BMJ Open Sport & Exercise Medicine

Effect of pseudoephedrine in sport: a systematic review

Kien V Trinh,[1] Jiin Kim,[2] Amanda Ritsma[1]

To cite: Trinh KV, Kim J, Ritsma A. Effect of pseudoephedrine in sport: a systematic review. *BMJ Open Sport Exerc Med* 2015;**1**:e000066. doi:10.1136/bmjsem-2015-000066

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjsem-2015-000066).

Accepted 18 November 2015

[1]Faculty of Medicine, McMaster University, Hamilton, Ontario, Canada
[2]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

Correspondence to
Dr Kien V Trinh;
trinhk@mcmaster.ca

ABSTRACT

Objective: Pseudoephedrine is a stimulant that can be purchased over-the-counter to relieve symptoms of nasal and sinus congestion. Owing to its similar composition to ephedrine and other amphetamines, pseudoephedrine mirrors some of its ergogenic effects. This study investigates its possible ergogenic effect through a systematic review. Our primary aim was to determine the effects of pseudoephedrine in sport and its potential for performance enhancement.

Design: We searched EMBASE, MEDLINE, PsychINFO and The Cochrane Library for trials conducted from their beginning to March 2015. Any published trial that used randomised assignment to the intervention and control groups in full text and measured pseudoephedrine as an independent variable were included.

Results: Overall, the review showed that the ergogenic effect of pseudoephedrine is dose-dependent. None of the reviewed studies showed an ergogenic effect at the therapeutic dose of the drug (60–120 mg); however, supratherapeutic doses (≥180 mg) yielded clinically significant results.

Conclusions: Owing to the limitations of the published studies in this field, we were unable to make any firm conclusions with respect to the overall effect of pseudoephedrine and its ergogenic effect. It is evident that there is a correlation between the dose administered and its ergogenic effects, but it is also evident that the side effects of using above the therapeutic dose outweigh the possible benefits of using pseudoephedrine in sport. Further research with larger sample sizes is required to determine the relationship between doses (≥180 mg) and concentrations in urine that cause an ergogenic effect.

BACKGROUND

During the 1995 Pan American Games, Silken Laumann sailed to victory with her teammates in the women's quadruple event.[1] Five days later, Laumann's drug screen showed levels of the prohibited stimulant pseudoephedrine (PSE), and the gold medal was revoked. It was later determined that Laumann had inadvertently taken over-the-counter PSE-containing medication for symptomatic relief of her cold.[1] Jack Uetrecht, a professor of pharmacy and medicine at the University of Toronto claimed that the dose and form Laumann took 'did not enhance performance', the officials of the games did not agree.[1] The banning of PSE has since become a highly debated topic in both the athletic and medical field.

PSE is a sympathomimetic amine that is readily available over-the-counter as a nasal and sinus decongestant.[2] Specifically, PSE activates adrenergic receptors in presynaptic neurons, which causes vasoconstriction. This decreases inflammation and mucous production[2] which relieves symptoms of the common cold. PSE has also been proposed to have ergogenic effects, likely due to its similarity to ephedrine and other central nervous system stimulants. These effects include increased muscle contractility, increased blood flow to skeletal muscles, increased glycogenesis, increased central nervous activation and heart rate, as well as decreased time to fatigue.[3] The International Olympic Committee and other organisations have banned the use of any substance that may enhance the sympathetic nervous system and, by its nature, have concluded that PSE has the potential to have this effect. Owing to the ergogenic nature of this drug, it is believed that it is a violation of the spirit of sport. Therefore, PSE was banned from use in competition.

