The World Anti-Doping Agency’s position on ergogenic and recovery pharmacological means and the major principles of their legal usage by athletes

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Summary
Pharmacological correction is focused on the improvement of athletes’ physical work capacity as well as on their adaptation to increased physical and psycho-emotional loads. The tasks of sports pharmacology in sport and particularly in the Olympic sport are considered as follows: correction of metabolic disorders aiming to maintain and improve physical work capacity of athletes; increase of body adaptation stability and immunological resistance to the effect of intensive, prolonged physical loads and psychological tension; improvement of adaptation to climate and time zone changes, i.e., jetlag prevention and correction; optimization of recovery processes after the loads of different direction, volume, and intensity; prevention of over-exertion and pathological states, related to the impact of physical loads.

This range of tasks necessitates the unavoidable usage of great number of pharmacological aids, influencing various components of metabolism in the body of athlete. It should be noted that any pharmacological aids, aimed at improvement of physical work capacity and optimization of the recovery processes, might be insufficiently effective or inefficient at all in the presence of pre-clinical occurring of pre-pathological states and diseases as well as in the absence of adequate dosage of physical loads.

While using various means for sports activity pharmacological support, it is necessary to clearly identify the metabolic component that they are influencing, the mechanisms of their action, and, ultimately, the nature of their impact on training process efficiency. Contraindications to the application of various pharmacological aids, their interactions, and potential side effects should be taken into account as well.

Based on the analysis of modern literature data and their own data, the authors of the article have formulated five basic principles to be followed while designing the programs for sports preparation under the aspects of pharmacological support.

The very first principle says that any pharmacological impacts, aimed at acceleration of the recovery processes after loads and increase of physical work capacity, are ineffective or minimally effective in the case of unreasonable prescription as well as in the absence of an adequate training process design. Assessment of the efficiency and the validity of training load setup, in its turn, should be based on the results of medico-pedagogical examination of an athlete in the course of long-term adaptation and appropriate remedial and pedagogical control.

The second principle describes application of pharmacological aids as accelerating the course of the natural recovery processes after loads and stimulating work capacity. While prescribing pharmacological means of such direction, one should clearly understand the objective of their usage, the main mechanisms of their action, and, on that basis, the direction of the impact on training process efficiency as well as contraindications, possible consequences of cross-interaction, and side effects. In order significantly to reduce the incidence of side effects, the gold standard and the “agent of choice” may be metabolic and metabolitotropic substances, which include, for instance, L-carnitine, succinic acid and its derivatives, and L-arginine based preparations and dietary supplements. It should be added that the value of the above listed substances with indirect or direct cardio-protective effect during intensive physical loads had increased significantly in 2015–2016 due to the WADA’s prohibition of trimetazidine and meldonium usage by athletes.

The third principle says that one should pay attention at such parameters of preparation actions as acute, cumulative, and delayed effects as well as differentiate the impacts upon power, capacity, economy, and reliability. The efficiency assessment of applied pharmacological means is of crucial importance depending on the period (stage) of training cycle, specialization, skill level, character of training, competitive load energy supply, initial functional state of athlete’s body as well as on anthropometric, sex, and age peculiarities.
The fourth one, in the context of training process intensification, deterioration of its ecological constituent, the increase in overall morbidity and the toughening of the WADA's requirements, describes the individualization of the formed pharmacological programs for sports preparation maintenance as becoming extremely important. It should be noted that the application of a complex of pharmacological ergogenic aids is expedient and the most effective when used during preparation of microcycles, necessarily varying with medicinal preparations and dietary supplements to properly follow settled tasks. Therefore, the methods of training should remain the major aspect in the achievement of optimal physical work capacity with pharmacological correction being an auxiliary, although, very important component.

And, finally, one should bear in mind that an athlete could be prescribed only registered preparations or dietary (food) supplements (as ergogenic aids or restorative agents) based on substances not prohibited by the Medical Commission of the International Olympic Committee, i.e., not included in the WADA's Prohibited List.

**Keywords:** sport, sports pharmacology, ergogenic aids, metabolitropical substances, anti-doping legislation.

Problem statement and its connection to important tasks of the study

The problem of athlete's body adaptation to progressive action of multiple repeated variants of physical load is becoming extremely significant during the long-term sports activities. The higher the athlete's skills level is, the closer body's functional state comes to the limit of its biological capacities and the less probable an adequate effect of applied variants of repeated training loads becomes; at the same time, the intensification of loads most frequently leads to excessive fatigue and diseases (Makarova, 2013). Unfavourable course of adaptation process may be accompanied by the signs of adaptogenic pathology, at which, as a result of adaptation mechanisms impairment, different degrees of homeostatic balance disturbance and even the degradation of tissues may be observed, resulting in deterioration of health and the competitive activity results (Quiles et al., 2009). These events contribute to premature withdrawal of talented athletes. Thus, it raises the necessity of biological structure-based innovative methods application and body functioning optimization in order to enhance the work capacity along with the risk reduction of work-related diseases. Actually, we are talking about extra-training medico-biological means, and, above all, the pharmacological ones.

