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Short communication

Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: A pilot study☆

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ABSTRACT

The efficacy of stimulant treatment in patients with substance use disorders and comorbid attention deficit hyperactivity disorder (ADHD) has been tested for cocaine and alcohol dependence but so far no studies have been conducted in amphetamine dependent individuals.

The present trial was a pilot study aiming to test the feasibility of treating amphetamine dependent patients with comorbid ADHD with central stimulant medication. The study was a double-blind, placebo controlled trial with parallel groups design comparing the efficacy of a fixed dose (72 mg) of OROS methylphenidate (MPH) with placebo (PL) in reducing ADHD symptoms in currently abstinent adults with amphetamine dependence and ADHD. Twenty-four treatment seeking patients who met the DSM IV criteria for amphetamine dependence and ADHD were randomized to MPH/PL. The trial was conducted at an outpatient facility with twice weekly visits, measuring ADHD symptoms and drug use. Patients rated their ADHD symptoms on a weekly basis and provided supervised urine specimens for drug toxicology twice weekly. All patients participated in weekly sessions of a skills training programme. Both the groups significantly reduced their self-rated ADHD symptoms during the 12-week treatment but there was no difference between the two treatment arms. Drug use, both measured by urine toxicology and self-report did not differ between the groups. No difference was found between the two groups with regards to craving for amphetamine or in retention in treatment. Larger studies with higher doses combined with individual dosage and longer follow-up periods are warranted.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is highly prevalent in populations with substance use disorders and associated with more severe course of the syndrome (Mariani and Levin, 2007). Methylphenidate (MPH) constitutes first line treatment for ADHD both in children and in adults. There have been several case reports and open label clinical trials of MPH for the treatment of patients with SUD and comorbid ADHD suggesting that treatment with MPH may lead to a reduction in drug use as well as in the ADHD symptoms (Levin et al., 1998; Castaneda et al., 2000; Somoza et al., 2004). So far, results from randomized controlled trials (RCT) of MPH in this population have been mixed (Schubiner et al., 2002; Carpentier et al., 2005; Levin et al., 2006, 2007; Wilens et al., 2008). However, the collective finding from these trials suggests that the use of central stimulant medication in substance dependent populations does not lead to an increase in craving or drug use.

The goal of the present study was to evaluate the feasibility of using MPH pharmacotherapy in adults with amphetamine dependence and ADHD. The main research question was to investigate the effects of MPH on the ADHD symptoms and its effect on relapse to amphetamine use, in a sample of chronic amphetamine dependent patients.

2. Methodology

2.1. Participants

Patients were recruited on a referral basis from outpatient addiction units in the Stockholm metropolitan region (pop. 2m). Amphetamine dependent patients newly diagnosed with ADHD were referred to the project manager and their eligibility was ascertained via phone interviews. Thirty-four treatment seeking patients (both male and female) were finally screened in person for the study. The participants were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM IV; APA, 1994) criteria for amphetamine dependence during the last 12-month period. Exclusion criteria included: (1) current or past DSM IV diagnosis of any other substance dependence except nicotine, (2) history of any major psychiatric disorder (e.g., schizophrenia and major depression) or any current psychiatric condition requiring medication, (3) use of any opioid medication or illicit opiates in the last

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month, (4) current use of benzodiazepines, (5) traces of any illicit substance in the urine (amphetamine, cannabis, cocaine [bensoylecgonine], and opiates), (6) serious somatic disease (e.g., severe hypertension), (7) pregnant or lactating women, (8) known hypersensitivity for methylphenidate and (9) IQ < 70. Potential participants underwent a physical examination including laboratory tests for hematology and liver function.

Patients gave their written informed consent to participate in the trial that was approved by the Regional Ethical Review Board in Stockholm and the Swedish Medical Products Agency, conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

2.2. Design

This study was a double-blind, placebo controlled, randomized trial comparing extended-release (OROS) MPH with placebo (PL). Twenty-four participants were randomized to either PL or MPH by the Karolinska University Hospital Pharmacy, using the Trombul software. The patients were required to stay abstinent from any psychoactive substance for a minimum of 4 weeks prior to inclusion. Abstinence was considered important for providing improved validity of the diagnosis of current and childhood ADHD (not substance related). This procedure was in concordance with the clinical guidelines in Sweden.

The trial duration was 13 weeks including baseline measurements and 12 weeks of treatment. The starting dose was 18 mg of MPH/PL which was titrated over period of 10 days to the maximum dose of 72 mg. For subjects who did not tolerate a dose increase the dosage was adjusted and continued at the tolerated level. Twice weekly the subjects visited the clinic and received medication (blister of 6–8 tablets) and provided a supervised urine specimen. Urine samples for amphetamines were analyzed twice weekly, cannabis, cocaine [bensoylecgonine] and opiates once weekly. Compliance to the trial was defined as consumption of 75% of the study medication as assessed by pill counts and by the presence of MPH in urine. All subjects participated once weekly in an individual skills training program which targeted risk for relapse in drug use and ADHD symptoms.

2.3. Measures

ADHD symptoms were assessed using the Conners' adult ADHD (Conners et al., 1999) self and observer rating scales (CAARS:SV and CAARS:O) once weekly. The Addiction Severity Index Scale (ASI; McLellan et al., 1992) measuring problem severity in e.g. physical health and substance use was administered pre- (week 0) and post-treatment (week 12).

