

Heuberger Jules A A C (Orcid ID: 0000-0001-7202-5088)

Cohen Adam F (Orcid ID: 0000-0001-7452-6222)

Dealing with doping. A plea for better science, governance and education

Jules A A C Heuberger¹, April Henning², Adam F Cohen³, Bengt Kayser⁴

¹ Centre for Human Drug Research, Leiden, The Netherlands

² Faculty of Health Sciences and Sport, University of Stirling, Scotland

³ DDCD Consulting, Oegstgeest, The Netherlands

⁴ Institute of Sports Science, University of Lausanne, Switzerland

Corresponding author: Jules Heuberger

jheuberger@chdr.nl

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A participant from the ancient Greek Olympics stepping into Tokyo's Olympic Stadium at the opening of the Games on 23 July 2021 would find the pageantry and competition familiar. Since doping-like behavior was prevalent at the time ¹, the athlete would be confused by the efforts to detect the use of substances in the body fluids of his fellow athletes. The anti-doping lab at the 2016 Summer Games in Rio de Janeiro operated on a 24-hour basis, requiring 5'500m² of space for its 30 mass spectrometry instruments and 700 staff ². Tokyo's organizers have announced an even more elaborate operation ³. Current anti-doping efforts are extensive, expensive, and complex ⁴. They not only concern the Olympic Games but competitive sport in general, also targeting non-Olympic athletes and, increasingly, amateurs ⁵.

For example, the common sense understanding of doping as intentionally cheating by enhancing performance with drugs to win belies, in part, the definition of doping offered by the World Anti-Doping Agency (WADA) (see Table 1). The Prohibited List (the List) ⁶ – a list of substances or methods athletes are not allowed to use either in-competition or at any time – covers nearly 400 substances with the ability to include almost a limitless number of substances. Many of which most non-medical experts have never heard of and do not know how or if they may enhance an athlete's performance.

This paper is aimed at specialized bio-medical professionals, but also the generalist. For the former, whether active in sport and anti-doping or not, our analysis contributes to the debate on how to proceed with anti-doping. A debate, as we will argue, that is highly needed to reform the current system. For the generalists, not necessarily directly involved in sports, they may be asked questions about or find themselves in situations involving substances that are on the List, for sports as well as for lifestyle. And there is the risk that a medical professional is unaware a patient is also an athlete and inadvertently prescribes a substance that could lead the athlete to violate an anti-doping rule (see ⁷). Medical professionals should therefore know about doping in sport and the functioning of anti-doping, but also of doping-like behavior in society in general, in order to be better equipped on how to act.

In analogy with the "war on drugs" – which has resulted in legislation forbidding or regulating psychotropic substances, categorizing them according to their alleged potential for harm, but largely driven by ideology-inspired reasoning ⁸ – we show that in sports the inclusion of substances on the List similarly lacks anchoring in scientific evidence. Anti-doping policymaking is not neutral but highly politicized. We examine the anti-doping system in terms of the underlying scientific evidence, its governance, and its social impact. While recognizing the important work realized over the last two decades by anti-doping efforts, we identify important deficiencies and intrinsic limitations, and argue there is need for more effective use of scientific evidence, greater transparency, more democracy and education, and a more inclusive and athlete-centered approach by the anti-doping movement.

Scientific evidence

The global anti-doping system stems from WADA, the global policymaking and harmonizing body for international sport. One of WADA's functions is publishing and updating the List, a process led by the Prohibited List expert group. The group's reasoning for the composition of the List is not made public but is ostensibly based on the three criteria laid out in the WADA Code (the main anti-doping policy document for global sport), of which a substance must

meet at least two to be included: 1) Potential or actual enhancement of athletic performance; 2) Potential or actual risk to athlete health; 3) Incompatibility with the “spirit of sport”⁹. The exact wording used in the official WADA documents is shown in Table 1 and is relevant in relation to some of the problems and challenges highlighted below.

The current anti-doping system is based on cutting edge science, such as state of the art testing technology that can detect ever tinier amounts of a prohibited substance or its metabolite in an athlete’s urine or blood sample. In other ways, however, the system is quite arbitrary. One key example of this is the List. The use of “potential” in criteria 1 and 2, the use of all-inclusive language elsewhere such as including non-approved substances – i.e. substances or methods in pre-clinical research or still to be discovered by science – on the List⁶, and the vague definition of the “spirit of sport” provide WADA nearly unlimited leeway in determining which substances are prohibited (see Table 1). A rigorous application of these principles to placebos concluded that even these could be added to the steadily lengthening list¹⁰.

Criterion 1: Enhancement

The current List includes many substances that are divided into classes. Table 2 gives an overview of these, as per the 2021 List, and lists example substances, the pharmacological effects deemed relevant in this context, and the alleged performance enhancing effects. Based on this overview, the treatment options for suboptimal sports performance seem extensive. This is in stark contrast to the reality of treating clinical patients, where most diseases have only a couple treatment options at best – not seldomly with limited efficacy – after years of pre-clinical and clinical research including thousands of healthy participants and patients. Indeed, a major scientific effort is required to show the clinical effects of a pharmacological agent, and still in many of these cases compounds fail to show a clinical benefit.

