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Lobeline Effects on Cognitive Performance in Adult ADHD

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Abstract

Objective—In preclinical studies, lobeline inhibited hyperactivity induced by nicotine and amphetamine, and improved performance and learning in studies utilizing radial-arm maze and spatial-discrimination water maze. This laboratory proof-of-concept study investigated lobeline as a treatment for ADHD symptoms in adults (31.11 ± 7.08 years).

Method—Using cognitive tasks and self-report measures, the effects of lobeline (0, 7.5, 15, or 30 mg, s.l.) and methylphenidate (0, 15, or 30 mg, p.o.) were assessed in nine volunteers with ADHD.

Results—Evidence suggested that lobeline could modestly improve working memory in adults with ADHD, but no significant improvement in attention was observed. Lobeline administration was associated with mild adverse side effects (nausea).

Conclusion—Further investigation of lobeline on working memory may be warranted.

Keywords

ADHD; lobeline; methylphenidate

Introduction

ADHD is a behavioral and neurocognitive disorder associated with abnormalities in central nervous system dopamine (DA) and norepinephrine (NE) neurotransmission (Sonuga-Barke, 2003), and nicotinic receptor dysfunction (Levin, 1992). Characterized by inattention, hyperactivity, and impulsivity (American Psychiatric Association [APA], 1994), ADHD is common in adults with prevalence rates estimated at 4.4% (Kessler et al., 2006).

The most commonly prescribed medications for ADHD are psychostimulants such as methylphenidate and amphetamine. These first-line therapeutic drugs modify DA and NE neurotransmission by increasing release from and inhibiting reuptake into their respective presynaptic terminals, increasing the extracellular concentrations of both monoamines (Volkow et al., 2001). Although highly effective, psychostimulants are not without side

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effects and risks, which include hypertension, insomnia, headaches, weight loss, and depressed rate of growth in children (Charach, Figueroa, Chen, Ickowicz, & Schachar, 2006; Hammerness, Perrin, Shelley-Abrahamson, & Wilens, 2011), and possibly increased tobacco use in some adolescents and young adults (Lambert & Hartsough, 1998). Also, concerns related to diversion of prescribed psychostimulants have been raised (McCabe et al., 2011). Atomoxetine, a selective NE transport inhibitor, is the first nonstimulant medication for ADHD approved by the Food and Drug Administration (FDA; Eiland & Guest, 2004). Although atomoxetine is efficacious in children and adults (Spencer et al., 1998), rates of suicidal ideation among children are reported to be high (Wooltorton, 2005), and potential liver function abnormalities have been observed (Diak & Senior, 2009). Also, antihypertensive medications, clonidine and guanfacine, are effective as ADHD treatments (Scahill et al., 2001). Clonidine and guanfacine act centrally as agonists at both α_1 and α_2 adrenergic receptors, inhibiting NE release through stimulation of α_2 autoreceptors located presynaptically on noradrenergic neurons in the prefrontal cortex (Arnsten and Dudley, 2005; Arnsten and Li, 2005). Long-acting forms of both clonidine and guanfacine are receiving increased attention as therapeutic agents for ADHD (Jain, Segal, Kollins, & Khayrallah, 2011; Wilens et al., 2012). While current treatments for ADHD are effective, they are not without risk, and not all patients respond adequately to currently approved medications. The development of additional nonstimulant medications for ADHD is clearly warranted.

The current study is the first prospective evaluation of the use of lobeline for ADHD. Lobeline, an alkaloidal component of the native plant, *Lobelia inflata*, is a novel compound that has been investigated in the treatment of drug abuse, including but not limited to methamphetamine, nicotine, cocaine, opioid, and alcohol abuse (Dwoskin & Crooks, 2002; Farook, Lewis, Gaddis, Littleton, & Barron, 2009; Miller et al., 2007; Polston, Cunningham, Rodvelt, & Miller, 2006). Lobeline inhibits nicotine-evoked DA and NE release from superfused rat striatal and hippocampal slices, respectively (Miller, Crooks, & Dwoskin, 2000). Lobeline also inhibits the function of the DA transporter located on the dopaminergic neuronal plasma membrane, and more potently inhibits vesicular monoamine transporter (VMAT2) function, which transports DA and NE into storage vesicles within the presynaptic terminal (Dwoskin & Crooks, 2002; Teng, Crooks, Sonsalla, & Dwoskin, 1997). Lobeline does not release DA from presynaptic terminals into the extracellular space, but alters the storage within the presynaptic terminal (Teng et al., 1997). Thus, from a neurochemical perspective, lobeline may have potential to benefit symptoms of ADHD, because it redistributes DA and NE stores within neurons (Dwoskin & Crooks, 2002).

