Enhancing Extinction Learning in Posttraumatic Stress Disorder With Brief Daily Imaginal Exposure and Methylene Blue:
A Randomized Controlled Trial

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ABSTRACT

Objective: The memory-enhancing drug methylene blue (MB) administered after extinction training improves fear extinction retention in rats and humans with claustrophobia. Robust findings from animal research, in combination with established safety and data showing MB-enhanced extinction in humans, provide a foundation to extend this work to extinction-based therapies for posttraumatic stress disorder (PTSD) such as prolonged exposure (PE).

Methods: Patients with chronic PTSD (*DSM-IV-TR*; N = 42) were randomly assigned to imaginal exposure plus MB (IE + MB), imaginal exposure plus placebo (IE + PBO), or waitlist (WL/standard PE) from September 2011 to April 2013. Following 5 daily, 50-minute imaginal exposure sessions, 260 mg of MB or PBO was administered. Waitlist controls received PE following 1-month follow-up. Patients were assessed using the independent evaluator–rated PTSD Symptom Scale–Interview version (primary outcome), patient-rated PTSD, trauma-related psychopathology, and functioning through 3-month follow-up.

Results: Both IE + MB and IE + PBO showed strong clinical gains that did not differ from standard PE at 3-month follow-up. MB-augmented exposure specifically enhanced independent evaluator–rated treatment response (number needed to treat = 7.5) and quality of life compared to placebo (effect size $d = 0.58$). Rate of change for IE + MB showed a delayed initial response followed by accelerated recovery, which differed from the linear pattern seen in IE + PBO. MB effects were facilitated by better working memory but not by changes in beliefs.

Conclusions: The findings provide preliminary efficacy for a brief IE treatment for PTSD and point to the potential utility of MB for enhancing outcome. Brief interventions and better tailoring of MB augmentation strategies, adjusting for observed patterns, may have the potential to reduce dropout, accelerate change, and improve outcomes.

Trial Registration: ClinicalTrials.gov identifier: NCT01188694

J Clin Psychiatry 2017;78(7):e782–e789
https://doi.org/10.4088/JCP.16m10936

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Despite the efficacy and effectiveness of exposure therapies for posttraumatic stress disorder (PTSD),[1,2] therapies such as prolonged exposure (PE) utilize nine to fifteen 90- to 120-minute sessions. A minority of patients discontinue before achieving remission, and, among completers, some have residual symptoms.[3] Accordingly, the next generation of precision medicine seeks to enhance the efficacy and efficiency of these psychotherapies, including using biological agents to more precisely augment therapeutic gains.

Methylene blue (MB), methylthioninium chloride, is an autoxidizing agent that enters living, metabolically active cells and stimulates mitochondrial oxidative metabolism and cerebral oxygen consumption.[4,5] Methylene blue is a US Food and Drug Administration (FDA)–grandfathered drug that has been used safely for years in humans when administered orally in doses of 1 to 4 mg/kg.[6–10] Instead of being selective for a single transmitter system or brain region, MB targets the synapses that require energy during postextinction memory consolidation.[11] Methylene blue improves memory consolidation[12,13] and, importantly, extinction memory in rats.[14,15] In humans, MB augments exposure therapy for claustrophobia, facilitating contextual memory and improving retention of extinction for those with low postexposure distress.[16] There is an FDA warning about using MB in conjunction with serotonergic drugs based on serotonin syndrome cases that have been reported after infusing MB as a surgical dye in patients undergoing parathyroid surgery. However, there are no reports of serotonin syndrome by oral MB administration. The dose for this study (260 mg) corresponds to its FDA-approved use for methemoglobinemia.

