



OFF-LABEL PRESCRIBING: AN UNSATISFACTORY SITUATION

Mag pharm Dr Silvia Hetz, aPhD

In this issue an Austrian hospital pharmacist acts as our Guest Editor in a survey of off-label prescribing. Her conclusions fully reflect the views put to us: the present free market arrangements do not support the needs of patients.

Introduction

Drug approval not only provides the treasured marketing authorisation but also a licence for which conditions, at which dosage and for which age of patient this medicinal product should be used. Whenever these conditions are abandoned the use of the drug is so

called “off-label”. In many settings off-label prescriptions are frequent and common, for example, in paediatrics, intensive care units or oncology. Although off-label use is always considered a problem, it is inevitable whenever therapeutic alternatives do not exist. Nevertheless, on average in

Europe there is little legal regulation. Physicians are left alone with a gap between their obligation to treat and a lack of suitably registered drugs. With an uneconomical cost-benefit ratio, the pharmaceutical industry does not feel urged to supply a satisfactory solution to the problem.

Austria: doctors are put in a difficult position

In Austria it is almost impossible to find an explicit legal framework for off-label prescribing. On one hand the Austrian Medicines Act “Ärzneimittelgesetz” states that only approved drugs may be marketed; on the other hand the Physicians Act “Ärztegesetz” obliges physicians to offer treatment to any patient. Furthermore no national or local guidelines or policies are in place. In our hospital we do not collect statistics on off-label prescribing but where therapeutic alternatives are lacking it is very frequent. It occurs daily in nearly every department of the hospital.

Doctors update themselves via congresses or professional journals about the state of the art of treatment, quite often with off-label therapies and are supposed to inform their patients and receive their consent as well as to take full responsibility for treatment failures. In fact serious consequences can arise from civil law and even criminal law for a physician if the suggested therapy is beyond the state of the art. Moreover they can lose their right to practise if accused of bodily injury. Until now no cases have been brought to court but doctors expect the judgements to be comparable to German precedents, which allow off-label use under certain circumstances.

There are no mechanisms for approving or monitoring off-label prescriptions in our pharmacy, our hospital or on a national level. A few initiatives exist such as an Austrian Society of Dermatology database on the internet, where doctors can report their experience with off-label treatments.

We have recently noticed that the pharmaceutical industry starts marketing new drugs long before the products are registered. The sales representatives try to get information about off-label prescribing and search for ways to sell their products before approval. They may argue that better therapies must not be delayed because of the time-consuming procedures of registration.

Summary

Thank you to everyone who contributed to this survey. It is less and less acceptable to treat children with drugs that have not been studied properly. It is the responsibility of the Medicines Agencies to offer a secure supply of medicines to all patients, including those groups of patients that do not stand for guaranteed profits. There is a need for institutions independent of marketing interests – for example universities – to push matters along on behalf of the European Agencies. The recently approved EU guidelines are certainly positive developments and are strongly welcomed. An increased number of drugs are expected to be licensed for children.

Off-label prescribing is regarded as necessary until suitably registered drugs are on the market. Drugs used off-label make the paediatric setting more prone to adverse drug events. This restrains prescribing, increases the risk of legal action, and worsens the risk of fatal events. A problem exists with reimbursement and hospital procurement systems that promote cheap drugs without proper pharmaceutical formulations for children.

In some countries the pharmaceutical industry is observed with much concern as it is thought to skilfully trigger the start of off-label use. Marketing authorisation holders take advantage of physicians, opinion leaders and associations in order to spread the news of promising off-label uses. When a new use is adopted it is inevitably on a poorly developed evidence base.

We need to face the fact that at present, the supply of sufficiently registered drugs is not satisfactory and that our means to secure it is inadequate. It shifts all the responsibility to satisfy the therapeutic needs of minor patient groups to the physician.

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The Norwegian Paediatric Association has national guidelines

There are no surveys on the use of unlicensed and off-label medicines in children in Norway, but we believe that it is the same as elsewhere. The use of unlicensed and off-label medicines is legal and is the responsibility of the prescribers. In any case questioning a prescriber's use of unlicensed and off-label medicines, the Norwegian Board of Health will decide whether or not it has been based on sound professional opinion, and if the hospital has adequate guidelines in the field.

Paediatricians are well aware of their responsibility and seek advice in the literature, among colleagues nationally and internationally and from pharmacists. In addition to local hospital guidelines, the Norwegian Paediatric Association has national guidelines, including the use of unlicensed and off-label medicines (www.barnelegeforeningen.no). Many hospitals refer to foreign paediatric formularies such as Medicines For Children and BNF-Children in their practice as well.

Imported unlicensed medicines are not tested by the Medicines Agency, wholesalers or the pharmacy. The wholesalers check that the supplier is a holder of a special manufacturers licence, import licence or distribution licence. The wholesalers are inspected and licensed by the Medicines Agency.