In preclinical behavioral studies, lobeline decreases (a) spontaneous locomotor activity (Miller et al., 2001), (b) the behavioral effects of nicotine (Miller et al., 2003), (c) methamphetamine-induced hyperactivity (Miller et al., 2001), and (d) methamphetamine self-administration (Harrod, Dwoskin, Crooks, Klebaur, & Bardo, 2001). Although lobeline produces cardiovascular effects, such as bradycardia or bradyarrhythmia, and has variable effects on blood pressure (Korczyn et al., 1969), these peripheral side effects occur only at doses that are much higher than doses that inhibit the behavioral effects of methamphetamine (Harrod et al., 2001). Lobeline may have effects similar to nicotine on cognition, based on studies utilizing radial-arm maze and spatial-discrimination water maze,

which showed that lobeline improved performance and learning in rats (Decker, Majchrzak, & Arneri, 1993; Levin & Christopher, 2003). Lobeline has been used for over 50 years as a smoking cessation agent (Ejrup, 1960; Kalyuzhny, 1968). While more recent evidence indicates lobeline is ineffective as a smoking cessation aid (Stead & Hughes, 2000), its extensive use in humans over the years, together with the successful completion of Phase I Clinical Trials, provides substantial safety and tolerability data for lobeline.

This study employed a double-blind, double-dummy, placebo-controlled, active comparator, within-participant design in adults with ADHD to determine the acute effects of lobeline on indices of attention, impulsivity, and working memory, as primary outcome measures. A positive control comparator, that is, methylphenidate, a medication with known efficacy for reducing ADHD symptoms in both clinical and research settings, was included in the experimental design. Secondary outcomes included physiological measures and self-report inventories that provided additional information concerning safety, abuse liability, and tolerability (e.g., appetite, side effects). We hypothesized that acute treatment with lobeline would improve measures of inattention and working memory, and decrease measures of impulsivity to a greater extent compared with placebo. We also hypothesized that lobeline would produce minimal changes in cardiovascular activity. The inclusion of methylphenidate as a positive control provided confirmation that the behavioral assays were sensitive to improvement on measures of attention, impulsivity, and working memory (Aron, Dowson, Sahakian, & Robbins, 2003; Heishman & Henningfield, 1991).

Method

Participants

A total of 42 adults (18 females, 24 males) were screened; 29 were screen failures, 4 withdrew during the laboratory study, and 9 completed the 7-day protocol (5 females, 4 males, ages 23–41 [31.11 ± 7.08 years]). The study was approved by the University of Kentucky Institutional Review Board and performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki. Participants gave written consent and were paid for their participation.

Criteria for study participation included adults aged 21 to 45 years, in general good health with childhood histories and current symptoms of ADHD, as confirmed by a clinical interview. The clinical interview consisted of a structured assessment based on the Diagnostic and Statistical Manual of Mental Disorders (4th ed., *DSM-IV*; APA, 1994) Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-1) supplemented by administration of the ADHD component of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic version (KSADS-E), in which participants gave a comprehensive history of their symptoms and administration of the Conners' Adult ADHD Rating Scale (CAARS). Participants had to be nonsmokers, not using any form of nicotine (confirmed with a carbon monoxide [CO] 9 breath analysis and salivary cotinine collected and assessed at baseline), and be able to suspend all current medications for 7 days prior to the start of the clinical trial except for short-acting ADHD medications, which are not taken for the duration of the laboratory study. Participants were informed that they would be screened for alcohol and other drug use, and that laboratory

sessions would be canceled if there was evidence of other drug use. Female participants could not be pregnant at the onset of screening and were required to use contraceptive measures to ensure that they would not become pregnant during the study.

Procedures

Screen and Lab Day

Participants who met the criteria above underwent a clinical screen that included a medical history and physical examination, including vital signs, weight, electrocardiography (ECG), complete blood count (CBC) with differential, liver functions, and urinalysis. At screening and prior to the start of each test day, participants provided urine samples for drug screening and breath samples for alcohol and CO analysis. Female participants received a beta human chorionic gonadotropin (β HCG) pregnancy test. Test sessions were approximately 4 hr in duration and consisted of six assessment batteries performed at baseline and every 30 min subsequently. Each assessment battery required 15 min to complete and was followed by a 15-min rest period.