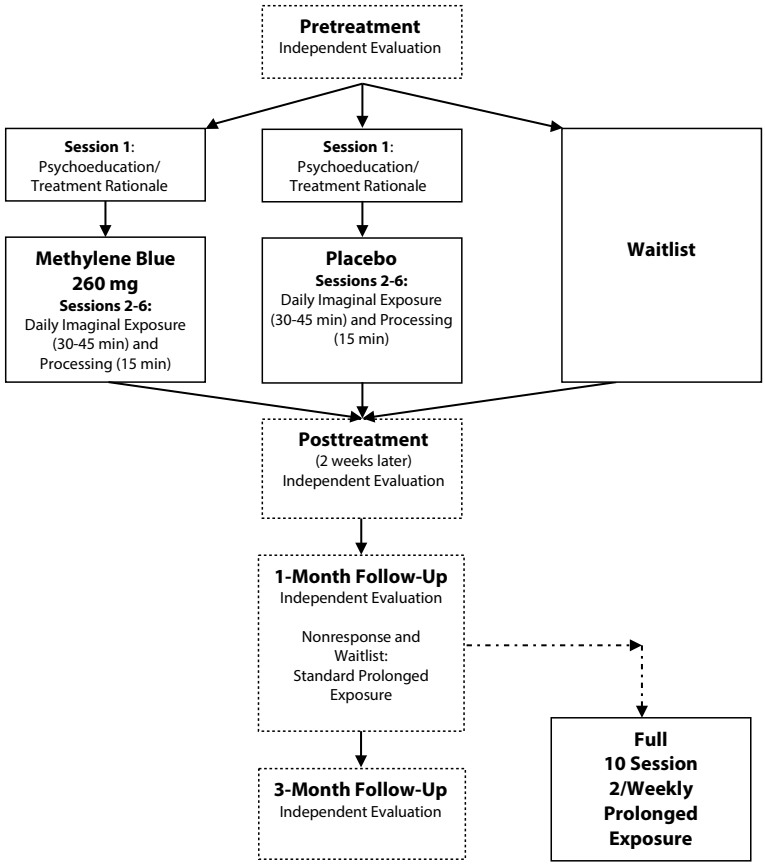
An activity-dependent metabolic approach to enhancing exposure is distinct from a transmitter-receptor pharmacology approach, exemplified by D-cycloserine, an *N*-methyl-D-aspartate (NMDA) agonist. D-cycloserine administered in conjunction with exposure sessions enhances the effects of exposure therapy for patients with low postexposure distress.[17–19] Given the extensive network of brain regions activated after extinction,[20] it is unlikely that extinction memory is limited to 1 transmitter system (eg, synapses with NMDA receptors). In contrast, MB effects are activity-dependent, enhancing energy metabolism in brain regions that are active during the postextinction consolidation phase.[21]

The present study examines the effects of MB augmentation of exposure therapy for chronic PTSD. A 6-session, 50-minute daily imaginal exposure protocol was used to examine the augmentation effects of MB versus placebo (PBO), compared to a waitlist control (WL) that later converted to standard PE (see Figure 1 for study design). Patients were followed through 3-month

Clinical Points

- The next generation of precision medicine will use targeted drugs, such as the memory-enhancer methylene blue, to augment psychotherapy.
- Augmentation of imaginal exposure therapy with methylene blue enhanced posttraumatic stress disorder (PTSD) response and quality of life, although optimal augmentation strategies need to be explored.
- A brief imaginal exposure version of prolonged exposure therapy offers a potentially viable PTSD treatment option.

Figure 1. Study Design



follow-up, measuring PTSD, trauma-related psychopathology, and general functioning. During acute treatment, daily measures of PTSD, depression, and negative beliefs were obtained to examine the differential trajectory or slope of the change between MB and PBO. Finally, possible mechanisms governing effects of MB were explored, examining the indirect effects of baseline working memory,[12,16] imaginal exposure distress,[16] and change in negative beliefs from first to last session.[22–24]

METHODS

Participants

Participants were 42 adults (30 women) with a primary *DSM-IV-TR* diagnosis of chronic PTSD. Exclusion criteria included current schizophrenia, delusional disorder, organic mental disorder, bipolar disorder, depression with psychotic features, active suicidal ideation severe enough to require immediate psychiatric treatment; substance dependence in the last 3 months; unwilling or unable to discontinue current trauma-focused psychotherapy or psychotropic medication (1 month free; 5 weeks free for fluoxetine); and unstable cardiovascular, autoimmune, endocrine, neurologic, renal, hepatic, retinal, gastrointestinal, or hematologic disorder or current seizure disorder or other medical contraindications for initiating MB, including pregnancy or conditions affecting drug absorption.

Participants were 19 to 65 years of age (mean = 37.5 years, SD = 12.4 years). The majority (78.6%) were white, 11.9% African American, 9.5% Hispanic, 9.5% Asian, and 4.8% Native American. Among participants, 54.7% had an undergraduate degree and 62.5% had a household income of less than $40,000/year. The index traumas (ie, worst reported trauma) were 28.6% nonsexual assault, 19.0% sexual assault, 11.9% car or other accident, 11.9% combat trauma, 9.5% natural disaster, 7.1% childhood sexual assault, 4.8% nonsexual childhood assault, and 7.1% other trauma. Approximately half (47.5%) had prior psychiatric treatment.

Design

Patients were randomly assigned from September 2011 to April 2013, using double-blind procedures for the active treatments, stratifying on PTSD severity (PTSD Symptom Scale–Interview version (PSS-I) < 30 vs PSS-I ≥ 30) to either 260 mg of MB (n = 15) or placebo (n = 16), each following 5 daily imaginal exposure (IE) sessions, or waitlist (n = 11). In WL, patients received 10-session PE, twice weekly, after the 1-month follow-up (Figure 2).

