Neuropsychopharmacology (2016) 41, 1191–1198
© 2016 American College of Neuropsychopharmacology. All rights reserved 0893-133X/16
www.neuropsychopharmacology.org

Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury

Thomas W McAllister*[,1,12], Ross Zafonte[2,12], Sonia Jain[3], Laura A Flashman[4], Mark S George[5], Gerald A Grant[6], Feng He[3], James B Lohr[7], Norberto Andaluz[8], Lanier Summerall[9], Martin P Paulus[10], Rema Raman[3] and Murray B Stein[11]

[1]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Brigham and Women's Hospital and Harvard Medical School, Boston MA, USA; [3]Department of Family Medicine and Public Health, Biostatistics Research Center, University of California, San Diego, CA, USA; [4]Department of Psychiatry, Neuropsychology Program, Geisel School of Medicine at Dartmouth, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [5]Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA; [6]Department of Neurosurgery, Stanford University/Lucile Packard Children's Hospital, Stanford CA, USA; [7]Department of Psychiatry, University of California, San Diego, CA, USA; [8]Department of Neurosurgery, College of Medicine/Mayfield Clinic, Neuroscience Institute, University of Cincinnati, Cincinnati, OH, USA; [9]Department of Psychiatry, Ralph H. Johnson VA Medical Center, Charleston, SC, USA; [10]Laureate Institute for Brain Research, Tulsa, OK, USA; [11]Department of Psychiatry and Department of Family Medicine and Public Health, University of California, San Diego, CA, USA

We report findings from a 12-week randomized double-blinded placebo-controlled trial of methylphenidate or galantamine to treat emotional and cognitive complaints in individuals ($n = 32$) with a history of PTSD, TBI, or both conditions. In this small pilot study, methylphenidate treatment was associated with clinically meaningful and statistically significant improvement compared with placebo on the primary outcome, a measure of cognitive complaints (Ruff Neurobehavioral Inventory—Postmorbid Cognitive Scale), as well as on the secondary outcomes reflecting post-concussive (Rivermead Post Concussive Symptom Questionnaire) and post-traumatic stress symptoms (Posttraumatic Stress Disorder Checklist). Treatment was well tolerated. These results suggest the need for a larger RCT to replicate and confirm these findings. Design considerations for such a trial should include the need for multiple sites to facilitate adequate recruitment and extension of the treatment and follow-up periods.
Neuropsychopharmacology (2016) **41,** 1191–1198; doi:10.1038/npp.2015.282; published online 28 October 2015

INTRODUCTION

Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are both prevalent consequences of traumatic events during deployment among US military personnel. One study indicated that US Army soldiers returning from year-long deployments in Iraq reported high rates of injuries with loss of consciousness (4.9%) and altered mental status (17.2%; Hoge *et al*, 2008) with the majority of these injuries judged to be mild TBI (mTBI). Moreover, there is a high level of co-occurrence of TBI and PTSD in this population. Many observational studies from both military and civilian settings (Hoge *et al*, 2008; Schneiderman *et al*, 2008) have firmly established an association between mTBI and PTSD (Hoge *et al*, 2008; Schneiderman *et al*, 2008; Bryan and Clemans, 2013; Bryan *et al*, 2013; Carlson *et al*, 2011; Hart *et al*, 2014; Stein and McAllister, 2009; Tanev *et al*, 2014; Wilk *et al*, 2012; Wisco *et al*, 2014; Yurgil *et al*, 2014). These observations signal not only a need for effective interventions for PTSD and mTBI occurring individually, but for interventions that have the potential to address both conditions at the same time.

Cognitive Symptoms in mTBI and PTSD

Although post-concussive (PCS) and post-traumatic stress (PTS) symptoms overlap in multiple domains (Stein and McAllister, 2009), cognitive complaints are particularly troublesome in both conditions. Individuals who suffer mTBI have acute cognitive effects, and a significant number of them have persistent symptoms (McMahon *et al*, 2014).

*Correspondence: Dr TW McAllister, Department of Psychiatry, Indiana University School of Medicine, 355W, 16th Street, Suite 4800, Indianapolis, IN 46202, USA, Tel: +1 317 963 7288, Fax: +1 317 963 7313, E-mail: twmcalli@iupui.edu
[12]These authors contributed equally to this work.
Received 6 March 2015; revised 15 June 2015; accepted 16 June 2015; accepted article preview online 11 September 2015

The DSM-5 diagnostic criteria for PTSD include cognitive symptoms related to memory and attention as part of the core clinical syndrome ('inability to recall an important aspect of the trauma'—one of the D criteria, and 'problems in concentration'—one of the E criteria). Furthermore, studies have shown that the memory deficits associated with PTSD are broader than the diagnostic criteria suggest; eg, PTSD is associated with deficits in verbal and visual memory for emotionally neutral information (Brewin *et al*, 2007). The attention deficits that characterize PTSD are well-documented and have been conceptualized as resulting from a combination of increased arousal and compromised inhibitory functions that are essential for attentional control (Falconer *et al*, 2008; Vasterling and Brailey, 2005).

