Title: Buspirone for the Treatment of Traumatic Brain Injury (TBI) Irritability and Aggression

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POST-TBI IRRITABILITY & AGGRESSION: BUILDING EVIDENCE-BASED APPROACHES TO MANAGEMENT

Buspirone for the Treatment of Chronic Post-TBI Irritability and Aggression: A 91-Day Single-Site, Flexible-Dose, Parallel Group, Randomized, Placebo-Controlled Trial"

1.0 BACKGROUND

The proposed research fits into the site's long-term plan to address knowledge gaps about TBI irritability and aggression. In this section, we summarize the current state of knowledge as it relates to conducting our two proposed study arms and our pilot data relevant to these studies.

Irritability and Aggression in General: Post-TBI behavior changes range in severity from irritability to physical outbursts, and are related to family members' perceived burden and stress.[15,76] Aggressive behaviors have been reported to be highly disruptive socially and vocationally,[15,36,53] a major family burden,[15] and an interference to receiving appropriate care.[36,54,55] In severe cases, behaviors may be so disruptive that one cannot live at home.[77]

What is irritability? Irritability descriptions include: *a tendency to be easily upset[16] and poorly controlled brief, external displays of temper.[33,35,78]* As essentially everyone is irritable at one time or another, irritability is generally considered abnormal when it is either *a new trait* or it is *more pronounced* and *present to an abnormal extent*.[33] Although it may be present with such problems as depression and anxiety, Snaith[35] describes this as an independent mood as opposed to just symptoms of such states. **What is Aggression?** Definitions of aggression describe: *an agitated state and loss of control resulting in a hostile, injurious or destructive act.[79-81]*

Post-TBI irritability is generally thought to result from an interaction between biological (premorbid and injury effects) and environmental factors.[25-28,82] Research focusing on irritable and aggressive behaviors occurring after TBI has started to paint a picture of the problem, its triggers, and possible treatments. Injury severity has not been consistently correlated with irritability.[18,36,41] Studies have found correlations of irritability with demographic (e.g., young age, lower education), [83,84] psychosocial (e.g., loss of job, social isolation, return to work),[35,85] psychological (e.g., depression),[86] and neuroanatomic (e.g., orbitofrontal, anterior temporal lobe, and cortical damage) factors.[7,36,87] Hammond et al.[50] have also found irritability to be highly associated with levels of social support, quality of marriage, availability of transportation, problems with insomnia, and incidence of fatigue. Self-ratings of irritability have been found to be associated with specific behaviors, including impaired initiation, forgetfulness, and trouble following conversations, [21] as well as tiring easily, particularly around people. Kim et al[36] reported that irritability was related to patients' perception that family members were inadequate in coping with illness, fear of job loss, and inadequate spiritual beliefs. Irritability may result from frustration and inability to cope with memory impairment, difficulty shifting cognitive tasks, or noxious stimuli,[16,17,86] and can impair successful communications with others. Prigatano[22] has suggested that irritability may be viewed as a reactionary behavioral disturbance.

Aggression related to TBI has been reported to have high associations with young age;[57] history of aggressive behavior;[57] impairments in verbal memory,[56] visuo-perceptual skills,[56] and executive-attention;[56] presence of major depression; [53] frontal lobe dysfunction; [53] and history of alcohol and substance abuse.[53]

Individuals with TBI may experience irritability without aggression, aggression without irritability, or both irritability and aggression. For example, in a study of caregivers of individuals one to two years post moderate-to-severe TBI, Kilmer, et al[23] found 73% reported aggression while 69% reported irritability (as assessed by the Neuropsychiatric Inventory). In our recent single-site study that enrolled individuals with irritability, 89% also had aggression.

Animal and clinical research has provided insight regarding brain structures, and neurotransmitters that may be involved in pathologic aggression.[88-96] However, much work still needs to be done through pharmacologic, neuroimaging, and psychological studies to better understand the relationship of irritability and aggression in TBI, as well as the pathophysiology, contribution of environmental factors, and response to treatments.

Measurement of Irritability and Aggression: A growing scientific interest in the clinical management of irritability and aggression following TBI has fostered the adaptation of existing measures developed for neurobehavioral assessment of other populations and the creation of new measures designed specifically for the assessment of neurobehavioral deficits in TBI. The current literature on TBI-related behavioral dysfunction has employed a variety of irritability, anger, and aggression measures shown to have well-established psychometric properties and good test-retest reliability, specifically: Agitated Behavior Scale,[64,97-101] Buss-Perry Aggression Questionnaire (the full version of Buss-Durkee Hostility Inventory),[102] Neurobehaviorial Rating Scale-Revised,[59,64,103] and Neuropsychiatric Inventory (NPI),[23,43,50,104-106] Overt Aggression Scale (OAS),[60,107,108] OAS-

Modified for Neurorehabilitation,[61,109] OAS-Modified for Outpatients,[34,40,110] Overt Behavior Scale,[62] State Trait Anger Expression Inventory-2,[47,48,63,111-113] TBI-Quality of Life (TBI-QOL) Anger bank items,[114] and St Andrew's-Swansea Neurobehavioural Outcome Scale (SASNOS).[115] Some of the measures are designed to be rated by an observer, while others are self-rated scales. Unlike most of these scales which measure a range of aggression as opposed to specifically measuring irritability, the NPI has 2 distinct domains for irritability and aggression. The NPI also provides information on frequency, severity, and caregiver distress about the symptom, making it particularly useful in TBI research.

In our previous work (amantadine single-site study),[43] the NPI Irritability and Aggression domains have demonstrated responsiveness to the interventions studied. For the current proposal, we will be using similar design and measures (NPI domains) to those used in our prior studies in order to be able to compare results across studies. As in our prior works, the NPI (an observer measure) has been adapted to allow collection from persons with TBI (with the permission of the instrument authors) and to allow collection of comparable observer and participant data. In addition to the NPI, we will also use the more recently developed measures (TBI-QOL Anger and SASNOS) with a goal of adding rigor to the measurement of results.

Pharmacologic Treatments for TBI Irritability and Aggression: Pharmacologic interventions are commonly used in the management of TBI neurobehavioral sequelae, including irritability and aggression. Despite this commonly used strategy, studies are lacking to provide the clinician direction in the pharmacologic management of irritability and aggression, specifically occurring after TBI. With the exception of a few studies (amantadine and carbamazepine studies; see Pilot Work), no randomized, controlled, double-blind, parallel group designed clinical trials have been conducted on medication treatments for chronic post-TBI irritability. Only a few studies (e.g., case series, open-label) have specifically studied the effect of medication treatments for chronic post-TBI irritability and aggression. [34,40,43,44,49,64,66,116-122] Several classes of medications hold promise, including *buspirone*.

Arciniegas et al.[51] identified ***buspirone*** as a medication with potential benefit in TBI for affective **lability or irritability** and **agitation and aggression**. The Guidelines for the Pharmacologic Treatment of Neurobehavioral Sequelae of TBI [52] provided a thorough evidence-based review that indicated there was **insufficient evidence to support any Standards**.

The results of this review and the definition of these terms are summarized below:

	Definition	Medication Evidence
Standards	Based on at least 1, well-designed class I study with an adequate sample, or overwhelming class II evidence, providing good evidence to support a recommendation	None
Guidelines	Based on well-designed class II studies with adequate samples, providing fair evidence to support a recommendation	Beta-blockers
Options	Based on class II or III studies, with additional grounds to support a recommendation	Methylphenidate, serotonin reuptake inhibitors (SSRIs), valproate, lithium, tricyclic antidepressants, ***buspirone***

It is apparent from review of the literature that pharmacologic studies that can move our field to the level of Standards for the treatment of post-traumatic behavioral issues are greatly needed. It is imperative to have several different treatments with a broad range of side effects available to use individually or concurrently, thereby allowing the clinician to select from a "menu" of likely effective treatments to tailor the drug selection to the patient in order to optimize effect and minimize side effects. Thus, the systematic study of several different classes of medications for this important and common problem is needed.

Through current and past TBIMS projects led by our PI, we have succeeded in our first steps in studying post-TBI irritability through: (1) identifying amantadine as a treatment for irritability, (2) conducting a multi-site study of amantadine for irritability,(3) studying the effect of carbamazepine on TBI irritability and aggression, (4) learning about environmental factors associated with irritability, (5) learning from individuals with brain injury and family members about their personal experiences, and (6) assessing the measurement of irritability and aggression.

