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The clinical pharmacology of performance enhancement and doping detection in sports

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**DISCUSSION AND
CONCLUSIONS**

Pharmaceutical research and development has mainly been driven by the discipline of medicine, and for good reason: there is a large societal benefit to be gained in being able to use pharmacological agents to treat diseases. This societal motivator is perhaps less strong in other disciplines where drugs are used, such as doping in sports, but the experience in medicine could nonetheless be applied to develop knowledge and evidence in these disciplines as well. One lesson learnt from clinical pharmacology in medicine is that biological systems are complex and that performing successful pharmacological interventions is therefore not straightforward. This complexity is for example reflected in the low success rate for market approval of new drugs in drug development, which is currently around 10-15%.¹ For these few successful drugs, there is sufficient evidence that there is a beneficial effect in a certain population and that this benefit outweighs the potential harm of the treatment (positive benefit-risk assessment). This benefit-risk assessment is the cornerstone for the approval of drugs, both for the FDA and EMA,^{2,3} and factors such as study design and choice of endpoints determine the strength of evidence and the uncertainties that drive this assessment. This is relevant as most doping substances are therapeutics, often approved for medical use (see the World Anti-Doping Agency (WADA) Prohibited List⁴), but for none of these substances the assessment was focused on improving sports performance. Sports performance, a product of biological systems, is also determined by a complex system of factors (take for example endurance performance⁵), meaning that the evidence available on the medical application of a drug is not sufficient for understanding its specific effects in sports or its benefit-risk ratio in that setting. In addition, where in medicine we can target the sub-optimally functioning system causing a disease, the physiological system of athletes has usually optimised (to some extent) for the specific task due to training. This makes improving the trained system possibly even more difficult, not in the least because it is not evident to determine which factor(s) in that system could be successfully targeted with a pharmacological intervention. Moreover, even in medicine seemingly simple and well-understood symptoms or diseases can prove complex to treat. The Cardiac Arrhythmia Suppression Trial (CAST) for example was designed to suppress premature ventricular complexes (PVC) after myocardial infarction to reduce mortality. Although antiarrhythmics encainide and flecainide indeed reduced occurrence of PVC,⁶ mortality actually

increased in the randomised, placebo-controlled trial that followed.⁷ And in chronic kidney disease, where erythropoietin production is reduced causing anaemia, restoring haemoglobin to almost normal levels using recombinant human erythropoietin has been shown to cause only modest improvement in patient-reported fatigue and more importantly, increase the risk of stroke compared to placebo treatment.⁸ Such (counter-intuitive) evidence shows that clinical pharmacology can be more complex than perhaps anticipated, and that randomised, placebo-controlled trials, using relevant clinical endpoints are needed to reveal the true effect of a treatment. Or to put it differently: it has proven difficult enough to pharmacologically improve physiological systems when they are in a diseased state, improving the system beyond the normal state requires at least a similar degree of thoroughness. However, the first two chapters of this thesis show that the evidence for performance enhancing effects of substances that are termed doping is limited. Evidence for effects of combinations of substances is virtually absent. For most substance classes no robust studies have been performed, for some classes there is evidence that there is no positive effect on performance, and for only 5 out of 23 classes there is evidence of a beneficial effect. Moreover, a meagre 11 studies including a total of 266 subjects form the total evidence-base for pharmacological performance enhancement, a large contrast with the amount of studies and subjects that substantiate the benefit of therapies in medicine. Despite this, the conviction of the positive effect of (the combination of) doping substances is strong, which is the driving factor for athletes to abuse these drugs. The discrepancy between this belief and the available evidence is striking, and an effort to generate this missing evidence is therefore necessary. As in regular medicine, this should start by studying effects of single substances in well-designed studies, and only if deemed relevant based on this evidence and the potential pharmacological mechanism, for combinations of substances. For one substance class, recombinant human erythropoietin (rHuEPO), we describe in this thesis a contribution to this effort. Interestingly, when we applied a randomised, placebo-controlled study design, we showed that although increases in haemoglobin lead to an improvement in several surrogate performance markers in athletes, this did not improve clinical outcome, i.e. endurance performance. It is unknown whether these findings also apply to professional athletes, as these could not be included in the study due to

