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BRIEF NOTES

Health risks related to illegal and on-line sale of drugs and food supplements: results of a survey on marketed products in Italy from 2011 to 2013

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Abstract

Objectives. The increasing illegal and on-line market of medicines and food supplements is helping the widespread diffusion of harmful counterfeit and forbidden products among consumers of developed countries. The objectives of this survey were the description of the main frauds recognized by public officers and the detection of illegal or counterfeit drugs and food supplements.

Methods. Medicines and food supplements found by Police forces on the illegal market or resulting from seizures made by Italian Customs authorities were visually inspected and analysed to evaluate their quality and the presence of other undeclared substances.

Results. The visual inspection and the chemical analysis revealed unsuitable packaging (mostly lacking of adequate information for consumers), absence of the declared active substances and presence of undeclared active substances. Products containing doping agents, illegal substances and active ingredients requiring medical supervision were found.

Conclusion. The present work confirmed the health risk associated with assumption of medicines purchased on the Internet and from the illegal supply chain and evidenced a new threat to consumer safety related to the presence of pharmaceutical active ingredients in food supplements claiming to contain only "natural ingredients".

Key words

- counterfeit medicines
- food supplements
- PDE5-i
- slimming agents
- doping agents

INTRODUCTION

Pharmaceutical counterfeiting is a well known problem in developing countries, where it touches worrying percentages [1-2] but it is often underestimated in developed countries, where it is spreading mostly from the on-line unauthorized distribution [3].

Italian legislation implementing the European Directive 2011/62/CE regarding the prevention of the diffusion of falsified medicinal products, prohibits the offer for a sale at a distance of prescription medicinal products and prescribes that all web pharmacies should have a common logo that is recognizable throughout the European Union.

Over the last few years the Italian Official Medicines Control Laboratory (OMCL) has been involved in the analytical control of a growing number of suspected samples seized by *Carabinieri NAS* (the Italian Police Force that deals with health related crimes) or by *Guardia di Finanza* (the Italian Police Force that deals with Financial Crimes) or by Customs Officers. In a previous work only the medicinal products copying the branded VIAGRA®, CIALIS® and LEVITRA® that contain the phosphodiesterase 5-inhibitors (PDE5-i) as active ingredients [4] were considered by the authors.

In this paper, the results of laboratory analysis performed on all kinds of suspicious medicines sent to the OMCL are reported. A number of food supplements suspected to fraudulently contain pharmaceutical active ingredients such as PDE5-i or slimming substances were also analysed. Finally, some unlabelled samples sized by customs agents were also analysed to look for the presence of pharmaceutical ingredients or other illegal substances.

MATERIALS AND METHODS

The samples considered in this paper came from seizures in gyms, sexy-shops and ethno-shops or from custom officers inspections of container shipment or

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postal packages addressed to private citizens as a result of on-line shopping. Each sample was registered, photographed and then carefully inspected to make some preliminary classification of the type of product (legal, illegal, counterfeit, etc.). Depending on the request of the authority involved in the seizure, samples were then analysed to ascertain only the qualitative or also the quantitative composition. In a low number of cases only a visual inspection was required.

Visual inspection of seized samples was performed following an internal procedure that, by means of a systematic observation, has the purpose to highlight all the differences with respect to the original sample (in the case of a counterfeit mimicking the branded medicine) or all the characteristics that suggest the product to be an illegal one. In particular, the presence of spelling errors on the label, discrepancies in expiry date or batch number between the secondary and the primary packaging, absence of the manufacturing name and country were checked, as suggested by World Health Organization guideline on pharmaceutical counterfeiting [1].

Qualitative analysis was performed on a liquid chromatograph equipped with a time-of-flight mass spectrometer detector (MS) (Agilent Technologies, Fast HPLC Mod. 1290 Infinity + Q-TOF Mod. G6520B with a Dual ESI source). For most of the samples a general in-house LC-MS Q-TOF screening method was used for chromatographic separation and accurate molecular mass values determination. From this value the most likely molecular formula of the unknown substance could be inferred and some possible molecular structures could be guessed. In a second step the detector was set in MS/MS mode, thus obtaining a mass spectrum which analysis allowed to confirm the identity of the substance (see analytical details in *Box 1*).

For quantitative analysis validated liquid chromatographic methods reported in the marketing authorization dossier of the corresponding legal products were employed. In some cases the analysis was performed on low price copies of brand-name drugs (*e.g.* Indian copies of VIAGRA® or CIALIS®): in such cases the extraction procedure was stressed to be sure to obtain the complete recovery of the active ingredient. For medicines copying the original products (mainly those against men impotence) infra-red spectroscopy and thermal analysis were also performed to detect the fraudulent replacement of the active ingredient with homologous molecules and to look for the presence of non-pharmaceutical or harmful excipients. In some cases, nuclear magnetic resonance (NMR) was used for a definitive identification of the active substance.

