

THE ETHICS OF PRESCRIBING OFF-LABEL DRUGS IN CHILDREN. THE DILEMMA OF SILDENAFIL

Laszlo-Zoltan Sztankovszky¹, Magdalena Iorga¹, Cristian Gheonea²,
Georgiana Russu³

¹Department of Preventive and Interdisciplinary Medicine,
“Gr. T. Popa” University of Medicine and Pharmacy, Iasi

²Pediatric Clinic, University of Medicine and Pharmacy, Craiova

³Department of Pediatric Cardiology, „Sf. Maria“ Children Emergency Hospital, Iasi

ABSTRACT

The off-label prescription means that medicines are administered by an unlicensed route, in an unlicensed formulation or dosage or to a child below the stated age range. The use of drugs in an off-label or unlicensed manner to treat children is widespread. Because many prescribed treatments for children have not been adequately tested in children, this population of patients remains a vulnerable one. On the one hand, prescribing off-label use drugs in children determines a lot of controversies but, on the other hand, without this possibility, could be deprived of a chance to be treated. The paper presents the widespread phenomenon of off-label use drugs in children, reflecting in scientific studies in USA and Europe. An important focus is on Romanian statistics of Sildenafil prescription and on dilemmatic use of it in pediatric cardiology unit.

Keywords: ethics, drugs, children, prescribing, off-label

INTRODUCTION

On an actual basis, humans spend only approximately 16 years as children, whereas they spend another part of their life as adults and seniority (60 to 80 years). In the age-based definition of “child”, adopted by the *Convention on the Rights of the Child*, the child is a person under the age of 18 years. According to the guidelines of the International Conference on Harmonization (ICH), we should distinguish between neonates (birth – 27 days), infants (28 days – 23 months), children (2-11 years) and adolescents (12-18 years). (1)

Along with pregnant women and infants children remain therapeutic orphans, because there are not many therapeutic indications that are unique to these vulnerable populations. Evaluating the potential safety of any off-label prescribing considered is probably the most challenging aspect for the pediatrician. The main sources of information to guide drug utilization are: *AMA* drug evaluations, *US*

Pharmacopeia, medical literature, clinical pharmacology/clinical pharmacy services, *US Food and Drug Administration* (FDA), the drug information services of various pharmaceuticals companies, drug company sales representatives, *Physicians’ Desk Reference* (PDR). Almost 70% of the entire PDR entries have either no existing dosing information for pediatric patients or explicit statements that the safety and efficacy in children have not been determined. In the best of circumstances, there are age-specific admonitions because of the lack of dosing information for infants and children. (2)

Even if a lot of scientific literature and research has been trying to point the different dilemmatic aspects of using drugs in minors (referring to trials, prescribing or use of drugs under the countries’ legislation) and some regulations have been adopted in order to regulate this issue, this challenge remains open to dilemmas. The Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal prod-

Corresponding author:

Magdalena Iorga, “Gr. T. Popa” University of Medicine and Pharmacy, 16 University St., Iasi

E-mail: magdalena.iorga@umfiiasi.ro

ucts for pediatric use required for medication to be ethically researched and made available for children aged 0-17 years. (3)

OFF-LABEL USE OF DRUGS FOR CHILDREN

The off-label and unlicensed use of drugs to treat children is a common practice that occurs either in hospitals or in the community. This problem derives from the fact that research for establishing drug efficacy and safety in children has not been carried out due to ethical problems, logistical difficulties, financial and legal concerns. (4)

The level of exposure to prescribed drugs was considerable at all ages and was highest in early childhood. Certain research supports the need for epidemiological studies on the reasons for drug use and for the evaluation of their pharmacological effects in children. (5,37)

Children are not included in trial for ethical reasons and because obtaining consent from parents is a very complex process, the caregivers must decide on behalf of their child. Trying to adapt to this situation, parents and pediatricians generally opt for standard care rather than trial participation. (6)

In normal conditions, the children are excluded from clinical trials of new molecules with therapeutic effect. Even though, when the drug is approved by the authorities, is just a matter of time until doctors use this medicine in pediatric patients. We do know that the practice of prescribing drugs for off-label conditions is found in approximately 50% of all physicians' prescribing. (7) The off-label prescription means that medicines are administered by an unlicensed route, in an unlicensed formulation or dosage or to a child below the stated age range. On the one hand, without this route, the child in need could be deprived of a chance to be treated. On the other hand, administering the unlicensed treatment could lead to unexpected effects, exposing the doctor to the malpraxis accusation. (8)

