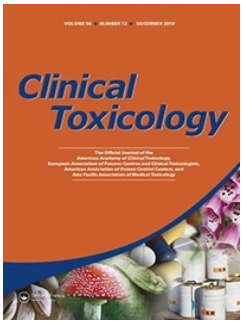

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An overview on performance and image enhancing drugs (PIEDs) confiscated in Italy in the period 2017–2019

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BASIC RESEARCH

An overview on performance and image enhancing drugs (PIEDs) confiscated in Italy in the period 2017–2019

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ABSTRACT

Context: The illegal market of counterfeit and falsified medicines and supplements containing unlabeled pharmaceuticals is expanding worldwide. They are usually referred to by the term "performance and image enhancing drugs" (PIEDs) and are mainly steroids, stimulants, hormones, and drugs for erectile dysfunction. PIEDs are easily accessible through the online or black markets. We analyzed over 400 such medicines confiscated in Italy in the period 2017–2019, to determine their composition.

Methods: Confiscated products were analyzed by gas chromatography/mass spectrometry and liquid chromatography/high-resolution mass spectrometry, in order to ascertain their composition and to evaluate the correspondence between what was declared on the label and the actual content, or to identify unknown products.

Results: The most commonly found substance was anabolic steroids, found in 64% of products, with 11% containing hormone modulators, 6% stimulants, 6% sexual enhancers (mainly sildenafil) and other drugs, including thyroid hormones, melanin stimulators, and vitamins. These substances were often in mixtures. The products were often mislabeled, containing contaminants in addition to the drug declared, or consisted of a drug completely different from the one reported on the label. Fifteen percent of products had a qualitative composition completely different from that declared, while 10% of products showed cross-contamination with other drugs, mainly testosterone esters, probably due to the presence of residues of other drugs in the production line. In addition, 11% of products were not labeled, so their purported composition was unknown.

Discussion: PIEDs pose a threat to public health. The main risks are related to the intrinsic toxicity of the substances found, especially when taken without a therapeutic indication. Another issue is related to the mislabeling of the fake medicines, and the poor-quality standard of counterfeit product preparation, with additional risks of the presence of other toxic ingredients or microbial contamination.

Conclusions: The use of counterfeit products is a public health concern, as it constitutes a high risk for consumer health. It is mainly caused by the uncontrolled use of steroids, stimulants, sexual enhancers, and other medicaments, without medical indication or supervision, with variable and unknown compositions and doses, as well as other contaminants as a result of the absence of good manufacturing practices.

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Introduction

The illegal market of counterfeit and falsified medicine and supplements containing substances not declared in the label is expanding worldwide. Substances generally abused for doping purposes are also used for a "lifestyle" motivation, mainly in developed, healthy countries. The main objectives of their use are to improve physical appearance, for diet, and to contrast erectile dysfunction. For these reasons, they are included in the wider classification of the performance and image enhancing drugs (PIEDs). PIEDs users include not only professional and amateur athletes but also fitness enthusiasts or students [1–3].

The most frequently used substances are androgenic anabolic steroids (AASs) and related substances, stimulants, and phosphodiesterase 5 inhibitors (PDE5I) [4,5]. Polydrug use of these substances often occurs [1–3,6]. The aim of their use is to achieve the desired physical effects, but also to counteract undesired side effects; for example, tamoxifene or sildenafil are used to contrast respectively gynecomastia or erectile dysfunction, both induced by the use of anabolic agents. The misuse of such substances, commonly in high dosages and without medical advice and surveillance, can result in unpredictable effects and constitutes a serious health risk. For instance, following the use of AASs, severe side effects on various organs and systems (cardiac, hepatic, reproductive) [7–10] and psychiatric disorders [11] are reported.

Illicit PIEDs are generally produced in clandestine laboratories and purchased on the black market [2,12–15], mainly

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Supplemental data for this article can be accessed here.

on the internet. In fact, purchasing on online platforms guarantees anonymity and does not require medical prescription or supervision, attractive features for people looking for those products.

This entails a high risk to the users' health, due to PIEDs production in unauthorized/clandestine laboratories, which are generally of substandard quality conditions. Fake medicines may contain fallacious active components, of low quality or in the wrong doses, high levels of contaminants and impurities, and can be mislabeled with respect to their composition.