It has been debated whether or not PSE is actually capable of generating any ergogenic effect. This continued debate has resulted in multiple changes to its position on the prohibited and/or monitoring list. Until 2004, PSE was included on the International Olympic Committee prohibited list. From 2004 to 2010, PSE was removed from the prohibited list, and later added to the monitoring list for in competition in 2010.[4] In this position, the use of PSE was considered doping if the urine concentration was greater than 150 µg while in competition.[4] Recently, as of 1 January 2015, PSE has been removed from the monitoring list.[4]

Despite potential risks and uncertainty on the ergogenic effects of PSE, athletes have

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

still been known to abuse PSE for its potential enhancement ability. Data collected by the World Anti Doping Association between 1996 and 2003 yielded 33 adverse analytical findings for PSE out of 52 347 in-competition analyses, or 4.1 positive controls per year.[4 5] In 2007 and 2008, that is, 3 years after PSE was removed from the prohibited list, the prevalence of PSE and ephedrine was determined in 16 335 in competition doping control samples.[4 5] The analyses resulted in 102 cases of PSE use or misuse.[4 5]

The purpose of this systematic review is to qualitatively consolidate the results of studies relating to the ergogenic effect of PSE in order to determine the validity of its ban from competition. Previous studies have yet to resolve the existing conflicting results, even when standardised testing methods are utilised.[6–8] Therefore, this article aims to clarify the relationship between PSE and sport enhancement on various parameters, specifically relating to drug dosage.

OBJECTIVES

To determine the effects of PSE in sport and its potential for performance enhancement.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Any published randomised control trial (RCT) in the English language, including cross-over studies. Owing to the controversy in this area, the authors felt that randomised controlled studies were the most appropriate research design to minimise bias to address the effectiveness of intervention. Studies were excluded if PSE was not the sole substance being administered to an athlete at a given time, or if the substance was not specifically being investigated for its ergogenic effects. This limitation was to ensure the data presented were not affected by any confounding variables.

Types of participants

Participants were male and female athletes of any level between age 18 and 65, with no other comorbid conditions.

Types of interventions

Studies must have used PSE as the only substance in the intervention. Studies that looked at other substances were included if athletes were not administered both substances simultaneously. The presence of a control and/or placebo group was also necessary for inclusion.

Types of outcome measures

Outcomes measured included any enhancement in sport above baseline such as timing, strength, time to fatigue and/or respiratory enhancement.

METHODS

Search strategy

We searched EMBASE, MEDLINE, PsycInfo and Cochrane Library databases for trials from their beginning to March 2015 (figure 1).

Study selection

At least two authors independently conducted citation identification, study selection and data abstraction. Disagreements were resolved through a third assessor.

Methodological assessment

At least two authors independently assessed each RCT for methodological quality and bias, based on the Cochrane's GRADE scale and the Cochrane's collaboration tool for assessing risk of bias.[9 10] Disagreements were resolved through a third assessor.

Data extraction

Two authors independently extracted raw data for demographics, descriptions of interventions and all outcomes to predesigned forms.

Data analysis

Data were retrieved and filed into abstraction forms. Differences between assessors were resolved by repeated review and consensus. The risk of bias of the RCT was assessed through the use the Cochrane collaboration's tool for assessing risk of bias. A third assessor resolved differences between assessors.

DESCRIPTION OF STUDIES/STUDY SELECTION

In consultation with two research librarians, we developed search strategies to identify potentially relevant studies from the EMBASE, MEDLINE, PsycInfo and Cochrane Library databases (see online supplementary appendix 1). We sought reports of RCTs, including cross-over trials, in relation to PSE use for its ergogenic effect. Clinical judgement was used to review the search and retrieve potentially relevant studies. Studies were excluded if they had co-interventions with other drugs (table 1).

METHODOLOGICAL QUALITY

Methodological quality was graded using two sets of criteria:

- Risk of bias: based on selection, performance, detection, attrition, reporting and other biases.[10]
- Cochrane GRADE table: began with highest quality rating for randomised trial evidence with downgrades to moderate, low or very low depending on the presence of limitations in design, indirectness of evidence, inconsistency of results, imprecision of results and high probability of publication bias.[9]

