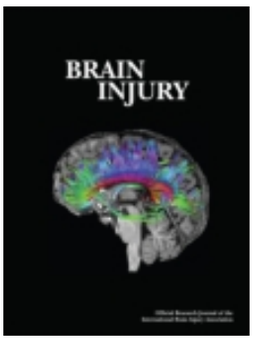

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ORIGINAL ARTICLE

Traumatic brain injury-related attention deficits: Treatment outcomes with lisdexamfetamine dimesylate (Vyvanse)

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Abstract

Background and objectives: Attention deficits are often among the most persistent and debilitating impairments resulting from traumatic brain injury (TBI). This study examined the effects of lisdexamfetamine dimesylate (Vyvanse) in treating attention deficits due to moderate-to-severe TBI. It was the first study of lisdexamfetamine dimesylate with this population and, in fact, was the first controlled trial in this area examining a stimulant medication option other than methylphenidate.

Methods: This was a 12-week, randomized, double-blind, placebo-controlled, cross-over trial. A total of 22 rigorously selected cases were enrolled, 13 of whom completed the trial. They were 16–42 years of age and had newly acquired attention deficits persisting for 6–34 months post-injury. They were assessed on a broad range of neuropsychological and behavioural measures at baseline, 6-weeks and at 12-weeks.

Results and conclusions: Positive treatment effects were found involving selective measures of sustained attention, working memory, response speed stability and endurance and in aspects of executive functioning. No major problems with safety or tolerability were observed. Some moderating treatment effects were found from a broad range of pre-treatment subject characteristics and injury variables examined. Avenues for further research and treatment applications in this area are discussed.

Keywords

Attention-deficit/hyperactivity disorder, head injury, neuropsychological effects, stimulant medication treatment

History

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Introduction

About two million incidents of traumatic brain injury (TBI) occur each year in the US (175–200 per 100 000 of the general population) [1]. Excluding cases with mild TBI, there are an estimated 62.3 per 100 000 individuals aged 15 and over who are living in the community with enduring functional impairments due to TBI [2]. This is clearly an important public health problem for which effective treatments continue to be sought.

Symptoms of inattentiveness, impulsivity and poor persistence have been observed in both children and adults following TBI. Indeed, these often are among the most prominent symptoms manifested and may contribute to interference in a variety of other functional domains. In a study by Levin et al. [3], increased rates of newly diagnosed Attention-Deficit/Hyperactivity Disorder (ADHD) were found in children post-TBI (ranging from 14.5% at 12 months to 18.3% at 24 months). The rates probably would have been even higher if considered in terms of selective symptoms rather than requiring that the full criteria for ADHD be present. There have been other studies establishing a significant causal link between TBI and secondary ADHD, with important moderating variables including the severity and location of injury, as well as psychosocial factors [4–6]. In general, more persistent attention deficits have been seen in children and adults with moderate or severe TBI rather than with milder injuries.

The underlying mechanisms producing ADHD symptoms post-TBI may be conceptualized in various ways. Injury to the frontal lobes is commonly known to produce changes in focused attention and response inhibition and probably accounts for the attention deficits in many cases. Injury to other specific areas may be involved, consistent with models of attention components and their mediation by different regions of the brain [7]. Another underlying defect in TBI often involves non-specific white matter shearing which may result in slower processing times, with indirect effects including diminished attention span, mental speed and stamina. Yet another possibility may include structural deficits in brain locations unrelated to attention that may result in assorted performance inefficiencies that, in turn, indirectly affect attentiveness by requiring greater effort (thereby lowering the threshold for mental fatigue).

In a study using functional magnetic resonance imaging (fMRI), Kramer et al. [8] examined long-range outcomes with

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respect to attention processing in children who sustained moderate–severe TBI in early childhood vs. a group of age-matched children with orthopaedic injuries. The children with TBI were found to activate similar networks of brain regions relevant to attention, albeit to a significantly greater extent in particular frontal and parietal regions compared to the controls. This may be viewed as suggesting a pattern of persistent compensatory activation in response to injury of underlying components. In an fMRI study of idiopathic (non-TBI related) ADHD in adults, Bush et al. [9] found evidence of more diffuse or scattered patterns of underlying neural activation under certain attention conditions compared to controls. Thus, it may be that attention deficits, whatever the cause, are associated with a less streamlined or efficient deployment of processes upon which attention depends.

There have been a few reports indicating positive effects associated with the use of stimulant medication to treat attention deficits following TBI [10–13]. Thus far, however, the evidence for the efficacy of stimulant medication based on controlled trials with this population has been limited and the mechanisms of action remain unclear [14, 15]. Most of the studies to date have lacked the necessary methodological rigour to permit clear conclusions about treatment effects, let alone possible mechanisms of action.

One possibility is that treatment with stimulant medication may produce increased activation of fronto-striatal brain regions that, although damaged, may be partially normalized by a heightened activation of spared zones. In an fMRI study of adults with non-TBI related ADHD, Bush et al. [16] found that psychostimulant medication (methylphenidate) produced increased activation in the dorsal anterior midcingulate cortex (daMCC) as well as dorsolateral prefrontal and parietal cortex, thereby normalizing what ordinarily may be *hypo-functioning* of these regions in ADHD. Based on the Kramer et al. [8] study noted above, it might be inferred that compensatory activation occurs to some extent naturally in TBI-related attention deficits. Perhaps stimulant medication helps to facilitate the process of compensatory activation, albeit in a more targeted or efficient fashion, such as by targeting dopamine transmission and synaptic plasticity in fronto-striatal regions [17]. Alternatively, stimulant medication use in acquired attention deficits may serve to activate secondary or backup neural circuits relevant to attention regulation. Or, rather than activating focusing or inhibitory mechanisms *per se*, there may be stimulant action on general alertness and arousal.

Thus far, studies examining the use of a stimulant such as methylphenidate to treat TBI-related attention deficits have found particular benefit in terms of improving slowed mental processing [12, 13]. In a randomized, cross-over, double-blind, placebo-controlled inpatient trial, Willmott and Ponsford [18] found that methylphenidate significantly enhanced processing speed within 2 weeks of treatment in 40 hospitalized adults with moderate-to-severe TBI.

The present study was a controlled clinical trial examining the effects of lisdexamfetamine dimesylate (Vyvanse) in the treatment of TBI-related attention deficits (Clinical Trials.gov, NCT01000064). It was based on a very carefully selected sample of individuals with moderate-to-severe TBI. It was chosen to eliminate cases with only mild TBI and focus instead on a group more likely to have persistent or chronic cognitive changes stemming from TBI. Extensive steps were taken to eliminate or minimize potentially confounding factors, making it one of the most rigorous studies thus far in this area. It was also the first controlled trial examining the treatment of TBI-related attention deficits with a stimulant medication other than methylphenidate. Lisdexamfetamine dimesylate (LDX), which acts as a prodrug to dextroamphetamine, is an FDA-approved medication for the treatment of ADHD. Efficacy in the treatment of idiopathic ADHD has been demonstrated in children, adolescents and adults [19–25].