The analysis of many different fake products containing sildenafil, as an example, demonstrated the presence of byproducts and aspartame, not declared in the label [16]. Indeed, falsified medicines do not undergo quality, safety, and efficacy control, as required by the EU authorization procedures.

Another concern is that supplements sold through irregular channels are prone to the addition in their composition of not-labeled PIEDs [17].

Moreover, the presence of unlabeled substances prohibited in sports can lead to adverse analytical findings in anti-doping controls [17].

On the website of the European Medicines Agency (EMA), there is a section dedicated to falsified drugs which report that the most frequently fake medicines in developed countries are "lifestyle" medicines, such as hormones and steroids [18]. EMA adopted a new directive on falsified medicines for human use in order to protect citizens' health, also dealing with internet sales of legal online pharmacies and approved retailers in the EU.

Also, World Health Organization (WHO) has drawn attention to this phenomenon; indeed, according to WHO surveillance report, products bought from illegal and unauthorized e-shops, increasingly popular in high and middle-income countries, often fail to meet quality standards and sometimes are released on the market without regulatory approval [19]. Studies published on the analyses of these preparations revealed that the active ingredients on the labels were substituted with other ones [13,20,21], whereas for other samples no active ingredient was detected at all [13,21,22].

In this study, we analyzed more than 400 exhibits, many of which consisted of dozens of packages of medicines, sold on the Internet or by clandestine retailers and seized in Italy by police officers from 2017 to 2019.

They had different pharmaceutical forms, as they were mainly tablets, injectable solutions, capsules, powders, and in a few cases, jelly preparations and plant extracts.

The injectable solutions were not sterile, with leaky caps that were sometimes rusted.

The products were analyzed in order to determine their compositions, and in some pilot selected cases, the correspondence with the amount of drug declared on the package.

Materials and methods

Samples

Samples were from 409 exhibits, coming from many confiscations carried out in different police operations performed by Carabinieri in the whole Italian territory. The confiscations were made at post offices or at storage warehouses of couriers for drugs coming from internet purchase orders; at home or storage facilities of suspect dealers; in clandestine laboratories; in gyms. Each individual case involved generally many packages of drugs of different classes, for example, several packages of anabolic steroids, stimulants, drugs against erectile dysfunction, hormone modulators. Each package consisted, in turn, of many tablets/capsules or various vials of liquids. Some of the packages were unlabeled.

No selection of the samples to be analyzed was made, which can, therefore, provide an overview of the general trend of counterfeit/illegal PIEDs in the Italian territory. The authorities made also 21 confiscations of peptide hormones (10 chorionic gonadotropins and 11 growth hormone packages), all "authentic" drugs from pharmaceutical companies, which were not analyzed.

Samples preparation and analysis

Many of the confiscations were constituted of multiple packages. 10% of the total number of units was analyzed in the case of multiple exhibits (packs of tablets, capsules, ampoules). Sample preparation varied according to the pharmaceutical form.

For qualitative identification, mainly in the unavailability of analytical standards, the analysis of samples and the data processing were carried out according to a previously published procedure, which was optimized for the identification of unknown samples [23].

This consisted of gas-chromatography/mass spectrometry (GC/MS) analysis and liquid chromatography-high resolution MS (LC-HRMS) analysis. This approach allowed to obtain and to study the information on the accurate mass of the unknown substance, obtaining its raw formula and its main fragments both in electron impact and in electrospray at high resolution, providing information on its molecular structure.

A quantitative determination of the active drug in the seized material was carried out only for some selected substances for which a certified analytical standard was available. Quantification was therefore performed on the exhibits containing sildenafil, ephedrine, oxandrolone, stanozolol, nandrolone decanoate, testosterone propionate, methenolone, and methandienone, by LC-HRMS, using the methods previously optimized and validated for the quantification of anabolic agents, stimulants and phosphodiesterase 5 inhibitors (PDE5I) [24,25].

Detailed information on reagents, standards, sample preparation, instrumental and analytical conditions are reported in the supplemental material.

Results

The analytical approach used allowed the identification of a wide range of substances belonging to different chemical classes in the confiscated products.