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

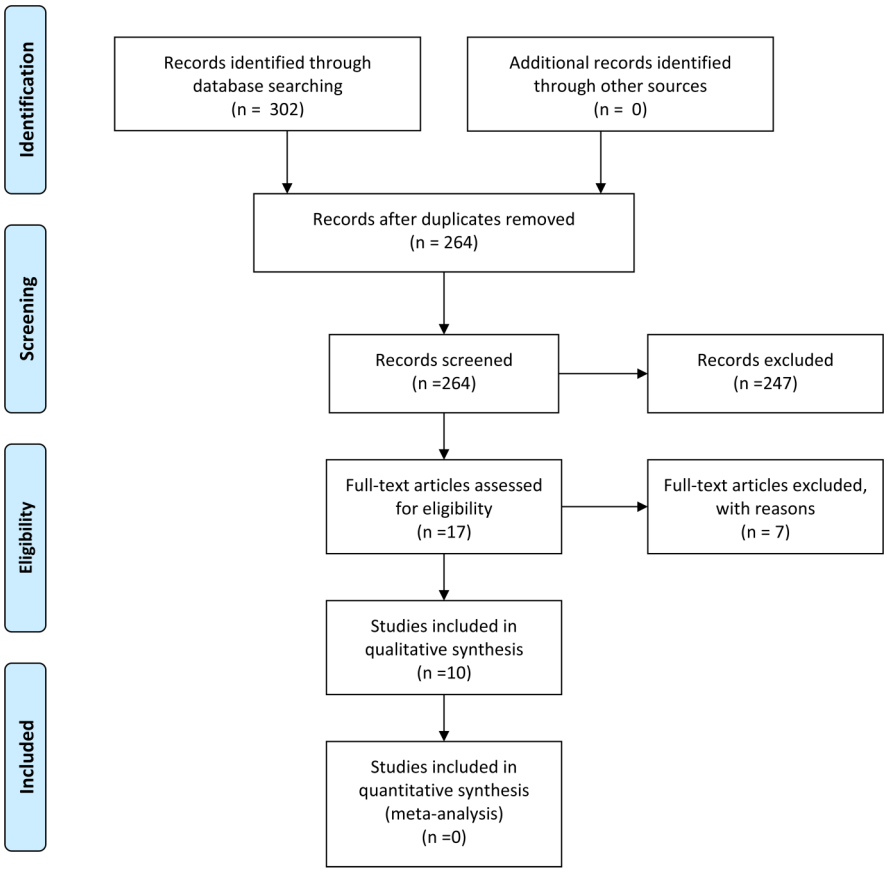

Figure 1 PRISMA 2009 flow diagram.

RESULTS

Out of 301 articles retrieved from EMBASE, MEDLINE, PsycInfo and The Cochrane Library, 39 duplicates were removed. From the 262 remaining, 17 studied the ergogenic effects of PSE and PSE-like substances. Of these 17, only 10 were devoted solely to studying the ergogenic effects of PSE and were used for this systematic review. Therefore, 10 remaining studies met all inclusion criteria (table 2).

Table 1 Excluded studies

Study	Reason for exclusion
Barroso *et al*[11]	Focuses on urinary threshold for detection of PSE
Bell and Jacobs[12]	Combined effect of caffeine and PSE studied
Bell *et al*[13]	Combined effect of caffeine and PSE studied
Chester *et al*[14]	Focuses on urinary threshold for detection of PSE
Jolley *et al*[15]	Focuses on influence of dehydration on PSE urinary levels
Pokrywka *et al*[16]	Focuses on frequency of PSE use
Spence *et al*[17]	Focuses on differences between effects of caffeine and PSE

PSE, pseudoephedrine.

Placebo versus PSE

Of the 10 chosen studies, 3 showed significant improvement in athletic performance.[20 24 25] These three studies used a supratherapeutic dose of at least 180 mg or 2.5 mg/kg of PSE, whereas the other studies used a therapeutic dose (60–120 mg or 1–2 mg/kg). The studies that used lower dosage of PSE showed no significant improvement for all measured parameters.[18 19 21–24 26 27] The authors compared both 60–120 mg or 1–2 mg/kg and ≥180 mg or 2.5 mg/kg of PSE to a placebo of similar appearance on the effects on maximal torque and peak power, decreased time to complete trial, and respiratory function. While the placebo and 60–120 mg or 1–2 mg/kg PSE categories showed no significant change, the ≥180 mg or 2.5 mg/kg PSE group showed significant improvement for all measured parameters. However, due to heterogeneity of the measurements selected in the trials, quantitative synthesis of data was not possible.

DISCUSSION

Our objective was to determine the effects of PSE on athletic performance in athletic individuals in good general health. Qualitative analysis showed overall positive results in favour of PSE over placebo for PSE doses ≥180 mg or 2.5 mg/kg. Doses below 180 mg or 2.5 mg/kg and placebos showed insignificant changes in athletic performance.

