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Doping in Sports, from Chemical to Genetic: A Technological Evolution or a Threat to Sport's Future?

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Abstract

The use of illicit drugs or techniques to enhance an athlete's physical or mental performance is known as doping, often driven by the desire to win. This review aims to highlight the latest advancements in the field of sport doping, including their methods of action and usage statistics. As per the World Anti-Doping Agency (WADA) data for 2021, chemical doping, particularly anabolic steroids, is the most common method used by athletes (accounting for 40%, with stanozolol being the most prominent at 15%). Genetic doping, specifically Erythropoietin Genetic Doping, has not raised any suspicion and is under consideration since the anti-doping program for the Tokyo 2021 Olympic Games. However, studies indicate that the costs and risks associated with genetic doping are significant, resulting in its declining popularity. Nevertheless, the number of scientific publications on genetic doping from 2018 to 2023 remains inadequate, particularly concerning the development of analytic methods to detect this violation of the international code. The doping issue is a permanent challenge as it affects multiple age groups, poses a risk to community health, and may impact future generations if genetic doping becomes easily accessible. Therefore, preventive education against doping is the only solution proposed worldwide.

Keywords: Chemical Doping, Genetic Doping, Anti-doping Violations, World Anti-Doping Agency Figures

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1. Introduction

Drug abuse to increase performance (PED – performance enhancing drugs) is a big issue in both competitive and leisure sports. The use of doping substances violates the spirit of fair play and represents a major health problem [1]. This situation has been documented in the sports world for several centuries, for example, in various populations existed ancestral customs where they used ginseng root, coca leaf, or mushroom derivatives to increase stamina, decrease fatigue, and increase fighting spirit [2].

Doping is defined as a violation of the World Anti-Doping Code, which includes using prohibited substances as demonstrated by laboratory studies, transporting or tampering with these compounds, or attempting to avoid any anti-doping control mechanism by failing to provide the required samples without justification [3]. Furthermore, the World Anti-Doping Agency (WADA) has put in place anti-doping policies with the purpose of protecting athletes' health and the integrity of sport, as well as to equalize the level of competitors, provide for appropriate sanctions in the case of non-compliance with, and the list of substances prohibited to athletes [4]. Doping is seen as a crime against nature, and the stigma of being punished discourages athletes from engaging in this unlawful and anti-sportive conduct. The reasons an athlete may utilize doping are many and diverse. Several writers have investigated the incentives that lead an athlete to take a forbidden drug or an unlawful procedure [5].

According to the findings of the doping tests, the proportion of samples containing prohibited drugs remained reasonably consistent before and after the establishment of the WADA (World Anti-Doping Agency). To date, most anti-doping policies have failed to take into consideration the unique characteristics of each sport in terms of drug misbehavior. Furthermore, prior to 1960, athletes, coaches, and doctors claimed to be unaware of the effects of

developing countries; however, the death of cyclist Tommy Simpson in 1967 changed the perspective, and the Olympic Committee began conducting increased anti-doping controls beginning in 1968 during the Olympic Games in Mexico [6].

The aim of this review is to highlight the issue of drug abuse in sports, particularly the use of performance-enhancing drugs (PEDs) and genetic doping, which violates the spirit of fair play and presents a significant health problem. In the second part, the definition of doping and the anti-doping policies put in place by the World Anti-Doping Agency (WADA) to protect athletes' health and the integrity of sport will be discussed. Furthermore, we will explore the reasons why athletes may use PEDs/Genetic and investigates the incentives that lead them to take prohibited drugs or unlawful procedures.

2. Definition of doping

Doping is typically defined as drugs of natural or synthetic origin that an athlete might use to increase his athletic performance. The term "dope" is derived from the English word dope - drugs. In sports, this idea is most likely the product of horse racing, since for the first time, performance-enhancing chemicals have been utilized on horses [7]. The World Anti-Doping Code definition of doping differs significantly. Its authors were unconcerned, stating that doping is an infraction of the anti-doping provisions included in the code itself. Furthermore, doping in the broadest sense may refer to not only drugs (illegal substances) but also prohibited procedures. Manipulation of blood and its components, for example. Transfusing an athlete with his or her own blood, for example, increases the availability of oxygen to the muscles and hence their performance [8]. The code specifies 10 anti-doping rule infractions for which an athlete, as well as their coach or doctor, may be disqualified. Both the use of forbidden drugs and the evasion or falsification of doping tests, the failure to notify their location, the distribution of prohibited substances, and so on are prohibited [9].

3. The World Anti-Doping Agency's History and Function (WADA)

WADA has been the central figure in all the recent doping crises. The World Anti-Doping Agency - that's how the World Anti-Doping Agency (WADA) is translated into English - was founded in 1999. The Tour de France multi-day cycling competition in 1998 provided the motivation for its formation, when illicit substances were identified in numerous competitors and team members [10]. The first World Conference on Doping in Sport was convened in Lausanne, Switzerland, in February 1999, and it was determined to establish an independent anti-doping agency to combat doping on a global scale. The International Olympic Committee and the governments of many nations established the agency toward the end of 1999. The World Anti-Doping Code and WADA worldwide standards were also accepted during the Second World Conference on Doping in 2003 in Copenhagen, Denmark [11]. WADA is in charge of doping monitoring in and out of major sports, as well as regulating the list of illegal drugs. Every year, the agency produces an updated version of the list. That gives it three months before it goes into effect. The current edition of the list is effective as of January 1, 2016. Her breakthroughs included the addition of meldonium to the list of forbidden substances, for which tennis star Maria Sharapova was banished for two years [12]. Furthermore, the World Anti-Doping Agency finances research into prohibited drugs and procedures in sport, prepares and distributes anti-doping equipment, and accredits anti-doping labs across the world. The revocation of a laboratory's accreditation might have major ramifications for the nation in which it is situated. As a result, the Moscow anti-doping laboratory was denied WADA certification in April. She has only been allowed to take blood tests since May of this year [13].

