Unlicensed and Off-label Drug Use in Children

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Niet-geregistreerd en 'off-label' geneesmiddelengebruik bij kinderen

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We try to tell ourselves the things we try to tell ourselves
to make ourselves forget
Adam Duritz

voor mijn ouders

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't Jong GW, Choonara I, Anker JN vd. FDAMA's Written Request list: Which medicines do children need? The Lancet, 2001; 357:398.

Chapter 1

Introduction and aims of the studies

1.1 Pharmacotherapy in children

In an ideal situation, marketed drugs should be studied in all potential users in accordance with contemporary concepts of drug therapy. Unfortunately, the current situation is far from ideal and this applies in particular to drugs used in children.
In 1967, Dr. Harry Shirkey used the term "therapeutic or pharmaceutical orphans" in his comment on the 1962 drug licensing system initiated by the Kefauver-Harris amendments.[1] He emphasized the ironical situation of a drug licensing system that was initiated by congenital malformations by thalidomide,[2] but subsequently failed in stimulating drug licensing in children.[3-5] However, many drugs that were released between 1962 and 1967 carried a clause like "Not to be used in children", since they had not been studied in children, despite the fact that they were effective against diseases that also occur in childhood. During the following 30 years, several reviews of the Physicians' Desk Reference (PDR) and the licensing information of new molecular entities (NME) have shown little change in the percentages of drugs with adequate pediatric labeling (Table 1).[6-10] Most drugs are not studied in children before introduction to the market, and are not available in applications for use in children. The US Food and Drug Administration (FDA) recognized the problem of absence of efficacy and safety data in children, and their position was clearly stated: "Drugs for use in children must be tested in children".[11]
This chapter will provide a general background on licensing procedures for drugs, the historical background both in Europe and the US and will subsequently discuss the difficulties for research regarding the efficacy and safety of drugs used in pediatrics.

Table 1 Reports on pediatric labeling

1973	Physicians's Desk Reference: 78% without sufficient pediatric labeling (Wilson, 1975)
1984-1989	New Molecular Entities: 80% without pediatric drug labeling (FDA 1989)
1991	Physician's Desk Reference: 81% without disclaimers or age restrictions (Gilman, 1992)
1992	New Molecular Entities: 79% of potential pediatric use unapproved (AAP, 1995)
1991-1994	New Molecular Entities: 71% without pediatric drug labeling (Cote, 1996)

1.2 Drug licensing

1.2.1 Aims of drug licensing

The purpose of licensing is to control the manufacturing, provision, promotion and supply of drugs[12] and to ensure their safety, quality and efficacy. The introduction of new drugs and the maintenance of an adequate system are major tasks of the governmental drug evaluation agencies. Not only since they need to guarantee drug safety and efficacy but also to provide legal protection for medical practitioners and patients.

1.2.2 Origin of drug licensing

The drug licensing process was introduced as a response to adverse drug reactions (ADRs) that occurred particularly in newborn infants (chloramphenicol-induced grey baby syndrome)[13] and the fetus (thalidomide-induced phocomelia).[2,14] Drug licensing systems were developed both in the US and in European countries, following the thalidomide disaster in the early 1960s in an effort to prevent other catastrophes.

More recently, the occurrence of serious drug related events in young children (sodium valproate-induced liver failure,[15 16] salicylates-induced Reye's syndrome)[17] clearly showed lack of impact of these regulations.

1.2.3 Licensing regulatory authorities

The European Medicines Evaluation Agency (EMEA) is responsible for drug licensing in the European Union (EU), and the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) is the licensing authority in the US. These agencies are responsible for the critical evaluation of new drugs, review of generic drugs and over-the-counter (OTC) drugs, and monitoring of the safety of drugs that are currently available (pharmaco-vigilance).

1.2.3.1 European Medicines Evaluation Agency

In 1995, a new European system for the authorization of medicinal products came into operation after many years of working towards a single European Union (EU) market for pharmaceuticals. This unified system is aimed to ensure availability of drugs under the same conditions in all EU countries with proper safeguards as to the safety, quality and efficacy of medicinal products.

The EMEA co-ordinates and supports the EU drug licensing system. Their main task is to co-ordinate the scientific evaluation of the safety, quality and efficacy of medicinal products for human and veterinary use throughout the European Union. The Committee for Proprietary Medicinal Products (CPMP) is part of the EMEA and combines the scientific expertise of the Member States to give opinions on the marketing of medicinal products. The EMEA has several working parties among which the Pharmacovigilance Working party who advices the committee on specific safety expertise.

The licensing system is based on two procedures; the centralised procedure and the decentralized (mutual recognition) procedure.[18] The centralised procedure is obligatory for medicinal products derived from biotechnology and optional for other new drugs. Under the centralised procedure, applications are submitted to the EMEA for evaluation by the CPMP. Assessment of the drug file is delegated by the CPMP to experts in two Member States (the "rapporteur" and "co-rapporteur"). The time limit for the evaluation procedure is 210 days. The CPMP considers the assessment report and votes about licensing authorization. Subsequently the EMEA forwards its opinion to the European Commission (EC) within 30 days, which makes the formal decision. An EC authorization is valid throughout the European Union and is usually given for five years. Applications for extension must be made to the EMEA three months before this five-year period expires.

The decentralized (mutual recognition) procedure applies to all drugs that do not follow the centralised procedure and is based on the previous multi-state procedure.[18] It applies the principle of mutual recognition by EU Member States. Under the decentralized procedure, an applicant may request to have an existing or new authorization in one Member State recognized by one or more other Member States. The applicant must submit identical applications to all relevant Member States. As soon as one Member State decides to evaluate the medicinal product (it then becomes the

"Reference Member State" (RMS)), it notifies this decision to the other Member States ("Concerned Member States" (CMS)) to which the application has been sent. The RMS subsequently sends a detailed assessment report to all Member States, which have 90 days to subscribe to the decision of the RMS. If the marketing authorization is not mutually recognized by other Member State, the points of disagreement are submitted to the CPMP for arbitration. The CPMP opinion is forwarded to the European Commission, which makes the final decision. Once the Commission decision is taken, it is binding. Also for member states which are not directly concerned at the time of the decision and which later receive a marketing authorization application for the same product. European enhancement of pediatric labeling was expressed in the CPMP Note for Guidance on Clinical Investigation of Medicinal Products in Children in 1997, in which the need for pediatric research and sufficient pediatric labeling was indicated. In December 2000, the council of Health Ministers adopted a council resolution which recognized the need for appropriate measures in the form of incentives, regulatory measurements and other supporting measures in respect of clinical research and development, regarding new medicinal products for children, and medicinal products already on the marked. In January 2001, a new CPMP Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population came into operation, which like the 1997 version encourages the pharmaceutical industry to investigate the safety and efficacy of a product in children if therapeutic benefit in the age group is likely, and to develop suitable formulations, even if the usage is likely to be small. A new EMEA/CPMP Paediatric Expert Group was formed to facilitate the CPMP and the EMEA regarding pediatric issues.

1.2.3.2 Food and Drug Administration

Historic perspective

In the US, the Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research (CDER) is responsible for review of all medicinal agents. In the US, the Food, Drug and Cosmetic Act (FDCA) of 1938 was initiated after the death of 107 children from sulfanilamide elixir, which contained diethylene glycol as a solvent. No toxicity testing had been done with the product before marketing. New drugs had to be labeled with adequate directions for use. The 1962 Kefauver-Harris amendments, resulting from the thalidomide disaster (fetal malformation (phocomelia) from maternal ingestion),[2,14] initiated the licensing process in the Food, Drug and Cosmetic Act (Title 21 US Code, Section 301-329, Public Law no 87-781, 1962). 'Substantial evidence of effectiveness' was required before a new drug could be approved for marketing. Substantial evidence was defined as consisting of 'adequate and well controlled investigations', including clinical investigations.

Table 2 US Drug legislation

1906	Prohibited alteration of misbranded products
1938	Drugs must be proven safe and have adequate directions for use
1962	Drugs also must be effective in the intended population
1979	Pediatric labeling emphasized
1994	Final Plan clarifies p ediatric labeling processes
1997	Pediatric Exclusivity Provision under FDAMA*
1998	Pediatric Rule
2002	Best Pharmaceuticals for Children Act (BPCA)

* FDA Modernization Act

Enhancement of pediatric labeling

The FDA has taken many measures to change the neglect of children in the assessment of the quality, efficacy and safety of drugs (Table 2). In 1979 the FDA determined that specific pediatric indications must be mentioned under the "Indications and Usage" section of the labeling, with appropriate pediatric dosage provided under the "Dosage and Administration" section. The information has to be based on well-controlled studies in the pediatric population. The "Pediatric Use" subsection was intended to improve drug labeling for pediatric patients, but the requirements further discouraged pediatric labeling and resulted in exclusionary language rather than the conduct of studies in children that would support child-appropriate information in the labeling.

The Orphan Drug Act in 1982 was designed to provide financial incentives for development of drugs for use in small patient populations (<200,000 patients per year). However, the Orphan Drug Act was not specially designed for pediatric patients.

In 1994, the FDA published the Final Plan for pediatric labeling.[19] The plan clarifies the FDA position on various procedures that can be used to get pediatric labeling of drugs. One procedure encompassed the extrapolation of adult efficacy data to children. Provisions for extrapolation were a similar course of disease between children and adults, similar effects and availability of additional information on pharmacokinetics, dynamics and safety that supports pediatric use. This plan was not very effective since 77 percent out of 430 submissions for labeling changes were not granted.

The 1997 Modernization Act (FDAMA) section 111 was designed to stimulate pediatric labeling, through a six months patent extension for drugs if additional pediatric studies for labeling purposes were performed. This requires the FDA to develop and maintain priority lists of drugs for which additional pediatric information may produce health benefits in the pediatric population. The FDA issues "Written Requests" for the drug products, which are considered as most useful and necessary in pediatric pharmacotherapy.

In 1998, the Pediatric Rule was published, which requires that all new drugs should be tested in the pediatric population, unless the manufacturer demonstrates that the product is likely to be unsafe or ineffective in children, or that pediatric studies are impossible, highly impractical, or that reasonable efforts to develop pediatric formulations have failed. For already licensed drugs, the FDA took the authority to require pediatric studies for drugs that are widely used or that are used in clinically relevant or life-threatening illnesses.

The Best Pharmaceuticals for Children Act (BPCA), which was recently accepted by the US congress, acts as a continuation of section 111 of FDAMA for an additional 5 years period (January 2002 - October 2007). An office of Pediatric Therapeutics will be established within the FDA to monitor and oversee activities dealing with pediatric research. It created an additional incentive for generic pharmaceutical companies by establishing a research fund for off-patent drug studies, which is administered by the National Institutes of Health and the FDA. The act also calls for the establishment of a foundation which purpose is to support pediatric research. BPCA grants a special priority status to labeling changes for children.

1.3 Pediatric drug research

1.3.1 Difficulties of pediatric drug research

There are several practical issues that complicate pediatric drug research. These include patient recruitment, consent procedures, lack of prior knowledge with respect to the (long term) toxic effects of drugs on developing tissues and growth, and different pharmacokinetics and -dynamics in children.[20] Besides, there is very limited experience with the conduction of clinical research in children.

1.3.1.1 Patient recruitment

There are problems in recruiting sufficient numbers of children in different age ranges, mostly because of reluctance of parents to give permission to let researchers use their children as study subjects. Modern study designs can minimize the number of subjects, but in pediatric studies patient recruitment frequently remains problematic. It is the most common cause of delays, increased costs and failure to complete drug trials. [21] The methods that researchers use to recruit patients for a clinical trial are critically important: if entry criteria make it likely that an insufficient number of subjects will be enrolled, or if the protocol is so difficult that few patients are likely to complete the study, it is irresponsible and unethical to expose subjects to the risks of enrollment, no matter how small (Table 3).[22] The success of recruitment of children is related to several factors;[23] but as a general rule inconvenience associated with study participation (including time, travel and discomfort) should be minimized.

Table 3 Pediatric patient recruitment success

Child and family	Perception of a real benefit to the child (not financial)
	Good patient-doctor relationship
	Clear and correct understanding what the trial is about
Study design	In- and exclusion criteria reasonable in relation to availability of patients
	Maintaining of ethical standards
Sources of recruitment	Motivation of colleagues to admit patients
	Information and reminders; e.g. through information meetings

1.3.1.2 Safety of drugs

For most new drugs there is a lack of knowledge on the long-term toxic effects of drugs on developing tissues and growth. But also other adverse reactions may occur predominantly in children. The history of pediatric pharmacology is illustrated by several major adverse drug reactions (ADRs) that occurred in young children (e.g. sodium valproate inducing liver failure,[15 16] salicylates-induced Reye's syndrome),[17] newborn infants (chloramphenicol inducing grey baby syndrome,[13] and benzyl alcohol inducing gasping syndrome)[24 25] and the fetus (thalidomide-induced phocomelia).[2 14] The importance of post-marketing surveillance of drug toxicity is well recognized in pediatric settings,[26-33] but is especially important in view of the overall lack of pre-marketing data. Several studies have shown growth impairment by pediatric use of insufficiently studied drugs. For example, the use of inhaled corticosteroids in asthma treatment has been associated with growth inhibition,[34] although sometimes the benefits of therapy may outweigh such risks.[35 36] Long term toxic effects of drugs are very difficult to study in a phase III-trial, and exposing children to drugs with an unknown

safety profile in clinical trials brings along insurveyable risks, which are often important reasons not to conduct pre-marketing trials.

1.3.1.3 Technical challenges

The small size of the child is one of the major technical problems in the conduct of experimental drug research. A major problem is the lack of cooperation of children in obtaining samples that require invasive techniques. Large efforts have to be made to comfort the child, to limit the complexity and duration of the testing, and to explain as clearly as possible why the child is subjected to the procedures and what the research is about. Obviously, this explanation is only possible in children who are old enough to understand. Blood sampling in pre-terms, neonates and infants has to be limited to the absolute minimum, and although alternatives such as monitoring of drug levels in saliva have been developed,[37,38] blood sampling remains unavoidable in many studies. The use of population pharmacokinetic techniques to obtain the necessary pharmacokinetic parameters, reduces the number of blood samples per child, but increases the number of children that need to be included. This method is not very useful for new drugs, but might facilitate research of drugs that are already commonly used in children.

1.3.1.4 Consent and ethics

'Consent' describes the positive agreement of a person who gives permission. It is normal practice to obtain informed consent from parents for research on children who are too small to decide for themselves. For consent to be valid, parents must be mentally competent, have received appropriate information, must be able to understand the information, and give consent voluntarily.

Consent procedures change as the child gets older. In general, if children have sufficient understanding and intelligence to understand what is proposed, it is their consent and not their parents', which is required.[39] The 1947 Nuremberg Code[40] sets out the principles of obtaining consent. Present guidelines are based on the World Medical Association's Declaration of Helsinki.[41] The Declaration of Helsinki states that, if possible, the child's consent should be obtained in addition to that of a parent. The underlying principle is that in research, as with medical treatment, the child should be included in the decision-making process as far as possible.

There are, however, particular difficulties in asking parents for consent to enroll their child in a research project. One problem relates not so much to the level of information given, but to the extent to which the information can be considered and understood. In addition, there is a problem of integrating the roles of caring pediatrician with that of clinical researcher.[42] It is very difficult to explain child and parents that a new treatment is unproven but potentially valuable, to gain consent for entry into a trial, and then explain that the patient has been randomized to standard therapy.

The declaration of Helsinki states "Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged for their effectiveness, efficiency, accessibility and quality". However, in pediatrics most 'methods' have hardly been studied. Ethical guidelines often state that if there is no expected therapeutic benefit to the child, no invasive drug studies should be conducted. Consequently, only sick

children can participate in invasive drug trials, aimed at cure of the disease they suffer from. Pediatric investigations must often afford an acceptable compromise between patient considerations and the quality and quantity of research.[43]
In 1995, the FDA provided basic new conditions for research in children, primarily founded on human rights. As children comprise a vulnerable population they must be protected from violation of their individual rights and from exposure to unnecessary risks (Table 4).[9]

Table 4 Basic ethical conditions for research in children

1.	The proposed research must be of value to children in general and, in most instances, to the individual child subject. The value may be a potential benefit in the treatment of the subject's disease, or may be improved understanding of basic biology of the disease state or of children in general.
2.	The research design must be appropriate for the stated purposes. Poorly designed research may not provide scientifically valid or useful data and may place the subjects at risk with no potential benefits.
3.	The research design must take into consideration the unique physiology, psychology, and pharmacology of children and their special needs and requirements as research subjects.
4.	The design should minimize risk while maximizing benefit.
5.	The study design must take in to account the racial, ethnic, gender, and socioeconomic characteristics of the children and their parents and, when appropriate, should include input from the community or appropriate advocacy representatives.
6.	The study must be designed to conform to the local, state, and federal laws of the jurisdiction of the study's location and the investigators' home jurisdiction, and to their local and national ethical guidelines.

1.3.1.5 Timing of research in children

The timing of clinical trials in children in relation to studies conducted in adults is related to the severity and specificity of the disease(s) to be treated, the degree of innovation of the medicinal product, potential risks and therapeutic alternatives. In the treatment of childhood diseases, the clinical testing may start in children before adults. For all other diseases, relevant safety and efficacy data from previous adult exposure are needed before proceeding with studies in children. In most cases, reasonable evidence of efficacy in adults is also needed to justify these studies in children (table 5).[44]

Table 5 Timing of specific categories of medicinal products

Diseases affecting exposure in children	Trials in children may start before any previous adult exposure
Diseases that primarily affect, have a different natural history in, or are of particular gravity in children	Trials in children needed in an early st age of clinical development, after demonstration of safety and reasonable (phase I/II) evidence of efficacy in adults
Diseases occurring in both adults and children, for which currently no treatment is available	Trials in children needed in an early stage of clinical development, after demonstration of safety and reasonable (phase I/II) evidence of efficacy in adults

1.3.1.6 Other problems

A very important issue is the general inexperience in conducting clinical trials in children. Both design and implementation of pediatric clinical trials require professionals with special training and experience, of whom there are too few. Besides, there is a lack of training programs in pediatric clinical pharmacology, both in the US and Europe.[45] The institution of (now) thirteen Pediatric Pharmacology Research Units (PPRUs)[46] funded by the US National Institutes of Health (NIH)[47] comply with the need of experience in pediatric clinical pharmacology.

1.3.2 Other sources of information

Without pediatric labeling, the rational selection and dosing of most drugs have to be made by the individual physician based mostly on extrapolation from adult labeling information.

1.3.2.1 Extrapolation from adult studies

The extrapolation of data from adults to children implies the assumption that children are simply "small adults".[43] The physical and maturation processes that occur in children distinguish them from adults. Both drug disposition and drug effects in children and especially infants may vary considerably from adults.[8] Ontogeny of drug absorption, metabolism and excretion limits the ability to extrapolate data from adults to children.[48] Formulas that have been used to extrapolate adult doses are based on weight (which is arbitrary and does not account for any specific differences in drug disposition between children and adults), or surface area,[49] which may give a better estimate for the dose in infants and children. However, doses extrapolated from adults overestimate the dose required for neonates and may underestimate the required dose in children. Adult-extrapolated dosing in children may therefore lead to either toxic effects from excessive doses or ineffective therapy from underdosing.[48]
Unfortunately it is not possible to predict the pediatric dosage requirements in the absence of adequate studies in children.[50] However, adult data are frequently a good starting-point for the prediction of the effect of a drug in infants and children. This prior prediction may minimize the number of samples that are required to estimate pharmacokinetic parameters in children. Data from adults may also assist predictions about the effect of specific disease states on drug disposition in children and metabolism-based drug interactions.

1.3.2.2 Obtaining information from the medical literature

Although the medical literature could be a source of information for the pharmacological treatment of children, physicians are often poorly trained in the critical evaluation of the medical literature while the reporting of clinical research in the medical literature is fraught with many deficiencies.[51-53] Common deficiencies are poor study design, incomplete documentation, questionable data collection methods, inappropriate statistical analysis, and indefensible conclusions.[54] Small numbers of subjects and limited stratification for various age groups further limit the application of medical literature to actual treatment decisions in children. Since journal editors and reviewers do not have access to all data when reviewing the results of a clinical trial, decisions that are based on the literature may lead to inadequate treatment. Drug labeling authorities on the other hand have access to all data prior to the labeling of the drug. The labeling information offers a clear and concise presentation of readily available and usable information approved by the licensing authorities as being substantial evidence of efficacy, safety and dose for the cited indications and age groups. The amount of information on the label, however, is of much importance. Use of hospital protocols and formularies may help, although even in the compilation of guidelines the insight in study design and execution is less complete than in registration. Large pediatric formularies, such as the Royal College of Paediatrics and Child Health

(RCPCH) and Neonatal and Paediatric Pharmacist's Group (NPPG) joint formulary "Medicines For Children",[55] which was published in 1999, are important improvements of the 'information problem', although frequent updating is the only guarantee for accuracy.

1.3.3 Consequences for pediatric pharmacotherapy

The fact that drug research in children is complicated by many factors has resulted in a lack of drugs that are sufficiently studied for use in children and consequently by inadequate pediatric labeling. Another logical consequence is the lack of pediatric formulations, especially for infants.[50,56] The drugs are often not available in appropriate dosage sizes, lack liquid formulations, and may taste peculiar to the child.[57] Dosage sizes are frequently based on the adult market, which forces physicians to prescribe fractions of tablets to children. Horn *et al.* [58] showed that splitting of tablets results in strong variability between doses, and recommended that solid dosage forms should not be cut.[59] To solve the formulation issue, many drugs that are frequently prescribed to children are modified in the pharmacy. This results in preparations that have a less well-documented and reproducible quality since it is difficult to determine the stability of various drugs at clinical important concentrations and practical storage conditions.[56] The patient's acceptance of a liquid dosage form depends on its palatability. In general, improving the taste may enhance compliance.[60-64]

1.4 Aims of the studies

Chapter 1 gives a general introduction to pediatric pharmacology in general, and the problems that accompany drug research in children in particular, and it provides an overview of drug legislation in Europe, and in the US. In **Chapter 2**, we will describe unlicensed and off-label drug use in children in hospital settings in the Netherlands and Europe. Distinction is made between a secondary, non-teaching (general) hospital setting, and a tertiary, academic hospital setting, in which over a certain period of time all prescriptions to inpatients will be assessed for unlicensed and off-label use. Central questions concern incidence and nature of unlicensed and off-label drug use in both settings, and which drugs are most frequently prescribed unlicensed or off-label. Comparison between five pediatric centers in England, Sweden, Germany, Italy and the Netherlands, as an initiative of the European Network for Drug Investigation in Children (ENDIC), will also be discussed. Drug prescribing in general practice, and the incidence and nature of unlicensed and off-label drug prescription to children by general practitioners will be assessed in **Chapter 3**, in the setting of the Integrated Primary Care Information database. Besides, we will assess the most important factors of influence on the prescription of drugs to children that are used outside the terms of the product license regarding the age of the patient in a nested case-control study. **Chapter 4** addresses the question related to unlicensed and off-label drug use in child- and adolescent psychiatry, and will describe trends in prescription of stimulants and antidepressants in children. **Chapter 5** will discuss adverse drug reactions in relation to unlicensed and off-label drug use. The question of relevance of unlicensed and off-label use of drugs in children in the light of negative health outcome is very important to address in this matter. We assess unlicensed and off-label use of drugs in an

adverse drug reaction (ADR) spontaneous reporting system in a case series. We also compare use of deptropine, an unlicensed drug, with other antihistaminics regarding neuropsychiatric adverse drug reactions. In **Chapter 6**, we evaluate the current situation regarding pediatric labeling of drug available in the Netherlands and drugs licensed through the European Medicines Evaluation Agency (EMEA). The efficiency of the FDA's Modernization Act will be assessed through an analysis for Written Requests issued by the FDA. **Chapter 7** is the concluding chapter in which the results of the previous studies are discussed. Recommendations about drug prioritizing for research, and other measures for the improvement of the current situation regarding pediatric labeling are made and suggestions for future research in this area are presented.

References

1. Shirkey HC. Therapeutic orphans. J Pediatr 1968;72:119-20.
2. McBride W. Thalidomide and congenital abnormalities. Lancet 1961;ii:1358.
3. Shirkey HC. Therapeutic orphans: who speaks for the children? South Med J 1970;63:1361-3.
4. Shirkey HC. The package dilemma. J Pediatr 1971;79:691-3.
5. Shirkey HC. Clinical pharmacology in pediatrics. Clin Pharmacol Ther 1972;13:827-30.
6. Wilson JT. Pragmatic assessment of medicines available for young children and pregnant or breast-feeding women. Basic and Therapeutic Aspects of Perinatal Pharmacology. New York, NY: Raven Press, 1975:411-21.
7. Offices of Drug Evaluation Statistical Report. Rockville, MD: Center for Drug Evaluation and Research. Food and Drug Administration; Public Health Service; US Dept of Health and Human Services, 1989.
8. Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates. A quiet frontier [comment]. Clin Pharmacokinet 1992;23:1-9.
9. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Committee on Drugs, American Academy of Pediatrics. Pediatrics 1995;95:286-94.
10. Cote CJ, Kauffman RE, Troendle GJ, Lambert GH. Is the "therapeutic orphan" about to be adopted? Pediatrics 1996;98:118-23.
11. Wilson JT. An update on the therapeutic orphan. Pediatrics 1999;104:585-90.
12. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. Br J Clin Pharmacol 1999;48:15-8.
13. Sutherland J. Fatal cardiovascular collaps of infants receiving large amounts of chloramphenicol. American Journal of Disease in Childhood 1959;97:761-7.
14. Lenz W. Thaladomide and congenital abnormalities. Lancet 1967;i:45.
15. Dreifuss FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid hepatic fatalities: a retrospective review. Neurology 1987;37:379-85.
16. Donat J, Bocchini J, Gonzalez E, Schwendimann R. Valproic acid and fatal hepatitis. Neurology 1979;29:273-4.
17. Starko KM, Ray CG, Dominguez LB, Stromberg WL, Woodall DF. Reye's syndrome and salicylate use. Pediatrics 1980;66:859-64.
18. Abraham J, Lewis G. Harmonising and competing for medicines regulation: how healthy are the European Union's systems of drug approval? Soc Sci Med 1999;48:1655-67.
19. 59 FR 64242: Food and Drug Administration, 1994.
20. Wilson JT, Kearns GL, Murphy D, Yaffe SJ. Paediatric labelling requirements. Implications for pharmacokinetic studies. Clin Pharmacokinet 1994;26:308-25.
21. Walson PD. Patient recruitment: US perspective. Pediatrics 1999;104:619-22.
22. Ross LF, Newburger JW, Sanders SP. Ethical issues in pediatric trials. Am Heart J 2001;142:233-6.
23. Hoppu K. Patient recruitment-European perspective. Pediatrics 1999;104:623-6.
24. Lovejoy FH, Jr. Fatal benzyl alcohol poisoning in neonatal intensive care units. A new concern for pediatricians. Am J Dis Child 1982;136:974-5.
25. Menon PA, Thach BT, Smith CH, Landt M, Roberts JL, Hillman RE, Hillman LS. Benzyl alcohol toxicity in a neonatal intensive care unit. Incidence, symptomatology, and mortality. Am J Perinatol 1984;1:288-92.
26. McKenzie MW, Stewart RB, Weiss CF, Cluff LE. A pharmacist-based study of the epidemiology of

adverse drug reactions in pediatric medicine patients. Am J Hosp Pharm 1973;30:898-903.
27. Whyte J, Greenan E. Drug usage and adverse drug reactions in paediatric patients. Acta Paediatr Scand 1977;66:767-75.
28. Choonara IA, Harris F. Adverse drug reactions in medical inpatients. Arch Dis Child 1984;59:578-80.
29. Mitchell AA, Goldman P, Shapiro S, Slone D. Drug utilization and reported adverse reactions inhospitalized children. Am J Epidemiol 1979;110:196-204.
30. Choonara I, Gill A, Nunn A. Drug toxicity and surveillance in children. Br J Clin Pharmacol 1996;42:407-10.
31. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. Acta Paediatr 1995;84:438-41.
32. Pirmohamed M, Madden S, Park BK. Idiosyncratic drug reactions. Metabolic bioactivation as a pathogenic mechanism. Clin Pharmacokinet 1996;31:215-30.
33. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol 2001;52:77-83.
34. Allen DB. Effect of inhaled beclomethasone dipropionate and budesonide on growth in children with asthma. Respir Med 1998;92 Suppl B:37-45.
35. Pedersen S. Do inhaled corticosteroids inhibit growth in children? Am J Respir Crit Care Med 2001;164:521-35.
36. Pedersen S. Assessing the effect of intranasal steroids on growth. J Allergy Clin Immunol 2001;108:S40-4.
37. Gorodischer R, Koren G. Salivary excretion of drugs in children: theoretical and practical issues in therapeutic drug monitoring. Dev Pharmacol Ther 1992;19:161-77.
38. de Wildt SN, Kerkvliet KT, Wezenberg MG, Ottink S, Hop WC, Vulto AG, Anker JN vd. Use of saliva in therapeutic drug monitoring of caffeine in preterm infants. Ther Drug Monit 2001;23:250-4.
39. McIntosh N, Bates P, Brykczynska G, Dunstan G, Goldman A, Harvey D, Larcher V, McCrae D, McKinnon A, Patton M, Saunders J, Shelley P. Guidelines for the ethical conduct of medical research involving children. Royal College of Paediatrics, Child Health: Ethics Advisory Committee. Arch Dis Child 2000;82:177-82.
40. The Nuremberg Code (1947). BMJ 1996;313:1448.
41. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2000;284:3043-5.
42. Eden OB. Informed consent. Consent difficult in paediatric oncology. BMJ 1994;308:272.
43. Kauffman RE, Kearns GL. Pharmacokinetic studies in paediatric patients. Clinical and ethical considerations. Clin Pharmacokinet 1992;23:10-29.
44. Autret E. European regulatory authorities and pediatric labeling. Pediatrics 1999;104:614-8.
45. Moore P. Children are not small adults. Lancet 1998;352:630.
46. Cohen SN. The Pediatric Pharmacology Research Unit (PPRU) Network and its role in meeting pediatric labeling needs. Pediatrics 1999;104:644-5.
47. RFA, NIH PPRU Network, 1993.
48. Christensen ML, Helms RA, Chesney RW. Is pediatric labeling really necessary? Pediatrics 1999;104:593-7.
49. Rane A. Drug desposition and action in infants and children. In: Yaffe SJ, Aranda JV, editors. Pediatric Pharmacology. Therapeutics Principles in Practice. New York, NY: WB Saunders, 1992:10-21.
50. Nahata MC. Pediatric drug formulations: challenges and potential solutions. Ann Pharmacother 1999;33:247-9.
51. Meinert CL, Tonascia S, Higgins K. Content of reports on clinical trials: a critical review. Control Clin Trials 1984;5:328-47.
52. Bland JM, Jones DR, Bennett S, Cook DG, Haines AP, MacFarlane AJ. Is the clinical trial evidence about new drugs statistically adequate? Br J Clin Pharmacol 1985;19:155-60.
53. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. A survey of three medical journals. N Engl J Med 1987;317:426-32.
54. Moss RL, Henry MC, Dimmitt RA, Rangel S, Geraghty N, Skarsgard ED. The role of prospective randomized clinical trials in pediatric surgery: state of the art? J Pediatr Surg 2001;36:1182-6.
55. The Royal College of Paediatrics and Child Health: Medicines for children. Hants, United Kingdom: B&MBC Books Ltd, Direct Books, 1999.
56. Nahata MC. Lack of pediatric drug formulations. Pediatrics 1999;104:607-9.
57. Crawford SY, Dombrowski SR. Extemporaneous compounding activities and the associated informational needs of pharmacists. Am J Hosp Pharm 1991;48:1205-10.
58. Horn LW, Kuhn RJ, Kanga JF. Evaluation of the reproducibility of tablet splitting to provide accurate doses for the pediatric population. The Journal of Pediatric Pharmacy Practice 1999;4:38-42.
59. McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. Pharmacotherapy 1998;18:193-7.

60. Powers JL, Gooch WM, 3rd, Oddo LP. Comparison of the palatability of the oral suspension of cefdinir vs. amoxicillin/clavulanate potassium, cefprozil and azithromycin in pediatric patients. Pediatr Infect Dis J 2000;19:S174-80.
61. Hutto CJ, Bratton TH. Palatability and cost comparison of five liquid corticosteroid formulations. J Pediatr Oncol Nurs 1999;16:74-7.
62. Matsui D, Lim R, Tschen T, Rieder MJ. Assessment of the palatability of beta-lactamase-resistant antibiotics in children. Arch Pediatr Adolesc Med 1997;151:599-602.
63. Matsui D, Barron A, Rieder MJ. Assessment of the palatability of antistaphylococcal antibiotics in pediatric volunteers. Ann Pharmacother 1996;30:586-8.
64. Dagan R, Shvartzman P, Liss Z. Variation in acceptance of common oral antibiotic suspensions. Pediatr Infect Dis J 1994;13:686-90.

Chapter 2
Unlicensed and off-label drug use in hospital settings

Chapter 2.1

Unlicensed and off-label drug use in an academic children's hospital

The treatment of pediatric patients with drugs in hospital is being impeded by a shortage in the availability of licensed drugs in an appropriate formulation. We have studied the extent of use of drugs that are not licensed for use in children (unlicensed) and drugs that are used outside the terms of the product license (off-label). We conducted this study in the setting of a Dutch academic children's hospital. In a prospective study of five weeks duration, we reviewed drug prescriptions in a pediatric ward and three intensive care units (ICUs). We classified the prescribed drugs into three main categories; licensed, unlicensed, and off-label, and determined the nature of their unlicensed and off-label use. 2139 courses of drugs were administered to 237 patients in 442 patient-days. Of 2139 prescriptions 725 (34%) were licensed, 1024 (48%) were unlicensed and 390 (18%) off-label. In 391 (90.3%) of 435 patient-days children received one or more courses of an unlicensed or off-label drug prescription in hospital. With regard to the availability of drugs of proven quality and adequate license for pediatric patients in hospital, dramatic shortcomings exist. As a result, drug legislation originally designed to protect patients and prescribing physicians against unsafe drug use and unjustified claims has turned into an insurmountable threshold to make proper drugs available for a vulnerable minority of patients.

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Introduction

Many commercially available drugs are only licensed for use in adults and are not used according to the product licensing in pediatric practice. Furthermore, for many drugs, the available formulations are unsuitable for pediatric use[1] and for many compounds in common use in pediatrics, preparations are not commercially available at all. The reasons for this situation are several. According to the modern standards of drug evaluation, obtaining a product license for a specific drug for a specific indication in a specific patient group necessitates extensive research. With children forming only a minority in the drug market, the profit driven drug industry by nature is reluctant to invest in pediatric drug studies. In addition, fear is growing for unforeseen and hard to study long-term side effects. As a result, drug legislation originally designed to protect patients and prescribing physicians against unsafe drug use and unjustified claims, has turned into a barrier to make proper drugs available for a vulnerable minority of patients.

Other reasons are the ethical problem of research in children, the reluctance of parents to allow their children to participate in drug trials, and the technical challenges small study subjects bring along. Possibly because of the underestimation of the problem, there is lack of funding from government, health care providers, and industry. As a result, pediatric drug trials are relatively scarce and in many cases contain only a limited number of patients.

Consequently, most drugs used in clinical practice in pediatrics are not licensed for children,[2-6] and this has lead to children being referred to as "therapeutic orphans".[7] Use of these drugs is sometimes based on the modification of adult formulations and dosage strengths and extrapolation of doses used in adults. This neglects the important differences between adults and children in development and drug metabolism and excretion.[8] Often, dosage regimens are based on clinical trials and published experience in children, although not submitted to licensing scrutiny.

Surveys in the UK by Choonara *et al.*, and by others, have shown that many drugs prescribed to children in pediatric, and especially neonatal care, are not licensed for children, or are prescribed "off-label" (i.e. outside the terms of the product license).[9-15] With tightening rules in medical practice and an increasing number of lawsuits, pediatricians are in an unenviable position. In the US, about 80% of all drugs approved for the market lack partial or complete information in the label pertaining to use in pediatric patients.[16-18] The US Food and Drug Administration (FDA) has implemented new regulations to increase the number of drugs available for pediatric use.[19 20] In Europe, similar changes are under discussion, currently only with very limited success.[21 22]

In contrast to many other European countries, most Dutch hospital pharmacies provide their pediatric wards with fully 'home made' pediatric formulations or modified commercial preparations (e.g. strength adapted suspensions, capsules) on a large scale. We wanted to investigate the licensing status of the drugs commonly used in a pediatric academic setting against this background. We therefore studied in detail all drugs prescribed in four hospital units in our academic children's hospital.