Pilot work (Hammond et al.):

The proposed studies are based on work recently completed by the applicant. Below we summarize some of the most relevant work from our group

Authors	Title	Conclusions
Definition & Measurement Studies		

Kilmer, Hammond et al. [23]	Use of NPI in TBI	• NPI is valid for use in TBI • Provides groundwork for the use of the NPI in TBI research and clinical monitoring
Kean, Malec, Hammond	Refining measurement of irritability and aggression in TBI	• NPI irritability and aggression items can be combined into a psychometrically sound scale • But may not adequately cover milder range • May need to be complemented with patient self-report
Hirsch & Hammond et al. [123]	Participatory Action Research: A conceptual model of irritability	• A conceptual model emerged in which irritability has four dimensions: affective/behavioral (especially in areas of self-regulation and impulse control); cognitive/perceptual (self-talk and ways of seeing the world); relational issues (interpersonal and family dynamics); and environmental (including environmental stimuli, time management, disruptions and routines, and cultural expectations). • In looking at *the impact of irritability* this analysis suggested that irritability primarily affects *the home – marriage, family, and domestic activities – and secondarily affects driving, working and participation in public activities*.
Hammond et al. [124]	Participatory Action Research: An in-depth look at the relational component of irritability	• Irritability associated with TBI is not just an individual but a family-system problem • Post-TBI treatment should include a comprehensive approach to improve family and other interpersonal interactions.
Hammond et al.[50]	Associations with irritability in TBI	• Identifies role of irritability in marriage quality and association with fatigue, social supports, and mood
Treatment Studies		
Hammond et al.[43]	Amantadine irritability & aggression single-site RCT	• Amantadine effective (as measured by NPI) and safe for reducing frequency and severity of post-TBI irritability and aggression
Hammond et al.	Carbamazepine irritability & aggression single-site RCT	• Study to be completed October 2012
Hammond et al.	Amantadine irritability multi-site RCT	• Study to be completed in summer of 2013

2.0 PROJECT RATIONALE AND SPECIFIC AIM

For the present project we have chosen to study a treatment for irritability and aggression (*buspirone*) and refine measurement of the *impact* of irritability and aggression (a separate study protocol). There are many other medications that may reduce irritability and aggression, and thus, this effort is only part of an ongoing, systematic approach to build an evidence-base to guide informed decision making. The investigators are committed to studying the effect of additional medications in the future, as well as continuing comprehensive, systematic study of post-TBI irritability and aggression. The current work fits additional pieces into a complex puzzle to address the treatment of these problematic behaviors. This body of work supports the priorities of the NIDRR Long-Range Plan [70] through the production of new scientific knowledge through research into pharmacologic interventions that can be used to improve options for achieving independence, social involvement, and function.

Specific Aim: Decrease irritability and aggression expressed by persons with TBI through the assessment of buspirone effectiveness for post-traumatic irritability and aggression and development of an irritability/aggression impact measure.

Target population: Persons with irritability and aggression following TBI and their families.

TREATMENT AND PLACEBO ARM:
"BUSPIRONE FOR THE TREATMENT OF CHRONIC POST-TBI IRRITABILITY & AGGRESSION: A 91-DAY SINGLE-SITE, FLEXIBLE-DOSE, PARALLEL GROUP, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL"

BuSpar® (buspirone) was introduced in the United States by Bristol-Myers Squibb in 1986 as a novel anxiolytic, receiving FDA approval for the treatment of Generalized Anxiety Disorder (GAD). Since the patent expired in 2001, BuSpar has been available in generic form. BUSP is an anxiolytic psychoactive drug of the azapirone chemical class that is unrelated pharmacologically to benzodiazepines, barbiturates, or other sedative and anxiolytic agents. Numerous studies in non-TBI populations have shown equivalent efficacy of BUSP and the benzodiazepines in treating GAD, and confirmed the preferential side effect profile of BUSP.

In using BUSP for the treatment of GAD, research suggests that it may also be helpful in reducing irritability and aggression. In fact, irritability has been identified as an early target symptom for positive response to BUSP for anxiety.[125] The literature suggests BUSP may be effective specifically for reducing aggression, agitation, and irritability associated with numerous psychiatric and neurologic disorders including case reports of effectiveness in TBI.[117-122,126-144]

The mechanism of BUSP effect on anxiety, mood and behavior is uncertain. BUSP is serotonergic with high affinity for serotonin 5-HT_{1A} receptors,[146] and also exerts dopaminergic (moderate affinity for D2-dopamine receptors) [146] and noradrenergic effects. [147,148] Serotonin, particularly the 5-HT_{1A} receptor, is implicated as a factor in animal and human models of aggression. Other agents that act on the 5-HT_{1A} receptors (such as high dose Beta 2-adrenergic blockers, lithium, and eltoprazine) appear to reduce aggression.[125] Despite its serotonergic effects, BUSP is not thought to have antidepressant properties, and is not approved by the US Food and Drug Administration for the treatment of depression. BUSP has no affinity for benzodiazepine receptors and does not affect GABA binding.

BUSP, well-known for its low side effects and drug interactions, has great potential for long-term use after TBI. BUSP is less sedating than other anxiolytics and does not produce significant functional cognitive or motor impairment. *With its favorable side effect profile, BUSP may carry advantages over many of the other agents commonly used to manage unwanted behaviors due to TBI, such as benzodiazepines,[149] antipsychotic agents, [150,151] anticonvulsants, [152] and serotonergic reuptake inhibitor (SSRI) antidepressants.[153-155]*

With the interpersonal disruption caused by irritability and aggression, it is critical to test potential treatments and generate knowledge about the positive and negative effects of these treatments. Which agents may be used in each individual differs based on numerous factors including medication effectiveness, side effect profiles, drug-drug interactions, and medical co-morbidities. Additionally, many individuals require multiple treatment approaches and often require multiple medications for optimal behavior control. Thus, there is need to rigorously study all potentially effective treatments to provide the basic knowledge upon which patients and physicians can determine the best approach for each individual. The literature suggests that medications may help reduce TBI irritability and/or aggression.[51,52] However, the evidence is sparse with few well-designed RCTs (Level I) (see **Pilot Data**).

Literature Review of BUSP in Non-TBI behavior:[126-145] Peer-reviewed studies of BUSP for mood and behavior in **non-TBI** populations used variable doses, generally increasing the dose every 2 to 4 days up to a maximum daily dose of 90mg. Effective treatment doses have ranged from 15-90 mg daily.

Literature Review of BUSP in TBI-related behavior: Level III evidence (case studies and retrospective case series) suggests that BUSP may improve a variety of adverse behaviors among individuals with TBI, including irritability, aggression, acute agitation, anxiety, and depression [117-122] as outlined below. Level I RCT evidence is needed is to guide clinical decisions.

Summary of Literature on BUSP for TBI Mood, Anxiety, and Behavioral Dyscontrol:

Author	LOE	N	Time Post-injury	Dose & Design	Measures	Results
Gualtierri CT 1991 [117]	III	14	Not stated	Retrospective summary of 14 cases (not clear if systematic review of all cases treated or based on recall) Dose: titrated to 45 mg/day	Clinical observation	Severe TBI: No improvement Mild TBI: 4 of 7 with extremely favorable response in anxiety, depression, irritability, somatic preoccupation, inattention, distractibility, intention tremor, & akathisia Well tolerated Max dose: 45 mg/day
Holzer JC 1998 [118]	III	1	Late (8 years)	60 mg / day over 4 months	Clinical observation	Ameliorated behaviors of spontaneous yelling, cursing, and assaultive behavior, and became able to participate in therapies and interact with others Well tolerated Max dose: 60 mg/day
Levine AM 1988 [119]	III	1	Acute	Started at 5 mg tid, advanced 2 days later to 10 mg tid (30 mg/day). Agitation resolved, but returned when dose decreased; resolved again when increased back up to 30 mg/day	Clinical observation	Agitation resolved Well tolerated Max dose: 30 mg/day
Mandoki 1994 [120]	III	1	Late	Started at 2.5 mg tid, advanced after 1 week to 5 mg tid (15 mg/day). Improved behaviors. After 1 month, increased to 30 mg/day, then 40 mg/day & eventually 50 mg/day.	Clinical observation	6 year old child who failed trials with most other medications due to failure of response or severe side effects Improved impulsivity, anxiety, nail biting, mouthing objects, focus, and hyperactivity No adverse side effects Max dose: 50 mg/day
Ratey JJ 1992[121]	III	2	Late	2 case studies Case 1 Dose: 5 mg bid Case 2 Dose: started at 5 mg bid, after 7 days increased to 5 mg tid reported response at 4 weeks	Clinical observation	Case 1: decreased hypersexuality, irritability, & aggression after 4 days, Case 2:Improved demeanor decreased frequency and intensity of aggressive outbursts, increased initiation after 4 weeks Well tolerated Max dose: 15 mg/day
Stanislav SW 1994 [122]	III	10	Late	Retrospective review Individuals in a psychiatric institution with verbal and physical aggression due to TBI and other causes 10–30 mg/day	Monthly behavioral therapy records	9 of 10 (90%) had improved behavior and aggression on BUSP; 6 (60%) had a 50% reduction in aggressive behaviors Well-tolerated Max Dose: 30 mg/day

Case reports suggest BUSP may reduce chronic TBI behavior problems. To date, there are no published studies of the use of BUSP specifically for post-TBI irritability or aggression that employ rigorous methodology. With our

large population base, behavior management expertise, and clinical trial experience, we are uniquely positioned to study BUSP in a randomized, double-blind, placebo-controlled manner specifically for irritability and aggression occurring in chronic TBI. As the first randomized, controlled trial of BUSP for irritability and aggression in chronic TBI, this study will be conducted as a single-site adequately powered study. In summary, support for BUSP as a post-TBI irritability and aggression treatment includes:

- Low side effect profile
- Availability of generic formulation creating wide availability at low cost
- Non-TBI population studies noted effectiveness of BUSP on aggression and irritability
- Case reports of BUSP efficacy for agitation and aggression in acute and chronic TBI

The present study will provide knowledge about the effect of BUSP on TBI irritability and aggression. Building on our success with three other RCTs for TBI irritability (single site carbamazepine, and single-site and multi-site amantadine studies), we are well positioned to move the field forward through continued systematic work in this area.

Summary of Drug-Specific Information

- **Pharmacokinetics and pharmacodynamics:** BUSP action may occur through the dopaminergic system or serotonin (5-hydroxytryptamine) receptor binding. It is rapidly absorbed with extensive first-pass metabolism. It is metabolized by the liver through oxidation via cytochrome P450 3A4 pathway, and excreted by the kidneys. Peak plasma concentration is reached in 40 to 90 minutes after single dose oral administration, with 2-3 hour half-life. 86% binds to plasma proteins. Within 24 hours, 29-63% is excreted in the urine and 18%-38% fecally.[146]
- **Side effects, cautions, drug interactions, monitoring, dosing:** Agents that may hasten or slow BUSP metabolism include: erythromycin, itraconazole, nefazodone, cimetidine, rifampin, and grapefruit juice. BUSP should not be co-administrated with monoamine oxidase inhibitors. Commonly observed untoward events include nausea (8% BUSP vs. 1% placebo), dizziness (3% vs. <1%), and nervousness (1% vs. <1%).[146]

2.1 RATIONALE AND SPECIFIC AIMS

There are many other medications that may reduce irritability and aggression, and thus, this effort is only part of an ongoing, systematic approach to build an evidence-base to guide informed decision making. The investigators are committed to studying the effect of additional medications in the future, as well as continuing comprehensive, systematic study of post-TBI irritability and aggression. The current work fits additional pieces into a complex puzzle to address the treatment of these problematic behaviors. This body of work supports the priorities of the NIDRR Long-Range Plan [70] through the production of new scientific knowledge through research into pharmacologic interventions that can be used to improve options for achieving independence, social involvement, and function.

Primary Aim: Assess treatment effects of buspirone (BUSP) on TBI irritability/aggression

Primary Hypothesis (Hypothesis 1a): Among individuals with TBI of >6 months duration and moderate-to-severe irritability, BUSP (15 mg daily dose with titration up to 60 mg daily as needed for irritability control) compared to placebo will result in a statistically significant ***greater proportion of responders*** as defined by a ***decrease of at least 3 points*** on the observer-rated Neuropsychiatric Inventory (NPI) Irritability domain scores from baseline to Day 91.
Hypothesis 1b: Among individuals with TBI of >6 months duration, BUSP (15 mg daily dose with titration up to 60 mg daily) will result in ***statistically significant improvement*** on scores of one or more of the following measures compared to placebo:
a) Observer and participant ratings of NPI and NPI-Distress *Irritability* domain scores,
b) Observer and participant ratings of NPI and NPI-Distress *Aggression* domain scores,
c) Participant ratings of TBI-QOL Anger bank,
d) Observer ratings of SASNOS Aggression, subscale,
e) Observer and participant ratings of Global Impression of Change,
f) Physician ratings of Clinical Global Impressions.

Secondary Aim: Assess the adverse events of BUSP in treating TBI irritability/aggression.
Hypothesis 2: BUSP will be well-tolerated as measured by number and types of the adverse events in the treatment group compared to the placebo group.

3.1 INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA
Closed head injury (impaired brain function resulting from externally inflicted trauma without penetrating injury as defined below) at least 6 months prior to enrollment Non-penetrating and meets Mayo Classification [156] of mild or moderate-severe brain injury with evidence from the medical record, clinician report, or detailed history provided by the participant or family. *(Note: Intoxication, sedation, intubation, or use of paralytics must be ruled out as causes of impaired consciousness)* **Moderate to Severe (one of more of the following)** Loss of consciousness of > 30 minutes Post-traumatic anterograde amnesia of ≥ 24 hours Worst Glasgow Coma Scale full score in first 24 hours < 13 (unless invalidated upon review, e.g., attributable to intoxication, sedation, systemic shock) Intracerebral hematoma, epidural hematoma, cerebral contusion, hemorrhagic contusion, subarachnoid hemorrhage, or brain stem injury **MILD (one of more of the following)** Loss of consciousness of momentary to < 30 minutes Post-traumatic anterograde amnesia of momentary to < 24 hours Depressed, basilar or linear skull fracture (dura intact)
Irritability that is either new or worse than level of irritability before the traumatic brain injury, by report of observer or person with TBI
Age at time of enrollment: 18 to 70 years
Voluntary informed consent of patient or guardian or legally-authorized representative and observer
Subject and observer willing to comply with the protocol
Observer-rated NPI Irritability Domain score 6 or greater to include only moderate-severe irritability
Medically and neurologically stable during the month prior to enrollment
If taking antidepressant, anxiolytic, hypnotic, or stimulant medications, no change anticipated in these medications during the month prior to enrollment
No change in therapies or medications planned during the 91-day participation
No surgeries planned during the 91-day participation
Vision, hearing, speech, motor function, and comprehension sufficient for compliance with all testing procedures and assessments
Observer (e.g.: family member, close friend, employer) with whom subject interacts sufficiently to observe occurrences of irritability. The observer interacts with the participant for a period long enough and of a nature to be able to judge the participant's irritability. The interactions would need to be adequate to judge observer distress over the irritability, severity of irritability and frequency of irritability on the following scale: < once weekly; once per week; several times per week, but not every day; essentially continuous.
EXCLUSION CRITERIA
Potential subject without a reliable observer
Penetrating head injury as defined by head injury due to gunshot, projectile or foreign object
Injury < 6 months prior to enrollment
Ingestion of buspirone during the month prior to enrollment
Inability to interact sufficiently for communication with caregiver
History of schizophrenia or psychosis
Diagnosis of progressive or additional neurologic disease
Clinical signs of active infection
Uncontrolled seizure disorder
Renal failure or creatinine clearance <55 mL/min (calculated using serum creatinine)
AST and ALT laboratory tests > 2x normal values