4. Doping types

4.1. Erythropoietin

Following its discovery in 1983 by American scientists, erythropoietin was born in the 2000s in the French laboratory of Château Malabri. The introduction of new forms prompted cyclist to utilize them. Erythropoietin is a hormone that promotes the generation of red blood cells from late progenitor cells and enhances bone marrow reticulocyte output in an oxygen-dependent manner. Erythropoietin is a synthetic version of the natural kidney hormone. It triggers the red blood cell maturation process once it enters the blood [14].

4.1.1. Mechanism of Action of EPO

EPO is a growth factor. Its activity, like that of any hormone, is mediated by attaching to a particular receptor known as EPO-R. EPO is a hydrophilic glycoprotein that is membranous. The EPO receiver is made up of a single chain dimer with a single transmembrane segment. This receptor contains an extracellular domain that ensures EPO fixation (two fixation sites of varying affinity, one of high affinity, nanomolar order, and the other of low affinity, micromolar order) and an intracellular region that activates the JAK/STAT signaling channel. The latter is expected to be phosphorylated at four distinct places and activates numerous intracellular relays (JAK/STAT5, PI3-kinase, Ras/MAP kinase pathways) that will eventually operate by inhibiting apoptosis and stimulating proliferation and differentiation of the target cell (Figure 1) [15]. This receptor is found in erythroid progenitors- they are present on a spectrum of cells spanning from mature BFU-E to erythroblasts, with the highest concentration on CFU-E - but also in megakaryocytes (blood-forming marrow cells). They may also be present in endothelial cells, nerve cells, and the placenta [16]. The attachment of the EPO ligand on its receptor causes a change in the latter's conformation and a rapprochement of the two receptor molecules (homodimerization). Both Janus kinases 2 (JAK2, tyrosine kinase) and the tyrosine EPO receptor are phosphorylated as a result of this. This causes the transcription factor STAT5, which is then phosphorylated by JAK2, to be fixed. The phosphorylated version of the transcription factor STAT5 will dimerize, move to the nucleus, and act on transcription.

4.2. Anabolic Steroids (testosterone, stanozolol, nandrolone, methenolone)

Anabolic steroids are pharmacological substances that replicate the effect of the male sex hormones testosterone

and dihydrotestosterone. Anabolic drugs increase protein synthesis inside cells, resulting in significant muscular tissue growth (usually this process is called anabolism). Steroid usage causes a large rise in muscle growth (5-10 kg per month), strength indicators, endurance, an increase in red blood cell formation, bone tissue strengthening, and a reduction in fat reserves. Steroids are still seen to be the most effective sort of doping in theory, but the difficulty is that athletes have learned to detect them quickly [17]. Steroids are hormones that are naturally found in the human body. Steroids are classified into three types based on their steroid chemical nucleus; Estrane nucleus (C18) compounds (Estrone and estrogens, which are female sex hormones released by the ovary), Andostrane C19 (Substances include testosterone and androgens, which are male sex hormones), Progesterone (C21) (Progestogens and corticosteroids are examples of compounds having a large nucleus). These three classes share a 4-cycle sterol core. These steroids are testosterone derivatives (Figure 2), a male sex hormone from the androgen family. When there is no ligand, the androgen receptor is found in the cytoplasm, where it forms a stable and inactive complex with chaperone molecules (HSP). At the cellular level, testosterone or DHT will be able to connect to the receptor in target tissues. This fixation results in the release of chaperone proteins (Hsp90) and the dimerization of the receptor, allowing it to enter the nucleus. It binds to certain sequences in the nucleus, resulting in the transcription of specific target genes (Figure 3) [18].

4.3. Diuretics (Chlorthalidone, Acetazolamide, Triamterin, Furosemide)

Diuretics are diuretics that are often used to treat muscular pain by removing excess fluid from the body. Because the impact is brief, it is usually utilized before a competition. Because anabolic steroids promote excessive fluid buildup, diuretics may be used throughout a steroid cycle. By considerably lowering the density of urine, intensive urination aids in the removal of other doping drugs from the body or masks their usage. As a consequence, it helps athletes lose weight quickly and improves their appearance [19].

4.4. Mental activity stimulants (cocaine, ephedrine, ecstasy and amphetamines)

Stimulants quickly affect the functional characteristics of the brain (activate the bioelectrical activity of the brain, modify conditioned reflexes, etc.) under circumstances of acute exposure, increasing endurance at physical labor. They have a quick stimulating impact in clinical usage and are frequently used in practice for the treatment of disorders characterized by sleepiness, lethargy, apathy, asthenia, and depression. The rise in functional capabilities of athletes under the influence of stimulants is mostly attributable to the inhibition of physiological regulators, to the limitations of functional reserve mobilization. These medications boost vitality, minimize weariness, and improve training or competition performance [20].