current WADA regulation. However, our study was the first to study effects on clinically relevant outcome measures in trained athletes, and there was no indication that the highest performing participants showed stronger effects of rHuEPO treatment. These findings emphasise, as we have seen in therapeutic studies, that pharmacological interventions induce complex effects which may be difficult to predict on a clinical level. Therefore, the selection of endpoints is critical for the interpretation and implications of findings, and our study in this respect touches upon another important shortcoming in doping research. Effects of a treatment should be evaluated based on relevant clinical outcome measures or validated surrogate markers, which is currently not always the case. One such often used surrogate marker in sports medicine, the lactate threshold, we have evaluated in this thesis, including the issues associated with the marker. By determining repeatability and the (limited) relation with actual sports performance, the value of such a marker as a surrogate endpoint can be better assessed. Finally, apart from evidence on the potential positive effects of doping substances, it is also relevant to gain knowledge on their safety profile. For rHuEPO we describe such a detailed assessment in this thesis, showing that endothelial activation occurs both through the pharmacological intervention alone and in combination with exercise, indicating a potential risk for athletes abusing these drugs. Summarizing these findings, we conclude that there is incomplete information and a clear lack of evidence for performance enhancement for the majority of substance classes on the Prohibited List, which could be considered alarming. A more systematic effort using well-designed research into doping substances could address these information gaps and thereby potentially reduce the unwanted use of substances that show no benefit on performance and/or evidence for negative effects. An additional problem that results from the lack of information, is that for all substances on the List there is a need for detection strategies and assays to catch cheating athletes. Not only is this an enormous operation that is very expensive and burdensome for both athletes and anti-doping agencies; in the final chapters of this thesis we show that the applied detection methods and procedures themselves are not without flaws and shortcomings either. The doping detection regulation that is in force therefore on top of all this does not unquestionably protect fair playing athletes or catch cheating athletes. Anti-doping efforts would greatly benefit from a more clinical pharmacological approach in this respect too, by making use of the

available (medical) knowledge and techniques. Overall, the combination of all of these uncertainties and shortcomings leads to a doping system that is not fully transparent, nor consistent, damaging both athletes and sports in general.

The conclusion that therefore must be drawn from all this is that sports medicine, just as regular medicine, needs to move towards a more evidence-based approach. This means implementing state-of-the-art study designs, with randomised, placebo-controlled, double blind set-ups and developing and using relevant biomarkers in these studies that measure and/or predict the pharmacological effect and accompanying impact on physiological performance and finally actual sports performance. The generated knowledge and evidence will benefit anti-doping efforts, improving decision-making and optimizing implemented procedures. For example, if there is strong evidence a substance class does not enhance performance, the class does not have to be prohibited. This evidence can in turn be used to prevent use through education, and detection efforts for these substances could be dropped. On the other hand, if there is strong evidence a substance class does enhance performance, the substance class should be prohibited, and all efforts should go into developing/improving reliable and robust detection methods, based on clinical pharmacological principles. If in addition there is also strong evidence of a health risk of such a class, this again can be used to deter use through education and targeted measurements of risk factors. The proposed shift would require, among others, revision of the WADA Code,⁹ but in many cases it would be possible to apply these evidence-based principles in the doping setting, perhaps with some minor modifications compared to regular medicine. If this approach is to be successful, a few obstacles may need to be overcome, and we will deal with three of these.

One evident obstacle is the amount of resources available for doping research, as the proposed studies and detection method development require funding. To be implemented structurally, a redistribution of funding will therefore be required. Some resources could be made available by focusing doping testing efforts only to the proven effective substances; a more structured and evidence-based approach to compiling the Prohibited List, would for example very likely result in a reduction of the enormous amount of substances on the List that need testing. Another source of funding might need to come from the business of sports itself. Astronomical sums are involved with many sport disciplines through media rights, salaries and sponsor

contracts. In order to keep sports fair, safe and sustainable, these parties need to be convinced of the motivation for the proposed changes, possibly opening the possibility to organise a part of these resources to flow to anti-doping efforts. For a sponsor for example, taking part in such a system might be interesting because of the publicity value of being associated with clean sports.

A second obstacle to implementing an evidence-based approach would be that new substances could be used by athletes while research is not yet concluded. We would argue that depending on how likely such a substance could enhance performance (based on the mechanism of action and (pre-)clinical studies), it can be placed on the Prohibited List until robust evidence is available, after which re-evaluation should take place. This evidence should contain information on the effect on sports performance as well as safety evaluations, generated in well-designed clinical studies using relevant outcome measures and taking into account the pharmacological mechanism of the substance. In the organised system we propose, this should not take more than a few years. So, if we look at the substances currently on the List, for many of these the required evidence could already have been available, as they have been on the Prohibited List for many years.

Finally, a potential obstacle would be that large trials are needed to power studies in order to detect very small beneficial effects that might be relevant for cheating athletes. As in regular medicine, this should be addressed by first establishing what a relevant effect would be and performing a power calculation for the number of subjects needed in a trial to detect such an effect. If it then turns out difficult to access a sufficiently large study population, combined and dedicated efforts should be made to deal with this problem, as is often the case in regular medicine. One consideration could be changing the current rules preventing elite athletes to participate in these trials.

Overall, there are challenges of implementing an evidence-based approach in doping research, but as described here they are not insurmountable. At the same time, we have shown in this thesis that the current approaches to doping regulation are undesirable. Moving towards an evidence-based approach in doping research will create better focused anti-doping efforts and will lead to more rational, transparent and objective doping regulation. This will only benefit athletes and spectators, and therefore in our view is the way forward.

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