Another distinguishing feature of the present study was the incorporation of fMRI methods to help elucidate not only underlying impairments, but also possible mechanisms of positive neural response to treatment. This report, however, focuses specifically on clinical outcomes based on a broad range of standardized cognitive and neurobehavioural measures. Data on safety and tolerability are also reported here. In addition, there is a detailed examination of pre-treatment subject characteristics (severity/pattern of brain injury, cognitive and behavioural symptom profiles, demographic factors) having possible moderating effects on treatment outcomes.

Methods

Subject selection

The study group consisted of individuals recently diagnosed with TBI presenting with persistent attention deficits. The specific inclusion/exclusion criteria used are listed below.

Inclusion criteria

- Males and females, aged 16–45;
- Closed head injury rated as moderate/severe based on Glasgow Coma Scale (GCS) rating, estimated post-traumatic amnesia, indications of intracranial injury on initial CT scan, etc.;
- Sustained 6–36 months earlier and considered to be neurologically stable;
- Persistent (>6 months) problems with focused or sustained attention (+1 SD or worse on Inattention component of ADHD self-ratings). Problems with attention/concentration rated as among most prominent cognitive changes; and
- Accompanying features may include disinhibition/hyperactivity symptoms and/or diminished arousal/speed/stamina

Exclusion criteria

- Penetrating head injury;
- Pre-injury history of diagnosed ADHD;
- Other psychiatric conditions such as mania or psychosis. Current post-traumatic stress disorder (PTSD) symptoms may be present but not so severe as to require pharmacologic treatment;
- Lifetime history of psychostimulant abuse or dependence. Other (non-psychostimulant) substance abuse within the past 6 months. Total lifetime drug use not exceeding five

times each for substances such as amphetamine, methamphetamine or cocaine;
- Prior treatment with psychostimulant medication;
- Tics or other contraindications for psychostimulant use including arteriosclerosis, cardiovascular disease, uncontrolled hypertension or hyperthyroidism, glaucoma, agitation and use of MAO inhibitor within 6 weeks;
- Current treatment with other psychotropic medication(s) within the past 6 weeks (but eligible thereafter);
- Estimated IQ <80;
- Sensory and/or motor impairment(s) seriously limiting testing options;
- Other neurological conditions including epilepsy, degenerative disorders, brain tumor or stroke;
- Physical conditions affecting arousal, activity level or stamina, including uncontrolled thyroid dysfunction, severe or symptomatic anaemia, autoimmune or metabolic disorders, untreated moderate/severe sleep apnea, etc.; and
- Persons for whom MRI scanning is contraindicated, including weight greater than 275 pounds (due to scanner table limitations), severe claustrophobia, implanted electronic medical devices (e.g. pacemaker, cochlear or other inner ear implant, deep brain stimulator), metallic foreign object in eye or rest of the body, aneurysm clips, non-removable metallic piercings and dental prosthetics. If a patient had a history of sheet metal work and there was no documented x-ray of the orbits since exposure, an x-ray was to be obtained to ensure that there were no metal fragments in the orbit.

Enrolment began in the autumn of 2009 and ended in the spring of 2013. Subjects were recruited through hospitals and clinics at Vanderbilt University Medical Centre in accordance with the protocol for this study approved by the Institutional Review Board for Human Subjects Research (IRB# 090563, Vanderbilt University). Most of the potential cases were identified through a careful review of medical records of patients with new TBI seen through the Vanderbilt Trauma Service and associated clinics within the time interval of interest (extending as far back as late 2006 at the start of the study). The initial screening of records narrowed the pool in terms of age, indications of moderate/severe TBI and whether any exclusion criteria were met. Other recruitment sites included the Vanderbilt-Stallworth Rehabilitation Hospital (an acute-care facility) and the Pi Beta Phi Rehabilitation Institute (a post-acute outpatient programme), each of which serve the rehabilitation needs of patients with various disabling conditions, including TBI.

What followed was a two-step process of further screening. Cases meeting the basic TBI criteria from record review were contacted via letter by their treating physician or service director informing them of the present study and asking them to consider participating in further screening to determine their eligibility. A form letter was used, specifically approved for this project by the IRB, which emphasized that there was no obligation to participate and that the decision either way would not influence future care at Vanderbilt. Candidates were then contacted by phone to further inform them of the study and to ask their permission to participate in a brief telephone screening (10–15 minutes) to get basic information concerning their potential eligibility. Issues of privacy and protection from coercion were carefully considered in how this was done. The phone contact was by a specially trained research assistant having no clinical involvement with the patient, thereby making it easier for the person to decline participation in the screening if not interested. A set script was followed, also approved by the IRB, which structured what was said as well as the content and sequence of the questions asked. The focus mainly had to do with determining whether there were continuing cognitive problems involving attention/concentration and to see if there were any disqualifying conditions. The aim was to identify potential candidates while at the same time sparing individuals of the unnecessary trouble of coming in person for a more in-depth screening visit (see below) if obvious problems with meeting inclusion/exclusion criteria could be identified beforehand.

Overall, a total of 87 potential cases were screened by phone. Of these, 32 were eliminated from further consideration (five for not reporting problems with attention, four with disqualifying co-morbid conditions, two with a drug abuse history, 19 with disqualifying medication treatment and two with an excluded device or implant). The remaining 55 cases were judged to be potentially appropriate and were invited to come in person for a final determination of eligibility. They were offered a small financial incentive and, if necessary, an offset of travel expenses to participate in the visit. They were encouraged to bring along a spouse or family member, if available, familiar with their functioning pre- and post-TBI.

A total of 35 cases came in for a screening visit (15 of the 55 invited were lost to follow-up and five elected not to participate further). Each underwent a semi-structured interview by the project neuropsychologist/principal investigator (MGT) to obtain more detailed information about the TBI (including any pre- or post-traumatic amnesia, immediate cognitive or behavioural changes) and any persisting problems with attention and related areas, including symptoms of overactivity/impulsivity or underactivity (fatigue, diminished speed/stamina), the presence of any co-morbid psychiatric conditions (depression, anxiety, etc.), as well as clarification of pre-morbid history. In addition, brief questionnaires were used in eliciting information on current cognitive and behavioural status. This included an ADHD symptom checklist developed by Barkley and Murphy [26] based on DSM-IV criteria. The checklist yielded separate indices for Inattentive and Hyperactive/Impulsive symptoms. A score of +1 SD or higher was used as the minimum cut-off for designating problems on either dimension. Participants also completed a Post-TBI Symptom Questionnaire, which further delved into mental functioning. Subject selection required that, categorically, attention problems were rated by the individual (and/or significant other) as among his/her most troubling cognitive symptoms persisting since the TBI. Each case was also screened in terms of having the necessary minimum IQ of 80. IQ was estimated with the Vocabulary sub-test of the Wechsler Adult Intelligence Scale-Forth Edition (WAIS-IV) and required a scaled score on it of 6 or higher.

