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POTENTIALLY DANGEROUS SIDE-EFFECTS OF DRUGS AND "BLACK BOX" WARNING SYSTEM

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Pharmacovigilance or collecting, monitoring, research, assessment and evaluation of information obtained from the manufacturer, health workers and patients about the adverses of the drugs, biological products, traditional medicines, with the aim to detect new information on the dangers of the drugs as well as prevention of new adverse side-effects harmful for the patients which is obligatory for the regulatory agencies, authorized by the authorities in almost every country. Modern trends of treating the patients in connection with rising number of new drugs in all pharmaceutical forms on the market demand continued improvement of the pharmacovigilance system with the accent on the feedback information towards the final consumers and doctors who prescribe them. One of very efficient communication tools between the regulation agency and final consumers/prescribers is created and implemented by Food and Drug Administration in the USA (FDA) called "boxed warning" – "black box". "Black box" warnings are the most serious warnings of FDA on the drugs, which point out potentially fatal, life threatening risks, or disabling side-effects of the drugs. It is named for the black border surrounding the text of the warning. The border was designed to draw attention on the warning and to emphasize it in relation to other information as a part of the drug packing. Looking into the studies monitoring the way the drugs with this kind of warning were used showed that explicit, well-publicized warning can change the prescribing habits of doctors and influence the patients to be more careful in using specific drugs or even classes of drugs. *Acta Medica Medianae 2011;50(3):69-73.*

Key words: *pharmacovigilance, FDA, "Black box" warnings, side-effects*

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Introduction

Bearing in mind the global trend of growth in numbers of new drugs in all forms, innovative and generic as well, together with the trend of constant growth of the number of prescribed drugs, it is of vital importance that medical professionals and final consumers are aware of all potential dangers that prescribing certain drug carries (1, 2). Pharmacovigilance systems which contain collecting, monitoring, research, assessment and evaluation of the information obtained by the manufacturer, health workers and patients on the adverse side-effects of the drugs, biological products, traditional medicines, with the aim to identify new information on the dangers of the drugs as well as prevention of adverse side-effects for the patients, have been developed in all serious health systems in the world (3).

World Health Organization (WHO) established the system of global monitoring of side-effects on the drugs in 1968, and insofar the system has involved 101 members. All members of the system send their reports to the collaboration centre of the World Health Organization to monitor the side-effects of drugs in Uppsala, where these information are processed, evaluated and updated in the international database. When there are several reports on the side-effects of a specific drug, this process can continue in the direction of sending a warning (safety alert) to the countries' members. This safety alert is, of course, sent only after detailed evaluation.

European Medical Agency (EMA) is responsible for pharmacovigilance in the European Union. EMA system "EudraVigilance" incorporates larger number of databases on adverse side-effects on drugs in the European Union (4).

Food and Drug Administration (FDA) is responsible for monitoring pharmacovigilance in the USA (5), but pharmacovigilance is also monitored by certain academic organizations such as Radar (6).

Medicines and Medical Devices Agency of Serbia (ALIMS) on its web page, concerning pharmacovigilance, constantly issues safety warnings on drugs distributed on our market (7).

However, the latest trends point out the need to improve the efficacy of reporting final consumers/prescribers of drugs, meaning the public, on serious adverse side-effects of drugs already on the market. European drug agency had already issued its plans on giving public access to the information in their database on the potential adverse side-effects of human and veterinarian drugs (8). On the other hand, FDA in the USA

already has a practice of the so-called "boxed warnings" or "black box" warning system on potentially dangerous adverse side-effects of the drug. In the following text we will use the term "black box" warning (9).

The concept of FDA "Black box" warning

Food and Drug Administration in the USA (Food and Drug Administration FDA or USFDA) is a part of the US Department of Health and Human Services and responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, food, cosmetics, and products that emit radiation as well as regulation of production, marketing and distribution of tobacco products. FDA is also responsible for improvement of public health by helping to speed up innovations that make medicines more effective, safer, and more affordable, and by helping the public get the accurate, science-based information they need to use medicines and foods. FDA also has responsibility for the reduction of tobacco use with the aim to improve health (10).

