

Analysis of OTC drugs adverse drug reactions spontaneously reported in 2018

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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

MARKUS KELLNER

**ANALYSIS OF OTC DRUGS ADVERSE DRUG REACTIONS
SPONTANEOUSLY REPORTED IN 2018**

Diploma thesis

Academic year:

2018/2019

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Prof. Darko Modun, MD, PhD

Split, September 2019

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1. INTRODUCTION

1.1. Self-medication

First, we need to comprehend the concept of self-care, in order to establish a better knowledge of self-medication. By definition of the World Health Organization (WHO) self-care is “what people do for themselves to establish and maintain health, prevent and deal with illness.” This concept comprises hygiene (general and personal), nutrition (type and quality of food eaten), lifestyle (sporting activities, leisure etc.), environmental factors (living conditions, social habits, etc.), socioeconomic factors (income level, cultural beliefs, etc.) and self-medication (1).

Consequently, self-medication is a specific component of self-care and is defined by WHO “as the selection and use of medicines, including herbal and traditional products by individuals to treat self-recognized illnesses or symptoms”. Furthermore, rather than acquiring medical advice from a health care professional, self-medication includes adoption of medicines, via the advice of a non-health professional person or by their own initiative. Unfortunately, this combines errors of responsible use, like sharing medicines and leftover drugs within the social circle and relatives or reusing old prescriptions to purchase medicines (1-3).

Self-medication and self-care are of increased global interest among the public, which has been influenced by several factors. Lack of health services, financial constraint, availability, accessibility, extensive advertisement of medicinal products, ignorance, misbelieves, as well as the possibility to treat or manage an illness through self-care are the most relevant. Moreover, other important factors are, patients’ satisfaction with the health care provider, purchasing prices of drugs, patients educational level, together with waiting times, high cost of private doctor’s consultations, age and gender (1, 4, 5).

Developing countries specifically struggle with prescription drugs being sold for self-medication without any professional supervision. This unapproved drug use is also one of the factors which are promoting occurrence of antimicrobial resistance. However, internationally, governments and health insurers are promoting self-care, and also self-medication when applied correctly and responsible. Therefore, pharmacists’ role is of crucial importance. Not only does the pharmacist supply and sell medicinal products and is part of a health care team, working in the hospital, community pharmacies, laboratory, the industry or in academic institutions, now there is also a need for more responsibility towards their customers and greater demand for accountability (1, 5-7).

1.1.1. Risks of self-medication

While the terms are often used interchangeably, we have to distinguish between ‘misuse’ and ‘abuse’ of a drug. Misuse is defined when a drug is used for a legitimate medical reason but in an incorrect manner, meaning it is either used for a prolonged time or at an increased dosage than recommended. Primarily misuse is therefore applicable to all drugs while, abuse is often associated with drugs containing opioids, antihistamines and laxatives. (8, 9).

Contrary, abuse is defined as the use of a drug for a non-medical reason, for example, to experience mind altering effects or to induce bodyweight loss. As mentioned earlier one can follow the other, and in many cases they actually can be used interchangeably, both describing incorrect use of an otherwise harmless drug. Incorrect use can be a consequence of incorrect self-diagnoses in the first place, as mentioned by a study of Ferris *et al.* which assessed the ability of women (with and without a previous physician-confirmed diagnosis of vaginal candidiasis) to self-diagnose this condition based on the reading of a classic case scenario. The majority of patients were unable to diagnose correctly upon reading the case scenario. Subjects may be using antifungals to treat diseases which may have comparable symptoms to vaginal candidiasis, but are possibly more serious (8-10).

Therefore, a faulty self-diagnosis, accompanied by the use of an ineffective non-prescription drug can mask symptoms of a potentially serious disease or medical condition, thereby delaying effective treatment. Furthermore, there are specific demographics like the elderly, children and pregnant women, that are at increased risk for irresponsible self-medication. Especially polypharmacy of over-the-counter (OTC) drugs and concomitant use of prescription drugs causing several harmful drug interactions, as well as non-compliance and prolonged use of OTCs, affect the elderly and increases their risk for adverse drug reactions (ADRs) (12-14).

Likewise, several non-prescription drugs are not recommended for the use in children with a certain age. However, a study by Kogan *et al.* reported common use of nonprescription drugs in over 50% of 3-year old pre schooled children in the 30 days prior to the survey. Especially neonates with enzyme deficiencies and different organ sensitivities are at increased risk to develop drug intoxication. Let alone that, during pregnancy indirect exposure of non-prescription drugs to the unborn child, has increased significantly, mostly as a consequence of effective advertising of products (15-17).

Eventually, the increased demand to self-medicate can undermine the patient physician relationship, while patients are mostly responsive to doctors’ guidance on non-

prescription medicines, those patients that are excluded from prescription fees, show less support for such an intervention. In fact, patients demand on prescribing decisions for non-prescription drugs may interfere with physician's treatment plans and lead to inappropriate prescriptions and polypharmacy. Likewise, some doctors in the UK even considered the endorsement of a non-prescription drug as breach in their National Health Service contract. Nevertheless, non-prescription drugs are advised to be used for self-limiting conditions for a short term. However, some exceptions have been proposed. For instance, paracetamol (acetaminophen), available as OTC drug, has been used in the long term management of osteoarthritis, in which case a diagnosis has been made by a physician (11, 18-20).

1.1.2. Benefits of self-medication

The deregulation of the non-prescription market causes many facets of self-medication to expand, which means an increase in market size for the pharma industry. Additionally, the switch of a drug to non-prescription status can protect it from generic competition. That is to say, increasing access to medications, favors the pharmaceutical industry. More importantly, self-medication causes health care cost reduction in health care systems, where government is the main payer of services (21-23).

Indeed, pharmacists support deregulation, establishing a more clinical role and greater professional status, through acquiring more therapeutic options and greater involvement with patients. In fact, growing confidence in the pharmacist to diagnose, treat and refer patients to the doctor, is supported by more doctors in Europe and in the UK. Further, patients themselves ask for greater availability to non-prescription medicines, since it is time saving, effective and economical (11, 24-27).

