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Limits to Research on Drugs and Sport

P.M. Clarkson and H.S. Thompson[a]

[a] Department of Exercise Science, School of Public Health and Health Sciences, Totman Building., University of Massachusetts, Amherst, MA 01003

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1. INTRODUCTION

Athletes have used several types of drugs to improve performance. This paper will address whether scientific research supports the use of these drugs. The limitations of research on drugs acting as stimulants (amphetamines, ephedrine, cocaine, and caffeine), drugs used to reduce tremor and anxiety (β-blockers), and drugs used for weight gain or loss (anabolic-androgenic steroids, β-$_2$ agonists, and diuretics) will be considered.

2.0. LIMITATIONS TO RESEARCH

2.1. Amphetamines

Studies on the effects of amphetamines on performance have yielded equivocal results [1-4]. Several authors reported that amphetamines improved performance [5-13], while others found no effect [14-18]. Early studies were not well controlled and many used small samples sizes. The small number of subjects is an important limitation because of the large inter-subject variability in the response to the drug. However, as a general pattern, it appears that the amphetamines may work by off-setting or masking the perception of fatigue.

The statistical analysis of several studies has been criticized, with some studies only reporting mean differences or percentages of subjects who showed improvement. Williams and Thompson [19] pointed out that for their study, a mean difference of about 3.5 % in endurance performance was found between the drug and the placebo trial but this was not statistically significant. However, it is important to know that some individuals show a positive response and document that the improved response is repeatable and not due to chance. In most studies, despite the lack of statistical significance, some subjects did improve. Laties and Weiss [20] stated that a 1% difference would be difficult to detect statistically but very meaningful for the athlete who shows that much improvement. They offer the example in running performance where the average time needed to run a mile decreased about 0.4 s/year making a 1% difference an important change. They stated "..he who can run 1% faster today than yesterday will suddenly be years ahead of his time."

The dose and timing of the dose may influence the results of the studies. Generally higher doses resulted in improved performance. However, this is not always the case as studies using

15 mg doses found no benefit to performance [19]. Sufficient time needs to be allowed between the dose and the assessment of performance. Those studies where the drug was administered 1-3 hours before testing [8,9] more commonly showed positive effects than when doses were administered sooner before the testing [21]. Also the duration of the exercise may be a factor such that studies using time to exhaustion tests lasting less than 4 minutes did not find an effect of the drug [18], but this is not always true [8,9].

Smith and Beecher [9] noted that subjects are generally aware that one of the trials involves the use of amphetamine. The amphetamine produces a sensation different from a placebo so subjects can discern when they have ingested the amphetamine. Therefore any positive effect with a drug trial could be attributed to the subjects "knowing" that they ingested the amphetamine and expecting to be helped by it. To overcome this, Smith and Beecher [9] also used secobarbital as well as a placebo so that subjects would notice a different sensation but not necessarily be able to discern which was the amphetamine. Some other studies have also used this strategy [14-16].

In the most recent study [12], although well-controlled with repeated observations on the same subjects, only 6 college student volunteers participated. A myriad of tests were performed and improvement was found for some tasks but not others. This may be due to the large inter-subject variability. In addition to the small sample size, the subjects were not trained athletes, although they were former high school athletes. This calls into question the motivation of untrained subjects to perform consistently at their maximal intensity. In studies where highly trained athletes were used as subjects, an increase in performance was found [8,9,13]. Without a high motivation level, most individuals may stop exercising before they are physiologically exhausted [22].

It is not clear why some studies find improved performance with amphetamine use and some do not. While factors such as the amount of the drug and timing of ingestion, use of athletes or non-athletes as subjects, and the type of exercise are factors, perhaps the most important reason is the high inter-individual response to the drug. Research should focus on reasons for this variability. Athletes are aware that amphetamines "work" for some individuals, but may not realize that it is a virtual "Russian roulette" as to whether the drug will work for them. Also, the sensation produced by the amphetamines may allow the athlete to believe that there is a benefit when there may not be.

Sufficient information exists to suggest that the drug does mask pain or fatigue in some cases. While this can produce a positive effect on performance, it could also diminish it. There may be a failure to detect warning signs for serious health complications [13]. During endurance events there is the danger of ignoring early signs of heat stroke. When soldiers were given amphetamines they ignored foot blisters [7]. On amphetamines, football players could ignore pain from injuries which may exacerbate the injury [20].