The rigorous screening procedure and the requirements for ongoing participation in the laboratory study led to the following screening failures: CAARS *T*-score less than 65 (8), body density index (BDI) of 16 or greater (7), body mass density (BMI) of 35 or greater (6), positive urine drug screen (UDS) on intake (2), and inability to commit to rigors of laboratory study (2).

Dosing

Shortly after arriving, participants received a low-fat meal, and 30 min later, the nurse observed participants swallowing a methylphenidate capsule (0, 15, or 30 mg, p.o.) with 150 ml of water. One hour later, the nurse administered lobeline tablets (0, 7.5, 15, or 30 mg, s.l.), asking the participant to hold the tablet sublingually for 30 s until dissolved. Sublingual doses were used because the safety had been demonstrated in clinical trials. Doses were administered such that methylphenidate and lobeline were not administered on the same test day. Inactive doses of both sublingual and oral formulations were given on placebo days. By staggering the dose administration, the full-time course was captured, and the peak response for both drugs was aligned within the same test hour of the session. A randomized dose design was used with five dose conditions tested across 7 laboratory days (about a 2-week period). The first session was designed as an active drug day that familiarized participants to the testing procedures under active drug conditions, but these data were not analyzed.

Measures

The 15-min assessment battery consisted of physiological measures, cognitive tasks, self-report measures, and lastly, a side-effects questionnaire. The battery was designed to monitor safety and measure/track effects on working memory, inhibition, attention, vigilance, and abuse liability. *Physiological measures* included heart rate, systolic and diastolic blood pressure (Dinamap; GC Medical), and physical movement measuring activity in units of mG of gravitational acceleration with an ActiTrac wrist monitor (IM Systems, Inc.; <http://www.intox.com>). *Cognitive tasks* included the Digit Span Backwards (DSB), for assessing

mental tracking and working memory; Stop Signal Reaction Test (SSRT), for measuring effects on inhibition; Two-Back Test, a measure of working memory using the CogState Clinical Trials (Version 5; © 2007 CogState Limited); and a 5-min Continuous Performance Task (CPT), a vigilance task that tracks Correct Responses and Misses, Incorrect and Missed Responses, and Reaction Time. *Self-report measures* for capturing drug effects and abuse liability included a Visual-Analog Scale (VAS), the Addiction Research Center Inventory–Short Form (ARCI; Martin, Solan, Sapira, & Jasinski, 1971), and Profile of Mood State (POMS). A *side-effects questionnaire* in a VAS format included symptoms associated with the administration of lobeline in previous clinical trials (as compared with placebo) and known methylphenidate side effects.

Statistical Approach

Statistical analysis—Subjective, observer-rated, performance tasks and physiological measures were analyzed using a two-factor model (Drug condition $\times$ Time) with an AR(1) covariance structure. The time course data for methylphenidate and lobeline were analyzed in separate analyses. Peak effects were calculated for individual participants and analyzed in a one-factor model (drug condition). Main effects and interaction effects were further explored by Tukey post hoc analyses comparing active doses with placebo. All analyses were conducted with Proc Mixed in SAS 9.2 (Cary, North Carolina) and were considered significant when $p \leq .05$.

Results

Cognitive Tasks

There were no significant main effects of dose or interactions between dose and time observed on any of the dependent measures from the CPT; however, there were significant main effects of time ($p \leq .01$) on Correct Responses (Hits), Missed Responses (Misses), Incorrect Responses (False Hits), Correct Misses, and Reaction Time (Hits), indicating that performance improved during the sessions. Post hoc analyses of peak effects indicate that methylphenidate at both 15- and 30-mg doses decreased Missed Responses. The time course analysis for the DSB and SSRT tests did not reveal significant main or interaction effects. Visual inspection of the results did not reveal any systematic dose- or time-related effects of methylphenidate or lobeline. However, the Tukey post hoc analyses suggested that numbers recalled in the DSB test was highest for the 7.5-mg dose of lobeline, approaching statistical significance ($p = .079$; see Table 1).

Side Effects

Noteworthy effects found in the VAS measures included a dose-related increase in “nausea,” which dissipated over the course of the session following administration of lobeline ($p < .05$); however, no such effects were observed following methylphenidate administration. Only the 30-mg dose of methylphenidate produced increases in “jittery” and “heart racing,” which decreased during the session while increasing reports of “full of energy” and decreasing reports of “sleepy.” “Bad drug effect” was reported only for lobeline, consistent with significant scores for “bad taste,” “bitter taste,” “oral numbness,” “numbness/tingling,” and “nausea” effects observed following lobeline, but not methylphenidate.

Methylphenidate, but not lobeline, significantly increased “nervousness” and “restlessness” ($p < .05$).