Specifically, headache, indigestion, constipation, cough/phlegm and colds (flu) are described as conditions, which patients demand to self-treat. Accordingly, increased access to H2-antagonists did not result in an increase in drug consumption or adverse drug reactions, nor did it cause obvious changes in hospital admissions for ulcer complications (28, 29).

1.2. OTC drugs

There is a relation between an increasing tendency towards the use of OTC drugs and an expansion of availability of OTCs, together with gained patient interest in self-care. In particular conditions of pain, the digestive system and cough appeared to be the most common reason for buying OTC medications. While consumers identify OTC drugs as safe,

they often have inadequate knowledge of the possible side effect profiles of the medications they are taking (30-32).

A questionnaire based study looking at elderly patients for example, found that three quarters of all participants, 392 (75.5 %) of the 519, considered OTC drugs as safe or mostly safe. Whereas a different study by Cuzzolin *et al.*, that included younger patients, found only 55,4 % of 613 participants, acknowledge non-prescription medications to be safe. Especially long term users of these medications underrated the potential physiological and pathological modifications or drug interactions. Appreciation of the benefits of OTC medications presented to be of greater importance to the patients, than their capability to cause damage. Indeed, frequently patients choose to prefer OTC drugs, because of prolonged waiting times in the physician's office (33-36).

More importantly, the chances of safer OTC drug use were increased when comprehensive advice was given by the pharmacist. Multiple analyses revealed, that the pharmacists represent the key source, providing information about the OTC medications. Only very few patients (46 (8.9 %) of 519) would buy OTC drugs without surveillance by a pharmacist. Therefore, pharmacists training and continuous education should emphasize the safety aspects of OTC medications, including potential interactions with prescription medicines. In fact, the survey indicated that pharmacists represent the most trusted source of information about OTC medications. However, if ADRs occur, patients tend to seek assistance from physicians. Further, special importance is warranted in the elderly, who are at an increased risk of ADRs because of age-related changes in pharmacokinetics and pharmacodynamics of drugs as well as deviation from normal compliance (36-40).

In Croatia, in order for new drugs to be granted marketing authorization the Agency for Medicinal Products and Medical Devices (HALMED) labels drugs as either a prescription only or not. Every authorized drug must fulfil quality, safety and efficacy standards which indicates it must be ratified by consistent and repeatable quality, of clinical efficacy and safety for patients. Precisely, OTC drugs are meant to treat symptoms and conditions that are recognized by patients and do not need medical supervision, meaning they are safe for self-medication (41).

Furthermore, HALMED determines an OTC drugs dispensary status, as they can be sold either in pharmacies or specialized retail stores of medicinal products. If a pharmacist however concludes that a particular OTC drugs could be harmful to a patient, he or she has the individual right to refuse the dispense of the drug. Since OTC drugs can contain more than one active substance, which can be of chemical or herbal origin, herbal medicinal products,

traditional herbal products and medicinal products with a well-established use can also be granted OTC status (41).

1.2.1. Analgesics

Anti-inflammatory drugs (NSAIDs) describes a group of drugs used to treat inflammation, pain and fever and are commonly used for diseases like osteoarthritis, rheumatic fever hyperuricemia and gout. NSAIDs act by inhibiting cyclooxygenases (COXs) that synthesize prostaglandins (PG) from arachidonic acid. We differentiate between, COX-1 and COX-2. COX-1, expressed essentially in most of the cells, it is the primary origin of prostanoids for variety of functions, such as hemostasis (42).

Furthermore, inhibition of COX-1, which is the leading cytoprotective isoform in gastric epithelial cells, causes most of the gastric adverse events and bleeding. Contrarily, COX-2 expression is induced by cytokine release, shear stress and tumor promoters, and therefore is more important in the formation of prostanoids, in inflammation and possibly in cancer. Therefore, COX-2 inhibition can worsen hypertension and increase the possibility for thrombotic events. Since most of the NSAIDs have a low pK value and are organic acids, they are largely well absorbed orally and mostly bound by plasma proteins, causing them to be excreted by glomerular filtration and tubular secretion. Plasma concentration and duration of drug effect seem to be in a confounding relationship, since NSAIDs accumulate in a low pH environment, like sites of inflammation (42).

NSAIDs are divided by their mechanism of action, as either being competitive, non-competitive, irreversible or mixed reversible, nonselective, inhibiting both COX-1 and COX-2, or COX-2 selective. Aspirin represents the only irreversible inhibitor of COX enzymes that is in clinical use, while all other NSAIDS bind COXs reversibly (42).

Numerous chemical derivatives of salicylates have been synthesized, since salicylic acid is too irritating to be used systemically. Among them is Aspirin, the acetate ester of salicylic acid. It fulfills its analgesic, antipyretic and anti-inflammatory effect through acetylation, making it a noncompetitive, irreversible inhibitor of COXs. Other salicylates act via the rather weak inhibition of COX enzymes and suppression of inflammatory up regulation of COX-2. Aspirin achieves its analgesic and antipyretic effect at doses of 325-1000 mg, when administered every 4-6 hours. While rarely used in inflammatory conditions such as arthritis, spondyloarthropathies and systemic lupus erythematosus, due to its inferior gastrointestinal safety profile, aspirin is effective for rheumatic fever at doses ranging from 4 to 8 g/d. Adults and children over 12 years, however, are recommended not to use more than

4g a day. In fact, aspirin inhibits platelets COX-1 enzymes for the remaining lifetime of the platelet for approximately 7-10 days, therefore inhibiting TxA2 production, decreasing the risk for cardiovascular occlusive events substantially in high risk patients. At the same time aspirin use, increases clotting time, can cause gastrointestinal bleeding, hypersensitivity reactions and should be avoided in children with an acute febrile illness, where it can cause a potentially life threatening condition called Reye Syndrome (42, 43).