Methods

Setting

Data were retrieved from four hospital units of the Sophia Children's Hospital in Rotterdam, The Netherlands, an academic children's hospital. This highly specialized hospital provides the Rotterdam region with care for children that are very seriously ill, and in need for specific care. During a 5-week period (February and March 1999) we prospectively investigated one large medium care unit and three intensive care units. These four hospital units were; MCU (Medium Care Unit, 56 beds/cribs), NICU (Neonatal Intensive Care Unit; 28 cribs), SICU (Surgical Intensive Care Unit; 18 beds/cribs) and PICU (Pediatric Intensive Care Unit; 14 beds/cribs).

Design

To determine the drug licensing status of drugs prescribed to children in this hospital, we prospectively gathered prescription data study in a dynamic cohort. We studied all patients that were hospitalized in one of the hospital units during the study period. We defined each event in which the prescriptions of an individual patient on a separate day have been investigated, as one 'patient-day'. Each hospital unit was studied for one day each week for five consecutive weeks, and was visited on a different day each week.

Data collection included: unit involved, week number, date of birth, age, weight, gender, diagnosis or reason of admission, drugs administered, form and route of administration, dose, frequency and indication for use. The use of the following drugs was not recorded: standard intravenous crystalloid fluids, blood products, total parental nutrition and oxygen therapy.

Classification

All drugs administered were assessed for licensing status by way of a classification system specially adapted to the Dutch situation, although largely based on a classification system described and used in previous published studies in the UK.[10]

In the main classification category four main groups of prescriptions were defined; (1) Proprietary medications, (2) generic, or non-propriety medication, (3) commercial formulations modified by the hospital pharmacy (Modified) and (4) medications manufactured by the hospital pharmacy (Home Label).

A prescription was automatically defined unlicensed if 'Modified' or 'Home Label' was applicable. In case of a modification, the commercial manufacturer would not be liable for the altered administered prescription, because the license of the original product is not applicable to the modified product. In case of a home label drug, no license was applicable, because it was produced by the hospital pharmacy itself. These prescriptions were not further classified for off-label use because the lack of proper information texts.

If a prescription was a propriety or generic product, we further classified for five other classification categories, namely age, dosage form & route of administration, daily dosage used, number of doses per day, and indication. If the prescription in one or more of the other classification categories was not according to registration, it was defined 'off-label'. Exceptions were made when the prescription was 'not licensed for

Table 1 Patient characteristics

Hospital unit (Number of beds / cribs)	MCU (56)	NICU (28)	SICU (18)	PICU (14)	Total (116)
Patients admitted	110	66	34	27	237
Gender					
Male	64	33	14	18	129
Female	46	33	20	9	108
Age					
Age range	4 d – 17 y	0 d – 6 m	6 d – 16 y	4 d –15 y	0 d – 17 y
Median age	4.5 y	12 d	54 d	2.2 y	8.5 m
Patient-days	186	130	70	49	435
Prescriptions	905	621	308	305	2139
Prescriptions per patient -day	4.9	4.8	4.4	6.2	4.9

MCU: Medium Care Unit; NICU: Neonatal Intensive Care Unit; SICU: Surgical Intensive Care Unit; PICU: Pediatric Intensive Care Unit.

use in children' or 'contra-indicated for use in children' (contra-indicated), or when doses for use in children were not mentioned in the reference (no information on use in children), in which case the prescription was defined 'unlicensed'.

The primary reference source used was the Repertorium 98/99 (an official Dutch compendium with approved drug information on drug specialties).[23] The alternative source of information was the Farmacotherapeutisch Kompas 98 (a compendium provided by the Dutch National Health Service),[24] which was used if the drug involved was not available as a proprietary medication, and therefore not mentioned in the Repertorium 98/99.

Results

During the 5-week study period in February and March 1999, 237 patients were included in the study in a total of 448 patient-days. The ages of the patients at admission ranged between 0 days and 17 years. Of 237 patients, 129 (54%) were male. The four hospital units admitted 110 (MCU), 64 (NICU), 33 (SICU), and 31 (PICU) patients, receiving 905, 621, 308, and 305 prescriptions, respectively (table 1). Fourteen patients switched from an intensive care unit to the MCU during hospitalization. Most important reasons for admission were: prematurity, BPD, cardiac mal-

Table 2 Number of prescriptions used in each licensing category

Category	Reason for unlicensed or off-label prescription	MCU (n=905)		NICU (n=621)		SICU (n=305)		PICU (n=308)		Total (n=2139)	
Licensed in children		375	*41%*	153	*24%*	100	*32%*	97	*32%*	725	
Off label **	Age/weight	58	*6%*	11	*2%*	22	*7%*	21	*7%*	112	*5%*
	Dose & Frequency	113	*12%*	72	*12%*	66	*22%*	29	*9%*	280	*13%*
	Indication	8	*1%*	18	*3%*	15	*5%*	3	*1%*	43	*2%*
	Route of administration & Dosage form	39	*4%*	19	*3%*	38	*12%*	3	*1%*	99	*5%*
Total off-label		170	*19%*	84	*14%*	88	*29%*	48	*16%*	390	*18%*
Unlicensed in children	No information on use in children §	112	*12%*	46	*7%*	33	*11%*	51	*17%*	242	*11%*
	Contra-indicated ‡	9	*1%*	5	*1%*	7	*2 %*	1	*<1%*	22	*1%*
	Manufactured or modified by the hospital pharmacy*	239	*26%*	333	*54%*	80	*26%*	108	*35%*	760	*36%*
	New drugs	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*
Total unlicensed		360	*40%*	384	*62%*	120	*39%*	160	*52%*	1024	*48%*

MCU: Medium Care Unit
NICU: Neonatal Intensive Care Unit
SICU: Surgical Intensive Care Unit
PICU: Pediatric Intensive Care Unit

§ No information on use in children is found in any subsection of the product license

‡ The product license indicates that the drug is contraindicated for use in children

* The prescription is prepared by the pharmacy, and no official product license is available for this formulation

** As drugs in the off-label category can be classified under more than one of the six bullet points, totals add up to more than the total number of off-label prescriptions for each unit.

Table 3 The 5 most frequently prescribed drugs in 4 different hospital units during the 5 weeks investigation period (%=percentage of all drug prescriptions in the hospital unit).

MCU	%	NICU	%	SICU	%	PICU	%	Total	%
Acetaminophen	4	Caffeine	11	Nystatin	17	Amphotericin B	9	Nystatin	5
Amphotericin B	3	Nystatin	9	Cisapride	8	Cisapride	7	Cisapride	4
Ondasetron	3	Vitamin D_3 & E	7	Acetaminophen	5	Acetaminophen	6	Acetaminophen	4
Furosemide	2	Ipratropium & Salbutamol	5	Cefotaxime	5	Cotrimoxazole	6	Caffeine	4
Spironolactone	2	Tobramycin	5	Furosemide	4	Furosemide	6	Furosemide	3

formations, oncology, cystic fibrosis, chronic renal failure, and asthmatics.

Of the 2139 prescriptions, 1024 were unlicensed (48%, 95%CI: 46-50), and 390 were off-label (18%, 95%CI: 17-20). 392 (90%, 95%CI: 87-93) of all 435 patient-days contained unlicensed drugs or off-label prescription. Of all prescriptions, 193 (9%) were commercial formulations modified by the hospital pharmacy ('modified'), and 567 (27%) were medications manufactured by the hospital pharmacy (Home Label). This percentage was even higher in NICU. 334 (16%) drug prescriptions were off-label for dose, and 100 (5%) were off-label for age (table 2).

A total of 189 drugs were prescribed, the most frequently encountered drugs in the study were nystatin, cisapride and acetaminophen (table 3). The most frequently encountered unlicensed drugs and off-label prescriptions in use were cisapride, caffeine and tobramycin (table 4). Off-label use is mainly due to use of different dose and frequency to that recommended in the product license. Ipratropium, budesonide and salbutamol are used in various combinations and dosage proportions. The components are dissolved in NaCl 0.9% by the hospital pharmacy, and then used in an aerosol.

Discussion

The licensing status of many of the drugs commonly used in our academic children's hospital is inadequate. Results show a high prevalence of unlicensed (44%) and off-label (15%) drug use in our medium care unit (MCU). We found even larger proportions of unlicensed and off-label drug use in intensive care, and especially in the neonatal intensive care unit (NICU), as expected. Lack of flexible pediatric formulations and lack of drugs properly licensed for new-borns and infants are important cofactors. We found a strikingly high use of 'Home Label' prescriptions in NICU (41%), which is mainly caused by the lack of flexible pediatric formulations, which the hospital pharmacy tries to overcome by manufacturing the needed formulations themselves.

We expected the number of drugs used (4.9 prescriptions per patient day) in the MCU to be lower than in the ICU's. However, no significant difference is found. This is probably due to the relatively high prevalence of chronic respiratory illness (cystic fibrosis, asthma) in this patient population.

Table 4 The 5 most frequently used unlicensed and off label drug prescriptions in 4 different hospital units during the 5-weeks investigation period.

MCU	NICU	SICU	PICU	Total
Pancreatin	Caffeine	Cisapride	Cisapride	Cisapride
Spironolactone	Vitamin D_3 & E	Gaviscon	Spironolactone	Caffeine
Furosemide	Ipratropium & Salbutamol	Acetaminophen	Ranitidine	Tobramycin
Tobramycin	Tobramycin	Morphine	Furosemide	Spironolactone
Phytomenadione	Dexamethasone	Phytomenadione	Trimeprazine	Furosemide

MCU: Medium Care Unit; NICU: Neonatal Intensive Care Unit;
SICU: Surgical Intensive Care Unit; PICU: Pediatric Intensive Care Unit.

Studies in the UK by Choonara *et al.* showed similar results concerning the licensing status of prescribed drugs.[11-14] When comparing our study to the UK studies, several aspects in design have to be considered. The extensive use of medications modified by the hospital pharmacy (modified) and formulations manufactured by the hospital pharmacy (home label) in the Netherlands compared to the studies performed in the UK results in very high percentages of unlicensed drug prescription. The difference between these studies is due to the pharmacy strategy to dedicate resources to clinical pharmacy service provision rather than manufacturing, which is followed by most departments in the United Kingdom. UK pharmacists are allowed to extemporaneously dispense any drug for an individual patient, but GMP regulations must rightly be followed if done on a larger scale. In the Netherlands, hospitals pharmacies often manufacture on a large scale for cost-saving reasons. Besides that, the number of drugs licensed for use in the Netherlands is smaller, also resulting in a higher proportion of modified medications and home label formulations; they together make up for 36% of all prescriptions. The method of data collection differed not only in length of study period, but also in data collection interval. In an international study in pediatric wards we participated in,[25] we used some of the data from this study. Preliminary results of this study have been reported in abbreviated form.26 The classification system used in these preliminary results was slightly different, but to facilitate comparison we adapted our data to the classification system used in the surveys by Choonara *et al.*[10]

It is important to recognize that off-label or unlicensed use of a drug may not be an inappropriate use (because of reasonable research based foundations of prescription protocol), but may be judged as such when the legal liability of the physician would be questioned in court, because the prescription is not in accordance with labeling information. In our pediatric wards, most drug use is based either on longstanding experience or evidence obtained from the literature. The majority of drugs are prescribed within established protocols. However, the same standards of efficacy and safety cannot be applied as for the adult population. Drugs that were prescribed while contraindicated or unlicensed for age may be particularly unsafe, considering the lack of research done in these drugs, and the potency of these drugs. They included vigabatrin (unlicensed in children < 10 kg.), and ciprofloxacin (contraindicated).

Results give a good impression of the extent of unlicensed and off-label drug prescription in very specialized pediatric care in the Netherlands. In general hospital pediatric care, and care provided to children by general practitioners, hardly any information is available on the extent of unlicensed and off-label drug prescription. We hope that future research in these areas will provide us of better knowledge of the extent of this problem.

We strongly support the FDA's Pediatric Rule.[19] Despite various gaps in these regulations, they are very important for the accomplishment of equality in safety and efficacy of pharmaceutical products in adults and children.[27 28] The extension of prescribing information of already licensed products with pediatric data is a matter of public interest and therefore should be solved between the industry and the medical community with public support. In return for public support, the license holder should be willing to develop flexible pediatric formulations (like droplets, suspensions,

linctus, different strengths, capsules etc). Older drugs that do not have a patent are however excluded from this rule, despite the fact that they are frequently used. A more difficult problem is to make currently unavailable preparations in need, more generally available. In most countries, according to GMP-regulations hospital pharmacies are not able to manufacture drugs on a larger scale than facilitation of its hospital(s) requires. It is of crucial importance to investigate whether manufacturers of generic drug products are able to produce certain products on a continent-wide scale (Europe, US), provided that the international pediatric community would be able to standardize their practices in order to make this effort economically reasonable. International collaboration could be realized and coordinated through organizations like the European Network for Drug Investigation in Children (ENDIC),[29] the American Society for Clinical Pharmacology & Therapeutics, the European Society for Clinical Pharmacology, and the Neonatal and Paediatric Pharmacists Group (NPPG) in the UK. We hope that drug regulation authorities would support this movement by facilitating an orphan status of such products, thereby reducing the investment risk of the producer. Accumulation of pediatric drug data could be an important strategy, given that efficacy and safety information becomes available beyond reasonable doubt and without very high financial risks for the license holder.

While drug regulations in general are intended for protection of patients and prescribing physicians, society should be willing to pay the price when side-effects of such regulations become counterproductive and unacceptable for children who constitute the future of the society. We have an obligation to investigate seriously every possibility to reverse this highly unfortunate situation in which the progress of medical care is not available for the most vulnerable and defenseless among us.

References

1. Nahata MC. Lack of pediatric drug formulations. Pediatrics 1999;104:607-9.
2. Prescribing unlicensed and off-label drugs fro unlicensed indications. Drug Ther Bull. 1992;35:97-9.
3. Nahata MC. Need for conducting research on medications unlabeled for use in pediatric patients. Ann Pharmacother 1994;28:1103-4.
4. Gervais A. Comment: medications unlabeled for use in children. Ann Pharmacother 1995;29:1052.
5. Kauffman RE. Status of drug approval processes and regulation of medications for children. Curr Opin Pediatr 1995;7:195-8.
6. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Committee on Drugs, American Academy of Pediatrics. Pediatrics 1995;95:286-94.
7. Shirkey H. Therapeutic orphans. J Pediatrics 1968;72:119-20.
8. Christensen ML, Helms RA, Chesney RW. Is pediatric labeling really necessary? Pediatrics. 1999; 104:593-7.
9. Nahata MC. Licensing of medicines for children in the USA. Paediatric and Perinatal Drug Therapy 1997;1:50-51.
10. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
11. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of "off-label" and unlicensed drugs in paediatric intensive care unit. Lancet 1996;347:549-50.
12. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. Bmj 1998;316:343-5.
13. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80:F142-4.
14. McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off label prescribing of drugs in general practice. Arch Dis Child 2000;83:498-501.
15. Chalumeau M, Treluyer JM, Salanave B, *et al.* Off label and unlicensed drug use among French office

based paediatricians. Arch Dis Child 2000;83:502-5.
16. Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates. A quiet frontier. Clin Pharmacokinet 1992;23:1-9.
17. Guidance for industry; Content and format for pediatric use supplements. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Washington, 1996:1-6.
18. Newman C, Hull D. Comment: regulations for pediatric labeling of prescription drugs. Ann Pharmacother 1997;31:1092-3.
19. Department of Health and Human Services. Food and Drug Administration. 21 CFR Parts 201, 312, 314, and 601. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients. Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research, 1998:66632-72.
20. Federal Register 21 CFR Part 201. Requirements on content and format of labeling for human prescription drugs and biologics: Requirements of prescription drug product labels; proposed rule. FDA, 2000.
21. Kmietowicz Z. Drug industry is unwilling to run trials in children. BMJ 2000;320:1362A.
22. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. Br J Clin Pharmacol 1999;48:15-8.
23. Dutch Society of Research-orientated Pharmaceutical Industry N, Dutch Society of the Phamaceutical industry of Selfcare medication and Healthproducts, Neprofarm. Repertorium 98/99, overview of by the Medication Evaluation Board registered information texts of pharmaceutical specialties. Repertorium. Utrecht: Nefarma & Neprofarm; 1998.
24. Central Medical Pharmaceutical Committee of the National Health service Council. Farmaceutisch Kompas 1998 (Pharmaceutical Compass 1998). Utrecht: National Health Service Council; 1998.
25. Conroy S, Choonara I, Impicciatore P, *et al.* Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000;320:79-82.
26. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, Anker JN vd. Unapproved and off-label use of drugs in a children's hospital [letter]. N Engl J Med 2000;343:1125.
27. The Pediatric Exclusivity Provision. Januari 2001 Status Report to Congress. Department of Health and Human Services. U.S. Food and Drug Administration. 2001.
28. Jong GW, Anker JN vd, Choonara I. FDAMA's written request list: medicines for children. Lancet 2001;357:398.
29. Bonati M, Choonara I, Hoppu K, Pons G, Seyberth H. Closing the gap in drug therapy. Lancet, 1999;353:1625.

Chapter 2.2

Unlicensed and off-label drug use in a pediatric ward of a general hospital in the Netherlands

Many drugs used in pediatric care are not licensed for that use, or are prescribed outside the terms of the product license (off-label). Studies in the UK and Europe showed a large number of unlicensed and off-label drug prescription in specialized pediatric health care centres. We determined the extent and nature of use of unlicensed drugs and off-label prescriptions in children in a general hospital in the Netherlands. We conducted a longitudinal prospective cohort study in a dynamic population consisting of patients admitted to the pediatric ward and the neonatology unit of a general hospital during a 19-weeks period. Drug licensing status of all prescriptions given to these patients was determined. A total of 1017 prescriptions were administered to 293 pediatric patients. 443 (44%) prescriptions were off-label, and 285 (28%) were for unlicensed drugs. 269 (92%) patients were given one or more drugs which were either unlicensed or prescribed in an off-label way. This study shows that the extent of unlicensed and off-label drug prescription in a pediatric ward and neonatology unit of a general hospital is large. Lack of pediatric drug labeling is therefore not solely a problem with drugs used in academic hospitals, but also in general hospitals.

Introduction

Adequate pharmacotherapy in children is complicated by lack of information,[1] lack of appropriate formulations,[2] and lack of drugs licensed for children.[3] Two major problems can be distinguished. Drug research in children, if performed at all, often takes place in small-scale post-marketing studies, and application for adjustment of licensing text is often not done. Lack of statistical power by small patient groups may be a problem, along with a lack of knowledge on long term toxic effects, challenges related to the size of the study subject (e.g. regarding blood sampling), problems with cooperation and communication, the issue of informed consent, a general lack of experience, lack of financial incentives, and a fear of legal liability. As a result, many of the drug preparations needed in pediatric clinical care do not have a license for use in children.[4] Moreover, many drugs have a formulation not suitable for use in children,[2] and some preparations commonly used in children are not commercially available. The aim of licensing is to ensure safety, quality and efficacy, but this goal is not met in children. Therefore, prescription of unlicensed drugs, or drugs that are licensed but used outside the terms of the product license ('off-label') is widespread in pediatric care. We earlier studied the extent of this 'unapproved' use of drugs in a specialized pediatric health care centre.[5] But since this hospital was not representative of all intramural pediatric care, we studied the extent of prescribing of unlicensed and off-label drug prescription in the pediatric ward and the neonatology unit of a general hospital in the Netherlands.

Methods

Setting and design

Data were gathered from the pediatric ward and the neonatology unit of the Reinier de Graaf Hospital, a general hospital in Delft, the Netherlands. This non-teaching hospital has a pediatric ward consisting of 27 beds and cribs, and a neonatology unit consisting of 27 cribs.

To determine the extent of prescribing of unlicensed drugs, and off-label drug prescription, we conducted a prospective cohort study during a 5-months period between March 1 and July 31, 2000. All patients hospitalized between March 1 and July 11, 2000, receiving drug prescriptions during the study period, were followed until one of the following endpoints: transfer to another hospital, discharge from the hospital, or end of the study period, whichever came first. Data were recorded on a daily basis. Details recorded included date of birth, gestation, weight, diagnosis or reason for admission, admission and discharge dates, start and duration of drug therapy, form and route of administration, dose, frequency, and indication for use. The use of the following drugs was not recorded: standard intravenous crystalloid fluids, flushes of sodium chloride 0.9% or heparin to maintain the patency of intravenous and arterial lines, blood products, total parental nutrition, and oxygen therapy.

Classification

Age was classified in line with the paediatric age definitions provided by the U.S. Food and Drug Administration (FDA),[6] but the categories "1 month -< 2 years" and "2 -<

12 years" were split because of the heterogeneity within these age groups.[7] Age groups used were: 0 -< 1 month; 1 -< 6 months; 6 months -< 2 years; 2 -< 6 years; 6 -< 12 years; 12 years and older.

We used a classification system largely adapted from the work of Choonara *et al.* to facilitate comparison.[8] We classified prescriptions into two main categories: licensed and unlicensed. The unlicensed category consisted of three separate groups: (1) Drugs that were contraindicated for use in children, (2) drugs preparations that were (a) manufactured (home label medications) or (b) modified by the hospital pharmacy, and (3) drugs that had an information text without dosage guidelines in children. All prescriptions that were formally licensed in children were analyzed for off-label use. The off-label category included all prescriptions that had a discrepancy with the information text for age (or weight), daily dosage and frequency, dosage form, route of administration, indication, or contraindication against use in a particular patient (e.g. use of ß-blockers in children with asthma). Some prescriptions were classified off-label for more than one reason.

As a reference source, we used the product information texts of the prescribed drugs, as provided by the Dutch Medicines Evaluation Board.

Analysis

All 1017 prescriptions were analyzed for unlicensed and off-label drug prescription by comparing each to the official labeling information text of the drug. Descriptive analyses were conducted for patient demographics, prescription data, and outcomes. Statistical comparison consisted of standard t-tests and Chi square-tests. All prescriptions were analyzed by two researchers independently; consensus was reached in all cases.

Results

All 293 patients (53% male) hospitalized between March 1, 2000 and July 11, 2000 were studied (Table 1). The age of the patients ranged between 0 days and 16.7 years, with a median of 0.9 years [Interquartile range (IQR); 0 - 6.2 years]. Duration of inpatient hospitalisation ranged between 1 and 79 days, with a median of 5 days [IQR 2-10]. Of all patients, 291 were discharged before the end of the study period. Most common reasons for admission were prematurity (n=30), apnea (n=27), sepsis (n=23), convulsions / epilepsy (n=12), pneumonia (n=12), dehydration (n=11), appendicitis (n=11) and constipation (n=9).

Table 1 Patient characteristics for the age groups, defined at the admission date of the patient to the pediatric ward or neonatology unit of the hospital.

Variable	Patients * (n=293)		Hospitalisation days ** (n=2551)		Prescriptions (n=1017)	
Age groups (%)						
0 -< 1 month	97	(33)	1 232	(48)	343	(34)
1 -< 6 months	34	(12)	448	(18)	175	(17)
6 months -< 2 years	43	(15)	189	(7)	129	(13)
2 -< 6 years	43	(15)	267	(10)	167	(16)
6 -< 12 years	43	(15)	199	(8)	105	(10)
12 years and older	33	(11)	216	(8)	98	(10)

* The age group indicates the age on the date of admission.

** The number of days patients were in a certain age group. Eighteen patients became 1 month old while in hospital.

Table 2 Number of prescriptions used in each licensing category

Category	Reason for unlicensed or off -label prescription	n=1017	
Licensed in children		289	(28.4%)
Off label [o]	Age/weight	161	(15.8%)
	Dose	248	(24.4%)
	Indication	25	(2.5%)
	Route of administration	1	(0.1%)
	Dosage form	3	(0.3%)
	Contraindicated	5	(0.5%)
Total off-label		*443*	*(43.6%)*
Unlicensed in children	**No information on use in children** [s]	37	(3.6%)
	Contra-indicated [r]	2	(0.2%)
	Modified preparation *	188	(18.5%)
	Manufactured by the hospital pharmacy	58	(5.7%)
	New drugs	0	(0.0%)
Total unlicensed		*285*	*(28.0%)*

[s] No information on use in children is found in any subsection of the product license
[r] The product license indicates that the drug is contraindicated for use in children
* The prescription is prepared by the pharmacy, and no official product license is available for this formulation
[o] As drugs in the off-label category can be classified under more than one of the six bullet points, totals add up to more than 1065 prescriptions

The patients received a total of 1017 prescriptions for 114 different drugs. The median number of prescriptions per patient was 3 (IQR 2-5). The most commonly administered drugs were acetaminophen (14%), cefotaxime (8%), amoxicillin (7%), caffeine (4%), and prednisolone (4%).

Two hundred and eighty nine (28%; 95%CI: 26-31) out of 1017 prescriptions were licensed drugs prescribed in a licensed way. In 728 (72%) of the prescriptions, drugs were either unlicensed (285; 28%), or drug prescriptions were off-label (443; 44%). Two hundred and sixty nine (92%) of all 293 patients received unlicensed drugs and/or off-label drug administrations. The hospital pharmacy manufactured 58 (6%) preparations ('home label medications'), and modified 188 (18%) preparations.

Most frequent reason for classifying 'unlicensed' was modification of the preparation by the hospital pharmacy (table 2). Off-label drug prescriptions were mostly off-label for dose, frequency and age or weight. On four occasions, a drug was prescribed 'as-needed'. We classified these prescriptions as 'licensed' if there were no other reasons for classifying the prescription unlicensed or off-label.

The three most commonly prescribed unlicensed and off-label drug prescriptions were acetaminophen, cefotaxime and amoxicillin (table 3). The use of acetaminophen in the age < 3 months was off-label for age, while above that age, off-label use was primarily related to the administered dose. The proportions in the mixture of salbutamol and ipratropium (and sometimes budesonide) into a single aerosol were determined individually, and preparations were separately made for each patient by the hospital pharmacy. The top-10 of unlicensed and off-label drug prescriptions

Table 3 Most frequently used unlicensed or off-label drug prescriptions

Drug	n (%)	Status
Acetaminophen	67 (7)	off-label for dose & frequenc y
	64 (6)	off-label for age/weight
Cefotaxime	46 (4)	off-label for dose & frequency
Amoxicillin	54 (5)	off-label for dose & frequency
Caffeine	40 (4)	manufactured or modified by the hospital pharmacy (UL)
Vitamin K	38 (4)	manufactured or modified by the hospital pharmacy (UL)
Cisapride	23 (2)	off-label for age/weight
Folic acid	21 (2)	manufactured or modifi ed by the hospital pharmacy (UL)
Ipratropium / salbutamol *	19 (2)	manufactured or modified by the hospital pharmacy (UL)
Salbutamol	17 (2)	off-label for age/weight
Budesonide	11 (1)	off-label for age/weight

UL = Unlicensed; * Ipratropium / salbutamol is a mixture of these two entities in a single aerosol

Table 4 Number of unlicensed and off-label drugs used within six age groups.

Variable	Unlicensed (n=285)	Off-label (n=443)	Total (n=1017)
Age groups (%)			
0 – < 1 month	128 (37)	176 (51)	343
1 – < 6 months	62 (35)	60 (34)	175
6 months - < 2 years	26 (20)	64 (50)	129
2 – < 6 years	24 (14)	72 (43)	167
6 – < 12 years	19 (18)	45 (43)	105
12 years and older	26 (27)	26 (27)	98

includes seven of the ten most frequently prescribed drugs.

The proportions of unlicensed and off-label prescriptions for each age group are shown in table 4. The number of home label medications and drugs modified by the hospital pharmacy (classified unlicensed) was much higher in newborns and small infants (0 -< 6 months); accounting for 35.2% of the prescriptions in these age groups, compared to 12.6% of the prescriptions in the older children. The number of patients receiving one or more unlicensed or off-label drug prescriptions is also higher in newborns and small infants; 98% of the patients in these age groups, compared to 88% in other children.

Discussion

This study shows that the extent of unlicensed and off-label drug prescribing is high in the setting of a general hospital. Our results disclosed that 28% of all prescriptions given during the study period were for unlicensed drugs, and 44% were off-label prescriptions. Even larger proportions of unlicensed and off-label drug prescribing were found in newborns and infants.

When comparing results of this study to the results of the other studies that surveyed unlicensed and off-label drug use, we saw a higher percentage of unlicensed and off-label drug use than in studies by Choonara *et al.*,[9-12] This is related to a much higher use of preparations manufactured or modified by the hospital pharmacy (24%) in our study. We also saw a higher proportion of unlicensed and off-label drug use than in our study in an academic children's hospital in the Netherlands.5 Despite the fact that academic children's hospitals often give specialized care to patients with rare diseases, unlicensed and off-label prescription of drugs was not lower in a general hospital. A high number of drug prescriptions were unlicensed because of modification or manufacturing by the hospital pharmacy (246). Due to a lack of flexible pediatric formulations, and a lack of drugs properly licensed for newborns and infants, hospital pharmacies are often obliged to adapt preparations to individual needs, or manufacture drugs that are not commercially available.

No conclusions can be drawn from the results regarding health risks for the exposed group of children. There is, however, a large suspicion of a higher risk for adverse drug reactions (ADRs) in children who receive unlicensed or off-label drug prescriptions.[13] Furthermore, it is important to recognize, that off-label or unlicensed use of a drug does not necessarily reflect inaccurate use (because of reasonable research based foundations). It may be judged as such, however, when the liability of the physician is questioned in court. In our pediatric wards, most drug use is based either on long-standing experience or evidence obtained from the literature. The majority of drugs are prescribed within established protocols. However, not the same standards of efficacy and safety can be applied as for the adult population.[13]

We support the FDA's Pediatric Rule, which states that new drug applications should contain data to support the use in all relevant patient populations (children in different age groups included), although we recognize important insufficiencies in the Rule.[14 15] We want to emphasize the need to include paediatric information in the labeling of new drug entities as early as possible. Most often, pre-marketing pediatric labeling will not be possible, but direct post-marketing involvement and development of safe, efficient and qualitative research methods will be essential to avoid unnecessary involvement of too large groups of patients, maladaptation of adult pharmacokinetics and uselessness of results due to poor study design, which is often a result of a lack of experience in pediatric drug studies.

The FDA's new proposed 'requirements on content and format of labeling for human prescription drugs and biologics' [16] contain important improvements in the information provided in the labeling information text regarding pediatric use. The European Medicines Evaluation Agency (EMEA)[17] is also actively involved in the development of better regulations for pediatric pharmacology, but the effectiveness of these measurements is questionable.[18 19]

Recent developments in the UK,[20] and Europe[21] regarding improvement of the current situation are promising, but safe and efficient drug therapy is still a long way ahead. Corporate initiation and funding - by the EU and US - of pediatric pharmacological research on new as well as older drugs, and globalization of labeling requirements and content and format of labeling information texts, might seem unreachable in the near future. Nevertheless, we have an obligation to seriously investigate every possibility to reverse this highly unfortunate situation in which progress of medical care is not available for our children.

References

1. t Jong GW, Eland IA, Stricker BHC, Anker JN vd. Information for paediatric use of medicines in a product information compendium. Paediatric and Perinatal Drug Therapy 2001;4:148-51.
2. Nahata MC. Lack of pediatric drug formulations. Pediatrics 1999;104:607-9.
3. Choonara I, Dunne J. Licensing of medicines. Arch Dis Child 1998;78:402-3.
4. Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates. A quiet frontier. Clin Pharmacokinet 1992;23:1-9.
5. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, Anker JN vd. Survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001;108:1089-93.
6. Guidance for industry; Content and format for pediatric use supplements. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Washington, 1996:1-6.
7. Nahata MC. New regulations for pediatric labeling of prescription drugs. Ann Pharmacother 1996;30:1032-3.
8. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
9. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of "off-label" and unlicensed drugs in paediatric intensive care unit [letter]. Lancet 1996;347:549-50.
10. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. Bmj 1998;316:343-5.
11. Conroy S. Development in relation to unlicensed and off label drug use. Paediatric and Perinatal Drug Therapy 1998;2:23-26.
12. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80:F142-4.
13. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. Acta Paediatr 1995;84:438-41.

14. The Pediatric Exclusivity Provision. January 2001 Status Report to Congress. Department of Health and Human Services. U.S. Food and Drug Administration, 2001.
15. t Jong GW, Anker JN vd, Choonara I. FDAMA's written request list: medicines for children. Lancet 2001;357:398.
16. Federal Register 21 CFR Part 201. Requirements on content and format of labeling for human prescription drugs and biologics: Requirements of prescription drug product labels; proposed rule. EMEA, 2000.
17. Herxheimer A. The European Medicines Evaluation Agency. BMJ 1996;312:394.
18. Kmietowicz Z. Drug industry is unwilling to run trials in children. BMJ 2000;320:1362A.
19. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. Br J Clin Pharmacol 1999;48:15-8.
20. Choonara I. Clinical trials of medicines in children. Us experience shows how to ensure that treatment of children is evidence based. BMJ 2000;321:1093-4.
21. Anker JN vd, Choonara I. ENDIC - European Network for Drug Investigation in Children. Peadiatric and Perinatal Drug Therapy 1999;3:15-16.

Chapter 2.3

Unlicensed and off-label drug use in pediatric wards in European countries

To determine the extent of use of unlicensed and off-label drugs in children in hospital in five European countries, we conducted a prospective study of drugs administered to children in general pediatric medical wards over four weeks in pediatric wards in five hospitals (one each in the United Kingdom, Sweden, Germany, Italy, and the Netherlands). For all children aged 4 days to 16 years admitted to general pediatric medical wards, the proportion of drugs that were used in an unlicensed or off-label manner was determined. 2262 drug prescriptions were administered to 624 children in the five hospitals. Almost half of all drug prescriptions (1036; 46%) were either unlicensed or off-label. Of these 1036, 872 were off-label and 164 were unlicensed. Over half of the patients (421; 67%) received an unlicensed or off-label drug prescription. Use of off-label or unlicensed drugs to treat children is widespread. This problem is likely to affect children throughout Europe and requires European action.

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Introduction

Many drugs used to treat children in hospital are either not licensed for use in children or are prescribed outside the terms of their product license (off-label prescribing).[1,2] Examples of use of off-label drugs include diazepam rectal solution in children under 1 year (not licensed for age group), amiloride tablets in any children (formulation), or rectal injection of lorazepam for a child with an acute seizure (route). An example of unlicensed use is the preparation of a suspension from a tablet by the hospital pharmacy.

Considerable concern exists within Europe[3] and the United States[4,5] about the use of unlicensed and off-label drugs in children. There is, however, little information available on the extent to which these types of treatments are used.

The extent of use of unlicensed and off-label drugs in the United Kingdom has been reported in a pediatric intensive care unit,[6] pediatric medical and surgical wards,[2] and a neonatal intensive care unit.[7] We wished to determine the extent of unlicensed and off-label drug use in several countries within the European Union. This is important in view of the new European guidance on the clinical investigation of medicinal products in children.[8]

Methods

We studied a pediatric medical ward in each of the participating centers (Derby, United Kingdom; Uppsala, Sweden; Marburg, Germany; Bergamo, Italy; Rotterdam, Netherlands) prospectively for four consecutive weeks during 1998. The wards in Derby and Bergamo admitted mainly general pediatric patients, with Derby including children who had had surgery. The wards in Marburg and Uppsala had a mixture of general pediatric and respiratory cases (including cystic fibrosis). The ward in Rotterdam had the fewest general pediatric cases, containing children with cardiac, oncological, renal, and respiratory disease.

Data on all patients admitted to the ward were collected by the investigator in each center. The child's age, date of birth, weight, and diagnosis were recorded as well as details of all drugs administered (route of administration, dose, and indication for use). We did not include standard intravenous replacement solutions, flushes of 0.9% sodium chloride or heparin, blood products, oxygen, or drugs in clinical trials.

We assessed all drugs administered to determine if their use was unlicensed and off-label using a previously described classification system.[1,2] Categories of unlicensed use were modification of licensed drugs (such as crushing tablets to prepare a suspension); drugs that are licensed but the formulation is manufactured under a special license (such as a liquid preparation of a drug that is licensed only in tablet form); new drugs available under a special manufacturing license (such as caffeine injections for apnoea of prematurity); use of chemicals as drugs when no pharmaceutical grade preparation is available; drugs used before a license has been granted; and imported drugs (drugs imported from a country where they are licensed). Off-label use included use of a drug in situations not covered by the product license or the summary of product characteristics; that is, at a different dose or frequency, in different clinical indications, in different age groups, administration by an alternative route, or in a for-

mulation not approved for use in children.

The primary reference sources for determining licensed indications were the Association of the British Pharmaceutical Industry's Data Sheet Compendium in the United Kingdom; the Swedish Physician's Desk Reference 1998 in Sweden; the Rote Liste 1996 and FachInfo compact disc (1997) in Germany; the Informatore Farmaceutico 1998 (national formulary) and technical leaflets in Italy; and the Repertorium 98/99 and Farmacotherapeutisch Kompas 1998 in the Netherlands.