Analysis of recent studies and publications

Physical work capacity stimulation and its methodology represent the key issues in sport area that cover different numerous aspects of sports training and constitute an integral part of recovery. Overcoming the difficulties, caused by the search for an optimal mode of training loads in individual sessions and micro-cycles that create adequate conditions for the course of the recovery and special adaptation processes, may be implemented in two directions: firstly, at the expense of proper optimization of educational and training process planning; secondly, by the means of task-oriented application of various means of physical and mental performance stimulation and improvement of the recovery processes. In this regard, one should bear in mind that, in order to exert their biological influence, the pharmacological means of such effect use the energy, which is mainly required to provide the motor activity of an athlete. Therefore, they should not be used unreasonably. To be specific, the knowledge of the regulations of recovery means application and work capacity stimulation (ergogenic aids) allow achieving high athletic results.

Professional level of athletes, especially elite ones, is achieved under the conditions of prolonged psychological stress, climate and time zone changes (desynchronosis), and constant increase of the intensity and the duration of physical loads. If we also consider the deterioration of environmental conditions as a result of man-made human activity, it becomes clear that athlete's body operates on the brink of reserve capacities (Antonio, Stout, 2002). Combined, simultaneous, or successive outcome of several factors leads to their mutual impact on the body. In response to the influence of adverse occupational-environmental factors of determined dose, intensity, and duration, the state of marginal tension of adaptation mechanisms with reversible maladaptation phenomena may develop as well (Makarova, 2013). Proceeding from structural-functional integrity of the compensatory and adaptive processes, one may suppose that, in response to the action of an extreme stimulus, an athlete develops the condition, which is characterized by the transition from marginally permissible tension of compensatory reactions that ensure homeostasis maintenance or the state of de-adaptation (Platonov, 2015). Thus, pharmacological support should prevent
the development of this phenomenon (Scharhag et al., 2013; Berlett, Levine, 2014).

Therefore, elaboration of means and methods for extreme state correction in athlete is the crucial problem of sports pharmacology as well as sports medicine, biochemistry, pathophysiology, etc. and requires interdisciplinary approaches to its solution. Ensuring improvement of general and special work capacity during considerable physical loads with the help of extra-training means of recovery and prevention of overtraining state will gradually become an important constituent for maintenance of athletes’ health and quality of life. Consequently, for the purpose of anticipated levelling, the side-effects of training and competitive processes over the last 20 years has appeared as an extremely “aggressive” system of post-load recovery that includes differently directed physical, psychological, and, especially, pharmacological effects, which are frequently lacking the common logic of application and may even contradict each other (Berlett, Levine, 2014). Under such conditions, the application of extra-training means, stimulating physical work capacity, should be extremely well-considered and based on actual homeostatic changes in the body of an athlete.

Objective of the work – formation of the main principles of pharmacological ergogenic aids application and recovery means in elite sport on the basis of metabolic mechanisms and physiological influence on the body with consideration of current requirements of the World Anti-Doping Agency (WADA).

Substantiating the methods of pharmacological means usage during intensive physical load

Due to the necessity of developing and introducing the means and methods of pharmacological correction, the task of their systematization, the possibilities of well-grounded application, and the study of their efficiency in the practice of elite sport became especially important. Medico-biological aspect of the problem of recovery and subsequent improvement of physical work capacity should be divided into two interrelated directions: 1) recovery of athletes in the course of educational and training process, followed by stimulation of general and special work capacity; 2) work capacity recovery after diseases, injuries, over-fatigue, i.e., proper medical rehabilitation. The first direction is pharmacologically correctional, whereas, the second one refers to the sphere of sports medicine (Nutritional ergogenic aids, 2004).

Methods of pharmacological influence on human body under the conditions of intensive sport activities, aimed at health maintenance of elite athletes, are based, in the first place, on the usage of WADA’s non-prohibited pharmacological means (pharmaceutical preparations and dietary supplements) (Scharhag et al., 2013), which contribute to acceleration of recovery processes and increase of physical work capacity; from the angle of biochemistry, those tend to enhance the degree of antioxidant protection of athlete’s body, reduce the severity of endotoxicosis syndrome, accelerate the processes of physiological vasculo- and angiogenesis and hematopoiesis, erythropoiesis, improve metabolic maintenance of muscular activity, including contractile activity of cardiac muscle through stabilization of metabolism in cardiomyocytes as well as stimulate improvement of the central nervous system functioning, etc. (Degtyareva et al., 2009; Gavrilova, Zemtsovsky, 2010).

