The clinical pharmacology of performance enhancement and doping detection in sports

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INTRODUCTION

Since the discovery of pharmacologically active plants and other products, these have been applied to treat disease.[1] But apart from therapeutic use, man has applied such substances for other purposes as well. Opium and coca for example were used in ancient times by priests in religious ceremonies for their euphoric effects, mushrooms and cacti were taken for spiritual reasons, and substances like alcohol, caffeine and nicotine have long been used recreationally (see for example[2–4]). One other distinct deployment of pharmacologically active agents has been in sports, a practice that also dates back to ancient times. In the old Greek Olympic Games, alcohol, mushrooms and sesame seeds were consumed to enhance performance, and stimulants were used by gladiators in Roman times against fatigue and injury.[5] Since those first applications of pharmacological products, our understanding of the involved mechanisms and the related science has evolved tremendously, and with this increase in pharmacological knowledge the possibility and need to determine whether substances are actually beneficial grew. This led to the conception of evidence-based medicine, of which the fundamental aim is to prevent patients from being treated with ineffective agents or getting exposed to unnecessary harm. Pioneers such as Archie Cochrane and Iain Chalmers postulated the importance of thoroughly evaluating the available evidence before implementing a certain treatment in medicine.[6] Such ideas led to the formation of systems to rate the quality of evidence for a treatment, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[7] and a similar system from the Oxford Centre for Evidence-Based Medicine (OCEBM), partly depicted in Table 1.[8]

According to this latter method, systematic reviews of randomised trials and randomised trials are considered the two strongest levels of evidence for the benefit of a treatment (level 1 and 2 evidence). These carry more weight than for example non-randomised controlled cohort studies, case-control studies, or mechanism-based reasoning. This shows the study design is very important in classifying the strength of the evidence, but an additional contributing factor is the knowledge about the link between the measured pharmacodynamic marker(s) in a study and the actual outcome that is being studied.[9] More specifically, evaluating the effect of a drug on a surrogate marker, for example levels of Tau protein for effects on Alzheimer's Disease, only gives a high level of evidence of a beneficial effect if there is a clear and proven link between the surrogate marker and the intended endpoint. In turn, to understand this link a thorough knowledge about the link between the biological mechanism of the drug and the clinical effect is needed. These two factors are schematically plotted in Figure 1, depicting that the basis for obtaining evidence on the beneficial effect of a drug is to increase the knowledge about the relation between mechanism of action, marker and clinical effect.[9]

This overall concept termed evidence-based medicine has been accepted as an essential part of medicine, crucial to ensuring good quality healthcare by making therapeutic decisions based on weighed and evaluated science. These principles are therefore indeed strictly applied for drugs intended for therapeutic use, and products will not be approved for medical use unless there is a high level of evidence for benefit in patients. Moreover, prescribing drugs without such a level of evidence is considered bad medical practice. However, when pharmacological agents are used in different contexts, these same standards are not applied as strictly. Both in recreational drug use and drug use in sports, there seems to be a discrepancy between the extent of use and the available evidence on the intended and harmful effects. In this thesis we focus on the use of pharmacological agents in sports (termed doping) and apply standards of evidence-based medicine and clinical pharmacology to doping research. That pharmacological agents are being used in sports is clear from the (many) confessions by athletes and the World Anti-Doping Agency (WADA) testing figures,[10] despite regulation aimed to ban or at least restrict doping use.[11] And so if these substances are being used in sports, it is important to acquire knowledge about the related effects and harms. The biological, methodological and pharmacological fundaments are the same as in therapeutics, so why should these basic principles not apply in doping research?

We believe they should, the problem is that these principles are not yet embedded in doping research, as can be seen from some examples of reactions to our research:

- A referee (vigorously) defending the WADA Prohibited List in response to our review on the evidence for effects of testosterone: '*Various testimonies during [legal] trials indicate that athletes use testosterone to recover faster. This is particularly valid for multiday events. The number of volunteers in many intervention studies is often too limited to demonstrate a marginal but still existing effect on performance.*

Most studies are underpowered when dealing with elite athletes due to the difficulty to access this population for obvious ethical and availability reasons. You cannot administer doping substance to elite and competing athletes, this would seriously contravene the rules in force.'

