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TABLE OF CONTENT

ETHICAL ISSUES REGARDING OFF - LABEL ADMINISTRATION OF ANTIBIOTICS

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Abstract

Off-label administration of a drug (uses not included in the approved product labeling regarding indications, patient populations, doses or routes of administrations) is generally accepted, but is not regulated in the legislation in Romania, nor in the European Union.

Starting from the classic example of the use of acetylasliclic acid in cardiology, many cases of off- label administration are already well known and practiced, reaching 40% cases in adults and even up to 90% cases in children. At the same time, antibiotic therapy is another example for off-label use, especially in the critically ill patients, where the increased incidence of infections with multidrug-resistant agents is one of the most common causes of antibiotic administration outside the authorized indications, when there are no therapeutic alternatives. However, the use of off - label antibiotics could be a cause of ethical concern, especially in vulnerable patients (children, elderly, pregnant women). Most of the time, many factors that could affect the efficacy, but especially the safety of off-label treatment have not been studied in the special categories of patients (pharmacokinetic / pharmacodynamic particularities, drug interactions, comorbidities).

For this reason, in order to ensure a safe and ethical antibiotic treatment, without inducing an increase in the risk of antibacterial resistance, the clinical decision must be based on relevant scientific evidence, after a proper evaluation of the risk-benefit ratio and in accordance with the specific guidelines.

Keywords: off - label, safety, ethics, antibiotics

Definitions

The use in medical practice of any medicine in any country is the result of an expensive long-term process carried out by pharmaceutical companies with the result of obtaining licensed medicinal products. The realization of license depends on national drug laws, which are derived from the relevant European directives and regulations. The originally tested and approved indications and dosages are printed in the package insert that must accompany the drug; drug use must be done in accordance to these approved indications. On the other hand, the practice of off-label use of medicines is widespread in clinical practice. Even if European Union developed most intensive activities concerning the off-label use of drugs, especially in children and adolescents, Directive 2004/27/EC does not define clear the term *off-label* use. However, in Annex I to its Guideline on Good Pharmacovigilance Practices, European Medicines Agency specifies that off-label use relates to "situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information" (European Medicines Agency, 2017). We usually consider that off-label / unlabeled use includes administration of a drug product in doses, patient populations, indications, or routes of administration that are not mentioned in the approved product labeling/Summary of Product Characteristics (Aronson & Ferner, 2017). For physician's prescriptive freedom, must be taken into consideration that approved and proven are not synonymous for a medical treatment (Lazzarin et al., 2008). Two tools have to be considered a physician's treatment option, namely product labeling and medical guidelines. Product labeling outlines the use of the medicine for prescribers and containes only approved indications, but has the principal inconvenience the imposibility to be easily updated. Specific guidelines have not a legally binding nature, but are easily updatable and contains scientific data about proven effectiveness of a treatment. Unlike, administration of an unlicensed product, which means a medicinal product for human use in respect of which no marketing authorization has been granted by a relevant licensing authority, off-label prescribing is not illegal or uncommon. Off-label use can be experimental, standard, or even state-of-the-art. It is common in many medical areas, such as oncology, psychiatry, and intensive care unit (Lenk & Duttge, 2014). Some examples include use of tramadol for erectile disfunctions, sildenafil for pulmonary hypertension or erythromycin as prokinetic agent (Martyn-St. James et al., 2015; Galiè et al., 2016; Maganti, Onyemere & Jones, 2003).

Off-label use of antibiotics

The available evidence suggests that antibiotics are often used in an off-label manner in a high frequency among patient populations, both pediatric and adult, but the percentages of off-label use are higher among pediatric patients. A study conducted in five European hospitals indicated that 39% of medications prescribed to the pediatric population were of off label use; other studies also showed that the incidences of off-label use and un-licensed drug use in the pediatric population were 11% in England, 29% in Netherlands, 33% in France, and 80% in Australia (Weda et al., 2017; Cuzzolin, Atzei & Fanos, 2006). The appropriate use of antibiotics has a fundamental role in controlling antibacterial resistance and in success of treatment of infections, since overprescription of antibiotics, as well as patient failure to comply with treatment regimens, has led to the development of drug resistant bacteria. Improper use of antibiotics was closely linked to the increase of *Streptococcus pneumoniae* resistance to penicillins up to 33%. Moreover, methicillin resistant *Staphylococcus aureus* (MRSA) in nasal cavities of children was increased up to 10 folds. In most of the cases, explanation of the increased resistance was related to an inappropriate administration of antibiotics (Creech, Kernodle & Alsentzer, 2005). Thus, it was demonstrated that sub – therapeutic doses of amoxicillin were associated not only with therapeutic failure due to bacterial adaptive phenomena, but also promotes mutation, induction and expression of bacterial resistance promoting genes with crossreactions with other beta- lactamines (Cortes, Pinas, Albarracin & Echenique, 2008).

