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 six-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 ($M_{change}=3.36$, $SD=7.26$), $p=0.005$, $d=1.46$. 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.

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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 six months. These include post-exertion malaise, muscle and joint pain, head-aches, 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 proven 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?" (pp. 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 (LDX) could be used to reduce executive functioning deficits in CFS patients who also present with clinically significant 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 (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 the symptoms of 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 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 child-bearing 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, etc.) 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 they 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 candidates, the

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[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.
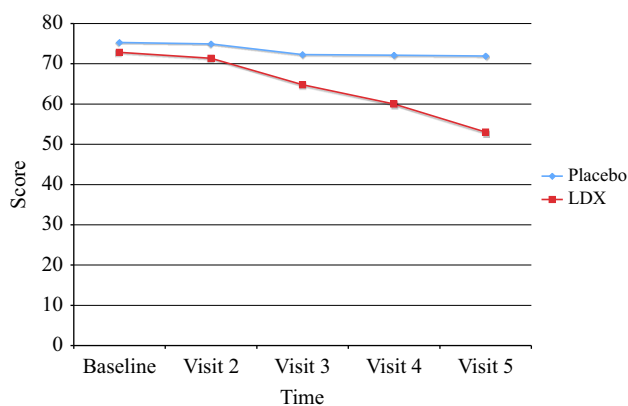
Fig. 1. Participants' cognitive impairment over the course of the trial, as assessed by the GEC of the BRIEF—A. *Note*: Lower scores denote better functioning.
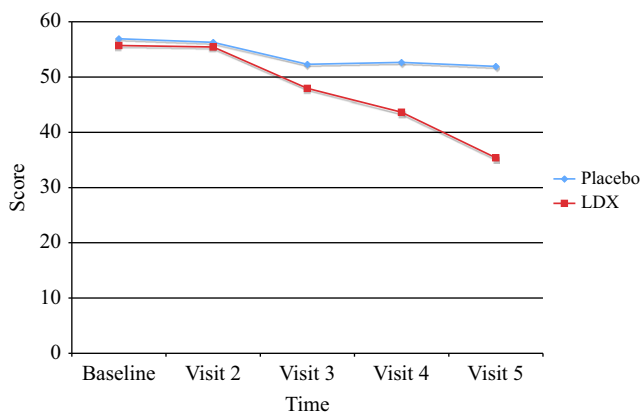

Fig. 2. Participants' fatigue symptoms over the course of the trial, as assessed by the Fatigue Severity Scale (FSS).

second visit was to obtain baseline assessments and to dispense the study medication and the next four were for dosage adjustment, medication dispensation and overall assessment.

2.5. Dosing

Participants were started with a single pill containing 30 mg of LDX or comparable placebo. To maintain the study blind, all LDX and placebo tablets were available in matching bottles obtained from the manufacturer and marked with 30, 50 or 70 mg and no visible differences were evident between the study medication and the placebo. If the PI determined that no significant adverse effects were exhibited at Visit 2, the dose was increased to 50 mg. If 50 mg dose was well tolerated, the dose was increased to 70 mg at Visit 3. If participants experienced adverse effects at this, or any, assigned dose, the dose was dropped to the level previously tolerated.

2.6. Assessments

2.6.1. Primary outcome measure: Executive functioning impairment

Executive functioning impairment was assessed with the Behavior Rating Inventory of Executive Function—Adult (BRIEF—A) (Roth et al., 2005). The BRIEF—A is a multifaceted assessment of adult (ages 18–90) executive functioning. The BRIEF—A includes nine clinical scales that assess behavioral, emotional, and metacognitive skills. It yields an overall score, the Global Executive Composite (GEC), which was used as the primary outcome measure in this study. The GEC is composed of two indices: the Behavioral Regulation Index (BRI), and the Metacognitive Index (MI). The BRI has four subscales: Inhibit, Shift, Emotional Control, and Self-Monitor. The MI has five subscales: Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials. Standard scores (*t* scores) are calculated for the overall score, the indices, and the subscales (Gioia et al., 2000).