Results

A total of 624 children were admitted to the general pediatric wards in the five participating centers and received 2262 drug prescriptions (Table 1). The prescribing habits in the five centers differed greatly. Paracetamol was the most widely prescribed drug and analgesic in four of the five centers. Dipyrone was frequently used in Italy only. Salbutamol and cefuroxime were both widely used (Table 2). Almost half of all drug prescriptions (1036) were either unlicensed or off-label (Table 1). Many more prescriptions were off-label (872) than unlicensed (164). The results were remarkably similar in Derby, Uppsala, and Marburg. Use of unlicensed and off-label drugs was greatest in Bergamo and Rotterdam, with Bergamo having the highest percentage of off-label prescriptions (66%) and Rotterdam the highest percentage of unlicensed prescriptions (14%).

Over half of the children (421; 67%) received an unlicensed or off-label drug prescription during their stay in hospital. Analgesics and bronchodilators were among the

Table 1 Patients and prescriptions in each center

	Derby		Uppsala		Marburg		Bergamo		Rotterdam		Total	
Patients	192		87		85		118		142		624	
Age range	21 days - 16 years		4 days - 15 years		28 days - 16 years		30 days - 12 years		4 days - 16 years		4 days - 16 years	
Prescriptions (mean)	798	(4.2)	185	(2.1)	224	(2.6)	398	(3.4)	657	(4.6)	2262	(3.6)
Unlicensed	58	7%	8	4%	8	4%	1	0%	89	14%	164	7%
Off-label	181	23%	49	26%	83	37%	263	66%	296	45%	872	39%
Patients receiving unlicensed or off-label prescription	109	57%	37	43%	46	54%	101	86%	128	90%	421	67%

Table 2 Five most frequently prescribed drugs in each center

	Derby	Uppsala	Marburg	Bergamo	Rotterdam
	Drug (%)	**Drug (%)**	**Drug (%)**	**Drug (%)**	**Drug (%)**
1st	Paracetamol (21)	Paracetamol (22)	Paracetamol (9)	Beclometazone (12)	Paracetamol (4)
2nd	Ibuprofen (10)	Cefuroxime (8)	Cholecalciferol (8)	Dipyrone (8)	Heparin (4)
3rd	Salbutamol (5)	Salbutamol (7)	Cefuroxime (7)	Salbutamol (8)	Amphotericin (3)
4th	Cyclizine (5)	Ibuprofen (6)	Salbutamol (7)	Paracetamol (7)	Pancreatin (2)
5th	Morphine (4)	Cotrimoxazole (5)	Xylometazoline (5)	Amoxycillin (6)	Spironolactone (2)

Table 3 Five most frequently prescribed off-label drugs in each center

	Derby		Uppsala		Marburg		Bergamo		Rotterdam	
	drug	**No***	**Drug**	**No***	**Drug**	**No***	**Drug**	**No***	**Drug**	**No***
1st	Cyclizine	38/42	Salbutamol	13/13	Budesonide	10/12	Beclomethasone	47/47	Heparin	28/28
2nd	Salbutamol	27/42	Paracetamol	13/41	Salbutamol	8/17	Salbutamol	28/32	Pancreatin	17/17
3rd	Morphine	26/33	Cotrimoxazole	4/10	Xylometazoline	8/15	Paracetamol	26/28	Spironolactone	17/17
4th	Ipratropium	15/15	Betamethasone	3/5	Paracetamol	7/20	Betamethasone	21/38	Frusemide	16/16
5th	Diazepam	13/13	Acetylcysteine	2/4	Chloral Hydrate	5/5	Amoxycillin	18/23	Tobramycin	15/16

* Number of off-label prescriptions / total number of prescriptions of drug in center

Table 4 Number of off-label prescriptions in each off-label subcategory

Category	Derby		Uppsala		Marburg		Bergamo		Rotterdam	
Age	79	(39%)	53	(88%)	23	(24%)	255	(58%)	18	(6%)
Dose & frequency	66	(32%)	1	(2%)	59	(61%)	33	(7%)	96	(31%)
Indication	36	(18%)	4	(7%)	7	(7%)	25	(6%)	13	(4%)
Route of administration	24	(12%)	2	(3%)	3	(3%)	49	(11%)	4	(1%)
Formulation	0	(0%)	0	(0%)	5	(5%)	80	(18%)	176	(57%)
Total	205		60		97		442		307	

Table 5 Examples of off-label use

Drug	Off-label use
Beclomethasone	Used in infants under 12 months. Licensed for 2 years and over in Italy
Fluticasone	250 l g twice daily in 4 year old. Maximum dose 100 l g twice daily
Trimeprazine	Used as sedative in child with pneumonia. Licensed fo r urticaria, pruritus, and pre -anaesthetic medication
Rifampicin	Used for enzyme induction in infant with biliary atresia
Salbutamol	Used two hourly (12 times daily). Licensed for 4 times daily
Tobramycin	Used once daily in neonate. Licensed for twic e daily

five most frequently prescribed off-label drugs in four centers (Table 3). The commonest category of off-label drug use was dose and frequency in three centers (Uppsala, Marburg, and Bergamo), accounting for more than half of off-label use. In the other two centers (Derby and Rotterdam) dose and frequency accounted for 31-32% of off-label drug use. The main category for off-label drug use in Rotterdam was formulation. Formulation was also an important category in Bergamo but not in the other centers. Age was the commonest category of off-label drug use in Derby (Table 4). Table 5 shows examples of off-label drug use.

In Bergamo, 53% of the children who received beclomethasone were under 12 months old, although it is licensed only for children aged 2 years and over in Italy.

Discussion

The drug use in the five pediatric wards differed. This is not surprising as each of the wards had different subspecialty interest and prescribing habits are different within each country.[9] Unlicensed drug use was highest in Rotterdam, which had the highest number of patients with complex diseases. Many of these children received drugs that are not available in a pediatric formulation and therefore had to be modified by the pharmacy department to make them suitable for administration to children. Stability data are rarely available for such products, which are rendered unlicensed by this modification. Dipyrone is no longer available in many European countries because of the risk of agranulocytosis.[10] It is, however, widely used in Italy. About half of the children in each of the five countries received drugs that are either unlicensed or off-label.

It is concerning that most bronchodilator drug prescriptions for children in hospital with asthma are off-label, since this is a common condition for which there has been considerable research. The efficacy of bronchodilators in children under the age of 2 years is variable, especially in infants under the age of 12 months. A particular problem was the widespread use of inhaled corticosteroids in children under the age of 2 years (off-label for age and dose); few data exist on the effect of inhaled corticosteroids on growth suppression in this age group. Studies are required to determine whether the off-label use of bronchodilators is justified by good scientific evidence.

The most common reasons for off-label use were that the medicine was prescribed at

a different dose or frequency, in a different formulation, or in an age group for which it had not been licensed. There were also some children who received the drug for a different indication or by an alternative route. It is ironic that it is children who are most likely to receive medicines that are either unlicensed or used off-label since the regulations for the licensing of medicines were introduced after cases of drug toxicity in the developing fetus (thalidomide) and newborn infant (chloramphenicol induced grey baby syndrome).[3]

Not all off-label drug use is inappropriate. Drug toxicity is more likely with aminoglycosides if they are used in neonates as recommended by the manufacturers at intervals of 8-12 hours rather than at longer intervals. In many cases, however, the risk of off-label drug use is not known because there are inadequate data. A recent study has shown that adverse drug reactions are an important problem in children after unlicensed or off-label drug prescriptions.[11]

The new European guidance on the clinical investigation of medicinal products in children encourages pharmaceutical companies that wish to introduce new products to investigate these in children when clinically appropriate. Changes have also been made in the United States to encourage pharmaceutical companies to carry out clinical trials in children. These changes in regulations may improve knowledge for new products, although a recent study found little improvement in new drugs licensed in Europe.[12] However, a major problem remains with many existing drugs commonly used in children. Health professionals concerned about the lack of information regarding the use of drugs in children are in a difficult situation. They need to raise awareness of the problem in society as a whole without causing undue anxiety among parents. To ensure that children are not exposed to unnecessary risks, controlled clinical trials are required to determine the most appropriate dose in children of different ages. A mechanism and infrastructure needs to be established to determine who will fund these trials. The European Network for Drug Investigation in Children has been established to try to improve this situation.[13] We feel that the European Union, national departments of health, and politicians as well as the European Medicines Evaluation Agency must take a more proactive role in getting drugs tested in children. If they fail to do so, children will continue to be denied the same rights as adults in relation to receiving treatment with drugs that have been fully tested.

References

1. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
2. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998;316:343-5.
3. Choonara I, Dunne J. Licensing of medicines. Arch Dis Child 1998;78:402-3.
4. Nahata MC. Licensing of medicines for children in the USA. Paediatric and Perinatal Drug Therapy 1997;1:50-51.
5. Cote CJ, Kauffman RE, Troendle GJ, Lambert GH. Is the "therapeutic orphan" about to be adopted? Pediatrics 1996;98:118-23.
6. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of "off-label" and unlicensed drugs in paediatric intensive care unit. Lancet 1996;347:549-50.
7. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80:F142-4.
8. European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit; Committee for Proprietary Medicinal Products. Note for Guidance on Clinical Investigation of

Medicinal Products in Children. EMEA, 1997.
9. Bonati M. Epidemiologic evaluation of drug use in children. J Clin Pharmacol 1994;34:300-5.
10. Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. The International Agranulocytosis and Aplastic Anemia Study. JAMA 1986;256:1749-57.
11. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 1999;88:965-8.
12. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. Br J Clin Pharmacol 1999;48:15-8.
13. Bonati M, Choonara I, Hoppu K, Pons G, Seyberth H. Closing the gap in drug therapy. Lancet 1999;353:1625.

Chapter 3
Drug prescribing in the general population

Chapter 3.1

Drugs prescribed to children in the general population

To describe the pattern of drug prescribing to children in the general population, we conducted a population-based cohort study in the Integrated Primary Care Information (IPCI) project, a prospectively gathered, automated general practitioners database in the Netherlands. All patients under 17 years of age, who were actively registered in the IPCI database, were followed for one life year during the period 1998-1999. Prescription patterns were assessed by age and gender. Drug use was unevenly distributed; 50.7% of the population received at least one prescription but 10% of the population received 50% of all drug prescriptions. Drugs were prescribed in 46.5% (95%CI: 46.2-46.8) of consultations. The proportion of drug users decreased from 73.9% (95%CI: 72.0-75.8) among 0-year-olds to 41.1% (95%CI: 40.3-41.8) in children between 8 and 13 years of age, and increased again to 57.1% (95%CI: 55.1-59.0) in 16-year-olds. Overall, the most frequently used drug types were systemic antibiotics, drugs for dermatological use, and respiratory drugs. This study showed that drug use is most extensive in children below two years of age, the age group for which least drugs are licensed.

Introduction

Drug consumption among children has been examined in only few studies.[1] Available reports have described drug utilization in hospital wards,[2-4] in hospital outpatients,[5] and prescribing by non-hospital based physicians.[6-10] Population-based information from primary care physicians, who in various countries deal with most of the health problems, is scarce. Recently, Madsen *et al.* [10] described pediatric drug utilization by means of the defined daily dose (DDD) method.[11] Although this DDD method is a useful tool for comparison of drug use between countries it does not allow for estimation of the actual prevalence or incidence of use in children since the defined daily dose is established only for adults. To obtain better insight into the prevalence of drug use in children we conducted a large cohort study in general practice.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with data from computer-based patient records of a group of 150 general practitioners (GPs) in the Netherlands. The GP plays a pivotal role in the Duch system of health care, specialists report their findings to the GP, who acts as a gatekeeper of medical care and information. Approximately 90% of the problems of the patient are addressed by the GP. Medical care, including prescription drugs, is essentially paid for by a combination of public (60%) and private insurers (40%). The type of insurance can be used as proxy for socio-economic status since publicly insured persons in general have wages less than 25,000.

The IPCI database is maintained by the department of Medical Informatics of the Erasmus Medical Center Rotterdam (EMCR) since 1992, and contains coded and anonymous data on gender, age, symptoms, diagnoses and findings, and on prescriptions, their indications and dosage regimen. Summaries of hospital discharge letters and information from clinical specialists are included as free text. Patient complaints and diagnoses are available both as free text and coded according to the International Classification for Primary Care (ICPC).[12] Prescription drugs are coded according to the Anatomical Therapeutic Chemical classification (ATC).[11] The data are entered and stored directly by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who ensures anonymity of the GP before further access is provided. To maximize completeness of information, GPs participating in the IPCI project are not allowed to maintain a system of paper records besides the electronic medical records. As of 2001, the IPCI database contains data on a cumulative number of approximately 500,000 patients. The system complies with European Union guidelines on the use of medical data for medical research and has proven valid for pharmaco-epidemiological research.[13]

Design

We conducted a population-based fixed cohort study in a dynamic source population of children, aged under 17 years, who were actively registered with one of the IPCI general practices. Each subject was followed for a fixed period of one year starting

from his birthday in 1998. For the final study population we retrieved all pharmacological prescriptions plus dosage regimens and indications written by the general practitioner during the follow-up period. Drugs were classified in broad groups according to the first position of the ATC-code, and in specific drug classes according to the first five positions of the ATC-code.

Analysis

For all subjects we determined the number of drug prescriptions and GP visits during the one year follow-up. Age was classified into groups: 0 - < 6 months; 6 - < 24 months; 2 - < 6 years; 6 - < 12 years; 12 years and older based on age at baseline except for 0 - 6 and 6 - 24 months old. Neonates contributed only 6 months to the 0 - 6 months category and then switched to the 6 - 24 months category. The prevalence of drug use was estimated per age group by dividing the number of users of certain classes of drugs by the number of persons in a specific age group. Ninety-five percent confidence intervals around prevalence estimates were based on the normal distribution. Chi-square statistics were used for comparisons of discrete variables.

Population characteristics

Results

The study population comprised 46,458 children (51.1% male, median age 8), who were all followed for one year. The insurance status was Sickfund for 49.5% (low status), and private insurance for 47.5% (intermediate / high status), as show in table 1. Of all children 66.8% consulted their GP at least once during the year (total number of consultations =101,833). The median number of consultations was 1 (interquartile range 0-3), with a mean of 2.2. The consultation frequency varied largely with age, the mean number of visits was 4.5 per year for 0-year-olds and then decreased quickly to 1.5 per year for 10- to 12-year-olds. For 16-year-olds the consultation frequency increased slightly to 2.5 visits per year. The percentage of females (68.0%) who had visited the GP during follow-up was significantly higher than the number of males (65.6%, p<0.001).

During the study period 73,051 pharmacological prescriptions were issued to the study population. Drug use was unevenly distributed; 50.7% of the population received at least one prescription (Table 1) but 10% of the population received 50% of all drug prescriptions. The proportion of drug users decreased from 73.9% (95%CI: 72.0-75.8) among 0-year-olds to 41.1% (95%CI: 40.3-

Table 1 Characteristics of study population

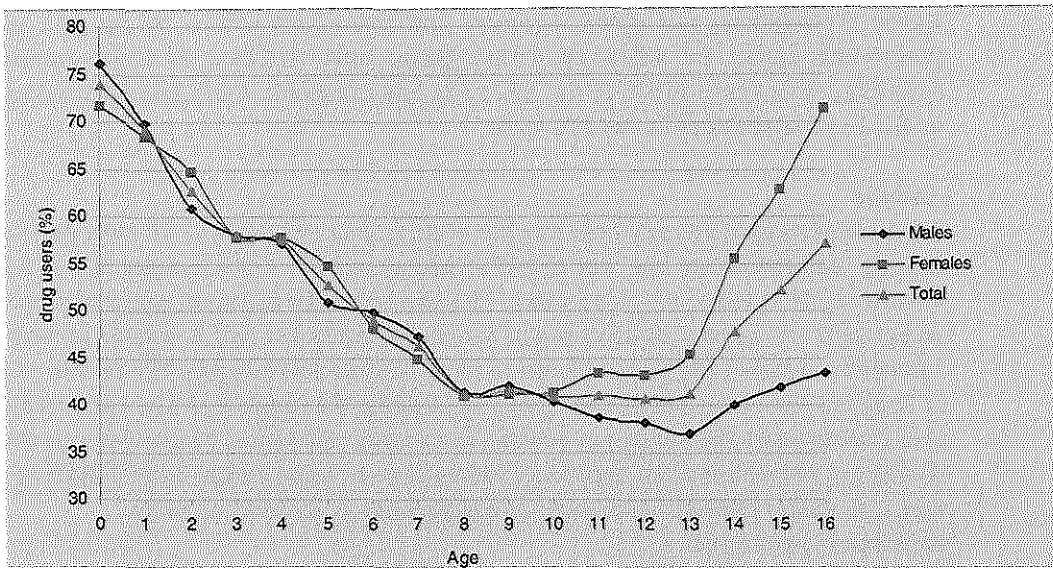
Variable	Total (n=46,458)	
Gender		
Male	51.1	
Female	48.9	
Age (IQR)	8	(4-12)
0 -< 6 months (%)	4.3	
6 -< 24 months (%)**	9.8	
2 -< 6 years (%)	24.1	
6 -< 12 years (%)	37.6	
≥ 12 year (%)	28.4	
*Insurance status**		
Sickfund (%)	49.5	
Private insurance (%)	47.5	
Unknown / Missing (%)	3.0	
Consultations (median [IQR])	1	[0 – 3]
0 (%)	33.2	
1-3 (%)	44.7	
4-6 (%)	11.5	
7-9 (%)	5.3	
10 and more (%)	5.3	
Prescriptions (median [IQR])	1	[0 – 2]
0 (%)	49.3	
1 (%)	18.1	
2-3 (%)	22.6	
4 and more (%)	10.0	

IQR = Interquartile range

* The insurance status of patient is used as a measure for socio-economic status (SES)

** Persons who start between 0-6 months of age can contribute to two age categories

Figure 1 Gender and age specific one-year prevalence of drug use



41.8) in children between 8 and 13 years of age, and increased again to 57.1% (95%CI: 55.1-59.0) in 16-year-olds (Figure 1). We did not observe gender differences in overall drug use for the younger age groups. In the older age groups however, differences did appear, accumulating to 71.3% (95%CI: 68.7-73.8) of 16-year-old females received prescriptions and only 43.4% (95%CI: 40.7-46.1) of 16-year-old males ($p < 0.001$). Drugs were prescribed in 46.5% (95%CI: 46.2-46.8) of consultations but this proportion varied from 40.4% for neonates (who had a high consultation rate) up to 49.1% for one-year olds, and 55.0% for 16-year olds.

Utilization by drug class

The most frequently prescribed drug groups were dermatological preparations (year prevalence of use: 23.4%, 95%CI: 23.1-23.8), respiratory drugs (year prevalence of use: 20.7%, 95%CI: 20.3-21.0), systemic antibiotics (year prevalence of use: 16.0%, 95%CI: 15.7-16.4) and analgesics (year prevalence of use: 7.8%, 95%CI: 7.5-8.0). Table 2 shows the prevalence rates for the most frequently used drug classes. The prevalence estimates for specific drug classes were highest for broad-spectrum penicillins (9.0%), acetaminophen (5.9%), respiratory sympaticomimetics (4.8%), antiallergic drugs (excl. corticosteroids) (4.8%), corticosteroids (inhalers) (4.4%) and antihistamines for respiratory use (3.9%).

Utilization by age and gender within drug classes

Prescription rates for each age group are shown in table 3, as well as the most frequently prescribed drug classes by age category. In neonates (0 - 6 months), use of drugs for the gastro-intestinal tract and metabolism was much higher than in the other groups. Candida albicans infections (neonatal sprue; miconazole and nystatin), vitamin K deficiency and gastro-esophagal reflux (cisapride) were the most common indications. In adolescents (12 years and older), we observed a relatively high use of NSAIDs such as ibuprofen and naproxen, antiallergic drugs (eyes) and oral contra-

Table 2 One-year prevalence of use of the most frequently prescribed drugs by drug class

Drug class	Number of users	Prevalence of use (%)	% Males	Mean age (SD)
Systemic antibiotics				
Broad-spectrum penicillins	4178	9.0	49	5.3 (4.1)
Macrolides	1545	3.3	51	5.3 (4.4)
Combination of penicillins and enzyme inhibitors	940	2.0	52	6.1 (4.4)
Beta-lactamase-sensitive penicillins	829	1.8	49	8.3 (4.9)
Tetracyclines	292	0.63	47	15.2 (1.7)
Drugs for dermatology				
Imidazole-derivates (e.g. miconazole)	1889	4.1	44	7.3 (5.5)
Other local antibiotics (e.g. fusidic acid, choramphenicol)	1380	3.0	52	7.3 (4.5)
Corticosteroids (class I)	1327	2.9	46	6.8 (4.9)
Corticosteroids (class II)	971	2.1	47	8.5 (5.0)
Other emolientics and protectives (e.g. vasilin)	794	1.7	53	15.2 (1.7)
Respiratory drugs				
Anti-allergic drugs (excl. corticosteroids)	2228	4.8	58	7.6 (4.5)
Sympaticomimetics (res piratory)	2227	4.8	50	6.8 (4.7)
Corticosteroids (inhalers)	2032	4.4	57	7.4 (4.5)
Other antihistamines for systemic use (e.g. deptropine)	1824	3.9	52	7.7 (5.3)
Fenothiazine-derivates (e.g. promethazine)	1055	2.3	54	6.4 (3.9)
All other ATC groups				
Paracetamol / Acetaminophen	2725	5.9	52	5.8 (4.4)
Antibiotics (eye)	1446	3.1	49	5.6 (5.1)
Propulsives (e.g. domperidon)	1029	2.2	48	6.3 (4.9)
Estrogens with progestagens	911	2.0	0	15.7 (1.2)
Corticosteroids with antimicrobiological agents (ear)	833	1.8	53	7.7 (4.4)
Osmotic laxantives	665	1.4	48	5.1 (4.0)

ceptives. Of females of 14 years and older, 30% used an oral contraceptive during the study period.

Drugs for dermatological use were widely used in all age groups. Topical drugs for acne were frequently used in adolescence, but topical corticosteroids were prescribed to both young and older children. The proportion of females using dermatological drugs was significantly higher than the proportion of males ($p < 0.001$), which was entirely attributable to the 12 - 16 year olds.

Twelve out of 40 most frequently prescribed drug classes were respiratory drugs. Users were predominantly males. Among anti-asthmatics, fixed combinations of sympaticomimetics and other anti-asthmatics, parasympathicolytics (ipratropium) and selective beta-2-sympathicomimetics (e.g. salbutamol) were predominantly prescribed to children less than five years of age; respectively 74, 73 and 80 percent. The most common indication for prescription of these medications was asthma (71%), followed by acute bronchitis / bronchiolitis (8%), and coughing (7%).

Systemic antibiotic use was highest in preschoolers; 50% of all prescriptions for antibiotics were issued to children under 5 years of age. Overall use was highest in 1-year-olds, with another peak at four years of age, which was related to acute tonsillitis. Most common indications for antibiotics were acute otitis media / myringitis (18%), acute bronchitis / bronchiolitis (14%), acute upper airway infections (8%), acute tonsillitis (7%), acute and chronic sinusitis (5%) and cystitis / urinary tract infections (5%). For the latter two indications, systemic antibiotics were predominantly prescribed to females (58 and 87 percent, respectively). Broad-spectrum penicillins were most frequently prescribed under 3 years of age (40%), tetracyclines on the other hand were mostly prescribed above 12 years of age (94%), mostly for the treatment of acne (38%), acute sinusitis (24%), and acute bronchitis / bronchiolitis (9%).

Analgesics for children consisted primarily of acetaminophen (paracetamol; 85%), as

Table 3 Prescription rate per year for each age group and the top-5 of drug classes used plus the most utilized individual drug in each class

Age group		0 -< 6 months	6 -< 24 months	2 -< 6 years	6 -< 12 years	12 years and older
Prescriptions		1.14	1.36	1.45	1.16	1.52
Males		1.21	1.44	1.48	1.22	1.13
Females		1.07	1.29	1.43	1.10	1.92
Top-5 of drugs used	1	A07AC	J01CA	J01CA	R03BA	G03AA
in age group (example)		(miconazole)	(amoxicillin)	(amoxicillin)	(beclomethasone)	(oral contraceptives)
	2	D01AC	N02BE	N02BE	R03AC	R03AC
		(miconazole; topical)	(paracetamol)	(paracetamol)	(salbutamol)	(salbutamol)
	3	S01AA	D01AC	R03BA	J01CA	R06AX
		(fusidic acid; eye)	(miconazole; topical)	(beclomethasone)	(amoxicillin)	(deptropine)
	4	A07AA	S01AA	R03AC	N02BE	D10AF
		(nystatin)	(fusidic acid; eye)	(salbutamol)	(paracetamol)	(clindamycin; topical)
	5	N02BE	R06AX	R01AA	R06AX	R03BA
		(paracetamol)	(deptropine)	(xylometazoline)	(deptropine)	(beclomethasone)

shown in table 2. Most common indications for prescription were acute otitis media / myringitis (27%), acute upper airway infections (17%), and fever (17%). Use of NSAIDs, including ibuprofen, and naproxen, was highest in adolescent females. Most common indications were menstrual pain (28%) and headaches (10%).

In general practice, the majority of drug prescription in children is restricted to a small group; 10% of the children accounts for 50% of drug prescriptions in one year. Most frequently prescribed drug classes were dermatologic preparations, respiratory drugs, systemic antibiotics and analgesics. Drug prescription varied highly with age and gender. In general, younger males and adolescent females consume most resources (prescriptions/consultations).

Other drug utilization studies in children have indicated similar prescription patterns. Although our population was restricted to 16 years of age, overall drug use was comparable between our study (50.7%) and two Danish studies in children 0 - 19 years of age (52.6% and 50.6% respectively).[10 14] Both studies showed a comparable peak in drug utilization among 1-year-olds, prescription rates of around 40% in 8 - 13 year olds, and systemic antibiotics, anti-asthmatics and drugs for dermatological use as most frequently used drugs. Thrane *et al.* also showed higher drug use in males under 10 year of age, but no significantly higher drug use in girls above 10 years of age (figure 1).[14] This may be related to the relatively high use of contraceptives by adolescent females in our population.

About forty-three percent of the most commonly prescribed drugs are systemic antibiotics and respiratory drugs; other studies in Denmark, Spain, Norway and the US showed similar numbers.[5 7 9 10] These drugs reflect treatment for the most common diagnoses among children in general practice, such as asthma, upper respiratory tract infections, lower respratory tract infections, otitis media, allergies, conjunctivitis and pneumonia.

Data on antibiotics are of special interest because of the environmental effects entailed in antibiotic overuse, mainly the introduction of bacterial resistance.15 Studies of antibiotic use among small children have shown a very high period prevalence, for example 79 percent in the first year of life in the US.[16] Only 25% of children received antibiotics in the first year of life, 34% of 1-year-olds and 28% of 2-year-olds which is lower than in Scandinavian studies.[10 14 17] Compared to the study by Bergus *et al.*,[16] we also found amoxicillin as the most frequently used drug (67%) among children under 20 months of age. Other frequently used antibiotics were macrolides (claritromycin, azitromycin; 15%) and amoxicillin clavulamic acid (12%), but almost none of the children received cephalosporines and sulphonamides. This underlines the restrictive antibiotic prescription in the Netherlands.

Discussion

In this study, we were interested in the general character and quality of drug prescription for children, while in other studies we specifically studied unlicensed and off-label drug use.[18] Several remarks related to the prescription patterns seen in this population are in place. Respiratory drug use was relatively high, when compared to other drug classes. Earlier research showed that off-label use of respiratory drugs is high, especially for anti-asthmatic use (e.g. corticosteroids and selective beta-2-ago-

nists), because of the 'high' minimum age indicated in the packet leaflet of these drugs. For example, 81% of prescriptions for ipratropium, a parasympathicolytic drug, was issued to children under six years of age, while the labeling of e.g. ipratropium provides no dosage recommendations for these children. Fluticasone, a corticosteroids used in asthma, is restricted to use in children from four years of age, while 25% of prescriptions were issued for children under four. Labeling information texts of many of the commonly used drugs for ophthalmologic use (i.e. fusidic acid, cromoglycate, and levocabastine), otological use (e.g. lidocaine, dexamethasone with framycetin and gramicidin) and respiratory use (i.e. terbutaline, cromoglycate) do not contain any information on use in children.[19]

Our study was conducted in a database with electronic medical records kept by general practitioners. In the Netherlands, most of the care (90%) is provided by the general practitioner, who also acts as a gatekeeper to secondary care. Specialists and hospitals inform the GP by letters, which are stored in the computer as free text. This means that we may miss specialist prescriptions, which will be more relevant to neonates, who are hospitalized more frequently. A second source of underestimation may be over the counter use of e.g. acetaminophen, which is frequently used as an antipyretic in the Netherlands. Finally, it should be noted that we analyzed drug prescriptions as opposed to drug dispensing; for that reason, we only approximate the actual drugs and dosing received.

Some commonly used drugs are not sufficiently studied regarding safety and efficacy, especially in younger age groups. The results of this study can be important for prioritizing the most essential drugs for pediatric development.

References

1. Bonati M. Epidemiologic evaluation of drug use in children. J Clin Pharmacol 1994;34:300-5.
2. Summers RS, Summers B. Drug prescribing in paediatrics at a teaching hospital serving a developing community. Ann Trop Paediatr 1986;6:129-33.
3. Mitchell AA, Lacouture PG, Shechan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. Pediatrics 1988;82:24-9.
4. Mitchell AA, Goldman P, Shapiro S, Slone D. Drug utilization and reported adverse reactions in hospitalized children. Am J Epidemiol 1979;110:196-204.
5. Olubadewo JO, Ikponmwamba A. Profile of prescription medication in a pediatric population. Drug Intell Clin Pharm 1988;22:999-1002.
6. Kennedy DL, Forbes MB. Drug therapy for ambulatory pediatric patients in 1979. Pediatrics 1982;70:26-9.
7. Sanz EJ, Bergman U, Dahlstrom M. Paediatric drug prescribing. A comparison of Tenerife (Canary Islands, Spain) and Sweden. Eur J Clin Pharmacol 1989;37:65-8.
8. Wessling A, Soderman P, Boethius G. Monitoring of drug prescriptions for children in the county of Jamtland and Sweden as a whole in 1977-1987. Acta Paediatr Scand 1991;80:944-52.
9. Straand J, Rokstad K, Heggedal U. Drug prescribing for children in general practice. A report from the More & Romsdal Prescription Study. Acta Paediatr 1998;87:218-24.
10. Madsen H, Andersen M, Hallas J. Drug prescribing among Danish children: a population-based study. Eur J Clin Pharmacol 2001;57:159-65.
11. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
12. Klinkman MS, Green LA. Using ICPC in a computer-based primary care information system. Fam Med 1995;27:449-56.
13. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
14. Thrane N, Steffensen FH, Mortensen JT, Schonheyder HC, Sorensen HT. A population-based study of

antibiotic prescriptions for Danish children. Pediatr Infect Dis J 1999;18:333-7.
15. Nyquist AC, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. Jama 1998;279:875-7.
16. Bergus GR, Levy SM, Kirchner HL, Warren JJ, Levy BT. A prospective study of antibiotic use and associated infections in young children. Paediatr Perinat Epidemiol 2001;15:61-7.
17. Rasmussen F. Use of antibiotics and prescription drugs in general during the first 9 years of life in a Swedish community. Paediatr Perinat Epidemiol 1988;2:346-58.
18. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, Anker JN vd. Survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001;108:1089-93.
19. t Jong GW, Eland IA, Stricker BHC, Anker JN vd. Information for paediatric use of medicines in a product information compendium. Paediatric and Perinatal Drug Therapy 2001;4:148-51.

Chapter 3.2

Unlicensed and off-label prescription of drugs to children in the general population

To determine the incidence and nature of unlicensed and off-label drug prescription to children in general practice in the Netherlands, we conducted a population-based cohort study in the setting of the Integrated Primary Care Information (IPCI) project, a prospectively gathered, automated general practitioners database in the Netherlands. All patients below 17 years of age, who were actively registered in the IPCI database during 1998 were selected. The study population consisted of a random sample of 25% of a potential source population of 53,706 patients. We evaluated all prescriptions given to the study population during 1998. A total of 17,453 prescriptions issued in 1998 to the study population were reviewed for unlicensed and off-label drug prescription. A total of 12,405 (71.1%) prescriptions concerned licensed drugs. Of the remaining 5048 prescriptions (28.9%), 2667 (15.3%) were prescriptions for unlicensed drugs, and 2381 (13.6%) were off-label prescriptions for licensed drugs. The one-year risk of an unlicensed or off-label prescription was 46% among children with at least one prescription. This population-based study showed that a large proportion of drugs prescribed by the general practitioner is unlicensed or licensed but prescribed in an off-label manner. Unlicensed and off-label drug prescription is therefore not limited to highly specialised pediatric clinical facilities, but also is an important issue in everyday pediatric care.

In press as:
Unlicensed and off-label prescription of drugs to children; population-based cohort study. t Jong GW, Eland IA, Sturkenboom MCJM, Anker JN vd, Stricker BHC. BMJ 2002

Introduction

Drugs are subject to licensing procedures to ensure their safety, efficacy and quality, but many drugs used to treat children in hospital are either not licensed ('unlicensed') or are prescribed outside the terms of the product license ('off-label').[1-5]
The extent and nature of unlicensed and off-label drug prescription in pediatric clinical care has been the subject of several surveys in Europe[1-7] and these consistently showed that a very large proportion of prescribed drugs are either unlicensed or used off-label. Little information is available about the situation in a general practice setting.[8,9] Only one single-practice study has been conducted so far, which showed 11% of drug prescriptions to be off-label or unlicensed.[9] We conducted a large cohort study in general practice by using computerised medical records available in the integrated primary care information (IPCI) database to assess the extent and nature of unlicensed and off-label drug prescription in children by general practitioners in the Netherlands.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with data from computer-based patient records of a group of 150 general practitioners (GPs) in the Netherlands. The database is maintained by the department of Medical Informatics of the Erasmus Medical Center Rotterdam (EMCR) since 1992, and contains coded and anonymous data on gender, age, unique patient identifier, practice, symptoms, diagnoses and findings, and on prescriptions, their indications and dosage regimen. Summaries of hospital discharge letters and information from clinical specialists are included as free text. Patient complaints and diagnoses are entered as text and coded according to the International Classification for Primary Care (ICPC).[10] Prescription drugs are coded according to the Anatomical Therapeutic Chemical classification (ATC).[11] The data are entered and stored directly by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who ensures anonymity of all information before further access is provided. To maximise completeness of information, GPs participating in the IPCI project are not allowed to have a system of paper records besides the electronic medical records. The IPCI database contains data on an accumulative number of 485 000 patients. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research.[12]

Design

We conducted a population-based cohort study in a dynamic population of children in the IPCI database who were permanently registered with one of the participating general practices between 1 January 1998 and 31 December 1998. In 1998, 53,702 children were registered in the IPCI database, for efficiency reasons we sampled 25%, which formed our final study population.
All subjects in the study population were followed from 1 January 1998 or date of

Table 1 Drug licensing categories

Category	Subcategory	Definition
Licensed in children		The drug is licensed for use in the patient, and given according to the product license
Licensed in children, but off-label	Age	The product license indicates that the drug is not indicated for use in children in a particular age (or weight) group
	Dose	The daily dose of the prescription is not in accordance with the product license
	Frequency	The frequency of the prescription is not in accordance with the product license
	Indication	The indication of the prescription is not in accordance with the product license
	Dosage form	The dosage form of the prescription is not in accordance with the product license
	Route of administration	The route of administration of the prescription is not in accordance with the product license
Unlicensed in children	"New" drugs	Drugs produced under a specials manufacturing license, which have not been subject to licensing regulations and therefore have no product license.
	No information on use in children	No information on use in children is found in any subsection of the product license
	Contra-indicated	The product license indicates that the drug is contraindicated for use in children
	Modified preparation	The prescription is prepared by the pharmacy, while no official product license is available for this formulation.

registration in the GP practice, whichever was latest, until the earliest of one of the following censoring points; death, reaching the age of 17 years, transferring out of the practice, or end of the study period.

Classification of prescriptions

From the prescription file, we extracted all prescriptions plus their dosage regimens and indications issued to our study population in 1998. All remaining prescriptions were classified regarding their licensing status.[6] Prescriptions for herbal drugs, non-pharmacological preparations and prescriptions for which no indication could be found were excluded.

The main, and mutually exclusive, classification categories were; "licensed", "licensed, but off-label" and "unlicensed" drugs. Prescriptions were classified as unlicensed drugs if they concerned: "new" drugs produced under a special manufacturing license; modifications to licensed drugs, drugs contraindicated for use in all children; and drugs for which no information was available on use in children (Table 1). Prescriptions were classified as off-label if the drug was prescribed: in a dose or dosage form other than specified in the product license; by an alternative route; for an age below the age recommendations or for an indication not included in the license. Prescriptions could fit into more than one off-label subgroup. As a reference source for classification we used the official product license, as approved by the Dutch Medicines Evaluation Board.