Critically ill patients constitute an important patient group vulnerable to multidrug-resistant bacteria and requires aggressive antimicrobial treatment. Their susceptibility to multidrug - resistant infections for which no labeled for indication or dose antibiotics are available may be one of the reasons for the off - label use of antibiotics. This phenomenon is somehow expected since many pathogens responsible for infections in critical care patients are resistant to most classes of antibiotics limiting the treatment options. Thus, 19 to 43% in adult critically ill patients were found to receive off-label prescriptions in one study (Tansarli, Rafailidis & Kapaskelis, 2012). In many cases, for these patients no effective alternatives are available in treatment armamentarium, therefore clinicians are obliged to resort to off – label use of antibiotics, either in dosages or indications. Frequently, off label antibiotic use was related to indications (up to 91% cases), compared to dose (8%) or route of administration (1%) (Lat et al., 2011). The main reasons for off - label use were unapproved indication (66%), dosing schedule (27%), and method of administration (17%) (Albaladejo et al., 2001).

In one analysis, it was found a high frequency of off - label administration of more aggresive antibiotics, such as colistin in critical care patients (Tansarli, Rafailidis & Kapaskelis, 2012). However, the increase of incidence of respiratory infections caused by multidrug resistant pathogens, along with unavailability or limited number of antibiotics for inhalation, has prompted the practice of off-label use of intravenous antibiotics for inhaled administration mainly in mechanically ventilated patients.

In many countries, colistin is available only as powder for injectable solutions. Recently, after Committee for Medicinal Products for Human Use (CHMP) assessment in 2017, colistin became available for intrathecal / intraventricular administration. Colistinmethate sodium, the precursor of colistin, is approved by European Medicines Agency (EMA) as dry powder for inhalation for management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged over 6 years. However, polymixyn E is recommended and frequently used in Intensive Care Units (ICUs) as adjunctive therapy of parenteral antibiotics in hospital - acquired pneumonia or ventilator-associated pneumonia produced by multidrug resistant *Pseudomonas aeruginosa* or *Acinetobacter baumannii* or carbapeneme - resistant gram negative bacteria (Kalil et al., 2016). Moreover, there are many examples of off - label use of antibiotics in clinical practice

including „old" drugs (e.g. amoxicillin + clavulanic acid, aminoglycosides, fluoroquinolones, etc) (Tansarli, Rafailidis & Kapaskelis, 2012), but also very new agents (e.g. oritavancin, dalbavancin, tedizolid, ceftolozane-tazobactam, ceftazidime- avibactam) (Bariola, Khadem & Nguyen, 2019). The most important concern in case of antibiotic drug use remains the safety issue, especially when adverse reactions are not documented in the product information document. Off-label use of antibiotics can also cause adverse drug reactions (ADRs) and even life – threatening adverse events with prolonged hospitalizations or even death. Taking into consideration again colistin example as an aerosolized anti-infective in critically ill patients, local adverse reactions (e.g. cough, wheezing, respiratory irritation, bronchoconstriction) have been reported (Le et al., 2010). FDA safety reports documented two cases of death after off - label use of aerosolized colistin. Systemic toxicity associated to the use of aerosolized colisitin was significantly lower compared to intravenous administration. In addition, possible environmental exposure and contamination for healthcare professionals were identified as risk factors after aerosolized antibiotics (Le et al., 2010).

Off - label use of fluoroquinolones in children is increased especially in the United States, even if safety aspects are still controversial. Since ciprofloxacin was contraindicated in children, pediatric clinical studies were limited during drug development process and safety information is based on animal toxicology data. However, data provided by post - marketing clinical experience revealed only mild to moderate transient side effects. Even so, physicians remain skeptical to use fluoroquinolones in pediatric patients (Patel & Goldman, 2016).

The most important concern in case of off - label use of antibiotics, irrespective of the antibacterial class, is the increased risk of emergence of bacterial resistance primarily in the adult population, especially when associated with an excessive and / or unnecessary use (Davido et al., 2016).

