Treatment Outcomes with Lisdexamfetamine Dimesylate (Vyvanse) in Children with Traumatic Brain Injury-Related Attention Deficits

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(Proposal)

Michael G. Tramontana, Ph.D.

Vanderbilt University

Introduction

Traumatic brain injury (TBI) is a major cause of cognitive handicaps and behavioral disabilities in the general population.[1-4] It is the leading cause of death and disability in the US for individuals under 25 years of age. There has been a growing awareness that even milder forms of TBI can result in persistent problems in mental functioning and overall quality of life. This is clearly an important public health problem for which effective treatments continue to be sought.

Attention deficits are often among the most persistent and debilitating impairments resulting from TBI. A multidisciplinary team at Vanderbilt University Medical Center recently completed a clinical trial examining the effects of lisdexamfetamine dimesylate (LDX; Vyvanse) in treating attention deficits due to moderate to severe TBI. The study was based on an Investigator Sponsored Trial funded by Shire Pharmaceuticals (IST-ALB-000236, Michael G. Tramontana, Ph.D., principal investigator). It was one of the most rigorous studies in this area to date, and was the first controlled study using lisdexamfetamine dimesylate with this population. The results of that trial were recently published (Tramontana et al.).[5] Briefly, positive treatment effects were found involving various 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.

The foregoing study highlighted the potential benefits of an option such as LDX in treating persons with TBI-related attention deficits. Treatment was for only a 6-week period (it was 12-week, randomized, double-blind, placebo-controlled, crossover trial), but yet it was enough to begin to impact on areas beyond narrowly defined aspects of attention. Conceivably, with more stable and better-regulated attention over time, individuals with TBI may be better able to derive benefit from other interventions, including therapies targeting other cognitive and behavioral areas affected. Overall, the study opened the door for further research and treatment applications in this area.

The previous trial dealt with individuals with TBI ranging from 16 to 42 years of age. We now propose performing a similar trial with children ranging from 6 to 16 years of age. This is a logical and important extension of the previous trial. Children in that age range comprise a major portion of the TBI population,[4] with most of the injuries resulting from falls, recreational

activities (including sports concussions), as well as motor vehicle accidents and pedestrian-motor vehicle accidents. Some are victims of violence. Impairments in attention can have a major adverse effect on learning and behavioral adjustment. Arguably, left untreated, these deficits can have an even more life-altering effect on achievement and future success than in the case of adults.

As far as pertinent background research, a study by Levin et al. demonstrated increased rates of newly diagnosed attention-deficit/hyperactivity disorder (ADHD) in children post-TBI (ranging from 14.5% at 12 months to 18.3% at 24 months). [6] The rates 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 many other studies establishing a significant causal link between TBI and attention deficits in children, with prevalence rates ranging from 20% - 46% and with persisting deficits lasting 4 -10 years or more.[7, 8] Important moderating variables have included the severity and location of injury, as well as age at the time of injury, IQ and psychosocial factors.

The underlying mechanisms producing attention deficits 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. Mirsky et al. articulated a four-component model of attention (*focus-execute, sustain, encode, shift)*[9] that has been applied widely in ADHD research. It has been cross-validated as applicable to children with TBI, with the underlying components affected to varying degrees depending on factors such as severity of injury.[10] The particular pattern of impairment based on this model has also been found to differ between children with TBI versus idiopathic ADHD.[11]

Another underlying defect in TBI often involves non-specific white matter shearing which may result in slower processing times, with indirect effects including limited attention span as well as diminished mental speed and stamina. Yet another possibility may include structural deficits in brain locations unrelated to attention that may result in assorted performance inefficiencies, which, in turn, indirectly affect attentiveness by requiring greater effort (thereby lowering the threshold for mental fatigue). All of these are similar to the mechanisms that were outlined in our study of adults. The difference with children is that the injuries can have major effects, not only on current functioning, but also in terms of subsequent brain development and longer-term functional organization. Skills and abilities in primary ascendance at the time of injury are especially vulnerable.

In a study using functional magnetic resonance imaging (fMRI), Kramer et al. examined long-range outcomes with respect to attention processing in children who sustained moderate-severe TBI in early childhood versus a group of age-matched children with orthopedic injuries.[12] 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.