Age was classified in line with the pediatric age definitions provided by the U.S. Food and Drug Administration (FDA),[13] but the categories "1 month - < 2 years" and "2 - < 12 years" were split because of heterogeneity within these age groups.[14] Age groups used were: 0 - < 1 month; 1 - < 6 months; 6 months - < 2 years; 2 - < 6 years; 6 - < 12 years; 12 years and older.

Analysis

Descriptive analyses were conducted for patient demographics, prescription data and

outcome. Statistical comparison consisted of independent 2-sample t-tests for continuous variables, and Chi square-tests or Fisher's exact test for discrete variables.

The study population comprised 13,426 children (51.7% male). During 1998, 64.8% of the children consulted their GPs at least once, the total number of consultations was 26,855, the median number was three consultations per year (Interquartile range (IQR) = 1-5). Significantly more girls than boys consulted their GPs ($p < 0.001$). A total of 18,400 pharmacological prescriptions were issued to the study population in 1998. We excluded 667 herbal prescriptions and 280 prescriptions for which no indication could be found were excluded from further analysis. This resulted in a final number of 17,453 prescriptions, which were issued to 45.7% of the patients (Table 2). For patients who received at least one drug, the median number of prescriptions per year was two (IQR = 1-4).

Results

The mean number of consultations per month for children in the age groups "0 - < 1 month", "1 - < 6 months" and "6 months - < 2 years" was 0.84, 0.39 and 0.33, respectively. This was twice as high ($p = 0.001$) as in the "2 - < 6 years", "6 - < 12 years" and "12 - < 16 years" groups (0.21, 0.14 and 0.15, respectively). The number of prescriptions per month was also higher in the younger age groups (0.21, 0.20 and 0.21, respectively) than in the older ones (0.14, 0.08 and 0.11, respectively).

Of the 17,452 pharmacological prescriptions, 12,405 (71.1%) were licensed for use in children, and prescribed in concordance with the product license. Of the remaining 5048 prescriptions (28.9%), 2667 (15.3%, 95%CI: 14.8-15.8) were prescriptions for unlicensed drugs, and 2381 (13.6%, 95%CI: 13.1-14.2) were off-label prescriptions for licensed drugs. Lack of information on use in children (8.3%), and deviance of recommended dosage (5.6%) were the most frequent reasons for unlicensed and off-label drug use, respectively (Table 3). The numbers of UL prescriptions were highest in the age groups "1 - < 6 months" and "7 months - < 2 years" (Table 4). The most frequent unlicensed and off-label prescriptions were fusidic acid (ophthalmic gel), salbutamol (aerosol), deptropine citrate, amoxicillin and fluticasone (aerosol) (Table 5). Drug classes in which drugs were most frequently prescribed unlicensed or off-label were bronchodilators and anti-asthmatics, ophthalmics, systemic antihistamines,

Table 2 Characteristics of patient-receiving children (46% of total) in the IPCI database in 1998

Variable	Prescription-receiving children (%)	Total study group
Gender		
Male	2990 (43.1)	6 941
Female	3151 (48.6)	6 485
Age groups*		
0 – < 1 month	40 (8.1)	491
1 – < 6 months	342 (35.9)	952
6 months – < 2 years	921 (49.6)	1856
2 – < 6 years	1797 (46.6)	3855
6 – < 12 years	1921 (36.4)	5274
12 years and older	1562 (37.2)	4195
No. of consultations		
0		4727
1-3	3181 (57.8)	6032
4-6	1490 (87.7)	1699
> 6	944 (97.5)	968

% = percentage of total population

* = totals do not add up to the total of the study group, since some patients contributed to several age groups.

Table 3 Classification of drugs.

Category	Subgroup	n=17453
Licensed in children		12405 (71.1%)
Off label * for:	Age	699 (4.0%)
	Dose	978 (5.6%)
	Frequency	279 (1.6%)
	Indication	565 (3.2%)
	Dosage form	190 (1.1%)
	Route of administration	4 (<0.1%)
	Total off-label prescriptions	2381 (13.6%)
Unlicensed in children	No information in product license on use in children [$]	1453 (8.3%)
	Contra-indicated in children	152 (0.9%)
	Modified preparation [£]	1062 (6.1%)
	New drugs	0 (0.0%)
	Total prescriptions for drugs unlicensed in children	2667 (15.3%)

[$] No information on use in children is found in any subsection of the product license

[£] Drugs produced under a specials manufacturing license, which have not been subject to licensing regulations and therefore have no product license

* As drugs in the off label category can be classified under more than one of the six bullet points, totals add up to more than 2381 prescriptions

Table 4 Number of drug prescriptions within each category

Variable	Unlicensed (%)	Off-label (%)	Total
Age groups			
0 – < 1 month	6 (13%)	1 (2%)	47
1 – < 6 months	137 (21%)	99 (15%)	665
6 months – < 2 years	540 (19%)	546 (20%)	2794
2 – < 6 years	676 (14%)	723 (15%)	4993
6 – < 12 years	659 (14%)	491 (11%)	4567
12 years and older	649 (15%)	521 (12%)	4386
Total	2667 (15%)	2381 (14%)	17453

% = percentage within age group

Table 5 Most frequent unlicensed (UL) and off-label (OL) prescription of drugs (n=5994).

	Drug entity	n	Primary classification
1	Fusidic acid	318	OL – Not indicated for age
2	Salbutamol	299	OL – Dosage OL – Not indicated for age
3	Deptropine	299	UL – Magistral preparation
4	Amoxicillin	209	OL – Dosage
5	Fluticasone	183	OL – Dosage
6	Terbutaline	154	OL – Dosage
7	Lidocaine	144	UL – No information
8	Sodium cromoglycate (ear drops)	129	UL – No information
9	Sodium cromoglycate (nasal spray)	119	UL – No information
10	Dexamethasone with antimicrobial agent Sofra dex® (ear drops)	115	UL – No information

systemic antibiotics and otologic drugs.

The baseline risk of a child to receive one or more unlicensed/ off-label prescriptions was 45.5% (95%CI: 44.3-46.8) for children who received at least one prescription during the one-year study period. For females, this risk was 18% higher (95%CI: 10-26) than for males. As compared to 6 to 12-years-old children, the relative risk of receiving unlicensed/off-label prescriptions was 2.6 (95%CI: 2.4-2.9) in 6 to 24-months-old children and 1.7 (95%CI: 1.6-1.9) in 2 to 6-year-old children. The risk of receiving an unlicensed/off-label prescription was 13.9% (95%CI: 13.5-14.3) per consultation.

Discussion

Although lower than in clinical studies, the one-year risk of off-label or unlicensed prescription was 46% to children that were prescribed drugs in general practice in

the Netherlands. This finding underscores the problems in pediatric pharmacology regarding the accuracy and adequacy of drug information in children.

A remarkably high number of prescriptions were off-label due to errors in the prescribed dosage (5.3%); this is surprising since the computer system supports the GP with correct dosage regimens and drug recommendations. The high percentage of modified preparations for children (6.1%) results from the lack of licensed pediatric formulations,[15 16] which is mainly compensated through modification of commercial preparations in the pharmacies.

We excluded 667 prescriptions for which we could not find an indication. This was motivated by the difficulty to determine correct dosage regimens from the product license of these prescriptions since they may depend on indication. 280 alternative drugs, such as homeopathic and herbal drugs, were excluded from the study, since there was no licensing authority evaluating efficacy of these preparations in 1998.

Although the risk of unlicensed and off-label drug use in children may be high, it is important to discuss the potential clinical impacts of these findings. Due to a thinner and better-hydrated skin, the rate and extent of drug absorption via the skin is increased in young infants. As a consequence, systemic toxicity may be observed with topical application of some drugs (e.g. lidocaine, corticosteroids) to children 8 to 12 months of age, in our children we found 56 infants (8% of children <12 months) who received topic applications that were classified unlicensed or off-label. Another complication may rise from the long-term use of respiratory corticosteroids, which could result in bone demineralisation and growth impairment in children,[17] especially in children that are younger than the minimal age that is indicated by the product license, or when the drug is systemically overdosed. Similarly, the use of highly dosed deptropine citrate in small children has been reported to cause hallucinations, agitation / aggressive behavior, ataxia and anxiety in children.[18] Many of the drugs that are frequently prescribed and classified by use as unlicensed or off-label will not be a actual threat to the health of the child and its recovery, but in general the risk of adverse drug reactions is higher in children who receive unlicensed or off-label drugs.[19]

Over the recent years several publications have indicated the urgent need of good evidence-based medicine, in adult as well as pediatric care. The European Medicines Control Agency's 1997 'Note for guidance on clinical investigations in children' for instance unmistakably reckons the widespread concern regarding performing clinical trials in children, particularly subjecting children to repeated invasive procedures.[20] However, no substantial measure have been taken by European authorities to enhance the industry's willingness to invest in pediatric research and to facilitate the development and improvement of clinical research sites in Europe. The Pediatric Pharmacological Research Units (PPRUs) in the US, which are funded by the National Institutes of Health, are an example of the lead the US has taken. We think the European community should take it's responsibility by active participation in the improvement of the pediatric licensing status of drugs commonly used in pediatrics.

In conclusion, this study showed that a considerable number of drugs that are prescribed to children in general practice are not licensed for use in children, or prescribed off-label. This proves that unlicensed and off-label prescription of drugs is

less than, but not limited to clinical care. This situation is hardly acceptable, and joined efforts should be taken to improve it. Not only because of the injustice done to children, but moreover since we cannot quantify or oversee the impact of the current situation on the health of our children.

References

1. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80:F142-4.
2. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. Bmj 1998;316:343-5.
3. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of "off-label" and unlicensed drugs in paediatric intensive care unit [letter]. Lancet 1996;347:549-50.
4. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, Anker J vd. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000;320:79-82.
5. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, Anker JN vd. Unapproved and off-label use of drugs in a children's hospital [letter]. N Engl J Med 2000;343:1125.
6. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
7. Chalumeau M, Treluyer JM, Salanave B, Assathiany R, Cheron G, Crocheton N, Rougeron C, Mares M, Breart G, Pons G. Off label and unlicensed drug use among french office based paediatricians. Arch Dis Child 2000;83:502-5.
8. Wilton LV, Pearce G, Mann RD. The use of newly prescribed drugs in children and adolescents prescribed in general practice. Pharmacoepidemiology and Drug Safety 1999;8:S37-45.
9. McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off label prescribing of drugs in general practice. Arch Dis Child 2000;83:498-501.
10. Klinkman MS, Green LA. Using ICPC in a computer-based primary care information system. Fam Med 1995;27:449-56.
11. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
12. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
13. Guidance for industry; Content and format for pediatric use supplements. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Washington, 1996:1-6.
14. Nahata MC. New regulations for pediatric labeling of prescription drugs. Ann Pharmacother 1996;30:1032-3.
15. Nahata MC. Lack of pediatric drug formulations. Pediatrics 1999;104:607-9.
16. Nahata MC. Pediatric drug formulations: challenges and potential solutions. Ann Pharmacother 1999;33:247-9.
17. Allen DB. Effect of inhaled beclomethasone dipropionate and budesonide on growth in children with asthma. Respir Med 1998;92 Suppl B:37-45.
18. Stricker BH, Prins AM, Schilte PP. Ernstige psychische bijwerkingen bij kinderen door gebruik van hoge doseringen deptropine. Ned Tijdschr Geneeskd 1992;136:1362-5.
19. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 1999;88:965-8.
20. European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit; Committee for Proprietary Medicinal Products. Note for Guidance on Clinical Investigation of Medicinal Products in Children. EMEA, 1997.

Chapter 3.3

Unlicensed and off-label prescription of respiratory drugs to children

Many respiratory drugs are not available in formulations suitable for infants and toddlers, and efficacy research is mostly restricted to older children. However, respiratory drugs are frequently used in children for common diseases like asthma, upper en lower respiratory tract infections, rhinitis and sinusitis. We therefore studied the unlicensed and off-label use of respiratory drugs in children. We conducted a population-based cohort study by using the computerized medical records in the Integrated Primary Care Information (IPCI) project. The study population comprised a random sample of all children aged under 16 years who were registered with a general practitioner in 1998. All prescriptions for respiratory drugs during the study period were classified according to licensing and off-label status. The study population comprised 13,426 patients (51.7% male, median age 8.67 years), of whom 2502 (19%) received 5253 prescriptions for respiratory drugs in 1998. A total of 3306 (62.9%) prescriptions concerned licensed drugs. Of the remaining 1947 prescriptions (37.1%), 882 (16.8%) were unlicensed for use in children, and 1065 (20.3%) were prescribed off-label. The one-year risk of an unlicensed or off-label prescription was 45% among children with at least one prescription for a respiratory drug. This population-based study showed that a large proportion of respiratory drugs prescribed by the general practitioner is unlicensed for use in children or licensed but prescribed in an off-label manner. These findings should prompt research into suitable formulations, dosages and efficacy of respiratory drugs in children.

Introduction

The extent and nature of unlicensed and off-label drug prescription in paediatric clinical care has been the subject of several surveys in Europe[1-7] and these consistently showed that a very large proportion of prescribed drugs are either unlicensed for use in children or used outside the terms of the product license ('off-label').
Respiratory drugs are used for several of the most common paediatric diseases such as asthma, upper and lower respiratory tract infections, rhinitis and sinusitis; conditions that are treated in general practice rather than clinical care.[8-12] Previous research of our group revealed that seventy percent of available respiratory drugs in the Netherlands are not fully licensed for use in children, and many of these (80%) are registered only for specific age/weight groups.[13] We conducted a large cohort study in general practice to assess the extent and nature of unlicensed and off-label prescription of respiratory drugs in children.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with data from computer-based patient records of a group of 150 general practitioners (GPs) in the Netherlands. Within the Netherlands, patients are registered to a single general practitioner and records from each general practitioner can be assumed complete for an individual patient. The database is maintained by the department of Medical Informatics of the Erasmus Medical Center Rotterdam (EMCR) since 1992, and contains coded and anonymous data on gender, age, symptoms, diagnoses and findings, and on prescriptions, their indications and dosage regimen. Summaries of hospital discharge letters and information from clinical specialists are included as free text. Patient complaints and diagnoses are entered as text and coded according to the International Classification for Primary Care (ICPC).[14] Prescription drugs are coded according to the Anatomical Therapeutic Chemical classification (ATC).[15] The data are entered and stored directly by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who ensures anonymity of all information before further access is provided. To maximize completeness of information, GPs participating in the IPCI project are not allowed to use paper records. As of 2001, the IPCI database contains data on a cumulative number of 485,000 patients. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research.[16]

Design

We conducted a population-based cohort study in a dynamic population of children in the IPCI database who were permanently registered with one of the participating general practices between 1 January 1998 and 31 December 1998.[17] In 1998, 53,702 children were registered in the IPCI database. Since our research required manual review of all prescriptions we randomly sampled 25% of the population, which formed our primary study population. All study subjects were followed from 1

January 1998, or the date of registration in the GP practice, whichever was latest, until the earliest of one of the following censoring points; death, reaching the age of 17 years, transferring out of the practice, or end of the study period.

Classification of prescriptions

From the prescription file, we extracted all prescriptions plus their dosage regimens and indications issued to our primary study population in 1998. Respiratory drugs were categorized into "nasal preparations" (ATC R01), "oropharyngeal preparations" (ATC R02), "anti-asthmatics" (ATC R03), "cough- and cold-medications" (ATC R05) and "antihistamines for systemic use" (ATC R06).

As part of a larger project,[17] all prescriptions for respiratory drugs were classified regarding their licensing status.[3] The main, and mutually exclusive, classification categories were; "licensed for children", "licensed, but used off-label" and "unlicensed for children" drugs. Prescriptions were classified as unlicensed drugs if they concerned: "new" drugs produced under a special manufacturing license; modifications to licensed drugs; drugs contraindicated for use in all children; and drugs for which no information was available on use in children. Prescriptions were classified as off-label if the drug was prescribed in a dose or dosage form other than specified in the product license; by an alternative route; for an age below the age recommendations or for an indication not included in the license. Prescriptions could fit into more than one off-label subgroup. As a reference source for classification we used the official product license, as approved by the Dutch Medicines Evaluation Board.

Age was classified in line with the paediatric age definitions provided by the U.S. Food and Drug Administration (FDA),[18] but the categories "1 month - < 2 years" and "2 - < 12 years" were split because of heterogeneity within these age groups.19 Age groups used were: 0 - < 1 month; 1 - < 6 months; 6 months - < 2 years; 2 - < 6 years; 6 - < 12 years; 12 years and older.

Analysis

Descriptive analyses were conducted for patient demographics, prescription data and outcome. Statistical comparison consisted of independent 2-sample t-tests for continuous variables, and Chi-square tests for discrete variables. Ninety-five percent confidence intervals around prevalence estimates were based on the normal distribution.

Results

The primary study population comprised 13,426 children (51.7% male) with a median age of 8 years and 8 months on the last day of follow-up. A total of 17,453 pharmacological prescriptions were issued to the study population in 1998. Of these, 5253 (30.1%) prescriptions concerned respiratory drugs. The respiratory prescriptions were issued to 2502 (18.6%) patients (Table 1). The median number of respiratory drug prescriptions among respiratory drug-using children was one (interquartile range (IQR) = 1-2). For anti-asthmatics (ATC R03), the median number of prescriptions was two per patient per year (IQR 1-3). Patients who received respiratory drugs were significantly younger than the rest of the study population ($p < 0.001$). The most frequently prescribed respiratory drugs were anti-asthmatics (40.7% of all

Table 1 Characteristics of study population (n=13,426).

Variable	Respiratory drug prescription -receiving children (n=2502)		Drug prescription -receiving children (n=6313) [$]		Total study population (n=13426)	
Gender						
Male	1318	(52.7%)	3066	(48.6%)	6 941	(51.7%)
Female	1184	(47.3%)	3247	(51.4%)	6 485	(48.3%)
Age groups[*]						
0 –< 1 month	1	(<0.1%)	40	(0.6%)	491	(3.7%)
1 – < 6 months	240	(9.6%)	342	(5.4%)	952	(7.1%)
6 months –< 2 years	581	(23.2%)	921	(14.6%)	1856	(13.8%)
2 –< 6 years	947	(37.8%)	1797	(28.5%)	3855	(28.7%)
6 –< 12 years	833	(33.3%)	1921	(30.4%)	5274	(39.3%)
12 years and older	552	(22.0%)	1562	(24.7%)	4195	(31.2%)

% = Percentage calculated on column total.
[*] = Totals do not add up to the total of the study group, since some patients contributed to several age groups.
[$] = All drug prescriptions over 1998, including respiratory drugs.

prescriptions), followed by systemic antihistamines (27.7%) and nasal preparations (23.2%). Largest subclasses of drugs - in numbers of prescriptions - were corticosteroids (18.0%), selective beta-2-sympaticomimetics (17.1%), systemic antihistamines (14.8%), sympaticomimetics for nasal use (12.7%) and phenothiazine-derivates (8.9%), as shown in table 2. The most frequently prescribed drugs were salbutamol (12.7%), xylomethazoline (12.7%), promethazine (7.4%), beclomethasone (6.5%), and fluticasone (6.5%). In terms of children who were exposed to these drugs, the distribution was slightly different, the highest percentage of exposure was to sympaticomimetics for nasal application (4.5% of children), followed by beta-2-sympaticomimetics for inhalation (4.2%) and systemic antihistamines (3.9%) (Table 2).

Of the 5253 prescriptions, 3306 (62.9%) were licensed for use in children, and prescribed in concordance with the product license. Of the remaining 1947 prescriptions (37.1%), 882 (16.8%, 95%CI: 15.8-17.8) were prescriptions for unlicensed drugs, and 1065 (20.3%, 95%CI: 19.2-21.4) were off-label prescriptions for licensed drugs. Modification of preparations (8.7%), and deviance of age/weight-restrictions (7.4%) were the most frequent reasons for unlicensed and off-label drug use, respectively (Table 3). Unlicensed and off-label drug use differed for the various respiratory drug classes (Table 4). Off-label use was especially high for anti-asthmatic drugs (39%),

Table 2 Respiratory drug utilization

Drug class	Prescriptions						Users			
	Total	% [$]	Unlicensed	% [#]	Off-label	% [#]	Total	% [$]	UL/OL [@]	% [#]
Corticosteroids (inhaled)	943	18.0			307	32.6	488	3.6	180	36.9
Beta-2-sympaticomimetics (inhaled)	898	17.1	162	18.0	300	33.4	561	4.2	318	56.7
Antihistamines (in different) [1]	776	14.8	299	38.5	49	6.3	517	3.9	267	51.6
Sympaticomimetics (nasal)	668	12.7	32	4.8	9	1.3	602	4.5	37	6.1
Pheothiazine-derivates	467	8.9	73	15.6	20	4.3	389	2.9	78	20.1
Corticosteroids (nasal)	276	5.3	141	51.1	4	1.4	182	1.4	94	51.6
Anti-allergic drugs (non-steroid)	200	3.8	119	59.5	4	2.0	120	0.9	75	62.5
Piperazine-derivates	175	3.3	15	8.6	7	4.0	119	0.9	15	12.6
Opium alkaloids and derivates	164	3.1	1	0.6	26	15.9	141	1.1	25	17.7
Parasympaticomimetics	112	2.1	7	6.3	100	89.3	88	0.7	84	95.5
Expectorants	98	1.9	34	34.7	20	20.4	93	0.7	74	79.6
Mucolytics [2]	81	1.5			28	34.6	71	0.5	26	36.6
Other drugs for nasal use [3]	75	1.4					57	0.4		
Other cough-suppressant drugs [4]	75	1.4			52	69.3	61	0.5	44	72.1
Sympaticomimetics + other anti-asthmatics [5]	69	1.3			68	98.6	50	0.4	50	100.0

[$] % of total number of respiratory prescriptions (n=5253) and patients in the cohort (n=13426)
[#] Row percentage
[@] Patients with an unlicensed or off-label prescription

[1] e.g. deptropine, ketotifen, and tefenadine
[2] e.g. acetylcysteine and brome hexin
[3] e.g. mupirocin and NaCl
[4] e.g. Pentoxyverine
[5] e.g. Fenoterol + ipratropium in Berodual®

Table 3 Licensing status classification of respiratory drugs

Category	Reason for unlicensed or off -label prescription	n=5253	
Licensed in children		3306	(62.8%)
Off label **	Age/weight	387	(7.3%)
	Dose	412	(7.8%)
	Frequency	199	(3.8%)
	Indication	237	(4.5%)
	Dosage form	58	(1.1%)
	Route of administration	0	(0.0%)
Total off-label		*1065*	*(20.3%)*
Unlicensed in children	No information on use in children §	347	(6.6%)
	Contra-indicated †	76	(1.4%)
	Modified preparation*	459	(8.7%)
	New drugs	0	(0.0%)
Total unlicensed		*882*	*(16.8%)*

§ No information on use in children is found in any subsection of the product license

† The product license indicates that the drug is contraindicated for use in children

* The prescription is prepared by the pharmacy, and no official product license is available for this formulation

** As drugs in the off-label category can be classified under more than one of the six bullet points, totals add up to more than 1065 prescriptions

and cough- and cold medication (30%). Anti-asthma drugs were frequently off-label for dose and/or indication or age/weight (14%, 10%, and 15%, respectively) and cough- and cold medication was mostly off-label for dose (19%). Unlicensed use was especially high for nose preparations and antihistamines for systemic use (24.0% and 26.4%, respectively), but off-label use was very low in these groups; primary reason for unlicensed drug use for both drug classes was modification of preparations by the pharmacy. The most frequent unlicensed and off-label prescribed drugs were salbutamol (inhaled), deptropine (syrup), fluticasone (inhaled), terbutaline (inhaled), and sodium cromoglycate (nasal spray) (Table 5).

Table 4 Number of drug prescriptions within licensing /off-label status

Variable	Unlicensed / off -label (%)		Licensed	
Age groups				
0 - < 1 month	0	(0.0%)	1	(100.0%)
1 - < 6 months	113	(67.7%)	54	(32.3%)
6 months - < 2 years	531	(64.8%)	289	(35.2%)
2 - < 6 years	583	(35.2%)	1074	(64.8%)
6 - < 12 years	422	(27.9%)	1089	(72.1%)
12 years and older	298	(27.2%)	799	(72.8%)
Drug classes				
Anti-asthmatics	1008	(47.1%)	1131	(52.9%)
Antihistamines for systemic u se	466	(32.0%)	991	(68.0%)
Nasal preparations	309	(25.3%)	910	(74.7%)
Cough- and cold medication	162	(38.1%)	263	(61.9%)
Oropharyngeal preparations	2	(15.4%)	11	(84.6%)
Total	1947	(37.1%)	3306	(62.9%)

% = Percentage within age group / drug class

Table 5 Most frequent unlicensed and off-label prescription of drugs (n=1947).

	Drug	N	(%)*	Primary classification
1	Salbutamol (inhaled)	299	(45%)	Off-label for age/weight Off-label for dose
2	Deptropine (syrup)	299	(100%)	Unlicensed; no information on use in children
3	Fluticasone (inhaled)	183	(54%)	Off-label for dose
4	Terbutaline (inhaled)	154	(89%)	Off-label for dose
5	Cromoglycate (nasal spray)	119	(100%)	Unlicensed; no information on use in children
6	Ipratropium (inhaled)	107	(95%)	Off-label for age/weight
7	Budesonide (nasal drops)	91	(100%)	Unlicensed; contra -indicated for use in children
8	Budesonide (inhaled)	80	(30%)	Off-label for indication
9	Fenoterol + ipratropium (inhaled)	68	(99%)	Off-label for age/weight
10	Beclomethasone (nasal drops)	50	(100%)	Unlicensed; no information on use in children

* Percentage of number of prescription for drug

The numbers of unlicensed and off-label prescriptions were highest in the age groups "1 - < 6 months" and "6 months - < 2 years" (Table 4). For children under 6 years of age, the risk of receiving unlicensed or off-label prescriptions was significantly higher than for older children; compared to children aged between 6 and 12 years, children in the age groups 1 - < 6 months, 6 - < 24 months, and 2 - < 6 years had a relative risk of 1.5 (95%CI: 1.0-2.2), 4.4 (95%CI: 3.7-5.1), and 2.1 (95%CI: 1.8-2.4) respectively.

The one-year risk of an unlicensed or off-label prescription was 45% (95%CI: 43-47) among children with at least one prescription for a respiratory drug. Males had a 15 percent (95%CI: 6-25) higher chance of receiving unlicensed or off-label prescriptions for anti-asthmatics than females. For other groups no significant differences were found.

For some infrequently used drugs (parasympaticomimetics and expectorants), the percentage of exposed children with at least one off-label of unlicensed prescription for this drug was highest (95% and 79% respectively). However also amongst the drugs with the highest exposure, the percentage of children with at least one off-label or unlicensed prescription was high; i.e. 57% amongst users of beta-2-sympaticomimetics and 52% among users of systemic antihistaminics (Table 2).

Discussion

This study showed a high one-year risk of unlicensed and off-label use of respiratory drugs among children who use these drugs (45%). In terms of prescription, 17% was unlicensed and 20% off-label. The percentages are slightly higher than the overall percentages in all classes of drugs (15% and 14%, respectively).[17] The risk of at least one off-label or unlicensed prescription was high amongst users of parasympaticometics, expectorants, inhalational sympaticomimetics and systemic antihistamines, and was higher for younger and males.

A remarkably high number of prescriptions were off-label due to "errors" in the prescribed daily dosage (7.8%); this is surprising since the computer system supports the GP with recommended dosing regimens. The licensing information text of many respiratory drugs provides physicians with dosage recommendations that are more restricted than the information text in common drug formularies like the Physician's Desk Reference in the US,[20] and the British National Formulary or the "Medicines for Children" formulary in the UK.[21] However, dose recommendations for paediatric use of many anti-asthmatics in these formularies are mostly experience based, and not so much evidence based. Although most unlicensed and off-label drug use will not result in any harm, bone demineralization and growth impairment has been reported following the long-term use of respiratory corticosteroids,[22] especially in children that are younger than the minimal age that is indicated by the product license, or when the drug is systemically overdosed. Similarly, the use of high doses of the antihistaminic deptropine citrate in small children has been reported to cause hallucinations, agitation / aggressive behavior, ataxia and anxiety in children.[23]

The high percentage of modified preparations for children (8.7%) is a direct result of the lack of licensed paediatric formulations,[24,25] which requires modification of commercial preparations in the pharmacies. The drug prescriptions that were off-label for

age were not checked for other off-label categories like indication and dosage, since these were not provided in the labeling information text. The dosage form therefore seems to be correct for most prescriptions, but especially in the younger children, the availability of suitable formulations is limited. Although there have been major advances in relation to different types of inhalers for children of different ages with asthma, such as the turbohaler, nebuhaler and volumatic inhaler,[26] knowledge of reproducibility of dose and lung disposition is limited.[27] Pressurized metered dose inhalers (pMDI)/spacers, and facemasks are needed for these children,[28] and parents have to be adequately instructed to be able to apply the drug. Dose variability for these drugs in small infants is large, and increased by complicating factors like bad cooperation by the wheezy infant.[29]

In conclusion, this study showed that a considerable number of drugs that are prescribed to children for very common respiratory diseases in childhood in general practice are not licensed for use in children, or prescribed off-label. This situation is hardly acceptable, and joined efforts should be taken to improve it.

References

1. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80:F142-4.
2. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. Bmj 1998;316:343-5.
3. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
4. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of "off-label" and unlicensed drugs in paediatric intensive care unit [letter]. Lancet 1996;347:549-50.
5. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, Anker J vd. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000;320:79-82.
6. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, Anker JN vd. Survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001;108:1089-93.
7. Chalumeau M, Treluyer JM, Salanave B, Assathiany R, Cheron G, Crocheton N, Rougeron C, Mares M, Breart G, Pons G. Off label and unlicensed drug use among french office based paediatricians. Arch Dis Child 2000;83:502-5.
8. Olubadewo JO, Ikponmwamba A. Profile of prescription medication in a pediatric population. Drug Intell Clin Pharm 1988;22:999-1002.
9. Sanz EJ, Bergman U, Dahlstrom M. Paediatric drug prescribing. A comparison of Tenerife (Canary Islands, Spain) and Sweden. Eur J Clin Pharmacol 1989;37:65-8.
10. Thrane N, Sorensen HT. A one-year population-based study of drug prescriptions for Danish children. Acta Paediatr 1999;88:1131-6.
11. Straand J, Rokstad K, Heggedal U. Drug prescribing for children in general practice. A report from the More & Romsdal Prescription Study. Acta Paediatr 1998;87:218-24.
12. Madsen H, Andersen M, Hallas J. Drug prescribing among Danish children: a population-based study. Eur J Clin Pharmacol 2001;57:159-65.
13. t Jong GW, Eland IA, Stricker BHC, Anker JN vd. Information for paediatric use of medicines in a product information compendium. Paediatric and Perinatal Drug Therapy 2001;4:148-51.
14. Klinkman MS, Green LA. Using ICPC in a computer-based primary care information system. Fam Med 1995;27:449-56.
15. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
16. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
17. t Jong GW, Eland IA, Sturkenboom MCJM, Anker JN vd, Stricker BHC. Unlicensed and off-label prescription of drugs to children; population-based cohort study. BMJ 2002;In press.
18. Guidance for industry; Content and format for pediatric use supplements. Food and Drug

Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Washington, 1996:1-6.
19. Nahata MC. New regulations for pediatric labeling of prescription drugs. Ann Pharmacother 1996;30:1032-3.
20. Physician's desk reference. 56th ed. Montvale, NJ: Medical Economics, 2001.
21. The Royal College of Paediatrics and Child Health: Medicines for children. Hants, United Kingdom: B&MBC Books Ltd, Direct Books, 1999.
22. Allen DB. Effect of inhaled beclomethasone dipropionate and budesonide on growth in children with asthma. Respir Med 1998;92 Suppl B:37-45.
23. Stricker BH, Prins AM, Schilte PP. Ernstige psychische bijwerkingen bij kinderen door gebruik van hoge doseringen deptropine. Ned Tijdschr Geneeskd 1992;136:1362-5.
24. Nahata MC. Lack of pediatric drug formulations. Pediatrics 1999;104:607-9.
25. Nahata MC. Pediatric drug formulations: challenges and potential solutions. Ann Pharmacother 1999;33:247-9.
26. O'Callaghan C, Barry P. Inhalation devices for young children. Paediatr Perinat Drug Ther 1997:57-65.
27. Janssens HM, Devadason SG, Hop WC, LeSouef PN, De Jongste JC, Tiddens HA. Variability of aerosol delivery via spacer devices in young asthmatic children in daily life. Eur Respir J 1999;13:787-91.
28. McCarthy TP. Use of 'Nebuhaler' and face-mask in young asthmatic children. Lancet 1990;335:983-4.
29. Janssens HM, Heijnen EM, de Jong VM, Hop WC, Holland WP, de Jongste JC, Tiddens HA. Aerosol delivery from spacers in wheezy infants: a daily life study. Eur Respir J 2000;16:850-6.

Chapter 3.4

Determinants for drug prescribing to children below the minimum licensed age

In the light of undesired effects that unlicensed and off-label drug use might have, it is necessary to study determinants that affect prescribing of such drugs. Prescription of drugs to children who are younger than the minimum licensed age may carry the highest risk of adverse reactions. To obtain insight into the factors that affect prescription of drugs below the minimal licensed age in children we conducted a population-based case-control study. The case-control study was nested in a cohort of 13,426 children aged 0 - 16 years, who were registered in the Integrated Primary Care Information (IPCI) project, a longitudinal observational general practitioners database in the Netherlands. Cases were all children who received a drug prescription below the minimum licensed age. To each case we matched up to four controls based on GP practice and patient age. As potential risk factors we evaluated use of health care resources, and acute and chronic morbidity. We identified 447 cases who were matched to 1,355 controls. Cases consulted their GPs significantly more often during the preceding half-year, had more drug prescriptions, and had more specialist referrals than controls. Respiratory diseases were the most important determinants for the prescription of drugs to below the minimum licensed age in children. In adolescents, migraine and other headaches were the most important reasons. This study showed that children suffering from respiratory disease or migraine have the highest risk of receiving a drug prescription below the minimum licensed age. Regulatory authorities and the pharmaceutical industry should be stimulated to improve evaluation of drug efficacy and safety in children.

Introduction

Although drugs play an important role in the treatment of children, many drugs are not licensed for use at all relevant ages and for all relevant indications.[1] This often results in the prescription of drugs that are either not licensed for use in children or are prescribed off-label. In recent years, several surveys in clinical as well as non-clinical settings have shown a high rate of unlicensed and off-label drug use in pediatrics.[2-8] In a previous study in primary care, almost thirty percent of all prescriptions in children between 0 and 16 years of age was either off-label or for an unlicensed drug.[9] In the Netherlands, general practitioners play a central role in the health care system and therefore they are informed of all relevant medical events. In order to identify risk factors for prescribing a drug to children below the minimum licensed age in general practice, we conducted a population-based nested case-control study.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with computer-based patient records from a group of 150 general practitioners (GPs) in the Netherlands. Within the Netherlands, patients are registered with a single general practitioner and records from each general practitioner can be assumed complete for an individual patient. The database is maintained by the department of Medical Informatics of the Erasmus Medical Center Rotterdam (EMCR) since 1992, and contains coded and anonymous data on gender, age, symptoms, diagnoses and findings, and on prescriptions, their indications and dosage regimens. Summaries of the hospital discharge letters and information from clinical specialists are included as free text. Patient complaints and diagnoses are entered as free text and coded according to the International Classification for Primary Care (ICPC).[10] Prescription drugs are coded according to the Anatomical Therapeutic Chemical classification (ATC).[11] Data are entered and stored directly by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who ensures anonymity of all information before further access is provided. To maximize completeness of information, GPs participating in the IPCI project are not allowed to have a system of paper records besides the electronic medical records. As of 2001, the IPCI database contains data on approximately 485,000 patients. The system complies with European Union guidelines on the use of medical data for medical research and is valid for pharmacoepidemiological research.[12]

Design

We conducted a nested case-control study in a randomly sampled cohort of 13,426 children, who were registered with one of the participating general practices between January 1 and December 31, 1998.

All cohort members were followed from January 1, 1998 or the date of registration in the GP practice, whichever was latest, until the earliest of one of the following censoring points; prescription of a drug to a patient below the minimum licensed age, death, reaching the age of 17 years, transferring out of the practice, or end of the

study period. All drug prescriptions issued to the cohort members during 1998 were evaluated manually to classify licensing status.

Cases and controls

We defined as cases all children who received at least one prescription for a drug below the minimum licensed age. The first prescription for such a drug was defined as the index date. Cases were excluded if they had less than 6 months of valid history before the index date. To each case, we matched up to four controls based on GP practice and age (+/- 3 months) who were allocated the same index date as the corresponding case. Also controls had to have at least 6 months of valid history before the index date.

