

Adverse effects of counterfeit drugs on public health

Hande Sipahi¹, Kübra Peltekoglu², Nazlı Şencan^{2*}

¹ Department of Toxicology, Faculty of Pharmacy, Yeditepe University,
34755 Istanbul, Turkey

²Pharmacoeconomics and Pharmacoepidemiology Research Center (PEPIRC),
Faculty of Pharmacy, Yeditepe University, 34755 Istanbul, Turkey

Abstract: In the last decades, growing number of counterfeit pharmaceuticals involve to global pharmaceutical market. The counterfeited drugs are substandard, poor quality copies of original products, so they pose a global and serious health risk which can lead to resistance to treatment, illness, disability and even death. Recently in Turkey, a counterfeit cancer drug has been realized from its package and it was reported that 95 patients did not get the treatment they supposed. Moreover, it is understood that, they are marketed not even in Turkey but also to the global market. Counterfeiting is a crime and a problem of all countries even developed or underdeveloped. Pharmacist and all healthcare professionals should be knowledgeable and vigilant on the importance of the adverse effects of counterfeited drugs. In this review, we have tried to draw attention to counterfeit drugs and their adverse effects on public health.

Key words: counterfeit medicines, adverse drug effects, pharmacy

Introduction

In the last decades, there have been a number of reports, literatures and comments on the counterfeit (fake) medicine (drugs) phenomena. According to World Health Organization (WHO), a counterfeit drug is defined as “a medicine which is deliberately and fraudulently mislabeled with respect to identity and/or source” (1). Also, Institute of Medicine (IOM) categories counterfeited drugs as falsified (a false representation of identity or source) and substandard drugs (not up to national specifications because of quality system failure) (2). Counterfeiting can be applied to both branded and generic products and counterfeit drugs may include products with correct or wrong ingredients, without active or insufficient active ingredients or with fake packaging (1). If there is something suspicious for a drug in terms of presentation like color, taste, crumbliness, shape, size or packaging such as language, medicine names, indicated dose strength, then it is most probably a counterfeit product (3).

It is clear that a growing number of counterfeit pharmaceuticals involve to global market including Turkey. In United States it is declared that, while the numbers of counterfeit pharmaceuticals were only 196 in 2002, it raised to 2054 in 2010 (4). The situation which is and should be categorized as crime is a problem for all countries even developed or underdeveloped. The criminals not only sabotage all populations’ health, they also violate the patient’s life. The counterfeit pharmaceuticals are dangerous in all ways and the outcomes are economic, clinical and humanistic (5).

Drugs sold without a prescription, self-medication, the shortage supply of drugs, ineffective cooperation among different stakeholders, poor and uneducated population may be indirect social factors which forms a basement for counterfeiting of drugs (6). WHO defines the reasons of counterfeiting of drugs as follows (1);

- The lack of appropriate drug legislation,
- Absence or weak drug regulation,
- Lack of regulation by exporting countries and within free trade zones,
- Inefficient cooperation between stakeholders,
- High prices of medicines,
- Weak enforcement and penal sanctions

The easiest way to sell counterfeit drugs is commerce by online pharmacy. Especially, the elderly, disabled and people unable to visit a pharmacist during normal working hours generally prefer to buy their medicines online. However people actually choose online pharmacies because of the speed and convenience, too. Moreover, the patient who are too embarrassed to discuss their condition with a healthcare professional and who don't want their family or employer to find out about their condition tend to use online pharmacies. In addition prices are typically lower compared with pharmacy and items are delivered direct to the door (3). A study performed in USA confirms that even the approved and accredited "web pharmacies" may also serve counterfeited drugs. In the research, it was reported to be 6 "approved", 10 "legally compliant", 10 "not recommended", 15 "highly not recommended", and 14 "not recommended" or "highly not recommended" drugs from 55 website pharmacies. The drugs purchased from internet were analyzed and only Viagra® failed in the tests. The mostly sold four other drugs (Lipitor, Celebrex, Nexium, Zolofit) passed the tests which researchers want to emphasize that "authorized web sites" drug quality is quite safe. (7). This research is an extraordinary study as in most countries do not have monitoring organizations on web pharmacies.