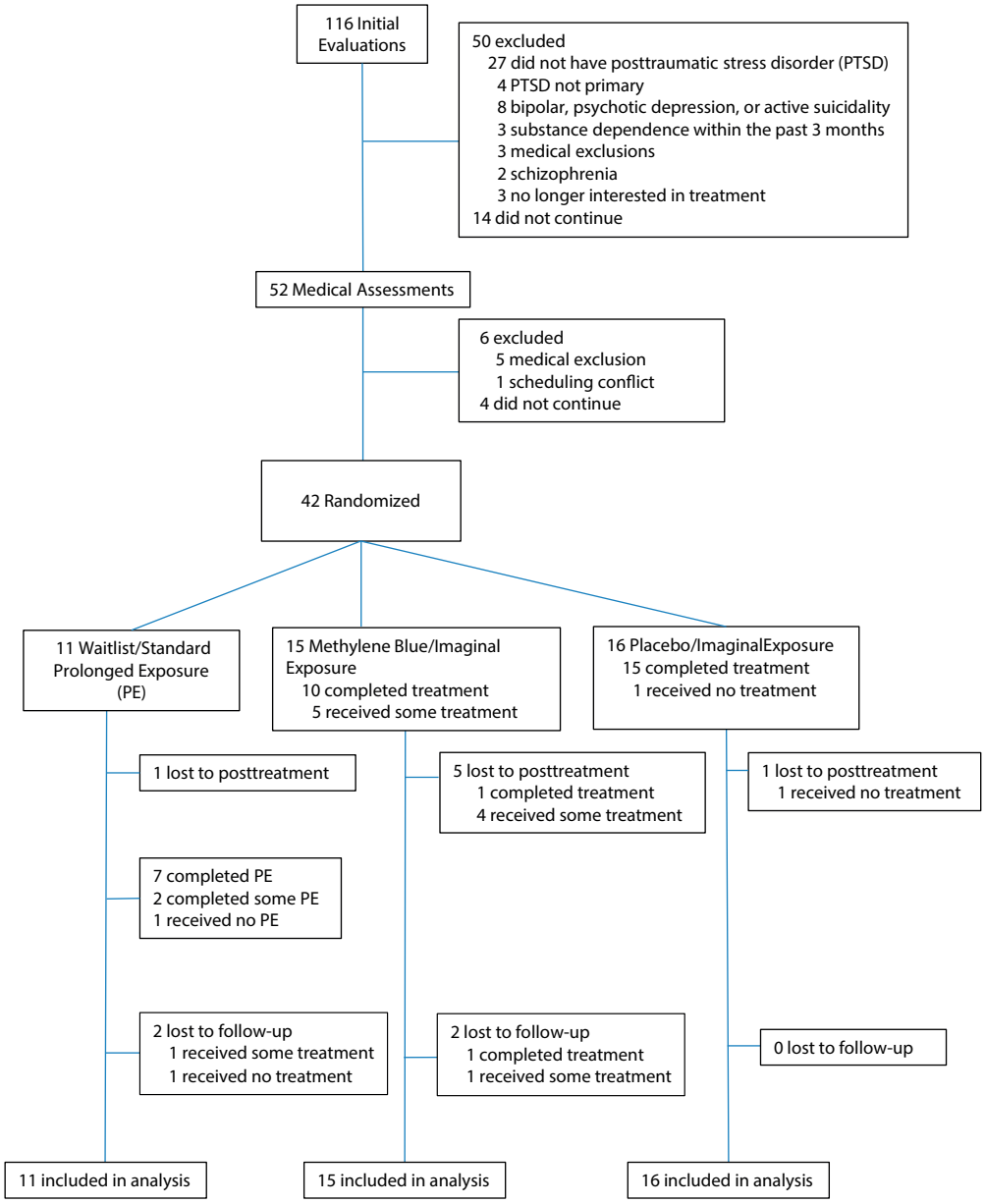
Interview Measures

PTSD Symptom Scale–Interview version (PSS-I).[25] The 17-item PSS-I scale rates *DSM-IV* criteria on a 0 to 3 scale, converging with other interview measures.[26] For a random subsample (14%), interrater reliability was assessed, with excellent agreement on severity (*intraclass correlation coefficient* (ICC) = 0.95, 95% CI = 0.81–1.00) and diagnosis (κ = 1.00).

Clinical Global Impressions–Improvement scale (CGI-I).[27] The CGI-I measures global improvement, from 1 (*very much improved*) to 7 (*very much worse*), and was used to calculate responder status. In a random subsample (14%), interrater agreement was high (ICC = 0.92, 95% CI = 0.68–0.99).

Structured Clinical Interview for DSM-IV (SCID-IV).[28] The SCID-IV was used to assess *DSM-IV* Axis I exclusion criteria. The SCID-IV has acceptable interrater reliabilities, with κ values between 0.70 and 0.94.[29,30]

Figure 2. CONSORT Diagram



Self-Report Measures

Patients reported symptoms from the previous 2 weeks at pretreatment, posttreatment, and 1-month and 3-month follow-up and from the past 24-hour interval for between sessions.

PTSD Symptom Scale–Self-Report (PSS-SR).[31] This 17-item measure assesses *DSM-IV* PTSD symptoms. It has good internal consistency, test-retest reliability, and diagnostic agreement with the SCID-IV.

Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR).[32] This 16-item measure assesses cognitive, anxiety, sleep, and appetite symptoms of depression. It has good internal consistency[33] and convergent validity.[34]

Posttraumatic Cognitions Inventory (PTCI).[35] This 36-item measure assesses dysfunctional posttrauma cognitions across self, world, and self-blame and yields a total score. Each of the 3 subscales has high internal consistency (0.97, 0.88, 0.86, respectively).

Automated Operation Span (OSPAN).[36] This computer-administered working memory capacity task has good internal consistency and test-retest reliability.

Short-Form Health Survey (SF-36).[37] This is a psychometrically validated 36-item measure of health status and outcomes.[38] The vitality and mental health subscales were selected to assess quality of life.

Sheehan Disability Scale (SDS).[39] The SDS assesses disability in 3 spheres: work, social/leisure activities, and

Table 1. Outcomes for Brief, Daily Imaginal Exposure + Methylene Blue (MB); Brief, Daily Imaginal Exposure + Placebo (PBO); and Waitlist/Standard Prolonged Exposure (WL/PE)[a]

	Pretreatment			Posttreatment			1-Month Follow-Up			3-Month Follow-Up		
Outcome	MB	PBO	WL	MB	PBO	WL	MB	PBO	WL	MB	PBO	WL/PE
PTSD severity (PSS-I)	32.07 (6.17)	31.38 (6.88)	32.73 (7.24)	17.10 (10.57)	14.67 (9.27)	29.60 (8.40)	10.33 (3.77)	13.33 (9.15)	28.33 (7.43)	7.63 (5.53)	10.93 (9.95)	7.25 (9.82)
PTSD diagnosis, %	100	100	100	30.0	33.3	90.0	11.1	33.3	88.9	0.0	13.3	12.5
Responder, %	0	0	0	70.0	86.7	10.0	100.0	93.3	22.2	100.0	86.7	100.0
PTSD severity (PSS-SR)	32.53 (7.83)	29.88 (7.28)	35.36 (7.84)	16.00 (12.06)	15.13 (9.49)	35.11 (6.03)	9.44 (8.09)	12.73 (8.16)	31.67 (8.12)	9.63 (10.29)	13.20 (11.70)	9.13 (11.29)
Depression (QIDS-SR)	13.27 (4.59)	12.81 (8.16)	13.82 (4.58)	7.55 (4.53)	8.40 (6.00)	13.11 (3.82)	6.00 (4.39)	6.53 (4.44)	12.44 (6.09)	5.00 (3.63)	6.80 (5.24)	4.13 (5.17)
Negative beliefs (PTCI)	141.33 (37.94)	142.88 (28.67)	145.91 (27.26)	100.56 (44.25)	109.13 (35.08)	150.67 (30.14)	90.56 (43.45)	107.00 (38.22)	148.78 (30.31)	75.88 (42.13)	108.60 (47.61)	82.75 (47.02)
Disability (SDS)	18.14 (6.51)	16.75 (6.63)	20.55 (4.80)	11.00 (7.23)	10.20 (7.88)	17.33 (7.73)	7.11 (6.97)	8.73 (9.20)	17.55 (7.73)	6.25 (6.20)	9.20 (6.91)	6.75 (7.76)
Quality of life (SF-36, mental)	43.33 (15.66)	40.78 (15.48)	35.00 (15.65)	56.11 (20.73)	59.00 (19.20)	35.56 (15.50)	67.22 (15.02)	56.83 (21.97)	41.11 (16.16)	73.75 (13.02)	59.67 (15.64)	72.50 (18.13)
Quality of life (SF-36, vitality)	30.14 (21.35)	35.81 (19.11)	26.33 (13.64)	47.22 (26.90)	49.58 (22.47)	27.78 (11.32)	59.03 (20.04)	49.17 (19.75)	23.84 (10.32)	66.41 (15.65)	51.25 (17.55)	59.38 (17.99)

[a]Values are presented as mean (SD) unless otherwise noted. Means and standard deviations are presented for observed values.
Abbreviations: PSS-I = PTSD Symptom Scale–Interview version, PSS-SR = PTSD Symptom Scale–Self-Report, PTCI = Posttraumatic Cognitions Inventory, PTSD = posttraumatic stress disorder, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Rated, SDS = Sheehan Disability Scale, SF-36 = Short-Form Health Survey.

family/home life, with a total score calculated for this study. The SDS has adequate reliability and validity.[40]

Subjective Units of Distress Scale (SUDS).[41] SUDS ratings were used to assess subjective distress level, using a 0 to 100 scale, from 0 (*no anxiety*) to 100 (*most anxious you can imagine*).

Medication Effects Form (MEF).[42] This 34-item scale assessed medication-related side effects, rated from 0 (*not present*) to 3 (*severe*). The MEF was administered 30 minutes after drug administration (end of session) and at the beginning of each subsequent treatment session.

