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Use of lisdexamfetamine dimesylate in treatment of executive functioning deficits and chronic fatigue syndrome: A double blind, placebo-controlled study

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ABSTRACT

The purpose of this study was to assess the efficacy of lisdexamfetamine dimesylate (LDX) for the treatment of executive functioning deficits in adults (ages 18–60) with chronic fatigue syndrome (CFS). The study's primary outcome measure was the Behavior Rating Inventory of Executive Function—Adult (BRIEF—A). Secondary outcome measures were standardized assessments of fatigue, pain and global functioning. Twenty-six adults who met criteria for CFS and had clinically significant executive functioning deficits were randomly assigned to a flexible morning dose (30, 50, 70 mg/day) of either placebo or LDX for a 6-week trial. The data were analyzed with standard analysis of variance (ANOVA) procedures. Participants in the LDX group showed significantly more positive change in BRIEF—A scores ($M_{change}=21.38$, $SD=15.85$) than those in the placebo group ($M_{change}=3.36$, $SD=7.26$). Participants in the active group also reported significantly less fatigue and generalized pain relative to the placebo group. Although future studies with LDX should examine whether these benefits generalize to larger, more diverse samples of patients, these results suggest that LDX could be a safe and efficacious treatment for the executive functioning deficits often associated with CFS. The possibility that dopaminergic medications could play an important role addressing the symptoms of CFS is also discussed.

1. Introduction

Chronic fatigue syndrome (CFS) affects millions of people each year (Centers for Disease Control and Prevention, 2009a, 2009b). Although it is often perceived to be a disorder characterized by only long-term, persistent fatigue that cannot be explained by another medical condition or by ongoing exertion, a variety of other symptoms are also typically present for at least 6 months. These include post-exertion malaise, muscle and joint pain, headaches, unrefreshing sleep, tender cervical or axillary lymph nodes, and a frequent or recurring sore throat (see Fukuda et al., 1994). For some patients, the most distressing symptoms of CFS are executive functioning deficits that include impaired short-term memory, delayed reaction time, and a subjective sensation of "mental fogginess". Combined with fatigue and pain, these executive function deficits can be debilitating, and it is estimated that they affect as many as 80% of all individuals who suffer from CFS (Afari and Buchwald, 2003; Short et al., 2002).

A variety of treatment options are available to patients with CFS, but none have proved to be universally effective. Among these options are cognitive-behavioral therapy, exercise therapy, dietary interventions, homeopathic treatments, and pharmacological interventions (see, e.g., Luyten et al., 2008). After reviewing the many available interventions, Van Houdenhove et al. (2010) called for investigations that examine intervention techniques that could be used to treat specific patient populations. Their hope was to begin answering the question of "what works for whom?" (p. 219). The present study was designed to contribute to the literature in this way.

Specifically, the present study was designed primarily to determine whether a common psychostimulant medication lisdexamfetamine dimesylate (LDX) could be used to reduce executive functioning deficits in CFS patients who also present with clinically significant

Abbreviations: AD/HD, Attention Deficit/Hyperactivity Disorder; ADHD-RS, Attention Deficit Hyperactivity Disorder Rating Scale; BRIEF—A, Behavioral Rating Inventory of Executive Function—Adult; CFS, Chronic Fatigue Syndrome; CGI—I, Clinical Global Impression Scale—Improvement; CGI—S, Clinical Global Impression Scale—Severity; FIQ, Fibromyalgia Impact Questionnaire; FMS, Fibromyalgia; FSS, Fatigue Severity Scale; LDX, lisdexamfeatmine dimesylate; RCBM, Rochester Center for Behavioral Medicine; XMRV, Xenotropic murine leukemia virus-related virus

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executive functioning deficits. LDX is a long-acting amphetamine-based pro-drug currently approved for the treatment of children, adolescents, and adults with attention deficit/hyperactivity disorder (ADHD) (Shire, 2010), but its efficacy for other conditions has not been widely studied. Psychostimulant medications have been used for many years to successfully treat executive functioning impairments among patients with conditions like ADHD (see, e.g., Young, 2007), and case-study evidence has suggested that they may hold promise for improving executive functioning in patients with CFS as well (Young and Redmond, 2007). However, no empirical studies to date have specifically examined whether the executive functioning deficits reported among the subgroup of patients with *both* CFS *and* clinically significant executive functioning deficits can be ameliorated with currently available pharmacological interventions.

A number of studies have demonstrated that some common pharmacological interventions (e.g., anti-depressant medications) have a degree of promise for treating a variety of the symptoms associated with CFS, including pain, fatigue, depressed mood, and sleep disturbances (Pae et al., 2009), but the extent to which these medications treat executive functioning deficits in patients with CFS remains unknown. Similarly, although the effect of psychostimulants on CFS patients has been explored to some extent, these studies have not fully explored the role of these drugs in improving executive functioning. For example, one study of 60 CFS patients compared twice daily methylphenidate treatment to placebo and found that nearly 20% of participants who took the psychostimulant experienced a clinically significant reduction in fatigue and inattention (Blockmans et al., 2006), but a similar study showed that low dose dexamphetamine reduced only fatigue in 90% of participants receiving active treatment compared to a reduction in 40% of those receiving placebo (Olson et al., 2003).