Counterfeiting types and risks;

Counterfeit pharmaceutical products may be produced with the correct ingredients, with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging, which all may have harmful effects to patients.

- *Products which have the wrong ingredients* may lead to increase the risk of accidental overdose and also drug interaction. For example, Priligy® as a short-acting selective serotonin reuptake inhibitor, the active ingredient dapoxetine has also been registered for the treatment of premature ejaculation in men, which made the drug more popular and form a gray market. Dean et al. analyzed the chemical content of the product sold on the internet, under the name of "Staying Powder RX", which claimed to contain "dapoxetine HCL/60 mg pills". It was found that sildenafil as impurity was detected in counterfeit derivative of Priligy sold on the internet (8). It is well known that sildenafil has interaction with hypertension and cardiovascular disease and also with other drugs. On the other hand

patients may not manage the dose with unknown ingredients and these counterfeit drugs may cause death. In another case report, 54 year old man was admitted to hospital with sweating, slurred speech, ataxia and confusion. On examination, severe hypoglycemia was associated with ingestion of counterfeit Cialis® (tadalafil, Eli Lilly). When compared with original Cialis manufactured by Eli Lilly, analytic measurements revealed that counterfeit Cialis contain high doses of glibenclamide (152.8 mg) and low doses of sildenafil (0.5 mg) instead of tadalafil (9). The patients who may use this counterfeit drug may cause to hypoglycemic coma which is a very serious mortality cause.

- *Products which have insufficient or no active ingredients* can also lead to serious adverse effects on human health. In 2005, thirty-one batches of illegal buprenorphine vials were seized by the Tehran police (10). Parenteral dosage forms of buprenorphine under different trade names such as “Temgesic®” and “Bungesic®” were the most popular illegal opioid drugs in Tehran. Based on analytical data, diacetylmorphine, acetylcodeine, and pheniramine were detected in all of samples. The presence of acetylcodeine could potentiate the convulsant effects of diacetylmorphine. Because of the absence of quality control and difficulties in differentiating counterfeited buprenorphine from genuine products, the use of counterfeited buprenorphine lead the opioid abusers to serious health risks (10).

Recently according to a daily newspaper, a nurse in Turkey has realized a counterfeit cancer drug because of its in inappropriate package, and then started the investigation process. In this event, it was found out that 95 patients did not get the treatment they supposed. The patients sew the criminals. It was reported that the criminals produce “so called pharmaceuticals” cooperatively with health workers. Moreover, it was understood that, this counterfeit cancer drugs were marketed not even in Turkey but also to the global market. This news showed that health care professionals and workers who are smart, brave and aware enough could save lives of patients and society (11). This was not only a criminal catch but also a social responsibility of health care professionals.

- *Products which have fake packaging* are another counterfeiting drug problem. In a study conducted in 2009, 14 amodiaquine and amoxicillin samples were evaluated to detect the presence of any counterfeit or substandard drugs in circulation. The products, including pediatric formu-

lations, were purchased from a total of 5 pharmacies from different geographical location, in Port Moresby, in Papua New Guinea by locals without disclosing the purpose. Results were quite remarkable as none of the samples collected from registered pharmacies were able to comply with the all of the evaluation criteria; visual evaluation, quality control specifications and product authenticity. 3/14 products were found to be counterfeits, 9/14 were substandard and 2/14 were substandard products and additionally suspected to be counterfeits (12).

- *Medicines which have correct active ingredients in different quantity from what is stated on the package* could lead serious adverse effects on human health, too. According to data from Brazilian Federal Police, Viagra® (sildenafil citrate, Pfizer) and Cialis® (tadalafil, Eli Lilly) which are used for male erectile dysfunction were the most counterfeited medicines in Brazilian pharmaceutical market during the period of 2007–2010. In a study conducted by Ortiz RS et al, the content of 43 original sildenafil citrate and tadalafil samples and 65 illegal sildenafil citrate and tadalafil samples have been examined. Results showed that counterfeit samples contain more sildenafil and tadalafil active ingredients compared to the original sample (13). Recently, Venhuis et al. had declared in their study, which is conducted on analyses of counterfeit drugs and dietary supplements and they have found that, dose to dose variations within a single package are quite remarkable and this unreliable ingredients and quality may pose serious health risk (14).