Treatment Approaches to Cognitive Complaints/Deficits

Little is known about the extent or nature of cognitive complaints in individuals with co-occurring PCS and PTS, yet the importance for the military and others with coexistent trauma cannot be overstated. Studies of mTBI have typically excluded individuals with PTSD, whereas studies of PTSD have typically excluded individuals with TBI. Literature on the pharmacological treatment of cognitive impairments after TBI has generally suggested two broad approaches involving either catecholaminergic or cholinergic augmentation (Arciniegas, 2006). With regard to catecholaminergic augmentation, methylphenidate (MPH; a stimulant that augments cerebral dopaminergic and noradrenergic function; Seeman and Madras, 1998) is generally regarded as the first-line treatment for impaired speed of processing, but may also benefit arousal, attention, and memory (Neurobehavioral Guidelines Working Group, 2006). Cholinesterase inhibitors have been used to augment cholinergic function in TBI patients and are posited to assist with memory and executive function (Tenovuo, 2005; Silver *et al*, 2006). Neither class of medication has been systematically studied in PTSD, although anecdotal clinical experience suggests that, for individuals with PTSD and cognitive complaints, MPH can produce clinical benefit without problematic exacerbations in anxiety. In addition, unique among currently available cholinesterase inhibitors, galantamine (GAL) is a positive allosteric modulator of nicotinic cholinergic receptors (nAChRs; Schilstrom *et al*, 2007). Stimulation of nAChRs in the ventral tegmental area activates midbrain dopamine neurons and augments dopaminergic tone, although in a less robust fashion than conventional dopamine agonists, thus mitigating the theoretical concern that such might exacerbate hyperarousal, anxiety, agitation, and sleep disturbance in individuals with PTSD. GAL has been shown to improve cognitive measures in Alzheimer's disease and possibly mild cognitive impairment (Wilcock *et al*, 2000; Loy and Schneider, 2006), and TBI in an open-label trial (Tenovuo, 2005).

Considering existing preclinical and clinical data, as well as gaps in the treatment literature for mTBI and PTSD, we initiated a randomized placebo-controlled trial of two pharmacotherapies—GAL or MPH—for reducing cognitive and emotional symptoms in individuals with mTBI, PTSD, and co-occurring mTBI and PTSD. We hypothesized that (i) treatment with MPH or GAL would be associated with greater reduction in cognitive complaints than placebo; (ii) MPH would result in greater improvement in executive function and processing speed than placebo; (iii) treatment with GAL would result in a greater improvement in the memory when compared with treatment with placebo; and (iv) either treatment would result in an improvement in symptoms characteristic of each disorder, ie, PCS and/or PTS symptoms, relative to placebo.

MATERIALS AND METHODS

Overview

In order to address the cognitive, emotional, and functional difficulties associated with PTSD and TBI, the Injury and Traumatic Stress (INTRuST) collaborative network was established and funded by the US Department of Defense (overall Principal Investigator and Consortium Director: Murray B. Stein MD, MPH). The present study (co-principal investigators Thomas McAllister MD and Ross Zafonte DO) was among the multisite trials conducted by the collaborative network. Seven sites from within the network participated in this trial.

Study Design

This was a multisite, double-blind, randomized-controlled trial (RCT) of GAL 12 mg bid or MPH 20 mg bid vs matching placebo for 12 weeks duration at 7 sites. This study used centralized randomization and shipping of study medications and concealed assignment of randomization status. Subjects were enrolled in the trial for 15 weeks (1 week of screening and baseline assessment, 12 weeks of treatment, 2 weeks of taper). Subjects completed major assessments at baseline (week 0) and post-treatment (week 12), and briefer interim assessments at weeks 4 and 8. The 12-week treatment period was followed by a 2-week taper, after which subjects returned to the clinic for a brief assessment.

Participants

The study population consisted of adults aged 18–55 years who met the following inclusion criteria: diagnosis of PTSD and/or history of mTBI (ie, history of mTBI or complicated mTBI as established by clinical interview), and clinically significant cognitive complaints (indicated by a T-score $\geqslant 60$ on the Postmorbid Cognitive Scale of the Ruff Neurobehavioral Inventory (RNBI; Ruff and Hibbard, 2003)). Exclusion criteria included sensitivity or previous adverse reaction to GAL, MPH, or other acetylcholinesterase inhibitor or stimulant medications, current or recent use of monoamine oxidase inhibitors, or medications that potentiate cholinergic function. Other psychotropic medication was permitted if the participant was on a stable dose for a minimum of 4 weeks prior to enrollment in the study. Women who were pregnant, planning to become pregnant, or lactating were excluded. Additional medical exclusions included history of glaucoma, cardiac conditions, such as bradycardia, AV block or history of taking medications associated with conduction abnormalities, seizure disorder (including post-traumatic epilepsy), or neurosurgery. Non-English-speaking subjects, those who scored a less than 70 scaled score on the Wide

Range Achievement Test, Reading Subtest (WRAT-3 Reading) or who had a lifetime history of psychotic disorder, bipolar disorder type I, stimulant abuse or dependence, tic disorder, alcohol use disorder (defined as MINI diagnosis of 'Alcohol Abuse', an AUDIT-C score of $\geqslant 5$ (Dawson *et al*, 2005)), substance use disorder in the past 6 months, current active suicidal ideation, and severe depressive symptoms (score of 20 or higher on the Patient Health Questionnaire-9 (PHQ9; Kroenke *et al*, 2001), were also excluded.