Acetaminophen, also known as paracetamol or N-acetyl-p-aminophenol is the active metabolite of phenacetin. It is often sold in fixed dose combinations together with aspirin, barbiturates, caffeine, vascular headache remedies, sleep aids, toothache remedies, antihistamines, antitussives, decongestants, expectorants, cold and flu preparations, and sore throat treatments. Mostly lacking anti-inflammatory activity, it acts as a noncompetitive reversible inhibitor at the peroxide site of COXs, inducing its antipyretic and analgesic effects. The diminished anti-inflammatory effect results from decreased COXs inhibition, that is due to the existence of high concentrations of peroxides at inflammation sites. While injectable and oral preparations are available, a typical dose contains 325-650 mg every 4-6 hours but should not exceed 4 g in healthy adults and children older than 12 or 2 g in chronic alcoholics in 24 hours. Acetaminophen is generally well tolerated; however multi-ingredient medications can cause drug interactions with toxic effects. Furthermore, over dosage of which two thirds are intentionally, can cause liver necrosis, resulting in nearly 80,000 emergency department visits and 30,000 hospitalizations annually in the U.S. Compared to aspirin, acetaminophens effects on the gastrointestinal system and platelets are reduced (42, 44, 45).

The potency of the phenylacetic acid derivative is considerably greater than that of other NSAIDs. Diclofenac has analgesic, antipyretic, and anti-inflammatory effects, its selectivity for COX-2 however, resembles that of celecoxib. Available as intravenous injection and oral tablets at daily doses of 50-150 mg, diclofenac is used for the long term symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, pain, primary dysmenorrhea and acute migraine. Temporary symptomatic treatment of pain for minor strains, sprains and bruises can be achieved with 1% topical gel/solution and a transdermal patch. Actinic keratosis can be treated with a 3 % gel. Postoperative inflammation succeeding cataract extraction and short-term alleviation for pain and photophobia after corneal refractive surgery are treated with an ophthalmic solution. Oral formulas are combined with misoprostol, a PGE1 analogue, in order to lower the prevalence

of gastrointestinal side effects like ulcers and erosions. Side effects occur 20% more common, as well as elevated liver enzymes, when compared to aspirin (42).

Ibuprofen is a propionic acid derivative and available alone and in various fixed dose combination with antihistamines, decongestants, famotidine, oxycodone, and hydrocodone. While ibuprofen is primarily applied for mild to moderate pain in 400mg oral formulations every 4-6 hours, for premature infants an injectable formulation is used to close patent ductus arteriosus. Maximum doses in adults should not exceed 3,2g/d, while the pediatric limit is at 2,4g/d. Special properties of ibuprofen may include its ability to slowly equilibrate with the synovial space, therefore having anti arthritic effects even after plasma levels decline. Moreover, ibuprofen has been shown to readily cross the placenta, in animal models. Studies also show there may be an increased risk for aseptic meningitis and ibuprofen is readily excreted in breast milk. Potency of ibuprofen seems to be equivalent to that of aspirin (42, 44).

Also a propionic acid derivative naproxen, seems to have its peak anti-inflammatory activity 2-4 weeks from onset of administration. As previously mentioned NSAIDs it is marketed alone, and in fixed dose combinations with pseudoephedrine, diphenhydramine, esomeprazole, and sumatriptan; as well as with lansoprazole. Mostly sold in oral formations containing 200-500 mg, it is indicated for juvenile and rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, pain primary dysmenorrhea, tendonitis, bursitis and acute gout attack. As with ibuprofen, naproxen crosses the placenta and shows up in the milk of lactating women and usage carries a risk for aseptic meningitis. Finally, in the elderly, naproxen has a higher free fraction and is excreted in less amounts, increasing the possibility for toxicity. Nevertheless, it seems to be better tolerated, than aspirin (42, 44).

1.3. Adverse drug reactions

According to the WHO an adverse drug reaction is defined as “any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy of disease or for the modification of physiological functions. Moreover, Edwards and Aronson define it as the following “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product (4, 46).

In HALMED’s definition however, an “adverse reaction is every response to a medicinal product which is noxious and unintended. This includes adverse reactions arising

from use of the product within or outside (including overdose, off-label use, misuse, abuse and medication errors) the terms of the marketing authorization or from occupational exposure.” Furthermore, HALMED differentiates an unexpected adverse reaction which is defined when,” the nature, severity or outcome of which is not is not consistent with the summary of product characteristics or the investigator’s brochure for medicinal products in clinical trials.” And an adverse event, that is “any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease coinciding with the administration of a medicinal product, but not necessarily in any causal relation to it “(47).

Finally, a serious adverse reaction/event is defined as “any adverse event or adverse reaction that is fatal, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or serious disability or incapacity, including a congenital anomaly/birth defect and other medically significant conditions.” Above all, a systematic review by Lazarou *et al.* 1998 implied that adverse drug reactions are between the fourth and sixth leading cause of death in the U.S. Additionally an approximated 2 million hospitalized patients have serious adverse drug reactions and 100,000 undergo fatal adverse drug reactions every year (47-49).

In particular, mortality is highest among the elderly, trending especially in ICU, emergency department, multi-specialty ward and general hospitals. In more than half of the cases fatal ADRs are specifically associated with drugs like Warfarin, aspirin, RAS inhibitors and digoxin. The most frequent detected fatal reactions for example, were intracranial hemorrhage, renal failure and gastrointestinal bleeding, which collectively account for more than 50% of fatal ADR. Furthermore, adverse drug reactions represent a critical cause of drug-related emergency visits that lead to hospitalization, or when happening during hospitalization, may protract the hospital visit. In consequence ADRs generate economic burden, influence quality of life, despite the fact, that more than half of ADRs are preventable. Increased unmasking of fatal ADR however, can be achieved with computer-based monitoring systems and other identification methods (48-54).

1.3.1. Reporting of ADRs

In order to continuously monitor the effects of medical drugs that have been licensed, the World Health Organization introduced National Centers (NCs) like HAMLED, that are WHO-approved pharmacovigilance centers in those countries partaking in the WHO Programme for international Drug Monitoring. According to HAMLED the pharmacovigilance centers are responsible for a variety of actions linked to “identification,

assessment, understanding, prevention and procedure in case of adverse reactions, as well as new information about the medicinal product safety.” In the Republic of Croatia, the qualified person responsible for pharmacovigilance can be “a medical doctor specialized in clinical pharmacology, or a medical doctor, or a doctor of dental medicine, or a graduate pharmacist, or a master of medical biochemistry, or a doctor of veterinary medicine with two years of experience in pharmacovigilance or two years of experience in his/her profession with appropriately documented training in pharmacovigilance “(4, 47).