2.6.2 Secondary outcome measures: Fatigue, pain, and global functioning

Fatigue was assessed with the Fatigue Severity Scale (FSS), a well-validated, nine-item measure of fatigue that was developed to assess daily fatigue in clinical populations (Krupp et al., 1989). Pain was assessed with the McGill Pain Questionnaire (MPQ)[2] (Strand et al., 2008). The MPQ is a multidimensional, quantitative assessment of self-reported pain. Overall functioning was assessed with the Fibromyalgia Impact Questionnaire (FIQ) and the Clinical Global Impression (Severity). The FIQ is a self-report measure of the impact of Fibromyalgia symptoms on daily life (Burckhardt et al., 1991). The CGI is a widely used measure of clinicians' judgments of patient improvement (Guy, 2000; Forkmann et al., 2011). These scales are all well-validated, widely used assessments of pain, fatigue, and the impact of symptoms on patients' daily life. Because LDX is traditionally used to treat ADHD, the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) was also used to quantify baseline levels of ADHD in the study population (Zhang et al., 2005).

2.7. Safety and tolerability analysis

In order to assess any differences in safety outcomes between the placebo and actively treated groups, heart rate, blood pressure and temperature were measured and compared. In addition, because stimulants have been noted to have anxiogenic effects, the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959) was included to evaluate anxiety in the active group relative to placebo.

2.8. Statistical procedures

Change in participants' levels of functioning on the primary and secondary outcome measures over the course of the trial was assessed with pre–post change scores. These scores were calculated by subtracting participants' endpoint scores on a given outcome measure (e.g., the BRIEF—A GEC) from their baseline scores on the same measure. These change scores showed the total change in score over the course of the trial, with higher values indicating a greater degree of change from baseline. Standard two-tailed parametric Analysis of Variance (ANOVA) tests were used to determine whether significant differences existed between the placebo and LDX groups, and a cut-off P-value of 0.05 was used in all cases. In some cases, further analysis with non-parametric procedures (i.e., the Mann–Whiney U test) was required to correct for heterogeneity of variance between groups. The magnitude of the differences between groups was assessed using Cohen's d, a standard measure of effect size.[3],[4]

3. Results

3.1. Primary outcome measure: Executive function impairment

The primary outcome measure was participants' level of change on the Global Executive Composite (GEC) of the BRIEF—A. These scores were calculated by subtracting participants' endpoint GEC scores from their initial baseline GEC scores. These change scores show the total change in executive functioning over the course of the trial. Higher values indicate improved executive functioning at the end of the trial compared to the beginning. These data were initially analyzed with a one-way, two-tailed ANOVA (*P*-value cut-off=0.05), but because Levene's test detected significant

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[2] The Brief Pain Inventory (BPI) was also initially included to assess participants' self-reported levels of pain. However, during the data collection phase of the trial, the BPI was incorrectly implemented and total pain scores could not be calculated. Therefore, these scores will not be reported in the results section.

[3] It is important to note that there was only a single primary outcome measure (the BRIEF—A GEC) with a variety of secondary subscales (e.g., the BRIEF—A BRI) and supporting secondary outcome measures (e.g., the FSS); therefore, correction for multiple testing was unnecessary for the primary outcome analysis (for rationale, see EMEA, 2002). For interested readers, a *very* conservative Bonferroni-type correction (p/n=0.05/7=0.007) was also applied to the inferential data, and the difference between the treatment and placebo groups on the GEC remained statistically significant.