Treatment Regimen

Identical-appearing capsules were administered orally, with b.i.d. dosing, for 12 weeks duration. The dosages, dosage regimen, and treatment period were largely modeled after those used in prior studies of GAL and MPH. GAL has a half-life of ~7–8 h and thus previous clinical trials have chosen twice daily dosing (Thompson, 2004). Twelve miligrams bid is considered as the maximum therapeutic dose. Higher doses were utilized in Alzheimer's trials but were associated with increased adverse events and rates of discontinuation (Thompson, 2004; Wilcock *et al*, 2000). The duration of treatment is consistent with duration of other pharmacotherapy trials (eg, Koontz and Baskys, 2005). The dose of MPH for this protocol is similar to that used in prior trials in TBI (Willmott and Ponsford, 2009) and at the higher dose is the equivalent of 0.28 mg/kg given twice daily, for a 70 kg man. The active treatment regimen was as follows:

Galantamine. GAL was initiated at 4 mg bid at week 0, increased to 8 mg bid at week 4, and finally increased to 12 mg bid at week 8 and then held constant until the major outcome assessment at week 12. The drug was tapered during weeks 12–14 (8 mg BID during week 13 and then 4 mg BID during week 14, and then discontinued).

Methylphenidate. MPH was initiated at 5 mg bid at week 0, increased to 10 mg bid at week 4, increased to 20 mg bid at week 8 and then held constant until the major outcome assessment at week 12. The drug was tapered during weeks 12–14 (10 mg BID during week 13; 5 mg BID during week 14, and then discontinued).

In the event of adverse effects believed to be associated with medication, participants' doses could be held at an intermediate dose (rather than proceeding with a scheduled increase) or decreased to the previous dose, but continued participation required a minimum dose of 4 mg bid GAL or 5 mg bid MPH).

Informed Consent

All participants gave written informed consent approved by their local IRB, as well as the Dartmouth College IRB, the UCSD IRB, and the Human Research Protections Office of the Department of Defense.

Assessments

The study included a repeated measures design with assessment points at baseline, 4, 8, and 12 weeks. Brief in-person visits occurred at weekly intervals, following the major assessment points to monitor the effects of increased dosage on clinical status. Medications were tapered after the week 12 visit, and the final brief study visit occurred at week 14.

The primary outcome for this study was the mean 12-week change in cognitive symptoms as measured by the RNBI Postmorbid Cognitive Scale (Ruff and Hibbard, 2003). Planned secondary analyses included change in cognitive performance (RVLT; Digit Symbol, Trails A and others) and symptoms associated with common co-morbid conditions including the Rivermead Post Concussive Symptoms Questionnaire (RPCSQ) to assess typical PCS symptoms, the Posttraumatic Stress Disorder Checklist (PCL-S) to assess PTS symptoms, and the PHQ9 to assess depressive symptoms.

Data Analysis

Descriptive analyses were performed to compare demographic and baseline characteristics among treatment groups. Categorical variables were evaluated using Fisher–Freeman–Halton Exact Test. Continuous variables were analyzed with analysis of variance test or a Kruskal–Wallis test, as appropriate.

The primary outcome (RNBI Postmorbid Cognitive Scale) was analyzed using an MMRM (mixed model repeated measures) approach based on a modified intent-to-treat (mITT) population. The mITT population was defined as randomized participants who were dispensed at least one dose of medication. Participants from the mITT population who were included in the MMRM model also required both a baseline and at least one post-baseline RNBI score. The model included as the dependent variable change from baseline in RNBI total score at each post-baseline visit (weeks 4, 8, and 12). Independent variables in the MMRM model included treatment, visit, treatment-by-visit interaction, RNBI total score at baseline, and the following pre-specified covariates: education, gender, age at baseline and diagnosis. Visits were treated as a categorical variable. Unstructured variance–covariance structure was used. Per protocol analysis was not performed owing to the small sample size.

Safety data were summarized overall and by treatment groups on the randomized subjects. A Fisher–Freeman–Halton Exact test was used to compare the number of subjects among groups who experienced at least one adverse event, overall and by MedDRA System Organ Class.

Other secondary efficacy outcomes (PCL-S, Rivermead, and PHQ9) were analyzed with an MMRM model analogous to the primary analysis. The model included the change from baseline at each follow-up visit as the dependent variable. Independent variables included treatment, visit, treatment-by-visit interaction, baseline score, and the following pre-specified covariates: education, gender, age at baseline, and diagnosis. Effect size (standardized mean) with confidence interval of change from baseline to week 12 was also computed for most measures.

All statistical analyses were performed in R version 3.0.2 (www.r-project.org). Because this is an early phase study, no adjustments were made for multiple comparisons, and a p-value of 0.05 was considered to be statistically significant.

RESULTS

Overview

The study was intended to enroll a total of 160 participants. However, as a result of slower enrollment than specified in the original scope of work and unanticipated difficulties obtaining study drug (owing to a temporary shortage of MPH suitable for packing as needed for this trial), the study was terminated early by the funding agency. At that time, 32 subjects had been randomized in the study, and their outcomes are described here.

