INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Fake anabolic androgenic steroids on the black market – Study protocol for a systematic review and meta-analysis on qualitative and quantitative analytical results found within the published literature

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Review question / Objective: **With this systematic literature review we aim to assess published data on the quality and quantity of anabolic androgenic steroids (AAS) found on the black market to further determine the proportion of fake drugs. To our knowledge this is the first systematic literature review analyzing the quality and quantity of blackmarked anabolic steroids within the published literature.**
Condition being studied: **AAS are synthetic, i.e. human-made, variations of the male sex hormone testosterone that are widely abused by athletes for their anabolic effect on muscles, thus are a convenient and easy method to improve body image and sport performance goals. Fake AAS, commonly acquired from the black market, pose a significant risk to individual and public health.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 November 2021 and was last updated on 15 December 2021 (registration number INPLASY2021110042).

INTRODUCTION

Review question / Objective: **With this systematic literature review we aim to assess published data on the quality and quantity of anabolic androgenic steroids (AAS) found on the black market to further determine the proportion of fake drugs. To our knowledge this is the first systematic literature review analyzing the quality and quantity of blackmarked anabolic steroids within the published literature.**

Rationale: **The effect of supraphysiologic doses of AAS on the muscle has been widely described and recognized in**

literature for decades (Bhasin et al. 1996). AAS belong to the broader group of image and performance enhancing drugs (IPEDs) and are widely abused to improve body image and sport performance goals (Mullen et al. 2020). Global lifetime prevalence of AAS use is estimated to be as high as 3.3% within the general population (Sagoe et al. 2014). Due to lack of reporting, precise prevalence and demographic information on the use of these substances is difficult to estimate (Bates 2016). The most common source of acquisition is the internet, which provides the perfect foundation for a counterfeit drug market (McBride, Carson and Coward 2018, Rahnema et al. 2014, Mullen et al. 2020). Isles and colleagues describe the term counterfeit medicine as closely associated and legally defined within intellectual property legislation and concentrates on trademark protection, whereas the term fake medicine best serves to communicate with the public to raise awareness on this topic (Isles et al. 2017). Those black-market substances may contain no active ingredient (inert), a wrong active ingredient (substituted), not all active ingredients or more active ingredients than are labelled (adulterated), or the labelled active ingredient(s) in another amount than labelled (substandard). Counterfeit and substandard products can potentially lead to negative health outcomes and are considered an individual and public health threat (Nieschlag and Vorona 2015, Solimini et al. 2017, Christou et al. 2017).

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METHODS

Search strategy: We will conduct a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) statement. We will search Pubmed/MEDLINE and Google Scholar for studies published before October 2021 that analyzed the quality and quantity of AAS to determine the proportions of substandard and counterfeit substances found on the black market. We will use the following search strategy with Boolean operators: ((fake) OR (counterfeit)) AND (anabolic steroids). For Google Scholar the same search terms are used without Boolean operators. Furthermore, we will continue to pursue relevant references of references and track electronic citations related to the topic manually to identify sources in obscure locations, also called snow-ball method (Greenhalgh and Peacock 2005).

Participant or population: Participants and population not applicable for this systematic literature review. Test subjects are anabolic steroids from the black market. Articles that analyze AAS can include substances that were acquired from different sources, such as directly from the black market (e.g. bought online), acquired from gym owners or athletes, or substances seized and analyzed by authorities.

Intervention: Not applicable for this systematic literature review.

Comparator: Not applicable for this systematic literature review.

Study designs to be included: One author (RM) will conduct the initial database search, extract the initial articles, and remove double records. A second author (PB) will independently crosscheck the initial search. Two reviewers (RM and PB) will screen each study independently by title and abstract based on the predefined eligibility criteria. Full texts of eligible studies will be reviewed by two reviewers (RM and LF) for data extraction. Disagreements in search results and study eligibility are resolved by consensus between the two reviewers. One author (AC) will assess the analytical methods used within eligible articles.

Eligibility criteria: Inclusion criteria are: (i) peer-reviewed original articles with full-text available, (ii) no restriction regarding country and date, (iii) articles in English language or with English abstracts, (iv) articles that present proportions of original and/or counterfeit and/or substandard drugs. We will exclude: (i) abstract-only papers as preceding papers, conferences, editorials, and author response theses and books, (ii) articles without full text available, (iii) articles where the exact composition of analyzed IPEDs is not provided by the author, (iv) to increase the homogeneity, article with mixed samples (e.g., if the analysis includes different classes of IPED) in which data on AAS are <25% of the analyzed substances.

Information sources: The following electronic databases will be included in the search: PubMed and Google Scholar. We will include studies up to October 2021.

Main outcome(s): The proportion of substandard and counterfeit AAS found in qualitative and quantitative analyzed samples from the black market. Definitions are available in section "other relevant information".

Additional outcome(s): - (i) The proportion of original AAS found in qualitative and quantitative analyzed samples from the black market (ii) The proportion of adulterated, substituted, and inert AAS for counterfeit substances. (iii) The proportion of over- or under-concentrated AAS for substandard substances. (iv) Assessment of the different analytical methods used to determine the quality and quantity of blackmarket AAS. Definitions are available in section "other relevant information".