[4] It is also important to note that an *a priori* power analysis was not conducted to determine whether the study had significant power to avoid type II errors. Retrospective power analysis is generally not recommended for these data (Nakagawa and Foster, 2004), and it was deemed unnecessary in this case because the results demonstrated that there were statistically significant differences between groups on the primary outcome measure. Thus, a power analysis would not have yielded any additional information about the data.
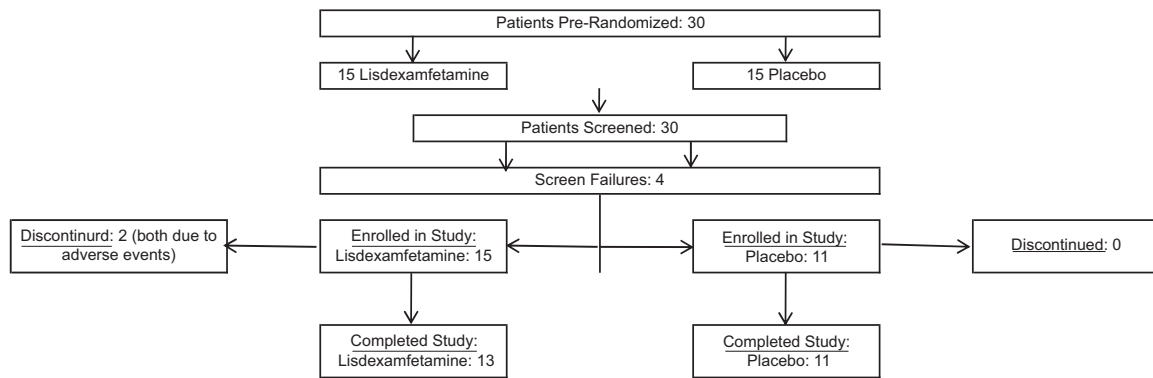
Fig. 3. Study patient disposition.

Table 1
Mean improvement of participants in the placebo and LDX groups on the primary outcome measure (BRIEF—A GEC) and its supporting subscales.

	Mean improvement (S.D.)		Inferential test	p-Value	Effect size
	Placebo	*LDX*			
Global executive composite	3.36 (7.26)	21.38 (15.85)	$U=22.50$	0.005	1.46
Subscales					
Metacognition index	4.09 (12.86)	23.31 (16.90)	$F(1, 22)=9.52$	0.005	1.28
Behavioral regulation index	4.46 (6.71)	15.69 (13.17)	$U=32.50$	0.024	1.07
Inhibit	3.27 (6.97)	13.00 (13.72)	$U=46.00$	0.138	0.89
Shift	−1.09 (9.50)	14.85 (15.64)	$F(1, 22)=8.67$	0.007	1.23
Emotional control	4.36 (8.23)	13.23 (12.30)	$F(1, 22)=4.13$	0.054	0.85
Self-monitor	4.46 (9.28)	10.23 (9.43)	$F(1, 22)=2.27$	0.146	0.62
Initiate	3.82 (8.67)	23.23 (16.82)	$F(1, 22)=11.92$	0.002	1.45
Working memory	1.09 (7.83)	21.46 (17.99)	$F(1, 22)=12.10$	0.002	1.47
Plan/organize	0.64 (12.59)	22.23 (14.81)	$F(1, 22)=14.50$	0.001	1.57
Task monitor	0.09 (7.35)	18.77 (17.28)	$U=22.00$	0.004	1.41
Organization of material	3.18 (7.49)	14.15 (12.11)	$F(1, 22)=6.80$	0.016	1.09

Note: The change scores were calculated by subtracting participants' endpoint scores from their initial baseline scores. These change scores show the total change in executive functioning over the course of the trial. Higher values indicate improved executive functioning at the end of the trial compared to the beginning. These data were initially analyzed with a one-way ANOVA. In cases where Levene's test detected heterogeneity of variance between groups, the scores were further analyzed with a Mann–Whitney U non-parametric ANOVA. "F" scores indicate a parametric ANOVA. "U" scores a non-parametric ANOVA. Cohen's d was used as the measure of effect size.

heterogeneity of variance between groups [$F(1, 22)=5.06$, $P=0.035$], these scores were further analyzed with a Mann–Whitney U non-parametric ANOVA. The results of this analysis showed that participants in the LDX group showed significantly more improvement in executive functioning ($M=21.38$, S.D.$=15.85$) than did participants in the placebo group ($M=3.36$, S.D.$=7.26$), $U=22.50$, $z=-2.84$, $P=0.005$, $d=1.46$. Fig. 1 is a graphical representation of participants' scores on the GEC over the course of the trial.

Additionally, Table 1 provides the complete descriptive and inferential statistics these same procedures yielded for each of the subscales that compose the BRIEF—A GEC. As the first three rows in Table 1 illustrate, the LDX group showed more improvement relative to placebo on the two indices of the GEC (BRI and MI). The differences between LDX and placebo were non-significant on the Inhibit and Self-Monitor subscales, but the LDX group showed more improvement relative to placebo on the remaining index subscales of the BRIEF—A: Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Material. In each case, participants in the LDX group showed more positive change than did participants in the placebo group, indicating that participants who took LDX improved relative to participants who took placebo.