The product marketing status (product illegally marketed, prescription-only medicine, doping substance [5] ingredient withdrawn from the market or banned as narcotic or psychotropic agent [6]) was assessed and on the base of the whole results of the analysis (visual inspection, qualitative and quantitative results) the final evaluation on the product was given.

Box 1
Details on screening method in the analysis of illegal/counterfeit medicines and food supplements.

Solvent extraction: methanol

LC parameters
Column: C18, 2.1x50 mm, 1.8 μm
Gradient elution: from 95/5v/v H_2O/CH_3CN + 0.1% formic acid to 5/95v/v H_2O/CH_3CN +0.1% formic acid in 15 min;
Flow rate = 0.4 mL/min;
Injection volume = 1 μL;
T column = 35°C

MS parameters
Source: Dual ESI in positive ion conditions
T gas(N_2) = 300°C
Drying gas = 10 L/min
Nebulizer = 40 psig
Fragmentor = 100V

MS-MS Targeted mode
Collision Offset Voltage = 30V

RESULTS AND DISCUSSION

Medicinal samples

Among all suspicious samples analysed by the Italian OMCL in the period 2011-2013, about one-third (34%) were medicines to treat erectile dysfunctions, requiring a prescription by a physician and strict medical supervision, because of the severe contraindications in case of previous stroke, heart or liver problems of the patient [7]. Thirty-seven per cent of the samples were substances mentioned in World Anti-Doping Agency (WADA) list [5], mainly anabolic steroids. Among them there was nandrolone decanoate that is listed in the Italian Tables of Forbidden Narcotic and Psychotropic Substances issued by the national Ministry of Health [6]. Special consideration was given to products containing substances with anorexiant activity (4%). Some of the analysed medicines declared to contain sibutramine, a substance forbidden from WADA list [5] and withdrawn from the market in 2010 for increasing the risk of serious cardiovascular events (such as heart attack or stroke) [8]. Among the other kind of medicines (29% of the analysed cases), 22% contained substances requiring a prescription by a physician.

Table 1 reports the observations deriving from the visual inspection of packaging and the outcomes of chemical analysis performed on the suspicious medicines and food supplements.

The visual inspection evidenced that most of the medicinal samples were lacking of outer packaging. Thus, no information about side effects, contraindications and interactions with other drugs was available to patients. In some cases the primary packaging was missing and tablets were loose in a plastic bag without any label. Primary packaging was broken or cut in 11% of cases, so that a more rapid degradation of the active substance was likely. Medicines improperly packaged may lack efficacy and produce unexpected effects. In 12% of the samples the batch number and the expiry date were not reported, illegible or inconsistent. Manufacturer's name and/or country of production were not reported in many cases, so that no traceability of the product was possible. Only in a small portion of samples the patient information leaflet and labels were in Italian, which would be mandatory for medicinal prod-

ucts marketed in Italy; in many cases the language used was not English either. Moreover 6% of samples had spelling mistakes in labels or leaflet. The composition of the medicinal product was not reported at all in 4% of the medicinal samples. Finally, an analysis of the origin of the products made on the basis of the indication on the packaging evidenced that about a third of the samples came from India. Obviously, in case of counterfeits, the information on the origin of the product could be false.

Counterfeit and illegal drugs are therefore harmful right from the packaging since all the information the patient needs for a safe use of the product is lacking.

The analytical results evidenced that 7% of the analysed medicinal products did not contain at all the labelled active ingredient and in few cases a different, undeclared active substance was found. Quantitative results indicated that 35% of the analysed samples contained an incorrect amount of active substance, generally lower.

The analysis performed on excipients resulted in the identification of different excipients with respect to the original branded sample (in particular for samples VIAGRA®- and CIALIS®-like) and in particular non-pharmaceutical excipients (such as gypsum) were found. In many cases undeclared lactose, that can cause problems to intolerant patients, was detected. Anyway it must be considered that any modification of a pharmaceutical formulation can affect the release of the active substance and so its bioavailability, thus, the replacement of the excipients without suitable studies may not be harmless [9].

Finally, in *Table 1* the evaluation on the counterfeiting of the samples is reported. Only a small portion of the products was considered legal and authentic (7%) on the basis of both the visual inspection and the analytical results. In 61% of cases the samples were illegal (unauthorized for marketing in Italy) and in 29% of cases they were counterfeit. In a small number of cases a doubtless evaluation was not possible (reported in the *Table* as I/C) because the difference between illegal and counterfeit, on the basis of the WHO definition of counterfeit [10] is often slight. For instance, when the quantity of active ingredient is less than the declared one it is not always clear if it is due to a sub-standard manufacture or to an intentional fraud.