FDA and other organizations in the USA dealing with pharmacovigilance have developed several communication tools to raise the consciousness on these adverse side-effects of the drugs. „Black box" warnings, ("black label" or „boxed" warning) is one of these tools used by FDA.

A black box warning is the strongest warning by the U.S. Food and Drug Administration (FDA) about any serious potentially fatal, life-threatening or permanently disabling adverse reaction of drugs (11).

The name itself comes from the black border surrounding the warning text. The border was designed to draw attention on the warning and to emphasize it in relation to other information as a part of the drug packing. This kind of warning must be a part of the drug packing, but also on the printed insert with the detailed information.

A black box warning means that there is enough evidence that the drug carries a significant risk of serious or even life-threatening adverse effects without definite cause-effect correlation. This kind of warning does not have to result from controlled clinical studies but caused by results of post-marketing drug research (12). This information is very important because most drugs having this warning have been used in everyday practice years before that; so, there is great experience on a large number of patients about the frequency of such side-effects. A research shows that approximately seven years pass after the drug's distribution on the market till the moment the warning is issued (13). Also, these postmarketing researches often initiate serious questions on the safety of a particular drug.

The system of postmarketing research of drugs enables the monitoring of the appearing of previous side-effects of the drug and its frequency. When side-effects are thus established, especially trained FDA experts look for the same side-effects of the same drug in the medical literature, in the data of the regulatory agencies of other countries, the data that WHO has, and through its own system "MedWatch" (electronic database on the adverse side-effects of drugs filled by medical proffesionals) (14).

The beforementioned experts look for more evidence which would, without question, point out that consuming particular drug is the cause of side-effects, not any other factors. They look for signs of time association – the same drug taken before the corresponding side-effect appears; coherence with the existing information; biological assurance – similar side-effect with drugs of the same class; consistence of correlation of the drug and the side-effect (result productivity); they look for specific correlations too (15). Based on everything that has been issued, FDA can expand the list of adverse side-effects of a drug as well as the frequency of the side-effects that are already known. If the side-effect is life-threatening or leads to disability, such side-effect, no matter its frequency, gets a "black box" warning.

FDA regulations are precise in setting three situations when this warning is issued. First, "black box" warning is issued when the adverse reactions of the drug are more serious than the drug benefits so the doctor prescribing the drug should carefully evaluate the final benefit for the patient. Therefore, in this category we can put permanently disabling or fatal side-effects. Other situation in which the warning is issued is when the drug has serious side-effects which can be prevented or reduced in frequency or severity by appropriate use of the drug, with careful monitoring and patient selection. The third situation in which the warning is issued is the obligatory notice for the doctor who has to pass particular certification in order to prescribe a certain drug or can issue it to the patient only under medical supervision (16).

According to the data of the USA market, out of 548 new drugs approved from 1975 until 1999, 8.2% have "Black box" warnings, and even 2.9% have been withdrawn from the market. And, as the number of drugs which are withdrawn from the market stays relatively constant, the number of drugs with this kind of warning has risen in the last decade (13, 17-19).

At the moment, approximately 350 drugs on the market of the USA have "Black box" warnings (20).

The influence of "Black box" warning on the prescribing habits of doctors

"Black box" warning does not represent any kind of prohibition in prescribing a drug by the doctor or the use of the drug by the patients, but it surely does give the reason for the doctor to think before prescribing it to the patient. Every drug prescription with this kind of warning should be followed with caution by the doctor, and the decision must be made with careful reflection on the relation of the potential risk and potential benefit for the patient. The warning should initiate the conversation between the doctor and the patient on the subject of drug safety, whether it was initiated by the doctor or the patient. In some cases the patient can notice early signs of adverse

reaction in time, and inform the doctor about it. This is the way to significantly prevent the emergence of serious side-effects of the drug. "Black box" warnings are of special importance to think about when, for example, serious side-effects can be prevented or reduced in frequency by proper use of the drug (for example, patient selection, careful follow-up, avoiding use of some drugs at the same time, and so on) (21).