Interventions

Brief, daily imaginal exposure (IE). Six 50-minute daily sessions of IE were conducted based on the PE manual.[43] No in vivo exposure or homework was included. Session 1 included a rationale for IE and common reactions to trauma. Sessions 2 to 6 focused on IE (30–45 minutes) and processing of the IE (15 minutes), with later sessions focused on the most distressing part of the memory and the final session including relapse prevention. Patients were treated by a masters-level or doctoral-level therapist, blind to study condition. Therapists were trained in a multiday training by E.B.F. Sessions were video recorded. A doctoral-level clinician blind to condition rated a randomly selected 10%. Therapists displayed excellent adherence (96%) and competence (91%).

Methylene blue and placebo. A 260-mg dosage of United States Pharmacopeia (USP)–grade MB (ScienceLab.com; Spectrum Chemicals) was selected based on 4 mg/kg as an effective memory-enhancing dose.[14,16] Because MB turns urine light green or blue, matching placebos contained an inert food dye (FD&C Blue No. 2). Methylene blue or PBO was administered post IE, with monitoring of SUDS, blood pressure, and heart rate. Guidelines for withholding administration of MB/PBO were (1) an unusually strong distress response during IE (ie, peak SUDS ≥ 95) and (2) a failure of that distress response to subside (ie, reduction < 25% of peak SUDS by the end of the session). One patient's MB dose at 1 session was withheld due to this rule.

Waitlist. Patients assigned to the WL condition started treatment after the 1-month follow-up, receiving a standard course of 10 twice-weekly PE sessions. The 3-month follow-up served as their posttreatment assessment.

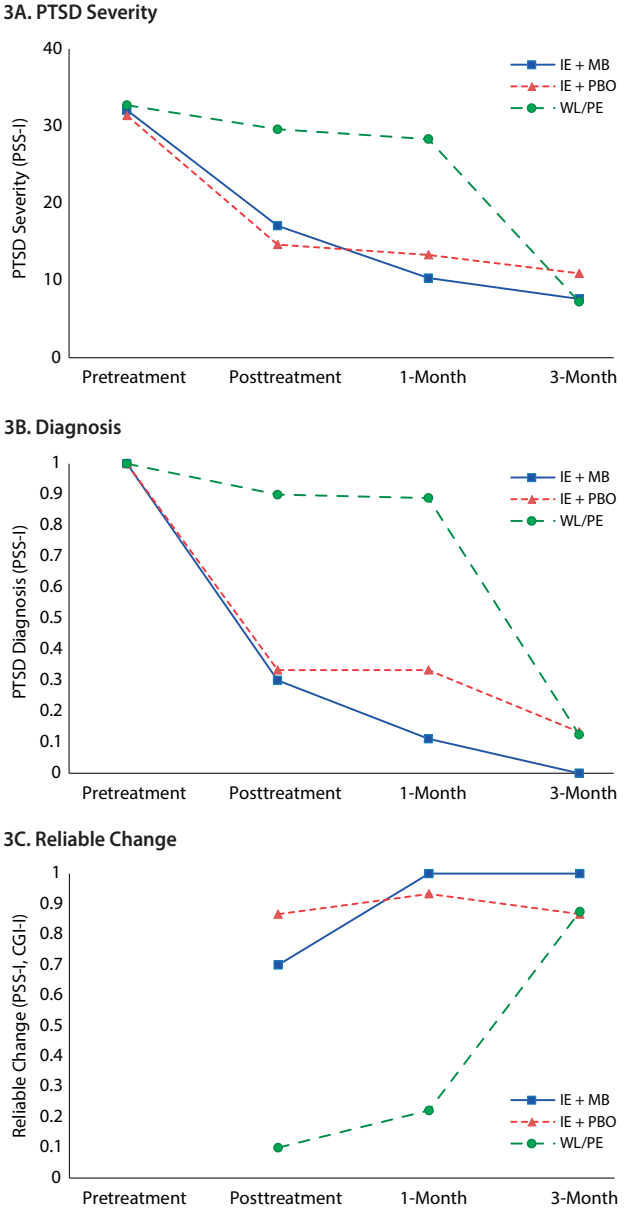
Procedures

The study was registered at ClinicalTrials.gov (identifier: NCT01188694) and was approved by the respective institutional review boards. Potential patients underwent a phone screen and were scheduled with an independent evaluator to assess PTSD (PSS-I) and exclusionary diagnoses (SCID-IV). Self-report measures (eg, PSS-SR, QIDS-SR, PTCI, SDS) were also completed. Eligibility was further determined via physical examination and laboratory panel from urine and blood samples, reviewed by each site's medical director. Eligible patients were randomly assigned using a computer program, with the double-blinding held by a single preparing pharmacy.

Prior to each session, patients completed the PSS-SR, QIDS-SR, PTCI, and MEF with reference to the last 24 hours. Heart rate and blood pressure were monitored before and after each session, and SUDS were monitored every 5 minutes during IE. The MEF was also completed after each drug administration session (sessions 2–6). The medical director administered the first MB/PBO dose, and the nurse administered MB/PBO thereafter. Patients remained on site for 30 minutes and were given an evening check-in call and a 24-hour contact number.