2. OBJECTIVES

To analyze adverse drug reactions reported to HALMED for OTC drugs in 2018.

3. SUBJECTS AND METHODS

This was a cross sectional study containing data on reported adverse drug reactions from Agency of Medicinal Products and Medical devices of Croatia (HALMED). An adverse drug reaction can be defined as damage directly initiated by the drug at normal doses, and in normal use. Data on adverse drug reaction reports was extracted from VigiBase, a pharmacovigilance database. VigiBase is the global database of World Health Organization, and which contains individual case safety reports (ICSRs). It is the largest database with over 20 million reports submitted by member countries. In Croatia, during the study period, physicians, pharmacists, other health care professionals and non-health care professionals (e.g. patients) were supposed to report ADRs.

The medicinal products database (available online in Croatian and English) was searched before requesting HALMED for the data reports. Inclusion criteria for database search was OTC Medicinal products. In 2019 overall 466 medicinal products were registered as OTC drugs, and were included in this study. Adverse drug reaction reports of OTC drugs from 1 January to 31 December 2018 were obtained.

The following data of ICSR were analyzed: reporter qualification (pharmacist, physician, consumer/non health professional or other health professional), patient gender and age, seriousness (included caused/prolonged hospitalization, life threatening, other and death), active substance name and concomitant therapy.

The reports data was exported into a spreadsheet using Microsoft Office Excel 2016, and descriptive statistical analysis was performed. Results are presented as whole numbers and proportions. Statistical analysis was performed using MedCalc software for Windows (v.11.5.1.0, MedCalc Software, Ostend, Belgium). Chi square test was used for comparing categorical variables and significance was set at $P < 0.05$.

4. RESULTS

In the examined period 165 ADRs reports were obtained for OTC drugs from HALMED. For 57 generic drugs at least one ADR was reported in 2018. Most commonly reported generic drugs were ibuprofen, 22 reports (13.3%) and paracetamol, 17 reports (10.2%). Concomitant therapy was reported in 25.3 % of the ADR, and in 74.7 % ($p < 0.001$) of the reports the only medicinal product that consumer used was OTC drug which caused the ADR.

Consumers that experienced ADR of OTC drugs were mainly female gender ($P=0.05$), as presented in Figure 1.

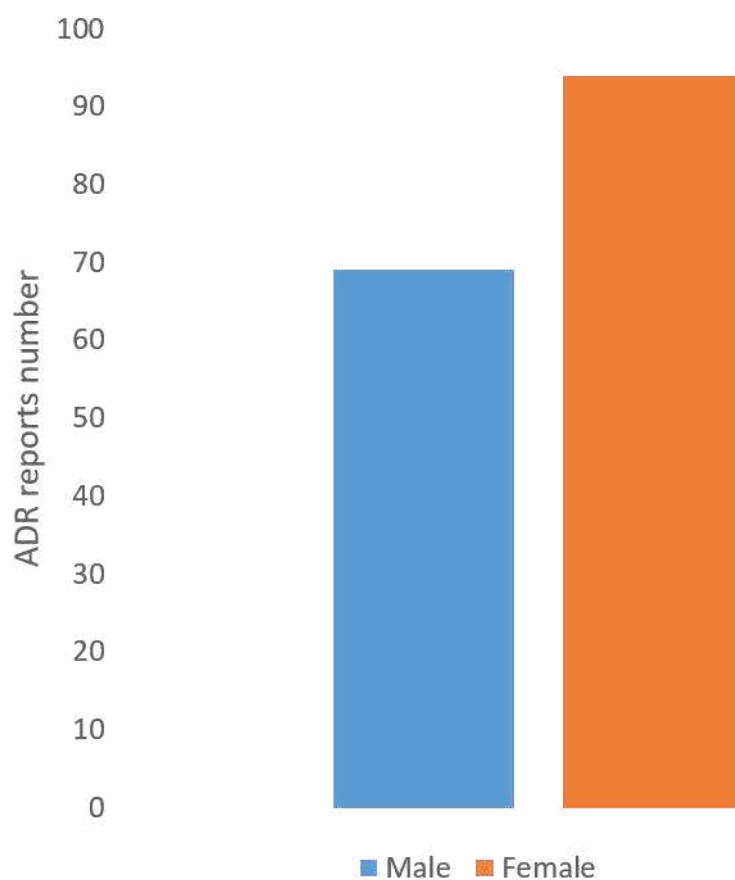


Figure 1. Gender of consumers that reported adverse drug reaction

Furthermore, consumers that experienced and reported ADR of OTC drugs were most commonly children under the age of 9 years, and this age group was followed by elderly (age groups > 60 years of age). Out of 47 ADRs that have been reported for children, 26 of them were accidental exposure to product by child. Number of ADR reports of each age group is presented in Figure 2.