Many researches have been conducted on the effects of these kinds of warnings on healthcare workers who prescribe the drugs. The research shows high level of warning on the healthcare workers who prescribe the drugs. As an example we can name prescribing rosiglizatone which was reduced by 70% after the "black box" warning (22). However, full efficiency of this warning is shown here, compared to other methods, because, although the adverse side-effects of this drug have been pointed out before in the media and professional publications, the influence on the prescribing habits of the doctors and direct reduction in its prescribing happened only after the "black box" warning (23).

The researches conducted in the USA say that doctors respect this kind of recommendation from 1 to 50% depending on the drug, but also about 40% of patients use some of the drugs which have this kind of warning. As there are about 350 drugs in the USA with "black box" warning, the doctors find it demanding to have in mind all the warnings in their everyday work, but for frequently prescribed drugs the effect is satisfactory (24). Therefore, these data surely show that the mere warning does not exclude the use of the drug completely, but its use in therapy is more serious and with precaution.

Other studies show great efficiency of this system, therefore, among others Weatherby LB et al. in their study conclude that explicit and well-publicized warning can change the habits of the doctors who prescribe the drugs (25).

Examples of drugs with "black box" warning

Looking into the drugs with "black box" warning one can conclude that among them there are drugs which are in widespread use in Serbia and often prescribed in everyday practice. Besides this, some of these drugs are on the positive list of the Republic Institute for Health Insurance. We will mention just a few examples of drugs as well as the reasons to issue such warning by FDA.

Whole classes of drugs with this warning are:

Antidepressant medications: all antidepressant medications have an increased risk of suicidal thinking and behavior, known as suicidality, in young adults aged 18 to 24 during initial treatment. This warning includes sertraline, paroxetine, escitalopram and other antidepressants.

Bisphosphonates: people who suffer from osteoporosis, taking bisphosphonates have an increased risk of getting atypical but serious fractures of femur. The majority of patients with these subtrochanteric and diaphyseal femur fractures have taken these medications for at least 5 years. Also, a large number of the treated patients who eventually fractured had "warning signs". The warning includes the most prescribed ones: alendronate, risedronate and ibandronate.

Fluoroquinolone antibiotics: people taking a fluoroquinolone antibiotic have an increased risk of tendinitis and tendon rupture, a serious injury that could cause permanent disability. The warning includes ciprofloxacine, levofloxacine, moxifloxacine and other medications containing fluoroquinolone.

Nonsteroidal antiinflammatory drugs: all unselective nonsteroidal antiinflammatory drugs (diclofenac, fenoprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen, piroxicam etc.), cause an increased risk of thrombose, myocardial infarction, and stroke, which can be fatal, and gastrointestinal bleeding, ulcers, and perforations which can be fatal. The risk increases with the prolongation of therapy. Selective NSAIL celecoxib is in this group.

Specific drugs with this kind of extra warning are:

Amiodarone: this antiarrhythmic exerts hepatic and pulmonary toxicity and is intended for use only in patients with life-threatening arrhythmia.

Olanzapine: elderly patients with dementia-related psychosis treated with olanzapine as well as other atypical antipsychotic drugs are at increased risk of death.

Rosiglitazone: patients with diabetes taking rosiglitazone have an increased risk of heart insufficiency or heart failure, or if they already have some heart disease are at great risk of heart failure.

Salmeterol: long-acting beta2 adrenergic agonist increases the risk of asthma-related death. Special attention should be paid to pediatric and adolescent patients.

Warfarine: can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose.

You can see the whole list of drugs with "black box" warning and detailed explanations on FDA web page.