Treatment effects with stimulant medication may also be conceptualized in various ways. One possibility is that it 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. 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 hypofunctioning of these regions in ADHD.[13] Based on the Kramer et al. study noted above, it might be inferred that compensatory activation occurs to some extent naturally in TBI-related attention deficits, perhaps especially in children. Stimulant medication may help 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.[14] 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.

There have been few studies examining the use of stimulant medication in treating TBI-related attention deficits in children. [15-18] Even fewer of these were controlled trials. All of them were very limited in terms of sample size and the scope of the outcomes examined. Nearly all of them focused specifically on methylphenidate as the stimulant treatment. Some positive effects were reported, but little can be concluded based on these studies due to methodological limitations. The dearth of studies here stands in contrast to the growing body of evidence noted above documenting the prevalence, pattern, and persistence of attention deficits due to TBI in children. At this point, more is known about treatment effects with adults, although the potential for lasting adverse effects from TBI-attention deficits is greater in children. The proposed study is intended to help fill this void.

This study will follow a design and methodology similar to what was done in the initial study, albeit adapted to the age range of the child sample. There will be some differences, however. The proposed study will not incorporate fMRI methods as was done in the initial trial. Instead, the focus will be on examining clinical outcomes based strictly on a broad range of standardized cognitive and neurobehavioral measures. That is intended not only to streamline the cost of the proposed study; it also will allow subject selection to be less restrictive. A number of otherwise suitable cases had to be excluded in the previous trial due to failing to meet criteria specifically having to do with the MRI scanning (e.g., no metal objects or implanted devices, claustrophobia, etc.). More generally, it was felt that there would be fewer potential problems with the participation or compliance of children if fMRI scans were not involved.

Also, unlike the initial trial, subject selection will not be restricted to only those with moderate-severe TBI. It will be extended to also include cases with milder TBI who have documented persistence in cognitive changes, including impaired attention. That would encompass many common cases of TBI, and greatly broaden the potential pool. Even if the attention deficits in these cases would not prove to be chronic, helping to enhance functioning in the earlier stages of recovery can have a beneficial effect on overall outcomes and limit secondary problems that might otherwise arise. Lastly, the interval from the time of injury to when a case is eligible for inclusion in the study will be reduced from 6 months to 2 months. This is intended to capture the child subjects earlier on in the recovery process. It will help reduce the attrition of potential cases who otherwise might be lost to follow-up or who wind up getting started on other treatments. Regardless of the exact point within the eligible time interval post-injury, it will be necessary that each case be judged to be neurologically stable but having persistent attention deficits.

This will be will be the first study to examine the use of LDX in treating attention deficits in children with TBI. It will be the most rigorous study to date examining stimulant medication treatment of any kind with this population. It is predicted that, as in the initial trial with adults, positive treatment effects will be found on a spectrum of outcomes having to do will attention and the various areas affected by it. Safety and tolerability with be carefully examined for the use of LDX in this clinical application. Also, as was done in the initial trial, treatment outcomes will be examined in terms of potentially moderating effects having to do with a broad range of pre-treatment subject characteristics and injury variables, including the pattern and severity of TBI, age of injury, as well certain cognitive and behavioral factors at baseline. In our previous trial with adults, subjects with greater functional limitations pretreatment (lower IQ, problems with executive functioning) showed better treatment response with LDX on some outcome indices.

Overall, this will be a novel study examining the treatment of TBI-related attention deficits in children. The primary aim is to conduct a sound clinical trial examining outcomes with LDX as the treatment, but the objectives of the study go beyond that. More broadly, the aim is to gain further insights into the nature of attention deficits and their treatment in children with TBI. Based on the existing research, there are likely to be unique relationships involving children with TBI versus idiopathic ADHD. The hope is that this trial will help inform and guide further investigations in this area.

Methods

Subject Selection

The subject sample is to consist of approximately 20 children diagnosed with TBI-related attention deficits. The specific selection criteria are noted below.

