Opinion Article

Anabolic Androgenic Steroids from underground market: drug quality and implications for research

Abstract:

Currently, a large portion of users of anabolic androgenic steroids purchase these drugs from non-legal sources, the so-called underground market. Seizure studies and analysis of these products show adulterations from 18 to 86%, plus potential serious contamination by heavy metals or microorganisms. Inadvertent abuse of underground market products can put users' health at additional risk, leading to more serious side effects or unknown adverse events. The poor quality of these products may also jeopardize proper verification of causality in case report studies or case series.

Article:

As we have seen in the history of anabolic androgenic steroids (AAS), there has been an increase in government enforcement laws, and the Controlled Substances Act III, voted by the US Congress in 1990, caused enormous bureaucratic difficulties for legal companies to produce and commercialize their original products [1]. Such difficulties consequently also contributed to the large and rapid growth of the underground market, and it is currently estimated that 50% of AAS sales in the US are clandestine (illicit) [1,2].

According to Parkinson AB. et al. (2006), 70.8% of 500 AAS users interviewed in the survey, obtained drugs from internet dealers, 24.2% from friends or gym dealers, 18.8% by mail order in foreign countries, 11.6% prescribed by physicians and 8.6% through internet legal and illegal pharmacies [3].

In this regard, brazilian researchers [4] from the University of Brasília and the Criminalistics Institute of the Federal Police published a short communication article about AAS counterfeit incidence in Brazil. The study presented data on laboratory assessment of AAS seized by the Federal Police from 2006 to 2011 [4].

Progressively, after 5 years of study, it was found that AAS seizure increased, as did the proportion of seized AAS that were chemically analyzed. Thus, in 2011 (last year of seizure), 1,468 samples were seized, of which 95% (1396) were analyzed and, as a result, 38.8% (570) were adulterated. In average of the 5 years (2006 to 2011), the authors stated that 31.7% of medicines seized and analyzed were somehow adulterated, not being exactly compatible with the information declared on label [4].

Four years later, the same author published a similar study [5] about analysis of drugs and supplements seized between 2011 and 2016, and followed the qualitative assessment guidelines of ANVISA (Brazilian National Health Regulatory Agency) and MAPA (Brazilian Ministry of Agriculture) [4,5].

Then, 328 samples were seized (87 in tablets, 83 aqueous suspensions and 158 oral solutions) which, according to the label, came from 17 different countries (in order of frequency: Paraguay, 154; Brazil, 30; USA, 24; Argentina, 22; Australia, 19; Spain: 13; unknown origin, 21) [5].

As a result, the authors observed a 42% overall average rate of adulteration/counterfeiting (understood as not being the exact one stated on the label, such as other AAS associated in the composition, other AAS that have not been declared, amount less than 50%, without legal registration, non-existent by ANVISA, counterfeit/inadequate packaging) [5].

Of the analyzed AAS seizures, oily solutions (injectable) had the highest adulteration rates (65.6%; 103 of 158 samples); of these, 65 did not contain any AAS in the composition, 22 contained AAS other than those stated, 9 were underdosed, 6 did not contain any of the stated AAS, and 1 contained other AAS in addition to what had been described by the label [5].

Furthermore, 28.7% of the oral tablets (25 of 87 samples) were counterfeit (13 were non-existent by ANVISA, 5 contained an AAS different from what had been declared, 4 contained no AAS, 2 contained doses lower than stated, and 1 contained other AAS in addition to what was stated) [5].

Aqueous suspensions had the lowest rates of adulteration/counterfeiting (injectable), with 10 of 83 samples (12.0%; where 6 were underdosed, 3 did not contain AAS, and 1 contained an AAS different from that stated on the label) [5].

When adding adulterated/counterfeit products with substandard products (i.e., products with the same quality, composition and packaging as the originals, but with a significant change in concentrations), the average overall rate of products considered "inadequate" increased to 53%. In these quantitative adulterations, 18 products that presented doses outside of those stated on the label (above or below 20% difference) were assessed as overdosed in 170% for orals, in 142% for aqueous suspensions and in 221% for oily solutions [5]

In different European countries, studies [6-12] already published over the last 15 years including laboratory assessment of seized underground market AAS, identified very high adulteration rates (**Table 1**):

Table 1- Adulteration/counterfeiting rate after laboratory analysis of seized underground market products (AAS)

Country	Year	Author	Counterfeiting rates
Germany	1997	Musshoff F. *et al. [6]*	35.7%
Germany	2000	Ritsch M. *et al. [7]*	37.5%
Germany	2008	Thevis M. *et al. [8]*	35.4%
Germany	2014	Krug O. *et al. [9]*	57.0%
Norway	2015	Hullstein IR. *et al. [10]*	18.0%
Belgium	2012	Coopman. *et al. [11]*	33.8%
Italy	2012	Pellegrini M. *et al. [12]*	86.6%

To better exemplify these data, in the study by Thevis M (2008) [8] on analyzes of underground market seized AAS, 25.7% had some type of adulteration, and so, out of 4 samples labeled "trenbolone" (an AAS highly sought after by professional and amateur bodybuilders, and which has no clinical studies performed on humans), none of the samples (SAM) contained only trenbolone:

SAM 67 (Trenabol):	SAM 68 (Trenabol depot):

- Trenbolone + T propionate + T phenylpropionate + Boldenone undecylate	- Trenbolone + T propionate + T phenylpropionate + Boldenone undecylate
SAM 69 (Tri-Trenabol 150): + Trenbolone enanthate + T propionate + T phenylpropionate + T enanthate	**SAM 70 (Trenabol 200):** + Trenbolone enanthate + T propionate + T phenylpropionate + T enanthate

(-) = did not contain; (+) = in addition to what was labeled just as trenbolone.

