Off label prescribing to children in primary care in Germany: retrospective cohort study

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Between 35% and 90% of the drugs prescribed to hospitalised children are either not licensed for children's use or are prescribed outside the terms of their product licence (off label prescribing).[1 2] Subsequent adverse reactions are more likely than with licensed products (6.0% *v* 3.9%).[3] We analysed the extent of prescribing off labelled products in a representative cohort of children in primary care.

Patients, methods, and results

We used the electronic database of prescriptions of Allgemeine Ortskrankenkasse, Baden-Württemberg. This health insurer covers more than four million people, 42% of the total population of the state. We retrospectively reviewed 1.74 million anonymous prescriptions written by 6886 office based doctors—specialists in paediatric, general, or internal medicine—between 1 January and 31 March 1999 for 455 661 patients aged 0-16 years.

Each prescription was represented by a numerical code, describing the drug's brand name, generic name, formulation, and content per dose unit. Our database did not contain diagnoses, dosage recommendations, or individually prepared drug formulations.

To assess the licence status of prescriptions we used the summary of product characteristics (Fach information) or drug lists provided by German pharmaceutical manufacturers' associations (Gelbe Liste or Rote Liste).

We categorised prescriptions by age group and the World Health Organization's anatomical, therapeutic, and chemical classification. A prescription was considered off label if the drug itself, its dose unit, or its formulation was not explicitly covered by documentation for the specific age group to which it was prescribed. Unlicensed drugs are not specified in the database because they are not automatically reimbursed by insurance.

Of 1740 238 prescriptions, 115 366 (6.6%) prescriptions for medical accessories, diets, and cosmetics and 32 866 with unidentifiable codes were excluded; the prescriptions with unidentifiable codes might have included an unknown number of unlicensed prescriptions but accounted for only 1.9% of the database.

Among the remaining 1 592 006 prescriptions for 10 452 different active ingredients, we found 210 528 (13.2%, 95% confidence interval 13.2% to 13.3%) off label prescriptions. The table shows the most common examples and some of the associated risks.

Three quarters of off label prescriptions (157 951) resulted from lack of information about use of the drugs among children or in particular age ranges. Of the off label prescriptions, 35 234 (16.7%) ignored

Most frequent off label drugs prescribed to outpatients aged 0-16 years for peroral, rectal, or nasal administration at the expense of Allgemeine Ortskrankenkasse, Baden-Württemberg, between January and March 1999

	0-11 months		1-2 years		3-6 years		7-11 years		12-16 years	
Rank	Drug	No	Drug	No	Drug	No	Drug	No	Drug	No
1	Xylometazoline or oxymetazoline*	217	Xylometazoline or oxymetazoline*	13 780	Xylometazoline or oxymetazoline*	3524	Cetylpyridinium††	2651	Tyrothricin mixtures††	4234
2	Herbal extract of ivy†	149	*Saccharomyces boulardii*	3 611	Dihydrocodeine**	2921	Sultiame	440	Cetylpyridinium mixtures††	3132
3	Pipenzolate	145	Salbutamol§	2 394	Tyrothricin mixtures††	1470	Codeine mixtures**	268	Ibuprofen*	1942
4	*Saccharomyces boulardii*	36	Mucolytic herbal formulations†	1 018	Cetylpyridinium††	664	Formoterol	243	Diclofenac††	1128
5	Acetylcysteine	32	Codeine mixtures**	730	Loratadine	477	Mucolytic herbal formulations†	232	Magaldrate	327
6	Cisapride‡	30	Dihydrocodeine**	687	Pipenzolate	415	Diclofenac††	227	Sultiame	220
7	Salbutamol§	24	Doxylamine mixtures (with or without paracetamol)	672	Fluticasone propionate	404	*Echinacea purpurea* formulations†	211	Extract of *Lichen islandicus*†	214
8	Terbutaline§	19	Pipenzolate	486	Mucolytic herbal formulations†	276	Extract of *Lichen islandicus*†	200	Mucolytic herbal formulations†	205
9	Antacids	19	Tetryzoline*	271	Diclofenac††	238	Dihydroergotamine	169	Crataegus and camphor formulations†	205
10	Ofloxacin¶	13	Cisapride‡	229	Ofloxacin¶	155	Antacids	156	Ofloxacin¶	179

*Prescribed amount of drug per dose exceeded the recommended dose.
†No dosage recommendations were available. Herbal formulations containing as much as 65% of ethanol by volume may cause significant concentrations of ethanol in babies and small children.
‡Cisapride is known to induce cardiac arrhythmias. It has been withdrawn.
§Efficacy and safety of β-2-sympathomimetics have not been proved in children younger than 18 months.
¶Use of the quinolone ofloxacin is not recommended during growth.
**For this age group no dosage is indicated in the SPC due to lacking pharmacokinetic data. Doses >3 mg/kg/day have been observed to produce respiratory depression, somnolence, or vomiting.
††Due to a lack of data, there are no dosage recommendations for children younger than 15 years, when diclofenac is administered systemically.