Meets criteria for alcohol or drug dependence within the preceding 3 months
Pregnancy (Beta-HCG + females of child-bearing potential); lactating females; sexually active females who do not agree to use birth control
Active concern of potential harm to self or others
Diagnosis of progressive or additional neurologic disease that affects brain function, except stroke that occurs at the same time as the TBI
Concurrent use of the following medicines at the time of enrollment due to potential for drug interaction: erythromycin, itrconazole, nefazodone, cimetidine, rifampin
Concurrent use of Monoamine Oxidase Inhibitors (MAOIs) or ingestion of MOAI within 4 weeks before starting study. Examples of MAOIs include: isocarboxazid (Marplan), phenelzine (Nardil), selegiline (Eldepryl), tranylcypromine (Parnate), and linezolid (Zyvox).
Concurrent use of benzodiazepine agents or ingestion of within 4 weeks before starting study. Examples include: alprazolam (Xanax), chlordiazepoxide (Librium), cinolazepam, clonazepam (Klonopin), clorazepate (Tranzene), diazepam (Valium), estazolam (ProSom), flurazepam (Dalmane), lorazepam (Ativan), medazepam, midazolam (Versed), temazepam (Restoril), triazolam (Halcion).
Concurrent use of high-dose serotonergic medicine (higher than 60 mg fluoxetine or equivalent)
Concurrent use of antidepressant Viibryd (vilazodone) (a selective serotonin reuptake inhibitor and and also a 5HT1A receptor partial agonist
Concurrent intake of grapefruit juice during study participation
Hypersensitivity/allergy to buspirone
Prior failed response (at least 4 weeks at minimum 30 mg/d) to buspirone
BRAIN Consumer Advisory Council member within early protocol development

4.1 ENROLLMENT/RANDOMIZATION

Target population: Persons living with TBI and irritability.
Sampling: Consecutive community and self-referrals to IU PM&R research office.
Recruitment: Recruitment will come from community and self-referrals from sources that include local brain injury clinics, psychologists, therapists, local healthcare providers, support groups, BIA-IN, physician letters to patients, flyers posted in clinics, handouts for clinic nurses and physicians, newsletters, hospital, medical school, and Indiana CTSI web sites, Craigslist.org, Researchmatch.org, Rehabilitation Hospital of Indiana's Facebook page, local and regional presentations. Recruitment may occur at the following sites: RHI and IUH hospitals and clinics, community agencies, and support groups. Clinicians will introduce the study to their patients whom they feel may be appropriate and provide them with the information needed to contact the research staff to learn more about the study. At the time of contact, the research staff will provide further information about the study. Interested potential participants will be scheduled for an in-person screening visit.
Informed consent: Potential participants or his or her guardian or legally-authorized representative will be consented in the usual and accepted manner. If the individual agrees to participate, the RA will obtain written informed consent prior to enrollment, treatment. The PI or co-investigator will also go over the study at the time of the baseline examination and ask if they have any concerns or questions. Inclusion and exclusion criteria will be confirmed and documented.
Screening for Eligibility: Medical record screening via a waiver of authorization for recruitment will be done prior to the participant signing the informed consent in order to view potential participants and determine eligibility. Injury information, communication status, medications and medical history will be obtained and reviewed for exclusion parameters. Laboratory assessments will be conducted to confirm qualification for the study. Potential participants will be invited to participate in this study if they have met the eligibility criteria. Basic demographic data will be collected about those who do not meet the inclusion criteria, and those who meet the criteria, but do not consent. A comparison will be conducted between participant and non-participant groups to determine if the groups differ.
Stratification: Randomization will be stratified on the presence of major or minor depression (defined by PHQ-9 total score $\geq$5) to ensure equal distribution of depression in the BUSP and placebo groups. This is important since depression is common after TBI, irritability is a primary symptom of depression, and BUSP has potential effect on depression. The study is not designed or powered to examine the effect of BUSP on depression. Participants will

have a 1:1 chance of receiving placebo or active treatment regardless of depression status. Our statistician will create a guide that assists the study pharmacist in the process of carrying out the stratified randomization.
Randomization: After successful screening, enrollment, and stratification, each participant will be assigned a study identification number that determines the double-blind treatment group according to the chronological order of entry into the study. Random assignment to either BUSP or placebo will be based on a computer-generated, block, randomization schedule produced by the statistician and maintained by the study pharmacist. Randomization will be blocked to force balance between the 2 groups (important if the study were stopped). The investigators and study staff will be blinded to the size of the blocks. Upon meeting all eligibility criteria, the RA will fax a completed randomization sheet to the study pharmacist that indicates the information needed for dispensing and stratification (study number, and total PHQ-9 score). The study pharmacist then looks at the randomization schedule and prepares the study medication to be dispensed. The study pharmacist will record the group assignment in the dispensing log.
Compensation: To help offset time and travel costs, participants and their observer will both receive $50 for the initial formal screening and $50 for the subsequent visits. Compensation will be provided in the form of check or gas gift card.

5.1 STUDY PROCEDURES

We propose an extended 91-day, outpatient, prospective, single-center, randomized (1:1 ratio and stratified by presence of depression), double-blind, placebo-controlled, adequately powered trial of the effects of BUSP for irritability (defined primarily by observer-rated NPI Irritability domain score) in individuals with TBI of > 6 months duration. Dosing will start at 15 mg daily and will be titrated up as needed to 60 mg daily in divided doses. On Day 8 the dose will automatically increase to 30 mg daily. Dose will be further adjusted upwards at Visits 2 and 3 if observer-rated NPI-Irritability domain score has not decreased by 80% of the baseline score (if decreased by 80% the current dose will be maintained). Four outcome assessment sessions will be conducted: Day 0 (Screening/ Baseline), Days 35 and 63 (interim evaluations), and Day 91 (final outcome). After completion of the final visit, the participants will be tapered off BUSP and offered a 1-month supply of BUSP (30 -45 mg/day) to allow them to determine if they would like to ask their physician to continue to prescribe it.
Treatment and Testing Timeline

	Randomized Controlled, Double-Blind Trial Days 1 -91				**Days 92-100**	**Days 101-131**
Visit 1: Baseline testing	**Visit 2 (Day 35)**: Interim testing & possible dose increase	**Visit 3 (Day 63)**: Interim testing & possible dose increase	**Visit 4 (Day 91):** Final testing		Taper off	Open Label

Double-Blind Study Drug Administration and Dosing Timeline

	Days 1-7 (starting dose)	**Days 8-35**	**Days 36-63**	**Days 64-91**	**Days 92-100 (taper)**	**Days 101-131 (open-label)**
Treatment Group N = 37	One 5mg BUSP pill three times daily (tid) **(15 mg/day)**	Two 5mg BUSP pill tid **(30 mg/day)**	Three 5mg BUSP pill tid **(45 mg/day)**	Four 5mg BUSP pill tid **(60 mg/day)**	Decrease dose every 3 days by 15 mg	BUSP 5 mg tid. After 1 week, two 5 mg tid
Placebo Group N = 37	1 placebo pill three times daily	2 placebo pills three times daily	3 placebo pills three times daily	4 placebo pills three times daily	Decrease dose every 3 days	BUSP 5 mg tid. After 1 week, two 5 mg tid

Dosing schedule assumes less than 80% improvement in NPI-Irritability domain score from baseline to listed assessment time point. If at least 80% improvement, the dose would not be increased at that visit.

Outcome Variables:

Primary Efficacy Measure
NPI Irritability domain rated by observer. NOTE: The primary analysis looks at the proportion that decrease ≥3 points to assess clinical significance in addition to statistical significance. This cut point of clinically meaningful change is based on clinical experience and

consumer input, and was utilized in our previous studies. A secondary analysis compares changes in NPI-Irritability using an ordinal scale.
Secondary Efficacy Measures
NPI- Irritability domain rated by observer and participant
NPI-Distress Irritability domain rated by observer and participant
NPI & NPI-Distress Agitation/Aggression Domain rated by observer and participant
TBI-QOL Anger item bank rated by participant
SASNOS rated by observer
Global Impression of Change rated by observer and participant
Clinical Global Impressions rated by clinician
Working Alliance Inventory – Short Revised rated by participant and Co-Investigator.