Conclusion

Based on the aforesaid, it is evident that the countries with the most advanced system of farmacovigilance also need constant improvement of the system. It is also necessary to monitor the side-effects through various different systems of report in order to have the proper results. Special attention must be paid to monitoring the adverse side-effects after they appear on the drug market because it is evident that spontaneous report by the healthcare workers or the pharmacists is not high enough, not even in the USA (only 1% of all cases). The emergence of a growing number of drugs on the market brings the healthcare workers into the situation that they simply cannot know all possible side-effects of the drug, especially those with low frequency. This is the reason why setting up such communication tool between the regulatory agency and the healthcare

worker and the pharmacist, and final consumers as well, has shown to be highly efficient. Additional drawing attention of the healthcare workers to the very serious side-effects of some drugs, no matter their frequency, such as "black box" warning, has shown to be a very good regulatory move by the FDA with the direct influence on the healthcare workers prescribing the drug. However, the warning had the direct influence on the final consumers as well, and this is very important effect which undoubtedly has direct influence on public health of the population. Also, having in mind a frequent use of some drugs in Serbia, which have been mentioned in this study as an example, we should seriously consider issuing similar methods on drug market in Serbia. And the fact is that many of beforementioned drugs with the "black box" warning can be bought in Serbia without prescription.

References

1. Reed SD, Califf RM, Schulman KA. How changes in drug-safety regulations affect the way drug and biotech companies invest in innovation. Health Aff (Millwood) 2006; 25: 1309-17. [CrossRef] [PubMed]
2. Stewart DW, Martin IM. Intended and unintended consequences of warning messages: a review and synthesis of empirical research. Journal of Public Policy & Marketing 1994; 13: 1-19.
3. Trontell A. Expecting the unexpected — drug safety, pharmacovigilance, and the prepared mind. N Engl J Med 2004; 351: 1385-7. [CrossRef] [PubMed]
4. Van Boxtel C, Santoso B and Edwards IR, editors. Drug benefits and risks - international textbook of clinical pharmacology. 2nd ed. Amsterdam: IOS Press; 2008.
5. Eudravigilance [eudravigilance.ema.europa.eu]. European Medicines Agency. Cited 2011 Aug 15. Available from: URL: http://eudravigilance.ema. europa.eu/ highres.htm
6. Food and Drug Administration's (FDA) [www.fda. gov]. United States Department of Health and Human Services. Cited 2011 Aug 16. Available from: URL: http://www.fda.gov
7. Bennett CL, Nebeker JR, Lyons EA, Samore MH, Feldman MD, McKoy JM, et al. The Research on Adverse Drug Events and Reports (RADAR) project. JAMA 2005; 293: 2131-40. [CrossRef] [PubMed]
8. Medicines and Medical Devices Agency of Serbia [www. alims.gov.rs]. Beograd: c 2005-2010 Copyright ALIMS. Cited 2011 Aug 15. Available from: http://www.alims .gov. rs/cir/farmakovigilanca/farmakovigilanca.php
9. European Medicines Agency (EMA) [www.ema. europa.eu/]. © 1995-2011 EMA. Cited 2011 Aug 15. Available from: http://www.ema.europa.eu/ema/ index. jsp?curl=pages/news_and_events/news
10. U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Warnings and precautions, contraindications, and boxed warning sections of labeling for human prescription drug and biological products - content and format". Retrieved 2010 Feb 21. Available from: http://www.fda.gov/cder/guidance/index.htm
11. Food and Drug Administration's (FDA) [www.fda. gov]. United States Department of Health and Human Services. Cited 2011 aug 15. Available from: http://www.fda.gov/AboutFDA/CentersOffices/defau lt.htm
12. Code of Federal Regulations Title 21: paragraph 201.57 (e) (2000).
13. Beach JE, Faich GA, Bormel FG, Sasinowski FJ. Black box warnings in prescription drug labeling: results of a survey of 206 drugs. Food Drug Law J 1998; 53: 403-11. [PubMed]
14. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. JAMA 2002; 287: 2215-20. [CrossRef] [PubMed]
15. Murphy S, Roberts R. "Black box" 101: How the Food and Drug Administration evaluates, communicates, and manages drug benefit/risk. J Allergy Clin Immunol 2006; 117: 34-9. [CrossRef] [PubMed]
16. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Warnings and precautions, contra indications, and boxed warning sections of labeling for human prescription drug and biological products - content and format. Rockville (USA): Fishers Lane; 2006.
17. Tufts Center for the Study of Drug Development. Drug safety withdrawals in the U.S. not linked to speed of FDA approval. Tufts CSDD Impact Report 2005; 7: 1-4.
18. Lasser KE, Seger DL, Yu DT, Karson AS, Fiskio JM, Seger AC, et al. Adherence to black box warnings for prescription medications in outpatients. Arch Intern Med 2006; 166: 338-44. [CrossRef] [PubMed]
19. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? JAMA 1999; 281: 1728-34. [CrossRef] [PubMed]
20. www.blackboxrx.com [http://blackboxrx.com]. Memphis: BlackBoxRX, LLC. Black box drug list. Cited 2011 August 15. Available from: http://blackboxrx.com/ index.php.
21. Marks NS, Weiss K. Boxed Warnings and other FDA communication tools. Am Fam Physician 2010; 81: 259. [PubMed]
22. Shah ND, Montori VM, Krumholz HM, Tu K, Alexander GC, Jackevicius CA. Geographic variation in the response to FDA Boxed warnings for Rosiglitazone. N Engl J Med 2010; 22: 2081-4. [CrossRef] [PubMed]
23. Cohen A, Rabbani A, Shah N, Alexander GC. Changes in glitazone use among office-based physicians in the United States, 2003-2009. Diabetes care 2010; 33: 823-5. [CrossRef] [PubMed]
24. Wagner AK, Chan KA, Dashevsky I, Raebel MA, Andrade SE, Lafata JE, et al. FDA drug prescribing warnings: is the black box half empty or half full?. Pharmacoepidemiol Drug Saf 2006; 15: 369-86. [CrossRef] [PubMed]
25. Weatherby LB, Nordstrom BL, Fife D, Walker AM. The impact of wording in "Dear doctor" letters and in black box labels. Clin Pharmacol Ther 2002; 72: 735-42. [CrossRef] [PubMed]