A recent systematic review evaluated the available high-level evidence of performance enhancement for the substance classes on the List, analogous with the required evidence for registration of disease treatments¹¹. Figure 1 shows a summary of these findings, after updating the data with recent studies^{12–15} that met the review criteria. The conclusions are: 1) for only 5 out of 18 substance classes is there evidence of some form of performance enhancing effect in randomized controlled settings with trained athletes, and for a 6th (glucocorticoids) in untrained subjects; 2) confirmed performance enhancing effects only concern muscle strength and power, sprint performance, and (shooting) accuracy for beta-blockers, and not for example endurance; and 3) the entire body of high-level evidence for performance enhancement of the substances on the List consists of twelve trials of sufficient quality and a total of 304 subjects. We conclude that there is little evidence of performance enhancement for the majority of substances and classes on the list. Such evidence is explicitly not required according to the WADA Code (WADC), which allows WADA to put almost anything on the list. The reasons for putting something on the List are not made public, but are ideally based upon systematic and careful abductive inference approaches as a surrogate for solid evidence from trials (see as an example¹⁶). However, there is reason to believe that other motives may also play a role in including substances. An example is meldonium. There is no evidence of performance improvement and no evidence of a relevant health risk in the dosage generally used by healthy physically active people^{11,17}. The inclusion of meldonium

on the List in January 2016 might thus be the reaction to the observation by WADA's monitoring program of meldonium's widespread use by athletes from Russia and other Eastern European countries, and the (warranted) suspicion of presumably endemic state-supported doping practices in Russia.

There are also blatant omissions from the List, including caffeine (one of the few substances for which there is clear evidence of performance enhancing effects¹⁸), and analgesics such as NSAIDs and tramadol. Such substances could be linked to at least two of the doping criteria with much less imagination than many of the substances currently on the List, complicating understanding of the List and begging for more transparency on the argumentation for decision-making. The remark of a former WADA president that a few espressos prior to a competition are fine but caffeine in pill form is not encapsulates well the underlying ideological stance¹⁹.

Anti-doping's objective is a celebration of clean champions. Reaching this ideal would require frequent testing for all these substances with perfect sensitivity and specificity (no false negatives nor positives). However, any laboratory test is limited by its imperfect sensitivity and specificity, which can vary between laboratories. Thus, the testing and detection systems not only generate frequent false negatives but may also generate false positive values (see for example^{20,21}) with dire (and sometimes criminal) consequences for athletic careers.

Criterion 2: Health

The second relevant factor is whether a substance can harm the athlete's health. In a general sense, any substance can jeopardize an athlete's health, or any person for that matter. The benefit-risk profile does not improve when substances are used off-label, as in a doping setting. Thus, for most substances on the List (but also all others) there is a risk of side effects, some more serious than others (Table 3). The requirement that a substance specifically may affect the health of an athlete is not supported by evidence, and without scientific evidence, the application of this criterion is equally arbitrary to that for enhancement.

Criterion 3: Spirit of sport

Unlike the previous two criteria, there is no pretense that the "spirit of sport" is based on scientific or medical evidence of any kind. Rather, it defines a moral high ground considered the ideal of sport. But this criterion lacks a precise legal definition^{22,23} and relies on a list of values that include elements of both enhancement and health²⁴, making it either redundant or a way of ensuring nearly any substance can be included on the List.

Why do athletes dope?

Given the relatively unknown enhancing effects and the potential for negative side effects, it may be unclear why athletes would engage in doping at all. Research has identified a range of motivations across competitive levels²⁵, though at the elite levels of sport, money was identified as a primary factor^{26,27}, making the drive to win greater than fear of the associated risks. Real prevalence of doping is impossible to measure, and estimates vary widely and may be flawed²⁸. However, prevalence models routinely show doping rates of 10-60% depending on country, sport and level²⁹⁻³¹. In any case, these numbers are much higher than those published by WADA reporting that only 1-2% of samples return positive, possibly giving the impression that the testing system is easy to beat³². Despite the high costs of developing, and

the complexity of carrying out a testing system, testing would indeed seem to be a weak deterrent for some athletes³³. Athletes may be tempted to use prohibited substances because the prohibited status seems to signify effectiveness and unintentionally promote a substance³⁴. A survey of Danish athletes found that 58% were interested in trying one of a list of 13 substances and 23% in trying either EPO, anabolic steroids, blood transfusions, or growth hormone³⁵. Athletes may also lose trust in the system if they perceive inequalities between countries' enforcement or if they feel their sport has a doping problem³⁶.

Twenty years of WADA

For most of the modern sport era, doping was an integral part of the game, first because it was not yet forbidden and then because anti-doping rules were not applied with much rigor³⁷. A series of highly mediatized doping scandals (Ben Johnson, Seoul Olympics 1988; Festina affair, Tour de France 1998) then progressively led up to the watershed decision in 1999 to set up the World Anti-Doping Agency³⁸. Over the last two decades WADA has strived for harmonization of anti-doping world-wide, with considerable though limited means relative to what the sport industry generates. WADA has been successful in many of its efforts, bolstered by the 191 state signatures to the UNESCO Convention Against Doping in Sports. A network of national anti-doping organizations (NADOs) and anti-doping laboratories now cooperate under the umbrella of WADA. This collective effort has led to sizable changes in doping behavior and prevalence²⁸. These well-intended anti-doping efforts have surely changed athletes' doping patterns and how doping is perceived by athletes and the public. After two decades, the question is by how much these achievements cover the objectives stated at the inception of WADA and what the outlook is for the coming decades. Several scholars analyzed the situation at WADA's 20-year anniversary and, on balance, tended to be rather critical³⁸⁻⁴¹.