Covariates

As potential determinants for prescribing drugs to patients below the minimum licensed age, we evaluated the number of consultations, pharmacological prescriptions, and referrals during the 6-month period preceding the index, plus all relevant pediatric diseases and common disorders for which the GP is often consulted. Information on morbidity was retrieved from both coded diagnoses and symptoms in the free text. The prevalence of all acute and chronic diseases on the index date was assessed by reference to these morbidity data.

Age was classified in line with the pediatric age definitions provided by the U.S. Food and Drug Administration (FDA),[13] but the categories "1 month -< 2 years" and "2 -< 12 years" were split because of the heterogeneity within these age groups.[14] Age groups used were: 0 -< 1 month; 1 -< 6 months; 6 months -< 2years; 2 -< 6 years; 6 -< 12 years; 12 years and older.

Statistics

Distributions of continuous and discrete variables were compared between cases and controls by means of standard t-tests and Chi-square tests respectively. To identify determinants for use of drugs under the minimum licensed age, we used univariate and multivariate conditional logistic regression analyses. All analyses were conducted using SPSS 10/PC.

Results

Within our study cohort of 13,426 children (51.7% male), we identified 515 (3.8%) patients who received prescriptions for drugs below the minimum licensed age. Eleven patients could not be matched to a control while 57 (11%) patients were excluded since they had less than 6 months of prior history. The resulting 447 cases were matched to 1,355 controls from the source population. The median age of the cases was 3 years (IQR: 0-12). There was no significant difference in gender between cases and controls. The most frequently prescribed drugs to children below the minimum licensed age were ipratropium, salbutamol, diclofenac, and budesonide (Table 1).

The risk of obtaining a prescription below the licensed age was thirty percent higher for children with a sickfund insurance (Table 1). The risk increased with more frequent use of health care resources, by 66% upon each additional consultation (inde-

Table 1 Top ten drugs prescribed to children younger than the minimal age among cases

Drug	Number (n=447)	%
Ipratropium	56	13%
Salbutamol	55	12%
Diclofenac	52	12%
Budesonide	46	10%
Fenoterol + ipratropium	34	8%
Cisapride	25	6%
Trimethoprim	13	3%
Ibuprofen	12	3%
Noscapine	9	2%
Piroxicam	8	2%

pendent of age/insurance and assuming a linear relationship) (OR 1.66, 95%CI: 1.54-1.79), and two-fold with each additional prescription (OR 2.0, 95%CI: 1.81-2.22). For the number of referrals to specialists, no significant extra risk was found when adjusted for gender, insurance and number of consultations (Table 2). The diseases that were significantly more prevalent in patients who received prescriptions for drugs below the minimum licensed age were mainly respiratory diseases: asthma, upper respiratory tract infections, lower respiratory tract infection, and rhinitis. In older children, migraine and other forms of headache (not tension-related) were important determinants (Table 3). Regurgitation in neonates was a significant determinant in children younger than 6 months (OR =9.7 (95%: 1.0-91)), which was mainly related to the use of cisapride in reflux esophagitis. When we adjusted for the number of consultations, the relative risk decreased to one for many diseases, except for asthma (10.9 (95%: 2.0-59.4) under 6 months, 10.4 (95%: 4.6-24.1) between 6 months and 2 years of age), and lower respiratory tract infections (5.3 (95%: 1.1-22.7) under 6 months, 2.2 (95%: 1.1-4.5) between 6 months and 2 years of age) in young children.

Table 2 Characteristics of study population

Variables	Cases (n=447)		Controls (n=1355)		OR_{crude} [95%CI]*
*Age group***					
1-< 6 months (%)	52	(11.6)	167	(12.6)	
6 months -< 2 years (%)	133	(29.8)	383	(28.3)	
2 -< 6 years (%)	89	(19.9)	263	(19.4)	
6 -< 12 years (%)	49	(11.0)	166	(12.3)	
12 years and older (%)	124	(27.7)	376	(27.7)	
Sex					
Male (%)	228	(51.0)	722	(53.3)	reference
Female (%)	219	(49.0)	633	(46.7)	1.1 [0.9-1.4]
Insurance status					
Private insurance	192	(43.0)	666	(49.2)	reference
Sickfund	232	(51.9)	618	(45.6)	**1.3 [1.0-1.7]**
Unknown / missing	23	(5.1)	71	(5.2)	
Consultations (median [IQR])	3	[2 - 5]	1	[0 – 2]	
0-2	198	(44.3)	1138	(84.0)	reference
3-4	131	(29.3)	133	(9.8)	**5.8 [4.3-8.0]**
5-6	67	(15.0)	50	(3.7)	**8.9 [5.6-13.9]**
> 6	51	(11.4)	34	(2.5)	**11.4 [6.8-18.9]**
Prescriptions (median [IQR])	2	[1 – 4]	1	[0 – 1]	
0-1	134	(30.0)	1086	(80.1)	reference
2-3	162	(36.2)	203	(15.0)	**8.9 [5.6-13.9]**
>3	154	(33.6)	66	(4.9)	**25.1 [16.3-38.8]**
Referrals					
0	372	(83.2)	1234	(91.1)	reference
1-2	63	(14.1)	118	(87)	**2.1 [1.5-2.9]**
>2	12	(2.6)	3	(0.2)	**23.8 [5.2-108.4]**

* Relative risk of receiving drugs that are not licensed for the age of the patient

** Controls were matched on age.
CI= confidence interval, OR= Odds ratio

Table 3 Association between co-morbidity and prescribing drugs to children below the minimum licensed age

Age group	1 -< 6 months			6 months -< 2 years			2 -< 6 years			6 -< 12 years			12 years and older		
Disease	case	control	OR [95%CI]	case	control	OR [95%CI]	case	control	OR [95%CI]	case	control	OR [95%CI]	case	control	OR [95%CI]
Asthma	17	8	**10.9 [3.5–33.9]**	56	36	**8.6 [4.6–15.8]**	37	32	**6.4 [3.1–13.2]**	13	18	**6.6 [2.3–19.1]**	10	11	2.2 [0.9–5.7]
Lower Respiratory Tract Infections	11	11	**2.9 [1.1–7.6]**	34	41	**3.6 [2.1–6.3]**	7	7	**3.2 [1.0–10.0]**	2	2	5.2 [0.7–41.0]	2	7	0.9 [0.2–4.7]
Upper Respiratory Tract Infections	16	30	**3.1 [1.3–7.5]**	37	54	**2.9 [1.7–5.2]**	12	24	1.7 [0.7–4.1]	1	4	0.8 [0.1–7.2]	6	6	**3.6 [1.1–11.9]**
Acute otitis media	6	12	1.4 [0.5–4.0]	31	49	2.0 [1.1–3.6]	8	17	1.3 [0.5–3.6]	1	4	1.2 [0.1–10.9]	2	5	2.5 [0.4–16.9]
Rhinitis	7	3	**9.7 [1.9–48.6]**	9	3	**12.0 [2.4–59.3]**	4	4	2.8 [0.5–14.6]	4	2	3.8 [0.6–22.6]	5	2	**11.8 [1.3–107.5]**
Impaired psychomotor development				4	7	2.2 [0.6–8.4]	4	6	1.8 [0.5–6.9]	6	3	**6.5 [1.5–27.7]**	2	6	1.4 [0.3–7.8]
Keratoconjunctivitis	4	7	1.5 [0.4–5.4]	11	16	**2.5 [1.1–5.8]**	3	8	1.2 [0.3–5.2]	2	2	5.7 [0.4–76.5]	7	5	3.0 [0.8–10.7]
Migraine													12	11	**4.3 [1.7–11.0]**
Headache (not migraine or sinusitis)										2	1	5.6 [0.4–68.4]	12	7	**5.0 [1.9–13.6]**

Adjusted for matching factors (GP practice, age) plus gender and insurance

Discussion

In this study, we showed that the risk of receiving prescriptions for drugs below the minimum licensed age is highest for young children who frequently visit their GP and suffer from asthma. Children with a sickfund insurance had a higher risk which possibly relates to the fact that they often have a low socio-economic background. Despite the high incidence of respiratory diseases and frequent prescription of respiratory drugs to children,[15-19] many of these drugs are not licensed for use in young children. Although most of these unlicensed and off-label drugs will not result in any harm, bone demineralization and growth impairment has been reported following the long-term use of respiratory corticosteroids,[20] especially in children who are younger than the minimal age that is indicated by the product license, or when the drug is systematically overdosed.

Most of the children cases who received a prescription below the minimum licensed age were either younger than 2 years of age (42%) or older than 12 years of age (23%). The drugs these children were prescribed comprised two different types, namely drugs that are not licensed / contra-indicated for use in children at all - used by children in the oldest age group (12 years and older) such as diclofenac, and drugs that are not indicated for use in children under a certain age, often a pre-school age (e.g. budesonide in asthmatic children under 6 years of age).

Several reasons for this situation may be recognized.[21] Because research in small children is complicated, the majority of drugs are not studied in small children.[22] Drugs that are not indicated for use in children under a certain age however are sometimes frequently used within these age groups, while safety and efficacy have not sufficiently been assessed to apply for licensing by the drug labeling authorities. Sometimes, there are good reasons for not prescribing such drugs to children below a certain age, for instance if a young child is not able to metabolize the drug or if the drug has been demonstrated not to be effective in certain age groups (e.g. tricyclic antidepressants in adolescents). Often however, drugs that might be useful have not been studied in children.

Over the recent years, several publications have indicated the urgent need for good evidence-based medicine, in adult as well as in pediatric care. The European Medicines Control Agency's 1997 'Note for guidance on clinical investigations in children' for instance unmistakably reflects the widespread concern regarding performing clinical trials in children, particularly when subjecting children to repeated invasive procedures. However, no substantial measures have been taken by European authorities to enhance the industry's willingness to invest in pediatric research and to facilitate the development and improvement of clinical research sites in Europe.

In conclusion, this study showed that the risk of receiving prescription for drugs below the minimum licensed age is high in young children with respiratory diseases, and in adolescents with e.g. migraine. These children may have a higher risk of adverse reactions. This situation is undesirable, and joined efforts should be taken to improve it.

References

1. Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates. A quiet frontier. Clin Pharmacokinet 1992;23:1-9.
2. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80:F142-4.
3. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998;316:343-5.
4. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
5. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of "off-label" and unlicensed drugs in paediatric intensive care unit [letter]. Lancet 1996;347:549-50.
6. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, Anker J vd. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000;320:79-82.
7. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, Anker JN vd. Unapproved and off-label use of drugs in a children's hospital [letter]. N Engl J Med 2000;343:1125.
8. Chalumeau M, Treluyer JM, Salanave B, Assathiany R, Cheron G, Crocheton N, Rougeron C, Mares M, Breart G, Pons G. Off label and unlicensed drug use among french office based paediatricians. Arch Dis Child 2000;83:502-5.
9. t Jong GW, Eland IA, Sturkenboom MCJM, Anker JN vd, Stricker BHC. Unlicensed and off-label prescription of drugs to children; population-based cohort study. BMJ 2002;In press.
10. Klinkman MS, Green LA. Using ICPC in a computer-based primary care information system. Fam Med 1995;27:449-56.
11. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
12. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
13. Guidance for industry; Content and format for pediatric use supplements. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Washington, 1996:1-6.
14. Nahata MC. New regulations for pediatric labeling of prescription drugs. Ann Pharmacother 1996;30:1032-3.
15. Summers RS, Summers B. Drug prescribing in paediatrics at a teaching hospital serving a developing community. Ann Trop Paediatr 1986;6:129-33.
16. Straand J, Rokstad K, Heggedal U. Drug prescribing for children in general practice. A report from the More & Romsdal Prescription Study. Acta Paediatr 1998;87:218-24.
17. Thrane N, Sorensen HT. A one-year population-based study of drug prescriptions for Danish children. Acta Paediatr 1999;88:1131-6.
18. Sanz EJ, Bergman U, Dahlstrom M. Paediatric drug prescribing. A comparison of Tenerife (Canary Islands, Spain) and Sweden. Eur J Clin Pharmacol 1989;37:65-8.
19. Madsen H, Andersen M, Hallas J. Drug prescribing among Danish children: a population-based study. Eur J Clin Pharmacol 2001;57:159-65.
20. Allen DB. Effect of inhaled beclomethasone dipropionate and budesonide on growth in children with asthma. Respir Med 1998;92 Suppl B:37-45.
21. Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. Br J Clin Pharmacol 2000;49:93-7.
22. t Jong GW, Eland IA, Stricker BHC, Anker JN vd. Information for paediatric use of medicines in a product information compendium. Paediatric and Perinatal Drug Therapy 2001;4:148-51.

Chapter 4
Stimulant and antidepressant use in children; unlicensed and off-label prescribing

Chapter 4

Stimulant and antidepressant use in children; unlicensed and off-label prescribing

Several studies in the US show a sharp increase in the use of psychotropic drugs in children, but little is known about the indications for use. We therefore determined the extent and nature of stimulant and antidepressant use in children in the Netherlands. We conducted a retrospective cohort study in the Integrated Primary Care Information (IPCI) project, a longitudinal observational database based on electronic medical records. Between 1995 and 2000, 81,618 children aged between 0 and 16 years were actively registered in the IPCI database. In this population, we estimated prevalence and incidence of stimulant and antidepressant use, and the indications for these drugs. Use of stimulants (methylphenidate) increased by a factor 7.7 between 1995 and 2000 to 4.9 users per 1,000 persons per year in 2000. Use of tricyclic antidepressants (TCAs) decreased, mostly since use for nocturnal enuresis decreased by a factor 4.6. However, the number of selective serotonin reuptake inhibitor (SSRI) users increased by a factor 5.4 during this period to 0.7 users per 1,000 persons per years in 2000. Twenty percent of stimulants, fourty-six percent of TCAs and thirty percent of SSRIs were prescribed off-label, mostly because they were not licensed for the indication for which they were used. Prescription of stimulants and SSRIs to children has increased during the second half of the 1990s in the Netherlands. Off-label use of stimulants and antidepressants is high mostly since these drugs are prescribed for indications they are not licensed for, or they are prescribed to children below the licensed age.

Introduction

Antidepressants and stimulants such as methylphenidate are among the most commonly prescribed psychotropic medications in children. Major concerns regarding these drugs include the lack of evidence regarding safety and efficacy of the majority of psychotropic agents in (especially younger) children, and the potential for overprescribing of stimulants such as methylphenidate (Ritalin®) in the treatment of attention-deficit/hyperactivity disorder.[1] Most of the antidepressants do not carry any specific labelling for the treatment of psychiatric conditions in children. Instead, the product labels of most antidepressants state that safety and efficacy have not been established in children. Moreover, various double-blind studies have shown that antidepressants are no more effective than placebos in treating depression in children and adolescents.[2] In recent years, the medical literature and popular press payed attention to increased pediatric usage of stimulants both in the US,[3,4] and in Europe.[5] Prescription rates of stimulants increased rapidly during the 1990s, with reported prevalences ranging between 3.6 and 4.9 percent in the US.[3,4,6] Still, little is known about pediatric use of stimulants and antidepressants in the general population. Therefore, we assessed the prescription patterns for stimulants and antidepressants, with a focus on time trends, gender, age differences, and off-label use of these drugs.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with data from computer-based patient records of a group of 150 general practitioners (GPs) in the Netherlands. The database is maintained by the Department of Medical Informatics of the Erasmus Medical Center Rotterdam (EMCR) since 1992, and contains coded and anonymous data on gender, age, symptoms, diagnoses and findings, and on prescriptions, their indications and dosage regimen. Summaries of the hospital discharge letters and information from clinical specialists are included as free text. Patient complaints and diagnoses are entered as text and coded according to the International Classification for Primary Care (ICPC).[7] Prescription drugs are coded according to the Anatomical Therapeutic Chemical classification (ATC).[8] The data are entered and stored directly by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who ensures anonymity of all information before further access is provided. To maximize completeness of information, GPs participating in the IPCI project are not allowed to have a system of paper records besides the electronic medical records. The IPCI database currently contains data on approximately 500,000 patients. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research.[9]

Design

We conducted a population-based cohort study in a dynamic population of children, who were registered with one of the IPCI general practices between January 1st, 1995 and January 1st, 2001. All subjects were followed from January 1st, 1995, or the date

of registration in the GP practice, whichever was latest until the earliest of one of the following censoring points; death, 17 years of age, transferring out of the practice, or date of last data sample.

Drug use

We identified all children, who used stimulants (ATC N06B) and antidepressants (ATC N06A) from the prescription file and retrieved the complete medical record for assessment of indication, and labeling status of prescriptions.

For each stimulant or antidepressant (tricyclic antidepressant (TCA), selective serotonin reuptake inhibitor (SSRI) or other antidepressant; e.g. moclobemide or trazodone) prescription, we assessed the indication from the indications as linked by the GP, or otherwise by manual inspection of the recorded symptoms and diagnoses. If the free text on symptoms, examinations and diagnoses did not yield a clear diagnosis, the indication was marked 'no indication'.

We assessed the licensing status of each stimulant and antidepressant prescription. In order to classify off-label status, we calculated the prescribed daily dose for each psychotropic prescription. Dosage & frequency, indication, and age of the patient at the moment of prescription were compared with the official product information text as provided by the Dutch Medicines Evaluation Board.[10 11] Since safety and efficacy had not been established for most of the antidepressants, most of them were unlicensed for use in children, if classification systems of earlier studies were used.[11 12] For this study, we classified the prescription off-label for age if the child was under 12 years of age in case of such an 'unlicensed' drug. For 12-16 year-olds, we used adult dosing regimens for off-label assessment. Prescriptions for which no indication was found, assessment for off-label use for indication was not conducted.

Covariates

Covariates of interest were age, gender, and health insurance as a proxy for socio-economic class. In the Netherlands, people with a higher income are privately insured, while others (except for all government employees) are insured through a public sickfund. The following age categories were created; (1) Preschoolers (0 through 5 years of age), (2) primary school-aged children (6 through 11 years of age), and (3) secondary / high school-aged children (12 through 16 years of age). During the period of follow-up persons could contribute time to multiple age categories.

Analysis

Comparisons between psychotropic drug users and non-users were conducted by using studentst-test for continuous variables and the Chi-square test for discrete variables. To describe utilization of antidepressants and stimulants we used the incidence and prevalence as frequency measures. Since TCA are used mostly for nocturnal enuresis, antidepressants used for this indication were excluded from the frequency estimates of psychtropic drug use. Incidence of drug use was estimated by dividing the number of new users (no previous use in the preceeding year) by the person-time of follow-up (person years; PY). The period-prevalence of use was calculated per year by dividing the number of users in one calendar year by the number of person years. 95%

confidence intervals were calculated on the basis of a Poisson distribution. In a next step we estimated age, gender and health insurance specific prevalence and incidence estimates. Incident use was estimated as prevalent use with non-use in the preceding calender year. Comparisons between strata were conducted by calculating prevalence and incidence ratios.

Results

Population characteristics

The source population comprised 81,618 children who accumulated a total of 229,396 person-years of follow-up. 379 children received 2130 prescriptions for stimulants and 265 children received 862 prescriptions for antidepressants during this period. TCAs were used by 114 (43.0% of antidepressant users) children for the treatment of nocturnal enuresis (NE) and by 58 children (21.8%) for the treatment of depression and anxiety (Non NE-related). SSRIs were prescribed to 87 (32.8%) children, and only 15 (5.7%) received other antidepressants. The most frequently used TCAs were imipramine (83% of NE-related and 39% of non -NE related TCA use), clomipramine (1% of NE-related and 23% of non -NE related TCA use) and amitriptyline (16% of NE-related and 21% of non -NE related TCA use). Paroxetine (58%), fluoxetine (20%), and fluvoxamine (18%) were the most frequently prescribed SSRIs. In the group of other antidepressants, moclobemide (48%) and mirtazapine (38%) were most frequently prescribed. Methylphenidate (Ritalin®) was the only stimulant prescribed, and accounted for all 2130 prescriptions. Four percent of all drug prescriptions studied were issued to preschoolers (0-5 years); percentages for stimulants and antidepressants were four and six percent, respectively.

Stimulant users were predominantly male (89.5%) and of lower socio-economic status, as measured by the type of insurance ($p=0.001$). Nocturnal enuresis-related antidepressant users were predominantly males (69%; $p<0.001$) but use of TCAs for NE was not related to socio-economic status (table 1). Use of antidepressants for non-NE related indications was distributed evenly among gender, but was higher in children of lower socio-economic status ($p=0.025$).

Time trends

The prevalence and incidence of stimulant and antidepressant prescriptions for children increased strongly during the study period. The numbers of stimulant users increased by a factor 7.7 between 1995 and 2000 from 0.64 to 4.90 users per 1,000 persons per year (PY) in 2000. The incidence increased by a factor 7.2 from 0.25 to 1.84 new users per 1,000 PY during the same period. For NE-related TCA use, the yearly prevalence of use decreased by a factor 6.9 from 1.53 to 0.32 users per 1,000 PY, whereas the yearly prevalence of not NE-related TCA use was stable during this period, with an average of 0.36 users per 1,000 PY. We observed a 5.4 fold increase in SSRI use up to 0.69 users per 1,000 PY. The incidence of use increased by a factor 8.1 to 0.52 new users per 1,000 PY, both in 2000 (figure 1), which was slightly at the expense of TCA use for not NE-related complaints that decreased by 40% to 0.32 new users per 1,000 PY.

In preschoolers, stimulant use increased by a factor 6.5 to 0.99 users per 1,000 PY;

Table 1 Characteristics of study population

Variable	Stimulant users (n=379)		TCAs for NE (n=114)		TCAs for non-NE (n=58)		SSRIs (n=87)		Total (n=81,618)
Age (median [IQR])	9.3 [7.3 – 11.7] [§]		8.6 [7.2 – 10.9] [§]		14.3 [10.3 – 16.3] [§]		15.1 [14.3 – 16.4] [§]		9.5 [4.8 – 14.7] [*]
Preschoolers (0-5 years)	38 (10)		11 (10)		6 (10)		2 (2)		
Elementary school children (6-11 years)	254 (67)		88 (77)		15 (26)		7 (8)		
Secondary school children (12-16 years)	87 (23)		15 (13)		37 (64)		78 (90)		
Gender		RR (95%CI)		RR (95%CI)		RR (95%CI)		RR (95%CI)	
Male (%)	**339 (89)**	8.1 (5.8-11.2)	**79 (69)**	2.0 (1.4-3.0)	25 (43)	0.7 (0.4-1.2)	**27 (31)**	0.4 (0.2-0.6)	51.1%
Female (%)	**40 (10)**	ref.	**35 (31)**	ref.	33 (57)	ref.	**60 (69)**	ref.	48.9%
Insurance form		RR (95%CI)		RR (95%CI)		RR (95%CI)		RR (95%CI)	
Sick Fund (%)	**224 (59)**	1.4 (1.2-1.8)	58 (51)	1.2 (0.8-1.7)	**39 (56)**	2.3 (1.3-4.2)	44 (51)	1.0 (0.6-1.50	50.9%
Private insurance (%)	**141 (37)**	ref.	45 (39)	ref.	**15 (34)**	ref.	40 (46)	ref.	45.8%
Unknown / Missing (%)	**14 (4)**		9 (10)		**4 (9)**		3 (3)		3.3%

TCAs = Tricyclic Antidepressants, NE = nocturnal enuresis, SSRIs = Selective Serotonin Reuptake Inhibitors, IQR = Interquartile range

[§] Age at the date of first prescription

[*] age at January 1st, 2000

Figure 1 Prevalence (solid line) and incidence (dashed line) of stimulant, TCA and SSRI prescriptions in the IPCI population between 1995 and 2000.

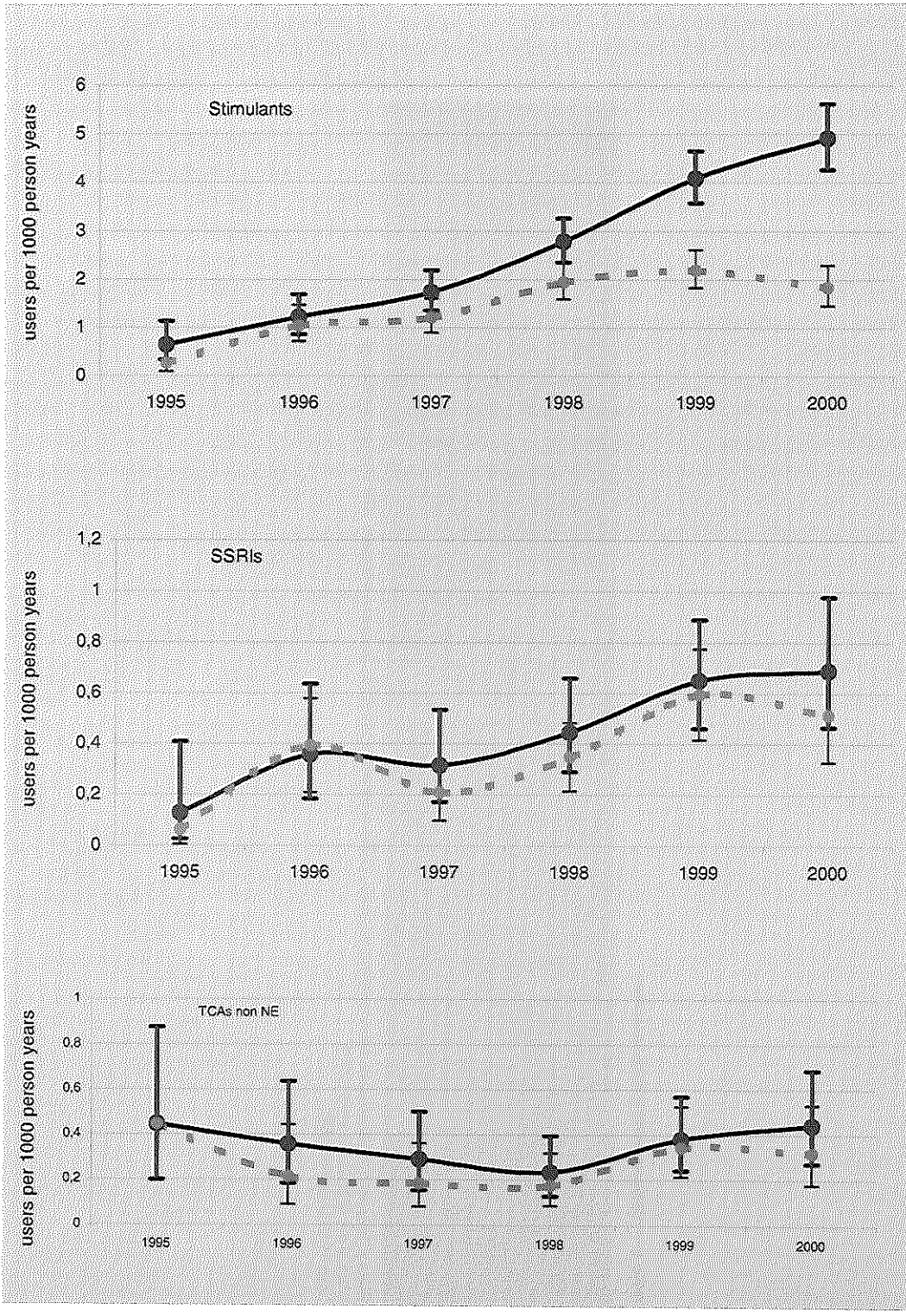


Table 2 Prescription trends in preschoolers and school-aged children

Variable	1995 (Rate)	1996 (Rate)	1997 (Rate)	1998 (Rate)	1999 (Rate)	2000 (Rate)
Prevalence per 1000 PY			Preschoolers (0 -5 years)			
Stimulants	0.2	0.5	0.5	0.6	1.1	1.0
TCAs (use not related to nocturnal enuresis)	0.2	0	0	0.1	0.1	0.1
SSRIs	0	0	0	0	0.1	0.1
			Primary school children (6 -11 years)			
Stimulants	1.5	2.1	3.4	5.4	7.6	8.8
TCA (use not related to nocturnal enuresis)	0.4	0.5	0.3	0.1	0.2	0.3
SSRIs	0	0	0	0.1	0.2	0.2
			Secondary school / high school children (12 -16 years)			
Stimulants	0.2	1.1	1.3	2.3	3.5	5.0
TCAs (use not related to nocturnal enuresis)	1.0	0.6	0.6	0.5	0.8	1.1
SSRIs	0.5	1.4	1.3	1.7	2.1	2.2

TCAs = Tricyclic Antidepressants, SSRIs = Selective Serotonin Reuptake Inhibitors

SSRIs were hardly used in this age group (table 2) and TCA use decreased. In NE-related TCA use, the decrease was roughly the same in preschoolers, primary school children and secondary / high school children while in not NE-related TCA use the decrease was much less in older children. The increase in stimulant use was high in 12-16 year olds, but highest in primary school children. Secular trends in utilization of TCAs, SSRIs and stimulants did not differ by gender.

Indication for prescription

For stimulants, the most common indication was attention-deficit/hyperactivity disorder (ADHD), which was the indication in 84% of the prescriptions in 296 (78%) patients. ADHD is a registered indication for stimulant use, as well as narcolepsy. Most common other indications used were "other problems behavior child" (6 patients), and "irritable/angry feeling/behavior" (5 patients). For 51 patients (13%), the indication for stimulant use could not be identified. For 38 (10%) patients, the indication seemed ADHD, but no clear diagnosis had been made. For TCAs, the most common indications were nocturnal enuresis (105 (61%) patients), followed by depression (10 (6%) patients), headache (11 (6%) patients), anorexia nervosa or boulimia (8 (5%) patients), state of anxiety/anxiety disorder (7 (4%) patients), ADHD (7 (4%) patients). For 13 (8%) patients no clear indication was found.

For SSRIs, depression was the most common indication (43 (49%) patients), followed by "state of anxiety/anxiety disorder" (11 patients) and "anorexia nervosa / boulimia" (8 patients). For 8 patients no clear indication was found.

Off-label prescription

Of stimulants, 19.7% was prescribed off-label, but off-label prescriptions amounted to 41.1% for antidepressants. Prescriptions were mainly off-label for indication - 80 and

Table 3 Off-label prescription of stimulants and antidepressants.

Classification	*Stimulants (n=2130)*		*TCAs (n=499)*		*SSRIs (n=305)*	
In accordance with the product license	1714	(80.5)	269	(53.9)	213	(69.8)
Off-label for age	80	(3.8)	21	(4.2)	15	(4.9)
Off-label for dosage	3	(0.1)	10	(2.0)	1	(0.3)
Off-label for indication	151	(7.1)	80	(16.0)	66	(21.6)
Off-label for age and indication	2	(0.1)	110	(22.0)	3	(1.0)
Off-label for age, dos age and indication			6	(1.2)		
No indication for use	190	(8.9)	15	(3.0)	11	(3.6)

TCAs = Tricyclic Antidepressants, SSRIs = Selective Serotonin Reuptake Inhibitors

* RR for non-NE related use only

88 percent of off-label prescriptions for stimulants and SSRIs, respectively (table 3). Stimulants were prescribed mostly off-label for indication in children aged 12-16 years (21%); 15 and 14% for 0-5 year olds and 6-11 year olds, respectively.

Discussion

In the Dutch population of children aged 0-16 years, the use of stimulants and SSRIs increased significantly between 1995 and 2000, whereas use of TCAs as antidepressant remained stable. Despite the increase in use the absolute utilization rates of stimulants and SSRIs are much lower than in the US. These findings confirm the results of a recent pharmacy based study in the Netherlands that reported a period prevalence for stimulants use of 7.4 per 1000 persons in 1999 (0-19 years of age), and an incidence rate of 3.4 per 1000.[5] The higher prevalence and incidence rates in that study (prevalence 7.4 versus 4.9/1000 and incidence 3.4 vs 1.8) can be explained by inclusion of prescriptions issued by specialists in a pharmacy dispensing database, that are not always included in the GP database. On the other hand , the denominator is less well-established in a pharmacy based database and no information is available on indications. We observed that the majority of stimulants (at least 84%) were prescribed for ADHD according to the licensed indication, but anti-depressants were often prescribed off-label for indication. Our results of a male predominance of treated attention-deficit/hyperactivity disorder and an increase of stimulant use in females are consistent with other studies.[3,5]

Despite current debates on off-label usage, prescriptions for both stimulants and SSRIs are strongly increasing in all age groups. Many articles have raised concerns about increases in the number of prescriptions of psychotropic drugs and consequent concerns of harmful effects that could be explained by potential overuse, inappropriate prescriber practices, and substitution for counseling or comprehensive therapy. A study by Jensen *et al.* suggests that many children with ADHD go undiagnosed and untreated,[13] whereas others treated with stimulant medications do not meet the diagnostic criteria for ADHD. However, potential positive influences of increased recognition and treatment of previously unrecognized mental disorders, improvements in access to psychiatric care, and increased education about the proper use of these medications must also be considered.[14] The attention that children with ADHD have received in the lay and medical press over the last decade has resulted in an increased recognition of children with symptoms of this disorder. Unfortunately, the thereupon-following pressure on doctors to assess new cases within time limits might be a factor leading to superficial practice, and diagnosing by undertrained physicians.14 Recent guidelines indicate that medication is best titrated against adverse and desirable effects, rather than body weight.[15] We question this approach since effectiveness and (long term) safety are uncertain. When reasonable evidence of safety and efficacy is established, clinicians should however not be deterred from using medications in young patients because of gaps in our knowledge of psychopharmacology in childhood. Unfortunately, the current situation is often different and long-term effects of use are unknown. Exploration of the impact of these psychotropic agents on, for instance, the developing brain is necessary, using technologies such as PET, NMS and functional MRI.[16]

The results of this utilization study is based on prescription records. Although this has given us the opportunity to study indications that are not available in dispersing data, we will have underestimated actual use. Psychiatrists and pediatricians prescribing will not be completely covered in the database, which bares a limitation.
In summary, we showed that prescribing of psychotropic medications to children is increasing in the primary care setting. Future studies should provide insight into diagnostic appropriateness and adverse and beneficial treatment outcomes for both stimulant and antidepressant usage.

References

1. Jensen PS, Bhatara VS, Vitiello B, Hoagwood K, Feil M, Burke LB. Psychoactive medication prescribing practices for U.S. children: gaps between research and clinical practice. J Am Acad Child Adolesc Psychiatry 1999;38:557-65.
2. Fisher RL, Fisher S. Antidepressants for children. Is scientific support necessary? J Nerv Ment Dis 1996;184:99-102.
3. Safer DJ, Zito JM, Fine EM. Increased methylpheridate usage for attention deficit disorder in the 1990s. Pediatrics 1996;98:1084-8.
4. Safer DJ, Krager JM. The increased rate of stimulant treatment for hyperactive/inattentive students in secondary schools. Pediatrics 1994;94:462-4.
5. Schirm E, Tobi H, Zito JM, de Jong-Van Den Berg LT. Psychotropic medication in children: a study from the netherlands. Pediatrics 2001;108:E25.
6. Zito JM, Safer DJ, dosReis S, Magder LS, Gardner JF, Zarin DA. Psychotherapeutic medication patterns for youths with attention- deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 1999;153:1257-63.
7. Klinkman MS, Green LA. Using ICPC in a computer-based primary care information system. Fam Med 1995;27:449-56.
8. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
9. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
10. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
11. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, Anker JN vd. Survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001;108:1089-93.
12. t Jong GW, Eland IA, Sturkenboom MCJM, Anker JN vd, Stricker BHC. Unlicensed and off-label prescription of drugs to children; population-based cohort study. BMJ 2002. In press.
13. Jensen PS, Kettle L, Roper MT, Sloan MT, Dulcan MK, Hoven C, Bird HR, Bauermeister JJ, Payne JD. Are stimulants overprescribed? Treatment of ADHD in four U.S. communities. J Am Acad Child Adolesc Psychiatry 1999;38:797-804.
14. Rushton JL, Whitmire JT. Pediatric stimulant and selective serotonin reuptake inhibitor prescription trends: 1992 to 1998. Arch Pediatr Adolesc Med 2001;155:560-5.
15. Hill P, Taylor E. An auditable protocol for treating attention deficit/hyperactivity disorder. Arch Dis Child 2001;84:404-9.
16. Vitiello B. Pediatric psychopharmacology and the interaction between drugs and the developing brain. Can J Psychiatry 1998;43:582-4.

Chapter 5
Adverse drug reactions in relation to unlicensed and off-label drug use

Chapter 5.1

Adverse events associated with unlicensed or off-label prescription; a case series

In pediatric care, unlicensed and off-label prescription of drugs is common. It has been suggested that off-label prescriptions increase the chance of adverse events. We studied adverse events attributed to off-label drug use notified to a spontaneous reporting system. All adverse events reported to the spontaneous Adverse Event Reporting System at the Columbus Children's Hospital, Ohio for children aged 0-16 years between January 1998 and September 2001 were reviewed for off-label drug use. FDA-approved labeling information texts were used as reference. A committee of experts assessed the causal relationship between the adverse event and use of off-label drugs. We excluded all drug withdrawals, drug-abuse syndromes, and intentional drug-overdoses. Five adverse events attributed to off-label drug use are described in detail. From the database, we extracted 282 reports of adverse events of which 142 were attributed to licensed drugs that were prescribed according to the product labelling text. Of the remaining 140 reports, 9 were excluded because of age, 25 as it concerned a deliberate overdose and 14 reports were excluded as the causal relationship was considered possible or unlikely, leaving 92 reports for analysis. Eleven (12%) of these reports concerned unlicensed drugs, 81 (88%) reports involved off-label prescription of the causal agent, of which 50 were off-label for age (62%), 34 off-label for indication (42%), 25 off-label for dose (31%), and 4 for route of administration (5%). This study shows that off-label use of drugs in children can lead to severe adverse events. The risk of off-label drug use may be higher than was previously assumed.