Drug use was assessed weekly using the Time-Line Follow-Back self-report interview (TLFB; Sobell and Sobell, 1992) and 7-point visual analog craving scale adapted from the Tiffany craving scale (Jayaram-Lindström et al., 2008). Urine toxicology was performed to detect amphetamines, cannabis, cocaine [bensoylecgonine] and opiates. The samples were screened for amphetamine by an immunoassay method with a cutoff level of 500 ng/ml. The confirmation analyses of the positive samples comprised amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine (reporting limit 300 ng/ml) and were performed using a liquid chromatography–tandem mass spectrometry method (Andersson et al., 2008). The same method was used for analysis of MPH in urine, as a measure of medication compliance.

Symptoms of depression and anxiety were measured by Beck's depression inventory-II (BDI-II; Beck et al., 1996) and Beck's Anxiety Inventory (BAI; Beck and Steer, 1993a). These were administered on three occasions: baseline, weeks 6 and 12. The Stroop-test (Golden and Freshwater, 2002) was also administered on three occasions: baseline, weeks 6 and 12 to measure the effect of treatment on reaction time and on directed attention. Adverse events (AEs) monitoring (interview and rating of intensity and duration) was carried out by the research nurse using a standardized form.

2.4. Statistical analysis

2.4.1. ADHD symptoms. The primary analysis of change in self- and observer-rated ADHD symptoms measured by CAARS was carried out according to completer analysis (used >75% of medication). Treatment efficacy was analyzed by *t*-test comparing MPH and placebo treated patients over 12 weeks. A secondary analysis was conducted according to the Intention-To-Treat (ITT) approach using the same statistical method.

2.4.2. Drug use. Relapse to amphetamine use as measured by (1) presence of amphetamine in urine, all missing urine samples were imputed as positive in the analysis, (2) TLFB, other amphetamine related measures were (3) retention in treatment, (4) cumulative abstinence and (5) craving for amphetamine. Use of other drugs was measured by (6) the presence of any illicit drugs for in urine and (7) TLFB for alcohol and any illicit drugs. All drug use measures were analyzed using *t*-test or Man–Whitney-test for non-parametrical data. Rate of continuous abstinence from amphetamine was computed by a Kaplan–Meier survival analysis according to ITT.

2.4.3. Other measures. Patients were compared on baseline characteristics using χ^2-tests for categorical characteristics and *t*-tests for continuous characteristics in order to assess efficiency of randomization procedure to ensure homogeneity between the two treatment groups. All additional outcome measures were analyzed using *t*-test or Mann–Whitney-test for non-parametrical data.

All the data analyses were performed using software program SPSS v.16.

3. Results

Participants were between 18 and 65 years of age (mean 37.4, SD 9.9) with chronic amphetamine use (mean 14.4 years MPH, 13.3 years PL) and an early debut in drug use (mean 14.4 years MPH, 13.8 years PL). The majority was male (18 men, 6 women), and lived on social welfare (71%).

There were no differences on any of the background variables (age, sex, means of living, age of onset of drug use or years of amphetamine use) (Table 1).

3.1. ADHD symptomatology

Change in self- and observer-reported ADHD symptoms in ITT analysis did not show any significant difference ($P = .137$, $P = .686$) between the two conditions (Table 1). Both groups showed a significant decline in their self-reported symptoms from baseline to week 12 (MPH-19.1 SD 13.2, PL-8.5 SD 19.8) in ITT analysis (Fig. 1).

3.2. Drug use

There was no difference between the MPH and the PL treated groups in terms of percentage of urines with no trace of amphetamine. In addition there was no difference between the groups in TLFB self-reported days of amphetamine use or in craving for amphetamine (Fig. 1). No difference was found in time to relapse, cumulative abstinence duration and retention in treatment (Table 1). There was no difference between the two groups in any of the measures for other drugs.

3.3. Other measures

There was no difference between the two groups (Table 1) in any of the other measures (BDI, BAI, and Stroop-test). Attrition was

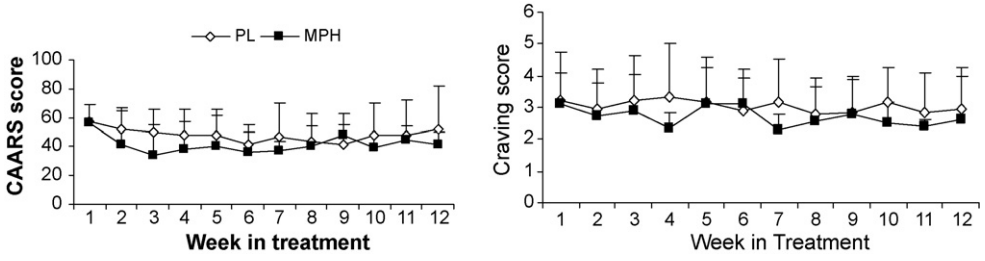

Fig. 1. The effects of methylphenidate (MPH) and placebo (PL) treatment as reflected in the Conners' adult ADHD self-report rating scale (CAARS) and a visual analog craving scale (maximum = 7) as a function of weeks in treatment.