A Placebo-Controlled Trial of Lisdexamfetamine in the Treatment of Comorbid Sluggish Cognitive Tempo and Adult ADHD

Lenard A. Adler, MD*; Terry L. Leon, MS, RN†; Taylor M. Sardoff, BA‡; Beth Krone, PhD§; Stephen V. Faraone, PhD¶; Michael J. Silverstein, MS∥; and Jeffrey H. Newcorn, MD¶

Objective: To examine the efficacy of lisdexamfetamine (LDX) versus placebo on behavioral attributes of sluggish cognitive tempo (SCT) in adults with attention-deficit/hyperactivity disorder (ADHD) and SCT.

Methods: In a randomized crossover trial conducted January 2016–April 2018, 38 adults with DSM-5 ADHD (via the Adult ADHD Clinical Diagnostic Scale v1.2) and SCT were recruited at 2 academic medical centers and assessed for symptoms of ADHD, SCT, executive function deficits, and functional impairment at baseline and weekly during treatment. Participants received 4 weeks of treatment with either LDX (30–70 mg/d; mean = 59.1 ± 14.8 mg/d) or matching placebo (mean = 66.6 ± 9.1 mg/d) with a 2-week washout before switching to the other arm. The ADHD Rating Scale and Barkley Adult ADHD Rating Scale–IV SCT subscale were coprimary outcome measures.

Results: There were moderately large treatment effects of LDX vs placebo on SCT ratings in both treatment periods (block 1 effect size = 0.68; block 2 effect size = 0.61), which reached significance only in block 1 owing to carryover effects of the first treatment epoch into the second. Significant effects were also seen for LDX over placebo in ADHD, executive function deficit, and functional impairment ratings, without order effects; no site differences were seen except on the Global Executive Complex score of the Behavior Rating Inventory of Executive Function—Adult Version. No moderating effects of sex, age, race, and ethnicity were seen.

Conclusions: Adults with ADHD and comorbid SCT had significant improvement after LDX vs placebo in ratings of SCT, ADHD, executive function deficits, and functional impairment. This is the first study to show improvement in SCT after stimulant therapy in adults with ADHD.

Trial Registration: ClinicalTrials.gov identifier: NCT02635035

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ABSTRACT

Sluggish cognitive tempo (SCT) describes individuals who are “dreamy,” “spacey,” slow moving, hypoactive, have difficulty initiating tasks, and often seem undermotivated and underaroused. Barkley has identified 9 cardinal symptoms of SCT: (1) prone to daydreaming, instead of concentrating; (2) trouble staying alert/aware in boring situations; (3) being easily confused; (4) being easily bored; (5) feeling spacey/in a fog; (6) frequently feeling lethargic; (7) being underactive/having less energy than others; (8) being slow moving; and (9) not processing information quickly/accurately.1 In a study of 1,249 individuals with and without attention-deficit/hyperactivity disorder (ADHD), Barkley identified individuals as having SCT if they had at least 5 of 9 symptoms rated often or very often on the 9-item SCT subscale from the Barkley Adult ADHD Rating Scale–IV: Self-Report (BAARS-IV; the Barkley SCT Scale).2 The prevalence of SCT in this subgroup was 5.8%, approximately half of whom had ADHD. Additionally, having SCT added to the impairment seen with ADHD, such that the cohort with ADHD and SCT was significantly more impaired overall and in 15 domains of impairment (including home, social, occupational, and educational).2 The results of this study suggest that SCT may be present and highly impairing in a large subgroup of adults with ADHD in a community sample, but SCT is not necessarily restricted to individuals with ADHD. In a meta-analysis by Becker et al,3 considering 23 independent studies including 19,000 participants, SCT was more strongly associated with the inattentive (IA) symptoms of ADHD than the hyperactive-impulsive symptoms (HI), in both children and adults. Other studies have found elevated levels of SCT in children with ADHD–combined type.4,5 Garner and coworkers evaluated parent and teacher reports in 322 children and adolescents for behavioral, emotional, and/or learning problems and found that SCT symptoms were greatest in youth with ADHD inattentive type, though they were also found in non-ADHD clinical groups.6 SCT symptoms have been thought to separate into cognitive (ie, daydreaming) and behavioral (ie, slowness, drowsiness) dimensions, with the behavioral dimension uniquely associated with learning/organization problems. Furthermore, studies have found a negative correlation between SCT and quality of life, an effect likely mediated...
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by the adverse consequences of SCT on executive function (EF). 7 Becker and Langberg 6 assessed parent and teacher ratings for 52 adolescents with ADHD and found that ADHD and SCT symptoms were highly correlated with ratings of EF. ADHD-HI symptoms were strongly associated with EF deficits in behavioral regulation, while ADHD-IA and SCT symptoms were unrelated to EF. As recent studies in community samples of adults and children have found high SCT in the absence of ADHD, the current thinking is that SCT might be a clinically meaningful condition not restricted to ADHD, with distinct underlying pathophysiology and treatment response. 1,4,9 Of note, although SCT is highly prevalent and associated with substantial impairment, it is not a primary driver of clinical treatment and is often not inquired about in the clinical evaluation, highlighting the need for appropriate identification and treatment.