Lastly, each candidate had to undergo a brief physical exam and review of medical history by the project physician (RLC). Enrolment was contingent on verifying the absence of contraindications for psychostimulant use as noted above (e.g. uncontrolled hypertension). Female patients of child-bearing

potential also had to have a negative serum pregnancy test in order to be enrolled. They were provided with education on avoiding pregnancy and what actions should be taken if they were to become pregnant while in the study.

Upon meeting all eligibility requirements, each candidate was taken through an informed consent process (parental approval was required for all cases of 16–17 years of age). Financial incentives and reimbursement of travel expenses were offered for participation in the study. Overall, a total of 22 cases were enrolled out of the 35 who completed the screening visit. There were eight cases who failed the more in-depth screening: Of these, two did not fully meet one or more of the inclusion criteria, four had disqualifying co-morbid conditions (including two with elevated blood pressure on exam) and two were being treated with excluded medications. In addition, there were two individuals lost to follow-up and three who elected not to participate further.

Study design

This was a randomized, double-blind, placebo-controlled, cross-over study. Cases meeting selection criteria were randomly assigned to one of two treatment sequences, alternating on whether stimulant treatment or placebo came first. Each phase was 6 weeks long, resulting in a total duration of 12 weeks. Comprehensive neurobehavioural and fMRI assessments occurred at baseline, 6 weeks and 12 weeks. Ratings of inattentive and hyperactive/impulsive symptoms were obtained during weekly visits.

Medication trial

Source

Medication was supplied by Shire Pharmaceuticals (Wayne, Pennsylvania). The Vanderbilt Investigational Drug Service (IDS) re-packaged the active medication to provide placebo and drug capsules identical in size and appearance. The IDS performed medication blinding and distribution to the research nurse.

Protocol

Individuals meeting screening criteria entered a pre-determined randomization scheme as designed by the IDS. Participants received LDX (see dosing below) or placebo for 6 weeks. At the end of 6 weeks (day 43 after treatment initiation) they were switched from the current agent (drug or placebo) to the alternative (drug or placebo). Following the manufacturer's guidelines, no taper or washout period was deemed necessary when stopping or switching from LDX (it has an elimination half-life of <1 hour). After completion of the full trial, individual participants were forwarded information from the IDS indicating the particular order of treatment in their case. (This permitted them the option of sharing their subjective experiences with their primary care provider, including any perceived benefits from LDX, in consideration of possibly pursuing further treatment on their own.) However, the blinding of project staff with respect to treatment order was maintained for all cases throughout the study until after the follow-up interview (see below) was completed with the final study subject.

Titration

Subjects in the LDX treatment phase of the protocol initiated dosing at 30 mg po on study day 1 and continued for week 1. If tolerated without indications of mild medication sensitivity (such as mild increases in anxiety, insomnia, etc.), the medication was increased to 50 mg at week 2 and again at week 3 to a maximum dosage of 70 mg. If there were indications of mild medication sensitivity at 30 mg, subjects remained on the 30 mg dose throughout the study unless they met safety end-points for withdrawal (see below) or unless they requested to exit the study. If a subject tolerated the 30 mg or 50 mg dose but reported tolerability problems after a dose increase, the dose was titrated downward to the prior tolerated dose level.

Weekly monitoring

Once enrolled, all cases underwent weekly (±3 days) clinical monitoring, drug trial implementation, as well as safety and compliance assessments by a research nurse at the Vanderbilt Clinical Trials Centre (CTC). Safety monitoring included the assessment of any self-reported adverse events (AEs), assessments of blood pressure, heart rate and weight, as well as psychiatric symptom assessment including suicidality. In addition, weekly self-ratings of inattentive and hyperactive/impulsive symptoms were obtained on a brief version of the Conners Adult ADHD Rating Scale (CAARS).

Safety end-points

These served as withdrawal criteria if met or exceeded. They included both psychiatric AEs (new onset suicidality, mania, psychosis or other serious reaction requiring psychiatric intervention) as well as medical AEs (above designated safety cut-off with respect to hypertension, tachycardia, etc., or any other evidence suggestive of a severe adverse effect of the study drug).

Post-study follow-up

Subjects were contacted by phone 2-weeks (±3 days) after the final study day to inquire about safety and to address any questions or concerns they may have had.

Note

Concomitant medications not listed in the exclusion criteria were permitted. No medications were changed or held for the purposes of entering the research study. If a participant's medical provider started the patient on a new medication and that medication was on the list of excluded medications, the subject was to exit the study. Inquiry as to possible medication changes/additions was specifically assessed as part of the monitoring of safety and compliance in weekly visits to the CTC.

Neurobehavioural assessment

All cases received one-time assessments on the following measures at baseline. These were used as covariates or component measures facilitating interpretation on other tests.

- Wechsler Abbreviated Scale of Intelligence (WASI; estimate of general intelligence);
- Frontal Systems Behavioural Evaluation (FrSBE; behavioural features of frontal lobe impairment);
- Wisconsin Cart Sorting Test (WCST; set maintenance/shifting; executive functioning); and
- Finger Oscillation (fine-motor speed/persistence).

The following were repeatable measures that were administered immediately before fMRI scans at baseline, 6 weeks (±3 days) and 12 weeks (±3 days):

- Trail Making Test-Part A (focus-execute*);
- Conners Continuous Performance Test (CPT; sustain*);
- Digit Span – Forward and Backward (encode*);
- Stroop Colour/Word Test; Trail Making Test-Part B (shift*);
- Digit Symbol-Coding, Letter Fluency, Category Fluency (processing speed/control);
- Paced Auditory Serial Addition Test (PASAT; working memory);
- Verbal Paired-Associate Learning, Benton Visual Retention Test (short-term memory);
- Conners Adult ADHD Rating Scale (CAARS)-Long Form (a brief form was also obtained during weekly visits to the CTC);
- Behaviour Rating Inventory of Executive Function–Adult Version (BRIEF-A);
- Quality-of-Life Inventory (QOLI); and
- Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI).

where * indicates one of four components of attention as outlined by Mirsky et al. [7]. Note: Descriptions and normative data for many of the tests can be found in a compendium of neuropsychological tests [27].