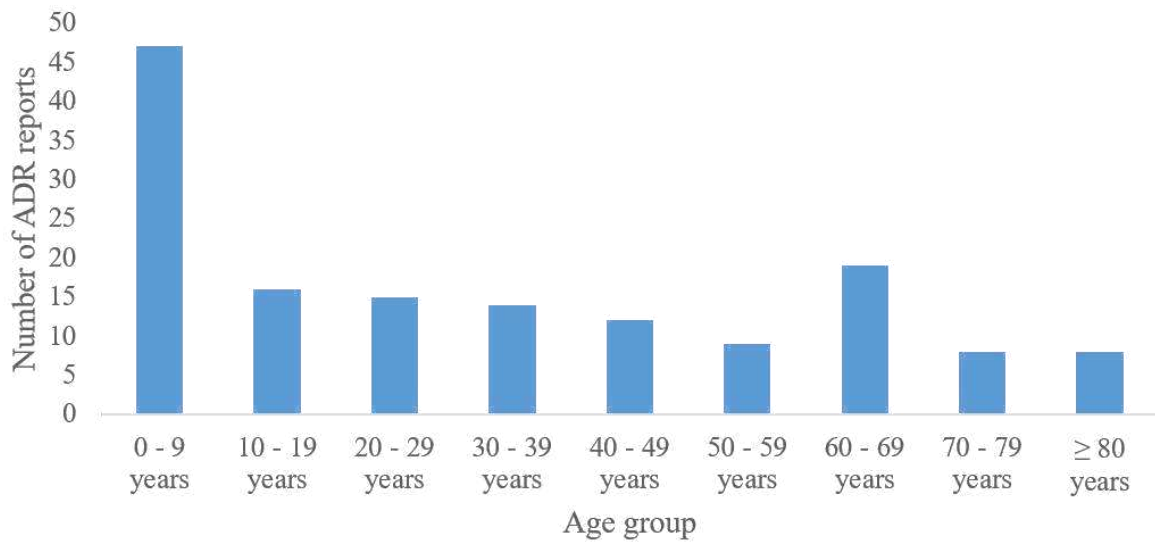


Figure 2. Age groups of consumers that reported adverse drug reaction

Figure 3 shows distribution of reporter qualification in 2018 OTC drugs ADR reports. Majority of the ADRs were reported to HALMED by pharmacists, followed by consumers. Other health care professionals reported only 6 ADRs during 2018, which accounts for 3.64% of all ADR reports.

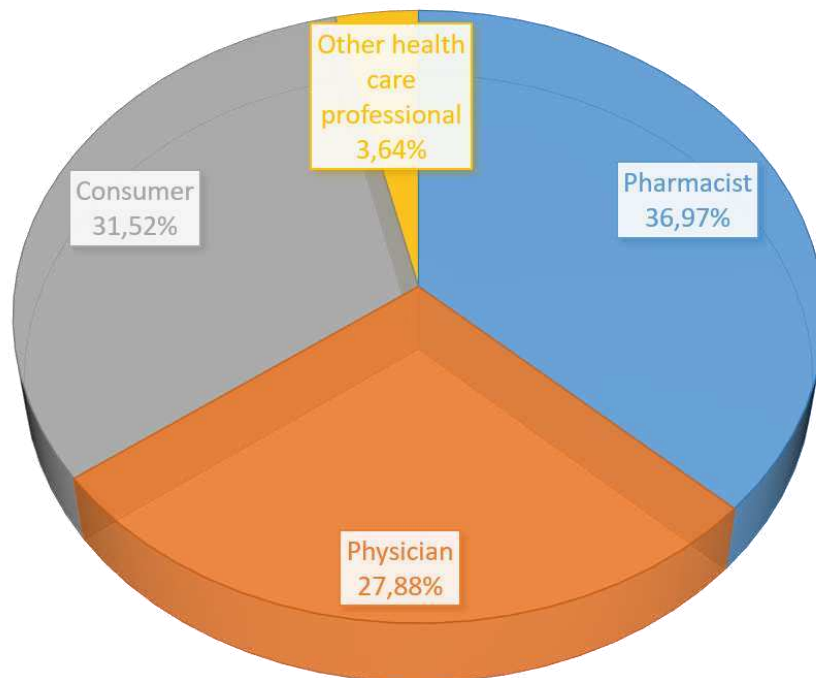


Figure 3. Distribution of reporter qualification for OTC drugs adverse drug reaction reports

Interestingly, more than 50 % of the reports included at least one of the seriousness criteria and were classified as serious. The distribution of ADR reports by seriousness is presented in Figure 4.