5. Prohibited doping techniques

5.1. Auto-transfusion and blood and component transfusion

Haemolybdenum is a blood transfusion, a kind of transfusion in which the recipient's bodily fluid is given to the recipient in the form of blood or its components. Various forms of transfusions are often linked with an increase in red blood cells and hemoglobin. Self-transfusion, in fact, increases the availability of oxygen to the muscles, enhancing their performance. This strategy is very useful for long-distance runners, bikers, and swimmers [8]. When employing an incompatible blood type, the athlete may suffer lethal results due to blood thickening and overloading of the circulatory system. This sort of doping is almost hard to detect. Blood doping is forbidden in sports both in and out of competition. The use of blood doping may be hazardous to an athlete's health. Athletes who utilize another person's blood are more likely to get viral illnesses such as hepatitis and HIV [21]3]. Furthermore, synthetic oxygen carriers are chemical molecules that are utilized to enhance the quantity of oxygen in the circulation. Perfluorates, hemoglobin-based oxygen carriers, and microencapsulated blood carriers are examples of such carriers. In and out of competition, artificial oxygen carriers are an illegal approach. They're used in medicine when actual blood isn't accessible, there's a danger of infection, or there's not enough time to check the compatibility of the donor and recipient's blood. Fever, reduced platelets, and blood poisoning are all possible side effects [22]. Plasma volume extenders (plasma expanders): used to treat shock induced by blood loss after surgery or trauma. Albumin, dextrane, hydroxyethylaminon, and mannitol are examples of such compounds. Both in and out of competition, this is regarded as a banned technique. Their usage may result in allergic reactions and anaphylactic shock [23]. The use of chemicals or procedures to affect the composition of urine or the sample is referred to as chemical and physical manipulation. Catheterization, urine replacement or sample manipulation, and the use of medications that restrict urination are all prohibited actions (for example, probenecid).

5.2. Doping via Genetics

Modifying the tissue of a specific individual, rather than the genetic features of germ cells, is the target of gene or genomic therapy. As a consequence, the use of gene therapy will not result in genetic changes in future generations [24]. According to research, this therapy technique may be beneficial in treating and even curing persons with severe immune system problems, hereditary forms of blindness, and some kinds of cancer. On the other side, this technology has been proposed for use in boosting athlete performance, and some reports claim that research is already ongoing to change human genes to increase sports performance [20]. Furthermore, the World Anti-Doping Agency is working to combat the issue of genetic doping in sports. To that reason, WADA hosted a genetic doping symposium in New York in March 2002. Experts, scientists, ethicists, athletes, and Olympic Movement leaders researched the issue and decided that there is a strong likelihood that this approach will be employed as a medication in the near future. As a consequence, genetic doping was added to the list of prohibited activities in 2003, and is described as the non-therapeutic use of genetically modified (altered) cells, genes, genetic components, or expression modulations capable of improving athletic performance. WADA also organized an

expert panel to research genetic doping in 2004. The group's mission is to continually examine the newest breakthroughs in gene therapy, develop techniques for detecting genetic doping, and convey the findings of these WADA-funded research initiatives to the public [17-25].

5.2.1. Sport-specific applications

The non-therapeutic application of genetic engineering to boost performance in sports events and other activities unrelated to the treatment of different illnesses is known as genetic doping. As with gene therapy, there are two basic approaches [26]: (1) Viruses that alter the human cell genome to meet the needs, (2) RNA interference - this approach involves blocking the activity of a certain gene without modifying it, with the option of "restarting" it by interventions at the RNA reading stage. Genetic doping, according to scientists, is exceedingly difficult to detect, but it has the potential to level the playing field for sports provided all competitors have equal access to these technologies. Olympic champion Eero Mäntiranta, for example, had a mutation that led his body to create an unusually large quantity of red blood cells. In fact, genetic doping is the introduction of a desired gene into an artificial virus. This virus may infect a person and cause a significant increase in the quantity of oxygen in the body, increasing his endurance. However, the effects may be disastrous: specialists are unsure about the method's safety. Doping increases a person's nervous and physical activity; therefore, the athletic outcomes may be spectacular. Those who do not depend on their own strength and strive to excite themselves in some manner do not always recognize that they are not only dishonest and anti-sportive, but also detrimental to their health. However, the intense drive to succeed leads to astounding creativity, and nothing ensures that the writers be discovered in all situations (Table 1) [27].

5.2.2. Scientific publications on genetic doping

We discovered that between 2018 and 2023, 3330 original papers on “Athletes and Doping” were published in trustworthy databases (Web of Science, Scopus, and Direct Science, for example). During the same time period, 30 books and 144 book chapters were published (Figure 4). We discovered a substantial difference in the total results after filtering on the basis of the keyword «Genetic Doping and Athletes». The amount of publications written on the topic demonstrates this plainly. In comparison, there are just 158 articles, 7 books, and 5 book chapters from 2018 to 2023.Simultaneously, research conducted in recent years suggests that the number of publications in the topic of “Athletes and Doping” has decreased dramatically. In comparison, there were 315 unique published papers in 2018, but just 227 in 2022. There are currently ten published articles in 2023. Books and book chapters, on the other hand, are always at the bottom of the pyramid (Figure 5).

From the viewpoint of genetic doping in athletes, we saw a decline in the quantity of papers on the subject. With 30 unique pieces in 2018, there will be 45 in 2019. While an article is published in 2023. On the contrary, scientific book and book chapter production tends to be low (Figure 6).

6. Doping control technique, organization

Doping control is the most crucial component of a complete program of actions to prevent athletes from using prohibited drugs (doping). District sport organizations (DSOs) must design and carry out in-competition and out-of-competition controls on athletes in the so-called "registered pool," according to the World Anti-Doping Code. We're talking about testing world-class athletes by international sports federations and WADA, as well as international and national athletes tested by national anti-doping agencies [28]. The anti-doping organization creates a control strategy and assigns the amount of samples for each sport. The approach comprises both non-competitive and competitive controls, as well as sample collection (blood and urine).

6.1. Testing for competition

The DSOs must coordinate the competition control procedure such that just one of them checks the event or competition. Athlete selection criteria are predetermined and based on the regulations of the individual international organization or tournament organizing body. Unless an international organization or tournament organizer has another doping control procedure in place, samples are normally gathered by the host country's [29]. Athletes who have been chosen for drug testing must give a urine sample immediately after the competition, in line with international testing regulations. The presence of chemicals forbidden for use during competition is checked in line with the list of prohibitions.