Between 1998 and 2010, 110.000 counterfeit products sales to wholesalers and then to pharmacy chain were detected. According to FDA's AERS (Adverse Event Reporting System) there is a significant association between "erythropoetin" and "drug ineffective". No other injectable had similar association with other drugs. After interviews with doctors and attorney, it is understood that low dose of drugs are labeled as high dose expensive ones, which did not helped patient to recover and reach the expected blood values (15). It is obvious that for treating the illnesses like cancer, more vigilance is needed for counterfeit drugs.

In a retrospective study performed in Singapore in 2008, laboratory tests of 15 patients admitted to hospital with severe hypoglycemia showed that the blood glibenclamide level was considerably high due to the use of a Chinese unlicensed aphrodisiac formulation (Power 1 Walnut). Based on the data, all of the patients were admitted to the emergency department

with neuroglycopenic symptoms about 12 to 36 h after ingestion of the pills. While the recommended maximum dose of glibenclamide for the treatment of Type 2 diabetes mellitus is 20 mg daily, most cases took a single dose of 93–98 mg of glibenclamide, which is about 4 times the maximal recommended dose (16). Furthermore, in 19 countries including Turkey, the quality of two main first line anti-tuberculosis medicines, isoniazid and rifampin, were assessed and 65 of 713 drugs purchased from pharmacies failed for requisite levels of active ingredients or disintegration. This could lead to an increase in drug resistance in these countries and consequently it is crucial to preventing the proliferation of falsified and substandard anti-tuberculosis drugs (17). Medicinal products expire date may also cause package related problems. Criminals may change the package or the claim of expire date on the package. As stability is an important part of quality and safety of drugs, many problems may occur.

- *Medicines without active ingredients* may lead failure of therapy. A report published in 2004 claimed that fluvoxamine (an antidepressant) and cyclobenzaprine HCl (a muscle relaxant) had been sold as ‘Triomune®’ or ‘Duovir®’, the two commonly prescribed antiretroviral brands in Democratic Republic of Congo. Many people with AIDS were reported to prefer counterfeit medicine because of the cheaper price (18).

- *Products which have impurities* could lead serious health problems. A 58 year old woman patient was found dead in her bed, in Canada in 2006. There was no reasonable cause of death. Unmarked packages and bags of pills were found which turned out to contain the hypnotic zolpidem, which is not available in Canada, the prescription anti-anxiety drug alprazolam and acetaminophen. After laboratory analyses, researchers found diphenhydramine (an OTC sedative), acetaminophen, mirtazapine (a prescription antidepressant), dextromethorphan (an OTC cough medicine) and methocarbamol (an OTC muscle relaxant). But most shocking were the dangerously high levels of metals, including aluminum (15 µg/g), phosphorus, titanium, tin, strontium, arsenic and other metals in the patient’s liver. The level of aluminum alone was 15 times higher than what’s considered normal (19). This example shows that in manufacturing processes, even the counterfeit drug is contaminated with toxic metals and caused a health hazard. This led the Canada government be more focused on the counterfeit drugs subject. Another event happened in China in 2010. In

a retrospective study, acute intraocular inflammation observed in 80 of a total of 116 patients after intravitreal injection of counterfeit bevacizumab. This was defined as a new syndrome; “Endotoxin induced Ocular Toxic Syndrome” (EOTS). It is understood that counterfeit bevacizumab caused the syndrome (20). The counterfeit bevacizumab had not been manufactured according to Good Manufacturing Practice (GMP) and medicine was contaminated and was not sterilized. Fortunately most of the cases, nearly %80 recovered.