Vital Signs

Analysis of the physiological measures, pulse, systolic and diastolic blood pressure, and mean arterial pressure taken during the session showed significant main effects of time ($p < .05$), but not dose or Dose $\times$ Time interactions for lobe-line. Methylphenidate produced a significant main effect on pulse and systolic blood pressure ($p < .05$). Both the 15- and 30-mg doses of methylphenidate attenuated a drop in pulse during the course of the session, whereas the 30-mg dose increased systolic blood pressure.

Discussion

Overall, the results indicate that lobeline does not have clear effects in improving cognitive performance in ADHD participants. However, the lack of robust effects of the positive control, methylphenidate, suggests that clear effects may be difficult to observe in a small sample of participants with the current battery of tests. The results were likely confounded because patients with more severe symptoms dropped out of the study because they could not discontinue their therapeutic psychostimulants. Furthermore, the selection of higher functioning adult ADHD participants who could stop their stimulant medication for the study may have affected the outcomes. Observations of the participants during test sessions suggest that the adverse bitter taste and numbness produced by sublingual lobeline was preoccupying and may have confounded assessment of drug effects on cognition.

In sum, deficiency in working memory is generally considered a primary cognitive deficit associated with ADHD (Barkley, 2006). Studies with adult ADHD have indicated relative weaknesses in working memory test measures compared with normal controls (Schoenlin & Engel, 2005). The current study demonstrates modest evidence that lobeline improves working memory in adults with ADHD. Investigation of lobeline in a new formulation with a reduced adverse side-effect profile may be warranted to determine whether the impact of lobeline on working memory can be better evaluated. A larger study is needed to make more definitive statements regarding the effect of lobeline on cognition in adult ADHD. Whether lobeline could have different effects based on individual differences such as participants with more severe inattention also may deserve further investigation.

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Table 1

Dose Effects of Methylphenidate and Lobeline on Cognitive and Physiological Measures.

	Placebo	MPD 15	MPD 30	LOB 7.5	LOB 15	LOB 30
	<i>M (SEM)</i>	<i>M (SEM)</i>	<i>M (SEM)</i>	<i>M (SEM)</i>	<i>M (SEM)</i>	<i>M (SEM)</i>
CPT Peak Max						
Correct Responses (Hits)	108.44 (4.17)	116.78 (2.15) ^a	118.00 (1.93) ^b	114.22 (2.48)	112.89 (2.82)	112.78 (2.90)
Missed Responses (Misses)	34.00 (6.27)	32.67 (6.77)	19.11 (3.39)	27.89 (3.70)	36.78 (6.99)	42.44 (5.45)
Incorrect Responses (False hits)	21.889 (2.11)	18.78 (2.58)	16.11 (1.73)	20.00 (2.44)	24.33 (3.38)	23.78 (2.15)
Correct Misses	488.11 (1.48)	491.11 (1.33)	491.44 (0.93)	486.78 (1.85)	488.67 (1.68)	487.40 (1.86)
Reaction Time Hits	396.04 (12.07)	383.90 (10.83)	381.60 (10.09)	381.47 (14.12)	383.76 (13.86)	385.05 (9.85)
Reaction Time Misses	541.89 (1.80)	540.66 (1.04)	541.54 (1.75)	541.79 (1.61)	539.62 (0.21)	539.71 (0.26)
Reaction Time False Hits	227.95 (8.35)	269.64 (14.12)	268.81 (19.76)	236.94 (12.56)	254.54 (24.24)	232.91 (12.97)
Digit Span Backwards						
Total score	11.44 (0.63)	12.11 (0.59)	12.22 (0.52)	12.67 (0.41) ^c	11.78 (0.49)	11.44 (0.53)
Physiological measures						
Pulse	75.98 (1.24)	79.74(2.19)	82.74 (2.43) ^d	77.91 (2.80)	77.97 (1.86)	77.46 (1.58)
Systolic BP	132.01 (4.15)	137.82 (3.56)	142.37 (3.16) ^e	138.40 (3.31)	137.11 (3.51)	136.46 (2.57)
Diastolic BP	78.94 (3.18)	80.04 (2.78)	83.89 (1.29)	78.18 (2.09)	79.76 (2.61)	81.22 (2.11)

Note: Data are peak max means (*SE*) unless otherwise indicated. CPT = Continuous Performance Task; MPD = methylphenidate; LOB = Lobeline.^a
p = 0.014;^b
p = 0.003;^c
p = 0.079;^d
p = 0.016;^e
p = 0.023.