Demographic and Pre-treatment Characteristics: Age, gender, marital status, ethnicity, educational level, time since injury, history of psychiatric disorder, previous TBI, cause of injury, CT scan findings, initial Glasgow Coma Scale score in ED, duration of post-traumatic amnesia (PTA), duration of loss of consciousness, socioeconomic status, employment status, substance use during the month prior to enrollment, relationship of observer to subject, medical history, overall function, severity of irritability, and presence of depression, anxiety or post-traumatic stress disorder (PTSD).

Efficacy Measures:

- **Neuropsychiatric Inventory (NPI & NPI-Distress):** The NPI[104] is a 40-item tool developed to assess behavioral abnormalities in individuals with dementia. Since its development, the NPI has been used in TBI populations to assess neurobehavioral dysfunction.[23,43,50] It is a fully structured observer interview that specifies verbatim the questions to be asked. The observer indicates if a specific behavior has been present during the past month or specified time period and if this represents a change from premorbid functioning. The most problematic behavior detected by the sub-questions is then used to grade the frequency and severity: behavior severity (1 = mild, 2 = moderate, 3 = severe) and frequency (1 = occasionally, less than once per week; 2 = often, about once per week; 3 = frequently, several times per week, but less than every day; 4 = very frequently, once or more per day or continuously) and the product (severity x frequency) is calculated (range 0-12). The NPI also assesses the caregiver's distress over the behaviors on a 6-point scale: 0 (no distress), 1 (minimal), 2 (mild), 3 (moderate), 4 (moderately severe), and 5 (very severe or extreme).

  For the present study, we will use the NPI Irritability and Aggression domains as outcome measures. The Irritability domain includes: bad temper, rapid mood changes, sudden anger, impatience, crankiness, argumentativeness. The Aggression domain includes: getting upset, resisting activities, stubborn, uncooperative, hard to handle, shouts, curses angrily, slams doors, kicks furniture, throws things, hurts or hits others.

  The NPI has established content and concurrent validity, as well as inter-rater (approximately 95% for both frequency and severity), test-retest (0.79 for frequency and 0.86 for severity), and internal consistency reliability (Cronbach's alpha of 0.88 for both).[104] The NPI-Distress has established content and concurrent validity, and inter-rater (0.96), test-retest (0.92), and internal consistency reliability.[105]

  Few scales exist to specifically assess irritability in neurologic disorders. Other available measures ask only about the presence or frequency of irritability. Only the NPI assesses the distress caused by the irritability. This multifaceted assessment of the problem makes the NPI ideal for the study of irritability in TBI, and specifically in this medication trial.

  The NPI has been used in several studies of persons with TBI, thus supporting the validity of the measure in this population.[24,43,50] The NPI Irritability and Agitation/Aggression domains were used in our single-site amantadine trial for post-traumatic irritability detecting differences between the treatment and placebo groups[43], as well as 2 ongoing trials. With permission of the instrument's author, we have created a participant version of the NPI. In the present study, we will again assess the frequency, severity, and distress over irritable and aggressive symptoms by both the observers (about the behavior of the individual with TBI) and the individuals with TBI (about themselves) using the same irritability and aggression domains of the NPI. The NPI takes approximately 5 minutes to administer.
- **TBI-Quality of Life (TBI-QOL) Anger:** TBI-QOL is composed of item banks and scales that reflect different health-related quality of life dimensions in TBI, [114] and is among the measures recommended by the Common Data Elements Workgroup.[157] The TBI-QOL Anger item bank includes hierarchically ordered items designed to measure the full continuum of anger in a way which is both sensitive and appropriate for TBI. The TBI-QOL Anger item bank is calibrated on the same log-linear scale with a similar bank in the Patient Reported Outcome Measurement Information System (PROMIS), allowing direct comparison between anger in TBI and anger in the general

population. The TBI-QOL Anger item bank can be administered as a computer-adaptive test, allowing precise measurement of self-reported anger using only 4-8 adaptively selected items. We include a letter from Dr. Tulsky supporting our use of TBI-QOL.

- **St Andrew's-Swansea Neurobehavioural Outcome Scale (SASNOS):** [115] SASNOS is a newly developed informant-rated measure designed specifically to assess neurobehavioral dysfunction in acquired brain injury as rated by an observer. SASNOS has a 5-factor conceptual framework based on the World Health Organization International Classification of Function (WHO ICF) that allows the measurement of a diverse range of NBD signs and symptoms in the following domains: interpersonal relationships, cognition, aggression, inhibition and communication. Initial validation suggests that the 49-item SASNOS is reliable and valid. The proposed study will utilize the aggression subscale, which includes 15 items and three subfactors: overt aggression (3 items), irritability (6 items), and provocative behavior (6 items). The aggression subscale demonstrates excellent test-retest reliability (ICC=.92) and internal consistency (alpha=.92), good inter-rater reliability (ICC=.80), and a strong statistical relationship with known measures, supporting its content, convergent, and divergent validity.
- **Global Impression of Change (GIC):** A Likert Scale rating impression of change (much improved, slightly improved, no change, slightly worse, or much worse) will be used for both participants and observers to rate their impression of change in the person with TBI.
- **Clinical Global Impressions (CGI):** The clinician's impression of change will be determined using the CGI. The CGI [158] is a highly sensitive,[159] standardized assessment tool used widely to assess psychopharmacology treatment response. The CGI is comprised of 3 subscales: Severity of Illness (SI), Global Improvement (GI), and Efficacy Index (EI). SI and GI are both rated on 7-point scales. The EI is rated on a 4-point scale that takes into account both beneficial effects and side effects. The CGI is rated by a clinician/investigator. The SI subscale is administered at initial assessment and then all three subscales are administered at follow-up assessments. To be considered effective, a treatment should lower the overall score in subsequent testing by at least 50%.[160] The CGI takes approximately 2 minutes for the clinician to score.

<u>Experimental Measure</u> (this measure to be developed after study completion, and thus, will be delayed in time from final analysis)

- **Aggression and Irritability Impact Measure (AIIM):** The AIIM is an experimental measure that will be developed and evaluated through the companion measurement study. It will consist of items assessing the degree to which irritability or aggression interferes with community participation activities. Specific community participation activities will be represented by items of the Participation Assessment with Recombined Tools-Objective (PART-O).[161] Additional items may be added after focus group review and cognitive interviewing that will take place prior to launching the study. The AIIM will be designed to assess specifically the degree to which irritability and aggression interfere with participation in contrast to the PART-O which assesses the extent of community participation in general. The beta version of the AIIM will be included in this Buspirone treatment study. It will be administered at the Baseline and Final visits as it is thought that the longer period is needed to allow time for changed impact. After refining it through psychometric studies, the final version of the AIIM will be extracted from the Beta version and analyzed as a dependent measure in the treatment arm to assess its responsiveness to the hypothesized treatment effect. The AIIM is included in the treatment arm only to assess its responsivity and not as an endpoint.
- **Working Alliance Inventory-Short Revised (WAI-SR):** The WAI-SR is a 12 item questionnaire with forms for completion by the person receiving treatment as well as by the provider. This measure of working or therapeutic alliance has been shown to predict the outcome of psychotherapeutic as well as rehabilitation interventions.[219] The WAI-SR is based on a factor analysis of the full WAI and has demonstrated reliability and validity.[220] The WAI-SR will be completed during the post-treatment assessment session at the end of the buspirone trial by the participant and by the research assistant who worked with the participant in the trial. Each of these individuals will complete the inventory independently without knowledge of each other's' responses. Data obtained from the WAI-SR will be evaluated as a covariate in analyses of outcome variables to assess for effects of buspirone relative to placebo.

<u>Stratification Measure</u>

- **Personal Health Questionnaire -- 9 (PHQ-9):** The PHQ-9[162] is a self-report questionnaire designed to assess depression through nine questions that come directly from the DSM-IV signs and symptoms of major depression (loss of interest, feeling down, sleep, fatigue, poor appetite, feeling bad about oneself, difficulty concentrating, moving slower, and thoughts of suicide). A total score is calculated to determine depression severity. Depression severity is broken down into the following categories: Severe (20-27); moderately severe (15-19); moderate (10-14); mild; (5-9) and none (0-4). The PHQ has good validity and reliability, and is sensitive to the presence of

depression.[162] A study by Fann et al.[163] found that the PHQ-9 was 93% sensitive and 89% specific for Major Depressive Disorder (MDD) in TBI. The PHQ-9, administered to the individual with TBI at each visit, is being used to capture the co-morbid presence of clinical depression which will be used for stratification of randomization and description of the sample, and to note change in depression with treatment. If a substantial number of participants have depression, a preliminary subanalysis of the effect of BUSP on PHQ-9 will be performed.