Participants

Figure 1 summarizes flow of subjects for this study. Although the inclusion and exclusion criteria were intentionally broad in order to attract a clinically representative sample, enrollment proved to be challenging. Seventy-five potential participants were screened across the 7 sites, 43 failed screening, and 32 were randomized and all were included in the intent-to-treat analyses. Common reasons for exclusion included co-morbid medical disorders, which were deemed exclusionary, and failure to reach inclusion threshold of cognitive complaints or deficits. Fifteen of the 32 randomized participants (47%) were civilians without history of military service. Distribution of military vs non-military participants did not differ across treatment groups. The participants were equally divided between those with PTSD only, TBI only, and both PTSD and TBI. In all individuals with PTSD, the diagnosis was present for at least 3 months. Twenty-seven percent of those with TBI reported blast exposure. Of those randomized, 10 dropped out before study completion. Dropout was highest in the placebo group ($n=5$), followed by GAL ($n=3$) and MPH ($n=2$). Reasons for dropout included adverse events ($n=3$ in the placebo group), non-compliance ($n=1$ in the GAL group), relocation ($n=1$ in the MPH group), other ($n=1$ in the MPH group), and lost to follow-up ($n=2$ in the GAL group and $n=1$ in the placebo group). Table 1 summarizes the demographic data of the participants included in the mITT analyses.

Safety and Tolerability

Overall the protocol was well tolerated. Among 32 randomized subjects, a total of 20 (62.5%) participants had at least one reported adverse event (7 in GAL, 6 in MPH, and 7 in Placebo, Fisher–Freeman–Halton Exact p-value >0.9999). A total 125 adverse events occurred, and no serious adverse events or deaths were reported in the study. There were no differences in rates of adverse events across the three treatment groups.

Primary Outcome Measure (Effect on Cognitive Symptoms)

Table 2 summarizes the results on the primary outcome measure. On the basis of the RNBI score, the treatment groups did not differ significantly in cognitive complaint severity at baseline. MPH treatment was associated with a significant improvement in cognitive complaints relative to placebo at all the three time points ($p=0.004$; 0.03; 0.036 at weeks 4, 8, and 12, respectively; effect size = 0.337 (95% CI = −0.642 to 1.304) at week 12). Treatment with GAL did not differ from placebo at any of the three time points.

Secondary Outcome Measures: Effect on Cognitive Function

MPH was associated with significant improvement on a measure of attention (Digit Symbol, $p=0.011$) relative to placebo. GAL was associated with significant improvement relative to placebo on a measure of episodic memory (long-delay recall of the RVLT, $p=0.011$).

Effect on PCS and Depressive Symptoms

Table 3 summarizes the results of treatment on depressive symptoms and PCS symptoms. MPH was associated with significant PCS symptom reduction relative to placebo at weeks 4, 8, and 12 ($p=0.047$; 0.01; 0.01, respectively; effect size = 0.886 (95% CI = −0.329 to 2.061) at week 12). GAL did not differ significantly

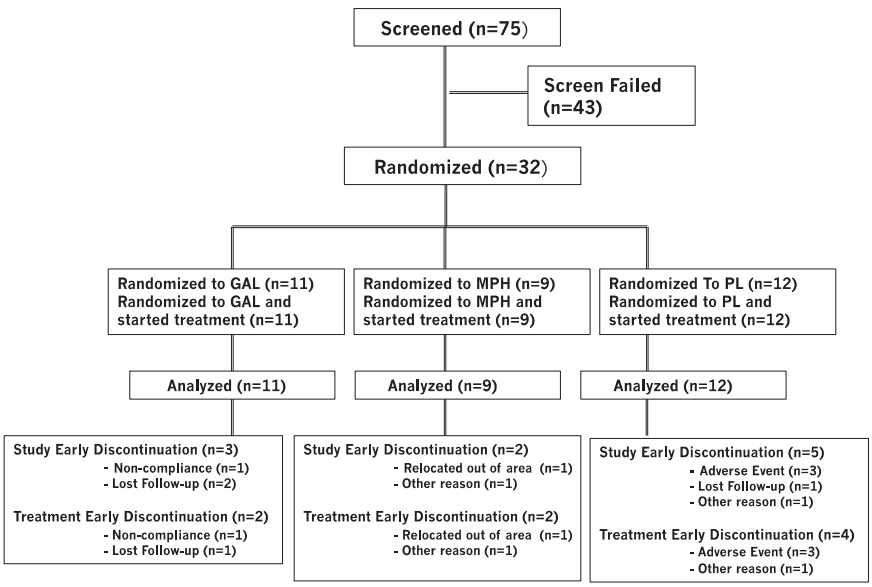

Figure 1 CONSORT diagram of subject study flow.

Table 1 Demographic and Baseline Summary

	GAL ($n=11$)	MPH ($n=9$)	Placebo ($n=12$)	Overall ($n=32$)	*p*-value
Baseline age	41.36 (9.06)	36.67 (9.33)	44.42 (8.18)	41.19 (9.09)	0.155
Education	15 (1.9)	14.22 (1.92)	14.5 (2.61)	14.59 (2.15)	0.724
Gender (male)	6 (54.55)	6 (66.67)	6 (50)	18 (56.25)	0.821
Ethnicity (Hispanic or Latino)	1 (9.09)	0 (0)	2 (16.67)	3 (9.38)	0.836
Race					
White	9 (81.82)	6 (66.67)	8 (66.67)	23 (71.88)	0.851
Black	1 (9.09)	2 (22.22)	2 (16.67)	5 (15.62)	—
Diagnosis					
mTBI/PTSD	3 (27.27)	2 (22.22)	2 (16.67)	7 (21.88)	0.97
mTBI	5 (45.45)	4 (44.44)	5 (41.67)	14 (43.75)	—
PTSD	3 (27.27)	3 (33.33)	5 (41.67)	11 (34.38)	—
Baseline RNBI	65.36 (10.11)	58.78 (11.67)	62.67 (11.55)	62.5 (11.07)	0.429
Baseline PCL-S	48.82 (20.74)	46.56 (10.63)	47.86 (16.55)	47.82 (16.31)	0.956
Baseline PHQ9	9.27 (4.76)	9.89 (5.06)	11.08 (5.3)	10.12 (4.95)	0.686
Baseline Rivermead					
RPQ3	3.67 (3)	5.38 (2.83)	3 (3.61)	3.96 (3.21)	0.307
RPQ13	27.89 (7.46)	30.88 (8.01)	28.11 (12.39)	28.88 (9.31)	0.782