The present study builds on these clinical observations and existing CFS research studies to explore the role of LDX in treating CFS. The primary objective of the present study was to examine whether LDX could be used to improve executive functioning among patients with *both* CFS *and* clinically significant executive functioning deficits. It was hypothesized that treatment with a daily dose of LDX would improve executive functioning deficits (vs. placebo) in adult patients with both CFS and clinically significant executive functioning impairments, as assessed by scores on the Behavioral Rating Inventory of Executive Function-Adult version (BRIEF-A). A secondary objective of the present study was to examine whether LDX could be used to improve fatigue, pain, and overall functioning among patients with both CFS and clinically significant executive functioning deficits. A secondary hypothesis was that a daily dose of LDX would improve fatigue, pain, and overall functioning (vs. placebo) in adult patients with both CFS and clinically significant executive functioning impairments. A tertiary aim of the study was to examine the safety and tolerability of LDX throughout the course of treatment. It was hypothesized that LDX would not differ in safety and tolerability relative to placebo.

2. Methods

The study was conducted at the Rochester Center for Behavioral Medicine (RCBM), a research and treatment center in suburban Detroit. RCBM actively participates in clinical care and new medication investigations. Clinical trials include multi-centered national trials and single site, investigator-initiated studies. The research unit is led by a board-certified psychiatrist and supported by an experienced team of clinical coordinators. Study medications were obtained from Shire's Investigator Sponsored Trial Operations Office. The Western Institutional Review Board (WIRB) oversaw the study and guided informed consent procedures.

2.1. Patient population

Study participants were recruited from local advertisements and the clinic's existing patient population. Participants ($N=26$) ranged in age from 21 to 59 ($M=45.10$). Twenty-five participants were female, and the male participant was randomly assigned to the placebo group. The participants were not monetarily compensated for their participation.

2.2. Inclusion criteria

In order to study changes in executive functioning associated with CFS, only adult participants (18–60 years old) with CFS and cognitive complaints were included in the trial. The CFS diagnosis was based on the participants' medical history and confirmed by the primary investigator using a clinical interview, brief physical examination, consultation of Fukuda et al.'s (1994) guidelines for CFS diagnosis, and the participant's responses to the Chronic Fatigue Syndrome checklist. Executive functioning impairment was formally assessed using the BRIEF—A, a widely accepted neuropsychological measure of executive impairment. Impairment was defined as a BRIEF—A Global Executive Composite score that was 1.5 standard deviations above standardized population mean, and all participants were required to score at that level of impairment or above. All participants were also required to be able to swallow study medication, display the ability to communicate effectively with the study team, and demonstrate the interest and capacity to fully comply with study procedures and restrictions. The Primary Investigator had final determination of these qualifications.

2.3. Exclusion criteria

Participants were excluded if their BRIEF—A Global Executive Composite scores were less than 1.5 standard deviations above the standardized population mean (a *t*-score less than 65). Participants were also excluded if they had been treated with any psychostimulant within the prior 6 months. Women of childbearing potential were excluded if they did not test negative for pregnancy at the screening visit, and they were excluded if they did not agree to use a medically accepted means of contraception during the study. Women who were currently breastfeeding were not allowed to participate.

Participants with severe comorbid psychiatric diagnoses (e.g., Axis I disorders such as mood disorders, anxiety disorders, post-traumatic stress disorder, obsessive-compulsive disorder) were excluded, as were participants with a history of psychosis, pervasive developmental disorders, severe Axis II disorders or severe substance dependence. The determination of participants' comorbidities was made subjectively through clinical interview and objectively through the Adult Self-Report Inventory-4, an assessment of psychiatric conditions.[1]

Participants were also excluded if they had a chronic or an acute medical condition or illness that could have been negatively affected by the study medication. Those with a history of hypothyroidism, hypertension, or a resting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg were ineligible. Participants on medications approved to treat fibromyalgia (duloxetine, milncipran, or pregabulin) were excluded at the pre-screening stage.

Participants who were directly affiliated with the study team, and those who were receiving treatment with an unregulated medication or had participated in a clinical trial within 30 days prior to screening, were also excluded. Individuals could not participate if they weighed less than 30 kg or more than 120 kg at the time of informed consent.

2.4. Study design

This was a randomized, single-center, double-blind, placebo-controlled study to evaluate the relative effectiveness of LDX administered as a flexible morning dose (30, 50, 70 mg/d) compared to placebo in participants with CFS. Potential study participants were prescreened with a telephone contact by a senior study coordinator. During the screening visit, the primary investigator administered the CFS Checklist and a study coordinator administered the BRIEF—A. Of all subjects screened, only two scored below the required threshold score for the BRIEF—A, and they were excluded. Also at the screening visit, each participant was assigned a randomized code number, which was used to determine whether the participant would be in the active or placebo arm. Participants were block randomized to LDX or placebo using an envelope allocation method, and 15 participants were randomly assigned to each group. Four participants were screen failures, but all had been randomly pre-assigned to the placebo group. Therefore, of the participants who completed the study, 15 were assigned to LDX and 11 to placebo (see Fig. 3). After the screening visit, the primary investigator gave individualized instructions to safely discontinue prohibited medications prior to starting study medication. Six visits were scheduled in total: the first visit was to screen

[1] There were no statistically significant differences between groups on the subscales of the ASRI, with the exception of the Bulimia subscale. There, a one-way ANOVA revealed that participants in the LDX group ($M=1.38$, S.D.$=1.56$) had *lower* scores than did participants in the placebo group ($M=3.30$, S.D.$=2.79$), $F(1, 22)=4.39$, $p=0.048$, $d=0.85$, suggesting the participants in the placebo group had a greater degree of disordered eating behavior than did those in the active group.