Descriptive Measures

- **Generalized Anxiety Disorder Assessment (GAD-7):** The GAD-7[164] is a self-report questionnaire used to screen and assess severity of generalized anxiety disorder. The interviewee is asked to rate the frequency of seven symptoms that link to the DSM-IV criteria for GAD. The GAD-7 will be administered at each visit to the person with TBI to detect co-morbid presence of anxiety disorder for description of the sample, and to note change in anxiety with treatment if baseline anxiety is associated with response to study drug. If a substantial number of participants have anxiety, a preliminary subanalysis of the effect of BUSP on GAD-7 will be performed.
- **PTSD Checklist Civilian (PCL-C):** The PCL[165] is a 17-item self-report measure linked to the DSM-IV symptoms of PTSD which is used for PTSD screening, diagnosing, and monitoring symptoms. Diagnosis can be made by determining whether an individual meets DSM-IV symptom criteria, i.e., at least 1 B item (questions 1-5), 3 C items (questions 6-12), and at least 2 D items (questions 13-17). There are three versions of the PCL: The PCL-M (military), the PCL-C (civilian; asks about PTSD symptoms in relation to any stressful events), and PCL-S (specific; asks about PTSD symptoms related to a specific event). With the PCL-C, the symptoms endorsed may not be specific to just one event, which is helpful when assessing survivors who have symptoms due to multiple events. PTSD will be assessed in this study to describe the sample. Thus, PCL-C, as opposed to the PCL-S, is utilized in the present study to detect co-morbid PTSD presence regardless of the inciting event and will be administered to the individual with TBI at the baseline visit for the purpose of characterizing the sample regarding the presence of PTSD. Administration takes 5-10 minutes.
- **Glasgow Outcome Scale Extended (GOS-E):** The GOS-E,[166] an extension of the Glasgow Outcome Scale (GOS), is a measure of overall disability following TBI. The total score from a structured interview provides an overall patient rating, classifying the patient into one of the following eight categories: Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability, Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, and Upper Good Recovery. The GOS-E has been shown to have good inter-rater reliability and content validity and to be more sensitive to change in mild to moderate TBI than the GOS. [166,167] The GOS-E will be used to describe baseline overall function and administered only at Visit 1.

Dosing Adjustments: For all participants, treatment will start at a total daily dose of 15mg BUSP or equivalent placebo, and increased automatically one week later to 30mg total daily dose or equivalent placebo tablets. If observer-rated NPI-Irritability score has decreased by at least 80% of the baseline score at either Visit 2 and 3 assessments then the dose will stay at the present dose. At the Day 91, visit the participant will be provided 9 days of tapering Study Drug and a 30-day supply of open-label BUSP. On Day 92, the participant will begin tapering off the study drug by decreasing to the next lowest dose every 3 days. On Day 101, they may start open label use. Further specifics regarding dose adjustments will be outlined in the Manual of Procedures. This dosing schedule is also depicted below:

Dose Adjustment Schedule

***Visit X* = Day on Study Drug**	**<80% improved observer NPI from baseline to *visit X***	**≥80% improved observer NPI from baseline to *visit X***
Day 1	15 mg daily or placebo equivalent	15 mg daily or placebo equivalent
Day 8	30 mg daily or placebo equivalent	30 mg daily or placebo equivalent
Day 36	45 mg daily or placebo equivalent	30 mg daily or placebo equivalent
Day 63	45 mg daily (or placebo equivalent) if ≥80% improved from baseline to visit 2 60 mg daily (or placebo equivalent) if ≤80% improved from baseline to visit 2	30 mg daily (or placebo equivalent) if ≥80% improved from baseline to visit 2 45mg daily (or placebo equivalent) if ≤80% improved from baseline to visit 2
Day 92	Begin taper	Begin taper
Day 101	15 mg daily	15 mg daily
Day 108	30 mg daily	30 mg daily

The above dosing schedule assumes that no changes in dose were made due to side effects or toxicity. BUSP has very few side effects and usually side effects will diminish within 3-4 days. Participants will be advised to notify the research staff if adverse changes are noted. When intolerable adverse events (AEs) occur, participants will be

instructed to reduce the dose to the next lowest tolerable dose or the study drug will be discontinued (depending on symptom severity). If intolerable symptoms have not subsided within 4 days or clinically appropriate time frame, the drug will be discontinued or titrated down further, whichever is most appropriate in the investigator's judgment. In the extremely unlikely event that the subject experiences signs or symptoms of life-threatening side effects, the study treatment will be withdrawn. The participant will be reassessed at the next visit or called for possible dose increase if symptoms have resolved or no longer appear to be related to study drug. Regardless of dose, testing will proceed according to the delineated schedule through to Day 91.

If the dose had been adjusted downward due to AE then at the scheduled Study Visit the dose would either stay the same as currently tolerated or advanced to the next dosing increment depending on the participant's clinical picture and time of the prior change in dose. If a participant is still having trouble adjusting to the last dose escalation, we will wait an additional week before trying to escalate to the next dose.

Blinding Procedure: The placebo pills will be identical in appearance, smell, and taste. Participants, family members, treating staff, physicians, RA/data collector and investigators will be blinded to group assignment until after the final study analyses. The dispensing pharmacist will be the only person unblinded.

Drug Identification in Emergency: The blind will not be broken until the end of the study unless medical treatment decisions depend on knowing the group assignment. Procedures for unblinding are outlined in the Manual of Procedures. An unblinding form prompts the clinician to think through all of the reasons for unblinding to ensure that unblinding is indeed necessary.

Formulation, Packaging, & Labeling: Generic buspirone hydrochloride will be used for the study. The placebo and active tablets will be identical in appearance and packaging and contain the same inactive ingredients. Pills will be dispensed in a pill bottle labeled appropriately with administration instructions, subject number, and emergency contact. To enhance compliance, the participants will be offered a pill dispenser box to help them lay out their medications for each week. We have found that such strategies are important for clinical trials involving individuals with TBI and cognitive impairment. Participants will be provided an additional 10 days of study drug to allow continued medication in unusual cases of not being able to come in during the treatment window. Participants will be asked to return any unused medication at each Study Visit. A 9-day supply of compound will be provided upon Day 91 for the purpose of weaning subjects from study medication on days 92-100. A 30-day supply of open-label BUSP will also be provided on day 91. Participants will be instructed that after taking all of the study drug taper supply, they may start the open label portion.

Storage: Designated research personnel are responsible for dispensing and accounting for all study compounds and exercising accepted medical and pharmaceutical practices. Records will be kept on inventory and dispensing record forms. Study compounds will be stored in a locked cabinet and used only as directed in this protocol.

Data Collection: Data are obtained primarily through participant and observer interviews and review of available medical records. The same interview sequence will be used each time.

Data Management: All data will be recorded on the case report form (CRF). The CRF and source data (labs, vitals, exams, adverse events) from each study visit will be reviewed by a study investigator for clinical significance and signed off. An online database using REDCap (**R**esearch **E**lectronic **D**ata **Cap**ture) will be developed and maintained by our Database Manager. Using a unique password, staff will run weekly data checks to allow for prompt data quality management, and generate monthly data completeness reports for discussion at monthly meetings of the investigators and RA with more frequent communication as needed.

Laboratory monitoring: Serum creatinine for Kidney Function, AST and ALT laboratory Tests, and pregnancy test (if female) will be obtained at the screening to assess eligibility. Further monitoring is not needed for BUSP.