Inclusion Criteria:

- Males and females ages 6 to 16
- Traumatic brain injury rated as mild/moderate/severe (based on *Glasgow Coma Scale*, estimated posttraumatic amnesia, indications of intracranial injury on CT scan, etc.)
- Sustained 2-36 months earlier
- Considered to be neurologically stable (absence of post-acute symptoms of confusion, disorientation, etc.)
- Persistent (> 2 months) problems with focused or sustained attention
- Problems with attention/concentration rated as among the most prominent cognitive changes
- Accompanying features may include diminished arousal/speed/stamina and/or hyperactivity/impulsivity symptoms.

Exclusion Criteria:

- Cases with primarily penetrating head trauma
- Pre-injury history of diagnosed ADHD (cases with questionable or selective features pre-injury may be considered as long as there is a clear worsening of symptoms)
- Pre-injury history of other neurodevelopmental disorders including intellectual disabilities, major communication disorders, or autismspectrum disorder
- Unstable or serious psychiatric conditions, such as psychotic symptoms. Concurrent problems with depression, anxiety, or posttraumatic stress disorder may be present but are judged to be stable and not so severe as to require pharmacologic treatment.
- Treatment with psychotropic medication(s), including stimulants, within the past 6 weeks, but eligible thereafter
- Lifetime history of stimulant abuse or dependence. Other (non-stimulant) substance abuse within the past 6 months
- Tics or other contraindications for psychostimulant use including cardiovascular disease, uncontrolled hypertension or hyperthyroidism, glaucoma, agitation, use of an MAO inhibitor within the past 6 weeks. Pregnancy would also be an exclusion for girls of childbearing age.
- Estimated IQ < 70
- Sensory and/or motor impairment(s) seriously limiting testing options
- Neurological conditions including uncontrolled epilepsy, degenerative disorders, brain tumor, or primary stroke
- Physical condition affecting arousal, activity level or stamina including uncontrolled thyroid dysfunction, severe or symptomatic anemia, autoimmune or metabolic disorders, untreated moderate/severe sleep apnea, etc.

Recruitment Plan:

Children for the study will be recruited from hospitals and clinics at Vanderbilt University Medical Center, including Vanderbilt Children's Hospital. It is anticipated that many of the potential cases will be identified through a careful review of medical records of patients with new TBI seen through the Pediatric Trauma Service and followed prospectively within the time interval of interest. The initial review of records will narrow the pool in terms of age, indications of mild/moderate/severe TBI, and whether any factors would exclude them from further consideration. Other recruitment sites will include Vanderbilt-Stallworth Rehabilitation Hospital, as well as various specialty services at Vanderbilt such as Pediatric Neurosurgery, Pediatric Neurology, Child Psychiatry, and the Sports Concussion Clinic. There are well-established collaborative relationships involving the investigative team and all these entities.

Screening Assessments/Enrollment:

What follows will be a two-step process of further screening. Parents of cases meeting the basic TBI criteria from record review will be contacted via letter informing them of the study

and asking them to consider participating in further screening to determine their child's eligibility. A form letter will be used (to be approved for this project by the Vanderbilt IRB) which will emphasize that there is no obligation to participate and that the decision either way will not influence their child's future care at Vanderbilt. Parents of candidates will then be 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 eligibility. Privacy and protection from coercion will be carefully maintained. The phone contact will be by a specially trained research assistant having no clinical involvement with the patient, thereby making it easier for the parent to decline participation in the screening if not interested. A set script will be followed (also to be approved by the IRB) which will structure the content and sequence of the questions asked. The focus will mainly have to do with determining whether there are continuing cognitive problems involving attention/concentration, and also to see if there are any disqualifying conditions. This will help to identify potential candidates while at the same time sparing individuals the unnecessary trouble of coming in person for a more in-depth screening visit (see below) if there are obvious problems in meeting inclusion/exclusion criteria that could be identified beforehand.