Interventions varied with respect of duration of treatment, doses of PSE, diet and type of exercise trial. For

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 2 Characteristics of included studies

Study	Design	Subject description	PSE dosage	Main Interventions	Outcome results
Gillies *et al*[18]	Double-blind RCT cross-over, single dose	Volunteer sample of 10 healthy male cyclists with no history of renal or other diseases	120 mg 90 min prior to testing	Group A (n=10) 120 mg PSE or placebo with exercise, 1-week washout period (2 trials) 120 PSE or placebo with no exercise (1 trial) Exercise: isometric muscle test (peak value) followed by 40 km cycling trial (time to completion)	No significant improvement in any parameters (isometric muscle function)
Swain *et al*[19]	Double-blind RCT, multiple-dose	Convenience sample of 20 male cyclists (18–35), cycling 50+ miles a week; 10 relevant to PSE	1 mg/kg, 2 mg/kg 60 min prior to testing	Group A (n=10) 1 mg/kg, 2 mg/kg or placebo with exercise, 1-week washout period (3 trials) Exercise: bicycle ergometer tests (time to exhaustion,VO_{2max}, peak pulse, and RPE)	No significant improvement in any parameters (VO_{2max}, time to exhaustion, peak BP and pulse) for either dose
Gill *et al*[20]	RCT cross-over, single dose	Volunteer sample of 22 healthy male athletes from university student population with no reported injuries prior to study	180 mg 45 min prior to testing	Group A (n=22) 180 mg PSE with exercise, 1-week washout period (1 trial) Placebo with exercise (1 trial) Exercise: Wingate test, isometric leg extension, bench press (peak value, heart rate)	Improved maximum torque, improved peak power of maximal cycling, improved respiratory function
Chester *et al*[21]	RCT cross-over, multiple dose	Recruited sample of 8 male endurance runners	60 mg, 6 doses over 36 h, 4 h prior to testing	Group A (n=8): 60 mg PSE or placebo with exercise, 1-week washout period (4 trials) Exercise: steady state exercise, 5000 m time trial (VO_{2max}, heart rate, BP, peak time) Statistical data not reported	No significant improvement in any parameters (VO_{2max}, heart rate, and respiratory exchange ratio)
Chu *et al*[22]	Double-blind RCT cross-over, single dose	Volunteer sample of 10 male, 9 female healthy university students (1 dropout)	120 mg, 2 h prior to testing	Group A (n=19) 120 mg PSE or placebo with exercise, 1-week washout period (2 trials) Exercise: Wingate test, MVC grip test, dorsiflexion test (peak power output)	No significant improvement in any parameters (force production, fatigue, power output)
Hodges *et al*[23]	Double-blind RCT cross-over, single dose	11 healthy male athletes	60 mg, 90 min prior to testing	Group A: (n=11) 60 mg PSE or placebo with exercise, 1-week washout period (3 trials) Exercise: 40% submaximal	No significant improvement in any parameters (peak power, total work, fatigue, heart rate)

Continued

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 2 Continued

Study	Design	Subject description	PSE dosage	Main Interventions	Outcome results
				cycling, 60% submaximal cycling, Wingate test (VO_{2peak}, peak power output, gross efficiency)	
Hodges *et al*[24]	Double-blind RCT cross-over, single dose	Volunteer sample of 7 male athletes from a university's athletic club (1 dropout)	2.5 mg/kg, 90 min prior to testing	Group A (n=7): 2.5 mg/kg PSE or placebo with exercise, 2–5-day washout period (2 trials) Exercise: 1500 m time trial (time to completion, blood parameters)	Significantly decreased time to completion trial by 2.1% with no reported side effects
Pritchard-Peschek *et al*[25]	Double-blind RCT cross-over, single dose	Volunteer sample of 6 trained male cyclists and triathletes	180 mg, 60 min prior to testing	Group A (n=6) 180 mg PSE or placebo with exercise, 2-week washout period (2 trials) Exercise: 70 kJ/kg standardised work time trial (time to completion)	Significantly decreased time to completion by 5.1%
Berry [26]	Double-blind RCT, cross-over, single dose	Recruited sample of 13 female student athletes from Utah Track and Field (2 dropouts)	2.5 mg/kg, 90 min prior to testing	Group A (n=13) 2.5 mg/kg PSE or placebo with exercise, 1-week washout period (2 trials) Exercise: 800 m run time trial (time to completion, heart rate, anxiety state)	No significant improvement in any parameters (time to completion, heart rate, level of anxiety)
Pritchard-Peschek *et al*[27]	Double-blind RCT, double-blind, cross-over, multiple dose	Volunteer sample of 10 trained male endurance cyclists from local cycling/triathlon clubs	2.3 mg/kg or 2.8 mg/kg, 60 min prior to testing	Group A (n=10) 2.3 mg/kg, 2.8 mg/kg, or placebo with exercise (3 trials) Exercise: 7 kJ kg−1BM work time trial (time to completion)	No significant improvement in any parameters (time to completion) for either dose