Study Sequence:

Visit 1: Screening and Baseline Testing
• Obtain signed, informed consent
• Screen for inclusion and exclusion criteria
• Review medical history collected in-person or via telephone
• Review Demographics collected in-person or via telephone
• Record review of systems and physical examination to include weight and height
• Vital signs*****
• Administer assessment measures to observer about individual with TBI: NPI & NPI-D Irritability& Agitation Domains, SASNOS, AIIM collected in-person or via telephone
• Confirm moderate to severe irritability per observer rated NPI Irritability Domain score ≥ 6
• Administer assessment measures to participant about self: NPI & NPI-D Irritability and Agitation Domains, TBI

QOL Anger, AIIM, PHQ-9, GAD-7, PCL-C collected in-person or via telephone
• Record Clinical Global Impressions
• Administer and score baseline GOS-E
• If meets all eligibility criteria (other than laboratory tests) then obtain serum creatinine, AST and ALT laboratory tests and serum pregnancy test for female
Confirm Eligibility and Randomize
• Confirm lab results are within limits of safety.
• Assign study ID number.
• Randomize
• Instruct on proper medication administration
• Dispense drug (15 mg/day x 1 week then 30 mg/day) via mailing study drug to participant
Call 1
• Confirm receipt of Fed-Ex study medication
• Review proper medication administration again & advise to start study drug the following day (Day 1)
• Instruct to bring in any remaining study medication to the next clinic visit
• Schedule next study visit
Call 2 (Day 7 +/- 3 days)
• Inquire about number of pills taken and any problems encountered, record adverse events, record any change in concomitant medications
• Increase dose to 30 mg/day as of Day 8 as planned and dispensed
Call 3, 4 and 5 (Days 14, 21, and 28 +/- 3 days)
• Inquire about number of pills taken and any problems encountered
• Record adverse events
• Record any change in concomitant medications
Visit 2 (Day 35 - 3 or + 7 days): Interim Evaluation in-person or via telephone
• Record number of remaining pills
• Collect unused medication
• Record any change in concomitant medications
• Record adverse events
• Vital signs*****
• Administer assessment measures to observer about individual with TBI: NPI & NPI-D Irritability & Agitation Domains, SASNOS, GIC
• Administer assessment measures to participant about self: NPI and NPI-D for Irritability & Agitation Domains, TBI-QOL Anger, PHQ-9, GAD-7, GIC
• Record Clinical Global Impressions
• Review medication instructions and dosing
• Advance drug dose (45 mg/day) unless prevented by adverse event or improved $\geq$80% on NPI-I
• Remind of next study visit
• Instruct to bring in any remaining study medication to the next study visit
Calls 6, 7, and 8 (Days 42, 49, and 56 +/- 3 days):
• Inquire about number of pills taken and any problems encountered, record adverse events, record any change in concomitant medications
Visit 3 (Day 63 - 3 or + 7 days): Interim Evaluation in-person or via telephone
• Record number of remaining pills
• Collect unused medication
• Record any change in concomitant medications
• Record adverse events
• Vital signs*****
• Administer assessment measures to observer about individual with TBI: NPI & NPI-D Irritability & Agitation Domains, GIC, SASNOS
• Administer assessment measures to participant about self: NPI and NPI-D for Irritability & Agitation Domains, TBI-QOL Anger, PHQ-9, GAD-7. GIC

• Record Clinical Global Impressions
• Review medication instructions and dosing
• Advance drug dose (60 mg/day) unless prevented by adverse event or improved ≥80% on NPI-I
• Remind of next study visit
• Instruct to bring in any remaining study medication to the next study visit
Calls 9, 10 , and 11 (Days 70, 77, and 84 +/- 3 days):
• Inquire about number of pills taken and any problems encountered, record adverse events, record any change in concomitant medications **Visit 4 (Day 91- 3 or + 7 days): Final Outcome Visit in-person or via telephone**
• Record number of remaining pills
• Collect unused medication
• Record any change in concomitant medications
• Record adverse events
• Vital signs*****
• Administer assessment measures to observer about individual with TBI: NPI & NPI-D Irritability & Agitation Domains, GIC, SASNOS, AIIM, Summary Questionnaire
• Administer assessment measures to participant about self: NPI & NPI-D Irritability & Agitation Domains, TBI QOL Anger, AIIM, PHQ-9, GAD-7, GIC, WAI-SR, Summary Questionnaire
• Record WAI-SR
• Record Clinical Global Impressions
• Ask if they think they have been receiving placebo or BUSP
• Encourage subject to make clinical appointment with rehabilitation physician for routine care and continued management, including addressing irritability as needed.
• Give subject 1-week supply of tapering dose BUSP and 1 month supply of open-label BUSP
Call 12 (Day 131+/- 7 days): Final Safety Call
• Inquire about any problems encountered during taper and open label and record adverse events
• Complete Study Completion Form

Summary of Measures and Who Will Respond:

Measure	Buspirone Study	Measurement Study	Observer	Participant	Clinician	Research Assistant
NPI & NPI-D Aggression	X	X (observer)	X	X		
NPI & NPI-D Irritability	X	X (observer)	X	X		
SASNOS	X	X	X			
TBI-Quality of Life-Anger	X	X		X		
Personal Health Questionnaire (PHQ-9)	X			X		
Generalized Anxiety Disorder (GAD-7)	X			X		
Aggression & Irritability Impact Measure (AIIM)	X	X	X	X		
PTSD Checklist Civilian (PCL-C)	X			X		
Glasgow Outcome Scale Extended (GOS-E)	X			X (or best source)		
Clinical Global Impressions (CGI)	X				X	
Global Impression of Change (GIC)	X		X	X		
Working Alliance Inventory-Short Revised (WAI-SR)	X	X		X		X

Schedule of Events:

Procedure	Baseline Visit 1	Calls***	Visit 2 Day 35 (-3 or + 7)	Visit 3 Day 63 (+/- 3 days)	Visit 4 Day 91 (-3 or + 7)
Informed consent	X				
Screen for eligibility criteria	X				
Past medical history	X				
Vital signs *****	X		X	X	X
Demographics	X				
Brief physical examination	X				
Pregnancy test for females*	X				
Laboratory tests: Serum creatinine and AST and ALT laboratory *	X				
Neuropsychiatric Inventory	X		X	X	X
TBI-QOL Anger	X		X	X	X
SASNOS	X		X	X	X
AIIM	X				X
PHQ-9	X		X	X	X
GAD-7	X		X	X	X
PCL-C	X				
GOS-E	X				
Clinical Global Impressions	X		X	X	X
Global Impression of Change			X	X	X
Working Alliance Inventory-Short Revised (WAI-SR)					X
Summary Questionnaire (Subject)					X
Summary Questionnaire (Observer)					X
Record concomitant meds	X	X	X	X	X
Study Completion Form****		X			
Assign study number**	X				
Randomization**	X				
Review proper medication use**	X	X	X	X	X
Dose adjustment**		X	X	X	X
Dispense drug**	X		X	X	X
Pill count**			X	X	X
Record adverse events**		X	X	X	X

*** These steps only performed if meets all eligibility criteria up to that point**
**** These steps only performed if meets all eligibility criteria**
***** Calls weekly**
****** Complete after telephone call 131**
******* Optional**

Drug Accountability: Compliance is enhanced through pill organizers, medication diaries, and frequent contacts (weekly contact). In the event that study personnel learn that a subject has not complied with the dosing schedule, the RA will try to resolve any concerns and encourage continuation in the study taking all doses as prescribed. The lack of compliance will be recorded on the relevant drug accountability case report form (CRF) for that subject.
Compliance: Pill counts will be performed at each visit. Compliance will be considered at least 75% medication consumption. If study medication compliance is at least 75% *and not more than 125%* over the course of the entire study, this will be considered compliant and would not represent a protocol deviation.

6.1/2 REPORTING OF ADVERSE EVENTS OR UNANTICIPATED PROBLEMS INVOLVING RISK TO PARTICIPANTS OR OTHERS

Side Effects and Adverse Events: All AEs encountered during the study will be recorded beginning at the time the informed consent form is signed. Participants will be encouraged to report each AE, and will be queried about AEs with each contact. All clinically significant changes in health status will be recorded and followed, including the date and time of onset, severity, relationship to study medication, the date of resolution (or the fact that the event is still continuing), the action taken, and the outcome. The PI will categorize each AE according to its severity (mild, moderate, severe) and suspected relationship to the study treatment. AEs not resolved at the completion of a protocol are followed until resolution or for duration as deemed appropriate by the Data Safety Monitoring Board (DSMB). Serious adverse events (SAEs) will be reported to the local IRB within 24 hours of the project staff becoming aware of the event. A study pager and call schedule will be maintained to assure timely communication.
Clinical and Safety Monitoring: The PI, Project Manager, Clinical Monitor, and DSMB, all with the training and experience to oversee the study conduct, will monitor the study in accordance with Good Clinical Practices. A Clinical Monitor from the Indiana CTSI will review record accuracy and completeness, check source documents, and evaluate study data (drug accountability, communication, and written records). The DSMB will monitor the study for purposes of safety and integrity, which will include review of AEs, SAEs, protocol deviations and violations, and data quality reports. A Manual of Procedure will be developed that specifies our procedures that guide dose adjustment and management of AEs, SAEs, and suicidal ideation.