A review demonstrates that up to 80% of prescriptions for children in hospital and in general practice are either unlicensed (without a license for children) or used off-label (outside the product license). (9)

But there is a need to study medicines, as data obtained in adults cannot be applied to children. Children are not little adults. Their physical development is characterized by metabolic particularities. Because many drugs are unlicensed in children, their doses are scaled down from those used in adults. Usually scaling down directly from an adult, using weight (mg/kg) as guidance, results in

a dose too small for infants and children, because elimination does not change in direct proportion to weight. (10) The disposition of drugs in children varies from that in adults, because children differ from adults pharmacokinetically and pharmacodynamically. Factors like growth, surface area, organogenesis, enzyme development, plasma and tissue binding, brain development, physiological and functional development and psychosocial issues need to inform the development of new medicines for children.

In Europe, only 35% of drugs are authorized for use in children. (11) Drugs most often used by children are respiratory drugs (30%), anti-infectives for systemic use (28%) and dermatologicals (12%). (12)

OFF-LABEL USE AS A WIDESPREAD PHENOMENON

The use of drugs in an off-label or unlicensed manner to treat children is a widespread phenomenon. Comparing both methods, drugs are more likely to be used in an off-label manner than in an unlicensed manner. The use of off-label and unlicensed drugs are applied in all the different pediatric wards surveyed and are extensive in many countries.

According to a survey, over two-thirds (67%) of 624 children admitted towards in five European hospitals received drugs prescribed in an unlicensed or off-label manner. 39% of the 2,262 drug prescriptions given to children were off-label. Therefore, the problem of off-label and unlicensed drug prescribing in children is a European problem that requires European action. According to one other study regarding off-label use in pediatric patients, the most vulnerable pediatric group – critically ill neonates and infants – has the highest exposure to drugs that are insufficiently documented with regard to efficacy, safety, and dosage; this situation underscores the need for clinical trials in these age groups. (13-15)

In France, a research paper targeted on the prescriptions of French office-based pediatricians revealed that 33% of these were used either in an unlicensed (4%) or an off-label (29%) manner. A total of 56% (N=550) pediatric patients received one or more off-label prescriptions. (16)

A study conducted in Great Britain by Turner (2008) proved that 25% of drug prescriptions in a regional Children's Hospital were either unlicensed or off-label. In 36% of the admissions, minor pa-

tients received one or more courses of an unlicensed or off-label treatment in hospital. (17)

In the United States, 80% of the drugs approved in five years (1984-1989) had no indication about being used in children. (18)

A study conducted in 2009 in Finland, in three wards (neonatal intensive care unit, general pediatric ward and pediatric surgical ward) showed that 76% of the children receiving a prescription had at least one off-label or unlicensed drug prescribed – 79% in the neonatal intensive care unit, 63% in the general ward and 91% in the surgical ward ($P = 0*014$). Of all prescriptions (629 prescriptions for 108 children), 51% were for licensed drugs, 36% for off-label and 13% for unlicensed drugs. International studies have shown similar extents of off-label and unlicensed-drug prescribing. (19)

In the Netherlands, a cohort study in the pediatric ward of a general hospital revealed that 44% of prescriptions were off-label, and 28% were for unlicensed drugs. 92% of patients received one or more unlicensed or off-label prescriptions, and this proportion was significantly higher in children below 6 months of age than in older children. (20)

In Israel, a study involving pediatric units from 2 hospitals has shown that the percentage of patients receiving unapproved drugs is over 80%. (21) A previous study of the researching team revealed a lower rate – about 42% of children received medicines that were off-label and/or unlicensed. (22)

One of the numerous studies developed in Germany regarding the use of drugs in children and adolescents revealed that the prevalence rate of off-label medication use among those who used medicines amounted to 40.2%. The rate is significantly higher in boys (41.4%), in children aged 3 to 6 years (48.7%). The research showed that 30% of the medicines prescribed were used off-label. Off-label medicine use was highest in preparations of the ATC-class “C00 Cardiovascular System”. For all origins of medicine, all age groups and all ATC-classes, under-dosing was the most frequent reason for off-label medicine use. (23)