Challenges for anti-doping

Some of the problems with anti-doping are due to how WADA is set up, its position relative to national governments, and the ideas it was predicated on at its founding. Others are related to the absence of sufficient democratic athlete representation in the policymaking process, the recent inclusion of non-elite athletes as targets of the anti-doping system, and the broader health and social implications of anti-doping for athletes and non-athletes.

Governance

WADA is not a truly independent organization, as it relies on national government signatories and the Olympic Movement for its funding, and its executive committee is comprised of members drawn equally from sport and civil society⁴². This presents a potential (and demonstrated) conflict of interest, as the decision-makers are drawn from the stakeholders it is meant to regulate. Even though WADA has recently introduced governance reforms, there are several areas where there remains room for improvement. Membership for several of WADA's committees, including key groups such as the Prohibited List expert group, is based on invitation or cooption, limiting transparency and accountability of the composition of these committees. Furthermore, because WADA is a non-governmental organization, it relies on cooperation with national governments to abide by the WADC and for other support such as national police power⁴². National governments, however, are in principle free to make their own national laws around doping, potentially undermining WADA's harmonization efforts and leading to a system where some countries have criminalized doping⁴³,

criminalized specific aspects of it ⁴⁴, or empowered NADOs to enforce anti-doping outside of organized sport, such as in gym settings ⁴⁵. Such laws risk drawing (amateur) athletes and gym-goers into the anti-doping system and/or the national criminal justice system. These differing laws can also lead to uneven levels of enforcement and confusion over what doping means in and outside the sport context, especially when sport and national policies conflict, such as in the legal status of cannabis, the use of anabolic steroids for aesthetic or anti-ageing purposes, or the use of cognitive enhancers by students. As a further example of discrepancies between national legislation, we point to the U.S.'s recent Rodchenkov Act, which has implications for anti-doping as it reaches beyond the U.S.'s borders.

Scientific inconsistency and secrecy

Apart from a lack of evidence (see above), the composition of the List is rather arbitrary. Most other sports rules are also arbitrary, which is fine as these are what define the game. But the WADC tries to root what is considered doping in (medical) science, which is not subjective or arbitrary. This leads to the situation where the List is potentially all-inclusive and covers vast amounts of substances, for many of which there is no evidence of performance enhancement, but omits other substances that are effective. Most of WADA's science-based decisions remain hidden and are not peer reviewed. For example, the biological passport for the longitudinal tracking of blood parameters to (indirectly) provide proof of blood-doping practice, uses Bayesian statistics based on algorithms of which the computer code is kept secret. All this is done by a system that is not transparent and increasingly extends itself into the lives of less competitive and even amateur athletes and beyond – without any independent body checking and weighing these regulations against existing universal human or national rights, including privacy. Although perhaps initially somewhat effective, the system may now have become unsustainable and runs the risk of also losing some of the positive effects it has had in sport ³⁹.

Policy overreach

WADA has taken a blanket approach to anti-doping, creating a policy that is (largely) the same for all sports and applies to athletes at all times. While this is an effort to harmonize policy and ensure consistency, it also assumes that all sports are enhanced in similar ways and athletes from all sports are equally likely to use any of the substances or methods on the List. The diversity of factors for performance across sports (e.g., oxygen transport in cycling, strength in powerlifting) and the potential enhancing effects of substances (Table 2) illustrate this is unlikely to be the case, yet the rules are the same. Further, the majority of anti-doping policies apply at all times, and athletes are prohibited from using – and can be tested for – most substances on the List at all times ⁹.

Athlete representation

Active athletes have limited representation within WADA and have little voice in how decisions are made, especially regarding the List. Non-elite and amateur athletes are almost completely left out of these processes, despite being subject to the WADC. Athletes are not given a choice whether to take part in the system, as it is a precondition to achieving international competitive levels, though increasingly this is applied at lower levels of competition ⁷. Amateur athletes as young as 12 and old as 80 years have been punished for anti-doping rule transgressions ⁷. As for other sport rules, athletes are expected to comply under the guise of fairness – the rules are the same for everyone. However, the stigma of

doping is so severe that athletes who oppose anti-doping rules may not be able to speak out for fear of being accused of doping, or at least sympathetic to it, and potentially losing team membership, sponsorships, or other sport relationships. As noted above, prevalence estimates indicate that a relatively high number of athletes may engage in doping, yet these athletes' voices and experiences are ignored unless they fall afoul of doping rules. Some sports leagues not governed by WADA, such as the professional sports leagues in North America, have collectively bargained anti-doping policies and come up with more tailored systems and regulations. While facing its own challenges, this does indicate that other policies are feasible ⁴⁶.

Social impact

The WADC may have regulatory effect only within sport, but its impacts can be felt much more widely, especially when coupled with broader fear-based messaging around health risks and cheating ⁴⁷. This becomes a broader social concern as anti-doping pushes beyond elite sport into the amateur and recreational levels of sport, as now included in the updated WADC ⁹. The inclusion of non-elite athletes in the anti-doping system further highlights the problems with an ideology-driven approach. As anti-doping expands beyond the elite levels of sport, the complexity of the List may lead some athletes to commit anti-doping rule violations unintentionally. When considering the number of substances prohibited and the various ways these can be ingested (e.g., on a doctor's prescription, in over-the-counter medicine, in dietary supplements, from food sources) it is likely this will increasingly occur. And unlike other types of sport rule violations, athletes who are found to violate an anti-doping rule face years-long bans from sport, even if use is inadvertent (possibly up to 40% of all cases, see ⁴⁸) or for medically-necessary reasons without a therapeutic use exemption – a documented exemption for specific medication that is on the List but is needed for treatment of a proven illness in an athlete. Athletes do have a right to appeal a ban through the Court of Arbitration for Sport, in which they must demonstrate their innocence rather than sport proving their guilt, as would be the case in most civil justice systems ⁴⁹. Such appeals can be costly, time-consuming, and difficult to navigate, resulting in a two-tier system where well-resourced athletes are better able to pursue appeals than those with lesser means ⁵⁰.