Norwegian doctors and pharmacist have tried to persuade the industry to keep some products suitable for children on the Norwegian market. In the 1980s our requests were heard sympathetically, especially by Norwegian and Scandinavian manufacturers. Nowadays the absence of some products seems to be profit-related.

On a daily basis the use of unlicensed and off-label medicines causes much bureaucracy. The doctors must apply for funding for the individual patient. The patient must pay for the medicines until the Norwegian Labour and Welfare Organisation has responded to the application. Paediatricians and pharmacists have asked the Health Department to review the rules to reduce the bureaucracy - with no success!

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Finland would like children's medicines tested and licensed

Off-label prescribing is allowed in Finland. There is not really any legal framework governing it. The only thing mentioned in the law is, for example when a physician writes a prescription for off-label use for a child, he/she has to confirm off-label dose by writing "SIC!" on the prescription.

We conducted a study in 2001 in which we evaluated the prescribing of off-label and unlicensed drugs in three paediatric wards in a tertiary hospital (Kuopio University Hospital) in Finland [1]. The paediatric wards were the neonatal intensive care unit, general paediatric ward and paediatric surgical ward. Of the 108 children with a prescription, 82 (76%) were prescribed at least one off-label or unlicensed drug; 79% in the NICU, 63% in the general ward and 91% in the surgical ward ($p=0.014$). Of all 629 prescriptions, 321 (51%) were for licensed drugs, 226 (36%) for off-label and 82 (13%) for unlicensed drugs.

Off-label prescribing is common in our hospital in every single ward. One example is pain management with epidural infusions and intrathecal injections for spinal anaesthesia. In both indications fentanyl is used in all patients although intrathecal use is not an indication of fentanyl.

One of the two goals of the Finnish National Agency for Medicines (NAM) as a partner of EU is the scientific evaluation and regulation of paediatric medicinal products. Paediatric pharmacotherapy is one of the areas where off-label use is common, and thus the aim of the NAM is to resolve this problem: children should have medicines that are tested and licensed for paediatric use [2].

To our knowledge there are no local policies about off-label prescribing. The only pressure on industry is the new regulation on medicinal products for paediatric use.

In Finland prescribers are under continuous indirect (subtle) pressure by the industry to use drugs in ways that are not licensed. The most common way is to invite opinion leaders to make presentations on different issues and to explain off-label use of products that are to the greatest advantage of companies. Moreover, opinion leaders are kept well informed all the time of any off-label use to which the products have been put.

1. Lindell-Osuagwu et al., submitted J Clin Pharm Therap.
2. www.europarl.europa.eu/oeil/file.jsp?id=5210532



⇒ Fentanyl: used intrathecally for pain management



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New legislation requires protocols in the Netherlands

In the Netherlands a new law on medicines came into force in July 2007. Off-label use is allowed, but under restriction: it is permitted by law if drugs are prescribed within established protocols. Physicians are obliged to consult a pharmacist if a prescription is not governed by a protocol. They must together draw up standards and protocols.

The extent of off-label use is substantial. In secondary and tertiary paediatric care between 50-80% of all drugs are prescribed off-label or unlicensed [1]. Not surprisingly, highest off-label use occurs in paediatric and neonatal intensive care wards. By far the most drug use is based either on long-standing experience or evidence obtained from literature.

Questions arise about the availability of drugs that will become available under the new Directive [3]. The Health Care Insurance Board (CVZ) has exclusive control over reimbursement of the Dutch healthcare system. Dutch pharmacies are allowed to prepare "homemade" formulations and to modify commercial preparations in order to suit the needs of children. The question of whether the CVZ will encourage the prescription of licensed but more expensive drugs is yet to be answered.

Finally, it is questioned whether more paediatric drug research really benefits children. Recently, a study group from Leiden University searched the literature to assess the effectiveness of a programme to encourage licensed formulations after the introduction of paediatric exclusivity laws in the USA [2]. Results show that children are infrequently given drugs granted paediatric exclusivity. Industry-sponsored research seemed to have focused on the most profitable part of the market. These findings warrant efforts to encourage research on drugs that really best serve paediatric patients.

1. 't Jong, et al. *Pediatrics*. 2001;108(5):1089-93.
2. Boots, et al. *Eur J Pediatr*. 2007;166(8):849-55.
3. www.europarl.europa.eu/oeil/file.jsp?id=5210532



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Perspective from a tertiary paediatric hospital in Ireland

Off-label prescribing is a legal and common practice in the Irish paediatric setting. While the Irish Medicines Board (IMB) controls the licensing of medicines, it has no role in the use of off-label or unlicensed medicines. The decision to use a medicine is the professional responsibility of the prescriber. To help and support prescribing decisions, authoritative references such as the British National Formulary for Children are used nationally, and thus, most prescribing is supported by evidence-based practice.