The few treatment studies of SCT in patients with ADHD to date have focused on children, rather than adults. Milich et al 10 investigated the use of methylphenidate for treatment of youth with ADHD-IA and did not find the medication to be effective for symptoms of inattention linked to SCT. One trial of methylphenidate in children with ADHD and SCT found that the response for SCT behaviors was lower than the response for core ADHD symptoms. 11 A more recent study (Froehlich et al 12) examined whether SCT behavioral attributes rated by teachers moderate the dose response to long-acting methylphenidate and, specifically, whether the moderating effect of SCT on medication response is distinct from that of ADHD subtype. Certain SCT behavioral attributes—eg, sluggish and sleepy—were associated with methylphenidate nonresponse, while daydreaming was not. Finally, Firat et al 13 assessed the effects of SCT and pretreatment ADHD severity among other variables on 1 month of open-label methylphenidate treatment response in children (n = 185); they found that parent- and teacher-rated ADHD-HI and SCT scores decreased after treatment. Older age positively affected the methylphenidate-SCT treatment response in both ratings. Like the results of Froehlich et al, 12 increased SCT scores were associated with decreased methylphenidate response in teacher ratings of ADHD.

A study of atomoxetine, a nonstimulant selective norepinephrine reuptake inhibitor, versus placebo in children with ADHD, dyslexia, and ADHD + dyslexia found that atomoxetine reduced SCT behavioral attributes in all groups, with the most significant change in the ADHD + dyslexia compared to the ADHD group. 14 Post hoc analyses revealed that controlling for changes in ADHD scores did not significantly influence changes in SCT scores.

No treatment trials have been conducted investigating treatment of SCT in adults with ADHD, and there have been no treatment trials of amphetamines in children or adults with SCT and ADHD. This is particularly important as a recent meta-analysis showed the amphetamine stimulant class to have the largest effect of all treatments for adults with ADHD. 15,16

The current study is a part of a 2-phase (phenotypic and treatment) examination of SCT and ADHD at 2 academic centers (NYU Grossman School of Medicine and Icahn School of Medicine at Mount Sinai). The phenotypic phase characterized SCT, ADHD, and EF symptoms in subjects who had ADHD and SCT versus those who had ADHD and were SCT negative. 17 An interim report of the NYU cohort seen in that study found that, similar to prior studies noted above in children and adults, individuals with both SCT and ADHD, versus adults with ADHD alone, have higher levels of inattentive symptoms and impairment.

We are now reporting data from the second phase of this study—the treatment phase. Subjects at NYU Grossman School of Medicine and Icahn School of Medicine at Mount Sinai who had both ADHD and SCT in the phenotypic phase were recruited into this crossover trial of LDX versus placebo. The goal of this study is to determine the efficacy of LDX on the nature and severity of ADHD symptoms and SCT behavioral indicators in adults with ADHD and SCT.