The effects of applying the majority of means and methods for correction of strenuous muscular activity are implemented through activation of specific and nonspecific mechanisms of recovery and stimulation of work capacity, general and special, in particular (Quiles et al., 2009). Usage of these means that belong to pharmacological ergogenic aids may significantly speed up the recovery processes, increase strength, endurance, improve coordination capacities, concentration, and other mental characteristics. Therefore, one of the main tasks of sports pharmacology is not the treatment but the mediated and target-specific impact on the competitive activity results through maintenance of numerous homeostatic components that determine professional qualities of the athlete provided that his/her health and quality of life are preserved (Gomez-Cabrera et al., 2008).

Taking into account the mechanism of pharmacological influence on physiological and biochemical processes that occur in the body, pharmacological ergogenic aids (PEA) may be divided into the following groups (Fig.). Application of PEA today is based on theoretical concept of the task-oriented metabolism regulation during physical loads by the means of expanding the “bottlenecks” of metabolic cycles with the help of some low molecular weight metabolites and stimulators of different elements of biosynthesis (Nutritional
ergogenic aids, 2004; Gomez-Cabrera et al., 2008; Scharhag et al., 2013).

In our opinion, five basic principles of pharmacological support in the practice of athletes’ preparation, which stem from the existing in the literature postulates, can be formulated (Nutritional ergogenic aids, 2004; Gorchakova, 2010; Platonov, 2015). **The very first principle** says that any pharmacological impacts, aimed at acceleration of the recovery processes after loads and increase of physical work capacity, are ineffective or minimally effective in the case of unreasonable prescription (unsound dose, preparation period, etc.) as well as in the absence of an adequate design of training loads of a certain intensity, energy orientation, and volume. Assessment of the efficiency and the validity of training load setup, in its turn, is based on the results of medico-pedagogical examination of an athlete in the course of long-term adaptation and appropriate remedial and pedagogical control.

**The second principle** describes creation of optimal conditions (including the usage of pharmacological means) that should provide acceleration of the course of natural recovery processes after loads and stimulation of work capacity. While prescribing pharmacological means, one should clearly understand the objective of their usage, the main mechanisms of their action (and, on that basis, the direction of the impact on training process efficiency) as well as contraindications, possible consequences of cross-interaction, side effects, and complications (Shilov, Knyazzeva, 2013). In order significantly to reduce the incidence of side effects, the gold standard and the “agent of choice” may be considered as metabolic and metabolitropic substances, which include, for instance, L-carnitine (such preparations as cardonat, karniel, agvantar; supplements CarniPlus, etc.), succinic acid and its derivatives (such preparations as meksidol, meksicor, limontar, armadin, nicomex, cytoflavin; supplements Yantavit, Yantarit, Mitomin, Yantarin-Sport, etc.), and L-arginine-based preparations and dietary supplements (such preparations as tivortin aspartate, tivorel, tivomax, angiobetarin, etc., supplements vasoton, L-arginine of different manufacturers, 500 mg and 1000 mg tablets or capsules). It should be added that the value of the above listed substances with indirect or direct cardioprotective effect during intensive physical loads had increased significantly in 2015–2016 due to the WADA’s prohibition of trimetazidine and meldonium usage by athletes.

**The third principle** says that, while applying pharmacological preparations for physical work capacity stimulation, one should take into consideration their acute, cumulative, and delayed effects as well as differentiated impact upon such parameters of physical work capacity as power, capacity, economy, mobilizability, and realizability, mechanism of preferential energy
supply of specific type of work, etc. (Gorchakova et al., 2010; Makarova, 2013). Low efficiency of pharmacological means for stimulation of work capacity and recovery may be observed in the case of unreasonable prescription (unsound dose of pharmacological substances, improper period of preparation, unaccounted preferential mechanism of energy supply during microcycle and mesocycle, etc.) or in the absence of adequate dosing of training loads. Well-reasoned prescription of PEA is also impossible in this case without the results of medico-pedagogical examination of an athlete in the course of long-term adaptation and appropriate remedial and pedagogical control at the given moment.