Next, potentially appropriate children and their parent(s) will be invited to come in person for a final determination of eligibility. Each will undergo 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 behavioral 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 premorbid history. In addition, questionnaires and rating forms will be used in eliciting detailed information on current cognitive and behavioral status. This will include behavior ratings on the Conners-3 Parent Form assessing ADHD and related areas. Selection will require a T-score of 65 or higher (+ 1.5 SD) on one or more of the following subscales: *Inattention, Hyperactivity/Impulsivity*, as well as *DSM-ADHD Inattentive Symptoms, DSM-ADHD Hyperactive-Impulsive Symptoms*. Parents will also complete a Post-TBI Symptom Questionnaire, which will further delve into mental functioning (children, ages 11 and older, will complete this as well). Subject selection will require that, categorically, attention problems be rated as among the most troubling cognitive symptoms persisting since the TBI. Each case will also be screened in terms of a having the necessary minimum IQ of 70. That will be estimated with the Vocabulary subtest of the Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V), and will require a scaled score on it of 4 or higher.

Lastly, each candidate will undergo a brief physical exam and review of medical history by the project physician. Enrollment is contingent on verifying the absence of any contraindications for psychostimulant use as noted above. Female patients of child bearing potential also must have a negative urine pregnancy test in order to be enrolled. Parents will be provided with information to help them guide their daughters on avoiding pregnancy and what actions should be taken if they were to become pregnant while in the study.

Upon meeting all eligibility requirements, parents will go through an informed consent process concerning their child's participation in the study. Any forms and procedures used will be approved by the Vanderbilt IRB.

Study Design

As in the initial study, this will be a randomized, double-blind, placebo-controlled, crossover trial. Following enrollment, each case will be randomly assigned to one of two treatment sequences, alternating on whether stimulant treatment or placebo comes first. Each phase will be 6 weeks long, resulting in a total duration of 12 weeks. Comprehensive neurobehavioral assessments will occur at baseline, 6 weeks, and 12 weeks. More streamlined behavior ratings along with safety monitoring and medication/placebo dispensing (see below) will be done during weekly visits.

Medication Trial

Source: Medication will be supplied by Shire Pharmaceuticals. The Vanderbilt Investigational Drug Service (IDS) will repackage the active medication to provide placebo and drug capsules identical in size (the smallest available) and appearance that will remain the same throughout the trial. The IDS will perform medication blinding and distribution to the study nurse.
Protocol: Enrolled children will enter a pre-determined randomization scheme as designed by the IDS. They will receive LDX (Vyvanse) 20-70 mg or placebo for 6 weeks. At the end of six weeks (day 43 after treatment initiation) each subject will switch from the current agent (drug or placebo) to the alternative (drug or placebo). Based on manufacturer's guidelines and clinical experience, no taper or washout period is deemed necessary either in switching from active drug to placebo or at termination of treatment.
Titration: All subjects in the LDX treatment phase of the protocol will initiate dosing at 20 mg po on study day 1 and continue on that for week 1. (The usual starting dose is 30 mg for children 6 years of age and older with idiopathic ADHD, but it was decided to begin with a more conservative starting point given the off-label use in the present trial.) If tolerated without indication of medication sensitivity (such as mild increases in anxiety, insomnia, weight loss, etc.), all subjects will be increased to 30 mg at week 2. Thereafter, if tolerated, they will be increased to 50 mg at week 3 and again at week 4 to a maximum dosage of 70 mg. Increments will be scaled back to a rate of 10 mg weekly at any point if there are concerns about possible medication sensitivity. Subjects will remain at the maximum tolerated dose for the remainder of the trial unless they meet safety endpoints for withdrawal (see below) or they request to exit the study. Cases with certain medical conditions (e.g., those with known or suspected renal dysfunction) will not be advanced to a daily dose beyond 50 mg. Weekly parent/subject ratings on the Clinical Global Impression-Severity (CGI-S) Scale (a standard measure of subjective treatment response used in clinical drug trials) will be taken into consideration in making dosing adjustments. If a subject tolerates lower dosing(s) but reports tolerability problems after a dose increase, the dose will be titrated downward to the prior tolerated dose level. Dosing adjustments may occur up to the start of week 6 if necessary. The same titration schedule and guidelines will apply during both the drug and placebo phases of the trial.
Safety Endpoints: These will serve as withdrawal criteria if met or exceeded. They include both psychiatric AEs (new onset suicidality, psychosis, or other serious reaction requiring psychiatric intervention) as well as medical AEs (above the designated safety cutoff with respect

to hypertension, tachycardia, etc., or any other evidence suggestive of a severe adverse effect of the study drug).