Pros and cons of off label use

Off - label drug use has many benefits for both healthcare professionals and patients. Sometimes it allows physicians to treat, particularly in cases when approved therapeutic options are unsuccessful and also allows patients to have earlier access to valuable medications (Gupta & Nayak, 2014). Another common reason for prescribing medicines outside the limits of their approved indications is convincing evidence on their effectiveness and safety in particular situations, such as rare diseases or "orphan" conditions (e.g. Tourette syndrome, Huntington's disease, myoclonus, muscular dystrophy). Children, pregnant women and elderly people are often exempt from clinical trials for a number of legal, ethical or practical reasons, so a wide variety of medications are not approved or specifically intended for these populations. Consequently, off - label prescribing is practiced in pediatric, geriatric and obstetrics when therapeutic alternatives for specific patient populations are not available. Off - label use was found to be up to 90% in hospitalized pediatric patients and lower (almost 40%) in adults (Gazarian et al., 2006). Off - label use is important not only to ensure the best treatment for patients, but also for discovery of new uses of existing drugs. Almost 57% of drug therapy innovations were discovered through off - label use in current medical practice (Demonaco, Ali & Hippel, 2006). Therefore, off - label use allows physicians to use existing drugs in an innovative manner when there is scientific evidence, although there has been no formal authorisation to supply appropriate medicines to vulnerable patient populations.

The main inconvenience is due to the fact that without an appropriate risk - benefit analysis and because it is not systematically evaluated by pharmaceutical industry, regulators, guideline formulators, off - label drug prescribing can jeopardize patient safety. Many

individual factors, such as age, comorbidities, polypharmacy, drug - disease interactions may be responsible for adverse reactions which can not be monitored due to a lack of controlled studies and observations (Mei et al., 2019). Therefore, an increased responsability for patients' well being is necessary since adverse events related to off - label drug use make physicians more vulnerable to potential legal sanctions. Other potential problems related to off - label prescribing may interest the healthcare system level (e.g. impossibility to compensate health care expenses) or pharmaceutical companies (e.g. promotion of off - label drugs by the manufacturers is not allowed) (table 1) (Goločorbin, Iliković & Mikov, 2015; Stahl, 2013; Weda et al., 2017).

Tabel 1. Benefits and risks of off - label prescribing (Stahl et al, 2013)

Benefits	**Risks**
✓ Use of evidence rather than regulations ✓ Use best practice rather than cost saving ✓ Ability to use lower/higher doses ✓ Ability to use in special populations, or in complex comorbid, treatment - resistant patients groups, not studied in clinical trials ✓ Ability to practice personalized medicine	✓ Need to better document informed consent ✓ Need to document scientific literature ✓ Confounding between off - label use and clinical research ✓ Lack of reimbursement

Current international legislation on off - label drug use

Although off - label drug use is legal in many countries, they do not have clear guidances about off - label uses of medicine and there is no consistency about off-label regulations between countries (Gupta & Nayak, 2014). Several countries have policy mechanisms related to the use of off - label drugs, such as practice guidelines, codes of ethics, financial mechanisms, and provision of published evidence. In Europe, ten countries (France, Germany, Greece, Hungary, Italy, Lithuania, the Netherlands, Spain, Sweden, and United Kingdom) have specific regulations or policy tools in place (table 2) (Weda et al., 2017).

Table 2. National regulation for off - label use in different European countries (Weda et al, 2017)

Country	National law	Type of regulation
Austria	Medical law and guidelines on the economic prescription of medicine and medical aids	Condition for off - label use in Austria
France	Law no. §2011-2012, december 29, 2011; regulation no. 2012 – 743 TRU	Regulation to "temporary recommendation for use"
Germany	Medical law 21 section 2 no.6	Exception on authorization requirement
Italy	Law 94/98, art. 3, subsection 2	Condition for off - label use in Italy
Spain	Law 41/2002 and Royal decree 1015/2009	Condition for off - label use in Spain
Switzerland	Swiss federal law on medicinal products and medical devices (art. 9, art. 26)	Temporary regulatory exemption Specification for physicians
United Kingdom	Professional legal guidelines	Specification for physicians

France has created regulation to "temporary recommendations for use" which has been implemented in 2012 with the aim to control off - label drug use by establishing patient monitoring and collecting data with permission from an expert committee, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), which is limited to 3 years (Emmerich, Dumarcet & Lorence, 2012).

In United Kingdom, the General Medical Council, which develops the prescribing guidance, recommends that a medicine should usually be prescribed in accordance with the terms of its license. However, unlicensed or off - label medicines may be prescribed when, based on an assessment of the individual patient, the prescriber concludes, that it is necessary for medical reasons to do so to meet the patient's specific needs. Moreover, National Institute for Health and Care Excellence announced in 2011 that it would provide in special circumstances, advice on the use of unlicensed and off - label medicines based on available evidence to inform decision-making by healthcare professionals (Shkopiak, 2012). According to Duch legislation, off - label use should be allowed only if it is the best treatment available to the patient. For example, when no licensed drug is available and off - label use is described in the medical literature and guidelines or if off - label use has been shown to be more effective than the licensed drug for the respective indication (Weda et al., 2017).