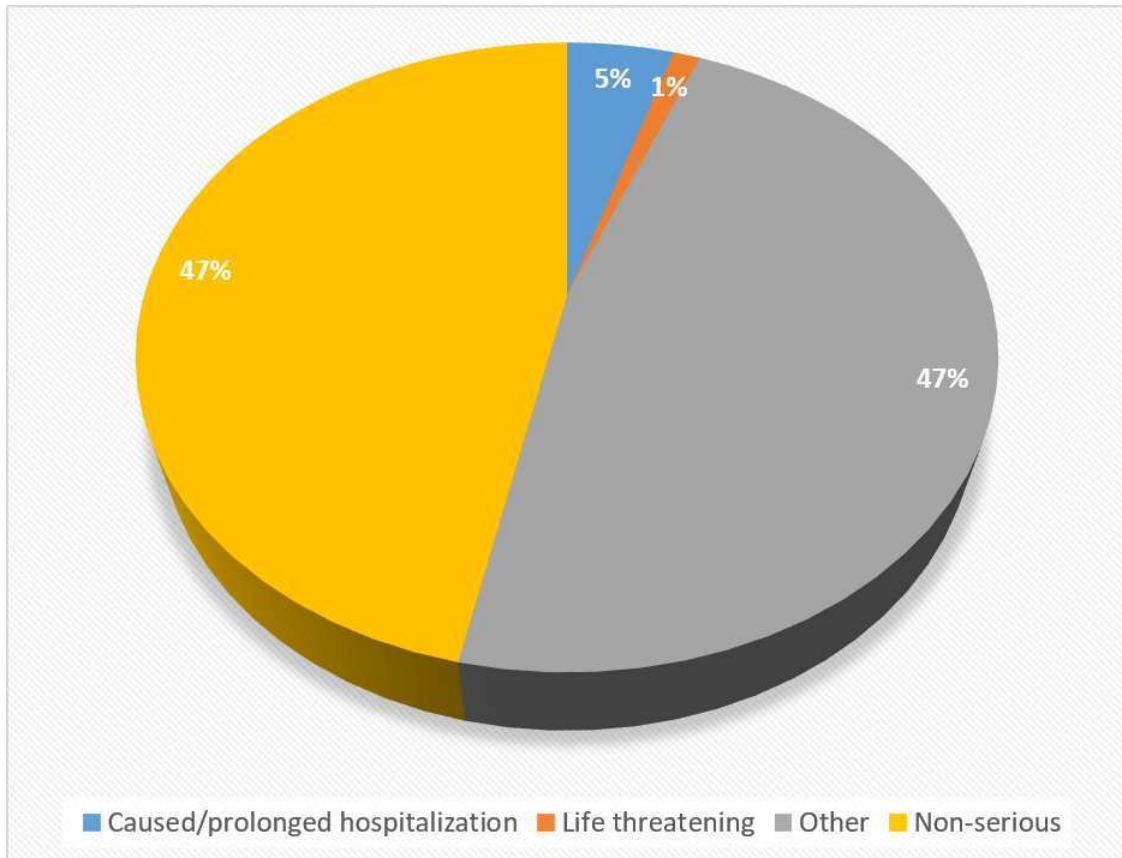


Figure 4. Distribution of adverse drug reaction reports by seriousness

5. DISCUSSION

In the examined period a total of 165 adverse drug reaction reports for OTC drugs were collected in HALMED. Interestingly, almost third of the reported adverse drug reactions were reported in pediatric age group (< 9 years). Furthermore, more than half of the pediatric adverse drug reaction reports were classified as accidental exposure to product by child. Out of all adverse drug reactions included in our study, it can be stated that accidental exposure to children could have been prevented in all of the cases. Therefore, both physicians, pharmacists and nurses should communicate to parent's ways how to improve childproofing mechanisms. The proposed childproofing mechanisms are to remember always to return drugs to a secure location immediately after use. Furthermore, the secure location should ideally be high and out of children's sight (55).

Study by Schoenewald *et al.* explored causes of pediatric accidental unsupervised ingestions of OTC drugs, as in United States of America every year poison centers receive more than 500000 reports of accidental/unsupervised exposure to drugs in children under 6 years of age. In the same study 60 % of caregivers reported that the drug involved in accidental unsupervised ingestion had not been in the normal storage location when accidental unsupervised ingestion occurred. Luckily, as presented also in our study, majority of the children did not experience any symptoms as a consequence of accidental unsupervised drug ingestion (55).

Ibuprofen was the OTC drug which adverse drug reactions were most commonly reported in 2018. Safety profile of ibuprofen has been well known, and has been studied extensively. However, a study published in 2018 by Walsh *et al.*, hypothesized that renal and gastrointestinal adverse drug reactions occur more often in infants younger than 6 months, when compared with infants older than 6 months. Furthermore, the authors assumed that ibuprofen would be associated with more adverse drug reactions than paracetamol in infants younger than 6 months. However, the results of this retrospective cohort study have showed that gastrointestinal and renal adverse drug reactions were not higher in younger group of infants (< 6 months) when compared to infants aged 6 to 12 months. Moreover, the results have showed that the number of adverse drug reactions in infants younger than 6 months was increased for the infants that have used ibuprofen when compared with infants that have used only paracetamol (56).

In the 2018 majority of the reports were obtained from pharmacists, and lowest number of the reports were obtained from other health care professionals (e.g. dental doctors and nurses). Furthermore, the number of reports obtained from the pharmacists was followed by the reports obtained from the consumers. The increase in the consumers reporting of

adverse drug reactions has been observed in previously conducted studies. Specifically, a smartphone application Web-Recognising Adverse Drug Reactions has been introduced in United Kingdom, the Netherlands and in Croatia between July 2015 and May 2016. A study published by Oosterhuis et al. compared app reports and reports received through conventional means from the same period. In the United Kingdom 28 % of the app reports were obtained from consumers, when compared to 18 % of consumers that conventionally reported adverse drug reactions, and in Croatia app reports from consumers was presented in 32 %, and conventional in 7 % of the reports. Therefore, it could be assumed that a large number of the consumers' reports noticed in our study could be a result of consumers use of Web-Recognising Adverse Drug Reactions smartphone application. However, the use of this application in Croatian adverse drug reaction reporting practice exceeds the scope of this study (57).

First limitation to our study is that only adverse drug reaction data collected in Croatia were included in our analysis. As OTC market differs significantly between diverse countries, even in European union, it is hard to compare our results with the results of adverse drug reaction reporting data of other countries. Furthermore, there is a possibility that a large number of adverse drug reactions occurred in 2018, and were not reported to national authority. This underreporting of adverse drug reaction has been recognized as a major issue worldwide. Therefore, in order to improve both consumers and health care professionals reporting practice it is important to support and conduct pharmacovigilance research.

6. CONCLUSION

1. In total 165 adverse drug reactions for OTC drugs were reported in 2018.
2. Most commonly reported generic drugs were ibuprofen, 22 reports (13.3%) and paracetamol, 17 reports (10.2%).
3. Concomitant therapy was reported in 25.3 % of the adverse drug reaction reports.
4. Consumers that experienced adverse drug reaction of OTC drugs were mainly female gender (P=0.05).
5. Out of 47 adverse drug reactions that have been reported for children, 26 of them were accidental exposure to product by child.
6. Pharmacists reported 36.97% of adverse drug reactions and consumers reported 31.52%.

7. REFERENCES

1. Essential Medicines and Health Products Information Portal [Internet]. Hague: Report of the 4th WHO Consultative Group on the Role of the Pharmacist. Available from: <http://apps.who.int/medicinedocs/en/d/Jwhozip32e/>
2. Montastruc JL, Bagheri H, Geraud T, Lapeyre-Mestre M. Pharmacovigilance of self-medication. *Therapie*. 1997;52:105-10.
3. Filho L, Antonio I, Lima-Costa MF, Uchoa E. Bambui Project: a qualitative approach to self-medication. *Cad Saude Publica*. 2004;20:1661-9.
4. Phalke VD, Phalke DB, Durgawale PM. Self-medication practices in rural Maharashtra. *Indian J Community Med*. 2006;31:34-5.
5. Ali Sherazi B, Mahmood KT, Amin F, Zaka M, Riaz M, Javed A. Prevalence and Measure of Self Medication: A Review. *J Pharm Sci Res*. 2012;4:1774-8.
6. Hughes L, Whittlesea C, Luscombe D. Patients' knowledge and perceptions of the side-effects of OTC medication. *J Clin Pharm Ther*. 2002;27:243-8.
7. Pagán JA, Ross S, Yau J, Polsky D. Self-medication and health insurance coverage in Mexico. *Health Policy*. 2006;75:170-7.
8. Hughes GF, McElnay JC, Hughes CM. Abuse and misuse of non-prescription drugs. *Pharm World Sci*. 1999;21:251-5.
9. Honig PK, Cantilena LR. Polypharmacy - Pharmacokinetic perspectives. *Clin Pharmacokinet*. 1994;26:85-90.
10. Ferris DG, Dekle C, Kitaker MS. Women's use of over-the-counter antifungal medications for gynecological symptoms. *J Fam Pract*. 1996;42: 595-600.
11. Bradley CP, Bond C. Increasing the number of drugs available over the counter: arguments for and against. *Br J Gen Pract*. 1995;45:553-6.
12. Honig PK, Gillespie BK. Clinical significance of pharmacokinetic drug interactions with over-the-counter (OTC) drugs. *Clin Pharmacokinet*. 1998;35:167-71.