There are also serious implications for athlete health as a result of zero-tolerance anti-doping policies and national laws. Anti-doping is already changing the doctor-patient relationship. Quality of care critically depends on this relationship, which responds to basic principles of medical deontology, including granting autonomy to the patient and, importantly, ensuring strict confidentiality. Anti-doping is changing this setting. For example, in France any physician who suspects that a patient is doping is obliged by law to denounce them to a medical board, illustrating the extraordinary reach of anti-doping (Articles L232-3 and 4 of the Sport Code). Consequently, an athlete becomes less likely to share doping behavior with their physician, which undermines an essential ethical tenet of the doctor-patient relationship and might cause harm from medical decisions by the doctor based on incomplete information or ill-performed doping. Because such an approach pushes use underground, athletes may need to rely on questionable sources and unsafe supplies of substances to avoid detection ⁵¹. Athletes and gym-goers may avoid disclosing their use to medical professionals, fearing either condemnation or that the doctor will lack knowledge of the substances to provide support for their use ^{52,53}. A positive test and/or sanction can lead to a range of emotional and mental issues ⁷, for which sanctioned athletes rarely receive organizational support to address ⁵⁴.

However, the stigma associated with doping can be severe^{55,56}, and even athletes who use only allowed methods of enhancement may be treated with suspicion^{57,58}.

A way forward

General public opinion does not want competitive sport to become a contest of sophisticated drug regimens but wants to continue to believe that talent, courage, and grit are the way to merited success. Sport actors believe that sports rankings (e.g., medals, world records) are valuable and constitute the main capital within the field³⁹. Anti-doping, therefore, strives to provide the spectatorship with competition that is considered fair. Tragically, however, by putting the bar too high (eradication of doping, clean athletes, clean Olympics) this proves impossible despite extraordinary (repressive) means, and after each Olympics the retesting of samples leads to medal reallocations, up to ten years later⁵⁹. This situation is likely to occur again after the Olympics in 2021, despite the large-scale anti-doping efforts being made in Tokyo.

Public opinion appears to remain in favor of anti-doping efforts but also resistant to changing the record-challenging and hyper-competitive aspects of sport that make it exciting to watch – the very things that may lead some athletes to use prohibited substances to enhance their performances with. Thus, we see a continuous cycle of regulation and experimentation generating an ever-growing List, with very little evidence that the substances on it affect performance at all. Inclusion on this List makes it more likely that athletes may use them because the inclusion suggests they may enhance performance.

Discussions about anti-doping policies often oppose two extremes: eradication or liberalization of doping. Neither is feasible, nor do we think they should be the goal. Surely, the current system requires reform, as aiming for perfection (i.e., eradication of doping) from an ideological perspective is a slippery slope towards a goal-justifies-the-means policy that risks inflicting more overall damage than it is supposed to prevent, of which we have highlighted examples and symptoms above. A more pragmatic stance, while striving to limit the damage to the individual and the collective, carries a promise for a more balanced result. An ethical analysis of what a more relaxed anti-doping rule would mean for sport showed that such a stance can be defended from a modern moral standpoint⁶⁰.

We do not claim we have the final solutions for this complex problem. Nevertheless, given the strong need for change, we here give a rough outline for a change that, on balance, could result in better anti-doping policy outcomes. This is in no way exhaustive or final. These proposals could be taken as a starting point by stakeholders from all relevant backgrounds, including scientific fields, governance, and education, to develop an improved system. With that, we hope this plea will be taken as a call to come together, with an open mind and new ideas, to find more efficient and appropriate solutions for this complex and ‘wicked’ problem.

The basis of this anti-doping system, like in regular medicine, should be a more evidence-based approach. This means that the third criterion for placing substances on the List, the ‘spirit of sport’, should be dropped because of its problematic fuzziness. Adequate trials and practically tested measures of performance and assessments of risk should then be performed to generate knowledge and improve decision-making for the List. High-quality clinical trials do not need to be onerous in sports⁶¹, which have all the sophisticated and

relevant measures of performance already institutionalized and regulated. Such trials need not to be performed for all 400 substances, but rather for the specific classes of substances, to evaluate whether that mechanism of action has any evidence for performance benefit. This would very likely shorten the List considerably. For substances not shown to be enhancing or unsafe, there is no need to separately consider harm beyond normative use, similar to how medicines are regulated.

For this approach to be successful, several obstacles need to be overcome. One obstacle is available resources; some resources will become available by dropping doping testing for substances that are removed from the List, but a structural source of funding might also need to come from sports itself. If parties involved are convinced of the value and promise of this evidence-based approach, redistribution of a small part of the funds in sports towards this goal could be acceptable. A second obstacle would be substance use by athletes prior to conclusive evidence being available. We would argue that, depending on the likelihood for the substance to be performance enhancing, these substances can be placed on the List until robust evidence is available. If organized well, this temporary situation for a specific substance should not exist for more than a few years. And in the rare case that a human trial would be truly ethically unacceptable, such a substance could remain on the List. Finally, a potential obstacle could be that powering studies to detect small beneficial effects would require large trials. If indeed large study populations are needed to detect a relevant effect and this would prove difficult, combined and dedicated efforts should be made to deal with this problem. One consideration could be allowing elite athletes to participate in such trials.