Data management: Extracted information will include first author's name, year of publication, country, sample collection period, analysis methods, sample information, analyzed classes of compounds and sample size, proportion of original, substandard, and counterfeit products and other remarks. Disagreements in data extraction are resolved by consensus between the two reviewers (RM and LF). Two team members (RM and LF) will review all data to ensure accuracy before analysis. Classification of prohibited substances are done according to the world anti-doping agency (WADA) prohibited list (Updated version as of 01 January 2021). We will further classify compounds according to the suggested classification of Neves (Neves and Caldas 2017), and Weber and colleagues (Weber et al. 2017) with adaptions into "original", "substandard" and "counterfeit". A subclassification of "counterfeit" substances into "adulterated", "substituted" and "inert", and "substandard" substances into "over- or under-concentrated" will be done. Definitions are available in section "other relevant information".

Quality assessment / Risk of bias analysis: Study quality will assessed by two reviewers (RM and PB) independently. Quality assessment for bias of analytical studies will be conducted using the ToxRtool (Toxicological dataReliability AssessmentTool) for in vitro studies (Schneider et al. 2009). Disagreements in quality assessment are resolved by consensus between the two reviewers. The ToxRTool was developed in Microsoft Excel® program and consists of two different parts, one for in vivo and one for in vitro data (Schneider et al. 2009). For this systematic literature review only the in vitro section is applicable. The tool comprises a list of 18 criteria with a maximum of 18 points for in vitro studies based on five groups of main criteria: i) test substance identification, ii) test system characterization, iii) study design description, iv) study results documentation, and v) plausibility of study design and results. Each of the 18 criteria must be assigned either a '1' (one point), i.e. 'criterion met', or a '0' (no point), i.e. 'criterion not met'. The total points assigned to a given study leads to a proposal of reliability category 1 to 3; 1) reliable without restrictions (15-18 points), 2) reliable with restrictions (11-14 points) or 3) not reliable (< 11 points) (Schneider et al. 2009). For this study, category 1 will be included in the meta-analysis without

discussion, category 2 will be discussed by the two reviewers (RM and PB) and inclusion for the meta-analysis will be resolved by consensus, category 3 will not be included in the meta-analysis but can be used as supportive information. Publication bias will be examined by funnel plots and Egger's test (Almeida et al. 2017)

Strategy of data synthesis: The pooled prevalence of counterfeit AAS and corresponding 95% confidence interval (CI) will be calculated using a random-effect model, using the procedure for meta-analysis of single proportions "metaprop" from the library "meta", provided in R software for statistical computing. The heterogeneity is evaluated by I2 statistic (Huedo-Medina et al. 2006). "Higgins and Thompson (2002) proposed a tentative classification of I2 values with the purpose of helping to interpret its magnitude. Thus, percentages of around 25% (I2 = 25), 50% (I2 = 50), and 75% (I2 = 75) would mean low, medium, and high heterogeneity, respectively" (Higgins et al. 2003, Higgins and Thompson 2002).

Subgroup analysis: Subgroups will be performed based on geographical regions.

Sensitivity analysis: Sensitivity analysis will be conducted to test the consistency of primary results by removing each study one by one.

Language: Articles in English language or with English abstracts are considered for this systematic review.

Country(ies) involved: This systematic review is carried out in Switzerland.

Other relevant information: Definitions Originals • Formulation detected fully matches the one declared on the label (Qualitative) • Levels of active pharmaceutical ingredients (AI) detected are between the defined range of the declared formulation defined by the individual article (Quantitative) Substandard • Formulation detected fully matches the one declared (Qualitative) • Levels of active pharmaceutical ingredients (AI) detected are not between the defined range of the declared formulation defined by the individual article (Quantitative) • Subclassification (Quantitative): - Over-concentrated: AI detected above defined range - Under-concentrated: AI detected below defined range Counterfeit • Formulations detected does not match the label (Qualitative) • Subclassification (Qualitative): - Inert: no AI present in the sample - Substituted: different AI than labelled present in the sample - Adulterated: not all or more AI than the labelled AI present in the sample.

Keywords: Anabolic androgenic steroids; AAS; fake; counterfeit; original; substandard; quality; quantity; black market; systematic review.

Dissemination plans: Dissemination will occur through publication of results in a peer-reviewed journal. Additional dissemination will occur through presentations at conferences regionally and nationally/internationally. Furthermore, this project will serve as a foundation for future prevention and harm reduction services within this field and will be disseminated on the respective web site when implemented.

Contributions of each author:

Author 1 - Raphael Magnolini - RM conceived the original idea. RM planned the literature search, data extraction and quality assessment. RM created the manuscript draft. RM contributed to refinement of the manuscript.
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Author 2 - Luis Falcato - LF provided methodological and statistical expertise. LF planned the statistical analysis. LF contributed to refinement of the manuscript.
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