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Kevin M. Strate

Philadelphia College of Osteopathic Medicine, kevinst@pcom.edu

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**Does the use of oral amphetamines reduce
cocaine use in cocaine-dependent
individuals?**

Kevin M. Strate, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not the use of oral amphetamines reduces cocaine use in cocaine-dependent individuals.

Study Design: Review of three English language randomized control trials (RCTs) published in 2001, 2003 and 2004.

Data Sources: 3 randomized controlled trials published after 1999 were obtained using PubMed, OVID, and Medline.

Outcomes Measured: The efficacy of using d-amphetamine to promote cocaine use cessation in cocaine-dependent individuals, determined using immunoassay and mass spectrometric analysis to identify cocaine metabolites in the participant's urine.

Results: Grabowski et al (2004) found a significant reduction in the use of cocaine in cocaine-dependent individuals, while Grabowski et al (2001) and Shearer et al were unable to show a significant reduction.

Conclusion: Evidence supporting the role of oral amphetamines in reducing cocaine use in cocaine-dependent individuals is inconclusive and conflicting at this time. However, further research and larger scale analysis is warranted and feasible considering the suggestive outcomes these studies represent.

Keywords: Cocaine-dependence, d-amphetamine, randomized-controlled trial, treatment

Introduction

Cocaine is a drug with increasing concern for abuse and dependence, with minimal available treatment options, that is in association with an array of psychiatric, medical, and individual social problems¹. The drug is coined "the caviar of street drugs," and given a reputation to be abused by celebrities, fashion models, and Wall Street traders². However, addiction is a disease that does not discriminate, affecting individuals of all backgrounds and socioeconomic status. The effects of cocaine not only occur during the "high", which only lasts about 15 minutes, but afterwards the negative effects take a toll on the heart, brain, and one's emotions². Considering the long-term damage consuming this drug has on the body, it is imperative to determine a way to help cocaine-dependent individuals overcome their addiction. This paper evaluates three double blind, randomized controlled trials determining the efficacy of Amphetamine (d-amphetamine) as an oral medication to promote cessation of cocaine use.

There are approximately 1.6 million current users of cocaine in the US, with the past-year prevalence of cocaine dependence is estimated to be 1.1%³. With such a high rate of addiction, it is alarming to consider the strain it has on our country's health care expenses. Although an

Strate, Oral Amphetamine in Cocaine-Dependent 2

estimation of annual healthcare cost due to cocaine-dependence is not recorded, it is included in the more than \$484 billion dollars that substance abuse as a whole costs our nation per year, as reported by the National Institute of Drug Abuse⁴. Health care practitioners are exposed to a large number of these patients on a daily basis.

Considering some people keep it hidden that they are abusing drugs, it is difficult to accurately depict. There is not an exact estimate available for healthcare visits due to cocaine-dependence; however, in 2009 NIDA reported an estimated 422,896 emergency room visits related to cocaine use⁵.

Cocaine addiction/dependence is proven to be in association with the stimulatory effect the drug has on the central nervous system's reward inducing center⁶. The sympathomimetic mechanism of action directly increases the activation of dopaminergic receptors, while also blocking the reuptake of norepinephrine and serotonin⁶. CNS stimulation from cocaine use has shown to increase harmful behavior in addicted individuals. These behaviors include psychosis, HIV and other transmittable disease risk-taking through unsafe sexual practice and injecting, compulsive binge behavior, violence, and other antisocial behaviors⁶.

Strate, Oral Amphetamine in Cocaine-Dependent 3

The drug effects can even change one's personality enough to alter their actions.

Stimulatory drugs, which are controlled substances, are the only class of medications that are showing promise as therapeutic agents for treatment of cocaine dependence. However, there is resistance in this field of research considering the addictive properties of these pharmaceutical medications⁶. Research and treatment are being conducted in other countries using other stimulant medications such as: Dopamine agonists, Methylphenidate, Modafinil, Armodafinil, and stimulant antidepressants such as Bupropion³. Cognitive-behavioral psychosocial therapy is also an adjunctive mainstay of treatment for cocaine dependence⁷. Currently there is not a drug of choice for promoting cessation of cocaine use in patients with cocaine-dependence. The medications previously listed have shown minimal efficacy in controlled studies. Research suggests that d-amphetamine may be used as an oral alternative to treat patients with cocaine-dependence with the goal to improve the likelihood of cessation.