De-blinding: Because placebo and active drug for all dosages will be packaged in opaque capsules of fixed size by the IDS, the study investigators and subjects will be blinded to drug/placebo status. IDS will provide this information to the PI or other medical personnel in the case of a patient medical emergency. If blinding is broken for this reason, the subject must exit the study.

After completion of the full trial, individual participants will be provided information from the IDS indicating the particular order of treatment in their case. This will allow them and their parents the option of sharing their subjective experiences with their primary care provider, including any perceived benefits from Vyvanse, in consideration of possibly pursuing further treatment on their own. However, the blinding of project staff with respect to treatment order will be maintained for all cases throughout the study until after the follow-up interview (see below) is completed on the final study subject.

Post-study follow-up: Parents (and subjects 11 years and older) will be 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.

Note. Concomitant medications not listed in the exclusion criteria will be permitted. No medications will be changed or held for the purposes of entering the research study. If a child is started on a new medication by their medical provider, and that medication is on the list of excluded medications, the patient will exit the study. Inquiry as to possible medication changes/additions will be specifically assessed as part of the monitoring of safety and compliance in weekly visits with the study nurse.

Neurobehavioral Assessments

All cases will receive a one-time assessment at baseline on the following measures. These will be used as covariates or component measures facilitating interpretation on other tests.

- Abbreviated Wechsler Intelligence Scale for Children- Fifth Edition (WISC-IV; general intelligence)
- Wisconsin Cart Sorting Test (set maintenance/shifting; executive functioning)
- Finger Oscillation (fine-motor speed/persistence)

The following are repeatable measures that will be administered at baseline, 6 weeks (+/-3 days), and 12 weeks (+/-3 days):

- Conner's Continuous Performance Test (sustained attention, delay, response modulation)
- Stroop Color-Word Test- Children's Version (set maintenance/shifting; regulation of competing response tendencies)
- Letter & Animal Word Fluency, WISC-V Coding (processing speed/mental control)
- Woodcock-Johnson Understanding Directions (listening comprehension, following spoken instructions)
- WISC- V Digit Span (working memory)
- Wide Range Assessment of Memory and Learning-2: Verbal Learning and Design Memory subtests (short-term auditory-verbal memory and visual memory)
- Conners-3 Parent and Self-Report Forms (ratings of ADHD symptoms and related areas)*

- Child Behavior Checklist (parent ratings of more general behavioral and emotional problems)
- Children's Depression Inventory-2 (self-report of depression symptoms)
- Children's Manifest Anxiety Scale-2 (self-report of anxiety symptoms)
- Behavior Rating Inventory of Executive Function (BRIEF) - Parent Report Form (also Self-Report Form for cases 11 years and older)

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* Short-forms of the Conners-3 will be obtained during weekly visits with the project nurse

Note. The above will provide a broad-based assessment of cognition and behavioral/emotional status, as well as focusing especially on attention-related areas. It incorporates measures assessing the four components in Musky's model of attention: *focus-execute, sustain, encode,* and *shift.* [9]

Classification of TBI Pattern and Severity

Brain injury measures will be based on medical record information (including head CT findings, Glasgow Coma Scale ratings, etc.) obtained during the medical care immediately following TBI. Subsequent clinical findings, when available, will be taken into consideration as well as information having to do with post-injury mental status obtained in the screening visit with potential candidates.

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

Cases will also be distinguished based on whether there are indications of white matter injury evident on CT. Cases with/without CT indications of frontal lobe injury will be differentiated as well. These determinations, as well as the final severity ratings, will made with the input of a physician with a specialty in the diagnosis and management of TBI in children.

Data Analyses

The double blind, crossover design allows for the assessment of both within-subjects and between subjects contrasts. The primary analyses will consist of multiple paired-samples t-tests comparing LDX versus placebo on each of the neurobehavioral dependent measures in the study.

No formal correction for multiple comparisons will be applied so as to not limit sensitivity in detecting possible treatment effects. A p value equal to, or less than, 0.05 will be considered statistically significant. All tests will be two-tailed. All analyses will be performed using Statistical Programs for the Social Sciences (SPSS for Windows, Version 21.0, IBM Corp, 2012).