Brain scans and functional brain imaging

All cases underwent magnetic resonance imaging of the brain. This included a structural (static) scan at baseline as well as fMRI at baseline, followed by fMRI scans at 6 weeks (±3 days) and 12 weeks (±3 days). Two stimulation task paradigms were administered during fMRI scans: the Multi-source Interference Task (MSIT) [28] and a Modified AX Continuous Performance Task (CPT-AX) [29]. Further details on the specific methods and findings with these components of the study are presented in a separate report under preparation.

Clinical determination of TBI pattern/severity

The brain injury measures used in the present report were based largely on medical record information (including head CT findings, Glasgow Coma Scale ratings, etc.) obtained during the emergency care and hospitalization immediately following TBI. Subsequent clinical findings, when available, were taken into consideration as well as information having to do with post-injury mental status obtained in the screening visit with potential candidates.

First, conventional score ranges on the Glasgow Coma Scale (GCS) were used in differentiating three levels of TBI severity: Cases with GCS scores of 13–15 were rated as having *mild* TBI; those with scores of 9–12 were rated as *moderate*; and those with scores of 8 and lower were rated as *severe*. Next, these designations were considered together with head CT findings. Any case rated as mild based on the GCS score alone was re-characterized as moderate if there was evidence of an intracranial brain injury documented by CT. Conversely, any case rated as severe based on the GCS score was upgraded to moderate in the absence of CT scan evidence of an intracranial injury. In addition, there had to be other evidence supporting an impression of a TBI of at least moderate severity, such as the presence of post-traumatic amnesia of 3 days or more that was not judged to be due simply to confounding factors such as sedation effects. The same was so for any case with a GCS score rated as moderate but who lacked CT evidence of intracranial injury. Taken together, these rules were used in defining a Composite Index of TBI Severity.

Cases were also distinguished based on whether there were indications of white matter injury evident on CT. Cases with/without CT indications of frontal lobe injury were differentiated as well. These determinations, as well as the final severity ratings, were made with the input of a board-certified trauma surgeon with a specialty in the diagnosis and management of TBI (OG).

Data analyses

The double blind cross-over design allowed for the assessment of both within-subjects and between subjects contrasts. The primary analyses consisted of multiple paired-samples *t*-tests comparing LDX vs. placebo on each of the neurobehavioural dependent measures in the study. No formal correction for multiple comparisons was applied so as to not limit sensitivity in detecting possible treatment effects. A *p*-value equal to or less than 0.05 was considered statistically significant. All tests were two-tailed. All analyses were performed using Statistical Programmes for the Social Sciences (SPSS for Windows, Version 21.0, IBM Corp, 2012).

Possible order effects (depending on whether drug treatment came before or after placebo) were examined though a separate analysis of variance (ANOVA) for each dependent measure using a two-factor model (treatment, order and treatment × order interaction). There were also applications of analysis of covariance (ANCOVA) to determine possible mediating or moderating effects of certain pre-treatment variables on treatment outcomes (demographics, brain injury variables, IQ and other cognitive factors, motor control integrity, behavioural symptom profiles and personality features).

Results

Subject characteristics

Of the 22 cases enrolled according to the criteria noted above, five were lost prior to the baseline assessment (moved, unable to contact, no-showed). Two cases were appropriate for the study but were left on hold (one was delayed due to scheduled surgeries; another case was incarcerated after the baseline assessment and completion of Week 1 in the protocol). Neither of them went on to complete the trial. Two cases had

Table I. Demographic and clinical information at screening.

Variable	Percentage	Mean (SD)	[Min, Max]
Demographic			
Gender	69% Male		
Race	84.6% Caucasian		
	15.4% African-American		
Age		28.85 (8.61)	[16, 42]
Employment status	76.9% Employed/Student		
	23.1% Unemployed		
Years of education		12.64 (1.76)	[11, 16]
Injury -related variables			
Cause of injury	69.2% MVA		
Months since injury		15.58 (9.99)	[6, 34]
Composite severity rating	53.8% Moderate		
	46.2% Severe		
White matter injury	50% Yes		
Frontal lobe injury	50% Yes		
Barkley & Murphy Ratings *Z*-scores			
Total		1.87 (0.91)	[0.15, 3.25]
Inattention		2.45 (1.49)	[−0.32, 4.2]
Hyperactivity/Impulsivity		0.80 (1.10)	[−0.86, 3.3]
Subjective complaints at screening			
Cognitive deficits (other)	100% Yes		
Under-activity/fatigue	23.1% Yes		
Pre-morbid inattention	15.4% Yes		

$n = 13$.
SD, standard deviation; Min, minimum; Max, maximum; MVA, motor vehicle accident.

to be withdrawn because of meeting end-point safety criteria for blood pressure (see the Safety and Tolerability section below). That left a total of 13 cases serving as the subject sample for the trial.

Table I shows various demographic and clinical characteristics of the total group of 13 cases at screening. They ranged from 16–42 years of age. There were nine males and four females. Education levels ranged from 11–16 years. The vast majority of the sample, 85%, was Caucasian; roughly 15% of the group was African-American. About a quarter of the group was unemployed and/or not in school. Based on the Composite Index of TBI Severity explained before, 54% of the cases were rated as moderate and 46% were rated as severe. Roughly half of the group had some form of white matter injury. Also, about half of the cases had some degree of frontal lobe injury. The majority of the injuries resulted from motor vehicle accidents. The length of time post-TBI for the group ranged from 6–34 months. As a group, self-ratings of ADHD symptoms at screening noted problems more with inattentive vs. hyperactive/impulsive behaviours (mean *z*-score = +2.45 vs. +0.80, respectively). About 23% of the group complained of concurrent problems with under-activity/fatigue. Only 15% of the group reported having a history of pre-injury attention problems (none to a degree resulting in formal treatment). Lastly, in addition to attention problems, all cases indicated having serious problems in at least one other cognitive domain.

After randomization, seven cases were assigned to the treatment condition in which they received LDX in the first 6 weeks and placebo in the second 6 weeks, whereas six cases received the opposite order. These sub-groups were generally equivalent in terms of the screening variables noted in Table I. An exception was that the sub-group treated with LDX in the second block tended to have a somewhat higher prevalence of cases rated as having severe vs. moderate TBI ($p = 0.05$)

There were specific protocol deviations (PDs) with three of the cases. One involved a 16-year-old male who did not return after the Week 10 visit. He had received LDX during the first 6-weeks, as well as full baseline and 6-week assessments, but there were no final assessments at the end of 12 weeks or at follow-up. Another case was a 34-year-old male whose involvement in the trial had to be cut short by 2 weeks in order for him to undergo urgent hip surgery. He underwent all the final assessments in the protocol after Week 10 which, in his case, was after completing 4 weeks on LDX in the second phase of the trial. Separate analyses are noted below comparing the results with/without these two PD cases. Another PD case was a 39 year old male who underwent full brain imaging and fMRI scanning at baseline but who had to be restricted from further scanning at 6 weeks and 12 weeks due to changes in university protocol involving scanning in cases with implants. However, he completed all aspects of the medication trial and neurobehavioural assessments in the study and was included in all the analyses noted below.