The fourth one outlines an individual usage of pharmacological means for improvement of athletes’ work capacity that should be based on the account of functional state of the major body systems and the stage of preparation within the annual macrocycle structure. Sports physician participation in individual selection of preparations and dietary supplements is mandatory (in cooperation with the coach who sets the tasks before the physician at each stage of preparation proceeding from the determined objectives of training character) (Nutritional ergogenic aids, 2004; Scharhag et al., 2013). In general, the selection of individual complex of pharmacological means for each athlete should be based, first of all, on a range of parameters, in particular, following the results of current and dynamic medico-biological studies, whereas important role belongs to the laboratory and functional diagnosis, since it allows to identify general metabolic link and a functional system, limiting physical work capacity of an athlete on the whole and at the given stage, in particular. At the same time, prophylactic measurements are taken to prevent the development or eliminate the main nonspecific symptoms of de-adaptation, which should include correction of the deficiency of functional reserves of neuroendocrine regulation, energy misbalance, improvement of structural and functional state of cellular and subcellular membranes, and antigenic-structural homeostasis (Platonov et al., 2010; Shilov, Knyazeva, 2013).

To review the above mentioned measurements, one should take into consideration not only the possibility of their implementation with account for time reserve (for instance, before the major competitions) and availability of sufficient efforts and finances but, above all, the stage and the period of preparation within annual macrocycle structure, sports event and specialization, skill level of an athlete, his / her age, and gender peculiarities, etc. Efficient and athlete health-oriented application of the complex of ergogenic aids and achievement of high sports result are possible as a consequence of strict pursuance of these principles only.

The fifth principle, due to constant toughening and changing of anti-doping rules, emphasizes keeping track of pharmacological means inclusion into the WADA’s Prohibited List. Striking examples of sports physicians’ non-compliance with anti-doping regulations were the juicy scandals of using trimetazidine (preductal) in 2015 and meldonium (mildronate) in 2016 by the world top athletes. In order to avoid such situations, one should thoroughly monitor the inclusion of these substances in the list of controlled ones, since there is high probability of their appearance in the WADA’s Prohibited List next year. For instance, for the year 2018, it (The 2018 Prohibited List) has already included actoprotector bemitil, the structural formula of 2-ethylsulfanyl-1-H-benimidazole (Aghajanian, Chizhov, 2003), which was the basis for Antihot supplement to be created back then (Gorchakova et al., 2010; Platonov, 2010). This supplement helps athletes to adapt during rapid temperature changes (Shabanov et al., 2008) and to avoid desynchronosis (Solodkov, 2013) under the conditions of middle and high altitude training, in particular (Solodkov et al., 2014). There is a considerable probability that this substance, useful for maintaining circadian rhythms and improving adaptation of professional athletes to severe environmental conditions (Solodkov, 2013), will be banned in 2019. Therefore, sports physicians and pharmacologists should be extremely careful in its prescriptions beginning from the second half of 2018. Besides, modern conditions demand knowledge of numerous pharmacological nuances from sports physcians that are necessary to timely identification of preparation formula, i.e., to be able to recognize if dietary supplement contains prohibited substance that has unsystematised chemical name on the label (for instance, geraniol, which is methylheptanamine, according to structure refers to banned specific stimulators of central nervous system; the same is inherent to designer steroids manufacturers, who deliberately put their unsystematised names on the package label). The best way to avoid similar
situations should be the presence of a full-time sports pharmacologist in the team.

Conclusions

1. Pharmacological ergogenic aids of metabolic and/or metabolitotropic character are the most efficient and the least toxic substances for application at the stages of athletes’ preparation.

2. The usage of any pharmacological means as the ergogenic aids necessitates an obligatory in-depth medico-biological examination as well as continuous control of athlete’s functional state and pedagogical indices that reflect general and special physical work capacity.

3. Formation of pharmacological programs of ergogenic nature should be highly individualized in relation to sports event, discipline, qualification, etc. and take into account personal attributes of individual athlete regarding functional activity of major organs and systems of the body that may limit work capacity stimulation as well as vary depending on the density and direction of micro- and macrocycles preparation.

4. Constant warning of sports physicians and pharmacologists with respect to the components of the World Anti-Doping Agency’s Prohibited List should be the essential constituent of preventing the breach of anti-doping legislation by Ukrainian athletes.

Prospects for further studies

Future researches should consist of creation and/or improvement of the lists of the main non-prohibited groups of pharmacological means with consideration of their impact on metabolic and physiological pathways of ergogenic capacity formation of the body during intensive physical loads. The constant search for new pharmacological ergogenic aids on the basis of state-of-the-art technologies (both by means of streamlined synthesis de novo and introduction of means, already available in clinical practice pharmacology that were not used in sport) as well as their further experimental and practical testings are of tremendous importance.

