EDITORIAL

Problems of Prescription Drug Use in Children

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Accompanying the article "Off-Label Use of Prescription Drugs in Childhood and Adolescence—an Analysis of Prescription Patterns in Germany" by Mühlbauer, Janhsen, Pichler, and Schoeller in this issue of Deutsches Ärzteblatt International

The pediatric health care study by Mühlbauer et al. that appears in this issue deserves our close attention: It reminds us once again of a longstanding public health problem, namely, the inadequate safety of prescription drug use in children (1). Pediatricians often give medicines in ways that do not conform with the product licence. The literature generally calls this practice "off-label use." Arising from the treating physicians' inadequate knowledge of the medicines that they prescribe, in both ambulatory and inpatient settings, off-label use doubles the frequency of adverse drug reactions, which are sometimes life-threatening (2, 3). As early as 1963, an American pharmacist and pediatrician, Harry C. Shirkey, complained that children risked becoming "therapeutic or pharmaceutical orphans" because many pediatric drugs had not been licensed (4). He felt it was unacceptable that safe and effective medicines should be withheld from this vulnerable group of patients. Yet it is only now, at the beginning of the 21st century, that laws and regulations are being put into effect at the national level and in the European Union as a whole to improve prescription in pediatrics (Directive 2001/20/EC of the European Parliament and Council relating to good clinical practice; 12th Amendment to the German Pharmaceuticals Act [Arzneimittelgesetz]; Regulation EC/1901/2006). Thus, the data from the year 2002 that Professor Mühlbauer and his colleagues have analyzed can still be considered an accurate reflection of the situation as it exists in 2008.

The prevalence of off-label use

In the past, the increasingly widespread off-label use of medications has been documented in other clinical disciplines (oncology, geriatrics). In order to raise awareness of the problem of off-label use in general, public institutions such as the German Federal Social Court (Bundessozialgericht) and the Joint Federal Committee (Gemeinsamer Bundesausschuss—the official self-governing body of health care providers, hospitals, and insurance carriers in Germany) now point more frequently to off-label use specifically in pediatrics. The impression is created that the term "off-label use" adequately describes the problem, and that it can be best solved by further regulations. It would now be appropriate to take the discussion back to its starting point and consider the general problem of drug medication and drug safety in children (5).

According to current standards, when a medicine is licensed, parameters are established for the indication, the dose, the age group, and the duration of treatment. The accompanying information for physicians includes warnings about potential harms. The data needed for this are acquired in industry-initiated efficacy and safety studies before authorization and are then submitted to the drug regulatory authority for critical review.

In contrast, scientific questions such as "proof of concept" are the driving elements in studies initiated by physicians and clinical researchers. Once the new knowledge obtained in such studies has been published in peer-reviewed journals, it is soon reflected in review articles, textbooks, and therapeutic guidelines.

A few recent examples of novel drug therapies in pediatrics can be named here: indomethacin for patent ductus arteriosus, caffeine for idiopathic apnea attacks, and methotraxate for juvenile idiopathic arthritis. The quality of the underlying studies, and/or the number of patients involved, often do not meet the regulatory requirements. Despite the legally instituted facilitating measures and incentives, it often happens that no drug manufacturer submits a licensing application with all of the required authorization documents. The off-label use of these medicines, with all implied risks, is thus a foregone conclusion, both in the maximal care setting of the intensive care unit and in specialized pediatric outpatient clinics. Depending on the patient's age and underlying disease, the percentage of off-label use varies from 30% to 90% (6).

Prescription practice in primary care

This problem in drug medication is present not just in the hospital, but also in primary care, as Mühlbauer et al. have clearly documented (1). Once these authors had determined, with great effort, the pediatric licensing status on the basis of the available Summary of Product Characteristics (SPC), they concluded that a major safety problem exists in the outpatient setting. As in the hospital, the problem is more severe among younger children. For all active agents used, the percentage of off-label use was 80% in neonates, 60% in infants, and a still too high 34% for the remaining ages (from toddlers to adolescents). These percentages are remarkable when one considers that the state of the available data enabled deviations from lincensed use to be detected only with regard to the age of the patient, and not at all with regard to the dose, method of administration, or indication.

It is perhaps understandable that children are often treated as if they were small adults when they have problems restricted to the sensory organs or the skin, but it is certainly no longer acceptable that potent cardiovascular drugs are necessarily given off label most of the time (1). These drugs are of essential importance in pediatric and neonatal intensive care units and in outpatient pediatric cardiology.

As one might expect, the traditional cough suppressants and medicines against the common cold are the drugs most commonly given in outpatient practice (1), and they are generally administered to preschool children as directed. Nonetheless, many of these drugs, which came on the market decades ago via a "historical" licensing mechanism, are not up to the current scientific standard (7), and combinations of them are still less so. These familiar old pediatric remedies can be obtained without a prescription but are not necessarily safe. The antitussive drug clubutinol, for example, was taken off the market very recently, after many years of use, because of the danger of cardiac arrhythmias. Even the on-label dose that was recommended at the time of its approval had not been carefully determined with dose-finding studies. Similar problems beset even the classic drugs paracetamol (acetaminophen) and salbutamol (8, 9).

An urgent call to action

In view of these numerous problems, action is clearly needed in Germany. Other European countries have already gone further than we have in this area. As a first step, it would be desirable for the drug manufacturers and the drug regulatory authorities to improve the product information, which is currently deficient in relation to pediatric use. In view of the widespread nature of off-label use in pediatrics, interest in prescription practice should be raised among pediatricians by increasing the number of presentations on this topic at the annual meetings of learned societies and in the board-exam preparation courses. Of course, the pediatric specialty societies should also intensify their health services research with respect to pharmacotherapy (10). It is urgently needed for government officials to assume a leading role in setting the agenda and to coordinate the activities of the responsible ministries and federal authorities on the one hand with those of the pharmaceutical industry and the pediatric specialty societies on the other. Mühlbauer's article gives a new impetus to this initiative. The German Parliament and the European Parliament and Commission are currently awaiting a report, due to appear in the next few months, concerning the implementation of laws and regulations for the improvement of drug medication in children.

Conflict of interest statement
The author declares that no conflict of interest exists as defined by the guidelines of the International Committee of Medical Journal Editors.

Manuscript submitted on 16 December 2008, revised version accepted on 16 December 2008.

Translated from the original German by Ethan Taub, M.D.

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Dtsch Arztebl Int 2009; 106(3): 23–4
DOI: 10.3238/arztebl.2009.0023

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