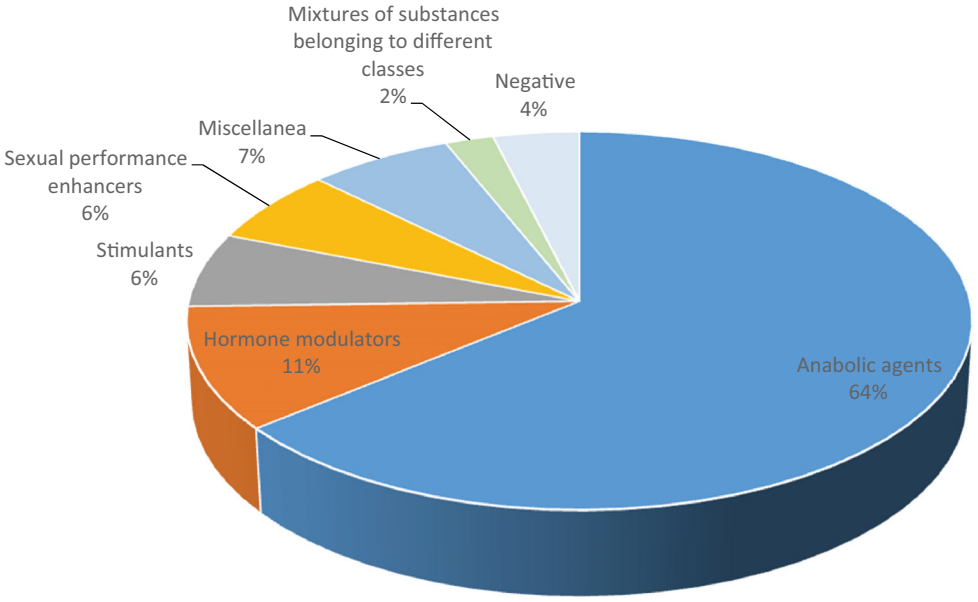

Figure 1. Pharmacological classes of substances identified in the illegal products analyzed.

Table 1. Androgen anabolic steroids identified in the products.

Substance identified	Number of samples	Mislabeling	No Label
Boldenone undecilenate	19	1	
Chlorodehydromethyltestosterone	8	1	1
Clenbuterol	5		
Drostanolone enanthate	5		
Drostanolone propionate	7	1	
Fluoxy mesterolone	2		
Mesterolone	4		
Methandienone	14	1	2
Metenolone	5	4	1
Metenolone enanthate	5	2	
Methyldrostanolone	2		
Metribolone	1		
Nandrolone decanoate	20		1
Nandrolone phenylpropionate	3	1	
Oxandrolone	14		1
Oxymetholone	6		
Stanozolol	43	3	4
Testosterone cypionate	8	1	
Testosterone decanoate	1	1	
Testosterone enanthate	17	4	3
Testosterone propionate	14	1	
Trenbolone acetate	11		
Trenbolone enanthate	7		
Trenbolone hexahydrobenzylcarbonate	2		
Mixtures	44	31	4
Mixtures of Testosterone esters	18	7	2
Mixtures of Nandrolone esters	2	1	1
Mixtures of Trenbolone esters	5	5	1
Mixtures of anabolic agents	14	13	
Mixture of anabolic agents and Other substances	5	5	

Figure 1 shows the pharmacological classes of the drugs identified and their percentages. More than half of the substances identified were AASs, whereas in other cases hormone modulators, stimulants, sexual performance enhancers, and other drugs were identified.

Table 1 summarizes the AASs detected in the samples analyzed, while Table 2 shows the substances belonging to other pharmacological classes.

No active drug was detected in sixteen of the products analyzed. The labels of these products, when present, reported the presence of testosterone cypionate, stanozolol, clenbuterol, fluoxymesterone, or a mixture of testosterone esters, and only oils for injection in a sample marketed with the name "Synthol," used to shape muscles.

In 15% of counterfeit medicines, the qualitative analysis demonstrated the presence of a substance different from the one declared on the label. 10% of them were contaminated with drugs other than those on the label. The percentages of mislabeled preparations are shown in Figure 2, divided between the different pharmacological classes.

Quantitative analysis was performed only for selected compounds, as described in the materials and methods

Table 2. Substances identified in the confiscations: hormone modulators, stimulants, sexual performance enhancers, others.