REFERENCES

FARMAKOLOGINIŲ ERGOGENINIŲ PREPARATŲ VARTOJIMO PRINCIPAI OLIMPINIAME SPORTE IR ANTIDOPINGO ĮSTATYMU REIKALAVIMAI

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SANTRAUKA

Sportininkams teikiama farmakologinė pagalba gerina jų darbingumą ir organizmo pritaikymą prie vis didėjančių fizinių ir psychoemocinių krūvių. Olimpinio sporto farmakologijos uždaviniai yra šie:
1. Metabolinės pažeidžios korekcija palaikant ir didinant sportininkų fizinį darbingumą.
2. Organizmo adaptacijos prie intensyvės ir ilgalaikės fizinės ir psichologinės įtampos poveikio ir imuninio pasipriešinimo didinimas.
3. Organizmo adaptacijos prie laiko ir klimatinių juostų kaitos didinimas, arba desynchronizuoto profilaktika ir korekcija.
4. Pervargimo ir patologinės būklės, susijusios su fizinių krūvių poveikiu, profilaktika.

Siekiant įgyvendinti tikslus, tenka vartoti daug farmakologinių preparatų, darančių įtaką įvairioms metabolizmo grandims sportininko organizme. Reikia atsižvelgti ir į tai, kad bet kurie farmakologiniai preparatai, kurie yra skirti fiziniam darbingumui didinti ir atsigavimui optimizuoti, yra nepakankami arba visai nefeifyktyvūs esant priešpatologinei organizmo būsenai, arba ligai, arba esant neadekvaciją fizinį krūvį dozavimui. Sportininkams, vartojantems farmakologinius preparatus, reikia gerai žinoti, kokios metabolizmo procesus jie veikia, kokie jų poveikio mechanizmai ir koks jų poveikis treniruojamų procesų efektyvinimui. Taip pat svarbu yra žinoti nepageidaučių šių preparatų vartojimo poveikį, jų poveikio pašalinį efektą.

Išanalizavę literatūros šaltinius ir apibendrinę savo tyrimo duomenis, autoriai suformuluvo šiuos pagrindinius principus, į kuriuos reikia atsižvelgti sudarant sportininkų farmakologinio aprūpinimo programą:
1. Visų pirma, bet koks farmakologinis poveikis, nukreiptas į atsigavimo po krūvių skatinimą ir fizinio darbingumo didinimą, bus neefektyvus arba minimaliai efektyvus jei šių preparatų vartojimas nebus pagrįstas, o treniruojamųjų procesas nebus adekvatus. Treniruojamų procesų efektyvumo ir pagrįstumo įvertinimas, suvokiant, turi būti pagrįstas sportininko pedagoginių ir medicinių tyrimų duomenimis.
2. Antra, vartojant farmakologinius preparatus turi būti skaitomi įvairūs atsigavimo procesai ir stimuliuojamųje darbingumą. Siekiant sportininkių labiau efektyvumo įvertinimui ir greičiau pasiekti optimalaus fizinio darbingumo, būtų svarbu tapti įvairiausių farmakologinių preparatų kūrėjų ir informuoti juos apie tai, kad per daug kartų naudojimas gali sukelti duris į neveikiamas preparatų vartojimą. Taip pat reikėtų žinoti, kaip jie veikia su neveikalių preparatais ir kurie preparatai gali būti naudojami kaip įvairiausių funkcinės funkcijos apimtis.
3. Trečia, intensyviai fiziniais krūvius, blogėjant ekologinėms sąlygoms, didėjant sergamumui ir griežtėjant WADA reikalavimus vis svarbesnis tampa sportininkų farmakologinio aprūpinimo programų individuālizavimas. Svarbu tai, kad ergogeninių poveikių farmakologinių preparatų kompleksas vartojimo būtų tikslinamas ir efektyvus rengimo metu taip pat būtų naudojamas arba maisto papildai, tokiu atveju naudojant jų efektyvumą. Taip pat reikėtų žinoti, kaip jie veikia su neveikalių preparatais ir kurie preparatai gali būti naudojami kaip įvairiausių šalutinių poveikio terapija. Taip pat būtų svarbu žinoti, kaip jie veikia su neveikalių preparatais ir kurie preparatai gali būti naudojami kaip įvairiausių šalutinių poveikio terapija.
4. Pagaliau reikia, kad sportininkams galima vartoti tik įregistruotus ergogeninius ir atsigavimą skatinančius preparatus arba maisto papildus, kurių sudėtyje neįkvieta WADA draudžiama medžiagų.

Raktažodžiai: sportas, sporto farmakologija, ergogeninės medžiagos, metabolinės substancijos antidopingo įstatymas.