13. Sihvo S, Klaukka T, Martikainen J. Frequency of daily over-the-counter drug use and potential clinically significant over-the-counter prescription drug interactions in the Finnish adult population. *Eur J Clin Pharmacol.* 2000;56:495-9.
14. Chrischilles EA, Lemke JH, Wallace RB. Prevalence and characteristics of multiple analgesic drug use in an elderly patient study group. *J Am Geriatr Soc.* 1990;38:979-84.
15. Chambers C. Over-the-counter medications: Risk and safety in pregnancy. *Semin Perinatol.* 2015;39(7):541-4.
16. Kogan MD, Pappas G, Yu SM, Kotelchuk M. Over-the-counter medication use among US preschool-age children. *JAMA.* 1994;272:1025-30.
17. Kacew S. Effect of over-the-counter drugs on the unborn child. What is known and how should this influence prescribing? *Paediatr Drugs.* 1999;1:75-80.
18. Bradley CP, Riaz A, Tobias RS. Patient attitudes to over-the-counter drug and possible professional responses to self-medication. *Fam Pract.* 1998;15:44-50.
19. Hughes CM, McElnay JC, Fleming GF. Benefits and risks of self medication. *Drug Saf.* 2001;24:1027-37.
20. Covington TR. Nonprescription Drug Therapy: Issues and Opportunities. *Am J Pharm Educ.* 2006;70:137.
21. Herxheimer A. Self-medication industry is determined to expand. *Lancet.* 1999;353:2136.
22. Hollenbeak CS. The effect of generic competition on prescription to over-the counter switching. *Pharmacoeconomics.* 1999;16:661-8.
23. Blenkinsopp A, Bradley C. Patients, society, and the increase in self-medication. *BMJ.* 1996;312:629-32.
24. Powis MG, Rogers PJ, Wood SM. United Kingdom community pharmacists' views on recent 'POM to 'P' switched medicines. *J Soc Admin Pharm.* 1996;13:188-97.

25. Erwin J, Britten N, Jones R. General practitioners' views on over the counter sales by community pharmacists. *BMJ*. 1996;312:617-8.
26. Sihvo S, Hemminki E, Ahonen R. Physicians' attitudes towards reclassifying drugs as over-the-counter. *Med Care*. 1999;37:518-25.
27. Keen PJ. POM to P: useful opportunity or unacceptable risk. *J R Soc Med*. 1994;87:422-5.
28. Bell HM, McElnay JC, Hughes CM. Societal perspectives on the role of the community pharmacist and community-based pharmaceutical services. *J Soc Admin Pharm*. 2000;17:119-28.
29. Andersen M, Schou JS. Safety implications of the over-the-counter availability of H₂-antagonists. *Drug Saf*. 1993;8:179-85.
30. The story of self-care and self-medication. 40 years of progress [Internet]. Nyon: Global self-care federation. Available from: <https://www.selfcarefederation.org/>
31. Bond C, Hannaford P. Issues related to monitoring the safety of over-the-counter (OTC) medicines. *Drug Saf*. 2003;26:1065–74.
32. Clark D, Layton D, Shakir SA. Monitoring the safety of over the counter drugs. We need a better way than spontaneous reports. *BMJ*. 2001;323:706–7.
33. Wawruch M, Kuzelova M, Foltanova T, Ondriasova E, Luha J, Dukat A et al. Characteristics of elderly patients who consider over-the-counter medications as safe. *Int J Clin Pharm*. 2013;35:121-8.
34. Cuzzolin L, Benoni G. Safety of non-prescription medicines: knowledge and attitudes of Italian pharmacy customers. *Pharm World Sci*. 2010;32:97–102.
35. Simoens S, Lobeau M, Verbeke K, van Aerschot A. Patient experiences of over-the-counter medicine purchases in Flemish community pharmacies. *Pharm World Sci*. 2009;31:450–7.
36. Bissell P, Ward PR, Noyce PR. Mapping the contours of risk: consumer perceptions of non-prescription medicines. *J Soc Adm Pharm*. 2000;17:136–42.
37. Volmer D, Lilja J, Hamilton D. How well informed are pharmacy customers in Estonia about minor illnesses and over-the-counter medicines. *Medicina (Kaunas)*. 2007;43:70–8.

38. Hanna LA, Hughes CM. Public's views on making decisions about over-the-counter medication and their attitudes towards evidence of effectiveness: a cross-sectional questionnaire study. *Patient Educ Couns*. 2011;83:345–51.
39. Guirguis K. The use of nonprescription medicines among elderly patients with chronic illness and their need for pharmacist interventions. *Consult Pharm*. 2010;25:433–9.
40. Bressler R, Bahl JJ. Principles of drug therapy for the elderly patient. *Mayo Clin Proc*. 2003;78:1564–77.
41. Agency for Medicinal Products and Medical Devices of Croatia [Internet]. Zagreb: OTC medicinal products. Available from: <http://www.halmed.hr/en/Lijekovi/Informacije-o-lijekovima/Bezreceptni-OTC-lijekovi/>
42. Grosser T, Smyth EM, Fitzgerald A. Pharmacotherapy of Inflammation, Fever, Pain and Gout. In: Brunton LL, Randa HD, Knollmann BC editors. *The pharmacological basis of therapeutics*. 13. edition. New York: Mc Graw Hill; 2018. p. 685-709.
43. Kalantzi KI, Tsoumani ME, Goudevenos IA, Tselepis AD. Pharmacodynamic properties of antiplatelet agents: current knowledge and future perspectives. *Expert Rev Clin Pharmacol*. 2012;5:319-36.
44. Blieden M, Paramore LC, Shah D, Ben-Joseph R. A perspective on the epidemiology of acetaminophen exposure and toxicity in the United States. *Expert Rev Clin Pharmacol*. 2014;7:341-8.
45. Moore N, Scheiman JM. Gastrointestinal safety and tolerability of oral non-aspirin over-the-counter analgesics. *Postgrad Med*. 2018;130:188-199.
46. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. *Lancet*. 2000;356:1255–9.
47. Agency for Medicinal Products and Medical Devices of Croatia [Internet]. Zagreb: Pharmacovigilance. Available from: <http://www.almp.hr/en/Farmakovigilancija/Sto-je-farmakovigilancija/Pojmovi/>
48. Lazarou J, Pomeranz BH, Corey PN. Prevalence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279:1200-5.
49. Erickson MA, Penning TM. Drug Toxicity and Poisoning. In: Brunton LL, Randa HD, Knollmann BC editors. *The pharmacological basis of therapeutics*. 13. edition. New York: Mc Graw Hill; 2018. p. 55-64.

