

Medical Liability for Off Label Use of Drugs in Romania

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Breaking the limits of the risks for the human body, health or even the life of the patient, as assumed by the pharmaceutical producers, by using a drug off label, for its side effects, in another purpose or even against the purpose for which the drug was authorized by the National Agency of Medicine and Medical Devices, is not in itself illegal if the off label use has the common consent of both the doctor and the patient for a treatment and only for a treatment which, although a spread procedure, has little or no scientific support. But if the patient is subjected to unreasonable risks, endangering his body, health or life beyond the possible benefits of the treatment, without being informed about the lack of scientific support, the doctor is liable not only for malpractice (civil medical liability) but also for a criminal offence.

Keywords: authorized chemical substances, drugs, off label, patient rights, medical consent, malpractice

The drug is a substance or a combination of substances which might be used through administration on humans for the prevention, diagnosis, treatment of diseases or for the restoration, correction, modification of the physiological functions. This means that the drug administration represents a chemical intervention on the human body which might have different effects upon it. Precisely due to these effects, the drug administration represents an exception from the principle of human body inviolability, which must ensure on the same time the protection of the public interest of the society and the protection of the private interest of the patient [1].

The protection of the public interest is achieved by the legality of the object of the medical contract (in our case, providing a medical service through the drug administration) or pharmaceutical contract (the sale of the drug). On basis of art. 1225 par.(3) and 1226 par.(2) of the Civil Code, this is a condition of validity for the legal acts in general, consisting on the fact that the legal operation (not only the operation, but also the concrete "good") is according to the public order and good morals because the respect for the human being (life, health, body integrity) is a necessity for the whole society and not only a private interest of the individuals. To that effect, some *goods* like cell, organ, tissue sampling and transplant are not in the *civil circuit* (they cannot be introduced on the market) and they cannot become material derived object [2] of an obligation of the contract (sale, exchange, mortgage); but other *goods* like chemical substances might be introduced in the *civil circuit* (they can be put on the market) as drugs (substances administrable to humans for medical treatment) and, as a consequence, might become material derived objects of a medical or pharmaceutical obligation of a contract only if they are authorized by the National Agency of Medicine and Medical Devices (ANMDM), following the procedure required by the art. 704-791 of the Law 95/2006 [3].

Of course, even if the administration of a certain drug is authorized by the National Agency of Medicine and Medical Devices, this does not represent an obligation for the patient, who has the right to freely appreciate whether its administration is according to his concrete interest and to express his consent which on the base of art. 1204 from the Civil Code must be: serious (it should not be expressed as a joke or by way of friendship, should not be too vague or expressed under a mental reserve known by the doctor), expressed knowingly (should be expressed by a person

with discernment) and free (it should not be affected by one of the faults of consent: error, fraud, violence, lesion).

The problem occurs when the chemical substance is medically used for a different purpose than the one for which the drug was authorized for and without a possible correct information of the patient, due to the lack of reliable scientific knowledge. The goal of the present study is the analysis of the legal consequence in Romania of off label use of drugs.

Experimental part

For the current study, we used the data posted on the site of the National Agency of Medicine and Medical Devices [4] about drugs authorized in Romania, but which were off label used and the Romanian jurisprudence on the matter [5].

Results and discussions

Based on the data obtained from the National Disease and Therapeutic Index, it is estimated that a percentage of 21% of the drugs were off label used in the United States of America in 2001, although most off label drug mentions (73%) had little or no scientific support. The most common off label used drugs among specific medications were gabapentin (83%) and amitriptyline hydrochloride (81%) and off label use was most frequent among cardiac medications (46%, excluding antihyperlipidemic and antihypertensive agents) and anticonvulsants (46%) [6].

In rheumatology the most commonly drug used off label is methotrexate, although there is limited evidence from controlled studies for its efficiency in this off label scenario [7] because methotrexate is authorized to be used to treat cancer, autoimmune diseases, ectopic pregnancy but may have many side effects, among which genitourinary side effects may seriously affect either sex (decreased libido, defective oogenesis and spermatogenesis is usually transient) but especially women may experience menstrual dysfunction, vaginal discharge, infertility or abortion [8].

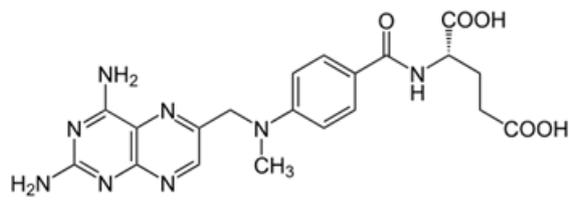


Fig. 1. methotrexate $C_{20}H_{22}N_8O_5$ [9]

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With the precise aim of producing this last dangerous side effect, methotrexate is used off label generally in combination with misoprostol [10]. Misoprostol is a prostaglandin E₁ analogue approved by the Food and Drug Administration to be taken orally only for the prevention and treatment of gastric ulcers, but, in practice, it has also become an important drug useful for elective medical abortion, cervical ripening before surgical abortion, evacuation of the uterus (in cases of embryonic or fetal death) and induction of labor [11].