BP, blood pressure; MVC, maximal voluntary contraction; PSE, pseudoephedrine; RCT, randomised control trial; RPE, rate of perceived exertion; VO_{2max}, maximum oxygen uptake.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 3 Risk of bias

Bias	Gilles *et al*[18]	Swain *et al*[19]	Gill *et al*[20]	Chester *et al*[21]	Chu *et al*[22]
Random sequence generation (selection bias)	Low risk 'randomly assigned'	Low risk 'randomised using block scheme'	Low risk 'randomly assigned'	Low risk 'Latin square design for subject assignment'	Low risk 'randomised'
Allocation concealment (selection bias)	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed
Blinding (performance bias and detection bias) All outcomes—patients?	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'double-blind'
Blinding (performance bias and detection bias) All outcomes—providers?	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'condition allocation was carried out by associate not involved in study'	Low risk 'double-blind'	Low risk 'double-blind'
Blinding (performance bias and detection bias) All outcomes—outcome assessors?	Unclear risk Not addressed	Unclear risk Not addressed	Low risk 'double-blind'	Unclear risk Not addressed	Unclear risk Not addressed
Incomplete outcome data (attrition bias) All outcomes—dropouts?	Low risk No dropouts	Low risk No dropouts	Low risk No dropouts	Low risk No dropouts	Low risk 1 drop out, addressed and justified
Incomplete outcome data (attrition bias) All outcomes—ITT analysis?	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Selective reporting (reporting bias)	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Similarity of baseline characteristics?	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics
Co-intervention avoided or similar?	Low risk No co-interventions	Low risk No co-interventions	Low risk Cross-over with adequate washout period	Low risk No co-interventions	Low risk Cross-over with adequate washout period
Compliance acceptable?	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable
Timing outcome assessments similar?	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups
Overall impression	Low risk	Low risk	Low risk	Low risk	Low risk

Continued

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 3 Continued

Bias	Hodges *et al*[23]	Hodges *et al*[24]	Pritchard-Peschek *et al*[25]	Berry[26]	Pritchard-Peschek *et al*[27]
Random sequence generation (selection bias)	Low risk 'randomly assigned'	Low risk 'randomised'	Low risk 'randomly assigned'	Low risk 'random trial'	Low risk 'randomised'
Allocation concealment (selection bias)	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed	Low risk 'member placed capsules in 2 different envelopes marked A or B, known only to this member'	Unclear risk Not addressed
Blinding (performance bias and detection bias) All outcomes—patients?	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'double-blind'
Blinding (performance bias and detection bias) All outcomes—providers?	Low risk 'double-blind'	Low risk 'double-blind'	Low risk 'double-blind'	High risk 'known to member of research team' assigning the envelopes A or B	Low risk 'double-blind'
Blinding (performance bias and detection bias) All outcomes—outcome assessors?	Unclear risk Not addressed	Unclear risk Not addressed	Unclear risk Not addressed	Low risk 'double-blind'	Unclear risk Not addressed
Incomplete outcome data (attrition bias) All outcomes—drop-outs?	Low risk No dropouts	High risk 1 out, not addressed nor justified	Low risk No dropouts	Low risk 2 dropouts, addressed and justified	Low risk No dropouts
Incomplete outcome data All outcomes—ITT analysis?	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Selective reporting (reporting bias)	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported	Low risk All prespecified outcomes reported
Similarity of baseline characteristics?	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics	Low risk No significant differences among baseline characteristics
Co-intervention avoided or similar?	Low risk Cross-over with adequate washout period	Low risk Cross-over with adequate washout period	Low risk Cross-over with adequate washout period	Low risk Cross-over with adequate washout period	Low risk Cross-over with adequate washout period
Compliance acceptable?	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable	Low risk Compliance with interventions acceptable
Timing outcome assessments similar?	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups	Low risk Outcomes measured at same time across groups
Overall impression	Low risk	Low risk	Low risk	Low risk	Low risk

