutamol, whereas for other drugs, differences were large, suggesting differing drug policies and physician attitudes in prescribing drugs.

#### Conclusions

Despite the increased attention paid to the issue of drug use in children and adolescents and the evidence produced and published on this topic in the last few years, the heterogeneity among drug utilisation studies is high, and the need for systematic and continuous monitoring of drug use in children remains strong. It can be concluded that 15 years after the first review, the state of art has changed little.

The epidemiological evaluation of drug prescriptions in children should therefore be improved, in particular in terms of methodological quality of studies performed. Prospective multinational collaborative studies aimed at collecting valid and comparable data should be performed to improve the rational use of drugs and to guarantee to children and their families safe and effective drug therapies.

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