The posttreatment assessment was completed approximately 2 weeks after session 6 by independent

Figure 3. Patterns of Response for Imaginal Exposure Plus Methylene Blue (IE + MB), Imaginal Exposure Plus Placebo (IE + PBO), and Waitlist Where, Between 1- and 3-Month Follow-Up, Full Prolonged Exposure Was Administered (WL/PE) Across Posttraumatic Stress Disorder (PTSD) Severity, Diagnosis, and Reliable Change



Abbreviations: CGI-I = Clinical Global Impressions–Improvement scale, PSS-I = PTSD Symptom Scale–Interview version.

evaluators (PSS-I, CGI), and patients completed self-report measures (PSS-SR, QIDS-SR, PTCI, SDS). At 1 month posttreatment (1-month follow-up), these same measures were completed and patients were classified as responders or nonresponders, using the Reliable Change Index, cutoff c.[44] Responders were defined as ≤ 23 on the PSS-I and ≤ 3 on the CGI-I. Nonresponders in either IE + MB or IE + PBO were offered 10 standard PE sessions at no cost. After the 1-month follow-up, patients in WL started twice-weekly PE for 5 weeks, with their posttreatment assessment being the 3-month follow-up. Final follow-up was at 3 months.

Data Analysis

All analyses were intent-to-treat, using mixed effects modeling for continuous outcomes and generalized linear mixed models (GLMM) for binary outcomes, using restricted maximum likelihood and quasi-likelihood techniques respectively. Pattern mixture models yielded no statistically significant evidence of informative missingness; therefore, all missing data points were treated as ignorable and randomly missing. Effect size d was calculated using on-average difference divided by the pooled standard deviation.

RESULTS

PTSD Outcomes

The pattern of PTSD change over time is shown in Table 1 and Figure 3. For our main outcome measure of evaluator-rated PTSD severity (PSS-I), there was a treatment × time interaction ($F_{3,90} = 11.65$, $P < .0001$); both IE + MB and IE + PBO were significantly different from WL at posttreatment and 1-month follow-up; neither differed from standard PE at 3-month follow-up. Both diagnostic and responder status mirrored these results, with significant differences between acute treatment (IE + MB, IE + PBO) and WL at posttreatment (diagnostic status: $F_{2,57} = 3.34$, $P = .04$; reliable change: $F_{2,57} = 5.47$, $P = .007$) and 1-month follow-up (diagnostic status: $F_{2,57} = 4.08$, $P = .02$; reliable change: $F_{2,57} = 4.85$, $P = .01$). However, at 3-month follow-up, effect sizes favoring IE + MB over IE + PBO emerged showing small to moderate effects. For PTSD severity and PTSD diagnosis, the differential effects (nonsignificant) were small ($d = 0.12$, $d = 0.29$, respectively) but were moderate for reliable change ($b = 0.29$, $t_{68} = 1.95$, $P = .05$, $d = 0.47$, number needed to treat = 7.5). Taken together, both brief interventions (IE + MB, IE + PBO) did not differ from standard PE at 3-month follow-up, with evidence of superiority of MB over PBO on reliable change.

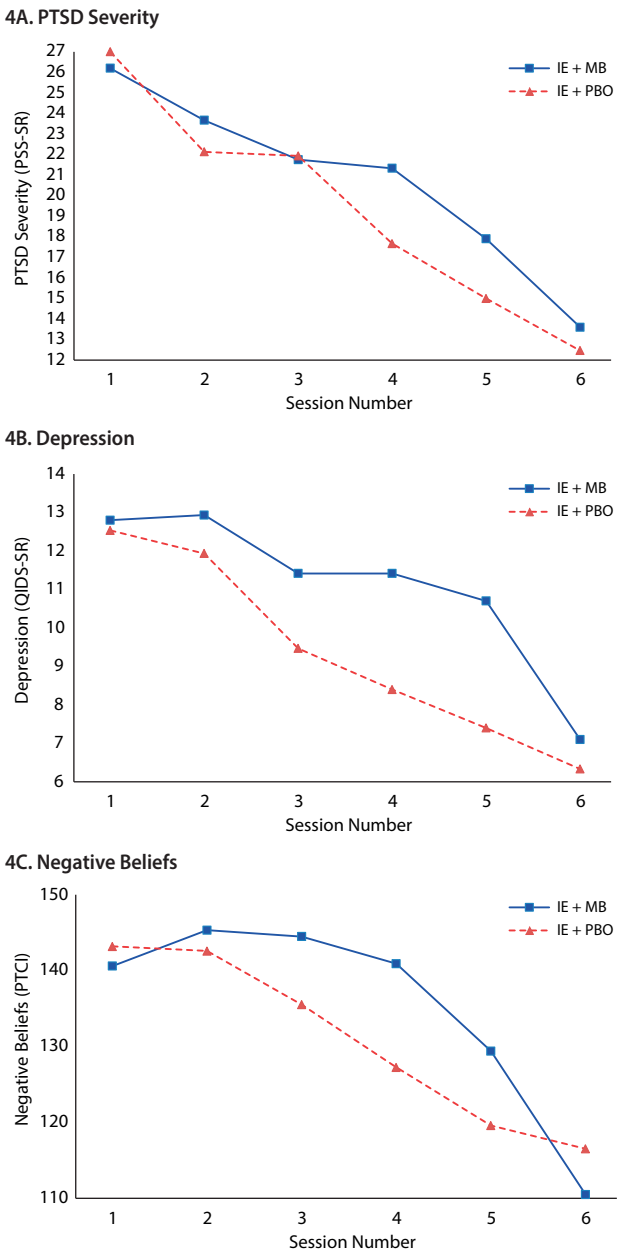
Secondary Outcomes: Depression, Beliefs, and Functioning