6.2. Out-of-competition controls

Out-of-competition controls are the responsibility of anti-doping agencies. Out-of-competition controls imply that any athlete may be chosen to be monitored at any time and at any location. Outside of competition, samples are analyzed in compliance with the list of banned substances and techniques [30].

6.3. Location information for athletes

To be accessible for out-of-competition controls, an athlete from a target group of athletes subject to controls must give precise location information. Location data is typically reported every three months, while country anti-doping authorities may have their own policies in place. If an athlete's plans change, they must notify the team as soon as possible. Athlete location information contains the athlete's home address, job schedule, training location, and competition schedules; in other words, it is information that assists anti-doping authorities in locating the athlete on the day specified for testing [31]. If an international or national athlete is among the athletes being tested, it is their obligation to submit information about their whereabouts. Failure to give correct location information is considered a breach of anti-doping regulations and will result in consequences being imposed on the athlete.

6.4. Sample storage and transportation

The samples (blood and urine) are kept at the anti-doping checkpoint before being transferred to the laboratory. Where athletes' identities are not available, samples are accompanied by suitable paperwork. Throughout the safety chain, the procedure of transporting the sample to the laboratory is continually recorded. The representative from

the laboratory signs for the sample and proceeds to record the security chain [32].

6.5. Examination of samples

The laboratory examines samples for the presence of drugs on the prohibited list. The laboratory sends the urinalysis findings to the Decentralized Autonomous Organization (DAO) within 10 working days of receiving the samples [28].

6.6. Processing of Results

The laboratory performing the sample analysis must provide the findings to the DAO in charge of interpreting the results, as well as the WADA. If an aberrant test result is discovered, the Results Management Authority confirms that the athlete got a therapeutic use permission for the chemical discovered in his urine and that the sample collection and examination processes were carried out in accordance with authorized guidelines [30].

- If the examination does not explain (or justify) the abnormal analysis result, the athlete will be advised in writing of the findings of the analysis and his or her rights about the analysis of Sample B.
- If a player wants a sample B analysis, he or she may attend to the lab in person or send a representative.
- If the results of sample B's analysis confirm the results of sample A's analysis, the DAO will continue with the other authorized steps, including conducting a hearing. During the hearing, it is assessed if a breach of the anti-doping rules occurred and whether consequences should be imposed. If the analysis of Sample B does not match the finding of Sample A, the initial result will be canceled, and no further action against the athlete would be taken.

Each DAO may have its own regulations for disclosing information about a punishment imposed on a sportsman. Subsequently, only highly qualified athletes were subject to doping control, and only during major national and international competitions, such control is already carried out not only during the competition period, but also during training sessions, and all people involved in sport, regardless of their sports equipment, are subject to doping control.

The doping control technique involves the selection of biological samples to be analyzed, the physical and chemical inspection of the samples obtained, the issue of a conclusion, and the enforcement of fines on violators. All parties must therefore assure cooperation in the fight against doping between sports organizations and authorities. They also collaborate in teaching, research, and health care to safeguard athletes and to promote anti-doping laws.

6.7. Genetic doping control

To preserve athletes' health and maintain equitable competing conditions, the International Olympic Committee, WADA, and International Sports Federations have recognized and prohibited performance-enhancing drugs and practices. As a consequence, they implemented a genetic control approach for athletes through a novel polymerase chain reaction technique for identifying erythropoietin (EPO) gene doping that was employed for the first time in Tokyo Olympic and Paralympic Games [33].

6.8. Example of Anti-Doping Test: Case of the 2022 World Cup-Qatar

FIFA revealed the numbers for its anti-doping equipment before and during the Qatar 2022 World Cup. The World Football Authority conducted 1433 inspections in total, 369 of which were performed during the FIFA World Cup, yielding 941 samples (Figure 7). FIFA also claims that since January 2022, each player on the quarter-finalist teams has been checked more than 4.5 times on average.

9. Prohibited drugs and use statistics

WADA's yearly list of illegal drugs is divided into three sections. In the first case, illegal drugs and procedures are forbidden both during and after the competition. Anabolic agents (S1), peptide hormones, growth factors such as substances and mimetics (S2), beta-2 agonists (S3), hormones and metabolic modulators (S4), diuretics (diuretics), and other masking agents are examples of these (S5). Manipulation of blood and its constituents is likewise banned at all times (M1), including techniques for transfusing blood to an athlete, even his own. Chemical and physical manipulations (M2) are already activities to substitute urine and/or change its qualities in the same group. Genetic doping (M3) is not permitted at any moment. Stimulants (S6), narcotics (S7), and cannabinoids (S8), such as hashish, marijuana, spices, and glucocorticoids, are only forbidden in competition (S9). The third section of the list includes alcohol (P1) and beta blockers (P2), both of which are restricted in specific activities, such as motorsport.

WADA develops and publishes yearly statistics reports on doping detections by certified labs as part of its anti-doping transparency function. The most recent of these reports is the 2021 report, which is now available on the Anti-Doping Agency website. He provides some intriguing facts on illegal substances, the usage of which sportsmen have been detected. In terms of frequency of usage, anabolic (S1) are the most popular. Anabolic steroids were utilized by almost one in every two athletes identified as dopers, accounting for 40% of all documented anti-doping violations. Anabolic drugs (including anabolic steroids) are used in medicine to help patients recover from significant long-term diseases, and in sports to help athletes gain muscle growth. Anabolic substances promote protein synthesis in the body, speed up the production and renewal of cells, tissues, and muscular structures, and therefore boost the body's anabolic activities (Table 2).