Figures 1 and 2 illustrate the mean *z*-scores for the total sample on the various neurobehavioural measures obtained at baseline. Using a *z*-score cut-off of −1.5 or less, examination of the results on the performance measures in Figure 1 revealed group deficits especially involving different facets of attentiveness. These were seen in terms of the rate of omission errors and perseverations on the Conners CPT. Reduced concentration and processing speed were evident on both the Trail Making Test and the PASAT. Deficits in other cognitive domains were relatively less prevalent or pronounced. Mean IQ scores for the group fell at average levels.

Inspection of Figure 2 indicates that there were significant degrees of self-rated ADHD-type symptoms on the CAARS,

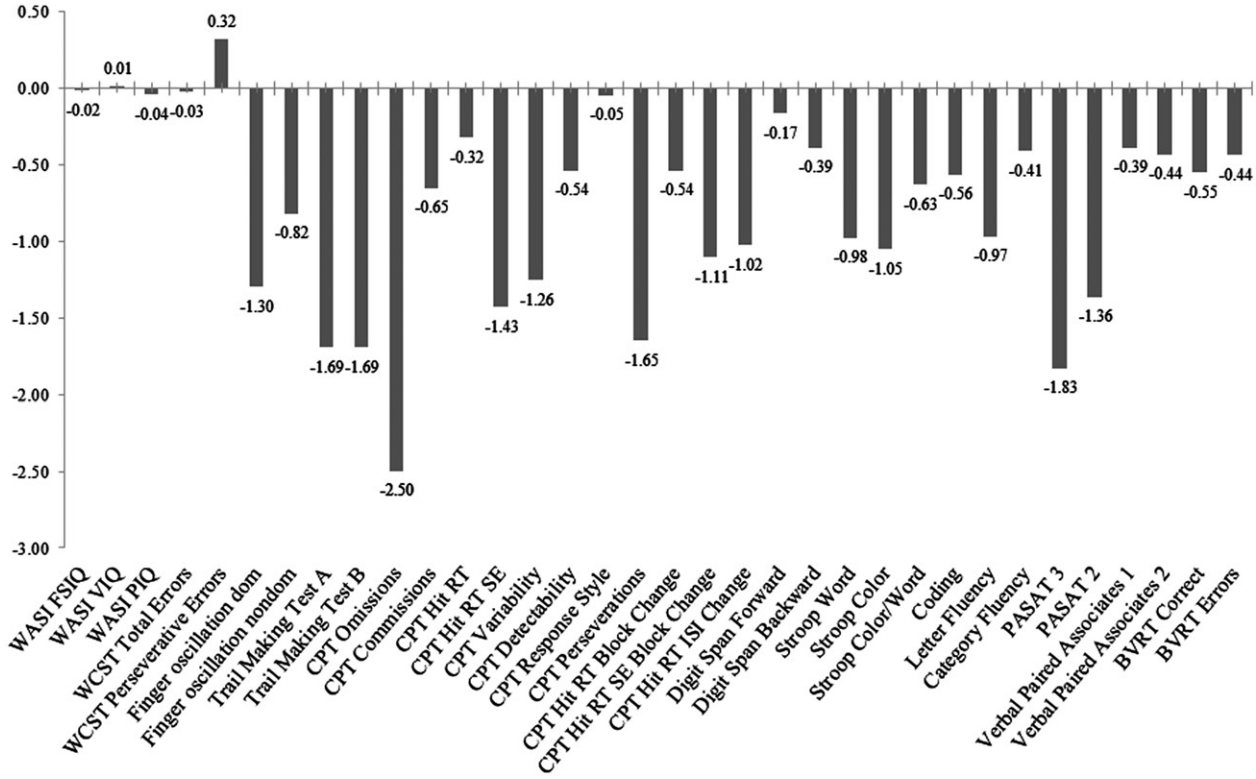

Figure 1. Baseline performance variable Z-scores
Note: Wechsler Abbreviated Scale of Intelligence (WASI); Verbal Index Quotient (VIQ); Performance Index Quotient (PIQ); Wisconsin Cart Sorting Test (WCST); Dominant Hand (Dom); Nondominant Hand (Nondom); Conners Continuous Performance Test (CPT); Reaction Time (RT); Standard Error (SE); Interstimulus Interval (ISI); Paced Auditory Serial Addition Test (PASAT, 3 second and 2 second ISI); Benton Visual Retention Test (BVRT).