- *Withdrawn drugs* also pose serious adverse effects on public health. Some drugs which are withdrawn from the market by legislations, creates a demand from gray market by the consumers who get used to take these drugs. A synthetic-type stimulant, fenethylline commonly known by the trade name “Captagon®” is one of the examples of the withdrawn counterfeiting. Captagon® was one of the most widely abused drugs in the Middle East. After its banning and withdrawal in 1988, the illicit production of drug has increased. Based on the analytical researches conducted on 124 batches of Captagon® tablets, it is found that while fenethylline was not detected in the Captagon® tablets, amphetamine, caffeine and several other substances was found in faked ones (21). The fake Captagon may be fine for abusers but again a threat for health. Another example is Acomplia® (rimonabant) which is used for weight-loss was withdrawn from the market at the end of 2008. The internet sales of the product contained rimonabant were significantly increased in spite of serious adverse events and lack of efficacy. When 5 suspected products were analyzed, the effective quantities of rimonabant were confirmed, additionally, one of the samples was found to contain low dose sibutramin (22).

Conclusion

Drugs must be safe, effective and should be used rationally in order to obtain the desired clinical and therapeutic outcome. However, it is known that nearly 5-7 % of the global drug market is counterfeited. It is also declared that in some countries pharmaceutical commerce market, counterfeit percentage is higher like 40-50% (23).

Millions of people die per year because of the poor quality drugs such as anti-infective products which can poses the risk of development of resistant to bacterial strains and lack of efficacy can increase mortality (24, 25).

The best way to strength global action against poor quality drug problem is firstly to have a “center” to play assertive role in the fight against falsified and substandard drugs (2) via to bring all of the information collected together from all the countries in the world as Uppsala Monitoring Center which is a Pharmacovigilance Collaborating Center of WHO for International Drug Monitoring (26). Moreover, there should be effective local drug regulatory authorities to control the illegal drug sales. For Turkey, government has started a fight with fake medicines and formed a unique system in 2010 (27). Every single manufactured or exported drug has a unique barcode and can be followed up from manufacture side to patient. Government declares that the system is useful and cost effective. On the other hand, for time being only reimbursed drugs are being chased. Drugs without prescriptions or vitamins and supplements are still at risk. In addition, outsell and expensive drugs such as cancer drugs are still favorite counterfeiting. Because local drug regulations are not enforced sufficiently, counterfeiting still seems to be a serious problem for Turkey and national urgent precautions are needed (28, 29).

As a result, considering the present public health situation in the world, for drug counterfeiting all related partners such as manufacturers, stakeholders, governments (authority), health care professionals (including physicians, nurses, pharmacists), patients and international NGO’s (Non-Governmental Organizations), WHO, IFPMA (International Federation of Pharmaceutical Manufacturers Association), and national and international consumers’ associations should realize their responsibility. It is obvious that awareness should be improved for all parts and especially for public. As public is the last consumer of these fake medicines, if patients resists to buy from internet or corners where there is no pharmacist and physician, it is more easy to wipe out the counterfeit medicines market. More should be done for educating the people against hazards and adverse effects of counterfeit drugs. All unwanted and unexpected adverse effects reporting and follow ups should as also be searched and examined if it is fake or not. Pharmacovigilance experts should also be educated from these perspectives, too. Education and awareness campaigns could be conducted for all partners. And the effectiveness of these attempts should also be measured, too. Another suggestion for protecting the public from adverse effects of counterfeit medicines is related to regulations: Giving hard punishment to these criminals as it is commit-

ted crime against public can also be a solution in decreasing the harm of fake medicines. Pharmacist and all health professionals should inform legal experts on the importance of the harm effects counterfeited medicines for people and public and emphasize the seriousness of the crime.

It is obvious that all health professionals who are involved in pharmaceutical chain have responsibilities. A collective work and awareness is needed so as to save and protect the rights of patients. Political, economic, legal, scientific and yet shortly a holistic approach is needed in this war. All parts involve in this “Fake Fight” have responsibilities. We cannot say that buying a fake watch or perfume or wine is less harmful to society. Either a drug or any other thing, that is counterfeited, is something dishonest. All fake products need similar attention and awareness (30).

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