SILDENAFIL OFF-LABEL ADMINISTRATION

Of the 2,130 prescriptions given during the 2-year period for 544 children from a pediatric cardiology ward, more than a half was either unlicensed (11%) or off-label (47%). While children aged 2-11 years received most of the unlicensed drug prescriptions (17%), neonates, who did not receive unlicensed drugs, were leading (64%) in the

use of off-label drugs. This study showed that the problem of off-label and unlicensed drug use also exists in pediatric cardiology. (24)

Sildenafil citrate is a medication originally created in 1989 by Pfizer Pharmaceuticals as a drug for treatment of hypertension and angina pectoris. Because Sildenafil citrate as a heart medication did not show promise, studies were stopped in 1992. (25)

By 1994, Terrett et al discovered during the trial studies of Sildenafil as a heart medicine that it also increased inflow of blood into the penis area, allowing men to reverse the lack of ability to get an erection. The drug acts by enhancing the smooth muscle relaxant effects of nitric oxide (NO), a chemical substance that is normally released in response to sexual stimulation. The smooth muscle relaxation allows increased blood flow into the penis leading to an erection when combined with exciting stimulus. (26)

The first phase of clinical trials under the direction of Osterloh (35) suggested that the drug had little effect on angina pectoris, but that it could induce significant penis erections. This drug is the first approved non-surgical treatment for erectile dysfunction that does not have to be either inserted or injected directly into the penis to achieve and keep an erection. The drug is not for use in children. (27)

The ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension (PHT) concludes that the use of Sildenafil in certain doses overcomes its risks in adults. Nevertheless, “off-label” uses of this product in higher doses not lead to improved results, while side effects are considerable.

Many studies present the use of Sildenafil to neonates and children with different cardiac problems. The researches present individual cases or cohort studies showing how dozens of cases have been successfully treated, thus Sildenafil represents a good therapeutic option. (28-32)

SILDENAFIL USE IN ROMANIA

The market of Sildenafil in Romania for 2013 increased with 23% comparing to 2014. (33) The approved form of sildenafil for PHT is the drug which has less than 1% total market share. Still, how much the other low-dose Sildenafil (25 mg) is used for erectile dysfunctions and how much off-label, including for pediatric children, is questionable.

The producers (of originals and generics) cannot promote off-label use of medication. However, ac-

according to ARPIM (Romanian Association of International Drug Manufacturers), medical representatives can offer “off-label” information in response to a spontaneous and explicit request from a health-care professional. (34)

In Romania, there is no comprehensive study regarding the off-label use of Sildenafil in children with PHT, but in the last two years there have been several media disputes involving the use of low-dose Sildenafil in pediatric hospitals. The leaflet of the drug specifies that the medicine is not proper for the use of women and children under the age of 18.

From the point of view of the Romanian National Medicine Agency, using “off-label” drugs is not prohibited, it represents a therapeutic option to the physician if there is no other alternative option, but one for which he assumes responsibility based on his own work experience, with respect to medical techniques and the rules of professional conduct regarding the use of “off-label”.

In respect of the above, in Romania – just as in other countries – the use of Sildenafil for children is not approved, not even for PHT. Nevertheless, taking into consideration the significance of “off-label” recommendations for pediatric patients in Europe, we can estimate that in Romania - where the adherence to strict therapeutic guidelines is less consistent than in Western Europe – in addition to the publicized cases in recent years, in important pediatric hospitals throughout the country, plus the significant consumption of the low-dose Sildenafil (other 25 mg Sildenafil), we can conclude that “off-

label” use of Sildenafil in children with cardiovascular disorders (such as PHT) is a fact, but one of insufficiently evaluated and studied magnitudes.

CONCLUSIONS

The off-label use in children is a widespread phenomenon. The level of exposure to prescribed drugs seems to be important at all ages and highest in early childhood. There are mainly two options which can be implemented as an interim arrangement. On the one hand, a consensus list of accepted off-label uses, backed up by scientific evidence, would at least partly relieve the work of physicians in the field. This list should be carefully updated. The second solution, as practiced in France, is the evaluation and approval of specific off-label uses by an official group of experts, in order to meet the needs of treatment (35). Both options would have the effect of helping physicians manage the ethical and legal dilemmas associated with the off-label use of drugs in children. (36) At the same time, this would probably lead to a safer and more homogeneous medical treatment for the concerned patients in different countries.

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