Objective

The objective of this selective EBM review is to determine whether or not the use of oral amphetamines can reduce cocaine use in cocaine-dependent individuals.

Methods

The criteria used for selection of the studies used were patients with cocaine-dependence who were seeking help in cessation of use and who were willing to participate in a controlled research trial. The intervention used was d-amphetamine 30mg and 60mg daily. The treatment group receiving d-amphetamine was compared to the control group who was receiving a visually matched placebo. The outcome measured was the efficacy of using d-amphetamine to promote cocaine use cessation in cocaine-dependent individuals.

This was determined using immunoassay and mass spectrometric analysis to identify cocaine metabolites in the participant's urine. The types of studies included were 3 randomized, double blind, and placebo controlled clinical trials.

The data sources used are 3 randomized controlled trials published after 1999 that were obtained using PubMed, OVID, and Medline. The keywords used in searches were "Cocaine-dependence", "d-amphetamine", "randomized-

controlled trial", and "treatment". All of the articles were written in English and published in peer-reviewed journals. The articles were selected based on their relevance to the clinical question and if they included patient oriented outcomes. The inclusion criteria involved were studies that were randomized, controlled, and double blind. The participants in the trials were cocaine-dependent, without an age requirement. The exclusion criteria in the RCTs were patients with medical comorbidities that could interfere with the study outcomes. All the studies utilized in this review deal with patient oriented outcomes (POEMS). The summary statistical analysis utilized in the studies reviewed included ANOVA, NNT, ABI, p-values, and F-score. Table 1 demonstrates the demographics of the participants in the study.

Outcome Measured

The outcome measured was the efficacy of using d-amphetamine to promote cocaine use cessation in cocaine-dependent individuals. This was determined by the absence of cocaine metabolites in that participant's urine. A urinalysis was conducted using laboratory immunoassay and mass spectrometry to identify benzoylecgonine, a metabolite of cocaine, at a cutoff of 300ng/mL.

Strate, Oral Amphetamine in Cocaine-Dependent 6

Table 1: Demographics and Characteristics of included studies

Study	Type	# of Pts.	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Grabowski ⁸ (2004)	Double blind RCT	94	18-50	Cocaine and heroin dependence diagnosis (DSM IV) in good health and without other psych diagnosis with normal cardiac function	Other significant medical diagnosis	32	15/30mg and 30/60mg of d-amphetamine per day and methadone x 26 weeks
Grabowski ⁷ (2001)	Double blind RCT	128	Not Specified	Cocaine-dependence diagnosis (DSM IV) in good medical health	Other psychiatric diagnosis	16	15/30mg and 30/60mg of d-amphetamine x 12 weeks
Shearer ⁶ (2003)	Double blind RCT	30	Not Specified	Cocaine dependence diagnosis (DSM-IV criteria) and a cocaine-positive urine sample or documented history of cocaine use	Other significant medical conditions likely to make trial participation hazardous (such as cardiovascular conditions and schizophrenia).	4	60mg of d-amphetamine per day x 14 weeks

Results

Three studies were included, two of which compared d-amphetamine therapy group against placebo group in cocaine-dependent individuals, and one that compared d-amphetamine therapy group against placebo group in cocaine and heroin-dependent individuals. Two of the studies did not specify an age parameter, but the third study restricted it to 18 to 50 years of age. To report conclusive data, individuals were presumptive for cocaine use if their benzoylecgonine (BZ) level was 300 ng/mL or greater on urine screening.

In the study by Grabowski et al (2001), three groups were analyzed. There was a group taking 0mg (placebo), 15/30mg d-amphetamine, and 30/60mg d-amphetamine. The trial was 12 weeks in duration and included 128 individuals. The proportion of urine screens that were positive at intake was 0.80, 0.68, and 0.65, respectively, for the individuals designated to each group previously listed. There was a dose-doubling phase that occurred at month two. For the complete sample, differences were not significant at the end of the study (Pearson $\chi^2=2.257$, $df=2$, $p=0.323$, $N=128$). When examining if there was a difference with dose as a variable, there still was no significance ($F=0.147$, $df=2.99$, $p=0.864$, $N=102$). However, all groups showed improvement. When the 16 individuals with negative urine