In this scenario, the care for the health of the athletes is the concern of the medical team and him or herself, while still allowing sports to fulfill their duty of care to athletes. Preventing use of ineffective substances based on rumored or anecdotal effects is difficult to regulate but would have no effect on the equal playing field. The best prevention of this would be compulsory education of medical teams and athletes as part of the new policy. Such programs and policies would need to be developed in consultation with both athletes and medical professionals. The educational programs could extend to the generalist medical professional so they would also be better equipped to recognize and deal with patients who are potentially doping.

Importantly, we also propose that WADA introduces more transparency with regard to the work of its various committees, such as the group deciding what to put on the List, as well as committees developing technical documents on doping sample analysis and interpretation. Secrecy is not a good housekeeper for good governance. Finally, we also propose to introduce more democratic principles into anti-doping governance with a larger and elected athlete representation.

Obviously, this outline remains a rough sketch for an updated anti-doping system, and clearly needs to be further detailed, considering the various subpopulations concerned – not only adult elite athletes but also, for example, minors, amateurs, and special Olympics participants who should be the topic of future work.

An important advantage of the proposed change would be that it would gradually alleviate the strong moralistic view of doping by changing an anti-doping rule violation into what could

then be seen as a technical error, more akin to other rule transgressions in sport. We need to deal with doping, limiting the harm to the individual and to society using reasonable means and in keeping with principles of democracy, transparency, and human rights.

The classical Greek athletes assumed that the rules for all their sports were dictated by the heroes or one of the Gods. This presumably made it easier for them to accept the rules without quarrelling, and indeed, universal acceptance of sport rules is just as essential today. Although we acknowledge the requirement for centralized dictation of rules, for doping and other medical-scientific aspects this is currently insufficient, and in some ways damaging. We advocate a new approach to the management of anti-doping rules based on science, education, democracy, transparency, and good governance. Some of these would not even have surprised our ancient Greek Olympian.

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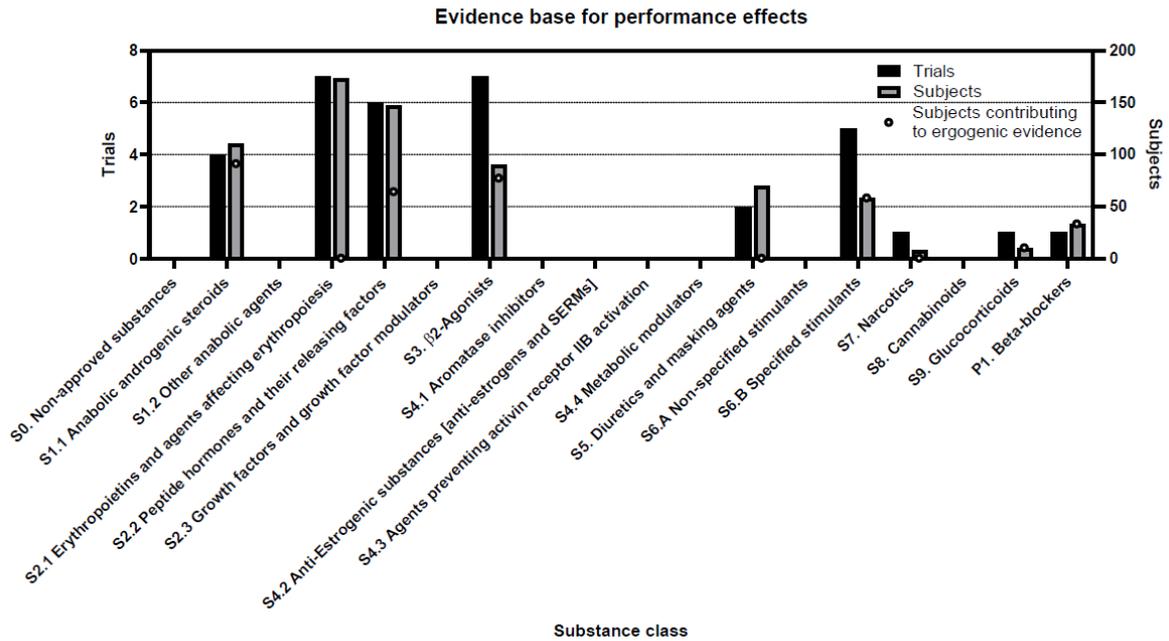


Figure 1. Graphical representation of the available high-level evidence for performance effects per substance class.

Number of published randomized, controlled trials investigating the effects of a substance (class) in well-trained subjects (left y-axis) and the total amount of subjects in these trials (right y-axis), regardless of the outcome of the trial (ergogenic or not). The circle for “Subject Improvement” indicates which portion of the total amount of subjects were part of trials actually showing convincing performance enhancing effects on relevant outcome parameters. Based on data reported previously (Heuberger and Cohen 2019), supplemented with most recent data, with permission from the authors.