- Dr. Olivier Rabin, WADA's science director, in The Times in response to our model-based publication describing the fundamental flaws in the salbutamol anti-doping procedures and the applied threshold level for triggering a violation:[12] '*... the organisation would vigorously defend its position and had already read the Leiden paper. "I read the article you refer to, and no, no concern at all. Nothing new as their model is based on three well-known studies," Rabin said. He added:* "WADA *has conducted several studies on salbutamol and continues to conduct studies on beta-2 agonists. We believe the current threshold is solid considering the scientific literature published on salbutamol over the past 20 years. Based upon the published and unpublished information in our possession, we see no reason to change the salbutamol threshold.*'
- In a letter to the editor regarding our publication of the effects of erythropoietin in cyclists:[13] '*In summary, the interpretation of their findings with* VO_{2peak} *testing and real-life competition is not convincing [...] In subjects with a similar training background and tested under carefully controlled laboratory conditions with a double-blind study design, erythropoietin clearly improves both* VO_{2peak} *and performance [in a time-to-exhaustion test] (7).*'

These examples indicate that several of the principles are being violated by experts in the field: classification of levels of evidence are not consistently applied, evidence that is available is not always recognised, and clinical relevancy is not determined based on validated (surrogate) markers. These issues should be overcome in order to provide a rational and evidence-based framework for doping research, and we feel that for a major part this is feasible. There are evident differences between therapeutics and doping (e.g. in terms of populations and existing regulation), and some of the described principles or methods might be more difficult or need more attention in the doping setting. But the fact that studies are underpowered to see small effects does not make evidence from n=1 trials (individual experience) stronger, nor can we accept an observed effect on surrogate markers to equal an effect on clinical outcome when this link is not sufficiently proven. In this thesis we therefore describe the initial setup for an updated doping research framework, and offer suggestions to reduce the gap that exists between this discipline and therapeutics. In the first chapters the foundation under doping is evaluated, where we investigate which evidence is available for pharmacological performance enhancement in sports and we describe a study investigating such effects for recombinant human erythropoietin in an evidence-based manner. A separate chapter describes that in the same study, we investigated the harmful effects of this treatment in athletes, showing that such studies could form the evidence-base for the benefit-risk assessment of a doping agent. Furthermore, we document the analysis of a commonly used surrogate marker and its relation to the clinical outcome of endurance performance to provide knowledge about the link between this marker and clinical effect. Finally, we discuss the detection of substances, a problem that is perhaps even more relevant to doping research than to therapeutics. Reliable and validated assays and related procedures here are paramount, and in the last two chapters we provide suggestions for improvement of several currently applied procedures and add to the available knowledge. In all chapters, state-of-the-art clinical pharmacological methodology is applied to address a particular doping problem, such as for example population pharmacokinetic modelling in the chapter on salbutamol detection. The combination of chapters shows that there is an overall lack of evidence in doping research, but also shows the feasibility of applying accepted standards from therapeutics to provide this necessary evidence. With that, this thesis aims to contribute to further evolution of this research field, just as the field of therapeutics has recently evolved towards evidence-based medicine.

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FIGURE 1 DIAGRAM OF TWO IMPORTANT FACTORS IN DRUG DEVELOPMENT Proving a clinical effect is done most rationally and efficiently by moving drugs to the upper right corner: obtaining a strong link between the molecular mechanism and the clinical effect, as well as measuring markers that relate to the clinical effect. With permission from Adam F. Cohen in Nature Reviews[9]

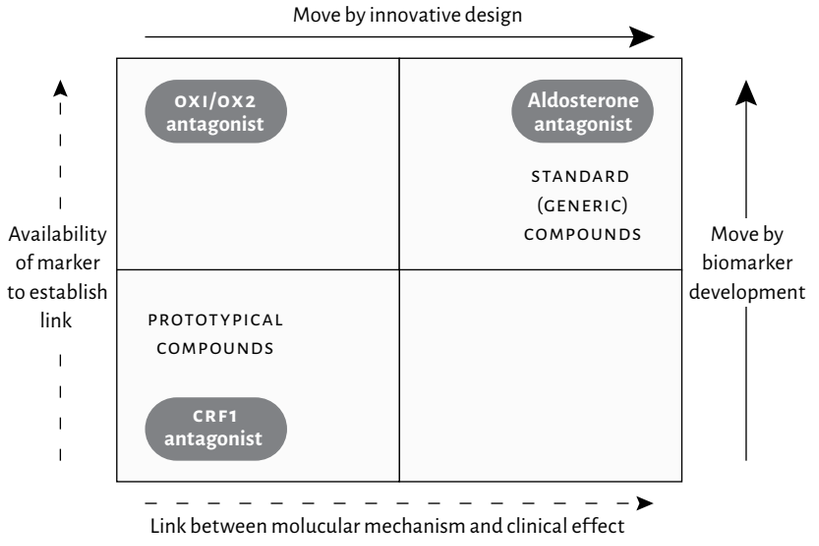

TABLE 1 OXFORD CENTRE FOR EVIDENCE-BASED MEDICINE 2011 LEVELS OF EVIDENCE

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort / follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning

** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.*
*** As always, a systematic review is generally better than an individual study.*