

ReviewForm3

JournalName:	<a href="#">JournalofAdvancesinMedicineandMedicalResearch</a>
ManuscriptNumber:	Ms_JAMMR_126852
TitleoftheManuscript:	Thefourdifferentanabolicscenarios:apotentialmandatorydistinctionforresearchandclinicalpractice
TypeoftheArticle	OpinionArticle

ReviewForm3

PART1:ReviewComments

CompulsoryREVISIONcomments	Reviewer’scomment	Author’s Feedback (Please correct the manuscript and highlight that part inthemanuscript.Itismandatorythatauthorsshouldwritehis/herfeedback here)
Please write a few sentences regarding the importance ofthismanuscriptforthescientificcommunity.Whyd o youlike(ordislike)thismanuscript? Aminimumof3-4 sentences may be required for this part.	<p>Themanuscriptconsistsoftotal10pages,includingthelistoftotal24literaturereferences.TheAuthors in theirnarrativereviewcommentaryoutline4possiblescenariosoftestosteroneand/orandrogen substances administration to humans, outlining their pros and cons and remarking ethical and legal issues that arise in each scenario. As such, the article is likely to raise interest in the Readers and adds original input into thestatusofknowledgeintherespectivediscipline. However,theAuthorsopenthethisfarunquestionably closedgatetodiscussionconcerningmakingitacceptableusingtestosteroneand/orandrogensubst ancesin casesthathavenostrict medicalindication,likeaestheticsor performedoping - thatthisfararerather univocally banned by the medical community. In contrast to the primum non nocere stand represented by the medical community, the Authors point at - questionable - benefits that may have resulted from testosterone and/or androgen substances treatments in healthy individuals, often applied in doses much higher than registered to be used in medicine. The Authors divide this phenomenon into “controlled” use of certain substances of known quality and “uncontrolled” use of unknown substances of questionable quality. In fact, as far as the legal system is concerned, there is in fact no difference between these scenarios. It is debatable whether it is ethically allowed to use and refer to the results of the experimental studies that were performed without medical need exposing the healthy participants to the possible health risks of overdosing the substances, even though the Authors argue that if controlled doses of controlled kindofsubstances are administered, suchnegativeeffects,especiallyoflastingnature, werenotdetected. I would suggest the Authors to stress more clearly in the text that currently in most countries the use of testosterone and/or androgen substances purely for aesthetic effect or performance improvement in otherwise healthy individuals (without medical indications) is associated with serious ethical and legal risks,inordertowarnmedicalprofessionalsnottoengageinsuchdubiousactivities.</p>	<p>Dear Reviewer,</p> <p>First, I would like to thank you for the time invested in reviewing this manuscript and for your valuable insights.</p> <p>However, I believe some clarifications are essential to maintain a focus on the data after your review.</p> <p>The article, as well understood in your review (“the article is likely to raise interest in the Readers and adds original input into the status of knowledge in the respective discipline”), has as its sole purpose the academic discussion of this topic, considering it is being conducted within a scientific journal.</p> <p>At no point did we “suggest a prescription” or “authorize prescriptions” for any purposes other than medical (e.g., aesthetics and performance enhancement). Prescription limitations are dictated by guidelines and council regulations, which is separate from an academic discussion on the topic.</p> <p>Additionally, since science is a self-constructing process, history shows us that “unquestionably closed doors” have often been reopened, leading to significant shifts in medical practice. Many treatments once considered highly beneficial revealed adverse effects over time, just as treatments initially ridiculed later became accepted practices within the “medical community.”</p> <p>Moreover, the term “medical community” does not constitute a study or scientific evidence applicable to an academic discussion; it is merely an authority argument.</p> <p>Many “positions” and “guidelines” are sometimes simply texts with scientific references, far from being thorough, systematic reviews using large databases to filter and summarize information, without “setting directives” (as the Cochrane Collaboration does, presenting evidence quality for decision-making). The medical professional must use this information (not just a stance) in collaboration with the patient.</p> <p>Medicine should be “guided by evidence” rather than “restricted” by “positions and guidelines from the medical community,” which has often proven to be mistaken historically. Without at least an academic space to propose new ideas, question established notions, and foster critical thinking—particularly in topics perceived as “unquestionably closed”—neither science nor medicine can evolve.</p> <p>The information on testosterone and anabolic steroid use in healthy young people, erroneously labeled as “questionable,” is derived from randomized controlled trials published in highly regarded journals by researchers with extensive publications in the field. The information has been drawn from findings within these studies, and in an academic</p>