To comprehend the function of anabolic in our bodies. The catabolic process is usually accompanied by the release of energy. Hormones control the severity of this process. For example, glucocorticoids (steroid hormones generated by the adrenal cortex) hasten protein and amino acid decomposition. Simultaneously, they block glucose catabolism and promote its anabolism. However, insulin, a pancreatic peptide hormone, enhances the intensity of glucose catabolism while inhibiting protein catabolism [34].

Catabolism, on the other hand, is the inverse of anabolism. It is the process of creating complex chemicals from simple elements. Proteins, lipids (fats and fat-like substances), polysaccharides, nucleic acids, and other high molecular weight cellular components are generated as a consequence of anabolism. Body tissues, particularly muscles, will be generated from them in the future. The

anabolic process involves a number of hormones and chemicals. For example, testosterone, the primary male sex hormone, is still among the anabolic agents most often utilized by athletes (it now occupies 15th place). However, stanozolol, a steroid medication, is the class leader in illegal drugs use (15%). WADA figures show that one in every five athletes found taking anabolic steroids did so. Stanozolol is an anabolic steroid that may penetrate a cell's nucleus and activate its genetic system. As a consequence, there is an increase in the synthesis of DNA, RNA, and structural proteins. It has the ability to both promote and repress anabolic processes. It promotes bone calcification. However, it, like other steroid medicines, has side effects that are harmful to the athlete's health. It should be emphasized that many people believe that stanozolol is one of the safest medications available. It is a modest androgen when compared to testosterone (male sexual hormone). As a result, the androgenic side effects of anabolic steroids should be reduced while using stanozolol.

We are specifically discussing virilization of the body, or the development of masculine secondary sexual traits in both men and women. The phenomena of "steroidal violence," which is related with the usage of anabolic steroids, should be mentioned here. Aggression and irritability are caused by an increase in the level of testosterone in the blood. At the same time, stanozolol's low androgenic activity renders it harmful for individuals with unstable mental health. Experts warn that this medicine is hazardous to the brain [35-37].

It has been utilized in sports for a long time. The athletic successes of Jamaican-born Canadian runner Ben Johnson in the 1980s disappointed another prominent athlete, Carl Lewis. He was also observed consuming the stimulant ephedrine. Johnson has deposed his colleague from the 100-meter management roles since 1985. However, Ben Johnson was dismissed in 1988 for taking stanozolol. Carl Lewis won gold at the Olympics in Seoul. Ben Johnson was subsequently sentenced to life in prison [42].

Stimulants (S6), often known as stimulants, have an effect on both the central and peripheral nervous systems. Ephedrine, pseudoephedrine, amphetamine, caffeine, strychnine, phenotropil, mesocarb (sydnocarb), and other comparable compounds are among them. Stimulants improve mental and physical performance, boost energy, and decrease weariness. Their method of action is to promote the passage of impulses inside the body. They release catecholamine neurotransmitters, principally noradrenaline (responsible for waking) and dopamine (a component of the "reward system"), and inhibit their recapture [38-39].

Stimulants placed second in anti-doping statistics. WADA believes that the use of stimulant drugs accounts for 15% of all infractions. Methylphenidate is the leader in this category, accounting for 20% of instances. It was originally used to treat nasal congestion in the 1940s and was not listed on the list of prohibited medications until 2010. It should be mentioned that methylphenidate was originally acquired from geraniums, but it is currently produced by synthesis. Methylphenidate has a lower potency than well-known stimulants like amphetamine and ephedrine, but it outperforms caffeine. Cocaine is the second most common drug (18%) [40].

Ephedrine, which first arrived in the late 1970s, is still one of the most popular stimulants, ranking sixth. During his usage in 1998, the famed Argentine player Diego Maradona was arrested and suspended for 15 months. Many of the stimulating ingredients, however, are included in cold medicines. Carl Lewis, a nine-time Olympic sprint and long jump champion as well as an eight-time world champion, was detected taking ephedrine and pseudoephedrine. He claimed, however, that he was unaware that the cold medicine he was taking included illegal substances.

The most common negative effect of stimulants are mental dependency, which is comparable to substance dependence. A abrupt refusal to take them causes melancholy, weariness, and sleepiness [41]. Caffeine and nicotine, by the way, are also stimulants. Nonetheless, they do not apply to illegal drugs [42]. WADA, however, continues to monitor their usage in order to discover abuses in sports. However, as well as several additional chemicals that may appear in future editions of the prohibited list.

Diuretics (S5) rank third in terms of number of applications (14%). Diuretics cause diuresis by interfering with the reabsorption of ions (mostly Na^+ and Cl^-) and water in the renal tubules. As the rate of urine generation rises, the liquid content of the body's tissues decreases. Diuretics (furosemide, amiloride, chlorthalidone, acetazolamide, and others) are used in sports for a variety of reasons.

Other illegal medications are eliminated from the body via urine. Increasing the density of urine also helps to conceal its usage. Diuretics may effectively reduce an athlete's body weight while competing in various weight divisions. Diuretics may make you look better in sports like fitness, figure skating, and gymnastics. Glucocorticoids (S9) account for 6% of the total and rank fourth on the list. Glucocorticoids have a wide range of effects on the body, including metabolism. They are steroids as well, but unlike "anabolic," they have a reverse catabolic effect and do not boost athletic performance when taken alone. However, we believe it is feasible in conjunction with other medications. Budesonide, which communicates nothing to the reader (29%), is first in terms of applicability. However, on the second, prednisolone (22%), prednisone (17%), and methylprednisolone (6%). As recently disclosed, Serena Williams is permitted to utilize all of these synthetic glucocorticoids.

