Letter to the Editor

Challenges in Establishing Causality in Anabolic Steroid Abuse

Dear Editor,

The misuse of AAS is well-documented to cause a wide range of adverse effects, varying from mild to severe, as demonstrated in the work of Parkinson AB and Evans NA. Their survey of 500 users revealed that only 0.8% reported no side effects [1]. Commonly reported issues include acne and increased skin oiliness, gynecomastia, mood and behavioral disturbances, sexual dysfunction, testicular atrophy, fluid retention, insomnia, localized pain at injection sites, skin striae, increased body hair, hair loss, voice deepening, clitoral hypertrophy, hypertension, and disruptions in cholesterol profiles and liver enzyme levels [1,2].

However, Goldman A. and Basaria S. [2] have argued that the more serious outcomes, particularly cardiovascular events, are primarily derived from studies with significant methodological limitations. These include reliance on case reports, case series, retrospective case-control analyses, cross-sectional research, and uncontrolled cohort studies. Fanaroff AC et al. (2020) further emphasize that without robust randomization, such evidence is insufficient to accurately evaluate the true risks and benefits of AAS use, undermining any proof-of-concept validity [3].

In addition, many confounding factors complicate the interpretation of findings in this field and should be critically addressed in academic discussions. These include the use of counterfeit or adulterated drugs sourced from underground markets (rates of adulteration can exceed 50% in some seized and chemically analyzed samples) [4], as well as the administration of excessive doses (up to 30 times the therapeutic range), long-term use spanning years, and polypharmacy involving either AAS or ancillary drugs [1]. Such combinations often heighten risks when substances like, diuretics, beta-agonists, insulin, or stimulants are involved [1,2]. Further complexities arise from variations in drug combinations, underlying mood or behavioral disorders, incomplete evaluations of clinical or laboratory histories, disregard for familial or personal health

risks, and the absence of medical supervision to guide safer practices or discontinuation, which could reduce preventable health complications [1,2,5-8].

Maybe some key questions can assist professionals and researchers in obtaining a clearer understanding of adverse health outcomes, particularly when analyzing non-randomized or uncontrolled studies. For example, in case reports, case series, case-control studies, surveys, cross-sectional analyses, or cohort studies, it is crucial to consider the patient's personal and family medical history prior to anabolic androgenic steroid (AAS) abuse [8]. Additionally, identifying the source of the substances used becomes paramount, as the quality and origin of these drugs (underdosed, overdosed, with biological contaminants, presence of heavy metals, substitution or addition of other substances) can significantly influence outcomes [4].

Another essential factor is determining whether the doses were moderate, slightly supraphysiological, or excessively abusive. It is also necessary to evaluate whether AAS or testosterone were used in isolation or combined with other legal substances, such as alcohol and tobacco, or illegal drugs, including cocaine, marijuana, methamphetamines, LSD, and ecstasy [8,9]. The duration of use, particularly the total lifetime exposure and the length of continuous supraphysiological dosing, further compounds the issue. Lastly, assessing whether health monitoring or professional supervision was in place to mitigate potential harms is vital for a more accurate evaluation of risks [6,8].

Based on logical reasoning, it is evident that prolonged, high-dose, and uninterrupted AAS abuse, often accompanied by polypharmacy involving legal and illegal substances, poses significant health risks [1,2]. Such behaviors, in the absence of medical supervision or monitoring, have been associated with severe outcomes, including fatalities [1,2]. However, while the dangers of this scenario are clear, pinpointing the specific contribution of AAS to these adverse events remains challenging. The chaotic and uncontrolled nature of such circumstances, marked by numerous confounding factors, complicates efforts to establish definitive and adequate causal relationships [1-4,8,9].

Disclaimer (Artificial intelligence)

The authors declare that generative AI was used only at the final stage of manuscript preparation (after writing) and exclusively for linguistic refinement in English Language (Name: ChatGPT; Version: GPT-4; Model: OpenAI's Large

Language Model; Source: OpenAI - https://openai.com). No original text was generated or substantively edited by the AI.

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