This pattern of no significant difference at 3-month follow-up for IE + MB versus standard PE or IE + PBO versus standard PE was also seen for depression (QIDS-SR), trauma-related negative beliefs (PTCI), disability (SDS), and quality of life (SF-36). At 3-month follow-up, effect sizes favoring IE + MB over IE + PBO showed small to moderate effects. For depression, negative beliefs, and disability, the differential effect sizes were not significant and small (respectively, $d = 0.05$, $d = 0.18$, and $d = 0.23$) but were moderate for quality of life mental health ($b = 28.34$, $t_{67} = 2.39$, $P = .02$, $d = 0.58$ and physical vitality ($b = 21.46$, $t_{67} = 1.90$, $P = .06$, $d = 0.46$).

Process of Change Across Sessions

Notably, for measures collected daily during brief imaginal exposure (PSS-SR, QIDS-SR, PTCI), the pattern of

Figure 4. Trajectories of Acute Session Change for Imaginal Exposure Plus Methylene Blue (IE + MB) Versus Imaginal Exposure Plus Placebo (IE + PBO) in Posttraumatic Stress Disorder (PTSD) Severity, Depression, and Negative Beliefs



Abbreviations: PSS-SR = PTSD Symptom Scale–Self-Report, PTCI = Posttraumatic Cognitions Inventory, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Rated.

change was different between IE + MB and IE + PBO (Figure 4). For depression, there was a difference between MB and PBO on slope (linear; $b = 2.56$, $t_{102} = 2.20$, $P = .04$, $d = 0.44$) and acceleration of slope (quadratic $b = -0.27$, $t_{102} = -1.65$, $P = .10$, $d = 0.33$). For negative beliefs, there was a difference between IE + MB and IE + PBO on slope ($b = 17.22$, $t_{102} = 3.05$, $P = .003$, $d = 0.60$) and acceleration of slope ($b = -2.50$, $t_{102} = -3.34$, $P = .001$, $d = 0.66$). In summary, IE + PBO showed linear trajectory with rate of change; whereas IE + MB had a quadratic trajectory of change, suggesting that IE + MB is potentially delaying and then later accelerating clinical gains in comparison to IE + PBO.

Tolerability of Methylene Blue

There were no severe adverse events (AEs). Four patients in IE + MB, 4 patients in IE + PBO, and 1 patient in WL experienced mild to moderate AEs during the trial. One AE (in IE + MB) resulted in treatment discontinuation; it was rated as potentially, but not definitely, related to the treatment and likely related to preexisting diagnostic comorbidity. Adverse events did not differ significantly across treatment conditions. Across sessions, patients in IE + MB reported more side effects (mean = 9.70, SD = 5.56) than those in IE + PBO (mean = 5.70, SD = 4.00; $F_{1,26} = 4.70$, $P = .04$, $d = 0.82$). As evidenced by the low observed means, side effects were rated as minimal. The most common side effect was urine or fecal discoloration, an expected byproduct.

Rates of dropout did not differ significantly between treatment conditions (IE + MB: 33.3%; IE + PBO: 6.3%; WL/standard PE: 36.4%). In IE + MB, the modal session dropout was after session 2 (after first administration of MB), and the mean was after session 3, suggesting early rather than late dropout; this was not statistically tested. Only 1 patient, in IE + PBO, chose to be retreated with standard PE, with this person's data removed for 3-month follow-up analyses.