Introduction

The benefits of pharmacotherapy are generally well studied, but there is less knowledge about the frequency and severity of adverse effects. For economical reasons, clinical trials are limited in size and duration, and therefore the full range of adverse drug reactions (ADRs) attributable to a certain agent is often unknown. Especially rare ADRs and chronic effects are easily missed. Thus, the findings of clinical trials, particularly with regard to ADRs, may not be generalizable.[1]

From the pediatrician's perspective, there is an additional major deficiency: the premarketing studies rarely evaluate pediatric populations. If pediatric studies are done, they often consist of very limited numbers of patients, and not all groups are covered. The relation of ADRs to the use of the drug outside the terms of regulatory approval (off-label use) has only been studied in one survey in the UK.[2] An increased, although non-significant risk was found between ADRs and off-label use of drugs in children. Adverse reactions to licensed drugs are monitored by spontaneous reporting of ADRs by prescribers and by post marketing surveillance by the manufacturer. Relatively little attention, however, is paid to the question whether such events may be caused by unlicensed or off-label drug use.[3] We studied adverse reactions attributed to off-label drug use notified to a spontaneous reporting system.

Methods

Setting

The Columbus Children's Hospital is a 300 beds/cribs hospital, affiliated with Ohio State University in Columbus, Ohio. The Spontaneous Adverse Event Reporting system in this hospital includes all spontaneously reported suspected adverse drug reactions since 1993. The system contains detailed clinical information regarding the adverse event, dosage, route of administration, formulation, and duration of use of the suspected drug. In addition, the system stores data on patient characteristics, comorbidity, and concurrent medication. Emergency department visits, hospital admission, ICU admission and home care visitations are included.

Analysis

All reports notified to the Spontaneous Adverse Event Reporting system during the 4-year-period between January 1st, 1998 and September 1st, 2001 were reviewed for use of unlicensed drugs or off-label prescription of licensed drugs. FDA-approved labeling information texts were used as a reference. Prescription of drugs that were contraindicated for use in children, or for which the pediatric use subsection indicated that safety and efficacy of the drug had not been established in children were classified 'unlicensed'. Prescription of drugs for which the age, the indication, dose & frequency, route of administration or dosage form was not in accordance with the licensed product was classified 'off-label'. A committee of experts including physicians as well as pharmacists assessed the causal relationship between the reported adverse events and unlicensed or off-label drug use. Reports regarding patients older than 16 years of age were excluded, as well as all drug withdrawal syndromes, drug-abuse syndromes, and complications of intentional overdoses.

Table 1 Characteristics of cases (n=92)

	Frequency	%
Severity		
increased monitoring	4	4%
treatment/intervention	44	48%
initial/prol. hospitalization	36	39%
near death	8	9%
Class		
known side effect	23	25%
unexpected effect	49	53%
drug interaction	2	2%
exaggeration	5	5%
overdosage	13	14%
Causality		
probable	51	55%
definite	41	45%
Gender		
male	49	53%
female	43	47%
Age groups		
< 1 month	2	2%
1- 6 months	11	12%
7 - 23 months	6	7%
2 - 5 years	19	21%
6 - 11 years	38	41%
12 - 16 years	16	17%
Unlicensed subcategory		
Contra-indicated	5	5%
No research conducted	6	7%
Off-label subcategory *	81	88%
Age	50	54%
Dose	25	27%
Indication	34	37%
Dosage form	0	0%
Route of administration	4	4%
Total	92	

* Numbers add up to more than 92 because more than one category may be involved

Results

Report characteristics

From the database, we gathered all 282 reports of suspected ADRs during the study period of which 142 (50%) concerned adverse events to licensed drugs that were prescribed according to the product labelling text. Of the remaining 140 reports, 9 (6%) were excluded because the patients were older than 16 year, 25 (18%) as it concerned an intentional overdose and 14 (10%) as the causal relationship was considered possible or unlikely. For the remaining 92 cases with unlicensed and off-label drug use (66%), characteristics are shown in table 1.

Of these, eleven (12%) cases concerned unlicensed drugs - of which five were contraindicated for use in children and for six no information was available regarding use in children. Eighty-one (88%) concerned off-label drug prescriptions. Five adverse events attributed to unlicensed or off-label drug use are described in detail because they demonstrate that the use of unlicensed drugs or off-label prescription of licensed drugs may lead to adverse events.

Case histories

Patient A

A two-day-old female (weight 3Kg) was sedated with 700 mg chloral hydrate (233

mg/kg) to facilitate an MRI. Following infusion she became lethargic, hypotensive, and hypothermic. Ventilation was suppressed with a respiratory rate of 30/minute and an arterial oxygen saturation of 90%. She was treated with intravenous fluids, warming and oxygen therapy. The use of chloral hydrate was off-label for age and dosage. Chloral hydrate is not licensed for children less than 1 month of age. In addition, the normal dose for children above 1 month of age is 60-75 mg/kg.

Patient B

Six-year-old male (weight 24Kg) who had an unremarkable medical history was admitted to the intensive care unit (ICU) after being hit by a car. He sustained multiple injuries including right parieto-occipital fracture with subdural hemorrhage, liver laceration, left distal femur fracture, right clavicle fracture and left great toe laceration. On the ICU paracetamol, mannitol, ranitidine and intravenous fluids were administered. On the second day of admission the patient experienced respiratory distress with tachypnea (ventilation 38/minute), nasal flaring and a blood oxygen saturation of 93% within minutes after his nightly codeine administration (dosage schedule 15 mg codeine i.v. every 3 hours). In addition he developed urticaria, involving most of his chest. He was treated with intravenous diphenhydramine, methylprednisolone and an aerosol containing salbutamol. Codeine use was discontinued and the patient recovered completely. Use of codeine was off-label for route of administration, since it was administered intravenously instead of orally.

Patient C

An eleven-year old male (weight 59Kg), with an unremarkable medical history, visited his physician and was treated with amoxicillin and naproxen for streptococcal pharyngitis and plantar fasciitis. One day later he received a triamcinolon injection. About 5-6 hours after injection, he developed a generalized rash and wheezing. The child's mother administered diphenhydramine because of wheezing. At the Emergency Department he received epinephrine and diphenhydramine with some relief. In addition, he received methylprednisolone, and within 15 minutes he developed a diffuse erythema multiforme, itching, and Quincke's edema. He was treated with famotidine, epinephrine and hydroxyzine and later with ranitidine, diphenhydramine, and epinephrine.

After six days physical examination still shows a diffuse, non-blanching, non-palpable, macular erythematous rash. Nevertheless, the patient again received 5 mg prednisone, followed by itching of feet, hands, and several new lesions on palm, forearms, which appeared 80 minutes later. He was treated with 25 mg diphenhydramine intravenously with relief of symptoms In this patient, use of methylprednisolone was off-label for age and indication. Streptococcal pharyngitis is not a licensed indication for use of corticosteroids in children.

Patient D

A sixteen-year-old male (weight 58Kg) with an osteosarcoma had an implantofix placed. For pain is his left leg, he received 10 mg of morphine intravenously. Within minutes he became unresponsive with perioral cyanosis and required artificial venti-

lation (oxygen blood saturation 76%). After 0.4 mg naloxone he recovered immediately. In this patient, use of morphine was off-label for dose and frequency.

Patient E

An eleven-year-old male (weight 32Kg) with attention deficit hyperactivity disorder presented with a slurred speech, difficulty of swallowing, shivering, and lethargy, followed by right fist clenching and right arm stiffness. The patient was unable to hold up his head or keep his eyes open. One day prior to presentation his medication had been changed from dextroamphetamine to 1.5 mg risperdone twice a day. He was treated with 25mg diphenhydramine intravenously with good initial response. Upon leaving the hospital, his symptoms returned after which he was admitted overnight for observation. No further reactions were noted. Risperdone is contraindicated for use in children.

Discussion

In this case series, we evaluated 92 reports of adverse reactions attributed to the use of off-label drugs. Turner *et al.* found ADRs in 6% of users of unlicensed drugs or off-label use of licensed drugs, and in 4% of users of licensed drugs,[2] and a higher occurrence of ADRs in unlicensed and off-label use in hospital settings. We were not able to determine the proportion of unlicensed and off-label use of drugs in the Columbus Children's, and therefore could not determine the relative risk of ADRs in unlicensed and off-label drug use in this setting.

The cases presented in the results give an impression of the effects of unlicensed and off-label drug use. The cases were selected because they were illustrative for several aspects of the problem that causes unlicensed and off-label drug use. In all five case histories, the adverse event was probably causally related to the unlicensed or off-label use of the suspected drug. This demonstrates that when drugs are not used in accordance with the product information text, this can lead to serious ADRs. Drug overdosing can be harmful and even life threatening, as is shown in patient A. In children, dosing errors occur much more frequently than in adults. Koren *et al.* reported seven of such cases and considered dosing errors as a "neglected iatrogenic disease in pediatrics".[6] Such errors may sometimes cause severe adverse events. Patient B is an example of the lack of suitable pediatric formulations. Because intravenous administration of codeine has not been proven safe and efficacious in children, administration of this drug is done with a formulation that is designed for use in adults. For many drugs, formulations for children have to be manufactured extemporaneously. Recently, Nahata *et al.* published priority listings for pediatric formulations for which no stability and / or compounding data were available.[7] That report contained some disturbing data indicating that there is lack of consistency of pharmacy practice and knowledge on the stability and safety of formulations.[8]

Patient C shows the consequences of drug use for indications that lack proper licensing. This practice is very common, especially in young children, where drugs are mostly licensed for few indications. Use for other indications is not studied, but as physicians use these drugs for many similar indications, the industry has no (financial) incentives to conduct research and to apply for labeling.

Patient D illustrates the effects of off-label dosing. The patient developed a severe adverse event after administration of morphine at a level well beyond the licensed dosage in children. Patient E shows the serious adverse effects following use of drugs that are not licensed for use in children. Especially in adolescence, physicians often treat patients with drugs that are licensed for use in adults, but not in children. Information in drug information texts is not always clear about the definition of 'children'.

Drug regulating authorities, like the US Food and Drug Administration (FDA), recognized the problem of unlicensed and off-label use as early as 1960, and they clearly stated; "Drugs for use in children must be tested in children".[9] However, over the following 40 years, several reviews of the Physicians' Desk Reference (PDR) and reviews of recently approved new molecular entities (NME) revealed little change in the proportion of registered drugs without pediatric labeling.[10-14] Introduction of new regulations to enhance pediatric labeling was rarely beneficial, and often had an adverse effect.[15,16] Most drugs are not studied in children before introduction to the market, and are not available in applications for use in children.

In conclusion, we gave some examples of adverse events, which were attributed to the use of unlicensed and off-label drug prescriptions in children. The use of unlicensed and off-label drugs in children is high. Although our case-series does not give insight into the frequency of adverse events by the use of unlicensed drugs and off-label prescriptions, the health risks associated with off-label drug use might be higher that is commonly assumed because only 50 percent of all reports were attributed to licensed drugs which were used according to the product information. Of course, we cannot exclude that this predominance of reports of adverse events attributed to unlicensed drugs or to off-label use of licensed drugs were caused by reporting bias. Such reporting bias might result if doctors more readily report adverse events to such drugs than to drugs that are used according to the product information. More emphasis should be given to adequate drug studies in children. Not only is there an ethical and legal imperative to study safety and efficacy in children of drugs of potential use in children, also a negative health outcome when using unlicensed drugs or off-label prescriptions should be an important motivation for a strong policy of licensing authorities regarding pediatric labeling.

References

1. Kaufman DW, Shapiro S. Epidemiological assessment of drug-induced disease. Lancet 2000; 356:1339-43.
2. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 1999;88:965-8.
3. Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. Br J Clin Pharmacol 2000;49:93-7.
4. Guidance for industry; Content and format for pediatric use supplements. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Washington, 1996:1-6.
5. Nahata MC. New regulations for pediatric labeling of prescription drugs. Ann Pharmacother 1996;30:1032-3.
6. Koren G, Barzilay Z, Greenwald M. Tenfold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. Pediatrics 1986;77:848-9.
7. Pai V, Nahata MC. Need for extemporaneous formulations in pediatric patients. J Pediatr Pharm Ther 2001;6:107-19.

8. Walson PD. "Pediatric" formulations. J Pediatr Pharm Ther 2001;2001(6):97-9.
9. Wilson JT. An update on the therapeutic orphan. Pediatrics 1999;104(3 Pt 2):585-90.
10. Wilson JT. Pragmatic assessment of medicines available for young children and pregnant or breast-feeding women. Basic and Therapeutic Aspects of Perinatal Pharmacology. New York, NY: Raven Press, 1975:411-21.
11. Offices of Drug Evaluation Statistical Report. Rockville, MD: Center for Drug Evaluation and Research. Food and Drug Administration; Public Health Service; US Dept of Health and Human Services, 1989.
12. Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates. A quiet frontier [comment]. Clin Pharmacokinet 1992;23(1):1-9.
13. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Committee on Drugs, American Academy of Pediatrics. Pediatrics 1995;95(2):286-94.
14. Cote CJ, Kauffman RE, Troendle GJ, Lambert GH. Is the "therapeutic orphan" about to be adopted? Pediatrics 1996;98(1):118-23.
15. The Pediatric Exclusivity Provision. January 2001 Status Report to Congress. Department of Health and Human Services. U.S. Food and Drug Administration, 2001.
16. t Jong GW, Anker JN vd, Choonara I. FDAMA's written request list: medicines for children. Lancet 2001;357(9253):398.

Chapter 5.2

Association of deptropine with neuropsychiatric events in children

Published case reports associated the antihistamine deptropine, which is unlicensed but regularly used for allergic rhinitis and asthma in children, with neuropsychiatric events. We conducted a retrospective cohort study to investigate this association. By using the computerized medical records of the Integrated Primary Care Information (IPCI) database we identified all prescriptions for systemic antihistamines issued to children between 1 and 10 years of age during the study period January 1st, 1995 and January 1st, 2000. The occurrence of hallucinations, confusion, agitation, aggressive behaviour or ataxia during use of antihistamines were assessed by medical reviewers who were blinded to exposure. The risk of any of these neuropsychiatric events during use of deptropine was compared to the risk of such events to other antihistamines that were also prescribed for respiratory indications. The final study cohort comprised 1657 users of deptropine and 4515 users of other antihistamines among which promethazine, ketotifen and loratidine were most frequently used. The incidence rate of neuropsychiatric reactions was 5.6 (95%CI: 1.6-19.3) times higher during use of deptropine than during use of other antihistamines. Deptropine was associated with an excess rate of 3.1 cases per 100 person-years of exposure. The incidence of neuropsychiatric reactions was 3.8 fold higher in the first episode of use than in subsequent episodes and was highest for children 2-10 years of age. Our study demonstrated that deptropine is associated with an increased risk of neuropsychiatric events in children. As this drug is not licensed for use in children and therapeutic alternatives are available, its use should be discouraged.

Introduction

Deptropine is an anticholinergic drug with anti H1-histaminergic, anti-serotonergic and central depressive action. Deptropine has been marketed in the Netherlands since 1962 for the treatment of symptomatic allergic rhinitis and chronic bronchitis but it was never specifically licensed for use in children. In 1992, a case-series reported on 16 children aged 1-10 years who developed hallucinations, agitation, aggressive behavior, ataxia or anxiety during use of deptropine.[1] The reported neuropsychiatric effects occurred within 1-3 days after administration and predominantly at high doses of deptropine. Following these reports of adverse reactions, deptropine was removed from the pediatric asthma guidelines. During the past years, there was a decrease in the prescription of deptropine to young children, but nevertheless prescription of deptropine is still substantial.[2] So far as we are aware, the association between deptropine and neuropsychiatric events has never been studied in an epidemiological study. Therefore, we investigated the incidence of neuropsychiatric reactions during use of deptropine and other antihistaminic agents.

Methods

Setting

This study was performed with data from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with computer-based patient records from a group of 150 general practitioners (GPs) in the Netherlands. The database is maintained by the department of Medical Informatics of the Erasmus Medical Center Rotterdam (EMCR) since 1992, and contains coded and anonymous data on gender, age, patient identification, GP identification, GP symptoms, diagnoses and findings, and on prescriptions, their indications and dosage regimen. Summaries of the hospital discharge letters and information from clinical specialists are included as free text. Patient complaints and diagnoses are entered as free text and coded according tot the International Classification for Primary Care (ICPC).[3] Prescription drugs are coded according to the Anatomical Therapeutic Chemical classification (ATC).[4] The data are entered and stored directly by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who ensures anonymity of all information before further access is provided. To maximize completeness of information, GPs participating in the IPCI project are not allowed to have a system of paper records besides the electronic medical records. As of January 2002, the IPCI database contains data on more than 500,000 patients. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research.5

Source and study population

The source population comprised all children aged 1-10 years during the study period between January 1st, 1995 and January 1st, 2000 who were registered with one of the GPs collaborating with IPCI. We excluded children less than one year of age, because recognition of neuropsychiatric events is very difficult in these young children. We selected all children from the source population who had been registered

with the GP for at least three months, and who received at least one prescription for a systemic antihistamine (ATC code R06A). The study cohort was divided into deptropine users and users of other systemic antihistamines. To deal with potential confounding by indication, we included only users of prescriptions of systemic antihistamines which were prescribed for respiratory indications.

Exposure definition and follow-up

Persons in the study cohort were followed from the prescription date of an antihistamine until the end of that prescription. The duration of each prescription was calculated from the prescribed quantity and dosing regimen. Consecutive prescriptions were combined into one treatment episode if the next prescription was prescribed within 30 days after the end of the previous prescription and if the dosage was the same. Follow-up stopped at the end of the last prescription in that episode, the prescription of a different antihistamine, the end of the study period, occurrence of a neuropsychiatric event, death or transferring out whichever was earliest.

Outcome definition

The neuropsychiatric outcomes of interest were identified from free text searches in the medical history of the child. The outcome of interest was defined as a notification of hallucinations, confusion, agitation, aggressive behaviour or ataxia. Potential cases were validated independently by two physicians through review of the medical record while being blinded to the type of exposure. Potential cases were excluded if the neuropsychiatric state could be explained by a concomitant disease or condition, such as severe infections, otitis media or fever. After review, we investigated for every outcome event whether it had occurred during or within 30 days after the duration of the prescription or outside this exposure window.

Covariates

Apart from the type of drug each antihistamine treatment episode was characterized by the following variables which were considered to be potential confounders or effect modifiers: age, gender, cumulative duration of prior use, dosage; indication; concomitant use of anti-asthmatics, antidepressants, acetaminophen, antibiotics, or vaccinations; presence of asthma.

Analyses

The incidence rate and 95% confidence intervals of neuropsychiatric outcomes were calculated per person-year of exposure and compared between deptropine and other antihistamines based on a Poisson distribution. If a child received more than one type of antihistamine during the study period, it contributed the corresponding person-time to each drug exposure category. All co-factors which were univariately associated with any of the specific outcomes at a p-value below 0.10, were included in the final multivariate Poisson regression model that was used to obtain the adjusted relative risk for each specific outcome during use of deptropine. In a second step we stratified by age to study potential effect modification. All statistical analyses were performed using SAS 6.2 and SPSS-PC 10.

Table 1 Patient characteristics

	Deptropine users (N=1657)	Other histaminic users with previous OCF use (n=4515)*
Gender (%)		
Male	52.7	53.0
Female	47.3	47.0
Insurance (%) *		
Private	38.7	41.5
Sickfund	54.6	55.9
Age mean (SD) (months)	30.6 (21.7)	64.2 (33.6)
Age category (%) **		
1-2 years	52.8	11.4
2-6 years	41.2	50.0
6-10 years	6.0	38.6
Total number of episodes	2568	7203
Person-time of exposure (years)	185.9	589.1
Episodes of same drug per person (%)		
1	51.0	65.4
2	22.9	18.1
3	11.9	7.6
4	6.7	3.8
5+	7.5	5.1
Most important indications for use (%)		
Coughing	27.0	25.6
Allergic rhinitis	0.1	11.0
Acute upper respiratory tract infection	16.7	10.0
Asthma	10.9	8.8
Acute bronchitis	12.2	2.8
Chronic bronchitis	1.7	1.8
Acute laryngitis/tracheitis	1.4	1.2
Unknown	25.7	35.3

* insurance status was unknown for some patients, ** age at time of first prescription

Results

The source population comprised 53,747 children between 1 and 10 years. In this population, we identified 1657 users of deptropine (3.1%) and 4515 users of other antihistamines (8.4%). Prescription rates of deptropine varied from 38 users per 1000 children per year in 1996 to 10 users per 1000 children in 2000. Deptropine users were significantly younger (median age: 13 months) than users of other antihistamines (median age: 70 months). The majority of deptropine users were £ 2 years of age whereas users of other systemic antihistamines were mostly between 2 and 6 years of age (table 1). Most of the children had only one episode of use of either deptropine or other anti-histamines. The duration of an average prescription episode was 27 days for deptropine and 30 days for other antihistamines. The most frequently used other systemic antihistamines were ketotifen with 24.1%, promethazine with 20.0%, loratidine with 13.8%, and cetirizine with 8.5% of total antihistamine exposure time. During exposure to antihistamines, we identified 11 cases of neuropsychiatric events that could not be explained by an underlying medical condition. Age was associated with the occurrence of the neuropsychiatric outcome; the incidence decreased with increasing age (p-trend<0.01). Concomitant use of antiasthmatics (RR=1.4, 95%CI: 0.4-5.3), the presence of asthma (RR=1.3, 95%CI: 0.4-4.4), female gender (RR=1.6, 95%CI: 0.5-5.3) and sickfund insurance (RR=2.1, 95%CI: 0.6-7.9) were associated with a slight but non-significantly increased risk of a neuropsychiatric event. None of the cases had used stimulants or antibiotics, and none of them had been vaccinated during the deptropine exposure window (Table 2).

Table 2 Incidence of neuro-psychiatric event by covariate status

	Person years	cases	Incidence per 1000 PY	RR	95%CI
Patient characteristics					
Age groups					
1-2 years	127.4	7	55.0	6.4	1.7-24.7
2-6 years	349.1	3	8.6	1.0	Reference
6-10 years	298.6	1	3.3	0.4	0.04-3.7
Health insurance *					
Private insurance	329.3	3	9.1	1.0	Reference
Sick fund	420.0	8	19.0	2.1	0.6-7.9
Gender					
Male	444.9	5	11.2	1.0	Reference
Female	330.2	6	18.2	1.6	0.5-5.3
Concomitant drug use					
Stimulants					
Non-users	770.0	11	14.3	1.0	Reference
Users	5.1	0	-	-	
	768.8	11	14.3	1.0	Reference
Vaccines					
Non-users					
Users	6.3	0	-	-	
Anti-asthmatics					
Non-users	612.2	8	13.1	1.0	Reference
Users	162.9	3	18.4	1.4	0.4-5.3
Acetaminophen					
Non-users	709.7	10	14.1	1.0	Reference
Users	65.4	1	15.3	1.0	0.1-8.5
Systemic antibiotics					
Non-users	646.8	11	14.6	1.0	Reference
Users	128.2	0	-	-	
Comorbidity					
Asthma					
No	538.3	7	13.0	1.0	Reference
Yes	236.8	4	16.9	1.3	0.4-4.4
Total	775.1	1	10.0		

* 5% of persons had no insurance mentioned, therefore the numbers do not add up to 100%.

Table 3 Association between use of deptropine and occurrence of neuro-psychiatric events

	Cases	PY	IR per 1000 PY	RR_{crude}	RR_{adj}	95%CI
Deptropine	7	185.9	37.7	5.5	5.6	1.6-19.3
Other antihistamines	4	589.1	6.8	1.0	1.0	Reference
1 - ≤ 2 years of age						
Deptropine	4	84.1	47.6	6.8	0.7	0.2-3.1
Other antihistamines	3	43.3	7.0	1.0	1.0	Reference
> 2 - 10 years of age						
Deptropine	3	101.8	25.0	13.6	16.3	1.1-158
Other antihistamines	1	545.9	1.83	1.0	1.0	Reference

* adjusted for gender, health insurance and anti-asthma medication

Seven neuropsychiatric events occurred during use of deptropine (IR: 37.7 per 1000 person-years) and 4 during use of other anti-histaminics (IR=6.8 cases per 1000 person-years). Use of deptropine increased the risk of neuropsychiatric effects more than five-fold (relative risk (RR) = 5.6; 95%CI: 1.6-19.3) and was associated with an excess incidence of 30.9 cases per 1000 PY of treatment. The corresponding number needed to harm was 446 prescriptions of deptropine for every neuropsychiatric event.

Most of the events occurred during the first episode with an incidence of 40 cases per 1000 person-years for deptropine during first use and 17 cases per 1000 person-years during subsequent prescriptions. Age significantly modified the relationship between use of deptropine and the occurrence of neuropsychiatric events. Among children of 1-2 years of age we did not observe an increase in risk but the risk was significantly elevated in 2-10 year-olds. (RR=16.3, 95%CI: 1,1-15.8). All seven cases occurring during use of deptropine were prescribed regular dosages, the mean was 0.05 mg/kg for 1-year-olds, and 0.03 mg/kg for older children.

Discussion

This study shows that pediatric use of deptropine is associated with an increased risk of neuropsychiatric events. A case series in 1992 described the occurrence of agitation, hallucinations, ataxia and aggression during use of deptropine in 16 children between the age of 1 and 10. It was suggested that the events were dose-related and could be explained by the antimuscarinic properties of the drug.[1] This has resulted in removal of deptropine from the pediatric asthma guidelines and to a subsequent decrease in usage. Following another report regarding the association of neuropsychiatric events with deptropine use,[6] an important information compendium in the Netherlands lowered the dosage regimen for all children to one-third of the original dose for all pediatric age groups.[7]

We did not identify overdosages in the cases during use of deptropine, if the guideline for preparation by pharmacists is used as a reference. The regimens in the prescriptions were compatible with the recommended dose of deptropine of 0.06 mg/kg/day for small children (< 2 years of age) and at 0.03 mg/kg/day for older children. It should be emphasized, however, that these dosage regimens may be too high. The license of deptropine was voluntarily withdrawn by the manufacturer years ago and since that time deptropine is unlicensed but still frequently prescribed. In view of the association with neuropsychiatric events, such a situation must be considered as undesirable.

Due to the observational nature of our cohort study, the validity of our results might be threatened by selection bias, information bias or confounding. The IPCI database gathers data from a large and complete source population. In the Dutch health care system, GPs receive all medical information on their patients from specialists and hospitals and this information is all registered in automated records. As anonymous study inclusion did not depend on the subject's or physician's decision but only on the presence of the prescription in the database and because all subjects who received a prescription for a systemic antihistamine during the study period were included, selection bias is highly unlikely. Moreover, the absence of exclusion criteria makes this study generalizable to the entire population of 1-10 year-old children. Information bias was unlikely because all prescriptions and morbidity were prospectively gathered by the GPs without knowledge of our later research hypotheses. The fact that the outcome was identified from computerized medical records, however, may have caused outcome misclassification (false negatives or false positives). Since the outcomes will not always be recognized and reported to the GP, we may have underestimated the incidence of neuropsychiatric events. We tried to minimize this problem by restric-

tion of our population to children of at least 12 months of age. Although we cannot exclude the possibility of false-positive misclassification of the outcome by parents who read the product information, this would not explain the risk increase to deptropine as also other antihistamines with respiratory indications report the potential for neuropsychiatric events in their product information. Some exposure misclassification may have occurred in the assessment of treatment duration. Most antihistamines are supplied as syrup and calculation of exact dosing regimens is difficult due to use of non-standardized quantity measures (spoons, cups etc.). Such exposure misclassification, however, would be non-differential and lead to a conservative estimate instead of an overestimation of the true risk. In each observational study confounding is an important factor to deal with, and therefore all co-factors were assessed in a time varying manner. In our study age and indication were important confounders and we dealt with them by adjustment and by using a comparison group with the same indications.

In conclusion our study confirms the hypothesis that use of deptropine is associated with neuropsychiatric events in children. As this drug is no longer licensed and because therapeutic alternatives are available, its use should be discouraged.

References

1. Stricker BH, Prins AM, Schilte PP. Ernstige psychische bijwerkingen bij kinderen door gebruik van hoge doseringen deptropine. Ned Tijdschr Geneeskd 1992;136:1362-5.
2. Schirm E, Gebben HJ, Tobi H, de Jong-van den Berg LT. Deptropine nog steeds voorgeschreven voor 0-4 jarigen. Ned Tijdschr Geneeskd 2000;144:2409-11.
3. Klinkman MS, Green LA. Using ICPC in a computer-based primary care information system. Fam Med 1995;27:449-56.
4. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
5. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bemmel JH. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
6. van Zoelen GA. Verontrustende toename van intoxicaties door deptropine. Ned Tijdschr Geneeskd 1996;140:98-99.
7. Central Medical Pharmaceutical Committee of the National Health service Council. Farmaceutisch Kompas 1998 (Pharmaceutical Compass 1998). 98 ed. Utrecht: National Health Service Council, 1998.

Chapter 6
Drug licensing and pediatric labeling

Chapter 6.1

Information for pediatric use of medicines in a product information compendium

Many of the medicines that are prescribed to children are not fully licensed for that use. We wanted to know the proportion of medicines that are licensed for use in children. Therefore, we assessed the pediatric licensing status of medicines in the Repertorium 98/99, the standard drug information compendium in the Netherlands. The medicines mentioned in the Repertorium 98/99 were assessed for their licensing status and categorized into five mutually exclusive groups: 'licensed for use in all children', 'licensed for use in some child age/weight groups', 'no pediatric use mentioned', 'not licensed for use in children', and 'no pediatric licensing necessary'. 1380 licensing texts were identified of which 223 are not used for the treatment of childhood diseases. Of the remaining 1157, only 339 (29%) were licensed for use in children of all ages. Many drugs were not licensed for use in children, often because of a lack of PK/PD data. We strongly recommend a mandatory 'pediatric use' subsection in all product information texts, which is already compulsory in the United States of America.

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Introduction

In co-operation with four other European groups, we earlier found a high prevalence of unlicensed and off-label drug use in children.[1] Many medicines used are not, or are insufficiently, licensed for use in children or are not used according to the product license ("off-label use").[2] Lack of financial support for pediatric drug research by pharmaceutical companies as well as governments, and lack of development of proper dosage forms for infants and neonates result in a high prevalence of unlicensed and off-label drug use.

Nearly 80% of the new molecular entities approved during 1984-1989 in the United States of America had no labeling for use in children.[3] Only 19% of the new molecular entities contained pediatric use information in the labeling at the time of drug approval during 1991-1995.[4] Choonara *et al.* showed that of the 45 new substances licensed in Europe since January 1995, 29 (64%) were of potential use in children but only 10 were licensed for pediatric use.[5] We conducted a study to assess the percentage of medicines that had a proper licensing text for use in children in the Repertorium 98/99,[6] the standard drug information compendium in the Netherlands.

Methods

The Repertorium 98/99 was selected, as it is the only drug information compendium in the Netherlands that gives a survey of the official scientific information texts of pharmaceutical proprietary medications approved by the Dutch Medicines Evaluation Board (MEB), the national labeling authority, or the European Medicines Evaluation Agency (EMEA), the European labeling authority that provides marketing authorization for most new pharmaceutical products since 1995. The Repertorium 98/99 is published by Nefarma and Neprofarm, which are the Dutch Society of Research-orientated Pharmaceutical Industry and the Dutch Society of the Pharmaceutical industry of Self-care medication and Health products, respectively. Together they represent most pharmaceutical companies in the Netherlands, and therefore the Repertorium 98/99 contains the scientific information text of almost all of the proprietary medications licensed in the Netherlands.

The subsections 'indications', 'dosage and route of administration', contra-indications', and 'warnings and precautions' of all information texts of the proprietary medications mentioned in the Repertorium 98/99 were analyzed regarding use in children. None of the products had a special subsection for 'pediatric use'.

Five mutually exclusive categories were defined regarding use in children, i.e. 'licensed for use in all children', 'licensed for use in some child age/weight groups', 'no pediatric use mentioned', 'not licensed for use in children' and 'no pediatric licensing necessary', respectively.

Firstly, the indications for use of the drug were analyzed regarding the probability of use in children. If highly unlikely, the product was categorized 'no pediatric licensing necessary'. An example of this category is FemoStop® (estradiol/dydrogesterone) for postmenopausal women. Secondly, all subsections were analyzed on disclaimers against use in children. If the product information contained a disclaimer against use in children or stated that too few pediatric data were available, it was called 'not

Table 1 Drug licensing status of use in children in the Dutch product information compendium.

Category	Number	%
Licensed for use in all children	339	29.3
Licensed for use in some child age/weight groups	257	22.2
No paediatric use mentioned	341	29.5
Not licensed for use in children	220	19.0
Total of drugs with potential use in children	1157	100
No pediatric licensing necessary	223	
Total number of drugs in the *Repertorium 98/99*	1380	

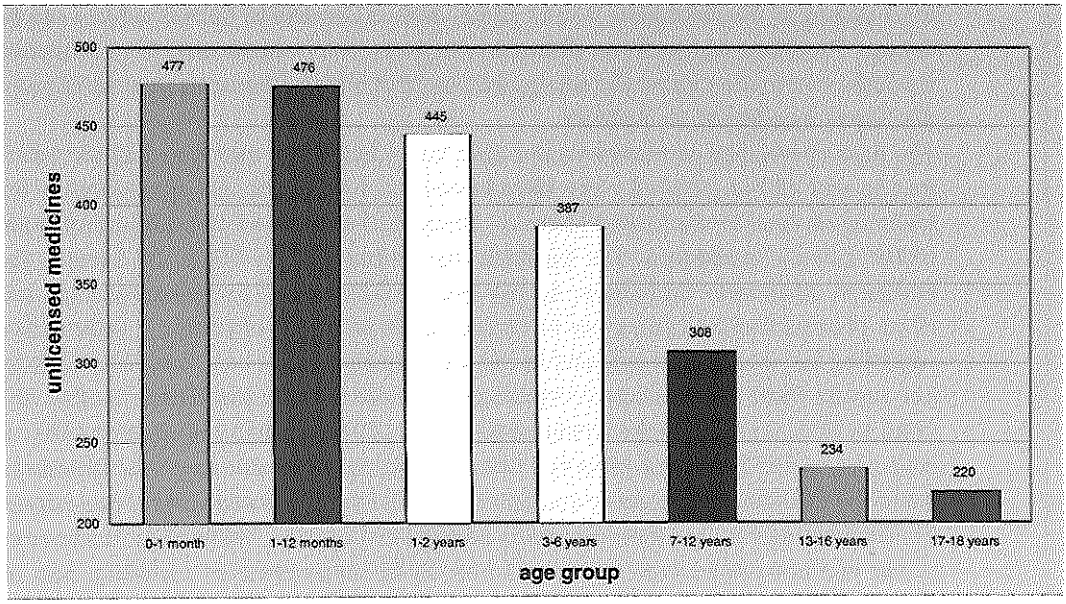
% of drugs with potential use in children

licensed for use in children'. If no pediatric use information was mentioned in any of the subsections of the information text, the product was categorized 'no pediatric use mentioned'. If there was a restriction on age or weight, the product was called 'licensed for use in some child age/weight groups' and the restriction was mentioned in the research form used for the study. If a drug was licensed for all pediatric age/weight groups the product was called 'licensed for use in all children'.
Not all restrictions on age were numerical, sometimes terms like neonates, toddlers, infants and children were used instead. We used the following definitions; 'new-born' (0-1 month), 'infant' (1 month up to 12 months), 'toddler' (1 year up to 2 years), 'small child' (3 years up to 6 years), 'child' (7 years up to 12 years) and 'adolescent' (13 years up to 18 years).

Results

The Repertorium 98/99 contains 1606 licensing texts. Some of them however were variants in dosage or dosage form of the same products. To obtain a conservative estimate of the percentage of unlicensed and off-label drug use, only the most child-friendly licensing text of a drug with the same Anatomical Therapeutic Chemical (ATC) classification7 was maintained, the others were removed from the analysis. A

Figure 1 Number of medicines not licensed for use in each age category



total of 1380 licensing texts were analyzed. Of all medicines with a potential use in children (n=1157), only 339 (29%) were 'licensed for use in all children'. Of the remaining 71%, 257 (22%) were 'licensed for use in some child age/weight groups', 341 (29.5%) gave no information at all on pediatric use whereas in 220 (19%) licensing texts contained too little information or a disclaimer against use in children (Table 1).