Table 1: Definition of doping, reasons for inclusion of substances and methods on the List, and examples of all-inclusiveness of WADA's formulation

	From the Code and the List ^{1,2}	Comments
Definition of doping	Art.1 of the 2021 version of The Code states: “Doping is defined as the occurrence of one or more of the anti-doping rule violations set forth in Article 2.1 through Article 2.11 of the Code”. Art. 2.1 through 2.11 then list different breaches ranging from “Presence of a Prohibited Substance or its Metabolites or Markers in an Athlete’s Sample” to “Acts by an Athlete or Other Person to Discourage or Retaliate Against Reporting to Authorities”.	This definition is an operational one, chosen for legal reasons. This formulation implies that doping is whatever WADA at any moment assesses it to be ³ . It does not correspond to the general understanding of what doping is – voluntary cheating by taking a forbidden substance.
Criteria for inclusion (2 of 3 is enough)	<p>“1. Medical or other scientific evidence, pharmacological effect or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or enhances sport performance;</p> <p>2. Medical or other scientific evidence, pharmacological effect or experience that the use of the substance or method represents an actual or potential health risk to the athlete;</p> <p>3. WADA’s determination that the use of the substance or method violates the ‘spirit of sport’ described in the introduction to the Code. ”</p>	<p>Doping is not defined by (potential) performance enhancing properties. A substance can also be on the list without satisfying criterion 1, in contrast to the public understanding of what doping is.</p> <p>The wording used in criteria 1 and 2 (“<i>experience</i>” and “<i>potential</i>”) and the inclusion of criterion 3 allow inclusion of just about anything on the List.</p> <p>The List is updated annually, with substances added, but sometimes also taken off the list. This implies that from one year to the next, a given substance may change its status from ‘not doping’ to ‘doping’, and vice versa.</p>

<p>The “spirit of sport” criterion</p>	<p>“Anti-doping programs seek to preserve what is intrinsically valuable about sport. This intrinsic value is often referred to as “the spirit of sport”. It is the essence of Olympism, the pursuit of human excellence through the dedicated perfection of each person’s natural talents. It is how we play true. The spirit of sport is the celebration of the human spirit, body and mind, and is reflected in values we find in and through sport, including: Ethics, fair play and honesty; Health; Excellence in performance; Character and education; Fun and joy; Teamwork; Dedication and commitment; Respect for rules and laws; Respect for self and other Participants; Courage; Community and solidarity. Doping is fundamentally contrary to the spirit of sport. ”</p>	<p>The “spirit of sport” criterion has been defended since it provides a common understanding of what is valued in modern sport ⁴. It has also been criticized for its lack of consistency. None of the listed items can be used to argue non-ambiguously against the use of some doping technology, in fact, if doping were allowed the same items could still apply. From a legal perspective this is highly problematic ^{5,6}.</p>
<p>Text excerpts illustrating the all-inclusiveness of the List</p>	<p>“Any pharmacological substance which is not addressed by any of the subsequent sections of the List and with no current approval by any governmental regulatory health authority for human therapeutic use (e.g. drugs under preclinical or clinical development or discontinued, designer drugs, substances approved only for veterinary use) is prohibited at all times”; “The following substances, and other substances with similar chemical structure or similar biological effect(s), are prohibited”; “The following diuretics and masking agents are prohibited, as are other substances with a similar chemical structure or similar biological effect(s) ”; “and other substances with a similar chemical structure or similar biological effect(s) ”.</p>	<p>These citations illustrate the all-inclusiveness of the List. Together with the three criteria used for inclusion, this way of formulating pre-emptively allows any unknown substances and methods to be considered as doping whenever observed or suspected to be used in the field. They also indirectly illustrate the underlying doxa of anti-doping, demanding an ideal of imaginary purity of the athlete ⁷.</p>

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Table 2. Substance classes on the 2021 Prohibited List, including examples substances, the their pharmacological effect and the alleged performance effect.

Substance class	Example substances	Pharmacological effect	Alleged performance effect
<i>Prohibited at all times</i>			
S0. Non-approved substances			
Non-approved substances	NA	NA	NA
S1. Anabolic agents			
S.1.1 Anabolic androgenic agents	Testosterone, epitestosterone, stanozolol, nandrolone	Testosterone-like effects activating the androgen receptor, increasing protein synthesis, and decreasing protein breakdown. Induce muscle growth.	Increase muscle strength, power.
S.1.2 Other anabolic agents	Clenbuterol, andarine, tibolone	Selective androgen receptor modulation/activation (SARMs), increasing protein synthesis and decreasing protein breakdown. Induce muscle growth. Clenbuterol is an exception, as it is not an androgen receptor but beta-2 adrenoreceptor agonist.	Increase muscle strength, power.
S.2 Peptide hormones, growth factors, related substances, and mimetics			
S2.1 Erythropoietins (epo) and agents affecting erythropoiesis	Erythropietins, xenon, daprodustat, luspatercept	Increase erythropoiesis, thereby increasing erythrocyte number and blood hemoglobin content.	Increase oxygen uptake and delivery, leading to improved endurance and peak performance, increased training effort and improved recovery.
S2.2 Peptide hormones and their releasing factors	Chorionic gonadotrophin (CG), luteinizing hormone (LH), corticotrophins (ACTH), growth hormone (GH)	CG and LH: Activation of LHCG receptor, leading to increased testosterone levels in males. ACTH: activation of the adrenal gland leading to increased cortisol, increasing free fatty acid	CG and LH: Increase muscle strength, power. ACTH: Improves endurance performance through improved energy consumption. Increase