METHODS

Study Design

This was a 10-week crossover trial, with 2 double-blind treatment periods consisting of 4 weeks each and an intervening 2-week single-blind placebo washout. During the first treatment period, subjects were randomized to receive either oral LDX or matching placebo washout. During the first week of a treatment period, LDX or placebo was given at a starting dose of 30 mg/d. Based on weekly assessments of clinical response and adverse effects, doses were increased or decreased during weeks 2 and 3 by 20-mg/d increments to a minimum of 30 mg/d and maximum of 70 mg/d. After week 3, the highest effective dose was maintained until the end of the treatment period.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) man or woman between the ages of 18 and 60 years; (2) met DSM-5 criteria for a primary diagnosis of inattentive or combined type ADHD as diagnosed via Adult ADHD Clinical Diagnostic Scale (ACDS) v1.2; and (3) demonstrated significant impairment, determined based on the norms of the Barkley Functional Impairment Scale (BFIS). The subgroup with SCT was required to have 5 or more items on the Barkley SCT Scale rated clinically significant and a total SCT symptom score of 26 or higher. Additionally, the group with SCT must have had clinically significant impairment in executive function. Impairment was determined by a T

Clinical Points

- Recognizing the symptoms of sluggish cognitive tempo (SCT) in adults with ADHD is complex, and there are no accepted treatments.
- Clinicians could consider lisdexamfetamine as a potential treatment option for adults with ADHD and SCT.
began with an assessment of childhood symptoms of ADHD and then probed an expanded set of recent (past year) symptoms, including all DSM-5 A1 and A2 symptoms. The scale includes developmentally relevant prompts and stem questions designed to capture DSM symptoms of ADHD as they present in childhood and adulthood. Based on participant responses, the clinician rates the symptom severity as 1 (never), 2 (mild), 3 (moderate), or 4 (severe).

The ACDS v1.2 has been expanded to include an additional 16 clinical prompts intended to assess executive function deficits (EFDs; 9 items) and emotional dyscontrol (ED; 4 items). ED includes behavioral descriptors of mood lability, irritability, and emotional overreactivity. As with the DSM-5 items, developmentally relevant prompts have been written for the EFD and ED items.

**ADHD-RS.** ADHD-RS\(^{23,24}\) is a semi-structured clinical interview to measure ADHD symptom severity in the last 1 to 2 weeks (and in this trial during the treatment phase, since the last rating). Adult interview prompts were incorporated to ensure adequate probing of symptoms; items are rated using a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The 9 inattentive and symptoms are summed and reported as the inattentive subscale (IA), and the 9 hyperactive-impulsive symptoms are also summed and reported as the hyperactive-impulsive (HI) subscale. The IA and HI subscales are added to obtain the ADHD-RS total score, which is the primary outcome measure in this trial, along with the total score on the Barkley SCT scale (see below).

**Barkley SCT scale.** The SCT subscale of the Barkley Adult ADHD Rating Scale\(^1\) is a 9-item self-report of SCT behavioral symptoms scored on a 4-point rating scale (1 = “never or rarely,” 2 = “sometimes,” 3 = “often,” and 4 = “very often,” with the latter two being the cutoff for clinical significance for each item). Subjects with SCT were required to have 5 or more items rated “often” or “very often,” with an additional study criterion requiring a total score of at least 26.

**BRIEF-A.** The Behavior Rating Inventory of Executive Function—Adult Version\(^{25}\) is a self-report composed of 9 clinical subscales designed to measure various aspects and deficits of executive function. The Metacognition Index (MI) is the sum of the initiate, working memory, plan/organize, task monitor, and organization of material subscales, and the Behavioral Regulation Index (BRI) is the sum of inhibit, shift, emotional control, and self-monitor subscales. The 2 indices, when combined, yield the Global Executive Complex (GEC) score. The GEC serves as a general measure of executive function. The GEC, BRI, MI, and individual subscales have been standardized, and T scores are used to describe severity. A T score of ≥65 is considered to represent clinically significant behavioral impairment in executive function.

**BFIS.** The Barkley Functional Impairment Rating Scale measures self-perceived, current impairment in 15 different major life activities (eg, completing chores, social interactions) using a 10-point Likert scale.\(^{26}\) Mean scores can be calculated to quantify impairment.
written informed consent prior to participation.

GAD and social anxiety disorder (n = 1). All subjects gave psychiatric diagnoses included generalized anxiety disorder (GAD; n = 3), obsessive-compulsive disorder (n = 1), and GAD and social anxiety disorder (n = 1). All subjects gave written informed consent prior to participation.