The medicines that were licensed for use in some child age/weight groups were subdivided into age categories as described in the methods. Figure 1 shows the number of medicines licensed for the children in the separate age categories.

Discussion

Approximately 71% of the medicines in the Repertorium 98/99 with a potential use in children are not fully licensed as such. The lack of scientific research on the pharmacokinetics and pharmacodynamics of many of these medicines in children may lead to trial-and-error based use, which endangers safety and efficacy. Many of the modern generation medicines, like ACE-inhibitors, have not been studied in children although they are relevant for therapy.

With these data no strong conclusion can be made on the exact number of medicines that need further investigation. Moreover, the Repertorium contains the names of products licensed by members of Nefarma and Neprofarm. It is unlikely, however, that our results cannot be extrapolated to all products licensed in the Netherlands. The categories 'licensed for use in some child age/weight groups' and 'not licensed for use in children' include medicines of two different classes. There are medicines that are preferably not used in particular child age/weight groups, e.g. because of organ immaturity, which have been studied well, but were considered as unsafe in the age/weight categories for which the licensing text contains a disclaimer. On the other hand, there are medicines that lack pharmacokinetic and pharmacodynamic data and need further investigation. Sometimes the licensing text is very explicit, but often the formulation of the disclaimer is very vague, and no conclusion on this subject can be drawn. Therefore we made no distinction between information texts that contained too little information about the use in children and information texts that contained a disclaimer against use in children.

The high prevalence of medicines that had 'no pediatric use mentioned' in the information text (30%) pleads for the introduction of a 'pediatric use' subsection in the information text. In the United States of America, the Food and Drug Administration (FDA) already introduced this 'pediatric use' subsection in 1979. In Europe, the European Medicines Evaluation Agency and national drug licensing agencies still allow pharmaceutical companies to register their products without any information regarding use in children included in the information text, as can be concluded from our results. Such a subsection is important, as pediatric use information is often difficult to find. Changes to the format and content of the product information texts, as proposed by the FDA's new proposed rule,8 would enable health care practitioners to prescribe medicines more safely and effectively. The amount, detail, and complexity of the labeling information have increased over the last decades. Technological advances in the products themselves and recognition of the importance of including new or

additional labeling information use of labeling in product liability and medical malpractice lawsuits, and increasing litigation costs are important causes. This has made it harder for health care practitioners to find specific information, and to discern the most critical information in product labeling. Suggestions in this Proposed Rule include a "Highlights of Prescribing Information" subsection and an index for the comprehensive prescribing information. We strongly support the suggestions, and hope the EMEA will seriously consider reviewing European regulations.

Children deserve an equal approach in drug licensing and equal quality of information. We regard the current situation regarding the availability of pediatric use information as insufficient.

References

1. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, Anker J vd. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000;320:79-82.
2. Kearns GL, Reed MD. Immediate action needed to improve labeling of prescription drugs for pediatric patients [editorial]. Ann Pharmacother 1997;31:249-51.
3. Kauffman R. Remarks to Counsel of Competitiveness. Washington: American Academy of Pediatrics, 1991.
4. Roberts R. Assessing safety in investigational drugs. Presentation at the Drug Information Association meeting. Gaithersburg, MD: Drug Information Association, 1996.
5. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. Br J Clin Pharmacol 1999;48:15-8.
6. Dutch Society of Research-orientated Pharmaceutical Industry N, Dutch Society of the Pharmaceutical industry of Self-care medication and Health products, Neprofarm. Repertorium 98/99, overview of by the Medication Evaluation Board registered information texts of pharmaceutical specialties. Utrecht: Nefarma & Neprofarm, 1998.
7. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
8. Federal Register 21 CFR Part 201. Requirements on content and format of labeling for human prescription drugs and biologics: Requirements of prescription drug product labels; proposed rule. CDER, 2000.

Chapter 6.2

Lack of effect of the European guidance on clinical investigation of medicines in children

To evaluate the licensing for pediatric use of new molecular entities (NMEs) granted a marketing authorization (product license). European Public Assessment Reports (EPARs) published on the Internet form January 1995 until May 2001 have been analyzed. Of 120 new substances licensed since January 1995, 70 (58%) were of potential use in children. Of these, only 17 were licensed for all pediatric use, and 15 for some pediatric age groups. Hence, the majority were probably not tested in pediatric age groups. Many of the new drugs granted marketing authorization lack sufficient pediatric labeling. The European Medicines Evaluation Agency should make an effort to improve this situation.

Introduction

Many new medicines and the vast majority of older medications have been approved without labeling for pediatric use.[1] The European guidance on clinical investigation of medicines in children states that 'children should not be given medicines which have not been evaluated for this age group'.[2] However, European legislation makes provision for physicians to use medicines that do not have a marketing authorization (unlicensed) and for purposes outside the terms of the marketing authorization (off-label). Consequently, many medicines are prescribed for children without specific knowledge of the dosage, metabolism, half-life and potential adverse effects.

The aim of the European drug licensing system is to give patients quick access to innovative new drugs, to facilitate the free movement of drugs within the EU, and to provide rigorous scientific evaluation of new products.[3] Since 1998, the system uses two licensing procedures: the centralized procedure via the European Medicines Control Agency (EMEA) and a decentralized procedure (mutual recognition), which enables manufacturers to seek simultaneous marketing authorization in concerned member states, provided that they already have marketing authorization in at least one member state. For all products approved under the centralized procedure, the EMEA issues the European Public Assessment Reports (EPARs). The EPAR reflects the scientific conclusion reached by the Committee for Proprietary Medicinal Products (CPMP) at the end of the centralized evaluation process and provides a summary of the grounds for the CPMP Opinion in favor of granting a marketing authorization for a specific medicinal product. It is made available by the EMEA for information to the public, after deletion of commercially confidential information. These reports give the reasons behind each approval, and contain a summary of product characteristics and the information to be included in the patient information leaflet.

In this study, we systematically reviewed the information contained in the EPARs to determine the current status with regard to labeling for pediatric use of new medicines granted a marketing authorization by the EU on recommendation by the EMEA.

Methods

The EMEA publishes all EPARs on the EMEA-website. All EPARs from January 1995 until May 2001 have been analyzed using Adobe® Acrobat Reader® 5.0.

From the EPARs, the following information was gathered: brand name and generic name of the drug, year of licensing ("date of decision" was used), manufacturer and its country of origin, dosage form(s), route(s) of administration and the main indications. Drugs were coded according to the Anatomical Therapeutic and Chemical classification (ATC).4 Several new molecular entities (NMEs) were licensed for more than one product, and mentioned in more than one EPAR. When the indication for use was the same for each product from one NME, they were assessed only once.

Firstly, applicability for pediatric use of drugs was established taking into account the prevalence of the target disease in the pediatric population and clinical outcome of the disease in children. Common indications for drugs, which were not taken into account, were diabetes mellitus type 2, Parkinson's disease, adult tumors, and reproduction enhancement because they do not apply to children. Secondly, when a drug

was of potential use in children, we assessed whether labeling for pediatric use and whether there was information in the summary of product characteristics concerning pediatric use. If the EPAR for an NME contained a disclaimer against use in children or stated that too few pediatric data were available, it was categorized as 'not licensed for use in children'. The product was categorized as 'no pediatric use mentioned' if none of the subsections of the EPAR mentioned anything about pediatric use. If there was a restriction on age (or weight), the product was categorized as 'licensed for use in some pediatric age groups' and the restriction was mentioned in the research form used for the study. The product was categorized as 'licensed for use in all children' if a drug was licensed for all pediatric age groups. Since we defined children between 0 and 16 years of age, all drugs that were not to be used in children under 17 year of age were defined 'not licensed for use in children'.

Results

Since the establishment of the EMEA in January 1995, 180 pharmaceutical products have been granted a Community Marketing Authorisation under the centralized procedure according to the EMEA-website. These brand products were applications of 123 new molecular entities (NMEs). One substance was licensed in 1995, 17 in 1996, 15 in 1997, 22 in 1998, 25 in 1999, 25 in 2000 and 18 in 2001 (up to June). The licensing procedure was undertaken by 53 manufacturers from 15 different countries, mainly from the US (50%), France (10%), the UK (9%) and Germany (9%).

The 123 NMEs belonged to ten different ATC groups; the most common being systemic anti-infectives (21%) and antineoplastic & immunosupressant agents (20%). Fourteen (11%) NMEs were HIV & Aids-related drugs (mostly antiretroviral) and ten (8%) were vaccines. For three NMEs (imiquimod, stavudine and HBVaxPro®), no EPAR could be found on the EMEA website.

Of the 120 remaining NMEs, 70 (58%) were of potential use in children (Table 1); 50 were not applicable for use in children (e.g. sildrenafil (Viagra®)). Of the drugs of potential use in children, only 17 (24%) were licensed for all relevant ages (table 2). The EPARs of 15 (21%) contained restrictions on age - 5 explicitly mentioned that the drug had not been tested under the minimal age-, 9 (13%) did not mention anything about use in children, and 29 (41%) were not licensed for use in children - of which 12 explicitly mentioned that the drug had not been tested in children.

Table 1 Licensing status of NMEs granted marketing authorization by the EU on recommendation of the EMEA

Category	Number	% of drugs with potential use in children
Licensed for use in all children	17	21%
Licensed for use in some pediatric age groups	15	19%
Explicit notice that the drug had not been tested in some pediatric age groups	*5*	
No pediatric use mentioned	9	14%
Not licensed for use in children	29	46%
Explicit notice that the drug had not been tested in children	*12*	
Total number of drugs with potential use in children	70	100%
Not applicable for use in children	50	
No EPAR found on EMEA website	3	
Total number of NMEs granted marketing authorization by the EMEA	123	

Table 2 Drugs fully approved for use in children by the EU on recommendation of the EMEA

NME	Therapeutic indication
Combined vaccine DTPw -HepB	Immunization
Combined vaccine DTPa -HepB	Immunization
Combined vaccine DTP -HepB-Poliomyelitis (HepB -IPV)	Immunization
Combined vaccine DTP -HepB-Poliomyelitis-HIB*	Immunization
Combined vaccine HIB* conj -HepB	Immunization
Combined vaccine HepA -HepB	Immunization
Streptococcus Pneu moniae vaccine	Immunization
Basiliximab	Immunosuppression
Epoetin beta	Anaemia
Imiglucerase	Gaucher's Disease
Mercaptamine bitartrate	Nephropathic cystinosis
Moroctocog alfa	Haemophilia A
Nevirapine	HIV
Palivizumab	Respiratory Syncytial (RS) Virus
Phenylbutyrate	Urea cycle disorders
Somatropin	Growth failure
Thyrotropin alfa	Hypothyroidism

* Haemophilus Influenza type B

Of the NMEs with age restrictions in the EPAR, one was off-label for children under three months of age, two under 2 years, four under 3, three under 4 and one under 6 years of age. This underlines the lack of appropriate licensing of drugs, especially in the younger age groups. Another two NMEs were restricted to children under 11 years, two under 12 years, and one under 15 years. Table 3 shows all relevant NMEs without a full pediatric license in each ATC drug class.

We compared the drug licensing status of drugs that were of US manufacturers with the US license as provided by the Food and Drug Administration (FDA). Since the FDA requires a 'pediatric subsection' in the labeling information text, none of the NMEs lacked information on use in children. Most of these drugs were not licensed for use in children in the US, except for mycophenolate-mofetil (immunosupressant), which was licensed for use in case of a kidney transplant in children. Several drugs were not licensed for the same indications; e.g. ribaverin was licensed in Europe for Hepatitis C although not in children, but in the US it was licensed for respiratory syncytial (RS) virus as well, for which it was licensed in children. One drug was licensed for use in children in the US, but not in Europe; Sirolimus (immunosupressant) was licensed in the US above 13 years of age, whereas in Europe, no pediatric license was available. Two NMEs were licensed in Europe for use in children, but not in the US - temozolomide (antineoplastic agent) was licensed in Europe in children above 2 years of age, and indinavir (antiretroviral agent) above 3 years of age. Overall, licensing for 9 out of 62 NMEs from US manufacturers differed when compared to the US licensing.

Discussion

Many of the new drugs that have been granted a marketing authorization in the EU during the past six years though the centralized procedure have not been sufficiently licensed for use in children. While the majority of drugs were of potential use in children, only 24% of these were licensed for all relevant pediatric age groups. Results of this survey disclose that most drugs that are indicated for diseases, which occur not only in adults but also in children, have not been approved by the EMEA for use in the pediatric population. At best it is stated that the drug has not been tested in children but often even that information is lacking.

Comparison to an earlier study by Impicciatore & Choonara that covered EPARs

Table 3 NMEs of possible use in children released by the EMEA without (complete) pediatric labeling

NME	Licensing status	Action
Drugs for metabolism		
Insulin	UL	Diabetes mellitus
Insulin aspartame	Age (6)	Diabetes mellitus
Insulin glargine	UL	Diabetes mellitus
Insulin lispro	NI	Diabetes mellitus
Drugs for blood and blood producing organs		
Darbepoetin alfa	Age (11)	Erythropoietin
Eptacog alfa	NI	Factor VIIa
Lepirudin	UL	Anticoagulant
Nonacog alfa	NI	Recombinant human factor IX
Drugs for heart and vessels		
Irbesartan	NI	Angiotensin II antagonist
Irbesartan + hydrochloric thiazide	UL	Angiotensin II antagonist
Telmisartan	UL	Angiotensin II antagonist
Systemic anti-infectives		
Amprenavir	Age (4)	HIV
Abacavir	NI	HIV
Abacavir + lamivudine	UL	HIV
Cidofovir	UL	CMV infection in HIV patients
Efavirenz	Age (3)	HIV
Fomivirsen	UL	CMV infection in HIV patients
Ganciclovir	UL	CMV infection in HIV patients
Hepacare vaccine	UL	Hepatitis B
Indinavir	Age (4)	HIV
Lamivudine	Age (3 months)	HIV
Lamivudine	UL	Hepatitis B
Lopinavir	Age (2)	HIV
Nelfinavir	Age (3)	HIV
Ribavirine	UL	Hepatitis C
Ritonavir	Age (2)	HIV
Saquinavir	UL	HIV
Twinrix adult	UL	Hepatitis A
Antineoplastic and immunosupressant agents		
Daclizumab	UL	Renal transplant rejection
Etanercept	Age (4)	Juvenile RA polyarthritis
Infliximab	UL	Crohn's Disease
Interferon alfa 1a	UL	Multiple Sclerosis
Interferon alfa con1	UL	Hepatitis C
Interferon beta	UL	Multiple Sclerosis
Mycophenolate-mofetil	NI	Transplant rejection
Peginterferon	UL	B-cell lymphoma
Rituximab	UL	B-cell lymphoma
Sirolimus	UL	Immunosupressant for organ transplant
Temozolomide	Age (3)	Brain tumors
Drugs for skeleton and –muscles		
Botulin toxin	UL	Spasticity
Leflunomide	UL	Rheumatoid arthritis
Drugs for the central nervous system		
Levacetylmethadone	Age (15)	Opiate addiction
Levetriazetam	UL	Anticonvulsant
Miscellaneous		
Desloratadine	Age (12)	Antihistamine
Deferiprone	Age (11)	Anti-inflammatory for conjunctivitis
Depreotide	UL	Iron overload in thalassaemia
Emedastine	Age (3)	Diagnostic (technetium scans)
Mangafodipil	UL	Diagnostic for liver lesions with MRI
Rasburicase	NI	Urate oxidase for hyperuraemic states in malignancy
Samarium lexidronam	NI	Radiotherapy for malignancy
Sevelamer	UL	Increased phosphate in haemodialysis, phosphate binder
Sulesomab	NI	Diagnostic for bone marrow infection
Sulfohexafluoride	UL	Aid for echocardiography

UL = unlicensed (not licensed for use in children),
NI = no information (no pediatric use mentioned),
Age = licensed for use in some pediatric age groups.

between 1995 and April 1998 is difficult because some EPARs were updated during the study period.5 Our survey shows an increase in marketing authorizations - from 45 between 1995 and 1998 to 68 between 1999 and May 2001 -, but no improve-

ment in the number of relevant drugs fully licensed for use in children (7/27 and 10/43 respectively), despite increasing attention to this problem.

Often a description was provided -mostly 'children' without age specification-, and we assumed that these drugs were not to be used in children aged 0 till 16 years. Avoidance of ambiguous terms like 'children', 'infants' and 'new-borns', and age specifications in months for new-borns and infants and in years for children would increase the accuracy of labeling information texts. The FDA has provided definitions for the age groups,[6] but since definitions are only advised by the EMEA, this problem is primarily European, as shown in the results. Clear indications of the reason for withholding an indication from certain patient groups would result in significant improvement in the labeling information text. The EMEA's format of the labeling information text still does not include a 'pediatric use subsection',[7] while the FDA introduced this in 1979, and is continuing to improve the format.[8] Similar changes in the European format of labeling information texts would certainly improve the clarity of provisions.

Clearly, earlier measures by the EMEA, such as the European guidance on clinical investigation of medicines in children,[2] are not effective. In general, the willingness of pharmaceutical companies to conduct pediatric research has not improved,[9] and the drugs for which pediatric labeling is requested, are often relatively irrelevant for use in the pediatric population.[10] The current regulations on content and format of labeling information texts allow much heterogeneity, which decreases legibility and accessibility of the information. The EMEA's new proposed review of the pharmaceutical legislation includes various important improvements, like acceleration of the authorization procedure, increased pharmaco-vigilance of marketed products, and various changes to the mutual recognition procedure.[11] However, no specific measures are reported regarding pediatric labeling, such as financial incentives for the pharmaceutical industry when applying for pediatric labeling - as is currently available in the US[12] - and review of the product information text regarding information on pediatric use. Therefore, a more strict approach regarding pediatric labeling should be considered.

References

1. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
2. European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit; Committee for Proprietary Medicinal Products. Note for Guidance on Clinical Investigation of Medicinal Products in Children. EMEA, 1997.
3. Herxheimer A. The European Medicines Evaluation Agency [editorial]. Bmj 1996;312:394.
4. Miller GC, Britt H. A new drug classification for computer systems: the ATC extension code. Int J Biomed Comput 1995;40:121-4.
5. Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. Br J Clin Pharmacol 1999;48:15-8.
6. Guidance for industry; Content and format for pediatric use supplements. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Washington, 1996:1-6.
7. t Jong GW, Eland IA, Stricker BHC, Anker JNvd. Information for paediatric use of medicines in a product information compendium. Paediatric and Perinatal Drug Therapy 2001;4:1-4.
8. Federal Register 21 CFR Part 201. Requirements on content and format of labeling for human prescription drugs and biologics: Requirements of prescription drug product labels; proposed rule,

2000.
9. Kmietowicz Z. Drug industry is unwilling to run trials in children. BMJ 2000;320:1362A.
10. t Jong GW, van den Anker JN, Choonara I. FDAMA's written request list: medicines for children. Lancet 2001;357:398.
11. Pharmaceutical Legislation Review 2001; Preliminary Remarks. London: European Medicines Evaluation Agency (EMEA), European Commission, 2001:1-74.
12. Department of Health and Human Services. Food and Drug Administration. 21 CFR Parts 201, 312, 314, and 601. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients. Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research., 1998:66632-72.

Chapter 6.3

FDAMA's Written Request list: Which medicines do children need?

Many drugs frequently used in infants and young children are not sufficiently studied for safety and efficacy for this age group. The FDA's Modernization Act provides a six-month extension of exclusivity to drug entities that are issued a Written Request by the FDA, and apply for additional pediatric labeling. We studied the usefulness and necessity of these drug entities for pediatric pharmacotherapy. Of 136 Written Requests issued in the study period, 36 (26%) were cardiovascular drugs. We welcome the developments that have resulted in more clinical trials of medicines in children. However, we also need to recognize the limitations of FDAMA whereby it is possible for 22 anti-hypertensives to be studied, when it is clear that this number of anti-hypertensives is not required in pediatric patients.

Introduction

Children are referred to as "therapeutic orphans" [1] as a result of the longstanding lack of appropriate medicines to treat their disease states. Information on use of medicines in pediatrics is inadequate, and we have an ethical obligation to rectify the current situation.[2] Many medicines used in pediatrics are not licensed, or are used outside the terms of the product license (off-label).[3] Over recent years various measures have been introduced to encourage pharmaceutical companies to conduct necessary research in children, and develop suitable pediatric formulations. In 1979 the US Food and Drug Administration (FDA) introduced labeling changes, which indicated that specific pediatric indications, if any, should be described in the indications and usage section of the labeling, with appropriate pediatric dosage provided in the dosage and administration session. Practical effect however was that many labels stated: "safety and effectiveness in children have not been established". In 1994 the FDA introduced the Pediatric Rule, which advocated extrapolation of adult efficacy data in some cases to pediatrics.[4] Provisions were that the course of the disease is sufficiently similar, the effects of the product (both good and bad) are sufficiently similar, and that further information (pharmacokinetic and -dynamic and safety data) supported pediatric use. This rule however was insufficient, since of 430 submissions for labeling changes, 77% did not obtain labeling improvements. The 1997 Modernization Act (FDAMA) section 111 attached six months of "pediatric exclusivity" to exclusivity or patent life of active moieties. It requires the FDA to develop and maintain priority lists of drugs for which additional pediatric information may produce health benefits in the pediatric population. The FDA issues "Written Requests" for the drug products they think are most useful and necessary in pediatric pharmacotherapy. These Written Requests are often issued after a Proposed Pediatric Study Request (PPSR) from industry.
In order to evaluate the effectiveness of this rule, we wanted to examine which drugs Written Requests were issued for, and whether these drugs are of important gain for pediatric pharmacotherapy.

Methods

We have examined which drugs Written Requests have been issued for between the initiation of the FDAMA in 1997 and September 2000. 136 Written Requests had been issued in that period, and were retrieved from the website of the FDA's Center for Drug Evaluation and Research (CDER).[5] Drug class, category and main indications were determined for all drugs on the Written Request list, using the Martindale Drug Reference.[6]

Results

Of 136 drugs that were issued a Written Request during the study period, 36 (26%) drug moieties were cardiovascular drugs as shown in the table. We also saw many antiviral drugs, mostly for the treatment of HIV. Drugs for the treatment of asthma were relatively underrepresented.

Table 1 Drug classes in the Food and Drug Administration's Written Request list

Drug Category	Number of drugs	Examples drug class	Number of drugs
Cardiovascular drugs	36 (26%)	Non-cardioselective â -blocker	12 (9%)
		Angiotensin converting enzyme -inhibitor	6 (4%)
		Carbonic Anhydrase Inhibitor	5 (4%)
		Cardioselective â -blocker	4 (3%)
Antiviral Drugs	12 (9%)	Protease inhibitor (HIV)	5 (4%)
		Nuclease Reverse Transcriptase Inhibitor (HIV)	4 (3%)
Analgesics, Anti-inflammatory Drugs and Antipyretics	12 (9%)	NSAID	7 (5%)
		Opioid Agonist	4 (3%)
Antidepressants	8 (6%)	SSRI	6 (4%)
Bronchodilator's and Anti- Asthmatic Drugs	7 (5%)	Leukotriene Antagonist or Inhibitor	4 (3%)
Lipid Regulation Drugs	5 (4%)	HMG-CoA-inhibitor	5 (4%)
Gastro-intestinal Drugs	5 (4%)	Proton Pump Inhibitor	2 (1%)

NSAID = non-steroidal anti-inflammatory drugs, SSRI = Selective Serotonin Reuptake Inhibitors

Discussion

While children experience heart disease, hypertension and hyperlipidemia, they are not a major cause of morbidity in the pediatric population. We suggest that the contribution of some drug classes is not in proportion with the actual need of these drugs in pediatric care. While many double-blind studies unanimously concluded that antidepressants are no more effective than placebos in treating depression in children and adolescents, six selective serotonin reuptake inhibitors (SSRIs) were issued Written Requests.[7] A large quantity of resources, money and effort currently is going into development of drugs to treat HIV infection both in adults and in children. Although an appraisable effort, the response to the HIV epidemic has tended to be highly politicized rather than managed as other serious life-threatening epidemics, as shown in the disproportionate number of nuclease reverse transcriptase inhibitors and protease inhibitors in the Written Request list (table 1). The number of bronchodilators and anti-asthmatic drugs however was surprisingly small, while especially in this group of diseases the need for appropriate drugs is high.[8]

Under FDAMA, a manufacturer who submits the pediatric studies required may received a 6 month extension of exclusivity or patent protection granted for that drug. The extension of exclusivity was intended as an extra financial incentive to study drugs in children that are really needed. However, financial benefits are likely to be considerable for some drugs, as the 6 months prolongation of exclusivity or patent protection applies to all formulations of the drug moiety whether appropriate for pediatric use or not. The January 2001 Status Report to Congress has indicated other gaps in the pediatric exclusivity provision, like a lack of incentives for some age groups, and it provides several suggestions for improvement.[9]

We welcome the developments that have resulted in more clinical trials of medicines in children. However, we also need to recognize the limitations of FDAMA whereby it is possible for 22 anti-hypertensives to be studied, when it is clear that number of anti-hypertensives are not required in pediatric patients. The FDA needs to be more proactive in ensuring that known medicines that are of greater clinical value to pediatric patients are studied, as specified in the ICH guidance on clinical investigation of medicinal products in children.

References

1. Shirkey HC. Therapeutic orphans. J Pediatr 1968;72:119-20.
2. Wilson JT. An update on the therapeutic orphan. Pediatrics 1999;104:585-90.
3. Choonara I, Dunne J. Licensing of medicines. Arch Dis Child 1998;78:402-3.
4. 59 FR 64242: Food and Drug Administration, 1994.
5. CDER Website: Food and Drug Administration: www.fda.gov/cder.
6. Martindale 32nd Edition, The Complete Drug Reference. London: Pharmaceutical Press, 1999.
7. Fisher RL, Fisher S. Antidepressants for children. Is scientific support necessary? J Nerv Ment Dis 1996;184:99-102.
8. Choonara I. Essential drugs for infants and children: European perspective. Pediatrics 1999;104:606.
9. The Pediatric Exclusivity Provision. January 2001 Status Report to Congress. Department of Health and Human Services. U.S. Food and Drug Administration, 2001.

Chapter 7

General discussion

7.1 Background

Many commercially available drugs are only licensed for use in adults and for many drugs the available formulations are unsuitable for pediatric use.[1] This reality leads to use of drugs which are unlicensed or off-label for use in children. There are several reasons for this highly unsatisfactory situation. Firstly, children represent only a small market in an absolute sense but also relatively as most children are healthy. Hence, from a commercial perspective it may not be profitable to invest in pediatric drug research. Secondly, fear is growing for unforeseen adverse effects and long-term toxicity which may be difficult to study. Therefore, the current requirements for licensing of a drug may have become a barrier to make proper drugs available to a vulnerable group of patients. Thirdly, there are ethical problems to conduct drug studies in children. In Europe the problems in pediatric drug use and research receive relatively little interest and there is a substantial lack of funding of pediatric drug research. As a result, pediatric drug trials are relatively scarce and often include only a limited number of patients. Despite the well-known thalidomide disaster, which happened already forty years ago and caused an epidemic of congenital malformations, very little has changed regarding the labeling of drugs in infants and children. Although the disaster has stimulated legislation of drug licensing, children ironically remain 'therapeutic orphans'. This is difficult to accept because many diseases in adults can also occur in children while pharmacokinetics and pharmacodynamics often differ. Prescription of drugs should be proven to be equally safe in children as in adults, and efficacy of the product should be thoroughly assessed for all probable users. Exposure of infants and children to drugs which are not proven to be safe and efficacious during growth and development, cannot always be prevented. Hence, the health implications of this 'therapeutic orphanhood' may be larger than is sometimes assumed.

The scope of this thesis was to assess the extent of the problem of unlicensed and off-label drug use in children both in clinical care as well as in general practice. Although it is just a first step on a lengthy road, we hope that results of our studies may revive awareness of the problem and stimulate adequate regulatory actions.

7.2 Methodological considerations

Before we change to the discussion on the consequences of our findings, there are two important methodological considerations which should be taken into account: classification and the consequences of the chosen study design.

Classification of unlicensed and off-label drug use

Over the last decade there have been many different terms for the prescription of drugs that are not fully licensed for use, or not in accordance with the labeling information text, (e.g. unlicensed, off-label, unapproved, off-license, unlabeled). Due to the variability in terminology, results from international studies on the extent of unlicensed and off-label use may be difficult to compare. In fact, the American literature considers many of our unlicensed categories as off-label use, and only considers drugs that are not licensed at all as unlicensed. The classification system applied in this the-

sis is mainly based on a system designed by Choonara et al. in the United Kingdom.[2] In this system, drugs classified as unlicensed for use in children comprise modifications of licensed drugs, drugs manufactured under a special license, and new drugs. Unlike this system, we also defined a drug with a labeling information text that does not contain any information on use of drugs in children as unlicensed for use in children, as well as drugs that are contraindicated for use in children. The differences in terminology may limit the possibility of comparison to overall rates of off-label plus unlicensed use but irrespective of these distinctions in (sub)classification, the totals of unlicensed and off-label drugs can be directly compared.

Study design

In epidemiology, there are several study designs to estimate occurrence of events and measures of association. Due to differences in settings and type of data collection, the designs of the studies described in this thesis vary. In the first study (chapter 2.1), the prescription data were collected ad-hoc on a once-a-week basis. For efficiency reasons each hospital unit was visited once a week, for five weeks, each week on a different day. In the second study (chapter 2.2), all prescription data issued on pediatric wards were collected longitudinally by pharmacy assistants. In the European study (chapter 2.3), the study design was already defined at the moment of our participation in this project. Despite differences in setting and design of these studies, classification of unlicensed and off-label use has been done equally in all studies, by the same investigator and based on official licensing reference information. These studies were mostly descriptive and did not analyse the association between the unlicensed or off-label status and potential determinants. Despite these differences however, all studies point to the same conclusion about the high proportion of unlicensed and off-label prescriptions in children. The studies described in chapters 3 and 4 are all based on data from the IPCI database. This population-based database with data from general practice has many advantages. Firstly, thanks to the pivotal role of the general practitioner in the Dutch health care system, all relevant medical data are usually available at the general practice. The presence of both prescription data and disease data facilitates studies on the association between drugs and disease. Secondly, as general practice data encompass the total population and are gathered prospectively without knowledge of later formulated research hypotheses, both selection bias and information bias are unlikely. Since the database contains information on drugs prescribed by general practitioners but not by specialists, however, some prescriptions from outpatient clinics are missed. This absence of specialist prescriptions may have resulted in underestimation of drug use in children in the general population although we think that such underestimation may be modest. Confounding was of little relevance in this thesis since most of the studies were descriptive, and frequency estimates were always stratified by age, gender and other relevant factors. In one analytic study on the association between neuropsychiatric effects and deptropine, we dealt with confounding by indication by the choice of a comparison group which received treatment for the same indication.

7.3 General discussion

Major findings

In this thesis we described the extent, nature, determinants and consequences of unlicensed and off-label drug use in children in both hospital- and community-based settings. From the results of these studies, we conclude that children often receive drugs which are unlicensed or off-label for use in children. Percentages are especially high in children's hospitals but also substantial in general practice.

The results from this thesis raise three major questions. Firstly, even if the proportion of unlicensed drug use or off-label use of licensed drugs is high, does this really matter? Secondly and if the answer to the first question is yes, what should we change or improve in the field of pediatric drug research? Thirdly, what regulatory requirements should be taken to ensure that the efficacy and safety of drug use in children is guaranteed?

Does the high proportion of unlicensed or off-label drug use in children really matter?

During our studies, the question arose whether this unlicensed or off-label use really mattered. After all, this situation is more or less stable since decades and there are no indications that this has led to a substantial increase in morbidity or mortality among children. Although this might seem reassuring, it is obvious from some of our studies that use of unlicensed or off-label drugs may cause adverse events which relate to this status. For instance, the use of deptropine for respiratory diseases in children led to an increased number of reports in the Netherlands of suspected neuropsychiatric adverse effects approximately 10 years ago. This was attributed to the relatively high doses which were then advised in children by pediatricians and in the national formulary.[3] As these dosages had not been formally tested in children, these advises were based on the personal experiences of some medical opinion leaders. Apparently, deptropine is still a cause of such effects as our study which is described in chapter 5 demonstrated that deptropine has a higher risk of neuropsychiatric effects than similar drugs used for the same indication. Although this does not prove that unlicensed or off-label use of drugs causes an overall increase in the risk of adverse reactions, there are certainly examples of such situations.

What should we do to improve pediatric drug research ?

As we discussed in the previous paragraph, the use of unlicensed drugs or off-label prescription of licensed drugs may have adverse consequences and should be discouraged as much as possible. Many of the unlicensed and off-label drugs which were used by children in our studies, however, are essential because children may have the same diseases as adults and may need similar treatment. As long as such drugs are not tested in children, their optimal dose is at best dependent on a good guess by experienced pediatricians or clinical pharmacologists. If we are lucky, such an empirical approach is confirmed by a favorable clinical response without much toxicity and structured in a well-written guideline. But it is also possible that every doctor decides alone on which dose he will start with. Such an approach, however, is probably rare nowadays. Nevertheless, the general absence of tested dosage schemes for the treat-

ment of diseases in childhood should be regarded as unethical and therefore, more pediatric drug studies are urgently needed. Such studies should prioritize on drugs of proven efficacy and effectiveness in the treatment of potentially life-threatening diseases in adults. Especially, if such drugs are clinically important but at the same time established causes of serious adverse reactions in adults, testing in children may be even more important unless the drug can be missed in children. Development of pediatric formulations for drugs and labeling of these formulations for use in children is another goal that has to be met. In general, drugs that are commonly used orally in small children should always be available in palatable, liquid formulations and in small dosage units.[4] The introduction of fast dissolving formulations and multiple unit system with small particle size are likely to facilitate administration of new drugs to children. Development of such formulations involving novel technology may require substantial investment. Similarly, injection vials of appropriate quantities/strengths are essential to minimize the risk of medication errors.[5] Research shows that errors which lead to an almost tenfold overdose by missing a decimal mostly occur in small children.[6]

If resources for pediatric drug research are limited, how should we choose our priorities? Obviously, we should prioritize on drugs which are essential to children. Selection of 'essential' drugs will always be a political process with economic implications. Nevertheless, the process must be driven primarily by the therapeutic needs of children. This means that we should prioritize on drugs which are used to treat life-threatening illnesses such as antibiotics and antineoplastic agents. Apart from the optimal dosing scheme, attention should be paid to child-friendly formulations and adequate labeling texts for children.

Recently, Nahata *et al.* published priority listings for pediatric formulations for which no stability and / or compounding data were available.[7] However, the report contains some disturbing data indicating there is lack of consistency of pharmacy practice and knowledge.[8] Lack of response from hospitals when asked for their common practice, as was the case in this survey, and the inconsistency of pharmacy practice and knowledge indicates a need for hospital associations to require such data to be collected and made available.

An important issue which has been raised in the past is whether it is ethical to perform studies in children. In our view, this is a fallacy or at best a misinterpretation of the consequences of such a perception in daily life. The real issue is whether it is ethical not to perform studies in children. As we already emphasized, many potentially life-threatening diseases which occur in adults (e.g. tuberculosis) may also occur in children. Many tuberculostatics, however, may cause severe adverse reactions. Hence, finding the optimal dose in children of different age and weight is important, both from the point of view of efficacy and safety. The situation in which no proper studies have been performed, will have as a consequence that doctors will try to find such a dose by a combination of dose estimation and trial and error. It is difficult to blame doctors for this as long as the pharmaceutical industry and government do not take their responsibility here. After all, they may have a very sick patient who is in urgent need of treatment. From the ethical point of view, this consequence of a general perception not to study drugs in children is too serious to deny.

What regulatory requirements should be taken to ensure that the efficacy and safety of drug use in children is guaranteed?

Necessity of pediatric labeling

Labeling of a drug indicates that there is substantial evidence from adequate and well-controlled clinical trials for the safe and effective use of that drug. Labeling provides important information on clinical pharmacology, indications and usage, contraindications, precautions, adverse effects, dosage, and administration. Unfortunately for children, most drug labeling contains the precautionary disclaimer that safety and efficacy in children have not been established. Extrapolation of data on safety and efficacy in children from the medical literature, or from data on safety and efficacy in adults can not be considered sufficient.[9] The child is not a small adult.[10] Therefore pediatric labeling is really necessary. Another, maybe even more important reason is the moral imperative of the assessment of safety and efficacy of drugs in all potential users. Pediatric labeling is the only way to ensure the safe and effective use of drugs in infants, children, and adolescents. The failure of the pharmaceutics industry to sponsor the necessary studies, the regulatory authorities to enforce their regulations, and the legislation to mandate that all drugs with potential use in children should be evaluated appropriately has allowed the child to remain a therapeutic orphan.[11]

The current drug licensing system has not fulfilled many of its goals. Considering the legal protection, the restrictions in application of drugs by the label would logically exclude any use of the drug beyond the label. The problem is, however, that several useful drugs for indications which have not formally been registered can only be used illegally in a formal sense. Considering the maintenance of drug safety and efficacy, the product information of the drug is often not the daily-life guidance for drug prescription by medical doctors as many of them resort to use of hospital protocols and medical literature. Drug labeling per se is not intended to set a standard for good medical practice. In fact, a physician might be held responsible for departure from accepted standards of care which are not formally registered and it may be considered as unethical to withhold adequate treatment which has not (yet) been registered. On the other hand, not following the instructions on the information text may also lead to legal problems.