		release and potentially sparing glycogen. Also increased glucocorticoid secretion. GH: activating cellular signaling pathways (including production of IGF-1), stimulating growth, cell reproduction and regeneration.	muscle strength, power, endurance performance through glucocorticoid effects. GH: Increases muscle strength, power, reduces body fat and improves lean body mass.
S2.3 Growth factors and growth factor modulators	Insulin-like (IGF-1), vascular endothelial (VEGF) and hepatocyte (HGF) growth factors.	Different factors affecting muscle protein synthesis/degradation, vascularization, energy utilization or regenerative capacity.	Increase muscle strength, power, endurance performance, recovery.
S3. Beta-2 agonists			
Beta-2 agonists	Formoterol, salbutamol, salmeterol, terbutaline	Activation of the beta-2 adreno receptor, leading to smooth muscle cell relaxation and muscle cell growth.	Increase muscle strength, power, and increase oxygen uptake and endurance performance.
S4. Hormone and metabolic modulators			
S4.1 Aromatase inhibitors	Exemestane, estolactone, 2-androstenol	Reduction of conversion (by aromatase) of androgens to estrogens, via inhibition of negative feedback on the hypothalamus, leading to higher testosterone levels.	Increase muscle strength, power
S4.2 Anti-estrogenic substances [anti-estrogens and selective estrogen receptor modulators (SERMs)]	Clomifene, cyclofenil, fulvestrant, tamoxifen	Effects on the estrogen receptor, through the hypothalamic-pituitary-testicular axis leading to increased testosterone.	Increase muscle strength, power
S4.3 Agents preventing activin receptor IIb activation	Bimagrumab, follistatin, stamulumab	Activation of the activin type 2b receptors, activating transcription leading to growth and cell differentiation.	Increase muscle strength, power

S4.4 Metabolic modulators	AICAR, insulins, meldonium, trimetazidine	Peroxisome proliferator-activated receptor (PPAR)- δ agonists and AMP-activated protein kinase (AMPK) activators: affecting energy expenditure and substrate utilization. Insulin: affecting glycogen storage and usage. Meldonium and trimetazidine: inhibition of free fatty acid oxidation.	PPAR and AMPK: Improve energy metabolism, thereby improving endurance performance. Insulins: Increase muscle strength, power, improve energy use. Meldonium and trimetazidine: improve endurance performance through energy metabolism.
S5. Diuretics and masking agents			
Diuretics and masking agents	Desmopressin, furosemide, hydrochlorothiazide	Affecting urine concentration or production through diuresis or affecting blood/plasma content.	<i>NA (supposedly interfering with doping detection)</i>
M1. Manipulation of blood and blood components			
Manipulation of blood and blood components	Administration of autologous or allogenic blood, blood products, perfluorochemicals. Intravascular manipulation of the blood.	Increasing oxygen-carrying capacity by increasing blood hemoglobin content or other oxygen-carrying entities.	Increase oxygen uptake and delivery, leading to improved endurance and peak performance.
M2. Chemical and physical manipulation			
Chemical and physical manipulation	Addition of proteases in doping control samples.	<i>NA</i>	<i>NA (supposedly tampering with doping control samples)</i>
M3. Gene and cell doping			
Gene and cell doping	Gene editing, silencing, use of genetically modified cells.	<i>NA</i>	Depending on the genes, effects could be as per any of the related substance classes.
Prohibited in-competition			
S6. Stimulants			
S6.1 Non-specified stimulants	Cocaine, amphetamine, methamphetamine, modafinil	Affecting neurotransmitter levels in the brain, among others dopamine and norepinephrine,	Increase muscle strength, power, endurance performance.

		leading to a variety of stimulant effects.	
S6.2 Specified stimulants	Strychnine, ephedrine, methylphenidate	Affecting neurotransmitter levels in the brain, among others dopamine and norepinephrine, leading to a variety of stimulant effects.	Increase muscle strength, power, endurance performance.
S7. Narcotics			
Narcotics	Buprenorphine, methadone, Morphine, oxycodone	Activation of the opioid receptor, leading to pain relief.	Ability to “go deeper” during performance by reduction of pain.
S8. Cannabinoids			
Cannabinoids	Tetrahydrocannabinol (THC)	Activation of the cannabinoid receptors, leading to a variety of effects including relaxation, increased heart rate, potential analgesia and psychotropic effects.	Improve performance when muscle relaxation is important, or where anxiety could impair performance.
S9. Glucocorticoids			
Glucocorticoids	Beclomethasone, budesonide, cortisone, prednisolone	Activation of the glucocorticoid receptor, leading to among others gluconeogenesis and other metabolic effects, and anti-inflammatory effects.	Increase muscle strength, power, endurance performance.
Prohibited in particular sports			
P1. Beta-blockers			
Beta-blockers	Pindolol, propranolol, sotalol, atenolol	Inhibition of beta adrenergic receptors, leading to decreased heart rate, muscle tone and tremor	Increase accuracy and concentration in sports where this is crucial (e.g. archery, golf, shooting).

Table 3. Substance classes on the 2021 Prohibited List and their reported side effects in the general or patient population (and not in athletes).