Substance identified	Number of samples	Mislabeling	No label
Hormone modulators			
Tamoxifene	11		
Clomiphene	8		
Ibutamoren (MK677)	6		
Anastrozole	4		1
Cardarine	3		
Letrozole	2		
Exemestane	3		
Raloxifene	2	1	
Ostarine	2		
Mixtures	8	5	2
Clomiphene, exemestane			
Cardarine, ostarine		1	
Dapoxetine, methandienone, rad 140		1	
Caffeine, clomiphene, exemestane, raloxifene			1
Caffeine, raloxifene			1
Ibutamoren, raloxifene, stanozolol		1	
Dapoxetine, ostarine, stanozolol		1	
Mesterolone, raloxifene, stanozolol		1	
Stimulants			
Caffeine	5	3	
Ephedrine	6		
Yohimbine	8		
Modafinil	1		
Sibutramine	2		
Mixtures	8	4	2
Caffeine, ephedrine (3 products)		2	
Caffeine, ephedrine, yohimbine			
Caffeine, ephedrine, sildenafil		1	
Caffeine, ephedrine, yohimbine, sildenafil		1	
Caffeine, clomiphene, exemestane, raloxifene			1
Caffeine, raloxifene			1
Sexual performance enhancers			
Sildenafil	15		2
Tadalafil	6		
Dapoxetine	2		
Homosildenafil	1		1
Mixtures	7	6	1
Sildenafil, thiosildenafil		1	
Caffeine, ephedrine, sildenafil		1	
Caffeine, ephedrine, yohimbine, sildenafil		1	
Dapoxetine, sildenafil			1
Dapoxetine, methandienone, stanozolol		1	
Dapoxetine, ostarine, stanozolol		1	
Dapoxetine, methandienone, RAD140 (SARM)		1	
Other substances			
Cannabis extracts	6		6
Melanotan II	4		2
Bremelanotide	4		4
Liothyronine	4		
Salbutamol	2		
Clenbuterol	1		
Thyroxine	1		
Cathechin	1		
Acetylsalicyclic acid	1		
Benzylsalicilate	1		
Lidocaine	1		1
Metformine	1		
Sulbutiamine	1		

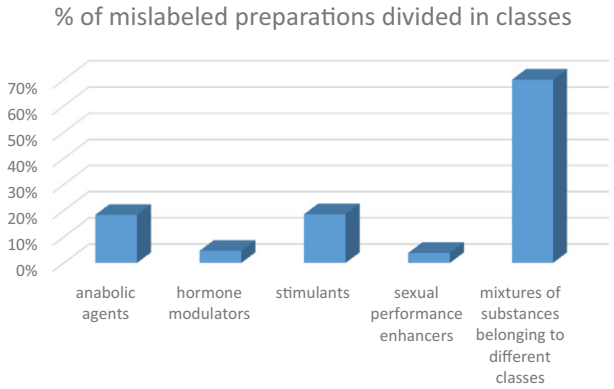

Figure 2. Mislabeled preparations among the different pharmacological classes.

section. The quantitative determinations showed discrepancies between the declared and the actual amount present in the preparation. For androgen anabolic steroids AASs, the quantitative content of the single compound was always lower than the one stated on the label. Nevertheless, these preparations generally consisted of mixtures of various AASs esters. Testosterone propionate concentration ranged from 20 to 100 mg/mL, testosterone decanoate from 10 to 100 mg/mL, testosterone enanthate from 10 to120 mg/mL. Stanozolol was detected in tablets at 1–10 mg, and in injectable depot preparation at 10–100 mg/mL. Methandienone was detected at 3–5 mg in tablets and methenolone at 1–5 mg. Sildenafil concentrations in the tablets ranged between 70 and 120 mg per table, while it was always reported as 100 mg preparations. Ephedrine amount ranged from 22 to 50 mg per capsule/tablet. In some of them its presence was not declared, other products reported its dosage at 25 mg.

Finally, the analyses of multiple samples from the same batch, or even from the same package, showed inconsistent quantitative results.

Discussion

The results obtained by the analysis of confiscated material demonstrated the threat for the public health of the clandestine market of PIEDs.

The threats are related to:

a. The intrinsic toxicity of a drug used out of its approved indication and without a pathological reason. The high number of confiscations is indicative of the spread of the phenomenon.
b. The mislabeling of the fake medicines, meaning that the users do not know exactly what they are taking and in which amount.
c. The poor-quality standard of fake product preparation, with no guarantee of GMP, with the inherent risks of the presence of toxic chemicals in the medicines, of cross-contamination with other drugs, and microbial contamination.

Indeed, the majority of the packages were provided with little or no information about their content, batch number, or expiry date. Not to mention that 11% of the products had no label reporting quali-quantitative information.