For continuous variable, mean (STD) was provided, and *p*-value is from ANOVA test or Kruskal–Wallis test, as appropriate. For categorical variable, *n* and percentage were provided, and *p*-value is from Fisher–Freeman–Halton Exact Test.

Table 2 Impact of Treatment on Cognitive Symptoms

	GAL vs Placebo	MPH vs Placebo
Week 4		
LS mean change	−3.4428	−14.3910
SEM	4.2976	4.8637
CI lower limit	−11.8659	−23.9237
CI upper limit	4.9804	−4.8582
p-value	0.4260	0.0043
Week 8		
LS mean change	−4.6532	−13.2199
SEM	5.3335	5.9657
CI lower limit	−15.1066	−24.9125
CI upper limit	5.8002	−1.5274
p-value	0.3862	0.0302
Week 12		
LS mean change	−6.3823	−12.0884
SEM	5.0987	5.6582
CI lower limit	−16.3757	−23.1783
CI upper limit	3.6110	−0.9984
p-value	0.2151	0.0364

Summary of Ruff Neurobehavioral Inventory (RNBI)—Postmorbid Cognitive Scale: change from baseline MMRM analysis.

from MPH or placebo at any of the time points. MPH was also associated with significant improvement in depressive symptoms relative to placebo at weeks 4, 8, and 12 ($p=0.01$; 0.01; 0.001, respectively; effect size = 0.497 (95% CI = −0.493 to 1.471) at week 12). GAL was associated with improvement in depressive symptoms relative to placebo at 12 weeks ($p=0.01$; effect size = 0.157 (95% CI = −0.893 to 1.228)).

Effect on PTSD Symptoms

Figure 2 summarizes the results of treatment on PTSD symptoms as measured by the PCL-S. MPH treatment was associated with significant improvement relative to placebo at weeks 4, 8, and 12 ($p=0.003$; 0.014; 0.007 respectively; effect size = 0.881 (95% CI = −0.148 to 1.883 at week 12), with a mean drop of 13 points at the 12-week point (range 3–22, SEM = 4.6). At no time point did GAL differ significantly from placebo on PTSD symptoms. Further analysis of the PCL-S scores, clustered according to the three dimensions of 'Re-experiencing' (items 1–5); 'Avoidance' (items 6–12); and 'Hyperarousal' (items 13–17) showed that the MPH effect was very similar across all three of these dimensions ($p=0.0144$; 0.0155; 0.0279 respectively, when compared with Placebo).

DISCUSSION

Overview

This is a preliminary study in a small sample of patients and thus inferences and conclusions must be considered tentative

Table 3 Impact of Treatment on Depressive Symptoms and Post-concussive Symptoms

	GAL vs Placebo	MPH vs Placebo
Summary of Patient Health Questionnaire − 9 (PHQ9): change from baseline MMRM analysis		
Week 4		
LS mean change	−3.2805	−5.7523
SEM	1.8977	2.0842
CI lower limit	−7.0000	−9.8374
CI upper limit	0.4390	−1.6673
p-value	0.0886	0.0075
Week 8		
LS mean change	−1.8700	−4.1254
SEM	1.3475	1.4877
CI lower limit	−4.5110	−7.0413
CI upper limit	0.7710	−1.2095
p-value	0.1699	0.0072
Week 12		
LS mean change	−3.9102	−5.6124
SEM	1.4752	1.6158
CI lower limit	−6.8016	−8.7793
CI upper limit	−1.0188	−2.4455
p-value	0.0101	0.0009
Summary of Rivermead Postconcussion Symptom Questionnaire (RPQ13): change from baseline MMRM analysis		
Week 4		
LS mean change	−5.3061	−9.6851
SEM	4.5370	4.7382
CI lower limit	−14.1985	−18.9719
CI upper limit	3.5863	−0.3983
p-value	0.2482	0.0467
Week 8		
LS mean change	−7.3752	−13.7272
SEM	4.9482	5.1607
CI lower limit	−17.0735	−23.8421
CI upper limit	2.3231	−3.6123
p-value	0.1429	0.0107
Week 12		
LS mean change	−6.7202	−12.0600
SEM	4.1718	4.3327
CI lower limit	−14.8968	−20.5520
CI upper limit	1.4564	−3.5681
p-value	0.1141	0.0078

and in need of replication. Nevertheless, the data are of interest from several perspectives. Our primary hypothesis was that both MPH and GAL would improve the perception of impaired cognition in patients with mTBI and/or PTSD. In this regard, MPH (but not GAL) did indeed result in a significant reduction relative to placebo in cognitive complaints based on the primary outcome measure, the RNBI Postmorbid Cognitive Scale.