ITT, intention to treat.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 4 Summary of findings

Pseudoephedrine vs control

***Patient or population*: male and female patient athletes with no comorbidities between 18 and 65**
***Settings*: track or gym**
***Intervention*: PSE effects on exercise**
***Comparison*: placebo effects on exercise**

Outcomes	Intervention			Number of participants (studies)	Quality of the evidence (GRADE)
	Placebo	PSE, 60–180 mg, 1–2 mg/kg	PSE, >180 mg or 2.5 mg/kg		
Time to completion (timed trial)	No statistically significant improvement in all studies[16 18 19 24–27]	No statistically significant improvement in all studies[18 19 26 27]	Significantly decreased time to completion by 5.1%[25] and 2.1%[24]	64 (7)[1618 19 24–27]	⊕⊕⊕○ **moderate** Limitations 0 Imprecision 0 Inconsistency 0 Indirectness −1* Other 0
Wingate test Peak anaerobic power	No statistically significant improvement in both studies[20 22]	No statistically significant improvement on study[22]	1.6% improvement (p=0.07)[20]	41 (2)[20 22]	⊕⊕○○ **low** Limitations 0 Imprecision −1† Inconsistency 0 Indirectness −1* Other 0
Peak power of maximal cycling	No statistically significant improvement in both studies[20 23]	No statistically significant improvement on study[23]	Improved peak power (p<0.01))[20]	33 (2)[20 23]	⊕⊕○○ **low** Limitations 0 Imprecision −1† Inconsistency 0 Indirectness −1* Other 0
Respiratory function	No statistically significant improvement in all studies[18–21 23]	No statistically significant improvement in all studies[18 19 21 23]	Significantly improved respiratory function (p=0.02, p=0.01 for FEV_1 and FVC)[20]	61 (5)[18–21 23]	⊕⊕⊕○ **moderate** Limitations 0 Imprecision 0 Inconsistency 0 Indirectness −1* Other 0
Isometric muscle test	No statistically significant improvement in both studies[18 20]	No statistically significant improvement in study[18]	Significantly improved isometric knee extension (p<0.03)[20]	32 (2)[18 20]	⊕⊕○○ **low** Limitations 0 Imprecision −1† Inconsistency 0 Indirectness −1* Other 0

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.
New findings
▶ Doses of PSE >180 mg or 2.5 mg/kg shows significant improvement in various athletic performance tests compared with control or doses 60–180 mg, 1–2 mg/kg.
▶ Both placebo and doses of PSE <180 mg or 2.5 mg/kg had no significant improvement in athletic performance.
▶ Improvement in athletic performance included: decreased time to completion in timed trials, increased peak anaerobic power, increased FEV_1 and FVC (lung function).
*No direct comparison of therapeutic doses in interventions.
†Small study group.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PSE, pseudoephedrine.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

instance, though Pritchard-Peschek *et al*[25] and Hodges *et al*[24] showed significant improvements in timed trials using PSE doses ≥180 mg or 2.5 mg/kg, the studies could not be meta-analysed as their interventions were different (1500 run[25] and 7 kJ/kg body mass work[24] time to completion, respectively). Owing to such heterogeneity, using the qualitative method of synthesising the evidence was more appropriate. However, this method is sensitive to how studies are categorised, as meeting the criterion of a certain level of evidence depends on the number of studies present in a category, methodology and risk of bias.