2.2. Ephedrine

Ephedrine is structurally related to the amphetamines [3] and functions as a stimulator to adrenergic receptors and the central nervous system [23,24]. Ephedrine, pseudoephedrine, and phenylpropanolamine are examples of the "ephedrines" [25]. Ephedrine increases myocardial contraction, cardiac output, and systolic blood pressure [24].

There are very limited data on the effects of ephedrine on performance. The few studies that have been done have reported little performance benefit from ingestion of ephedrine [26,27,28]. Two of these studies did not use trained athletes [26,27], and all probably used a

dose less than that used by athletes. Further studies are needed to examine various doses of ephedrine in highly trained subjects.

Recent attention to ephedrine stems from its potential use as a "fat burner." Studies have documented that ephedrine is effective in increasing thermogenesis and fat loss. In 1993, *The International Journal of Obesity* devoted a volume (volume #17 suppl. #1) to studies of the effects of ephedrine on thermogenesis and weight loss in obese individuals. Despite use of ephedrine to promote lean tissue and fat loss in athletes, there are no studies to document the effectiveness of ephedrine in this group.

2.3. Cocaine

Cocaine has not been found to benefit performance. However, the few recent studies that have examined the effects of cocaine on exercise performance are not well controlled, such as using coca chewing to induce cocaine into the body in a culture where coca chewing is acceptable [20-32]. One early study [33] found that cocaine ingested 15 minutes before a cycling ergometry test did not improve performance. The time of ingestion may have been too close to the testing. More recent studies of coca chewing showed some physiological differences (higher ventilation, increased plasma free fatty acid levels, increased blood levels of catecholamines) during exercise [31,32], but performance was not assessed, other than VO_2 max which was not affected. Probably the reason for the lack of research is that cocaine is a controlled and addictive drug, and it would be difficult to get approval by most human subjects review committees to undertake such studies. However, animal studies have also not shown performance benefits from cocaine ingestion (cf. 1).

Cocaine might detrimentally affect performance because the euphoria cocaine produces may cause athletes to perform poorly but think they are performing well. Heightened peripheral reflexes produced by cocaine could impair function [34]. Animal studies have shown that injecting cocaine resulted in altered muscle glycogen metabolism during exercise such that glycogenolysis was increased, causing greater lactate levels and earlier fatigue [1]. There is concern that cocaine can result in addiction which would ultimately cause physical deterioration and impair performance [34].

2.4. Caffeine

Because several excellent reviews have been published on caffeine [1,35-39], this will only briefly be mentioned here. Moderate doses of caffeine (5-6 mg/kg body weight) taken about 1 hour before exercise have been shown to improve performance, with the exception of sprint exercise lasting less than 90 s, high intensity exercise (>90% VO_2 max), and incremental exercise tests. There is a large inter-subject variability in the response, however. Limitations of studies include the lack of research on females and the lack of field tests. Furthermore, the mechanisms to explain the ergogenic effect across a wide variety of exercise types remains to be determined.

2.5. Beta-blockers

The β-blockers reduce stimulatory effects of the sympathetic nervous system by preventing binding of epinephrine to its receptors, thereby reducing heart rate and tremor [39]. Athletes and performers use β-blockers to reduce anxiety and increase steadiness. Because of the role in reducing cardiovascular response, β-blockers will generally impair exercise performance when the exercise is physiologically stressful [40]. However, β-blockers improve performance

in any activity that is not physiologically challenging but requires accuracy, such as pistol shooting, archery, and musical performance. Most of the studies confirming the effectiveness of β-blockers on performance have been double-blind and placebo controlled, using trained individuals in simulated competition. Improvement with β-blockers has been found for pistol shooting, ski-jumping, and musical performance [41-51].

These drugs result in large variations in inter-individual response. In some individuals, β-blockers produce such a decrease in heart rate that performance is negatively affected [48,50]. Thus, although too much anxiety will impair performance, some anxiety appears necessary. Studies are needed to examine the effects of various doses in different individuals to ascertain the reason for the large inter-individual difference.