Table 1: Potential is defined as the relative easy to use the gene in an athletic setting in relation to the expected effect [27]

Genes	Potential	Risks Controlled	Risks uncontrolled
Erythropoietin	++++	±	++++
Insulin-like growth factor (IGF-1)	++	-	++++
Vascular endothelial growth factor (VEGF, Fibroblast growth factor (FGF)	+	±	++++
Growth hormone (GH)	+	-	++++
Myostatin/fallistatin	++++	?	++++
Endorphins, Enkephalins	+	?	++++

Range: ++++: easy to use, great potential, difficult to use, little effect expected. Risk is the health risks for the user when such a gene is introduced. Range: ++++: potentially dangerous for health

Table 2: Substances Identified in ADAMS as AAFs (Adverse Analytical Findings) in Each Drug Class (All Sports) [38]

Substance Group	Occurrences	% of all ADAMS reported findings
S1 Anabolic Agents	875	40%
S6 Stimulants	348	16%
S5 Diuretics and Other Masking Agents	310	14%
S4 Hormone and Metabolic Modulators	247	11%
S9 Glucocorticoids	124	6%
S3 Beta-2 Agonists	68	3%
S8 Cannabinoids	92	4%
S2 Peptide Hormones, Growth Factors and Related Substances	98	4%
S7 Narcotics	22	1%
P1 Beta-Blockers	9	0.4%
M1 Enhancement of Oxygen Transfer	4	0.2%
M2 Chemical and Physical Manipulation	0	0%
Total	**2197**	

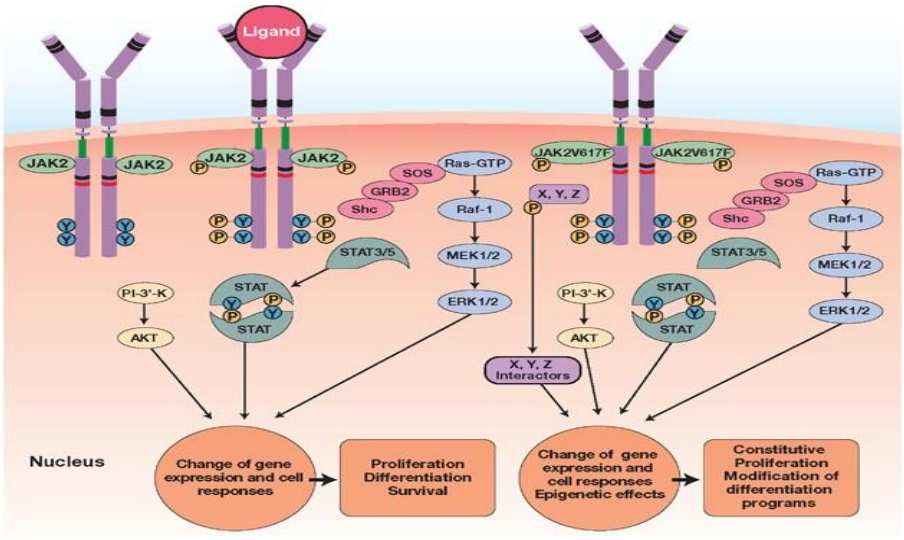

Figure 1: The EPO and JAK/STAT signaling pathways [15]

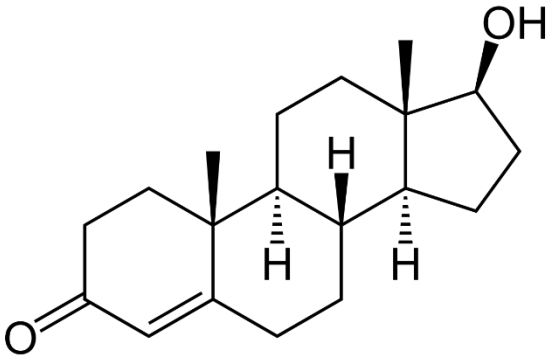

Figure 2: Testosterone structure (Bhasin et al., 2021) [19]

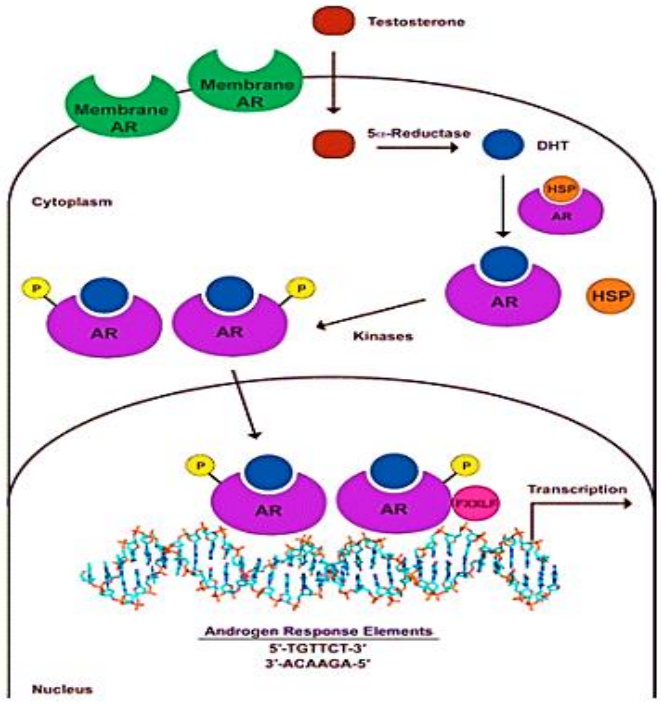

Figure 3: Activation of the androgen receptor by testosterone [20]
DHT (dihydrosterone), HSP (heat stock protein: thermal shock protein or chaperone protein), P (phosphorylation site), AR (androgen receptor)