Off label prescription of drugs is often the only choice which physicians have, because several essential drugs may not have been licensed for use in children. When undertaking off label prescribing, decisions should be made based upon rational scientific theory, expert medical opinion or controlled clinical trials, although validity of these sources may often prove to be weak. The physician is obligated to be aware of the content of the package insert and give it due consideration (e.g. precautions, contraindication and warnings).

Suggestions for improvement

Improvement of the licensing system will require huge efforts and the mobilization of political pressure, publicity regarding the subject, and willingness of the responsible policy makers to recognize the severity of the problem. In general, new financial incentives for the industry to conduct pediatric research are important, especially for

orphan drugs.[12] In Europe however, financial incentives are forbidden for orphan drug development.[13] Since history has demonstrated that willingness of the industry to start trials in children is largely lacking,[14] financial incentives may be needed to stimulate pediatric labeling. Regulations that would oblige companies to pediatric labeling, and development of pediatric formulations would certainly improve the current situation, unless the applicant for licensing is able to convince the regulatory agencies that the product in unlikely to be used in children. Overall, it is defensible to require that drugs which are registered for diseases in adults which also occur in children can only be registered after adequate pediatric drug studies.
The format of the labeling information text of drugs in Europe still lacks a "pediatric use" subsection. Results are that information texts of many of the drugs which were granted marketing authorization do not contain any information on use in children. Format changes, such as recently proposed in the USA,[15] could strongly improve the amount and quality of information available in the information text. Such a subsection is important as information on pediatric use is often difficult to find. The amount, detail and complexity of the labelling information have increased over the last decades. Technological advances of the products themselves and recognition of the importance of including new or additional labelling information, use of labelling in product liability and medical malpractice lawsuits, and increasing litigation costs are important causes. This has made it more difficult for health care practitioners to find specific information, and to discern the most critical information in product labelling. Suggestions in this Proposed Rule include a "Highlights of Prescribing Information" subsection and an index for the comprehensive prescribing information. We strongly support the suggestions, and hope the EMEA will seriously consider reviewing European regulations.

Unlicensed and off-label drug use

Unfortunately, this message has been proclaimed before but has not (yet) led to the action needed to "solve" this problem. The relevance of unlicensed and off-label drug use in pediatrics has long been recognized by many pediatricians, pharmacists, researchers and representatives of government and industry. Regarding the pharmaceutical industry, we cannot expect them to simply change there policies regardless of costs, for they are profit-driven organizations. On the other hand, every organization should prevent her product from improper, unsafe and inefficacious use as much as possible. Difficulties in pediatric pharmacology research are illegitimate motivations for not conducting pediatric research.
Although governments recognize the problem, the measures that have been taken have not been very efficient yet. Development of regulations to assure that new drugs will have all relevant labeling is an important goal. However, the promotion of additional pediatric labeling for drugs that are already used in children should not be forgotten. This is especially important if the patent/exclusivity is expired, and if drugs are not frequently used in children but play an important role in certain diseases or disorders - so called 'orphan drugs'.
Currently, the European Medicines Evaluation Agency is working on new guidelines regarding the research of drugs in children. The intention is to make a subsection in

which a dosing scheme for use in children is given for every drug which may be used in this group. For drugs which are not used in children (e.g. sildenafil), this is explicitly stated. The implementation of such a guideline may prove to be a substantial step forward.

References

1. Nahata MC. Lack of pediatric drug formulations. Pediatrics 1999;104:607-9.
2. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. Paediatric and Perinatal Drug Therapy 1997;2:52-55.
3. Stricker BHCh, Prins AM, Schilte PP. Ernstige psychische bijwerkingen bij kinderen door gebruik van hoge doseringen deptropine. Ned Tijdschr Geneeskd 1992;136:1362-5.
4. Breitkreutz J, Wessel T, Boos J. Dosage forms for perioral drug administration to children. Paediatr Perinat Drug Ther 1999;3:25-33.
5. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. Jama 2001;285:2114-20.
6. Koren G, Barzilay Z, Greenwald M. Tenfold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. Pediatrics 1986;77:848-9.
7. Pai V, Nahata MC. Need for extemporaneous formulations in pediatric patients. J Pediatr Pharm Ther 2001;6:107-19.
8. Walson PD. "Pediatric" formulations. J Pediatr Pharm Ther 2001;2001(6):97-9.
9. Christensen ML, Helms RA, Chesney RW. Is pediatric labeling really necessary? Pediatrics 1999;104:593-7.
10. Yaffe SJ, Aranda JV. Introduction and historical perspective. In: Yaffe SJ, Aranda JV, editors. Pediatric Pharmacology; Therapeutic Principles In Practice. 2nd ed. Washington: W.B. Saunders Company, 1992:3-9.
11. Shirkey HC. Therapeutic orphans. J Pediatr 1968;72:119-20.
12. Garattini S, Bertele V. Adjusting Europe's drug regulation to public health needs. Lancet 2001;358:64-7.
13. Regulation (EC) no 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Off J Eur Comm 1999;no L 018 of Jan 22:1-5.
14. Kmietowicz Z. Drug industry is unwilling to run trials in children. BMJ 2000;320:1362A.
15. Federal Register 21 CFR Part 201. Requirements on content and format of labeling for human prescription drugs and biologics: Requirements of prescription drug product labels; proposed rule. CDER, 2000.

Chapter 8

Summary (Samenvatting)

Summary

This thesis described the incidence, nature, determining factors and consequences of unlicensed and off-label drug use in children in hospital-based and community-based settings. We defined drugs "unlicensed (for use in children)" if after evaluation by the Dutch Medicines Control Agency or the European Medicines Control Agency (EMEA), no approval had been granted by government for use of the drug in children or if no license for use of the drug was available at all. Off-label prescription concerns the prescription outside the terms of the product license regarding the age of the patient, the indication, route of administration, dosage form, dose & frequency of administration, en when the use of the drug was contra-indicated for use in the child.

Chapter 1 provides an overview of the current state of pharmacotherapy in children *(Chapter 1.1)*, pediatric drug research and pediatric labeling, and described the aims of the studies. *Chapter 1.2* gives an overview of the current drug licensing regulations, and various initiatives taken to change the current situation, and *Chapter 1.3* describes the major practical and ethical problems pediatric pharmacology research is confronted with. Chapter 1.4 denotes the five objectives of the studies presented in this thesis. Our first objective was to determine the incidence and nature of unlicensed and off-label drug use in academic children's hospitals, a pediatric ward of a non-teaching hospital, and in the general population. Secondly, we intended to investigate which factors are of influence on unlicensed and off-label prescribing. Thirdly, we wanted to explore the possibility of a relation of unlicensed and off-label drug prescription and a negative health outcome. Our fourth object was to investigate the pediatric licensing status of drugs that are available in the Netherlands, and fifthly, to evaluate the efficiency of the current European system of marketing autorization (drug licensing), as well as the measures that have been taken in the US to improve the current situation.

In **Chapter 2**, we describe the unlicensed and off-label drug use in children in hospital-based settings in the Netherlands, and in Europe. Distinction is made between secondary and tertiary care, with general, non-teaching hospitals as secondary and academic, teaching hospitals as tertiary care. In *Chapter 2.1*, a survey in the Sophia Children's Hospital, a tertiary care children's hospital in the Netherlands is described. In a prospective study of five weeks duration, we reviewed drug prescriptions in a pediatric ward and three intensive care units (ICUs). We classified the prescritions into three main categories; licensed, unlicensed, and off-label, and determined the nature of their unlicensed and off-label use. During the study period, 2139 courses of drugs were administered to 237 patients in 435 patient-days. Of 2139 prescriptions, 725 (34%) were licensed, 1024 (48%) were unlicensed and 390 (18%) off-label. In 391 (90%) of 435 patient-days, children received one or more courses of an unlicensed or off-label drug prescription in hospital. This study showed a high incidence of unlicensed and off-label drug use in tertiary care. We also conducted a study in the neonatal and pediatric wards of the Reinier de Graaf Hospital, a non-teaching general hospital, which is described in *Chapter 2.2*. We conducted a longitudinal prospective cohort study in a dynamic population consisting of patients admitted to

the pediatric and neonatology ward during a 19-weeks period. Drug licensing status of all prescriptions given to these patients was determined. A total of 1017 prescriptions were administered to 293 pediatric patients. 443 (44%) prescriptions were off-label, and 285 (28%) were for unlicensed drugs. 269 (92%) patients were given one or more drugs which were either unlicensed or prescribed in an off-label way. This study shows that the extent of unlicensed and off-label drug prescription in a pediatric ward and neonatology unit of a general hospital is large. Lack of pediatric drug labeling is therefore not solely a problem with drugs used in academic pediatric hospitals, but also in pediatric wards of general hospitals. The number of unlicensed and off-label prescriptions was higher than expected, when compared to academic pediatric hospital. In *Chapter 2.3*, we compared unlicensed and off-label drug use in five European countries. We conducted a prospective study of drugs administered to children in academic pediatric wards over four weeks in five hospitals (one each in the United Kingdom, Sweden, Germany, Italy, and the Netherlands). For all children aged 4 days to 16 years admitted to pediatric wards, the proportion of drugs that were used in an unlicensed or off-label manner was determined. 2262 drug prescriptions were administered to 624 children in the five hospitals. Almost half of all drug prescriptions were either off-label (39%) or unlicensed (7%). Over half of the patients (67%) received an unlicensed or off-label drug prescription. This survey showed that use of off-label or unlicensed drugs to treat children is widespread. However, there are large differences in drug utilization between countries participating, and also in the numbers of drugs licensed for use in children, the availability of pediatric formulations, and the freedom of hospital pharmacies regarding modification and manufacturing of formulations themselves.

Chapter 3 discusses drug prescribing to children in general practice, and the incidence and nature of unlicensed and off-label drug prescription to children by general practitioners. The Integrated Primary Care Information (IPCI) database, a prospectively gathered, automated general practitioners database in the Netherlands was used as a setting. In *Chapter 3.1*, we describe the pattern of drug prescribing to children in the general population. All patients between 0 and 16 years of age, who were actively registered in the IPCI database, were followed for one life year during the period 1998-1999. Prescription patterns were assessed by age and gender and individual drugs. Drug use was unevenly distributed: 50.7% of the population received at least one prescription but 10% of the population received 50% of all drug prescriptions. Drugs were prescribed in 46.5% (95% CI: 46.2-46.8) of consultations. The proportion of drug users decreased from 73.9% (95%CI: 72.0-75.8) among 0-years-old children to 41.1% (95%CI: 40.3 - 41.8) in children between 8 and 13 years of age but increased again to 57.1% (95%CI: 55.1 - 59.0) in 16-year-old children. Overall, the most frequently used drug types were systemic antibiotics, drugs for dermatological use, and respiratory drugs. This study showed that drug use is most extensive in children below two years of age, paradoxically the age group for which the least number of drugs are licensed. *Chapter 3.2* describes the proportion and nature of unlicensed and off-label drug use in the general population. During 1998, all patients below 17 years of age, who were actively registered in the IPCI database, were select-

ed. The study population consisted of a random sample of 25 percent of a potential source population of 53,706 patients. A total of 17,453 prescriptions issued in 1998 to the study population were reviewed for unlicensed and off-label drug prescription. 2667 (15.3%) were prescriptions for unlicensed drugs, and 2381 (13.6%) were off-label prescriptions for licensed drugs. The one-year risk of an unlicensed or off-label prescription was 46% among children with at least one prescription. This population-based study showed that a large proportion of drugs prescribed by the general practitioner is unlicensed or licensed but prescribed in an off-label manner. Unlicensed and off-label drug prescription is therefore not limited to highly specialized pediatric clinical facilities, but is also an important issue in everyday pediatric care. Since many respiratory drugs are not available in formulations suitable for infants and toddlers while respiratory drugs are frequently used in children for common diseases like asthma, upper en lower respiratory tract infections, rhinitis and sinusitis, we studied the unlicensed and off-label use of respiratory drugs in children in *Chapter 3.3*. The data in this chapter were derived from the results of the survey described in chapter 3.2. 2502 (19%) Patients received 5253 prescriptions for respiratory drugs in 1998. 882 (16.8%) were unlicensed for use in children, and 1065 (20.3%) were prescribed off-label. This population-based study showed that a large proportion of respiratory drugs prescribed by the general practitioner is unlicensed for use in children or licensed but prescribed in an off-label manner. In *Chapter 3.4*, we conducted a population-based case-control study to obtain insight into the factors that affect prescription of drugs below the minimum licensed age in children. The case-control study was nested in the cohort described in Chapter 3.2 and 3.3. Cases were all children who received a drug prescription below the minimum licensed age. To each case we matched up to four controls based on GP practice and patient age. As potential risk factors we evaluated use of health care resources, and acute and chronic morbidity. We identified 447 cases, who were matched to 1355 controls. Cases consulted their GPs significantly more often during the preceding half-year, had more drug prescriptions, and had more specialist referrals than controls. Respiratory diseases were the most important determinants for the prescription of drugs to below the minimum licensed age in children. In adolescents, migraine and other types of headache were the most important reasons.

Chapter 4 addresses the question related to unlicensed and off-label drug use in child- and adolescent psychiatry, and describes trends in prescription of stimulants and antidepressants in children. We conducted a retrospective cohort study in the IPCI database. Between 1995 and 2000, 81,618 children aged between 0 and 16 years were actively registered in the IPCI database. In this population, we estimated prevalence and incidence of stimulant and antidepressant use, and the indications for these drugs. Use of stimulants (methylphenidate) increased by 770 percent between 1995 and 2000 to 4.9 users per 1,000 persons per year in 2000. Use of tricyclic antidepressants (TCAs) decreased, mostly since use for nocturnal enuresis decreased. However, the number of users of selective serotonin reuptake inhibitors (SSRI) increased by 540 percent during this period to 0.7 users per 1,000 persons per years in 2000. Twenty percent of stimulants, 46% of TCAs and 30% of SSRIs were pre-

scribed off-label, mostly because they were not licensed for the respective indications.

Chapter 5 discusses adverse drug reactions in relation to unlicensed and off-label drug use. In *Chapter 5.1*, we describe the relation between the occurrence of adverse drug events and off-label prescription of the potentially causal agent. We studied adverse events attributed to off-label drug use notified to a spontaneous reporting system for children aged 0-16 years between January 1998 and September 2001. Five adverse events attributed to off-label drug use were described in detail. From the database, we extracted 282 reports of adverse events of which 142 were attributed to licensed drugs that were prescribed according to the product labelling text. Of the remaining 140 reports, 9 were excluded because of age, 25 as it concerned a deliberate overdose and 14 reports were excluded as the causal relationship was considered possible or unlikely, leaving 92 reports for analyses. Eleven (12%) of these reports concerned unlicensed drugs, 81 (88%) reports involved off-label prescription of the causal agent, of which 50 were off-label for age (62%), 34 off-label for indication (42%), 25 off-label for dose (31%), and 4 for route of administration (5%). This study shows that off-label use of drugs in children can lead to severe adverse events. The risk of off-label drug use may be higher than was previously assumed.
Several case reports revealed that use of the antihistamine deptropine, which is unlicensed but used regularly for allergic rhinitis and asthma in children, may cause neuropsychiatric reactions in children. In *Chapter 5.2*, we conducted a retrospective cohort study to assess the extent of this association. By using the computerized medical records of the Integrated Primary Care Information (IPCI) database we identified all prescriptions for systemic antihistamines issued to children of 1 to 10 years of age between 1995 and 2000. The neuropsychiatric adverse effects that we considered were agitation, anxiety, and hallucinations. The occurrence of these events were assessed during the legend duration of antihistamines and compared between deptropine exposure and exposure to other systemic antihistamines prescribed for respiratory indications. The final study cohort comprised 1657 users of deptropine and 4515 users of other anti-histaminics among which promethazine, ketotifen and loratidine were most frequently used. The incidence rate of neuropsychiatric reactions was 5.6 fold (95%CI: 1.6-19.3) higher during use of deptropine with an excess rate of 3.1 cases per 100 person-years of exposure. The incidence of neuropsychiatric reactions was 3.8 fold higher in the first episode of use than in subsequent episodes and was highest for children 2-10 years of age. Our study demonstrated that deptropine is associated with an increased risk of neuropsychiatric events in children. As this drug is not licensed for use in children and therapeutic alternatives are available, its use should be discouraged.

In **Chapter 6**, we evaluate the current situation regarding pediatric labeling of drugs available in the Netherlands and drugs licensed by the European Medicines Evaluation Agency (EMEA), as well as the efficiency of the FDA's Modernization Act (FDAMA). In *Chapter 6.1*, we assessed the pediatric licensing status of medicines in the Repertorium 98/99, a drug information compendium in the Netherlands. We analyzed 1380 licensing texts of which 223 pertained to drugs that were not used for the

treatment of childhood diseases. Of the remaining 1157, only 339 (29%) were licensed for use in children of all ages. In *Chapter 6.2*, we evaluated the licensing for pediatric use of new molecular entities (NMEs). Hereto, European Public Assessment Reports (EPARs) published on the Internet from January 1995 until May 2001 were analyzed. Of 120 new substances licensed since January 1995, 70 (58%) were of potential use in children. Of these, only 17 were licensed for all pediatric use, and 15 for some pediatric age groups. Hence, the majority, were probably not tested in pediatric age groups. Many of the new drugs granted marketing authorization lack sufficient pediatric labelling. In *Chapter 6.3*, we studied the usefulness and necessity of drug entities for pediatric pharmacotherapy. Of 136 Written Requests issued in the study period, 36 (26%) were for cardiovascular drugs. We need to recognize the limitations of FDAMA, which makes it possible to study 22 antihypertensives for use in children while it is clear that this number of anti-hypertensives is not needed for pediatric patients. The overall conclusion of this thesis is that there are several good reasons for enhancing labelling requirements for use of drugs in children.

Chapter 7 addresses methodological considerations, the major findings of our studies, and considers the subject of this thesis in a general discussion. Three major issues are discussed; the relevance of unlicensed and off-label drug use, the improvements to enhance pediatric pharmacology research, and regulatory requirements to change the current situation.

Samenvatting

Dit proefschrift beschrijft de incidentie en determinanten van niet-geregistreerd en off-label geneesmiddelengebruik bij kinderen in het ziekenhuis en in de huisartspraktijk, alsmede de consequenties daarvan voor de gezondheid van de gebruikers. Wij definieerden geneesmiddelen als "niet-geregistreerd" voor kinderen wanneer er na beoordeling door het College ter Beoordeling van Geneesmiddelen (CBG), of de European Medicines Evaluation Agency (EMEA), bij registratie geen toestemming werd verleend voor het gebruik van het geneesmiddel door kinderen of indien het geneesmiddel voor geen enkele indicatie of leeftijdsgroep geregistreerd werd. Het "off-label" voorschrijven van een geneesmiddel werd gedefinieerd als een voorschrift aan een kind van een geregistreerd geneesmiddel beneden de in de productinformatie vermelde minimum leeftijd of voor een niet-geregistreerde indicatie, toedieningsweg of -vorm, dosering of frequentie van doseren.

Hoofdstuk 1 geeft een overzicht van de huidige situatie betreffende farmacotherapie bij kinderen (*Hoofdstuk 1.1*), geneesmiddelenonderzoek en -registratie bij kinderen en beschrijft de doelstellingen van de studies. *Hoofdstuk 1.2* geeft een overzicht van de regelgeving aangaande registratie van geneesmiddelen voor kinderen, en bespreekt verscheidene initiatieven die zijn genomen om de huidige situatie te verbeteren. *Hoofdstuk 1.3* beschrijft de belangrijkste praktische en ethische problemen bij het doen van farmacologisch onderzoek bij kinderen. In *Hoofdstuk 1.4* worden de vijf doelstellingen gegeven van de studies die in dit proefschrift beschreven staan. De eerste doelstelling was het bepalen van de incidentie van niet-geregistreerd en 'off-label' geneesmiddelengebruik bij kinderen in een academisch kinderziekenhuis (het Sophia Kinderziekenhuis in Rotterdam), in een algemeen ziekenhuis (het Reinier de Graaf Gasthuis in Delft), en bij kinderen behandeld door de huisarts. Daarnaast werd onderzocht welke factoren van invloed zijn op het niet-geregistreerd en off-label voorschrijven van geneesmiddelen bij kinderen. Ten derde werd de relatie onderzocht tussen het gebruik van niet-geregistreerde en off-label voorschriften en de eventuele negatieve gevolgen voor de gezondheid van kinderen. Het vierde doel was om te bepalen in hoeverre geneesmiddelen, die in Nederland geregistreerd zijn, ook bij kinderen gebruikt mogen worden volgens de productinformatier. De vijfde doelstelling was om de doelmatigheid te beoordelen van het huidige Europese systeem van marketing autorisatie (geneesmiddelenregistratie), alsmede van enkele van de maatregelen die in de Verenigde Staten zijn genomen om de huidige situatie met betrekking tot de registratie van geneesmiddelen bij kinderen aldaar te verbeteren.

In **Hoofdstuk 2** beschrijven we het niet-geregistreerd en off-label gebruik van geneesmiddelen bij kinderen in ziekenhuizen in Nederland en in Europa. Onderscheid is gemaakt tussen tweedelijns (algemeen ziekenhuis) en derdelijns zorg (academisch ziekenhuis). In *Hoofdstuk 2.1* wordt een onderzoek beschreven in een centrum voor derdelijnszorg, het Sophia Kinderziekenhuis in Rotterdam. In een prospectieve studie van vijf weken werden de voorschriften van drie medium care units (MCUs) en drie intensive care units (ICUs) onderzocht. We classificeerden deze voorschriften in drie categorieën: geregistreerd-, niet-geregistreerd-, en (geregistreerd doch) off-label

gebruik bij kinderen. Daarnaast bepaalden we het type niet-geregistreerd of off-label voorschrijven. Gedurende de studie-periode werden 2139 geneesmiddelen voorgeschreven aan 237 patiënten gedurende 435 patiëntendagen. Daarvan waren 725 geneesmiddelen (34%) geregistreerd, 1024 (48%) niet-geregistreerd, en 390 (18%) off-label voor gebruik bij kinderen. Gedurende 391 (90%) van de 435 patiëntendagen ontving de patiënt een of meer voorschriften die niet-geregistreerd danwel off-label waren. Deze studie laat zien dat veel van de geneesmiddelen, die voorgeschreven worden in de derdelijns zorg, niet geregistreerd of off-label zijn. We deden ditzelfde onderzoek ook op de kinderafdeling van een tweedelijns ziekenhuis, het Reinier de Graaf Gasthuis in Delft, middels een longitudinale, prospectieve cohort studie bij patiënten, die gedurende een periode van 19 weken werden opgenomen op de kinderafdeling en de pasgeborenen afdeling (*Hoofdstuk 2.2*). Van alle geneesmiddelen die werden voorgeschreven, werd de registratiestatus bepaald. Een totaal van 1017 geneesmiddelen werd voorgeschreven aan 293 patiënten, waaronder 443 (44%) off-label voorschriften en 285 (28%) voor niet-geregistreerde middelen. 269 (92%) patiënten kregen tijdens hun verblijf één of meerdere niet-geregistreerde of off-label geneesmiddelen. Alhoewel het onderzoek één ziekenhuis betrof, suggereert deze studie dat er veel geneesmiddelen niet-geregistreerd of off-label worden voorgeschreven in de tweedelijns kindergeneeskundige zorg. In *Hoofdstuk 2.3* vergelijken we niet-geregistreerd en off-label geneesmiddelengebruik in vijf Europese landen. We deden een prospectieve studie op de kinderafdelingen in vijf derdelijns ziekenhuizen in het Verenigd Koninkrijk, Zweden, Duitsland, Italië en Nederland. Voor alle kinderen (in de leeftijd tussen 4 dagen en 16 jaar), die waren opgenomen op medium care units gedurende vier weken, werd het aantal niet-geregistreerde en off-label voorgeschreven geneesmiddelen bepaald. Aan 624 kinderen in deze vijf ziekenhuizen werden gedurende de studieperiode 2262 geneesmiddelen voorgeschreven. Bijna de helft van alle voorschriften waren ofwel off-label (39%), ofwel niet-geregistreerd (7%). Tweederde van de patiënten ontving tenminste één niet-geregistreerd of off-label geneesmiddel. Dit onderzoek laat zien dat niet-geregistreerd en off-label voorschrijven van geneesmiddelen bij kinderen wijdverbreid is, maar dat er grote verschillen zijn in dergelijk geneesmiddelengebruik tussen de onderzochte ziekenhuizen binnen de deelnemende landen. Bovendien zijn ook de aantallen geregistreerde geneesmiddelen, de beschikbaarheid van kindertoepassingen van geneesmiddelen en de vrijheid van ziekenhuisapothekers om geneesmiddelen aan te passen voor gebruik bij kinderen sterk verschillend.

Hoofdstuk 3 bespreekt het voorschrijven van geneesmiddelen aan kinderen in de eerste lijn, en de incidentie van niet-geregistreerd en off-label voorschrijven door de huisarts. Hiertoe werd gebruik gemaakt van het Integrated Primary Care Information (ICPI) project, een database met prospectief verzamelde geautomatiseerde gegevens van Nederlandse huisartsen. In *Hoofdstuk 3.1* wordt het voorschrijven van geneesmiddelen door huisartsen aan kinderen beschreven. Alle patiënten tussen 0 en 16 jaar werden een jaar lang gevolgd in de periode 1998-1999. Leeftijd- en geslachtspecifieke voorschrijfpatronen werden hierbij geanalyseerd. Geneesmiddelengebruik was ongelijk verdeeld: 50,7% van de populatie ontving tenminste één voorschrift,

maar 10% van de populatie ontving 50% van de voorschriften. Geneesmiddelen werden voorgeschreven tijdens 46,5% van de consulten. Het aantal kinderen dat geneesmiddelen gebruikte, nam af van 73,9% onder 0-jarigen tot 41,1% onder 8- tot 13-jarigen, maar nam weer toe tot 57,1% onder 16-jarigen. Antibiotica, middelen voor dermatologisch gebruik en respiratoire geneesmiddelen werden het meest frequent voorgeschreven. Deze studie laat zien dat geneesmiddelengebruik het meest uitgebreid is bij kinderen onder de leeftijd van 2 jaar, paradoxaal genoeg ook de leeftijdsgroep waarvoor de minste geneesmiddelen zijn geregistreerd. *Hoofdstuk 3.2* beschrijft de incidentie van niet-geregistreerd en off-label geneesmiddelengebruik in de eerste lijn. Gedurende 1998 werd 25% van alle patiënten jonger dan 17 jaar in IPCI gevolgd. Alle 17.453 voorschriften van deze 13.426 patiënten werden beoordeeld op off-label of niet-geregistreerd gebruik. Hiervan waren 2667 (15,3%) voorschriften voor geneesmiddelen die niet geregistreerd zijn voor gebruik bij kinderen, en 2381 (13,6%) waren off-label voorschriften voor geregistreerde geneesmiddelen. Het risico op het voorgeschreven krijgen van een niet-geregistreerd of off-label geneesmiddel was 46% voor kinderen met tenminste één voorschrift. Deze studie liet zien dat een aanzienlijk deel van de voorschriften off-label zijn danwel geneesmiddelen betreffen die niet geregistreerd zijn voor gebruik in kinderen. Niet-geregistreerd geneesmiddelengebruik is daarom niet beperkt tot de specialistische zorg die in een ziekenhuis geboden wordt aan kinderen maar ook een belangrijk aandachtspunt in de pediatrische zorg die dagelijks door de huisarts geboden wordt. Veel respiratoire geneesmiddelen zijn niet beschikbaar in toepassingsvormen voor gebruik bij kleine kinderen terwijl deze middelen veel gebruikt worden voor de behandeling van veel voorkomende ziektes als asthma, bovenste en onderste luchtweginfecties, rhinitis en sinusitis. Daarom werd het niet-geregistreerd en off-label gebruik van respiratoire geneesmiddelen door kinderen bestudeerd (*Hoofdstuk 3.3*). Hierbij ontvingen 2502 kinderen 5253 voorschiften voor respiratoire geneesmiddelen in 1998, waarvan er 882 (16,8%) niet geregistreerd waren voor gebruik in kinderen, en 1065 (20,3%) off-label waren voorgeschreven. Dit percentage was aanzienlijk hoger dan bij de voorschriften voor overige geneesmiddelen. In *Hoofdstuk 3.4* deden we onderzoek naar de factoren die van invloed zijn op het voorschrijven van geneesmiddelen onder de leeftijd waar ze voor geregistreerd zijn, middels een patiënt-controle onderzoek. Patiënten waren alle kinderen die een geneesmiddel hadden gehad terwijl ze jonger waren dan de minimum leeftijd waarvoor het middel geregistreerd is. Als potentiële risicofactoren evalueerden we bezoeken aan en verwijzingen door de huisarts, acute en chronische ziekten. 447 van dergelijke patiënten werden geïdentificeerd, waarvoor 1355 controles werden geselecteerd. Casus bezochten hun huisarts significant meer gedurende het voorafgaande halfjaar, kregen meer geneesmiddelen voorgeschreven en werden vaker verwezen dan controles. Respiratoire aandoeningen waren de belangrijkste determinanten voor het voorschijven van geneesmiddelen onder de minimale geregistreerde leeftijd bij kinderen. Bij adolescenten waren migraine en andere vormen van hoofdpijn de belangrijkste redenen van voorschrijven onder de minimum leeftijd in de productinformatie.

Hoofdstuk 4 beschrijft het voorschrijven van antidepressiva en stimulantia bij

kinderen, alsmede het niet-geregistreerd en off-label gebruik van deze geneesmiddelen, middels een retrospectieve cohortstudie in de IPCI database. Tussen 1995 en 2000 waren 81.618 kinderen (0-16 jaar) geregistreerd in IPCI, en in deze populatie werd prevalentie en incidentie van stimulantia en antidepressivagebruik bepaald, alsmede de indicatie voor gebruik. Gebruik van stimulantia (methylfenidaat) nam toe met een factor 7,7 tussen 1995 en 2000 tot 4,9 gebruikers per 1000 persoonsjaren in het jaar 2000. Het gebruik van tricyclische antidepressiva (TCAs) nam af, vooral omdat gebruik voor de behandeling van enuresis nocturna afnam. Echter, het aantal gebruikers van selective serotonine reuptake inhibitors (SSRIs) nam toe met een factor 5.4 gedurende deze periode tot 0.7 gebruikers per 1000 persoonsjaren in het jaar 2000. Twintig procent van de stimulantia, 46% van de TCAs en 30% van de SSRIs werden off-label voorgeschreven, vooral voor niet-geregistreerde indicaties.

Hoofdstuk 5 bespreekt bijwerkingen van geneesmiddelen in relatie tot niet-geregistreerd en off-label gebruik. In *Hoofdstuk 5.1* beschrijven we de relatie tussen het optreden van bijwerkingen en off-label voorschrijven van het mogelijk veroorzakende geneesmiddel. We bestudeerden bijwerkingen bij kinderen tussen 0 en 16 jaar, die in de studieperiode tussen januari 1998 en september 2001 gemeld waren. Het betrof 282 meldingen, waarvan er in 142 gevallen sprake was van geregistreerd geneesmiddelgebruik. Twaalf procent van deze meldingen betrof geneesmiddelen die niet-geregistreerd waren en 88% betrof off-label gebruik. Binnen deze laatste groep was 62% off-label voor leeftijd, 42% voor indicatie, 31% voor dosering, en 5% voor toedieningsweg. Deze studie laat zien dat off-label gebruik van geneesmiddelen in kinderen kan leiden tot ernstige bijwerkingen maar geeft geen inzicht in de frequentie hiervan.
Uit verscheidene gepubliceerde ziektegeschiedenissen blijkt dat het gebruik van het antihistaminicum deptropine, dat niet meer geregistreerd is maar nog steeds gebruikt wordt voor behandeling van allergische rhinitis en asthma, neuropsychiatrische bijwerkingen kan veroorzaken bij kinderen. In *Hoofdstuk 5.2*, wordt een retrospectieve studie beschreven, die verricht werd om de omvang van dit probleem in kaart te brengen. Alle voorschriften van respiratoire antihistaminica voor kinderen in de leeftijd van 1 tot 10 jaar tussen 1995 en 2000 werden hiertoe verzameld. De neuropsychiatrische bijwerkingen, die bestudeerd werden, waren agitatie, angst en hallucinaties. Het cohort bestond uit 1657 gebruikers van deptropine en 4515 gebruikers van andere antihistaminica, waaronder promethazine, ketotifen en loratadine het meest frequent gebruikt werden. De incidentie van neuropsychiatrische reacties was bijna zes keer verhoogd tijdens gebruik van deptropine, vooral in de eerste episode van gebruik. Het risico was het hoogst bij kinderen tussen 2 en 10 jaar. Aangezien dit middel niet geregistreerd is voor gebruik in kinderen en bovendien therapeutische alternatieven aanwezig zijn, moet gebruik van deptropine ontraden worden.

In **Hoofdstuk 6** wordt de huidige situatie besproken van registratie van geneesmiddelen voor kinderen in Nederland en van geneesmiddelen, die geregistreerd werden via de European Medicines Evaluation Agency (EMEA). Tevens wordt ingegaan op de situatie in de Verenigde Staten met FDA's Modernization Act (FDAMA). In *Hoofdstuk 6.1*

1380 productinformatie-teksten, waarvan 223 geneesmiddelen betroffen die niet gebruikt worden voor behandeling van ziekten bij kinderen. Van de overigen 1157 waren slechts 339 (29%) geregistreerd voor kinderen van alle leeftijden. In *Hoofdstuk 6.2* evalueerden we de registratie voor gebruik bij kinderen van nieuwe geneesmiddelen. Daartoe werden European Public Assessment Reports (EPARs) bestudeerd, die gepubliceerd waren op het internet in de studieperiode van januari 1995 tot mei 2001. Van de 120 nieuwe geneesmiddelen, waren 70 (58%) van potentiële betekenis voor de behandeling van kinderen. Hiervan waren slechts 17 middelen geregistreerd voor alle leeftijden, en 15 voor sommige pediatrische leeftijdsgroepen. In *Hoofdstuk 6.3* bestudeerden we het nut en de noodzaak van bepaalde geneesmiddelen voor de kindergeneeskunde. Ook wordt hierin het nut besproken van de 136 Written Requests die gedurende de studie periode in het kader van de FDAMA werden ingediend. Zesendertig van deze verzoeken van de farmaceutische industrie (26%) betroffen cardiovasculaire geneesmiddelen, waarvan 22 voor antihypertensiva. Gezien dit grote aantal en de lage prevalentie van hypertensie bij kinderen, mag men zich afvragen of de FDAMA niet haar doel voorbijschiet.

In **Hoofdstuk 7** worden de methodologische overwegingen besproken, alsmede de belangrijkste bevindingen van de studies uit dit proefschrift. Drie belangrijke onderwerpen worden besproken. Ten eerste, de relevantie van niet-geregistreerd en off-label gebruik bij kinderen. Ten tweede, mogelijke verbeteringen ter bevordering van farmacologisch onderzoek bij kinderen. Ten derde wordt besproken welke mogelijke maatregelen op gebied van de regelgeving genomen moeten worden om de huidige situatie met betrekking tot de toepassing van geneesmiddelen bij kinderen te verbeteren.

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About the author

Geert Willem 't Jong was born on April 10, 1977 in Sliedrecht, the Netherlands. He graduated in 1995 from the "Christelijke Scholengemeenschap De Lage Waard" in Papendrecht. In the same year, he started his study at the medical school of Erasmus University Rotterdam, in Rotterdam, The Netherlands. During this period, he participated in a research project of the Department of Pediatrics, Division of Neonatology (head: Prof.dr. J.N. van den Anker) on unlicensed and off-label drug use in children in the Sophia Children's Hospital in Rotterdam, the Netherlands, and graduated in 1999. In 2000, he started the work described in this thesis at the Departments of Pediatrics (head: Prof.dr. H.A. Büller), and Epidemiology & Biostatistics (head: Prof.dr. A. Hofman). During this period, he worked as a trainee in Derby, United Kingdom (head: Prof.dr. I. Choonara) on the evaluation of an American incentive for pediatric labeling, and in Columbus, Ohio (head: Prof.dr. J.N. van den Anker) on unlicensed and off-label prescription in a spontaneous adverse drug event reporting system. In May 2002, he will start his internships in order to finish his medical training.