Strate, Oral Amphetamine in Cocaine-Dependent 8

drug screen from initial screening (entry of study) who continued to be negative throughout the study were excluded, there was a difference in the pattern of cocaine use. The data for month 1 was similar to the complete sample, but differences emerged after the dose was doubled. The 60mg group showed fewer BZ-positive urine screens than placebo group during month 3 ($F=4.577$, $df=1.9$, $p=0.061$, $N=11$), but this data was not significant. The study reported six subjects that stated medication side effects as a reason for discontinuation of therapy. These included changes in their appetite and muscle twitches or movements. The study concludes that there was an absence of adverse effects that diminishes concerns for this treatment, but caution is essential⁷.

In the study Grabowski et al (2004), three groups were involved in the study, 0mg, 15/30mg, and 30/60mg of d-amphetamine. Of the 94 subjects who began the medical treatment, 62 remained at the end of the study. This study also included a dose-doubling phase at month two. Analysis comparing the single to doubled dose phases indicated that the 30/60-dose group significantly reduced cocaine use when compared to the other groups (Interaction $F=4.34$, $df=2.56$, $p=0.0176$; Cohen's effect-size $f=0.394$). The side effects noted were changes in appetite, constipation, and

Strate, Oral Amphetamine in Cocaine-Dependent 9

drowsiness, leading to only a 2% dropout rate. The safety concern was of cardiovascular origin, requiring each subject to be evaluated by a cardiologist prior to initiation of therapy⁸.

In the study Shearer et al, the 30 subjects were cocaine and heroin-dependent and were divided into two groups, 0mg (placebo) or 60mg d-amphetamine. The proportion of positive urine samples declined in the treatment group from 94% at baseline to 56% and 69% during the study. The placebo group's positive urine samples remained constant at 79% throughout the study. The between-group difference at the final week 14 was 22.4% ($\chi^2=1.7$, $p=0.2$), not showing significant difference. As calculated by the results of the study, for every 10 subjects treated with oral amphetamines, one more would discontinue cocaine use when compared to placebo (NNT represented in Table 2). The commonly reported side effects during this study were insomnia and disturbed sleep, however they did not differ between groups⁶.

Table 2: Clinical Efficacy of Using d-amphetamine to treat Cocaine-Dependence

Study	CER (0mg)	EER (60mg)	ABI	NNT
Shearer et al	21%	31%	10%	10

CER- control event rate, EER- experimental event rate, ABI- absolute benefit increase, NNT- number needed to treat

Discussion

Although all trials do not show significant evidence, they imply that d-amphetamine at higher doses (60mg) could be a potentially safe and effective treatment to reduce cocaine use in cocaine-dependent individuals. However, the possibility of adverse events may lead to skepticism. Insurance companies currently cover the cost of d-amphetamine for most individuals for the treatment of attention deficit disorder. However, it has not been approved for this application. Considering the fact that this medication is CNS stimulating in nature, there is also potential for abuse.

The study by Shearer et al was too small to confidently evaluate the efficacy of d-amphetamine in relation to placebo in reducing cocaine use, cravings and related harms⁶. The size of the study is a limiting factor in this field of research. Grabowski et al (2004) found a significant reduction in the use of cocaine in cocaine-dependent individuals, while Grabowski et al (2001) and Shearer et al were unable to show a significant reduction. Furthermore, as a whole, these studies give support to merit future controlled studies to evaluate the utility of d-amphetamine in the management of cocaine dependence.

Conclusion

Evidence supporting the role of oral amphetamines in reducing cocaine use in cocaine-dependent individuals is inconclusive and conflicting at this time. Nevertheless, further research and larger scale analysis is warranted and feasible considering the suggestive outcomes these studies represent.

Future studies should attempt to increase the amount of participants and put particular emphasis on patients with cocaine-dependence alone, instead of subjects with multiple drug dependencies. Higher dosing at 60mg daily d-amphetamine appears to be the more promising treatment. Focus on comparing placebo to the higher dose in a controlled setting could show more profound statistical outcomes. Also, the duration of the studies should be lengthened to prove safety of this treatment for long-term control. Although the results of these studies are modest, treatment with d-amphetamine shows more promising outcomes than other previously researched medications in treating the serious problem of cocaine-dependence and abuse.

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