All studies were assessed to have a low risk of bias (table 3). For their quality of evidence, the studies were downgraded from high level of evidence to moderate, low or very low depending on the presence of limitations in design, indirectness of evidence, inconsistency of results, imprecision of results and probability of publication bias with the Cochrane GRADE scale (table 4). All studies were RCT in design and implementation and had a low likelihood of bias; thus, none of the studies showed limitations in design. The results of all parameters were also consistent based on dose; only PSE doses ≥180 mg or 2.5 mg/kg showed significant results, while placebo and doses below 180 mg or 2.5 mg/kg did not. However, only two studies measured the parameters of Wingate test, peak power of maximal cycling and isometric muscle test, leading to small sample sizes. We believe that high quality of evidence should be reserved for conclusions in which the likelihood of making an incorrect reference is small, that is, having consistent findings in multiple sampled studies with low risk of bias. Thus, these categories were downgraded from high-to-moderate quality due to their risk of imprecision. Publication bias of the studies was unclear to assess as only published trials were available through literature search. Additionally, none of the studies directly compared the effects of variable therapeutic doses of PSE. The question of whether higher doses of PSE impact athletic performance would have been more directly addressed if studies had two explicit interventions—a high and low therapeutic PSE dose group—and a control placebo group. This would allow direct analysis between the variables and strengthen the studies' quality of evidence. Thus, all evidence was downgraded in quality due to the indirectness.

The approach to summarising the literature has several strengths. We used a comprehensive, librarian-assisted search of multiple databases. Healthcare professionals decided on article relevance and assessed quality. At least two people extracted the data and the principal investigator verified data entry.

The effect of PSE on athletic performance is a highly debated subject in both the medical and athletic fields. The findings of this review are useful for the design and planning of a larger clinical trial that assesses the effect of PSE on performance with a focus on a direct comparison of doses. PSE has been on and off the WADA guidelines for some time, and present evidence does not indisputably support the banning of PSE at a lower dose. Thus, a large-scale study should be conducted to formulate an approach to this question.

AUTHORS' CONCLUSIONS

Implications for practice

The authors of this review conclude that there is moderate evidence suggesting that higher doses of PSE may be more beneficial than inactive placebo pills or lower doses in enhancing athletic performance. Therefore, these findings should be considered throughout the process of developing substance laws in competition. This would provide a more accurate maximum use of PSE to be considered as doping or whether it has a place on the monitoring list. Since PSE is present in over-the-counter decongestants, changes may allow athletes to take appropriate doses for symptomatic relief while taking the necessary precautions to avoid doping allegations and harmful side effects.

Implications for research

The banning of substances in competition is a highly debated and continually changing field. Therefore, there is need for a large, high-quality RCT to determine the role of dosing of PSE on enhancing athletic performance.

Implications for an updated systematic review

There is no recent systematic review on the effects of PSE on athletic performance. Thus, a current systematic review on this topic is necessary to summarise the current findings on PSE use and doping regulations.

Contributors JK and AR ran the literature search, analysed and chose the relevant studies, critiqued their methodology and quality of evidence, and formed relevant conclusions. KVT analysed and chose the relevant studies, critiqued their methodology and quality of evidence, and formed relevant conclusions. All authors proofread the paper.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES

1. Schneider AJ, Butcher R. An ethical analysis of drug testing. In: W Wilson, E Derse, eds. *Doping in elite sport: the politics of drugs in the Olympic Movement*. Champaign-Urbana, IL: Human Kinetics, 2001;129–52.
2. Fitch K. Proscribed drugs at the Olympic Games: permitted use and misuse (doping) by athletes. *Clin Med* 2012;12:257–60.
3. Clarkson PM, Thompson HS. Drugs and sport. *Sports Med* 1997;24:366–84.
4. Welcome to the List Wada Prohibited List. (n.d.). Retrieved 1 April 2015. http://list.wada-ama.org/