		<p>discussion, such sources should suffice.</p> <p>To “refute” or qualify this information as “questionable” from an academic perspective, additional randomized controlled studies should be conducted to document risks and potential adverse effects. This would then allow well-grounded arguments to be included in the text.</p> <p>Most “severe adverse effects” cited in literature reviews come from case reports, case series, cross-sectional, and cohort studies without controls. From an evidence-based medicine standpoint, these types of studies are limited in establishing causality.</p> <p>There is, therefore, a clear “gap” in the literature. High-quality studies in controlled environments with moderate supra-physiological doses over the short to medium term did not find severe adverse effects, while other studies with questionable methodological quality suggest serious side effects. However, the latter often reflect different conditions—unregulated substances, mixed substance use, lack of systematic follow-up—different from what has been studied in controlled trials.</p> <p>Certainly, there are critiques—like any scientific evidence—regarding the duration (up to six months), isolated use (not combined in large polypharmacy), moderate doses (up to six times the replacement dose), etc. But again, this information is derived from multiple randomized controlled trials, which makes it a discussion of information rather than a “recommendation for use.”</p> <p>If studied without harm in a randomized controlled trial and not refuted (or only questioned in a different scenario, and by low-quality evidence), I believe that the traditional medical principle of “primum non nocere” has been respected. At no point was it stated that “there is no risk,” only that “no serious adverse effects were detected,” which are distinctly different propositions.</p> <p>Based on evidence-based medicine principles of internal and external validity, and high-quality evidence offering a closer approach to truth, this concept can be cautiously applied to similar scenarios. This has been the practice over time. As we know, less than 15% of current cardiology evidence comes from “Grade 1A” sources, as previously published multiple times in respected journals, including JAMA and BMJ (see references below). Guidelines and positions not based on adequately systematized information reviews can be questionable and, as noted by various authors, even erroneous.</p> <p>DOI: 10.1136/bmj-2021-066045</p> <p>DOI: 10.1136/bmj.n2833</p> <p>DOI: 10.1177/2047487319885197</p> <p>DOI:10.1001/jama.2019.1122</p> <p>The requested “need” for additional emphasis on the fact that prescription for non-therapeutic purposes is not recommended by medical entities and carries ethical and legal concerns does not seem clear. This is already stated in the abstract: “However, such uses remain controversial and are not widely endorsed by medical organizations due to ethical and safety concerns.” Furthermore, in the “third scenario,” we</p>
--	--	---

ReviewForm3

		<p>clearly mention: “Many professional societies and medical councils, however, do not recommend non-therapeutic use (for aesthetics or performance) due to a ‘lack of evidence of safety and efficacy...)</p> <p>Personally, and thus stepping out of the academic discussion, I agree with what appears to be a personal position emphasizing the need for caution, highlighting potential risks, misuse, and lack of long-term evidence. I also believe that other methods of enhancing performance, such as physical training, proper nutrition, supplementation, sleep, and stress management, carry far less risk.</p> <p>Regarding the 1976 reference, Prof. Dr. Charles Kochakian, often considered the “modern father” of anabolic steroids (and with several publications in PubMed to his name), authored a classic book on this subject, containing numerous descriptions of clinical studies for therapeutic purposes, which has even been published in other languages without translation, such as German and Russian. Most anabolic steroid studies were published between 1960-1990; hence, in this field, I believe it is more beneficial to focus on study methodology than publication date. Much of our information on therapeutic use (“authorized” by “medical community”) dates from this period, and for this community, it is considered valid, regarding the date of publication.</p> <p>Note: The text has been updated, with the term PEDs (performance-enhancing drugs) highlighted in yellow for clarity.</p> <p>Note2: Title suggested accepted <b>“Possible scenarios of testosterone and anabolic androgenic steroids use in and outside medicine”</b></p> <p>In conclusion, the manuscript aims solely to promote academic discussion on a topic often regarded as taboo or forbidden, and not, as suggested, to provide any “recommendation for supraphysiological use.”</p> <p>I hope that we may at least begin to open, within an academic discussion, doors that have thus far remained unquestionably closed</p> <p>Thank you again for your time in reviewing the manuscript and reading my responses to your comments.</p> <p>Best Regards, LUCAS</p>
Is the title of the article suitable? (If not please suggest an alternative title)	No, title is not clear enough - a title like “Possible scenarios of testosterone and anabolic androgenic steroids use in and outside medicine” would be more appropriate.	
Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here.	Yes - the abstract mirrors the key theses presented by the Authors in the main text.	
Are subsections and structure of the manuscript appropriate?	Yes - the structure of the manuscript is logical.	

ReviewForm3

Please write a few sentences regarding the scientific correctness of this manuscript. Why do you think that this manuscript is scientifically robust and technically sound? A minimum of 3-4 sentences may be required for this part.	The line of argumentation presented by the Authors is clear enough. It is easy to follow as the Authors divided the text into parts referring to various scenarios they discuss. The Authors present their theses using the scientific, objective approach.	
Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.	The literature references are numerous, most of them reasonably recent. However, there are some superannuated, e.g. stemming from 1976, and it would be reasonable to find some newer ones in their place.	
Minor REVISION comments		
Is the language/English quality of the articles suitable for scholarly communications?	All abbreviations shall be explained while used for the first time in the text, e.g. PEDs. The overall quality of English language used is good, the style is objective, suitable for a scientific paper.	
Optional/General comments		

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	(If yes, Kindly please write down the ethical issues here in details)	