In support of the subjective improvement in cognitive function, MPH was also associated with significant improvement in objective tests of attention and speed of information processing, domains known to be responsive to stimulants, including MPH, in other populations with cognitive complaints and deficits such as attention deficit disorder (MTA Working Group, 1999; Advokat, 2010). GAL was associated with improved episodic memory, also consistent with previous work in other populations such as Alzheimer's disease where this agent is FDA approved for treatment of the episodic memory problems that are the hallmark of that disorder. This profile of cognitive enhancement with these two agents is consistent with the proposed neurobiology of underlying mechanisms of cognitive complaints and deficits in TBI (McAllister and Arciniegas, 2002; Arciniegas, 2006; 2007; Chew and Zafonte, 2009), and the shared neurobiological underpinnings of symptom overlap in TBI and PTSD (Stein and McAllister, 2009).

Also of interest is the observed impact of MPH treatment on other symptom domains. PCS symptoms as measured by the Rivermead Post Concussive Questionnaire were significantly reduced in the MPH group. This may not be overly surprising given the non-specificity of PCS symptoms and the shared symptom profile of mTBI and PTSD that has been noted previously (Stein and McAllister, 2009; McAllister and Stein, 2010). The drop in depressive symptoms on the PHQ9 is also noteworthy given the well-described high rates of co-morbid depression in both TBI (Silver *et al*, 2009; Jorge *et al*, 2004) and PTSD (Hankin *et al*, 1999; Brady *et al*, 2000). Although transient elevations in mood can certainly be seen with use of MPH, it is not believed to be a robust antidepressant, and the mood effects are not thought to be long-lasting (Parker *et al*, 2013). In this study, nevertheless, the reduction in PHQ9 scores was seen at the 4-week time point, and remained low over the subsequent 8 weeks suggesting that short-lived mood-elevating effects of MPH are unlikely to be the sole source of this improvement.

Perhaps the most interesting and surprising observation from this study, however, was the robust drop in PCL-S scores associated with MPH treatment. As with the improvement described above in other domains, this drop occurred early and was sustained throughout the duration of the study. Not only was the drop highly statistically significant, but it was clinically significant (with a large effect size >0.8) as well with an average 13-point drop on the PCL-S for subjects who received MPH. This is a remarkably robust reduction in symptoms that far exceeds the effect size seen for currently marketed agents used to treat PTSD. Despite this being a small study, both the rapidity and the magnitude of response of PTSD symptoms to MPH mandates that larger RCTs be conducted to determine the reproducibility of these results and the possible benefits of this drug.

This study has several limitations that must be considered. The sample size is small and thus as noted earlier, any conclusions are tentative pending larger studies. Screening and enrollment were surprisingly challenging across all the 7 sites, raising a question about how generalizable our small sample is to other populations. On the other hand, we

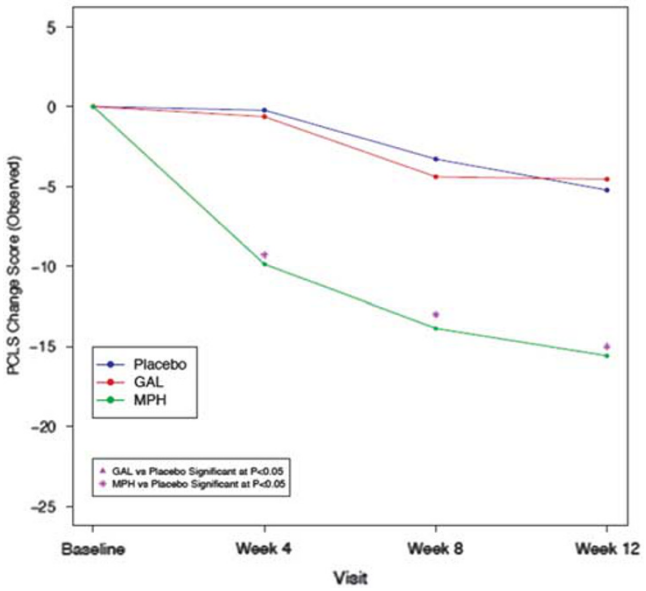

Figure 2 PTSD Checklist—Specific Event Version (PCL-S) change from baseline (observed) plot.

specifically opted to include those with TBI, PTSD, and both PTSD and mTBI in an effort to make our results as applicable to the OEF/OIF cohort as possible. Generalizability of these findings to a pure sample of OEF/OIF participants is not clear, as 47% of this sample was not military personnel, and 27% of the TBI sample was exposed to blast. The fact that these robust and statistically significant findings were found in even this small a sample provides evidence of the magnitude of the results, and argues for the importance of further investigations in this area. Given the chronic cognitive deficits, perceived cognitive symptoms, and possible clinical improvements observed in this study, replication with a much larger sample is imperative. There are several factors that lend credibility to these preliminary findings. The pervasive and consistent treatment effect across domains—subjective and objective—in the MPH group is particularly noteworthy. Furthermore, the improvement in cognitive complaints is supported by gains in cognitive performance in domains where one would expect to see MPH effects. The very broad spectrum of symptom improvement—spanning cognitive and emotional domains—seen with MPH is of great interest, particularly given that chronic post-concussive complaints are notoriously difficult to treat. Should additional studies replicate these findings, the relatively inexpensive nature of MPH is also worth noting.