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

5. Thevis M, Sigmund G, Geyer H, *et al*. Stimulants and doping in sport. *Endocrinol Metab Clin North Am* 2010;39:89–105.
6. Tokish JM, Kocher MS, Hawkins RJ. Ergogenic aids: a review of basic science, performance, side effects, and status in sports. *Am J Sports Med* 2004;32:1543–53.
7. Williams AD, Cribb PJ, Cooke MB, *et al*. The effect of ephedra and caffeine on maximal strength and power in resistance-trained athletes. *J Strength Cond Res* 2008;22:464–70.
8. Salerno SM, Jackson JL, Berbano EP. Effect of oral pseudoephedrine on blood pressure and heart rate: a meta-analysis. *Arch Intern Med* 2005;165:1686–94.
9. Guyatt GH, Oxman AD, Montori V, *et al*. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* 2011;64:1277–82.
10. Higgins JP, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
11. Barroso O, Goudreault D, Carbó Banús ML, *et al*. Determination of urinary concentrations of pseudoephedrine and cathine after therapeutic administration of pseudoephedrine containing medications to healthy subjects: implications for doping control analysis of these stimulants banned in sport. *Drug Test Anal* 2012;4:320–9.
12. Bell DG, Jacobs I. Combined caffeine and ephedrine ingestion improves run times of Canadian Forces Warrior Test. *Aviat Space Environ Med* 1999;70:325–9.
13. Bell DG, Jacobs I, McLellan TM, *et al*. Thermal regulation in the heat during exercise after caffeine and ephedrine ingestion. *Aviat Space Environ Med* 1999;70:583–8.
14. Chester N, Mottram DR, Reilly T, *et al*. Elimination of ephedrines in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004;57:62–7.
15. Jolley D, Dawson B, Maloney SK, *et al*. Hydration and urinary pseudoephedrine levels after a simulated team game. *Int J Sport Nutr Exerc Metab* 2014;24:325–32.
16. Pokrywka A, Tszyrsznic W, Kwiatkowska DJ. Problems of the use of pseudoephedrine by athletes. *Int J Sports Med* 2009;30:569–72.
17. Spence A, Sim M, Landers G, *et al*. A comparison of caffeine versus pseudoephedrine on cycling time-trial performance. *Int J Sport Nutr Exerc Metab* 2013;23:507–12.
18. Gillies H, Derman WE, Noakes TD, *et al*. Pseudoephedrine is without ergogenic effects during prolonged exercise. *J Appl Physiol* 1996;81:2611–17.
19. Swain RA, Harsha DM, Baenziger J, *et al*. Do pseudoephedrine or phenylpropanolamine improve maximum oxygen uptake and time to exhaustion? *Clin J Sport Med* 1997;7:168–73.
20. Gill ND, Shield A, Blazevich AJ, *et al*. Muscular and cardiorespiratory effects of pseudoephedrine in human athletes. *Br J Clin Pharmacol* 2000;50:205–13.
21. Chester N, Reilly T, Mottram DR. Physiological, subjective and performance effects of pseudoephedrine and phenylpropanolamine during endurance running exercise. *Int J Sports Med* 2003;24:3–8.
22. Chu KS, Doherty TJ, Parise G, *et al*. A moderate dose of pseudoephedrine does not alter muscle contraction strength or anaerobic power. *Clin J Sport Med* 2002;12:387–90.
23. Hodges AN, Lynn BM, Bula JE, *et al*. Effects of pseudoephedrine on maximal cycling power and submaximal cycling efficiency. *Med Sci Sports Exerc* 2003;35:1316–19.
24. Hodges K, Hancock S, Currell K, *et al*. Pseudoephedrine enhances performance in 1500-m runners. *Med Sci Sports Exerc* 2006;38:329–33.
25. Pritchard-Peschek KR, Jenkins DG, Osborne MA, *et al*. Pseudoephedrine ingestion and cycling time-trial performance. *Int J Sport Nutr Exerc Metab* 2010;20:132–8.
26. Berry C. Effect of Pseudoephedrine on 800-Meter Run Times of NCAA Division I Women Athletes. 2011. http://digitalcommons.usu.edu/cgi/viewcontent.cgi?article=2115&context=etd
27. Pritchard-Peschek KR, Jenkins DG, Osborne MA, *et al*. The dose–response relationship between pseudoephedrine ingestion and exercise performance. *J Sci Med Sport* 2014;17:531–4.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2015-000066 on 21 December 2015. Downloaded from http://bmjopensem.bmj.com/ on April 17, 2024 by guest. Protected by copyright.