Substance class	Potential adverse effects
S0. Non-approved substances	
Non-approved substances	NA
S1. Anabolic agents	
S.1.1 Anabolic androgenic agents	Some of the reported side effects include: Increased sexual drive, acne, increased body hair, increase in aggressive behavior. Testicular atrophy, reduced semen production and quality, infertility, gynecomastia. Cardiomyopathy, atrial fibrillation, QT dispersion, cerebrovascular accident, myocardial infarction, disturbances of the hemostatic system ventricular thrombosis and systemic embolism, and acute heart failure. Liver disorders, mood disorders. (Summarized from ¹)
S.1.2 Other anabolic agents	Clenbuterol: See Beta-2 agonists. SARMs: Better safety profile than AAS, but potentially liver toxicity and decreases in HDL cholesterol (summarized from ²)
S.2 Peptide hormones, growth factors, related substances, and mimetics	
S2.1 Erythropoietins (epo) and agents affecting erythropoiesis	Thrombotic events, including stroke. High hematocrit levels resulting from these agents can also cause heart failure, myocardial infarction, and seizures. (summarized from ³)
S2.2 Peptide hormones and their releasing factors	HCG, LH and GnRH will influence testosterone levels in males. Side effects will be mainly related to increased and decreased testosterone levels (possibly similar to, but milder than described under AAS). Corticotrophins and releasing factors: increased susceptibility to infections, Cushing syndrome, hypertension, mental disorders (see SmPC Synacthen ⁴) Growth hormone and releasing factors: hypertension, diabetes, carpal tunnel syndrome, congestive heart failure, edema, neuropathy. (summarized from ⁵)
S2.3 Growth factors and growth factor modulators	There are many different growth factors listed, the majority with little clinical data available. Side effect profile will likely depend on the type of growth factor and it's mechanism. For example, ICG-1 will have side effects similar to those of growth hormone, in addition to hypoglycemia, seizures, jaw pain, myalgia, headaches, increased liver and kidney mass, and altered liver function (summarized from ⁵)
S3. Beta-2 agonists	
Beta-2 agonists	Tremor, tachycardia, nausea, dizziness, nervousness. (based on reports from ^{6,7})
S4. Hormone and metabolic modulators	

S4.1 Aromatase inhibitors	Arthralgia, fatigue, hot flashes, muscle or joint stiffness, myalgia, osteoporosis. (summarized from ⁸)
S4.2 Anti-estrogenic substances [anti-estrogens and selective estrogen receptor modulators (SERMs)]	Hot flushes, carcinoma, venous thromboembolic events, embolism, arthralgia, endometrial polyps (summarized from ⁹)
S4.3 Agents preventing activin receptor IIb activation	Involuntary muscle contractions, diarrhea, bone weakness, vascular side effects (summarized from ¹⁰ and ¹¹)
S4.4 Metabolic modulators	PPARdelta and AMPK activators: no registered compounds and lack of clinical data. Insulin: hypoglycemia, potentially leading to loss of consciousness, coma, seizures (summarized from ⁵) Meldonium and trimetazidine: gastric or esophageal burning, muscular cramps, dizziness, effort induced discomfort, depression, sedation and/or drowsiness, palpitations, visual disturbances, anorexia, and hyperorexia. (summarized from ¹²)
S5. Diuretics and masking agents	
Diuretics and masking agents	Mainly related to fluid and electrolyte imbalances, e.g. hyponatremia, hyperkalemia, extracellular fluid volume depletion and related hypotension, formation of precipitation in urine leading to stone formation, headache, nausea, vomiting, diarrhea, dizziness. (summarized from ¹³)
M1. Manipulation of blood and blood components	
Manipulation of blood and blood components	Similar to side effects related to increased hemoglobin content for erythropoietins. Immune reactions to products.
M2. Chemical and physical manipulation	
Chemical and physical manipulation	<i>NA (no substance administered)</i>
M3. Gene and cell doping	
Gene and cell doping	To the technique: immune reactions, problems related to disruption of genes. Other adverse effects could be related to the specific gene function.
S6. Stimulants	
S6.1 Non-specified stimulants	Confusion, delirium, sweating, palpitations, pupil dilation, rapid breathing, hypertension, tachycardia, tremors, muscle and joint pain, headaches, anxiety. Myocardial pathology (including cardiac arrest), heat stroke. Mood effects, paranoia, stroke, seizures, dependence. (summarized from ¹⁴)

S6.2 Specified stimulants	Headache, dizziness, irritability, anxiety, tremor, and psychosis. Higher doses (overdose) can cause restlessness and anxiety, dizziness, insomnia, tremor, rapid pulse, sweating, respiratory difficulties, confusion, hallucinations, delirium, and convulsions. Abnormally high blood pressure and rapid, irregular heartbeat. (summarized from ¹⁴)
S7. Narcotics	
Narcotics	Nausea, dizziness, sedation, vomiting, constipation, and respiratory depression. (summarized from ¹⁵)
S8. Cannabinoids	
Cannabinoids	Decreased ability to concentrate and maintain attention. Impaired information processing and reaction time. Nausea, vomiting, dry mouth, paranoia, psychosis. (summarized from ¹⁶)
S9. Glucocorticoids	
Glucocorticoids	Skin atrophy, disturbed wound healing, osteoporosis, muscle atrophy/myopathy, cataract, glaucoma, diabetes mellitus, adrenal insufficiency, mood disorder, psychosis, hypertension, dyslipidemia, and a reduced fibrinolytic potential, peptic ulcers, upper gastrointestinal bleeding, pancreatitis and oral candidiasis. (summarized from ¹⁷)
P1. Beta-blockers	
Beta-blockers	Bronchospasm, heart failure, prolonged hypoglycemia, bradycardia, heart block, intermittent claudication, Raynaud's phenomenon, depression, fatigue, nightmares. (summarized from ¹⁸)

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