3.2. Secondary outcome measures: Fatigue, pain, and functioning

The FSS, MPQ, and FIQ were used to assess participants' improvement in fatigue, pain, and FMS impact. For each participant, change scores on the FSS, MPQ, FIQ, CGI-S, and ADHD-RS were calculated by subtracting participants' endpoint scores on each measure from their baseline scores on the same measure. These calculations illustrate the total change in score over the course of the trial, and higher values indicate more change from baseline. These data were then analyzed with one-way, two-tailed univariate ANOVAs (P-value cut-off$=0.05$).[5] Relative to participants in the placebo group, those in the LDX group showed a statistically more improvement on the FSS, MPQ, CGI-S, and ADHD-RS. These change scores indicate that participants who took LDX had less fatigue, less pain, higher overall functioning, and fewer ADHD symptoms at the end of the trial compared to baseline, relative to participants who took placebo. Table 2 provides the full listing of means, standard deviations, and the inferential statistical information yielded by these procedures for all the scales. For the sake of brevity, they are not listed here as well. Fig. 2 shows participants' scores on the FSS over the course of the trial.

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[5] Following the recommendation of EMEA (2002), correction for multiple testing was not applied to these secondary outcome analyses. However, for the interested readers, a very conservative Bonferroni correction ($0.05/n$) would yield a cutoff p-value of 0.00833. By this stricter criterion, the participants in the LDX group would still have shown more improvement on the FSS than participants in the placebo group, indicating that by the strictest criteria LDX reduced fatigue relative to placebo.

3.3. Safety and tolerability analysis

Significant adverse events were not encountered in this study. The most common treatment-emergent adverse events included: headache (LDX: 15.38%/Placebo: 7.7%), dry mouth (LDX: 7.7%/Placebo: 0%), and insomnia (LDX: 7.7%/Placebo: 0%). Two participants discontinued the study due to adverse events [insomnia (at visit 3), anxiety (at visit 5)]. Vital signs among the treated group varied minimally compared to the placebo group. These findings were consistent with data collected during the LDX pivotal trials in adults with ADHD (Adler, 2007). A full exploration of treatment-emergent adverse events can be found in Table 3.

Change scores in pulse rate, temperature, blood pressure, and anxiety (as assessed by the HAS) were calculated by subtracting participants' endpoint scores on each safety measure from their baseline scores on the same measure. These calculations illustrate the total change in score over the course of the trial, and higher values indicate more change from baseline. These data were analyzed with separate one-way, two-tailed univariate ANOVAs (P-value cut-off$=0.05$). These analyses revealed that participants in the LDX group showed more change in pulse ($M=-8.75$, S.D.$=9.11$) than did participants in the placebo group ($M=1.82$, S.D.$=9.68$), $F(1, 22)=7.28$, $P=0.013$, $d=1.13$; however, the endpoint pulse rates did not differ between groups [LDX: $M=77.77$, S.D.$=13.41$; placebo: $M=75.27$, S.D.$=12.55$, $F(1, 22)=0.22$, $P=0.644$]. The negative change score for participants in the LDX group revealed a higher endpoint than baseline pulse, indicating that participants in the LDX group initially had lower pulse rates than participants in the placebo group. LDX then raised these rates to the level of those in the placebo group. There were no additional statistically significant differences between the LDX and placebo groups on the safety measures, including the measure of anxiety.

Table 2
Mean improvement of participants in the placebo and LDX groups on the secondary outcome measures.

	Mean improvement (S.D.)		F (1, 22)	p-Value	Effect size
	Placebo	*LDX*			
FSS	5.00 (11.73)	20.92 (14.71)	8.37	0.008	1.20
McGill	2.45 (9.53)	10.38 (8.84)	4.47	0.046	0.86
FIQ	8.83 (18.14)	20.90 (25.54)	1.60	0.219	0.54
CGI_S	0.64 (0.92)	1.92 (1.50)	6.20	0.022	1.03
ADHDRS	8.73 (7.80)	18.17 (11.95)	4.93	0.038	0.94
HAM-A	6.18 (8.28)	11.31 (9.74)	1.89	0.183	0.57

Note: The change scores were calculated by subtracting participants' endpoint scores from their initial baseline scores. These change scores show the total change on the secondary outcome measures over the course of the trial. Higher values indicate improvement at the end of the trial compared to the beginning. These data were analyzed with a one-way ANOVA. The F-value indicates the results of the inferential test. Cohen's d was used as the measure of effect size.