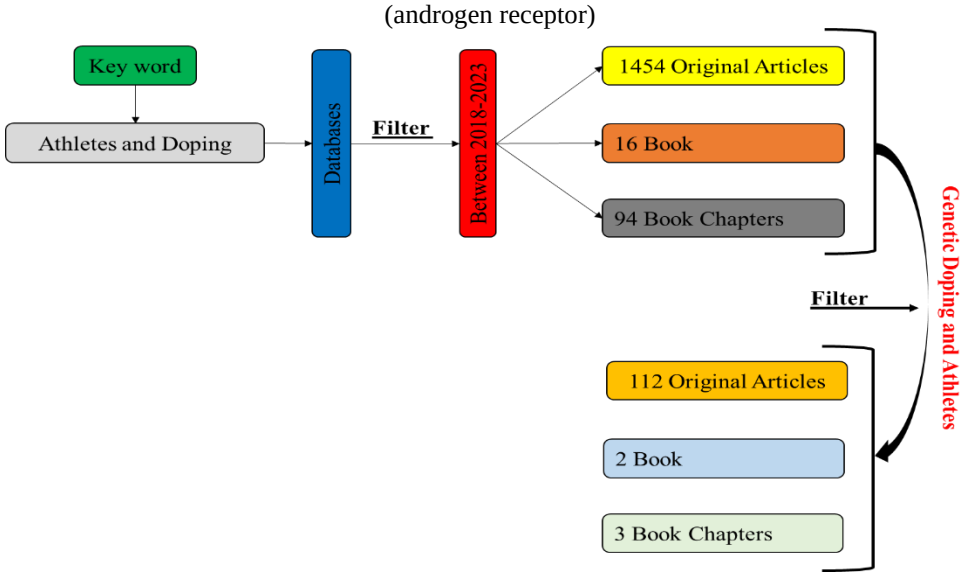

Figure 4: Procedure for searching for published publications about "Athletes and Doping" and for "Genetic Doping and Athletes"

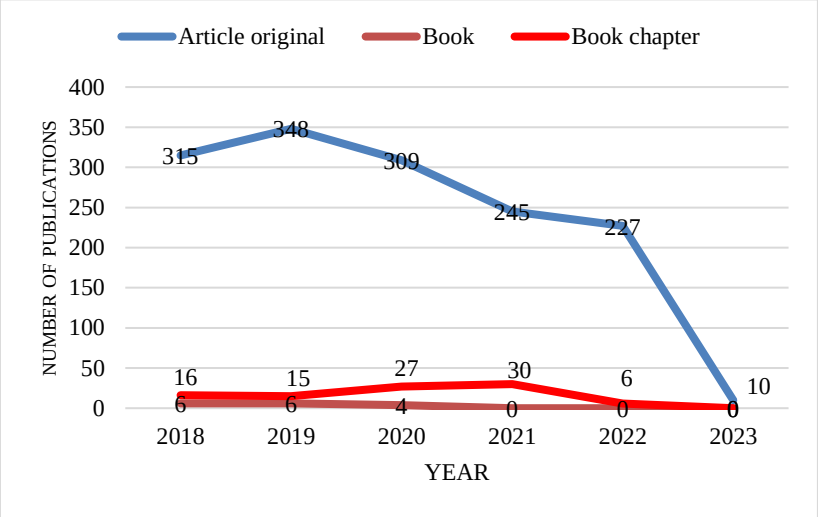

Figure 5: The number of articles regarding "Athletes and Doping" (2018-2023)

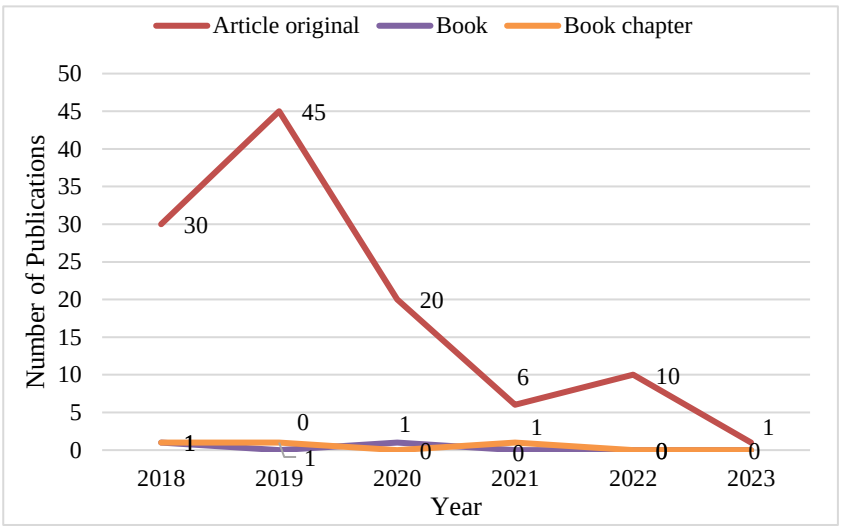

Figure 6: Amount of literature on genetic doping in athletics (2018-2023)

