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Editors' view

Off-label and unlicensed prescribing for children: have we made any progress?

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Unlicensed drugs are those that do not have marketing authorization. Off-label use is prescribing outside the terms of the product licence, for example in a different indication, age group, dose or route to that which is approved by the regulatory authority. In 1999, Collier wrote an editorial for the *Journal*, in which he considered the problems raised by off-label and unlicensed prescribing for children. He concluded that "the current widespread use of products outside [licensed] conditions disadvantages children and is unacceptable" (1). Has anything changed over the last 8 years? Data from the UK suggest that in primary care about 11% of drugs prescribed for children are used off label (2). Higher figures have been found in the Netherlands (29%) (3) and France (33%) (4). The rate of off-label use for children in hospital was close to 40% in a survey of five European hospitals (5) and even higher in hospitalized neonates.

These patterns of prescribing are almost inevitable, given the lack of evidence of efficacy for many drugs in children and the need to treat serious diseases. However, the statistics hide different degrees of risk. There used to be little incentive for pharmaceutical companies to investigate the efficacy and safety of their agents before marketing; usually, they merely published a disclaimer in the prescribing information that the medicine "is not approved for use in children". Even when an evidence base for both efficacy and safety subsequently accrues, the cost of applying for an extension to the licence may be too great for the company to justify, given the likely size of the new market. For many potential treatments, the population that requires the medicine is so small that trials can only be carried out by recruitment of children from large numbers of centres. It is not surprising that the perceived ethical, technical, and logistic difficulties of carrying out research in children has restricted the available evidence on many medicines (6). Fortunately, incentives to pharmaceutical companies in the USA and Europe to carry out research in children and the formation of paediatric clinical pharmacology research networks, such as those in the UK (6), USA, and Canada (7), are beginning to address these shortcomings. In Europe there are several developments. Among these, Medicines for Children - The European Paediatric Initiative (8) has proposed wide-ranging changes to the way that medicines are licensed for use in children. The under-reporting of adverse drug effects in paediatric populations has also prompted a guideline on pharmacovigilance for medicines used by children, which came into force in January 2007 (9).

In the meantime, we are left to navigate a path through the potential minefield of paediatric prescribing. Children are not simply young adults, and the extrapolation of adult data to paediatric populations relies on many assumptions. Drug dosages for different age groups are adjusted on the basis of weight or surface area, in order to avoid ineffective or potentially toxic regimens; there are different patterns and outcomes of disease in children compared with adults; and there is a dearth of information on patterns of adverse reactions and potential long-term toxicity from medicines in children. There are conflicting data about the risks of serious adverse reactions from the use of off-label and unlicensed medicines in children (10), and the true picture is compounded by under-reporting.

Since the publication of Collier's editorial, sources of information for safe and effective prescribing in children have improved considerably. In the UK, The National Service Framework for Children, Young People and Maternity Services (11) established a standard on medicines for children. More recently, the introduction of the

British National Formulary for Children (BNFC) (12) in 2005 has given UK prescibers a handbook of evidence-based guidance and expert opinion (when there is inadequate evidence) to improve the quality of paediatric prescribing.

In day-to-day clinical practice, the prescriber is still left with dilemmas. Off-label prescribing and the use of unlicensed drugs in children is acceptable when there is no suitable alternative. Following the recommendations in consensus guidelines, such as those in the BNFC, is an important safeguard, although not a guarantee of either safety or efficacy. There is then the issue of responsibility for informing the parent or young adult about off-label or unlicensed use of a medicine. Both the prescriber and the pharmacist who dispenses the prescription have a role in providing information for patients and carers, although the relationship between them is unclear. In this issue of the *Journal*, Stewart *et al.* (13) have explored the attitudes of community pharmacists to this problem. Although the proportion of questionnaires returned was low, the sample was believed to be representative of the demographics of UK community pharmacists. The results suggest a high degree of awareness of the potential problems surrounding off-label and unlicensed prescribing, but only a minority of pharmacists said that they would contact the prescriber to check the prescription if they had concerns. The General Medical Council (UK) guidance on prescribing (14) states that a "When current practice supports the use of a medicine in this way [off label] it may not be necessary to draw attention to the licence when seeking consent [to treat]". Many pharmacists believe that they have a role in informing parents that medicines are being prescribed off-label. It is clear that in order to avoid distress and concern among parents and older children, these responsibilities need to be clarified. Use of the BNFC in the UK, and similar authoritative publications in other countries would be a good place to start when deciding whether a discussion about off-label or unlicenced indications should be undertaken.

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