4. Discussion

Chronic Fatigue Syndrome is a poorly understood condition that afflicts millions and has no clear treatment (Pae et al., 2009). As a result, researchers have recently called for new approaches to treatment (and treatment investigations) that are targeted toward specific subsets of the larger population of CFS patients (Van Houdenhove et al., 2010). The subset of interest in the present study was those CFS patients who also have clinically significant deficits in executive functioning, and the present study was designed in a way that begins to answer the call for specialized treatment. Although the research to date has been somewhat inconclusive about the degree to which pharmacological interventions can be used to treat all of the symptoms of CFS (Luyten et al., 2008), clinical observations have suggested that psychostimulant medication could be used to treat some of the executive functioning deficits associated with CFS (see Young, 2007; Young and Redmond, 2007). This present study examined this question empirically by investigating whether LDX could ameliorate the executive functioning deficits among the subset of patients with both CFS and clinically significant deficits in executive functioning.

Patients with chronic fatigue syndrome and executive functioning impairments were recruited into a double-blind study and randomized to either LDX or placebo. The safety and tolerability analysis demonstrated satisfactory safety and tolerability for the active group. Relative to participants in the placebo group, those who took LDX showed significantly more improvement in executive functioning, as assessed by the present study's primary outcome measure, the BRIEF—A. Relative to the placebo group, participants who took LDX also showed significantly more improvement in fatigue, pain, and global functioning, as assessed by the FSS, MPQ, and CGI.

4.1. Limitations

This study does have a number of limitations that warrant further discussion. The first of these limitations is that the study was relatively small ($N=26$), and it was conducted at only a single site. Future research should be conducted at multiple sites and include greater numbers of participants to assess the generalizability of these findings to all patients with both CFS and clinically significant executive functioning deficits. It is noteworthy, however, that statistically significant differences were achieved between treatment groups despite the small sample size used in this study. It is a testament to the efficacy of the treatment, as a larger sample would have been made statistically significant differences easier to achieve between groups. Another limitation of the present study is that the randomization resulted in an imbalance in the number of participants in the active arm relative to the placebo arm. This occurred because the conditions were randomly pre-assigned to all potential participants at the screening visit. By chance, the only four screen failures were pre-assigned to the placebo group.

Table 3
Primary and secondary outcome measures.

	Scale	Assessment
Primary	**Behavior Rating Inventory of Executive Function—Adult (BRIEF—A)**	Executive function
Secondary	**Fatigue Severity Scale (FSS)**	Fatigue
	McGill Pain Questionnaire (MPQ)	Pain
	Fibromyalgia Impact Questionnaire (FIQ)	Fibromyalgia impact
	Clinical Global Impression—Severity (CGI-S)	Global functioning
	Attention Deficit/Hyperactivity Disorder Rating Scale (ADHDRS)	AD/HD symptoms
	Hamilton Anxiety Scale (HAM-A)	Anxiety

Another limitation is that the results suggest, on the surface, somewhat conflicting results on the secondary outcome measures of pain. Namely, participants who took LDX showed significantly greater reduction in pain than did participants in the placebo group, but this was only the case on one of the two assessments of pain (the MPQ). Based on the results of the FIQ, there were no statistically significant differences in the impact of pain on functioning; however, this result may actually reflect an important impact of the measurements itself. The FIQ as the name implies, the *impact* of fibromyalgia symptoms (i.e., pain) on daily life. This is somewhat different than a direct measure of pain. Fibromylagia is a much more thoroughly studied condition than CFS, and three medications, duloxetine, pregabalin and minalciprin are currently approved as fibromyalgia treatments. The pivotal studies for these agents demonstrated improvements in pain but only minalciprin showed superiority to placebo on cognitive measures (Van Seventer et al., 2006; Wohlreich and Watkin, 2003; Clauw et al., 2008). Because these existing treatments for pain already exist for patients with fibromyalgia alone, the most important finding of the current study remains the fact that LDX improved *executive functioning in CFS patients* over placebo. Reducing the impact of fibromyalgia would certainly have been a benefit, but it was not the primary aim of this study.