POTENCIJALNO OPASNI NEŽELJENI EFEKTI LEKOVA I „BLACK BOX" SISTEM UPOZORENJA

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Farmakovigilanca ili prikupljanje, praćenje, istraživanje, ocenjivanje i vrednovanje informacija dobijenih od strane proizvođača, zdravstvenih radnika i bolesnika o negativnim efektima lekova, bioloških proizvoda, tradicionalnih lekova, a sa ciljem identifikovanja novih informacija o opasnosti u vezi sa lekovima, kao i sprečavanjem štetnih posledica po bolesnika obaveza je regulatornih agencija, ovlašćenih od strane nadležnih državnih organa, u gotovo svim zemljama. Savremeni trendovi lečenja bolesnika, u sprezi sa sve većim brojem novih lekova u svim farmaceutskim oblicima na tržištu, zahtevaju kontinuirano poboljšanje sistema farmakovigilance, sa sve većim akcentom na povratne informacije prema finalnim potrošačima i propisivačima. Jedan od jako efikasnih komunikacionih alata između regulatorne agencije i finalnih potrošača/ propisvača osmislila je i implementirala Administracija za hranu i lekove SAD-a (FDA) pod nazivom – uokvireno upozorenje („black box"). „Black box" upozorenja su najozbiljnija upozorenja FDA za lekove, koje ukazuje na potencijalno fatalne, opasne po život, ili onesposobljavajuće neželjene efekte lekova. Sam naziv potiče od crnog okvira koji okružuje tekst upozorenja. Okvir je dizajniran da privuče pažnju na upozorenje i da ga posebno naglasi u odnosu na ostale informacije, koje mogu biti prisutne u pakovanju leka. Uvidom u studije koje su pratile način korišćenja lekova sa ovakvim upozorenjem evidentno je da eksplicitno, dobro publikovano upozorenje može promeniti propisivačke navike lekara i uticati na bolesnike da opreznije koriste određene lekove ili čitave klase lekova. *Acta Medica Medianae 2011;50(3):69-73.*

***Ključne reči**: farmakovigilanca, FDA, „Black box" upozorenja, neželjeni efekti*