2.6. Anabolic-Androgenic Steroids (AAS)

The most apparent limitation to the research on AAS abuse in athletes stems from problems with study design. While many early studies examining the ergogenic effects of AAS employed double-blind controlled designs [52-57], others either had no control group [58], were not blind [58,59] or only used a single-blind design [60-62]. A controlled double-blind cross-over was used by only a few investigators [52,63-67].

Even when the double-blind protocol is used, there can be other problems. Subjects often detect the difference between AAS or a placebo because of the profound psychological and motivational effects of AAS use [63,65,68]. Crist *et al.* [63], Freed *et al.* [65], and Bhasin [64] found that, during the use of a double-blind cross-over design, their subjects were able to detect and predict when they received the steroid based on the psychological and physiological changes associated with AAS use. The potential motivational effects of AAS, real and perceived, appear to play a significant role in double-blind studies, making strength gains attributable only to AAS use difficult to quantify.

Though recent literature has focused on the psychological rather than ergogenic effects of AAS use, it is not immune to design problems. Much of the association between AAS use and mental instability or psychoses is derived from case studies [69-71] or a few investigations which questioned current AAS users about their psychological profiles [72-75]. Presently, only one study has attempted to examine prospectively the psychological effects of AAS use with a blinded, placebo-controlled investigation [76].

The psychological studies are further muddled with the finding that other drug use often accompanies AAS use [77,78]. Bahrke and Yesalis [79] have suggested that a triad exists between AAS use, weight training and behavioural changes, thereby masking the effects of AAS use alone. The impact of this triad on the interpretation of psychological changes associated with AAS abuse has been ignored in the literature.

Epidemiological reports of the incidence of AAS use in a variety of populations have primarily used cross-sectional designs with self-reporting questionnaires [80-84]. With the exception of the use the National Household Survey on Drug Abuse database [83], the questionnaires used in incidence reports are not standardized, but vary from study to study. Though self-reports have been validated for recreational drug use [85], their use in determining AAS abuse is problematic for two reasons: comparisons between studies are difficult and the accuracy of self-reporting, particularly in adolescent populations, has been questioned [83]. The possibility of under-reporting AAS use is also of concern.

In their detailed review of the contradictions apparent in the early AAS literature, Haupt and Rovere [86] reported that if the training experience of the subjects was controlled, the

studies exhibited a consistent pattern: the ergogenic effects of AAS were only seen in previously weight trained subjects who continued training during AAS use. A recent study [64] that controlled several parameters used subjects experienced with weight-lifting and placed them into two groups: one group continued resistance training and one did not. Although both groups showed muscle mass and strength gains with testosterone injections, the exercising group had the greater gains.

Controlling for trained vs. non-trained may not be enough. Trained individuals may train for power alone, using primarily anaerobic training (weight-lifters and powerlifters), or for physique which encompasses both weight and aerobic components (bodybuilders). Many studies have failed to account for these differences, confounding their results. Given the concerns that anaerobic and aerobic training may affect mood states (for review see 79) and other factors such as lipid profiles [87] differently, subjects with varying training history should be controlled.

Poor control of dietary factors is another problem with the AAS literature. While some studies report supplementing their subjects with protein [57,61,88], few studies have considered dietary factors. Although some investigations have recorded the nutritional intake of their subjects [97,89-91], only one study actually controlled dietary intake [64]

The other prominent limitation in the literature with respect to subject populations arises from the increasing use of AAS in young and female athletes with little or no scientific data on these populations. The ethical issues present in the knowledgeable administration of AAS to adults are increased in children, but the report that 250,000 to 500,000 young adult males are currently using AAS [92] prompts concern about the fact that little is known about their impact on adolescents. The same is true for female athletes. Strauss and colleagues [93] suggested that studies in women are "virtually nonexistent, largely because women athletes are reluctant to reveal their steroid use because of social pressure against it."

Users of AAS often consume 5-10 times the maximal recommended daily dose in addition to "stacking" multiple drugs [94]. Only three controlled studies approximated such dosages [64,66,67], while most studies recruit current users and do not exert control over the dose, frequency or type of drug taken. Crist *et al.* [63] completed one of the few early studies to find no increase in strength with AAS use even though their subjects were weight-trained. This is probably because they only dosed with 100 mg Nandrolone/week for three weeks, much lower than is thought to be consumed by athletes using AAS [94].