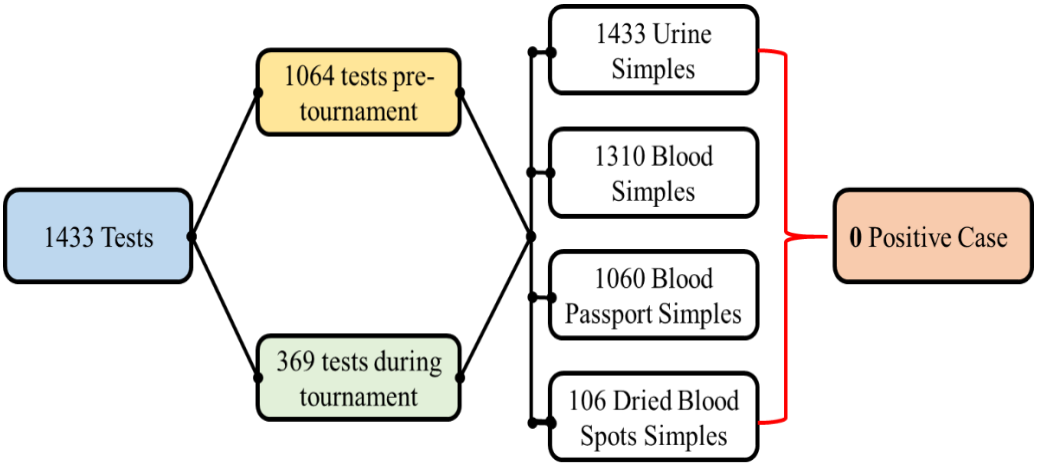

Figure 7: FIFA anti-doping procedure during Qatar-2022 World Cup

Hormones and metabolic modulators (S4) ranked third with 11%. This category also contains the meldonium disscovered in Maria Sharapova's possession. However, since it has been on the list since 2016, it is not indicated in the statistics. Tamoxifen is the first. Some compounds are classified as antagonists or agonists in biochemistry and pharmacology. Tamoxifen acts by inhibiting estrogen receptors. Estrogens are feminine sex hormones that are also generated in the male body. Tamoxifen is used with anabolic steroids. Its goal is to prevent the negative consequences of testosterone conversion into estrogen. Excess testosterone is produced in the body when anabolic steroids are used. It is diverted by flavouring because it cannot be entirely digested in a conventional manner. As a consequence, testosterone (male sex hormone) becomes estrogen (female sex hormone). For male athletes, this poses a danger to feminization: the development of female sexual features. Tamoxifen inhibits the development of this undesirable condition by blocking estrogen receptors.

Norwegian athletes with asthma who win numerous international contests use beta-2 agonists from group S3. Asthmatics account for 69% of Norwegian Olympic medalists. But, of course, the Norwegians are unconcerned since they all have license to take these substances. And whether the medications they use offer them an advantage over their rivals is a point of contention that has yet to be addressed. Beta-2 agonists rank sixth in statistics and are abused in 4% of cases. To begin, agonists are chemicals (drugs) that enhance or stimulate the functional activity of a certain kind of receptor. Although the hormones and neurotransmitters indicated above are agonists, it is not common to refer to them as such. In respiratory tract cells, beta-2 agonists activate beta-2 adrenergic receptors. They are referred to as beta-2 since there are also beta-1 and beta-3. Beta-1 receptors are found in salivary glands, heart area tissues, and a few other places. Beta-3 receptors are present mostly in fat fibers, which are responsible for fat storage and exchange for other substances and organs.

Thus, beta-2 agonists, by interacting with beta-2-adrenoceptors, contribute to bronchial expansion, which improves gas exchanges and, as a result, provides an edge over other athletes. But only if we're talking about a healthy athlete utilizing drugs, not a true asthmatic. 4% of the abuse is attributed to Group S2, which comprises peptide hormones and growth factors. It is controlled by erythropoietin, a kidney hormone. It regulates erythropoiesis (formation of red blood cells by erythrocytes). Lance Armstrong, an American cyclist, was banned for life in 2012 for drug usage and distribution. Armstrong not only utilized, but also disseminated erythropoietin to his coworkers. Erythropoietin stimulates red blood cell formation and raises hemoglobin levels in the blood. As a consequence, the athlete's physical performance improves as the oxygen supply to the muscles improves. It is utilized in endurance sports such as long distance running, cycling, walking, cross country skiing, and biathlon.

Cannabinoids (S8) round out the list of chemicals that passed the 1% threshold, having been used by 4% of athletes who tested positive for doping. Marijuana is supposed to enable athletes to minimize pre-debut excitement and relax. At the same time, it causes addiction and smoking, both of which have serious implications. In 2009, American swimmer Michael Phelps, a 23-time Olympic winner, was convicted of marijuana use and prohibited from competition for three months [43].

10. Preventive solutions against sports doping

Models of various types of physical culture and sports activities in the organization of primary prevention of doping among adolescents and youth contain the following components: psychophysical component; anti-doping propaganda; sports and educational staff training. Based on worldwide experience, numerous techniques to mitigating harmful social phenomena may be distinguished [44]: (1) Knowledge approach: disseminating information on the harmful effects of doping on individuals and society, as well as the destructive nature and dangers of such behavior, (2) Doping is considered to be the result of a problem and underdevelopment of the emotional domain; the focus of preventative interventions is on the development of thinking and self-regulation abilities, as well as the development of so-called "emotional intelligence"; and (3) The interpretation of illegal drug consumption as a consequence of a lack of crucial vital skills, an inability to cope constructively with issues and accomplish goals via other methods; the focus of preventative efforts on the development of these skills and abilities, (4) The importance of social variables is emphasized. This method to preventive aims to enhance the ability to resist the harmful effect of the social environment, as well as to normalize interactions between children and adolescents and their peers and adults, (5) Instilled in young people the importance of health as a source of well-being, as well as the necessity to maintain a healthy lifestyle, (6) Involve young people in activities and ideals that are incompatible with the use of illegal drugs.

11. Conclusions

Sport is a component of society and reflects the events that occur in a person's life. It is a noble habit that is currently being undermined by the employment of fraudulent ways to improve performance in sports competitions. Social workers and psychologists believe that the concept of "chemical or genetic doping behavior" is a psychological issue in the first place, since the athlete's obsession for winning overrides his morality, leading him to employ doping methods to overcome performance concerns. To resolve this concern, it is necessary to more actively implement educational programs for the primary prevention of drug use (doping) in sport among young people, as well as to ensure the social adaptation of young athletes and their integration into the sports environment in accordance with educational objectives. As a result, the legal framework of current international standards, as well as the global infrastructure of anti-doping policies, must be aligned to keep up with the technological evolution of doping methods.

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