These findings also raise questions about the potential mechanism(s) underlying the symptom improvement observed in this study. Preclinical data indicate that MPH can enhance fear extinction, (Abraham *et al*, 2012) suggesting one such possible mechanism. If this is, indeed, the mechanism of action of MPH on reducing PTSD symptoms, then one might consider designing a future trial where MPH (vs placebo) is administered in conjunction with exposure therapy. But other animal models of PTSD also show benefits of MPH that may or may not involve facilitation of fear extinction (Aga-Mizrachi *et al*, 2014), pointing to the need to further explore mechanisms of action.

Positive findings in pharmacological trials in PTSD have been notoriously difficult to discern, with many drugs tested recently failing to differentiate from placebo (Howlett and Stein, 2015). Yet in this trial MPH was associated with a robustly positive impact on PTS (and PCS) symptoms and, importantly, was well tolerated by study participants. One of the concerns raised by several of the IRBs associated with the study was the belief that use of stimulants in individuals with PTSD might exacerbate existing difficulties with hyperarousal and sleep, leading to clinical deterioration. On the contrary, the observed rate of adverse events in the MPH group did not differ from placebo, and much of the improvement in the measured domains was driven by improvement in the PTSD group. These findings are of particular interest given anecdotal reports of widespread prescribing of MPH by clinicians working with veterans and military personnel with PTSD, and highlight the pressing need for additional research to determine the utility and safety of this drug (or other drugs with potentially overlapping mechanisms of action, such as atomoxetine) in this patient population.

FUNDING AND DISCLOSURE

This study was funded by the United States Department of Defense grant W81XWH08-2-0159. MBS reports consulting income in the past 3 years from Janssen Pharmaceutica, Pfizer, and Tonix Pharmaceuticals; and income for editorial work for *Biological Psychiatry* and *UpToDate*. RZ has received compensation from Demos Medical Publishing, as well as Oakstone Institute for educational products. The remaining authors declare no conflict of interest.

ACKNOWLEDGMENTS

We acknowledge Laura Burns, Leigh Chesnut, Judith Frazier, Mary Hynes, and Michael Macklin, for their contributions to this work. We are also grateful to the members of the Data Safety Monitoring Board, chaired by Gerald van Belle, PhD, for their careful oversight of the study.

REFERENCES

Abraham AD, Cunningham CL, Lattal KM (2012). Methylphenidate enhances extinction of contextual fear. *Learn Mem* **19**: 67–72.

Advokat C (2010). What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). *Neurosci Biobehav Rev* **34**: 1256–1266.

Aga-Mizrachi S, Cymerblit-Sabba A, Gurman O, Balan A, Shwam G, Deshe R *et al* (2014). Methylphenidate and desipramine combined treatment improves PTSD symptomatology in a rat model. *Transl Psychiatry* **4**: e447.

Arciniegas D, McAllister T, Kaufer D (2007). Cognitive Impairment. In: Coffey CE, McAllister TW, Silver JM (eds). *Guide to Neuropsychiatric Therapeutics*, Lippincott Williams & Wilkins: Philadelphia, PA, USA, pp 24–78.

Arciniegas DB, Silver JM (2006). Pharmacotherapy of posttraumatic cognitive impairments. *Behav Neurol* **17**: 25–42.

Brady KT, Killeen TK, Brewerton T, Lucerini S (2000). Comorbidity of psychiatric disorders and posttraumatic stress disorder. *J Clin Psychiatry* **61**: 22–32.

Brewin CR, Kleiner JS, Vasterling JJ, Field AP (2007). Memory for emotionally neutral information in posttraumatic stress disorder: a meta-analytic investigation. *J Abnorm Psychol* **116**: 448–463.

Bryan CJ, Clemans TA (2013). Repetitive traumatic brain injury, psychological symptoms, and suicide risk in a clinical sample of deployed military personnel. *JAMA Psychiatry* **70**: 686–691.

Bryan CJ, Clemans TA, Hernandez AM, Rudd MD (2013). Loss of consciousness, depression, posttraumatic stress disorder, and suicide risk among deployed military personnel with mild traumatic brain injury. *J Head Trauma Rehabil* **28**: 13–20.

Carlson KF, Kehle SM, Meis LA, Greer N, Macdonald R, Rutks I *et al* (2011). Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. *J Head Trauma Rehabil* **26**: 103–115.

Chew E, Zafonte RD (2009). Pharmacological management of neurobehavioral disorders following traumatic brain injury–a state-of-the-art review. *J Rehabil Res Dev* **46**: 851–879.

Dawson DA, Grant BF, Stinson FS (2005). The AUDIT-C: screening for alcohol use disorders and risk drinking in the presence of other psychiatric disorders. *Compr Psychiatry* **46**: 405–416.

Falconer E, Bryant R, Felmingham KL, Kemp AH, Gordon E, Peduto A *et al* (2008). The neural networks of inhibitory control in posttraumatic stress disorder. *J Psychiatry Neurosci* **33**: 413–422.