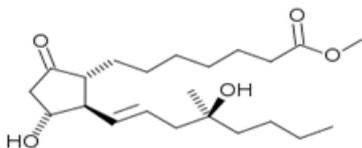


Fig. 2. misoprostol
C₂₂H₃₈O₅ [12]

Because in obstetrical and gynecologic practice it is used as an off label drug in both abortion and induction of labor, the US Food and Drug Administration had issued warnings that hospital use of misoprostol (for cervical ripening, induction of labor, or for the treatment of serious postpartum hemorrhage) outside of the approved indication may also be associated with meconium passage, meconium staining of amniotic fluid, and cesarean delivery and that maternal shock, maternal death, fetal bradycardia, and fetal death have also been reported with the use of misoprostol [13].

Ignoring such warnings from the government and the manufacturer itself against this off-label use, nurses at a Californian hospital administered to Rebecca Blasco a gastric ulcer medication to induce labor by forceful contractions during labor, which compromises blood flow to the fetus, who suffered a lack of oxygen during labor, which led to developmental issues for the infant Abigail Blasco. For this, the victim obtained \$70 million arbitration award against the company which owned the hospital and the health maintenance organization [14].

A similar situation occurred in Romania, where in 2008 a doctor at the Tura Municipal Hospital administered to a pregnant woman Cytotec, a gastric ulcer medication, to induce labor during which the newborn suffered a lack of oxygen. But in Romania the case was not settled by arbitration, instead it was trailed as a criminal offence in the criminal court.

As far as this present study is concerned, the problem in this case was that of the use of Cytotec. Misoprostol is a generic drug now authorized in Romania under four different brand-names: 1) Artrotec 75 (a combination of diclofenacum and misoprostolum) produced by PFIZER EUROPE MA EEIG – Great Britain and authorized in 2005 for gastric ulcer treatment (the misoprostol component) [15], 2) Medabon (a combination of mifepristonium and mesoprostolul) produced by SUN PHARMACEUTICAL INDUSTRIES EUROPE B.V. – Netherland authorized only in 2012 for abortion but not as an oral but as a vaginal form of the medication [16], 3) Misodel 200 micrograme produced by FERRING GMBH – Germany authorized only in 2014 for labor induction but, again, not as an oral but as a vaginal form of the medication [17], 4) Typogyne 400 micrograme produced by EXELGYN - France authorized in 2013 for abortion as an oral form of the medication [18]. But not even at present misoprostol is not authorized in Romania under the American brand-name of Cytotec, produced only for gastric ulcer treatment which was orally administrated and off label used to induce labor. Moreover, the doctor did not inform the patient about the risks to the pregnant woman or to the fetus that the off label use of this

unauthorized drug in Romania may present, about which even the American producer Searle warned in 2000. Although the medical expertise and testimony proved only a high rate of probability but not the certainty that the use of Cytotec produced the lack of oxygen for the newborn, the court concluded that the doctor was guilty for not informing his patient of the risks involved, as required by the art. 649 of the Law 95/2006 and art. 6 of the Law 46/2003[19]. Being a doctor in a public hospital, he was tried as a public servant and condemned for the criminal offence of abuse in service against the interests of persons on the basis of art. 246 of the 1969 Penal Code, and also for malpractice (the civil medical liability). The problem is that even though the responsibility for malpractice acts committed by the employees belongs to the hospital and the public health care system [20] (exactly as in the Californian case, where the damages were awarded against the company which owned the hospital and the health maintenance organization and not against the nurses who administered the drug), the Turda Public Hospital was condemned only on basis of art. 1000 (3) of the 1864 Civil Cod as a guarantee that his employee will execute his obligation.

Conclusions

The risks of medical treatment are due not only to the scientific and technical level of medicine but also to the drugs needed to be administered. Breaking the limits of those risks, as assumed by the producers, by using off label the drug for its side effects, in another purpose or even against the purpose for which the drug was authorized by the National Agency of Medicine and Medical Devices, is not in itself illegal if the off label use has the common consent of both the doctor and the patient for a treatment and only for a treatment which, although is a spread procedure, has little or no scientific support. But if the patient is subjected to unreasonable risks, over the limits assumed by the producers and authorized by the National Agency of Medicine and Medical Devices, without being informed about the lack of scientific support, the doctor is liable for medical malpractice and criminal offence.

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In articolul

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ERRATA

Due to a regrettable mistake, in the article

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published in Rev. Chim. (Bucharest), 68, no. 12, 2017, p. 2823, it mistakenly appeared,
at authors, the name OANA ALEXANDRESCU which must be replaced with OANA ANASTASESCU.