Still, in this same study, of the 5 samples labeled as "nandrolone", 100% also had some type of adulteration:

SAM 11:	**SAM 19:**	**SAM 20:**	**SAM 38:**	**SAM 62:**
- Nandrolone + T enanthate	- Nandrolone + T enanthate	- Nandrolone + T enanthate + T cypionate	- Nandrolone + T enanthate	+ Nandrolone + T propionate

(-) = did not contain; (+) = in addition to what was labeled just as nandrolone.

Llewellyn W [13], "Anabolics" book author (a large compilation of empiric and scientific information about AAS, currently in its 11th edition), published in 2007, carried out a laboratory analysis, at a licensed and certified company, of 14 AAS purchased from the underground market from different clandestine laboratories. Thus, four laboratory tests (qualitative and quantitative) were carried out with these drugs: 1) Contamination by heavy metals (arsenic, lead, tin); 2) Quantitative dosage assessment (labels versus assessed in the test); 3) Steroidal contaminants (steroidal components other than AAS, translating low product quality); 4) Oily vehicle assessment (if any flavoring was identified, it would be a strong indication that it was a cooking oil and not a pharmacological product).

As a result of the laboratory assessments carried out, the author observed that: 1) 21% showed contamination by heavy metals; 2) 64% had AAS concentrations above or below 20% of what was declared on the label; 3) 57% failed the steroid component purity test (other impurities, irregularities in the component used); 4) 14% used components (possibly cooking oil) other than pharmaceutical oil vehicles.

Thus, Llewellyn W. [13] concluded that, in general, underground market AAS, according to the analysis performed, would not be suitable substitutes for products from the pharmaceutical industry (heavy metal contamination, concentration change, low quality raw material made with non-pharmaceutical vehicles). He also added in his conclusions that if another purchase were made from different underground suppliers and laboratories, possibly the results that were observed in this analysis would also be different, due to product quality inconsistency.

As seen from described data, adulteration rates, whether only from incomplete labeling information, or reaching extremes of contamination by heavy metals and microorganisms, are quite high, and cannot be predicted or guaranteed solely by the word of a seller or the purposes of a buyer of such products for use [3-5,13].

However, due to high demand and profitability, lack of information and adequate guidance, many consumers are in this market (seeking better prices, greater product concentration, diversity of drugs and convenience to buy), and most are not aware of the health risks that an adulterated or contaminated product can cause [3-5,13-15].

In this market, regarding the similar names given, numerous drugs produced, in general, are not found in the licit market. However, this production is always carried out clandestinely (i.e., not licensed production sites, not regulated and/or inspected by health agencies), and is mostly sold to athletes, bodybuilders and recreational practitioners by close contacts or through social networks [13-15]

In the manufacturing process of underground market AAS, raw materials from countries with low market regulation (inspection) are generally used (common in Southeast Asia), in particular with regard to the quality and production processes of pharmacological components. With drugs and raw materials, dealers and couriers ("mules") enter the borders of higher regulation countries (e.g., the USA and Europe) using different routes (cars, buses, trucks, shipping containers), and deliver the material for manufacturing the final products to sales units (glasses, blisters, ampoules, capsules), generally carried out in small laboratories (not to attract attention) and with homemade machinery [13-15].

Differently, while the underground market in general aims at "profit", the traditional pharmaceutical industry and western medicine have always aimed at the constancy of quality aspects of drugs to be used in human beings for therapeutic purposes, such as product safety. With this objective, and aligned with the medical thinking of "Primum non nocere" (first, do no harm), drugs must be used to treat diseases and not to cause harm, which could potentially occur due to product contamination by microorganisms, heavy metals, non-pharmaceutical vehicles, quantity adulteration, etc, [13-15].

In this way, drugs for human use are only produced under government approval and by certified companies, which are highly regulated and routinely inspected. Furthermore, the raw materials used in production come only from suppliers who are also certified and regularly inspected [13-15].

The environment (production site) is always under strict contamination control (personal protection, positive air flow), and it is mandatory that the product to be produced is sterilized. The final product, i.e., the drug that will be directed to consumers, sold licitly in controlled medicine pharmacies and distributors, contains only what is described on their label qualitatively and quantitatively, with potentially very small margins of error (close to zero) [13-15].

In the underground market, we observe the opposite of what happens in the pharmaceutical industry, i.e., raw materials originated from non-certified sources: drugs are produced at home, without sterility, with the handling of products by untrained personnel, exponentially increasing the chances of quantitative and qualitative irregularities as well as contamination by heavy metals or microorganisms [13-15].

If we could compare underground market drugs with those that are produced at a high cost and high technology by the pharmaceutical industry, it would be very clear that most of these products would not be suitable for human consumption [13-15].

The inappropriate composition of underground market AAS increases the discussion about what exactly we are seeing in scientific studies (in particular case reports, cross-sectional studies or longitudinal user follow-up studies) that report harm or adverse effects of AAS use [8, 16,17]

Some authors [16] have long highlighted the extreme relevance of the topic, however, interestingly, most studies that have been published previously (especially case reports and case series, users cohort studies, or case-control studies of health outcomes) often does not even mention the users source of drug acquisition; and this, as we have seen, could mask the results of adverse effects that were seen, given the high chance that overdoses and/or toxic contaminations are also potential causal agents of the observed health outcome.

To conclude, two aspects are extremely relevant, the first is the need for physicians attention to the poor quality of these products, which can put the users health at risk by leading to more side effects or unknown adverse events. The second is the adequate detecting impediment of causality (adverse health outcomes) in several studies already published, specially case reports, which did not take into account the use of these poor quality adulterated products.

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