CGI-S. Overall impairment was also assessed by the CGI-S scale, a widely used clinician-rated measure of global ADHD impairment that uses a 7-point Likert rating (1 = normal, 7 = among the most severely ill patients).27

Participants
Thirty-nine participants with comorbid ADHD and SCT were recruited to participate in this study. Ratings for 1 subject were excluded secondary to significant adherence violations with treatment on multiple visits; data on 38 subjects were included in the analyses (see Figure 1). Participants were drawn from 2 academic medical centers, New York University Grossman School of Medicine (n = 23) and Icahn School of Medicine at Mount Sinai (n = 15). Thirty-four percent of the subjects had inattentive presentation of ADHD, while 66% had the combined presentation. Four percent of the subjects had inattentive presentation of ADHD, while 66% had the combined presentation. There were no significant demographic differences between sites, except for a higher proportion of Latino subjects at NYU (Pearson $\chi^2 = 6.6087, P = .010$). Participants had a mean age of 34.6 ± 10.1 years, and 53% (n = 20) were Caucasian; 34% were male and 66% were female. Comorbid current psychiatric diagnoses included generalized anxiety disorder (GAD; n = 3), obsessive-compulsive disorder (n = 1), and GAD and social anxiety disorder (n = 1). All subjects gave written informed consent prior to participation.

Data Analysis
Demographic data were analyzed using logistic regression for continuous variables and Pearson $\chi^2$ tests for categorical variables. Clinical trial outcomes data were analyzed with negative binomial regression with generalized estimating equations and robust standard errors. A negative binomial model was chosen because our outcome measures were limited to positive integers. We used generalized estimating equations with robust standard errors to account for correlations between visits.

RESULTS
Titration patterns of LDX and placebo were similar in the 2 blocks, with slightly more subjects having their dose reduced by 1 step (20 mg) during treatment with LDX (n = 5) than placebo (n = 2). The mean (SD) overall titrated dose of LDX was 59.1 (14.8) mg/d, while the mean overall titrated dose of placebo was 66.6 (9.1) mg/d. The mean placebo dose was significantly higher than the mean LDX dose by 7.5 (15.4) mg/d ($P = .0037$). There were moderately large effects of LDX over placebo on SCT ratings in both treatment epochs (Figure 2) (block 1 effect size [ES]: Cohen $d = 0.68, P = .008$; block 2 ES = 0.61, $P = .10$), which reached significance only in block 1. There were significant carryover effects of both LDX and placebo treatment following block 1 such that SCT ratings did not return to baseline; therefore, SCT results are presented separately for the 2 treatment blocks (Figure 2). For all other measures, no significant order effects were seen, and results from the 2 blocks were combined and presented as LDX vs placebo (see Table 1). Significant effects were seen for LDX over placebo for total ADHD symptoms, EF, and functional impairment ratings (all $P < .05$). Significant effects were also seen for LDX over placebo on IA and HI subscales of the ADHD-RS (IA: sequence effect: $\chi^2 = 1.04, P = .31$; drug effect: $\chi^2 = 9.54, P = .0001$; ES: 0.92; HI: sequence effect: $\chi^2 = 1.15, P = .28$; drug effect: $\chi^2 = 5.32, P = .02$; ES: 0.53). No
lost significance (t = 1.63, P = .21; drug effect block 1: χ^21 = 6.26, P = .01; drug effect block 2: χ^21 = 7.33, P = .007; effect size block 1: 0.97; block 2: 0.91).

To examine the relationship between changes in ADHD and SCT symptoms, we examined correlations between the BRIEF GEC and SCT ratings. A significant association (r = .91, P = .007) was found between the change in ADHD total symptoms and the association between BRIEF GEC and SCT symptoms, which remained significant (r = .91, P = .007; effect size block 1: 0.97; block 2: 0.91).

To examine ADHD total symptoms by treatment block, we compared the mean changes in ADHD-RS total scores for LDX and placebo. The mean changes for ADHD-RS total scores were LDX: −7.56% (9.8); placebo: −2.2% (11.4). (Changes over treatment: systolic BP: χ^21 = 4.33, P = .04; diastolic BP: χ^21 = 13.78, P = .0001; pulse: χ^21 = 13.78, P = .0001).

DISCUSSION

Adults with comorbid ADHD and SCT significantly improved in ratings of SCT, ADHD, EF, and impairment when treated with LDX vs placebo. The SCT findings were present in both treatment epochs, with a moderately large ES; however, an order effect was seen with larger placebo effects in block 1 than block 2 that limited statistical significance to block 1. In addition, there were also carryover effects, and SCT ratings failed to return to baseline for both treatments.
in block 2. Consequently, group differences in ADHD ratings only reached significance in block 1.