The analytical results demonstrated many qualitative and quantitative discrepancies with what was reported on the labels, in agreement with other authors' findings [13,20–22].

The compound declared was in some cases replaced with a similar one, such as a different steroid ester, for example, testosterone cypionate instead of testosterone enanthate, or a substance belonging to the same class, for example, methandienone replacing oxandrolone. In other samples, the label was completely misleading. This was the case, for example, of some capsules in which the presence of aspirin was declared along with the stimulant drugs ephedrine and caffeine, where acetylsalicylic acid was replaced with sildenafil; another preparation claiming to contain only natural herbal extracts, contained instead sildenafil and thiosildenafil. In other cases, the label on the tablets reported that they contained oxandrolone, while more than 50% of them, in the same package, contained methenolone enanthate. Some preparations consisted of a mixture of active ingredients, from two up to thirteen compounds identified, instead of the single one declared; these products appeared to be contaminated with traces of other drugs.

Lastly, the quantitative determinations also showed discrepancies between the declared and the actual amount present in the preparation. In addition, the analyses of multiple samples from the same batch, despite the same label information, showed different quantitative results.

These findings may be due to various factors:

- The poor quality of the production steps, with a badly mixing of the ingredients, which leads to a lack of homogeneity of the product. This can give an account of the different quali-quantitative results even in the same batch.
- No decontamination of the production line, which leads to the presence of many contaminating substances.
- In general, a lack of attention paid during the production/packaging/labeling phases, in which the medicines can be completely substituted with others. This is evident in those cases where there is not the label on the packaging.

Moreover, there is no guarantee of sterility during the production/packaging phases. This is of particular concern considering the fact that many of them are injectable solutions.

All those findings confirm the threat to health due to the use of these products.

Firstly, because the majority of these substances have their own toxicity and adverse effects [7–11,26–29], especially when taken without a therapeutic indication, no medical supervision or when the results of the clinical trials did not allow their release on the market. This is the case of Melanotan II, an oligopeptide used to enhance melanin production, the use of which has been associated with the onset of melanoma [27,28]. As a further example, the anorectic compound sibutramine, contained in two confiscations, was withdrawn from the EU market in 2010 for some deaths related to its use. In the case of AASs, most of the time the actual quantitative content of a single steroid was lower than stated, but the preparations were made of mixtures of different esters or different steroids (e.g., in the case of testosterone or trenbolone). This can lead to the intake of high amounts of AASs, with several possible health risks [7–11,29], as they mutually boost their activity.

Moreover, additional risks are related to the use of multiple substances, also due to the unpredictable qualitative content of uncontrolled preparations, with possible drug-drug interactions. For example, in some preparations without labels, ephedrine was present in concentrations at the highest therapeutic range. This can cause cardiac diseases [29], especially if this substance is unknowingly mixed with other stimulant drugs.

In addition, the quantitative deviation from the expected content, the large variation among apparently similar preparations, and the absence of any active substance in some of them, may cause the user to compensate by consuming greater quantities of the product, with additional risks of side effects and overdosage.

The types of substances identified were evenly distributed over 3 years of the study, and no particular trend or differences between the confiscated products over the years was found.

A limitation of the study can be that it involved samples confiscated in a single national territory. Anyway, the majority of samples were imported from abroad, and can, therefore, be considered as a snapshot of the international situation. Another limitation can be that only qualitative analyses on the majority of samples were performed, due to the lack of the analytical standards for all the substances. Nevertheless, the scope of the study was to have an overview of the typologies of illicit PIEDs that circulate in the EU territory. Quantitative analyses were performed on some selected drugs, as a pilot study to assess the accuracy of the clandestine production. As a result, this study demonstrated a low level of accuracy, including quantitative composition, even within the same batch of preparation.

Conclusions

The analysis of over 400 PIEDs products from the illicit market demonstrated the high risk to public health of the distribution/purchase/use of these preparations. Many of them were mislabeled, having a different composition than the one declared, or were not labeled at all. They were not produced following GMP, with subsequent risks related to the possible presence of microbial contamination, and did not undergo regulatory and pharmacovigilance rules. Even more concerning, they are used in the absence of a therapeutic indication, medical supervision, and are easily accessible to young people.

Supplementary data

A complete description of the materials and methods used is available as Supplementary data.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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