Underlying all of the other limiting factors already discussed is the ethical issue of studying a controlled substance which is often taken in very large doses. The increased reliance on AAS by high school aged athletes [92,95] prompted Perry and colleagues [96] to suggest that "it is no longer acceptable to think it unethical to administer large doses of anabolic steroids in controlled studies when there is a world-wide epidemic of anabolic steroid use among athletes at all levels of competition." One recent and very well-controlled study did evaluate the effects of a supraphysiological dose of testosterone (600 mg injection weekly for 6 weeks) during a resistance training programme and found that these doses, especially when combined with resistance training, resulted in an increase in fat-free mass, muscle size, and muscle strength [64]. Although this study used men who had experienced weight-lifting, they were not competitive. The effects of supraphysiological doses in highly trained athletes remains to be determined.

2.7. β_2 -Agonists

These drugs act as stimulants by binding to the β_2 adrenergic receptors. When used in aerosol form, β_2 agonists are relatively selective for β_2 receptors of the bronchial muscles and are therefore used in the treatment of asthma. Studies of aerosol therapeutic doses generally show no performance benefits [97,98], but some studies have reported an ergogenic effect [99,100]. However, the interest in β_2 agonists stems from their purported use to increase muscle mass when ingested. Clenbuterol appears to increase muscle hypertrophy and decrease fat deposition in animal models [101-103]. Several studies of β_2 agonists effects in untrained human subjects have reported increased strength gains [104-107].

Well controlled studies have shown that β_2 agonists by oral administration may be effective in increasing muscle strength. However, the studies are limited as they have not been done with trained athletes. The mechanisms to explain these changes have not been examined. Data on effects of aerosol doses of β_2- agonists have generally shown no improvement in performance, but again studies are limited. It is not known whether these drugs will enhance muscle mass, strength, or performance in highly trained athletes when given doses that will likely exert an effect. Like all drugs mentioned so far, there appears to be a large and unexplained inter-subject variability in the response to the drug.

2.8. Diuretics

Diuretics are used in sports where body weight is an important component, such as wrestling, light weight rowing, body-building, and horse riding. Diuretics can increase weight loss by about 3-4% over a 24-hour period [4,108]. Diuretics result in dehydration which could detrimentally affect performance by disturbing cardiovascular function, electrolyte balance, and thermoregulation [108,109-112]. These disturbances may be more severe with diuretic-induced dehydration than other methods of inducing dehydration [108,109,110].

For sports like light-weight rowing, the physiological changes resulting from diuretics could impair performance. When there is not sufficient time to rehydrate between the weigh-in and the competition, as in the case of certain types of wrestling competitions, wrestling performance could be impaired [109,112]. However, no studies have examined possible performance decrements in the field. In other types of wrestling competitions, there is sufficient time to rehydrate between the weigh-in and the competition so that effects of dehydration on performance would be minimal. Also performance of jockeys and body-builders may not be negatively affected by dehydration. However, little is known about the consequences of long term use and frequency of use of diuretics in athletes. In a recent report [113] a body builder who abused diuretics presented with hypotension and hyperkalaemia. Further studies are needed to assess diuretic-induced performance decrements in trained athletes in field situations as well as the long term health consequences of diuretic use.

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Discussion: Limits to Research on Drugs and Sport

D.A. Cowan:
In your conclusion, you say that most drugs are ineffective in increasing performance in sport. May I ask whether you would care just to modify that to simply not proven at the present time?

P.M. Clarkson:
Most drugs are ineffective for some subjects and effective for others; some athletes show improvement. We do not know if these subjects will improve performance consistently when given a drug, but we do know that some subjects show no effect, some subjects show a large effect. When I say that drugs are possibly ineffective I mean they may be ineffective for a particular athlete, but may be more effective for another athlete. A particular athlete may be benefited or harmed.

J.R. Barbany:
I should like to know your opinion about the use of ginseng in sport because -as you know- there is a controversy and I think that it could be considered more an ergogenic aid than doping in sport.