Possible order effects (depending on whether drug treatment comes before or after placebo) will be examined though a separate analysis of variance (ANOVA) for each dependent measure using a two-factor model (treatment, order, and treatment x order interaction).

There will also be 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, behavioral symptom profiles and personality features). We anticipate that the distribution of cases in terms of TBI severity will permit an analysis of comparative treatment outcomes for children with mild versus moderate versus severe brain injuries.

Also, safety data will be examined carefully based on weekly visits over the course of the trial. Comparisons will be made on LDX versus placebo for indices such as blood pressure and heart rate, side effects (insomnia, decreased appetite or weight loss, etc.) or significant adverse events, if any.

Safety Monitoring

Because this is a clinical trial of an FDA-approved medication with a favorable safety profile, there will be no independent data safety monitoring board (DSMB) or Safety Officer for this study. Patient safety will be monitored using best practice clinical care standards.

Safety Assessment: Patients will undergo weekly (+/-3 days) monitoring by the project nurse. Safety monitoring will include assessment of any self- or parent-reported adverse events (AEs), assessments of blood pressure, heart rate and weight, as well as psychiatric symptom assessment including suicidality.

Safety Endpoints: Safety endpoints will serve as withdrawal criteria if met or exceeded. They include:

Psychiatric

- New onset suicidality
- Mania
- Psychosis
- Other acute and serious reaction requiring immediate psychiatric intervention

Medical

- Hypertension (SBP and/or DBP greater than 95th percentile for child's age on two or more consecutive readings separated by at least 10 minutes)

- Tachycardia (symptomatic tachycardia or sustained heart rate greater than 150% of resting baseline heart rate on two or more consecutive readings separated by at least 10 minutes)
- Chest pain (judged by the study physician to be of likely cardiac origin)
- Other evidence suggestive of severe adverse effect of study drug
- Significant weight loss (> 10% compared to baseline level, and which persists despite downward titration
- Pregnancy
- Introduction of a medication by subject's medical provider if that medication is on the list of excluded medications

Parents will be provided with contact information and instructions of what to do if questions or concerns regarding possible problems or safety issues should arise. Adverse medical events will be brought to the attention of the project physician who will initiate appropriate follow-up action as needed. All adverse events will also be communicated immediately to the PI (see below), Withdrawn patients and their parents will be provided with an explanation for their withdrawal and will be referred to an appropriate care provider for clinical management as needed.

Safety Reports: All adverse events (AEs) will be communicated immediately to the PI for follow-up review. Severe adverse events (SAEs) will be reported to the PI, IRB and study sponsor according to IRB guidelines.

The following are types of events that require reporting to the IRB. If the event does not fit the categories, the event is not reportable to the IRB; however, it may be reportable to the sponsor.

a) Any event that requires prompt reporting to the sponsor, in accordance with the protocol (e.g., serious adverse events);
b) Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
c) Deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant;
d) Publication in the literature, safety monitoring report including a Data and Safety Monitoring Report, interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
e) Adverse event that is both a serious adverse event and an unexpected adverse event, which in the Investigator's opinion is more likely than not to be related to the research procedures;
f) Breech in confidentiality that may involve risk to that individual or others;
g) Complaint of a participant that indicates an unanticipated risk or which cannot be resolved by the research staff; or
h) Other event that is unanticipated, involved risk to participants or others and was possibly related to the research procedures.

Stopping Rules: Due to the pilot nature of this study, small sample size, favorable safety profile of the intervention, and crossover endpoint design, there will be no interim analyses or stopping rules for the study. Because similar preparations of amphetamine have been used clinically in

this population by the current investigators and other investigators, there is reasonably sufficient clinical experience to indicate that there will be no high proportion of SAEs or safety concerns.

Privacy/Confidentiality

Subjects will have code numbers and will not be identified by name. Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor, and their agents. This confidentiality extends to biological sample tests, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The results of the research study may be published, but subjects' names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the principal investigators will keep records in locked cabinets and on password-protected computers and results of tests will be coded to prevent association with subjects' names.

Timeline

- Startup – 3 months
- Trial implementation and data collection – 30 months
- Data analysis and reporting – 3 months

Total: 3 years

Key Project Personnel

(See Appendix 1)

Budget

(See Appendix 2)

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