Indirect Effects of Memory, Distress, and Beliefs

Pretreatment working memory capacity (OSPAN) moderated changes between IE + MB and IE + PBO on PTSD severity (PSS-SR; $b = -10.39$, $t_{54} = -2.44$, $P = .02$, $d = 0.66$), depression ($b = -4.93$, $t_{54} = -2.09$, $P = .04$, $d = 0.57$), negative beliefs (PTCI; $b = -39.37$, $t_{54} = -2.95$, $P = .004$, $d = 0.80$), and disability ($b = 6.33$, $t_{53} = -1.83$, $P = .07$, $d = 0.50$), such that those in IE + MB with better working memory made superior clinical gains. Distress at the end of session 2, showed a trend toward an indirect effect for depression ($b = 3.58$, $t_{63} = 1.83$, $P = .07$, $d = 0.46$), such that those in IE + MB with higher distress showed less reduction in depression than those in IE + PBO. Change in negative beliefs mediated changes between IE + MB and IE + PBO on PTSD severity (PSS-I; $b = 7.19$, $t_{63} = 2.71$, $P = .009$, $d = 0.68$), depression ($b = 5.78$, $t_{63} = 3.09$, $P = .003$, $d = 0.78$), and disability ($b = 10.24$, $t_{62} = 3.83$, $P < .001$, $d = 0.97$), such that, although cognitive changes mediated the effects of IE + PBO, they did not mediate the effects of IE + MB.

DISCUSSION

The present study provides preliminary evidence for the efficacy of brief IE with MB or PBO, yielding no difference across multiple indices compared to the standard PE protocol. Initial evidence also points to small to moderate differences favoring IE + MB over IE + PBO at follow-up, an altered trajectory of change for patients taking MB, and potentially different mechanisms driving MB-augmented

exposure. MB was generally well tolerated as evidenced by few adverse events and only minor side effects.

The efficacy of brief, daily IE is novel in its use of a simplified intervention and is consistent with the growing literature showing that shortened interventions produce meaningful clinical gains in PTSD.[22,45,46] Further, the low dropout rate (6.3% in IE + PBO) suggests that this intervention may have applications for populations at risk for dropout.

MB-augmented IE initially showed a slower rate of change, particularly for depression and negative beliefs, which accelerated over the course of treatment, whereas IE + PBO showed a linear pattern of change. Consistent with prior literature,[16,47] MB in the early sessions may delay initial gains by consolidating the distress experienced in initial exposures rather than extinction learning that may occur over repeated sessions. Indeed, fear expression activates a neural network involving the amygdala and anterior cingulate cortex, whereas memory for fear extinction activates the ventromedial prefrontal cortex and hippocampus.[48] Accordingly, during early sessions, MB would be expected to facilitate "fear-expression," whereas during later sessions, MB would facilitate the "fear-extinction" neural network. Consistent with this interpretation is the early dropout in MB. Administering MB only in the later sessions of exposure may lead to better therapeutic outcomes. Further, gains for those receiving MB-augmented exposure may continue following treatment, as evidenced by higher reliable change for MB versus placebo at 3-month follow-up.

Working memory capacity and change in negative beliefs emerged as differential predictors of MB versus PBO response. Patients with better working memory made stronger clinical gains in IE + MB than those in IE + PBO. Consistent with the memory-enhancing properties of MB,[12,49] perhaps patients with better working memory of the extinction learning in sessions show stronger clinical gains. In contrast, consistent with other studies,[47] self-reported distress after IE did not differentially predict outcome, with the exception of a trend for depression. As seen in D-cycloserine, specific extinction-learning indices have not been consistently linked to enhanced exposure outcome.[50] Finally, consistent with the growing evidence that cognitive shifts drive PTSD reductions in PE,[22–24] changes in negative beliefs were associated with greater change in IE + PBO. However, this was not the case for IE + MB, arguing for a divergent mechanism underlying these effects.[16]

This was a small clinical trial powered to detect large effects, limiting the generalizability of the findings. Analyses such as dropout may have emerged as significant if the sample size was larger, as these are based on only a few people. Augmentation using MB was limited by IE efficacy, leaving little room to detect differential effects. The dosage and timing of MB were not manipulated. Other doses or administration protocols may yield larger effects. A strategy of MB administration in the late but not the early sessions may have helped mitigate undesired early effects.

This trial provides preliminary evidence for efficacy of a 50-minute, 6-session imaginal exposure intervention for PTSD, related psychopathology, and functioning. There was evidence that MB improved final outcomes, although effect sizes were small to moderate. Better tailoring of MB augmentation to the late phase of exposure sessions may reduce dropout, further accelerate change, and improve outcomes.

Submitted: May 11, 2016; accepted October 24, 2016.

Published online: July 5, 2017.

Potential conflicts of interest: None.

Funding/support: This work was funded by R34MH087375 (PI: Zoellner) from the National Institute of Mental Health.

Role of the sponsor: The study sponsor had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Acknowledgments: We thank Ashley Banner, BA (University of Texas [UT]); Lindsay Kramer, BS (University of Washington [UW]); and Hillary Smith, BA, BS (UW), for their work on organizing the implementation of the study. We would also like to thank the medical directors and nurses who helped with this study: Elizabeth Alexander, MD (UW); Pilar Cristancho, MD (University of Pennsylvania [UPenn]); Donald Garcia, MD (UT); Michell Gerbozy, RN (UT); Alice Friedman, RNNP (UW); Patricia Imms, RN (UPenn); Joshua McDavid, MD (UW); and Beverly Nolan, RN (UT). None of these individuals reported any conflicts of interest.

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