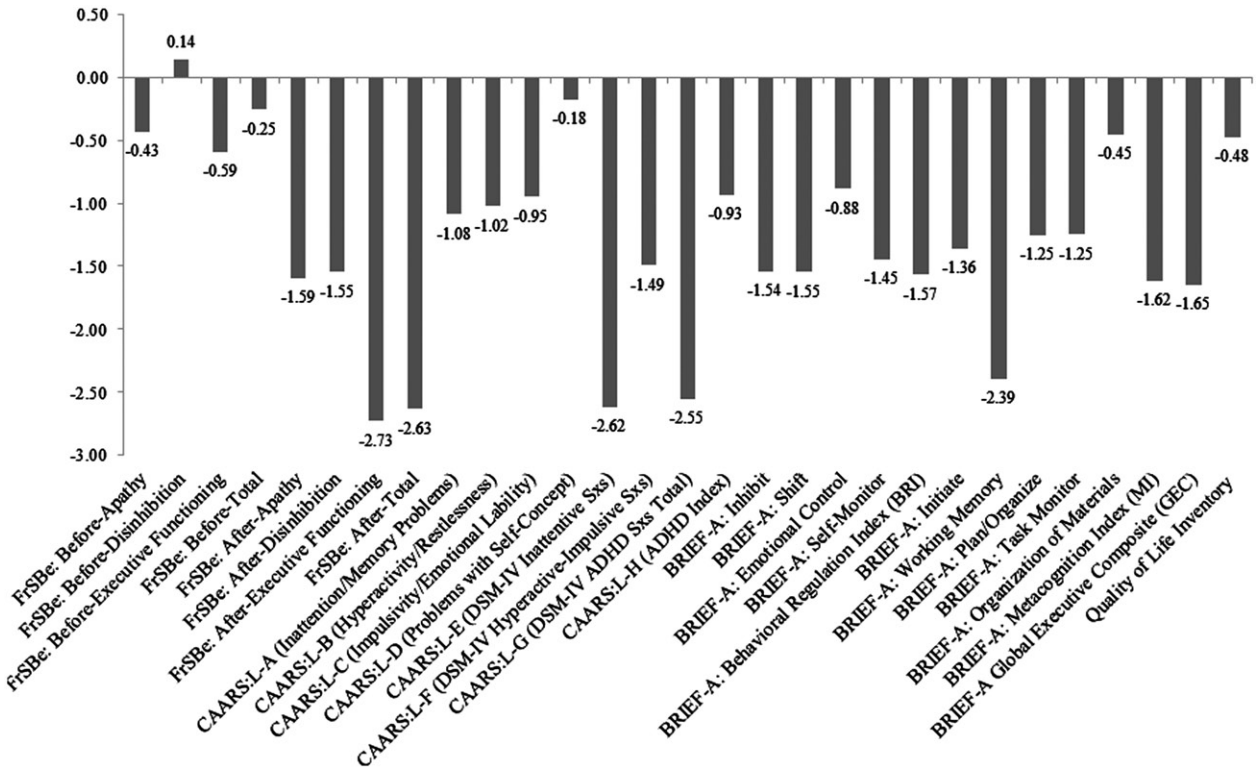

Figure 2. Baseline behavioural variable Z-scores
Note: Frontal Systems Behavioral Evaluation (FrSBE); Conners Adult ADHD Rating Scale: Long Form (CAARS:L); Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV); Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A).

together with behavioural indicators of frontal lobe dysfunction on the FrSBE (noted post-injury vs. pre-injury) and executive function deficits on the BRIEF-A. In addition, not shown in Figure 2, there were minimal-to-moderate levels of self-rated depression and anxiety for the group as a whole at baseline. The breakdown of cases falling at different raw score ranges on the BDI-II was as follows: Minimal = 4, Mild = 4, Moderate = 4, Severe = 1. On the BAI, the breakdown was: Minimal = 3, Mild = 4, Moderate = 6.

Thus, this study had succeeded in recruiting a group of individuals with serious but varying forms of brain injury for whom deficits in attention and related areas were, in fact, among their most prominent areas of dysfunction.

At baseline, cases receiving LDX treatment in the first 6-weeks vs. second 6-weeks had rated themselves as having significantly more problems on different aspects of the FrSBE (Total Score, Executive Functioning, Disinhibition) prior to treatment. The two sub-groups were otherwise equivalent on the other pre-treatment neurobehavioural measures.

Safety and tolerability

As noted above, two cases had to exit the study due to exceeding safety end-points for blood pressure (BP >149 for systolic BP and/or >99 for diastolic BP). In both cases, this occurred after Week 1 in the trial (one case was on LDX at the time and the other was on placebo). Both cases had relatively high BP readings at baseline (144/81 and 140/80).

For the remaining 13 cases, mean BP levels were somewhat higher during the 6 weeks on LDX vs. the 6 weeks on placebo. That was the case both with systolic BP (124.5 vs. 118.3, respectively) and diastolic BP (71.9 vs. 68.5, respectively). Mean heart rate was also somewhat higher (80.4 vs. 73.8, respectively). However, none of these differences were statistically significant when analysed in terms of repeated measures ANOVA based on treatment (on/off LDX), time (weeks 1–6) or treatment × time interaction.

In terms of dosing, nine out of 13 of the cases tolerated being titrated up to the maximum maintenance dose of 70 mg LDX. Following the conservative titration protocol noted above, it turned out that two cases were maintained at 30 mg and two cases at 50 mg. All cases on placebo were taken to the maximum maintenance level. Two cases on LDX had to be titrated downward due to tolerance issues. One case was decreased from 70 mg to 50 mg due to complaints of erectile dysfunction; there were no further complaints following the reduction. The other case was dropped back from 50 mg to 30 mg due to concerns regarding a susceptibility to unstable BP.

Table II shows the various side-effects that were monitored in weekly visits and their occurrence when on LDX vs. placebo. Reports of decreased appetite and actual weight loss of 5 lbs or greater were noted more during the 6 weeks on LDX vs. placebo, but the differences were not statistically significant ($p = 0.125$ and 0.070, respectively). Other side-effects while on LDX were absent or very infrequent.

Treatment outcomes

Dependent samples *t*-tests were conducted comparing mean performance after 6 weeks of treatment on LDX vs. placebo for each of the neurobehavioural measures. That involved a large number of comparisons given the broad-based assessments that were performed. Table III summarizes the main significant findings. On LDX, there were fewer Perseverations on the Conners CPT ($p = 0.053$). There were also better scores on the Conners CPT involving Hit Reaction Time (RT) Block Change (indicating less slowing in RT as the test progressed; $p = 0.052$) and less Hit RT Inter-Stimulus Interval (ISI) Change (indicating less variability in RT depending on speed of presentation; $p = 0.047$). There was better performance on vs. off LDX on WAIS-IV Digit Span-Backward ($p = 0.003$). There also were lower self-ratings of Inattentive symptoms on the CAARS-Long Form ($p = 0.040$). Across these different outcome measures, the rates ranged from

Table II. Safety and tolerability.

Side-effects assessed/reported	LDX	Placebo
Weight loss[a]	7	1
Decreased appetite	5	1
Insomnia	2	5
Dry mouth	2	2
Diarrhoea		
Nausea		
Feeling jittery		
Tremors		
Anxiety	1	
Agitation		
Restlessness		1
Shortness of breath		
Excessive sweating		
Erectile dysfunction	1	

$n = 13$.
LDX, lisdexamfetamine dimesylate.
[a]Defined by loss of 5 lbs or more over the 6-week treatment period.

Table III. Summary of main treatment differences.

	Mean (SD)			
Variable	On LDX	Off LDX	*t*	*p* Value
Conners CPT				
Perseverations *T*-score	50.23 (6.67)	59.76 (17.29)	−2.16	0.053
Hit RT Block Change *T*-score	47.70 (7.47)	54.21 (7.68)	−2.17	0.052
Hit RT ISI Change *T*-score	58.08 (17.92)	65.93 (17.61)	−2.24	0.047
Hit RT Standard Error *T*-score	54.26 (18.21)	64.04 (15.68)	−2.27	0.047[a]
Digit Span-Backward Scaled-score	11.60 (3.86)	9.40 (4.40)	4.13	0.003
CAARS:L-Inattention/ Memory Problems *T*-score	51.25 (13.29)	56.33 (12.39)	−2.33	0.040
BRIEF-A Sub-scale				
Organization of Materials *T*-score	48.55 (7.95)	56.00 (12.76)	−2.27	0.047[a]

$n = 12$, except for Digit Span Backward SS ($n = 10$). Significant differences were based on $p = 0.05$ or less.
SD, Standard deviation; LDX, lisdexamfetamine dimesylate; CPT, Continuous Performance Test; RT, Reaction Time; ISI, Inter-stimulus Interval; CAARS:L, Conners Adult ADHD Rating Scale: Long form; BRIEF-A, Behaviour Rating Inventory of Executive Function–Adult Version.
[a]*p* Value obtained with removal of the two cases with protocol deviations.