The magnitude of effects of LDX on ADHD symptoms in this trial in adults with ADHD and SCT is quite similar to that seen in other studies of LDX in adult ADHD, and specifically in patients with ADHD and EFD.\textsuperscript{17} This study extends the efficacy of LDX to subjects with ADHD and SCT. Although we found moderate to large ESs for both ADHD symptoms and SCT ratings, the baseline to endpoint change scores for the two types of ratings were only modestly correlated, sharing 24% of their variance; the regression analysis presented above suggests that the relationship between ADHD and SCT scores may be driven by changes in EFD scores. This provides further evidence that SCT is not simply another measure of ADHD and suggests the possibility that different patient characteristics and/or mechanisms (such as EFD) may moderate or mediate the response of ADHD and SCT symptoms to LDX and other medications. These findings highlight the importance of assessing for the presence of SCT and EFD at baseline in patients with ADHD, and to also monitor the potential response of ADHD, SCT, and EFD symptoms throughout treatment. As EFDs have been shown to be responsive to cognitive behavioral therapy in combination with pharmacotherapy in adults with ADHD, it remains to be seen whether such a combination would also be an effective treatment strategy to optimize symptom reduction in adults with ADHD and SCT.\textsuperscript{29,30}

The finding of a small but significantly higher final dose of placebo versus LDX is not surprising, as clinicians could clinically titrate the dose, and the smaller response to placebo led to higher up-titration in the placebo group. Finally, the small but nonsignificant increases in blood pressure and pulse, along with the other adverse events we observed, were like those seen in prior trials of LDX in adult ADHD.\textsuperscript{31}

Several studies described above have examined potential moderating effects of ADHD symptoms, or lack thereof, on SCT behavioral attributes in children treated with methylphenidate or atomoxetine. As noted above, we found that one-fourth of the effect of LDX on SCT ratings can be potentially accounted for by changes in ADHD ratings—suggesting partial distinctiveness of the two constructs. However, it is difficult to fully examine potential moderating effects in our trial as all our subjects had ADHD and SCT. Differences in findings in this study from those studies that examined potential moderating factors in children could be due to (1) our studying adults, (2) our studying effects of amphetamine versus methylphenidate or atomoxetine, (3) differences in the rating instrument used or the raters (teacher/parent/SCT scale), (4) absence of a placebo control group (Firat and coworkers\textsuperscript{13} and the SCT cohort in McBurnett and colleagues\textsuperscript{14}) and (5) inclusion of a comorbid diagnosis (dyslexia) (McBurnett et al\textsuperscript{14}).

Several additional caveats should be noted. We specifically weighted our sample toward having EFD with the requirement for having a significant M1 cutoff on the BRIEF, and also toward having more significant SCT symptoms by requiring a total score of $\geq 26$ on the Barkley SCT scale in addition to the standard threshold of $\geq 5/9$ symptoms. Furthermore, the finding of an order effect in both LDX and placebo treated subjects such that ratings did not fully return to baseline after washout of block 1 drug is of note. Such carryover effects are a potential liability of any crossover design trial and are not specific to trials of ADHD or SCT. However, a prior crossover design study of LDX versus mixed amphetamine salts did not see such carryover effects.\textsuperscript{32} Nevertheless, moderate to large effects were seen for LDX over placebo in both treatment epochs. Our sample was not large enough to fully examine potential differential effects of ADHD subtype or symptom subsets on the LDX treatment effect; however, treatment effects on IA symptoms were twice as large as on HI symptoms, which might be due to potential effects of the enrichment of the sample with SCT and EFD symptoms. Nor could we evaluate the extent to which enrollment in prior adult ADHD treatment trials or receiving treatment at a tertiary center, such as those conducting this study, may have affected the results. These issues may the foci of future investigations.

In summary, this is the first study to find treatment effects of stimulants on SCT behavioral attributes in adults with ADHD and SCT. Future trials should examine potential mitigating effects of EFD symptoms on response and should be conducted with parallel designs to mitigate any potential for carryover effect. Additionally, the responsiveness of SCT in other conditions or as stand-alone disorder to ADHD treatments remains a potential line of investigation.