Licensed medicines, off-label use or evidence-based. Which is most important?

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Medicines are licensed for use in humans by regulatory authorities. The concept of licensing is that it helps ensure that medicines are safe, effective and of an adequate quality for regular use.[1] Licensing was introduced due to concerns about safety not to ensure that medicines are effective. It was a response to specific examples of drug toxicity, notably the grey baby syndrome in neonates following the use of the antibiotic chloramphenicol and phocomelia in the developing fetus following ingestion of thalidomide by pregnant women.[2] Within the UK, the Medicines Act was passed in 1968. The licensing of medicines is both a control on products of public interest as well as an authorisation to sell for pharmaceutical companies. Pharmaceutical companies are only allowed to promote licensed medicines. Prescribers, however, are free to prescribe the most appropriate medicine for their patient. This should be based on the best available scientific evidence. Medicines can be licensed (authorised) by either national regulatory agencies (national route) or the European Medicines Agency (centralised route). It is only once they are licensed, that they can be marketed and made available to patients.[1]

OFF-LABEL USE

In the late 90s, there were several studies documenting the extent of off-label and unlicensed use of medicines in paediatric inpatients.[3] These studies highlighted that many medicines used in paediatric patients are off-label, that is, used in a manner different to that recommended in the product licence. Off-label use may relate to use at a different dose or frequency, by a different route, or in a different age group for that which is authorised. Additionally, medicines may also be used for different indications to those contained within the product licence. Following the initial studies within the UK, there were studies involving different European countries and subsequently countries outside of Europe.[3] These studies all showed that off-label drug use was common in paediatric patients, both in hospital and in the community. This off-label use can increase the possibility of an adverse drug reaction occurring.[2]

In response to the widespread concern regarding the extensive off-label use of medicines in the paediatric population, legislation was passed both in Europe and North America to encourage pharmaceutical companies to study clinically required medications within the paediatric population.[4] Since this legislation was introduced, numerous studies have continued to be performed in different countries around the world documenting off-label drug use. Off-label drug use in paediatric patients, however, is already well documented. Further studies of off-label drug prevalence utilisation are not currently needed, whereas we do need appropriate comparative studies evaluating the safety and efficacy of off-label versus on-label drugs.

EVIDENCE-BASED PRESCRIBING

One of the major concerns regarding off-label use, in particular in paediatric patients, was not that medicines were unauthorised but rather there was an insufficient evidence base for the use of many medicines in children. It was the lack of an evidence base that most concerned health professionals specifically interested in this problem.[5] Evidence-based medicine had become accepted with adult patients and the concern was that paediatric patients were being ignored. The evidence-based practice of prescribing medicines appropriately is increasingly being recognised as a major issue, not only in low and lower-middle income countries but also in upper-middle and high-income countries.

The importance of evidence-based medicine is highlighted in the paper by De Bruyne *et al*, which looks at first-generation antihistamines.[6] They highlight that although these medicines are licensed, there is a large variability in labelled indications and licensing ages in different countries in Europe. This raises questions concerning the regulatory process. The same available data has been evaluated differently by different countries. Additionally, the evidence basis for the use of medicines in these indications is questionable. The first-generation antihistamines were licensed a long time ago. One would anticipate that the requirements for licensing are more thorough now than previously. However, it is important to recognise, however, that for a medicine to be licensed, one only has to show that it is more effective than placebo. The lack of a requirement for studies comparing the new drug to established treatment has been raised as a major weakness of the European regulatory process.[1] It has been suggested that evaluating 'added therapeutic value' should be added to the current criteria for drug evaluation of quality, efficacy and safety.[1]

The main message of the paper is that, it is the evidence base for the use of medicine for a specific disease that is the most important issue. Knowledge must guide the medical decisions and not the marketing status (licence). Researchers should stop studying the epidemiology of off-label drug use in children. Their independent research would have a far greater impact if they studied the evidence basis for many current practices in prescribing and also whether medicines are prescribed rationally or not. For their part, medicine agencies must put patients' and public health services' interest first with more determination.[1]

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