7.1/2 STUDY WITHDRAWAL/DISCONTINUATION

Subject Withdrawal: Subjects may discontinue or withdraw from the study for any of the following reasons: (1) subject's request, (2) adverse event requiring treatment discontinuation, (3) investigator deems necessary. If a subject withdraws or is discontinued for any reason, they will be asked if they will return to the site as soon as possible where all Final Visit assessments will be conducted as is necessary for an intent-to-treat analysis.
Termination of the Study: If the PI or DSMB discovers conditions arising during the course of the study which indicate that the clinical investigation should be halted, the study may be terminated after appropriate consultation and discussion. Conditions that may warrant study termination include, but are not limited to, the discovery of a significant, unexpected and unacceptable risk to the subjects, failure to enroll subjects at an acceptable rate, insufficient adherence to the protocol requirements, or completion of study objectives.

8.1 STATISTICAL CONSIDERATIONS

General Considerations: Statistical analyses for this study will be the responsibility of the study statistician working through the Department of Biostatistics. Safety and efficacy analyses will be conducted on all evaluable patients. Parameter estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using number of patients, frequency, and percentages. Additional exploratory analyses of the data will be conducted as deemed appropriate. Changes from this analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are detailed below. Standard statistical methods will be employed. Descriptive statistics, including means and standard deviations, or counts and percentages will be calculated. As a majority of the outcome variables are measured on the ordinal (Likert) scale, nonparametric statistical tests will be employed. The SAS® software, version 9.3,[166] will be used. A p-value of less than 0.05 will be considered statistically significant unless otherwise noted. Analysis plans specific to each hypothesis are further discussed below.
Analysis Sets: The definitions of the study populations are listed below:

Population	Definition
Intention-to-Treat	All patients who meet the eligibility criteria and are registered for the study irrespective of their compliance to the planned course of treatment.
Per Protocol Set	All patients who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations.

Population	Definition
Safety	All patients receiving at least one dose of study drug are included in the analysis of safety, unless otherwise noted.

Participant Characteristics: Participant demographics and baseline characteristics will be listed and summarized for the Intent-to-Treat population, including age, gender, ethnicity, height, weight and medical history. Demographic and baseline measurements will be compared between the two groups. Variables measured on an interval scale (e.g., age) will be compared between the two groups with a Student's t-test. Variables that are not normally distributed will be tested with the Wilcoxon rank sum test. The chi-square test or Fisher's exact test will be employed for variables measured on the nominal scale (e.g., gender).
Concomitant Medications: Concomitant medications will be summarized.
Participant Disposition: Disposition will be tabulated showing the number of those entered and discontinued for any reason. Reasons for discontinuation will be listed and summarized.
Compliance: Number of subjects who are compliant with respect to pill taking (defined as ≥ 75% of prescribed study medication consumption) will be reported.
Subject Replacements: Subjects who discontinue the study will not be replaced.
Sample Size: The sample size is based on the sample size needed for the primary and secondary efficacy analyses. For the primary outcome (proportion of participants who have a decrease of at least 3 points in their Irritability Domain Score), thirty-three participants per group are necessary to detect a difference of 40% having a successful decrease in irritability in one group versus 80% in the other, using a chi-square test with a power of 90% and an alpha of 0.05. This is the effect size we observed in our prior amantadine single-site study.[43] For the secondary outcomes, the sample size for the Wilcoxon rank sum test was calculated using the formulas derived by Noether.[167] Thirty-three people are needed in each group to ensure a power of 80%, with an alpha of 0.05, and p = probability(Y>X) = 0.70, where Y and X are random samples from the two populations (groups). Under the null hypothesis p = 0.50. To allow for a 10% loss-to-follow up, *37 participants will be enrolled into each of the 2 study arms for a total sample of 74.*
Available Sample and Back-up Plan to Achieve Recruitment Numbers: Based on several assessments, we expect to recruit according to our timeline as we have in our prior studies. The PI has successfully conducted several similar pharmacologic studies for irritability in this population which have run according to timeline and provided insight to recruitment obstacles and solutions. In two similar single-site studies, the PI was able to enroll 76 participants over 3.5 years with only a 5% drop out rate. A similar study is near completion at IU with enrollment progressing ahead of schedule. We have ample access to the target population to satisfactorily recruit. Recruitment reports are reviewed by the research team monthly and compared to benchmarks. If/when recruitment falls below benchmark, an action plan will be implemented. If recruitment lags behind benchmarks, we will repeat our intense local advertisement efforts (to both clinicians and persons with brain injury), expand the advertisement to nearby communities, expand our recruitment across Indiana, and provide targeted education about our study and irritability in general to clinicians and persons with brain injury across the state. If necessary, we can extend involvement in this study to other PM&R specialists and psychologists in the region or to nearby residential facilities. If for some reason we still lack adequate recruitment, we will discuss potential options with our NIDRR project officer, such as contracting with another center.
Subject participation duration: 131 days (including open-label); **Study Duration:** 5 years.
Efficacy Analyses:
Hypothesis 1a: Among individuals with TBI of >6 months duration and moderate-to-severe irritability, BUSP compared to placebo will result in a statistically significant greater proportion of responders as defined by a decrease of at least 3 points on the observer-rated Neuropsychiatric Inventory (NPI) Irritability domain scores from baseline to Day 91.
Hypothesis 1b: Among individuals with TBI of >6 months duration, BUSP will result in statistically significant improvement in scores of one or more of the following measures compared to placebo: a) observer and participant ratings of NPI and NPI-Distress Irritability domain scores, b) observer and participant ratings of NPI and NPI-Distress Aggression domain scores, c) participant ratings of TBI-QOL Anger bank, d) observer ratings of SASNOS, e) observer and participant ratings of Global Impression of Change, f) physician ratings of Clinical Global Impressions.
The primary analysis will be intention-to-treat. For Hypothesis 1a, the primary outcome, the percent of participants who are considered to have meaningful reduction in irritability (decrease of at least 3 points in the NPI Irritability Domain Score) from baseline to 91 days, will be compared between the two groups (those receiving active drug and

placebo) using a chi-square test. A logistic regression model will be used to adjust for depression and possible demographic and baseline differences between the two groups and a post-hoc secondary analysis will examine the factors (including depression and anxiety) influencing the effect of BUSP on the primary outcome by including group interaction in the logistic model. For Hypothesis 1b, the change in the observer-rated NPI Irritability Domain Score from baseline to 91 days will be compared between the two groups using a Wilcoxon rank sum (Mann-Whitney) test for ordered categories. The secondary outcomes will also be compared between the two groups using Wilcoxon rank sum tests. For the secondary outcomes, Hochberg's step-up Bonferroni method will be used to control for multiple testing. Secondary analyses will include repeating the analyses above using the PPS population. Wilcoxon rank sum tests will also be performed for separate subgroups such as females, males, participants with injury caused by motor vehicle crashes or falls to test whether BUSP can be efficacious for these separate subgroups. In addition, if a substantial number of participants have depression, a preliminary analysis of the effect of BUSP on PHQ-9 may be performed. The effect of BUSP on GAD-7 will also be performed.

Safety Analysis: Hypothesis 2: *BUSP will be tolerated as measured by number and types of the adverse events in the treatment group compared to the placebo group.*

Safety analyses will be conducted in the Safety Population. For Hypothesis 2, the percent of adverse events will be compared between the two groups using the chi-square test or the Fisher's exact test. In this analysis, no adjustments will be made for multiple testing.

Interim Analyses: No interim analyses are planned unless the DSMB deems it necessary.

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