Our Lady's Children's Hospital caters for all children, from premature infants up to adolescents. Off-label prescribing occurs in all areas and disciplines but especially in intensive care and neonatology. A study by the Pharmacy Department found that 56% of all doses administered in the intensive care unit were off-label, with a similar figure of 54% in a baby ward. The younger the child, the number of medicinal products licensed decreases.

Paediatric physicians reluctantly accept the unsatisfactory state of affairs. The decision to prescribe off-label is made where the benefit to the child outweighs any potential risks. Indeed to have a licensed medicine available for a specific indication and age group is considered an unexpected bonus! It is important for each hospital to have a policy for unlicensed medicines and off-label use of medicines, ideally endorsed by its Drugs and Therapeutics Committee.

Rationalisation of product lines by large pharmaceutical companies and the discontinuation of older drugs has a significant impact on paediatrics. Ireland's small population of children means that our market is insufficient to justify an expensive license renewal and so the product disappears off our shelves. Despite protests from healthcare professionals, manufacturers know that we will import it from another EU country where it is licensed, so that patients are not deprived of the medicine.

It is illegal to promote medicinal products outside of their licensed indications and pharmaceutical companies are careful about this.



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National safety initiative in Sweden

Sweden is part of the Scandinavian Paediatric Pharmacy Group, www.sppg.net. This year a national initiative on patient safety on paediatric drugs is running with approximately 16 teams (pharmacists, nurses and physicians) from different paediatric hospitals around Sweden, meeting up to apply patient safety strategies to the drug use process.

Off-label use of medicine is part of the free prescribing rights of the physician. However, the pharmaceutical benefit boards for reimbursement can specify therapy restrictions in primary care drugs. No national guidelines exist for off-label prescribing.

Rane et al. showed that in a paediatric hospital setting (Uppsala), 67% of the paediatric patients received at least one off-label drug, which corresponded to the frequency of the other countries in the study [1].

A study of the primary care off-label prescribing to children in Stockholm county showed that for 90% of the most-prescribed drugs, 70% were used off-label in dermatology and 5.4% of systemic drugs were used off-label [2].

At our hospital we have started to retrospectively review drug charts for paediatric off-label drugs since many off-label drugs are used infrequently in paediatrics. We are collecting information regarding the volume of prescribing, investigating the known literature, compiling data from our clinical cases and interviewing parents to learn more about the safety issues of off-label prescribing.

There is no known pressure except market forces and the Paediatric Use Marketing Authorisation (PUMA) [3] and the Medicines use Investigation for the Children of Europe (MICE) initiatives, which promote registration of paediatric products. MICE has been merged into Paediatric Directive 1901/2006/EC of last year, which gives many incentives to produce paediatric medicines [4].

1. Conroy. *BMJ*. 2000;320(7227):79-82
2. Ufer, et al. *Eur J Clin Pharmacol*. 2003;58(11):779-83
3. emea.europa.eu/htms/human/paediatrics/pumas.htm
4. www.europarl.europa.eu/oeil/file.jsp?id=5210532

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Off-label prescribing is as yet unregulated in Slovenia

Off-label prescribing is a problem. It is tolerated in Slovenia although there is no basis for it in law. In paediatrics it is estimated that around 60% of drugs are prescribed off-label. In theory, legal action against the prescriber is possible both from the patient and from the insurance company.

No national guidelines or policies are in place for approving and monitoring this behaviour at the national, hospital, clinician or pharmacy level. However, in local guidelines we recommend the dosage according to clinical studies and the literature. These may vary from the official summary of products' characteristics.

The international regulations on drugs are at the moment the only mechanism that forces the industry to licence drugs for paediatric use properly. The officially licensed product information should be updated more frequently, based on wider studies.



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Off-label use not covered by the law in Poland

The off-label use of medicines is a problem in Poland. The major area is paediatrics, especially in oncology and haematology. Drugs not licensed in Poland also belong to a special group. In clinical practice exceptions concern mainly the age of patients, dosage and administration route.

By law, every drug administered other than according to the license, should be treated as a medical experiment. The procedures of a clinical trial are required, such as approval from a bioethics committee. However the law is often ignored.

The doctor who prescribes the drug is always responsible for its use. There are no standard Polish procedures for how to act if such a treatment is not appropriate. It depends on the practice in the hospital or clinic (e.g. written patient permission for off-label use and application to the bioethics committee).

Pharmaceutical companies are always extending the therapeutic recommendations, especially with new, expensive drugs. Information about clinical effectiveness spreads much faster among doctors than can be controlled by the existing legislation, and the bureaucracy is cumbersome.

If clinically relevant actions could be made legal by simple procedures and manufacturers were obliged to investigate drugs in special patient groups (children, the elderly), the scale of off-label use of medicines could be reduced.

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