Hankin CS, Spiro A, Miller DR, Kazis L (1999). Mental disorders and mental health treatment among US Department of Veterans Affairs outpatients: the Veterans Health Study. *Am J Psychiatry* **156**: 1924–1930.

Hart T, Benn EK, Bagiella E, Arenth P, Dikmen S, Hesdorffer DC *et al* (2014). Early trajectory of psychiatric symptoms after traumatic brain injury: relationship to patient and injury characteristics. *J Neurotrauma* **31**: 610–617.

Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* **358**: 453–463.

Howlett JR, Stein MB (2015). Novel prevention and treatment approaches to PTSD. In: Liberzon I and Ressler KJ (eds). *Neurobiology of PTSD*, Oxford University Press: Oxford, UK.

Jorge RE, Robinson RG, Moser D, Tateno A, Crespo-Facorro B, Arndt S (2004). Major depression following traumatic brain injury. *Arch Gen Psychiatry* **61**: 42–50.

Koontz J, Baskys A (2005). Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study. *Am J Alzheimers Dis Other Demen* **20**: 295–302.

Kroenke K, Spitzer RL, Williams JB (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* **16**: 606–613.

Loy C, Schneider L (2006). Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev* CD001747 (doi:10.1002/14651858.CD001747.pub3).

McAllister TW, Arciniegas D (2002). Evaluation and treatment of postconcussive symptoms. *NeuroRehabilitation* **17**: 265–283.

McAllister TW, Stein MB (2010). Effects of psychological and biomechanical trauma on brain and behavior. *Ann N Y Acad Sci* **1208**: 46–57.

McMahon P, Hricik A, Yue JK, Puccio AM, Inoue T, Lingsma HF *et al* (2014). Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. *J Neurotrauma* **31**: 26–33.

MTA Working Group (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry* **56**: 1073–1086.

Neurobehavioral Guidelines Working Group, Warden DL, Gordon B, McAllister TW, Silver JM, Barth JT *et al* (2006). Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma* **23**: 1468–1501.

Parker G, Brotchie H, McClure G, Fletcher K (2013). Psychostimulants for managing unipolar and bipolar treatment-resistant melancholic depression: a medium-term evaluation of cost benefits. *J Affect Disord* **151**: 360–364.

Ruff RM, Hibbard KM (2003). *RNBI, Ruff Neurobehavioral Inventory: Professional Manual*. Psychological Assessment Resources: Lutz, FL, USA.

Schilstrom B, Ivanov VB, Wiker C *et al* (2007). Galantamine enhances dopaminergic neurotransmission in vivo via allosteric potentiation of nicotinic acetylcholine receptors. *Neuropsychopharmacology* **32**: 43–53.

Schneiderman AI, Braver ER, Kang HK (2008). Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol* **167**: 1446–1452.

Seeman P, Madras BK (1998). Anti-hyperactivity medication: methylphenidate and amphetamine. *Mol Psychiatry* **3**: 386–396.

Silver JM, Koumaras B, Chen M, Mirski D, Potkin SG, Reyes P *et al* (2006). Effects of rivastigmine on cognitive function in patients with traumatic brain injury. *Neurology* **67**: 748–755.

Silver JM, McAllister TW, Arciniegas DB (2009). Depression and cognitive complaints following mild traumatic brain injury. *Am J Psychiatry* **166**: 653–661.

Stein MB, McAllister TW (2009). Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *Am J Psychiatry* **166**: 768–776.

Tanev KS, Pentel KZ, Kredlow MA, Charney ME (2014). PTSD and TBI co-morbidity: Scope, clinical presentation and treatment options. *Brain Inj* **28**: 261–270.

Tenovuo O (2005). Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury-clinical experience in 111 patients. *Prog Neuropsychopharmacol Biol Psychiatry* **29**: 61–67.

Thompson S, Lanctot K, Herrmann N (2004). The benefits and risks associated with cholinesterase inhibitor therapy in Alzheimer's disease. *Expert Opin Drug Saf* **3**: 425–440.

Vasterling JJ, Brailey K (2005). Neuropsychological findings in adults with PTSD. In: Vasterling JJ, Brewin CR (eds). *Neuropsychology of PTSD: Biological, Cognitive, and Clinical Perspectives*. Guilford Press: New York, NY, USA, pp 178–207.

Wilcock GK, Lilienfeld S, Gaens E (2000). Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *BMJ* **321**: 1445–1449.

Wilk JE, Herrell RK, Wynn GH, Riviere LA, Hoge CW (2012). Mild traumatic brain injury (concussion), posttraumatic stress disorder, and depression in U.S. soldiers involved in combat deployments: association with postdeployment symptoms. *Psychosom Med* **74**: 249–257.

Willmott C, Ponsford J (2009). Efficacy of methylphenidate in the rehabilitation of attention following traumatic brain injury: a randomised, crossover, double blind, placebo controlled inpatient trial. *J Neurol Neurosurg Psychiatry* **80**: 552–557.

Wisco BE, Marx BP, Holowka DW, Vasterling JJ, Han SC, Chen MS *et al* (2014). Traumatic brain injury, PTSD, and current suicidal ideation among Iraq and Afghanistan U.S. veterans. *J Trauma Stress* **27**: 244–248.

Yurgil KA, Barkauskas DA, Vasterling JJ, Nievergelt CM, Larson GE, Schork NJ *et al* (2014). Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty marines. *JAMA Psychiatry* **71**: 149–157.