In addition, Australia, Singapore, India and China have practice guidelines for the use of off - label drugs. Guiding principles before prescribing off - label drugs developed in 2013 by Council of Australian Therapeutic Advisory Groups (CATAG) include: need of high - quality medical evidence to determine effectiveness of off - label use, consider it when all other therapeutic options are unavailable / unsuitable or not tolerated, need to monitor outcomes, effectiveness, and safety. Patient must be involved in the decision-making process. In India, off-label prescribing is illegal according to the Amendments to the Indian law (Mudur, 2004). In Singapore, physicians are required to treat their patients according to general methods and only use authorized medicines for appropriate indications, and prescribing medicines for use outside the terms of their license must be made on sufficient evidence base or experience, stating the advantages of and reasons for off - label use.

Since a clear description of off - label prescribing in China is not available, a expert consensus was intended to increase awareness of off - label use among healthcare professionals and to provide a practical and explicit approach, based on the following process: use of supportive evidence, an assessment made by an expert group, approval by ethics committee, obtaining informed consent, safety monitoring (Zhang, Li & Zeng, 2012).

Ethical issues on off - label drug use

As in clinical research, off - label prescribing rise different ethical issues. For the protection of patients in clinical trials, ethical principles listed in *The Nuremberg Code*, *The Belmont Report* and *The Declaration of Helsinki* are well known and implemented. While off -label use does not necessarily fall under the laws of human experimentation per se, the dichotomy in the laws concerning off - label drug use fails to sufficiently protect the patient resulting in ethical concerns.

Therefore, between allowing physicians to practice their "state - of - art" medical practice and also protecting the best interests of their patients is a fine line. Doctors should be attentive in selection of the appropriate approach to off - label use based on the urgency of the patient's situation, availability of alternative treatments, as well as patient populations or how long the respective off - label drug is prescribed (Dresser & Frader, 2009). Relating to the ethical aspect of the issue, the five principles of medical ethics of Beaucamp and Childress model of modern bioethics are:

- *Autonomy* for patients with ability to make own decisions and free of controlling pressures;

- *Beneficence* and *nonmaleficence* in order to ensure patients' safety and the benefit of new, effective drugs for specific patient groups, as well as the overall population;
- *Fidelity* and *justice* for both patients and physicians, means trust and honesty.

By contrast with clinical research with the aim to develop new treatments for future patients, off - label prescribing is targeting on best available therapy for a particular patient. Doctors should balance the patient's individual needs and characteristics with available scientific evidence when deciding whether to prescribe a drug for an off - label use. They have to evaluate if there is sufficient scientific evidence to justify the off - label prescribing or to press for additional research when available data is lacking (Dresser & Frader, 2009). Generally, a doctor is obligated only to provide a patient with clinical information and has no legal duty to inform a patient of a drug's regulatory status. However, to reduce the risk that patients consider themselves under - informed, and to protect against associated liability, physicians should be required to inform their patients of the off - label use of their treatment, and obtain consent, explaining the possible risks (Holley, 2009). In addition, medical organizations came with the goal of helping physicians for appropriate ethical judgment about off - label prescribing for the benefit of the patients (Eichler, Abadie, Raine & Salmonson, 2009).

On the other hand, all the medical actions in case of off - label use of a medicine must be taken into account to offer additional protection against malpractice claims, and these includes again: a good knowledge of medical guidelines and information about medical treatment, with reputable peer reviewed literature reflecting sound scientific evidence and information of the patient about off - label prescription (and not intended for medical research) (Riley & Basilius, 2007).

Conclusions

Off - label drug prescribing is a widely accepted practice and is not malpractice, and may constitute even a „standard of care" in some cases, especially in special patient populations. The off - label use of antibiotics is also occasionally inevitable. But since we are facing with an continuously increse of antibacterial resistance, the off - label prescribing of antibiotics should be made with precautions. This should be limited to special patients groups, such as critically ill patients more vulnerable to multi - drug resistant bacteria. However, irrespective of off - label treatment prescribed, physician should demonstrate good and updated knowledge of the newest medical scientific guidelines. Moreover, they should inform patient about the off - label medication and to explain the benefits and possible risks associated with their treatment. In the absence of specific laws to cover off - label drug use, physicians shoud be prudent, well-reasoned and to follow ethical standards in order to help their patients.

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