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recommendations on active ingredient, dose units, or formulations for a specific age group—for example, quinolones in children and xylometazoline 1% formulations for babies.

The proportion of off label prescriptions was highest for 1-2 year olds (68 791 (17.9%, 17.8% to 18.1%) prescriptions) and lowest for 7-11 year olds (40 539 (10.5%, 10.4% to 10.6%) prescriptions).

Of the 181 914 (8.8%) prescriptions for topical treatments of the skin, eye, or ear, 116 060 (63.8%, 63.6% to 64.0%) were off label. The active ingredients of the most commonly prescribed systemic off label drugs are shown in the table.

Off label prescribing was common for cardiovascular drugs (3646; 55.2%, 53.9% to 56.4%), drugs for genitourinary disorders (1869; 48.5%, 46.9% to 50.1%), anti-inflammatory agents (7194; 45.0%, 45.2% to 46.0%), antidepressants (246; 36.6%, 33.0% to 40.4%), and antidementia (11; 34.4%, 18.6% to 53.2%), antiepileptic (932; 14.2%, 13.3% to 15.0%), and antipsychotic drugs (54; 10.2%, 7.8% to 13.2%).

Comment

We found that 13.2% of prescriptions for a representative group of children in primary care in Germany were off label. Although we could not detect off label use due to dosage or indication with this database, the proportion of prescriptions that were off label was similar to that in much smaller studies that analysed dosage and diagnoses.[4 5] Our data show that efforts to improve the quality of pharmacotherapy in children should not exclude widely marketed and firmly established drugs.

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Contributors: MS, KM, and CG designed the study. PS provided access to Allgemeine Ortskrankenkasse, Baden-Württemberg, and gave information concerning drug prescription patterns in outpatients. HS matched the file with prescription data to another database including the anatomical, therapeutic, and chemical classification of the World Health Organization. BK and HM provided computer based analyses. RB designed the study, coordinated study procedures, determined licence status of prescriptions, analysed the results, and wrote the paper. CG is guarantor.

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Unlicensed and off label drug use by children in the community: cross sectional study

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Studies in various hospital settings showed that many drugs taken by children either are not licensed or are used outside the terms of the product licence.[1–3] Information on the extent of paediatric labelling of drugs taken by children in the community is, however, limited and based on small study populations.[4 5] We studied drugs taken by children in the community, based on the pharmacy records of prescriptions from both general practitioners and outpatient departments. We aimed to determine the number of prescriptions for unlicensed drugs for children in the community and to investigate paediatric labelling of all drugs with a product licence to determine the extent of off label use.

Participants, methods, and results

In the Netherlands people commonly register with one pharmacy, from which they obtain their drugs, including those prescribed as outpatients. Excluded are drugs used during hospital stays and those bought over the counter. We obtained our data on dispensing from the InterAction database, which covers part of the northern Netherlands.

We selected all prescriptions for children aged 0-16 years in 2000. Dutch pharmacies are allowed to prepare their own formulations and to modify commercial preparations. These pharmacy based preparations are exempt from licensing, and we classified them as unlicensed. For each prescription of a licensed drug (all remaining prescriptions) we examined the official licence information—the summary of product characteristics—in detail. We determined whether the summary mentioned use in children and, if so, the minimum age. When age was unspecified we set it at a minimum of 0 years. If use in children was not mentioned or was advised against without an indication of age, we set the minimum age at 18 years. We considered that a drug with a product licence was used according to the label if the summary of product characteristics stated that it could be used in children, and if the child was of the minimum age for use or older; otherwise we considered the drug was used off label. As information about indications was not available, we were not able to distinguish between different indications in the summary.

We analysed 68 019 prescriptions for 19 283 children aged 0-16 years. General practitioners were responsible for 56 961 (83.7%) of the prescriptions; the remainder came from specialists. Unlicensed drugs amounted to 16.6% (11 288) of the total pre-