Perhaps the most important limitation of the present study is the make-up of the participant sample. One limitation of the sample is that there were no male participants in the treatment group and only one in the placebo group. This dearth of male participants does somewhat reflect the expected demographics of CFS (i.e., many more women seek treatment for CFS), but future studies should examine samples with a higher proportion of male participants in order to determine if LDX has the same effects for men as it does for women. A second limitation of the sample was the high degree of ADHD *symptoms* observed in the sample. Although participants entered the study on the basis of their CFS and cognitive impairment symptoms alone, RCBM is known to specialize in ADHD treatment, and some participants may have been drawn to it for this reason. A specific effort was made to recruit from outside the clinic's existing population to counter the possibility of an overrepresentation of ADHD patients.

Despite the precautions, 62% of participants scored above the threshold for ADHD on the ADHD-RS. It is important to note, however, that these threshold scores differ from an ADHD *diagnosis*. To obtain such a diagnosis, participants' core ADHD symptoms would have needed to be evident by the age of seven and would have needed to cause functional impairment. A specific clinical interview to determine these diagnostic criteria was not conducted during this study, and so there was no way to determine whether the participants actually had ADHD. More importantly, 38% of the participants in this study decidedly did *not* meet the cutoff criteria for ADHD. Moreover, fatigue is not part of the ADHD diagnostic criteria, and few studies have examined the effect of LDX on fatigue. So while some study participants may indeed have met criteria for ADHD, many did not. As such, the findings of the present study continue to support the assertion that LDX offers benefit for individuals with CFS and executive functioning impairments by alleviating symptoms beyond those for which the medication is currently indicated. To help understand the relationship between CFS, executive functioning impairments, and ADHD symptoms, future studies of LDX should more directly assess ADHD diagnostic criteria.

4.2. Conclusion

These results of this study suggest that LDX safely exerts beneficial effects on executive functioning among patients with both CFS and clinically significant executive functioning impairments. The results also suggest that LDX improves fatigue, pain, and global functioning (but not fibromyalgia impact) in the same population. Although the mechanism by which these benefits are achieved remains unclear, it is not beyond speculation. In terms of pain, LDX may reduce pain by improving individuals' ability to filter out painful stimuli without having a direct analgesic effect (see e.g., Schweitzer et al., 2004; Sussman, 2008). In terms of executive functioning, like other stimulants, LDX centrally modulates dopaminergic and noradrenergic systems in the pre-frontal cortex, a phenomenon that has been associated with improved cognition in individuals with ADHD (Kengay et al., 2004). It may be the case that LDX has a similarly positive effect on cognition in non-ADHD populations as well. The modulation of dopamine circuits translates clinically into an anti-fatigue effect, and although this property has been previously identified (Kooij et al., 2001; Adler et al., 2010), the present study is the first to demonstrate that LDX ameliorates cognitive impairments and fatigue in a population in which CFS and executive functioning impairments are the primary clinical symptoms.

Whatever the explanation, the present study demonstrated that treatment with LDX brought about significant improvements in executive functioning, fatigue, pain, and global functioning among participants with both CFS and clinically significant deficits in executive functioning. While psychostimulants have long been available, LDX offers a number of advantages over other psychostimulants. Whereas some short-acting agents have been hampered by concerns about safety, tolerability and diversion, LDX is a pro-drug with long-acting effects, properties that limit the likelihood of diversion and misuse (Lasser et al., 2010). Moreover, it has been used extensively in clinical populations since its release to the marketplace, and the present study demonstrates that it is safe and well tolerated among participants with both CFS and clinically significant executive functioning deficits. Although it does not appear to be curative, further studies should be undertaken to assess the rate of relapse following cessation of treatment. Observations in the clinic thus far suggest the benefits are sustained only with ongoing treatment.

Overall, CFS remains a high prevalence condition without a universal treatment. The present study, however, demonstrates the ongoing promise of new pharmacological interventions and gives reason for longer and larger multi-center studies to further replicate and extend the encouraging results achieved here.

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