50. Patel NS, Patel TK, Patel PB, Naik VN, Tripathi CB. Hospitalizations due to preventable adverse reactions-a systematic review. *Eur J Clin Pharmacol.* 2017;73:385–98.
51. Patel TK, Patel PB. Mortality among patients due to adverse drug reactions that lead to hospitalization: a meta-analysis. *Eur J Clin Pharmacol.* 2018;74:819-32.
52. Patel H, Bell D, Molokhia M, Srishanmuganathan J, Patel M, Car J et al. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998–2005. *BMC Clin Pharmacol.* 2007;7:9.
53. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One* 2009;4:4439.
54. Suh DC, Woodall BS, Shin SK, Hermes-De Santis ER. Clinical and economic impact of adverse drug reactions in hospitalized patients. *Ann Pharmacother.* 2000;34:1373-9.
55. Schoenewald S, Ross S, Bloom L, Shah M, Lynch J, Lin CL et al. New insights into root causes of pediatric accidental unsupervised ingestions of over-the-counter medications. *Clin Toxicol (Phila).* 2013;51:930-6.
56. Walsh P, Rothenberg SJ, Bang H. Safety of ibuprofen in infants younger than six months: A retrospective cohort study. *PLoS One.* 2018;13(6):0199493.
57. Oosterhuis I, Taavola H, Tregunno PM, Mas P, Gama S, Newbould V et al. Characteristics, Quality and Contribution to Signal Detection of Spontaneous Reports of Adverse Drug Reactions Via the WEB-RADR Mobile Application: A Descriptive Cross-Sectional Study. *Drug Saf.* 2018;41:969-78.

8. SUMMARY

Objectives: Self-medication and self-care are of increased global interest among the public, which has been influenced by several factors. Lack of health services, financial constraint, availability, accessibility, extensive advertisement of medicinal products, ignorance, misbelieves, as well as the possibility to treat or manage an illness through self-care are the most relevant. However, OTC drugs used in self-medication process could also cause adverse drug reactions and we aimed to analyze their reports from Croatia in year 2018.

Patients and Methods: Overall, 466 medicinal products were registered as OTC drugs in Croatia, and were included in this study. Adverse drug reaction reports of OTC drugs from 1 January to 31 December 2018 were obtained. The following data were analyzed: reporter qualification, patient gender and age, seriousness, active substance name and concomitant therapy.

Results: In total 165 adverse drug reactions for OTC drugs were reported in 2018. Most commonly reported generic drugs were ibuprofen, 22 reports (13.3%) and paracetamol, 17 reports (10.2%). Concomitant therapy was reported in 25.3 % of the adverse drug reaction reports. Consumers that experienced adverse drug reaction of OTC drugs were mainly female gender ($P=0.05$). Out of 47 adverse drug reactions that have been reported for children, 26 of them were accidental exposure to product by child. Pharmacists reported 36.97% of adverse drug reactions and consumers reported 31.52%.

Conclusion: Accidental exposure to OTC drugs by child observed in our study could have been prevented and childproofing mechanisms should be communicated to parents.

9. CROATIAN SUMMARY

Naslov: Analiza sumnji na prijave nuspojava bezreceptnih lijekova u 2018. godini

Ciljevi: Samoliječenje i skrb o vlastitom zdravlju ima rastući interes javnosti, pod utjecajem različitih faktora. Nedostatak zdravstvene usluge, financijski utjecaj, dostupnost lijekova te opširno reklamiranje bezreceptnih lijekova su neki od najčešćih faktora koji utječu na popularnost samoliječenja. Međutim, bezreceptni lijekovi koji se koriste u svrhu samoliječenja također uzrokuju nuspojave, a cilj ovog istraživanja bio je analizirati prijave tih nuspojava iz Hrvatske u 2018. Cilj ovog istraživanja bio je analizirati sumnje na nuspojave bezreceptnih lijekova prijavljene u 2018. godini.

Pacijenti i metode: Ukupno je 2018. godini na tržištu u Republici Hrvatskoj bilo registrirano 466 lijekova, koji su uključeni u ovo istraživanje. Prijave sumnji na nuspojave bezreceptnih lijekova zaprimljene od 1. siječnja do 31. prosinca 2018. uključene su u ovo istraživanje.

Rezultati: Ukupno je prijavljeno 165 sumnji na nuspojave bezreceptnih lijekova u promatranom periodu. Najčešći generički lijekovi uključeni u prijave su ibuprofen s 22 prijave (13,3%) i paracetamol sa 17 prijava (10,2%). Drugi lijekovi u terapiji prijavljeni su u 25,3% slučajeva. Korisnici bezreceptnih lijekova su bili većinom ženskog spola ($P=0,05$). Od 47 sumnji na nuspojave lijekova prijavljenih u djece, 26 je bilo slučajnih izloženosti lijeka djetetu. Ljekarnici su prijavili 36,97% sumnji na nuspojave, a sami korisnici 31,52%.

Zaključak: Slučajna izloženost bezreceptnih lijekova djeci uočena u ovome istraživanju može se prevenirati, mehanizmi za zaštitu djece trebali bi biti objašnjeni pacijentima.

10. CURRICULUM VITAE

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