P.M. Clarkson:
As I understand it, certain ginseng preparations contain some ephedrine. In fact, Linford Christie tested positive for ephedrine and, it was thought this was because he was drinking ginseng tea at the Olympic Village.

M.H. Williams:
We just completed a study with one form of ginseng, the so-called "Siberian ginseng", and we basically found no effect on physiologic or metabolic responses to exercise or on an all-out peak VO_2max test. However, the dosage we gave and the limited time -six weeks- may have been too short, and we dealt with only one form of ginseng. There is an excellent review by Mike Bahrke and William Morgan in Sports Medicine and essentially they conclude that there is very little data to support the efficacy of ginseng to enhance performance.

J.P. Clarys:
Could you comment on the "muscle mass contouring" effect of ephedrine. I am using this term because we all agree that ephedrine is a fat burner, but I am not sure we all agree on considering ephedrine a muscle mass improver.

P.M. Clarkson:
I think you are absolutely right. Part of the problem is that the data on its use as a fat burner have come from studies where the intent was to show weight loss and fat loss, not muscle mass gain. There are no studies that have actually looked at muscle mass gain in humans, only in animals. Concerning contour, if one loses fat, the illusion is that there is more muscle mass. Whether this actually happens in any athletes, we do not know. There are no studies on athletes. I am not sure of its efficacy in athletes who already are very lean.

F. Brouns:

I have a question about your opinion on the types of performance testing. When referring to ephedrine and related substances, you said there are conflicting data. Many of the studies in the past have been done as open-end performance trials, which, in fact, determines endurance capacity and not endurance performance. Most of these data come from non-validated performance tests.

P.M. Clarkson:

You are absolutely right. Many studies use time-to-exhaustion tests with untrained individuals, and these tests notoriously have a high degree of variability, especially in unmotivated subjects.

B. Ekblom:

You discussed the problem of having responders and nonresponders in the use of anabolic steroids. We know that we have responders and nonresponders in all types of tests on anything we give to people. Do you think they have controlled for the basic concentration of testosterone and other hormones when you have responders and nonresponders?

P.M. Clarkson:

I think that is part of the problem. This is why the study by Bhasin *et al.* is quite good. They took subjects who were well matched and they controlled the diet, which is something other studies usually have not done. The Bhasin *et al.* study was a very well controlled study.

M. Orme:

Moving away from the area of sports medicine, there is good data on interindividual variation in response to non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis. Some patients will respond to one drug but not to another when there is no obvious difference in the pharmacology of the drugs. There is also evidence that some patients can respond to one drug at one point in time and yet a year later can be non-responders. There are also reasons for drug response such as social circumstances, diet etc which cannot be readily controlled.

In the case of beta blockers there is good evidence that the anti-anginal response (but not the anti-hypertensive response) is correlated with the plasma level of the drug. However some drugs have active metabolites (eg oxprenolol) which will confuse the situation.

T.D. Fahey:

Could you comment on the interaction between testing and training as a possible mechanism for subject variability in the response to a drug? In the case of anabolic steroids users, the anabolic steroids may allow athletes to train harder and thus, when they are tested, there is a possibility that they may be overtrained.

P.M. Clarkson:

This is another good point which brings me back to the Bhasin *et al.* study in the sense that they took subjects who were not overtraining, started them all on a consistent exercise program and then found results that were fairly clear. The training level of the subjects is an important consideration.

A. Batterham:

Will Hopkins (who is a statistician out of New Zealand) has done some work looking at performance differences between gold, silver and bronze medallists in elite sports and among the placers in various track and field events, and has shown that the differences between different types of medal or between winning and losing represents an effect size in statistical terms of 0.1 or less of a standard deviation. This relates to the question of how to demonstrate effectiveness or ineffectiveness of drugs. What it means is that if we are searching for such small effects that could make a difference between winning and losing, that in order to adequately power our studies statistically, we are going to need huge sample sizes in the experimental and the control groups. So, it is very easy to accept the ineffectiveness of drugs or any other intervention when it is just that the statistical power of the study is not enough.

P.M. Clarkson:

Basically, that is true. You may not find that a small increase in performance is statistically significant but it is very meaningful for a particular athlete.