Food supplements

Food supplements are quite a different matter. In Italy they are not subjected to the same marketing regulations as medicinal products but they should however be notified to the Italian Ministry of Health to be legally marketed in the country [11]. *Table 1* evidences that most of food supplements analysed were not notified to the Ministry of Health (86%) and 28% of them contained undisclosed pharmaceutical substances.

The packaging examination confirmed the same quality problems observed on medicines. All the actives found in food supplements and natural herbal remedies were prescription-only or forbidden substances. In this case the risk for public health is more serious, because the consumer ignores the risk, being convinced to assume a "natural" product without any side-effect. It is worth making some special remarks about the re-

Table 1
Quality evaluation (packaging visual inspection and analytical results) performed on medicinal samples and food supplements purchased by citizens over the Internet market and seized by Customs or seized on the illegal market in Italy from 2011 to 2013

Visual inspection	**% of failures in medicines (105 samples tested)**	**% of failures in food supplements (29 samples tested)**
Outer packaging missing[1]	72	10
Immediate packaging missing	3	0
Immediate packaging damaged	11	14
Expiry date and/or batch number missing, illegible or inconsistent[2]	12	34
Manufacturer's name and/or manufacturing country missing	37	55
Label not in Italian	79	24
Mistakes on label	6	14
No label at all	4	0
Illegal product[3]	**61**	**86**
Analytical results		
Absence of the labelled active substance	7 (% of 91 samples)	NA[4]
OOS[4] assay	35 (% on 55 samples)	NA
Presence of an undeclared pharmaceutical active substances	12 (% on 91 samples)	28
Counterfeit product	**29 + 3** (I/C)[5]	**28**

[1] The leaflet was missing in almost all the samples.
[2] The batch number and/or the expiry date on the immediate and outer packaging were inconsistent.
[3] Products with no marketing authorization in Italy (for medicines) or no notification to the Italian Ministry of Health (for food supplements).
[4] Out of specifications: < 90% or > 110% of the label claim.
[5] Illegal/Counterfeit medicine.
NA: not applicable.

sults of the analysis on dietary supplements. In many weight-loss promising supplements the analysis showed the presence of sibutramine and phenolphthalein. The first is the same slimming agent found in some illegal medicines that has been withdrawn from the European and American market [8]; the second was used in the past as a laxative, but later it has been banned for its suspected cancerogenic effect [12, 13]. In food products promising the enhancing of sexual performances and advertised as all-natural alternatives to prescription drugs, sildenafil and tadalafil, the active ingredients of VIAGRA® and CIALIS® respectively, were found. Also their analogous dimethyl-sildenafil, hydroxy-homosildenafil and hydroxy-tiohomosildenafil were detected. For these analogous clinical trials are not available, thus at the moment it is impossible to know their toxicity and possible adverse reactions. Moreover, food supplements containing hidden pharmaceutical ingredients are a serious risk also for the potential toxic interactions with other medications.

Unlabelled vials

Five type of unlabelled glass vials containing a white powder and differing only for the colour of the cap were seized by Italian Customs and analysed by the Italian OMCL. Three of them were found to contain mannitol for injection. This sugar alcohol is used as a masking agent in doping owing to its diuretic effect and it is reported in WADA list [5]. In one sample the growth hormone somatropin and mannitol were found. In the last sample the GHRP-2 (growth hormone releasing peptide-2), a peptide registered in Japan as medicine for the treatment of juvenile growth failure [14] and illegally used as doping agent to induce the endogenous increase of the growth hormone [15] was detected. In this last case, a confirmation of the structure was obtained by NMR [16]. All the substances found in these vials can be dangerous to consumers and the absence of any information (qualitative and quantitative composition, manufacturer's name, batch number and expiry date) makes these samples even more dangerous.

CONCLUSIONS

The results of this survey evidence that most of the samples seized by Italian Police Forces and customs authorities or bought on the web by Italian citizens, contain doping agents and banned substances or prescription-only drugs. Buying medicines on-line or out of the legal supply chain is usually considered a way to save money and to avoid medical prescription, but it results in an illegal and dangerous action. An increasing risk for public health is also coming from food supplements. These products that are perceived by consumers as being completely riskless owing to their labelling suggesting a "100% natural" composition often showed to contain active pharmaceutical substances.

The aim of this paper is to prompt physicians to warn their patients about the risks of purchasing medicines and food supplements from the on-line illegal pharmacies or from illicit sources. Moreover, authorities, physicians and consumers should be aware not only of the intrinsic hazard of doping agents but also of the possible counterfeiting of doping products: undeclared mix of different substances with possible toxic interactions, the use of new molecules without established toxicity studies. This survey in Italy probably reflects the situation of many other European Countries [17] and indicates that an urgent combined action is needed from Official Medicines Control Laboratories, Health Authorities, Police Forces, Professional organizations and Consumers Associations.

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Conflict of interest statement

The authors have no conflict of interest to disclose.

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