

Project Review

“Pharmacological manipulation of the central nervous system: Evidence of performance benefits and implications for the list of prohibited substances”

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The fatigue that accompanies prolonged exercise is most often ascribed to events occurring in the periphery (glycogen depletion, dehydration). Recent evidence, however, suggests that the central nervous system (CNS) plays a critical role, especially during exercise in the heat. This is an important consideration, as many major championships take place during the summer, often in countries with warm climates.

Many stimulants acting on the CNS are included in the WADA Prohibited List; they can enhance performance and may pose a risk to health. Pharmacological manipulation of the CNS function can influence mood, the sensation of effort and/or thermal stress, cognitive function and tolerance to pain and discomfort. Drugs that manipulate brain neurotransmitters, in particular serotonin, dopamine and noradrenaline, have been shown to influence exercise performance, but many of these agents are not currently included on the Prohibited List. Many of these drugs are used in the treatment and management of a wide variety of psychiatric disorders, so the pharmaceutical industry is constantly producing novel, more selective and more powerful agents, with the potential for marked effects on exercise performance. Athletes may have legitimate reasons for their use (under Therapeutic Use Exemption; TUE), but the inappropriate use of these agents by athletes to enhance performance is a distinct possibility.

These drugs, which are readily accessible over the internet, may also pose a risk to health as the normal limits to body temperature may be exceeded. At least one high profile death during the Tour de France has been ascribed to hyperthermia consequent upon amphetamine use.

This project will investigate the performance effects of drugs affecting the CNS, and will also consider the various factors (gender, environment etc) that may influence their efficacy. These findings will help determine the suitability of this class of drugs for future inclusion on the Prohibited List.

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Results and Conclusions

Stimulant medications enhance the activity of the central and peripheral nervous systems, producing a variety of effects including increased alertness, motivation and arousal, elevated heart rate and blood pressure, altered mood and the perception of a diminished requirement for food and sleep. Since these responses are likely to influence athletic performance, the aim of this project was to examine evidence that pharmacological manipulation of the central nervous system (CNS) can produce improvements in exercise performance. Anecdotal reports, evidence from screening procedures used by WADA-accredited laboratories, as well as TUE application statistics, provide some evidence that athletes may be increasingly turning drugs of this nature. Of course, athletes may have legitimate reasons for the use of these drugs, but these agents may also be used with the sole aim to enhance performance. Of particular concern would be medications employed in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.

The present series of studies provide clear evidence to support the inclusion of Bupropion on future Prohibited Lists. The findings of the studies presented here, along with our previously published work, demonstrate that bupropion can produce a significant, measureable and consistent improvement in exercise performance in warm conditions when taken at the maximal therapeutic dose (+7-9% vs a placebo condition). This response is apparent in both male and female participants, and does not appear to be influenced by pre-exercise nutritional intake. Increased exercise performance following administration of bupropion was associated with the attainment of higher core temperatures and heart rates during the later stages of exercise. This occurs without any apparent change in the subjects' perceived exertion or thermal stress. It is distinctly possible that the use of bupropion and methylphenidate by athletes competing in warm conditions will increase susceptibility to heat illness and potentially fatal heat stroke.

Contrary to the findings of a recently published report, ingestion of tyrosine (the precursor of dopamine) produced no effect on physical performance during an exhaustive cycle test; this response may be due to rate limiting steps in catecholamine synthesis from tyrosine. The administration of the Parkinson's drug, Sinemet (containing L-Dopa), also failed to significantly influence exercise performance, but performance may have been limited by side effects reported by some participants. S-adenosylmethionine (SAM) has become popular as an alternative therapy for the treatment/management of depression and other related disorders. Despite some effects on the physiological response to exercise, there was no evidence of a benefit to exercise performance following a 7 days of administration.

In conclusion, it appears that bupropion can produce a measureable and consistent improvement in exercise performance in warm conditions when taken at the maximal therapeutic dose. With this in mind, inclusion of bupropion on future Prohibited Lists appears to be warranted. Substances that alter catecholamine production do not appear to consistently influence performance, but further investigation is justified.

8) Publications/presentations related to the project

Peer-reviewed publications

Roelands B, Watson P, Cordery PAA, Decoster S, Debaste E, Maughan RJ, Meeusen R. A dopamine/noradrenaline reuptake inhibitor improves performance in the heat, but only at the maximum therapeutic dose. *Scandinavian Journal of Medicine and Science in Sports* 22: 93-8, 2012.

Cordery P, Peirce N, Maughan RJ, Watson P. The role of central catecholamines in the development of fatigue during prolonged exercise in women. *Applied Physiology, Nutrition, and Metabolism* (in preparation)

Cordery P, James LJ, Peirce N, Maughan RJ, Watson P. Effect of an acute dose of a dopamine precursor on time trial performance in warm conditions. *Journal of Applied Physiology* (in preparation)

Cordery P, Maughan RJ, Watson P. The effects of one week of oral S-adenosylmethionine supplementation on cycling performance and thermoregulation in warm conditions. *International Journal of Sports Nutrition and Exercise Metabolism* (in preparation)

Conference presentations

Roelands B, Watson P, Cordery P, Decoster S, Debaste E, Meeusen R. Is there a dose-response effect of a dual DA/NA reuptake inhibitor on performance and thermoregulation in the heat? Annual Congress of the European College of Sport Science. Liverpool 2011.

Cordery P, Watson P, Peirce N, Maughan RJ. The role of central catecholamines in the development of fatigue during prolonged exercise in women. Proc Physiol Soc 27, PC302. Physiology Society Summer Meeting. Edinburgh 2012.

Watson P, Enever S, Page A, Stockwell J, Maughan RJ. Tyrosine supplementation does not influence the capacity to perform prolonged exercise in a warm environment. The Physiological Society; Biomedical Basis of Elite Performance. London 2012.

Cordery P, Maughan RJ, Watson P. The effects of one week of oral S-adenosylmethionine supplementation on cycling performance and thermoregulation in warm conditions. International Sport & Exercise Nutrition Conference. Newcastle 2012.