31–46% of the cases demonstrating a positive difference of 1 SD or more when on LDX vs. placebo. For the Perseverations score on the Conners CPT, 23% of the cases actually had a positive treatment difference of 2 SD or more.

Re-analysis of the above, excluding the two cases with protocol deviations (PDs), yielded very similar results. The same differences on vs. off treatment with LDX were found in terms of both Perseverations and Hit RT ISI Change on the Conners CPT ($p = 0.053$ and 0.022, respectively) and on WAIS-IV Digit Span-Backward ($p = 0.007$). However, the difference involving self-rated symptoms of Inattentiveness on the CAARS-Long Form dropped to a marginal level ($p = 0.061$). The difference involving the Hit RT Block Change was no longer significant ($p = 0.103$), although there was now a significant difference on the Hit RT Standard Error, another measure of response speed variability on the Conners CPT ($p = 0.047$). Treatment differences on the Conners CPT simply involving overall Hit Reaction Time were only marginal, with or without the two PD cases ($p = 0.144$ and 0.063, respectively). Lastly, without the two PD cases, there was now significantly better self-appraisal on vs. off LDX involving the Organization of Materials sub-scale of the BRIEF-A ($p = 0.047$).

The order of treatment (whether LDX was received in the first vs. the second 6-week period) made little difference in outcomes. This was analysed through separate ANOVAs examining both treatment effects and order effects on each of the dependent measures. The only exceptions had to do with the results on sub-sections of the BRIEF-A. For the Organization of Materials sub-scale, there was both a significant effect for treatment and a significant treatment × order interaction. That was so both with the two PD cases ($p = 0.001$ and 0.029, respectively) and without them ($p = 0.039$ and 0.002, respectively). There was overall improvement on this measure with treatment, but there was more of a drop in self-reported problems for those cases who received LDX in the first 6 weeks vs. the second 6 weeks. A similar interaction effect was obtained on the Initiate sub-scale of the BRIEF-A, both with and without the two PD cases ($p = 0.008$ and 0.012, respectively). However, the cases who received LDX in the first 6 weeks vs. the second 6 weeks happened to have started off with higher levels of self-rated problems with task initiation.

Moderating effects

There were few differences in treatment outcomes based on demographic factors. One of these had to do with a significant treatment × age interaction on the Colour/Word section of the Stroop Test, a measure involving the regulation of competing response tendencies ($p = 0.02$). The pattern was for older vs. younger cases to show *greater* benefit on this measure due to treatment with LDX. There also was indication of a moderating effect on some measures due to education level. This was seen especially in terms of variability measures on the Conners CPT, such as the Hit RT ISI Change (one of the areas of positive outcome noted above), for which there was a significant treatment interaction with years of education ($p = 0.02$). Treatment with LDX had more of a positive effect on this measure for cases having *fewer* years of education. As for race, there was too little variation on that factor in this sample for meaningful comparisons to be made.

Moderating effects were also examined in terms of various factors having to do with the severity and pattern of brain injury. Overall, there was a lack of consistent or clearly interpretable differences in treatment outcomes due to differences in TBI severity, whether based solely on the GCS or in terms of the Composite Index TBI Severity defined above. The same was true with respect to differentiating TBI cases based on whether there were CT scan indications of white matter injury and/or frontal lobe injury.

The cognitive and neurobehavioural measures used in the present study typically correlate to varying degrees with each other. That is especially the case with measures of global intelligence, which tend to share significant portions of variance with many neuropsychological tests [27]. That was certainly the case in this study, in that estimated Full Scale IQ, based on the WASI at baseline, correlated significantly with 15/28 (54%) of the performance measures assessing outcomes. In the case of Perseverations on the Conners CPT (one of the main measures with positive treatment effects noted above), there was a significant treatment interaction with IQ ($p = 0.01$). Off LDX, cases with lower vs. higher pre-treatment IQ performed more poorly in terms of CPT Perseverations. On LDX, however, performance on this variable improved to the extent of nullifying differences in outcome due to IQ. A similar interaction affecting treatment outcomes on Conners CPT Perseverations was seen with another cognitive measure administered at baseline, the Wisconsin Card Sorting Test (WCST)-Categories Achieved ($p = 0.03$). Off LDX, cases who solved fewer vs. more WCST categories at baseline tended to produce more CPT Perseverations when evaluated 6 months later. However, on LDX, they benefitted relatively more on that outcome measure compared to those cases who were more adept in conceptual reasoning on the WCST pre-treatment. The same type of interaction involving WCST Categories Achieved was seen for another outcome measure having positive treatment effects, CPT Hit RT Block Change ($p = 0.05$).

Analyses were also performed examining differences in outcomes due to other various pre-treatment factors in the study. The overall severity of ADHD symptoms at screening, based on self-ratings on the Barkley and Murphy Scales, had little effect in predicting treatment response. However, there were some predictive findings pertaining to self-rated ADHD symptoms based on the CAARS obtained at baseline. Treatment with LDX made more of a positive difference in Quality-of-Life ratings for cases reporting *more* problems with Impulsivity/Lability on the CAARS pre-treatment ($p = 0.02$). A similar effect on Quality-of-Life was seen with pre-treatment self-ratings of Disinhibition on the FrSBE as the predictor ($p = 0.01$). Predictive relationships with treatment outcomes were also seen with self-ratings of executive functioning on the BRIEF-A obtained at baseline. There was a significant interaction involving the Global Executive Composite, the overall summary score on the BRIEF-A, and treatment effects on Digit Span-Backward ($p = 0.016$), another one of the main areas with a positive outcome noted above. Cases reporting greater overall pre-treatment problems with executive functioning tended to

show *more* of a benefit from LDX on this outcome measure. Similar interaction effects were seen with selective sub-scales on the BRIEF-A, as in the case of scores on the Inhibit scale predicting treatment outcomes on measures such as Category Word Fluency and self-ratings of depression on the BDI-II ($p = 0.013$ and 0.031, respectively). In each case, those with greater pre-treatment problems with inhibition showed a *greater* relative benefit from treatment.

There was insufficient variation in the sample for meaningful comparisons to be made based on whether or not there was report of under-activity/fatigue at screening ($n = 3$) or whether there was a history of pre-injury attention problems ($n = 2$). Pre-treatment self-ratings of depression or anxiety made little difference in treatment outcomes. One difference had to do with treatment effects on self-ratings of Planning/Organization on the BRIEF-A. Cases with *lower* self-ratings of depression on the BDI-II pre-treatment tended to do better on vs. off LDX in terms of perceived planning and organization abilities ($p = 0.03$).

Discussion

Deficits in attention and related areas constituted major problems for participants in this study. These were, in fact, among the more prominent deficits seen in a heterogeneous group of individuals with moderate-to-severe TBI. Yes, these subjects were selected, in part, on the basis of having persisting attention deficits post-TBI. Nonetheless, it was noteworthy that attention deficits stood out among the functional problems they had, despite the presence of widely varying differences in terms of assorted pre-injury and injury-related factors.

Positive treatment effects with LDX were noted in various aspects of attention, both in terms of self-ratings and performance measures assessing different facets of attention regulation. Performance benefits were seen especially in terms of different aspects of sustained attention as assessed on the Conners CPT. Thus, with respect to Mirsky's model of different components of attention, it was the *sustain* element that was especially affected. There was a positive impact on working memory or the *encode* element in Mirsky's model, as seen with the improved performance on WAIS-IV Digit Span while on LDX. However, the fact that it was Digit Span-Backward that improved, not Digit Span-Forward, suggested that the benefit was more evident where more *effortful* concentration was involved. Improvements in processing speed (a finding reported in some other studies examining psychostimulant treatment effects in TBI) were seen, but mainly in terms of response speed *stability* or consistency and endurance, rather than in terms of simple speed of execution, *per se*.

Other findings included improvements in self-reported aspects of executive functioning, such as task organization, noted in some of the analyses. Treatment was for only a 6-week period in the present study, but yet it was enough to begin to impact on areas beyond narrowly defined aspects of attention. Perhaps positive treatment effects would have been more evident in other areas, including ratings of mood and quality-of-life, if there were improved functioning extending for a longer period of time and affecting more aspects of the individual's life. Also, conceivably, with more stable and better-regulated attention over time, individuals with TBI may be better able to derive benefit from other interventions, including rehabilitation therapies targeting other cognitive areas affected.

Treatment with LDX appeared to be generally safe and tolerable when applied to this sample of persons with TBI. There were no major adverse events from either a physical or psychiatric standpoint. Two subjects had to exit the study due to meeting safety end-points for blood pressure, but each of them had relatively high BP readings to begin with, and they met the end-points after a week into the study whether they were on LDX or placebo at the time. There was a trend for higher BP and heart rate readings on LDX vs. placebo for the group as a whole, but the differences were not found to be statistically significant. The same was so with respect to reports of weight loss (5 lbs or more) and decreased appetite while on LDX vs. placebo. Perhaps these differences would have been significant in a larger sample. In any event, no novel side-effects were found with LDX in this TBI sample compared to what is ordinarily reported in the treatment of idiopathic ADHD [19, 21, 23, 25].

An important aspect of the study was the examination of various pre-treatment factors as they related to treatment outcomes. Cases with more serious challenges pre-treatment (lower IQ and education, executive function deficits and greater indications of impulsivity/disinhibition) showed a relatively *greater* treatment benefit from LDX in some of the analyses. These observations provided some insights into pre-treatment differences in persons with TBI, possibly having an important bearing on treatment outcomes. However, keep in mind that these predictive relationships were drawn from a fairly large number of analyses. For the most part, the positive treatment effects and suggestive trends identified in this study did not depend greatly on various pre-treatment factors. That was the case with the various brain injury variables as examined in this report (severity, CT indications of white matter or frontal lobe injury). However, elucidating predictive relationships involving brain injury factors likely depends on having a larger sample of cases and/or the incorporation of imaging methods providing more precise and quantitative means of revealing important underlying structural and functional differences.

The present trial was among the most rigorous studies so far examining the assessment and treatment of attention deficits in TBI. The use of a cross-over design was appropriate here given that the randomized subject sample consisted solely of cases determined to be neurologically stable and who were a minimum of 6-months post-TBI at baseline [15]. It was the first study of LDX (Vyvanse) with this population and, in fact, was the first controlled trial examining stimulant medication treatment in TBI using an option other than methylphenidate. Other distinguishing features had to do with the very broad-based neurobehavioural measures used in the study and the incorporation of fMRI methods in examining underlying neural mechanisms of response (a report dealing specifically with the scan findings is under preparation).

The chief methodological limitation of this study was the sample size. The very strict selection criteria that were used limited what was otherwise a much larger pool of potential

TBI cases. Excluding cases based on various factors (metal implants precluding MRI scanning, certain co-morbid physical or mental conditions or various concurrent treatments) had to do more with issues of control and methodological rigour in the present study rather than necessarily constituting restrictions that would have to be applied in actual clinical practise. That being said, it was all the more noteworthy that various significant treatment effects were revealed in this trial despite the relatively small sample of cases. Many outcome measures were examined (which surely increased the likelihood of finding some effects), but a point was made of limiting what was reported here to outcomes that had some consistency across the different analyses.

Overall, this was an initial trial with LDX in this population that yielded some promising findings requiring further study and delineation in future trials. Going forward, there should be consideration of broadening the selection of individuals with TBI. Future studies should include cases with milder TBI who have documented persistence in cognitive changes, including impaired attention. This would encompass many common cases of TBI, such as most sports-related concussions. Even if the attention deficits in these cases do not prove to be chronic, helping to enhance functioning in the earlier stages of recovery may have a beneficial effect on overall outcomes and limit secondary problems that might otherwise arise (e.g. frustration and loss of self-esteem, disruption of pursuing personal goals). The scope should also be broadened to include the examination of treatment outcomes in terms of TBI occurring at younger ages. The present study dealt with individuals with TBI ranging from 16–42 years of age. An obvious and important extension would be to evaluate the effects of LDX on children and adolescents with TBI.

TBI is a major cause of persistent and debilitating handicaps in the general population. Advances in emergency medical care have resulted in major positive strides in survival but, with that, there has been a higher prevalence of persons surviving with serious cognitive and neurobehavioural disabilities. Many of them will have persisting deficits in attention and the many other areas of functioning they may affect. The present study highlighted some positive effects of a treatment option such as lisdexamfetamine dimesylate and opens the door to further examining its potential benefits in treating persons with TBI-related attention deficits.

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