Effects of Post-Session Administration of Methylene Blue on Fear Extinction and Contextual Memory in Adults With Claustrophobia

Michael J. Telch, Ph.D.

Aleksandra K. Bruchey, Ph.D.

David Rosenfield, Ph.D.

Adam R. Cobb, M.A.

Jasper Smits, Ph.D.

Sandra Pahl, Ph.D.

F. Gonzalez-Lima, Ph.D.

Objective: Preclinical studies have shown that low-dose methylene blue increases mitochondrial cytochrome oxidase activity in the brain and improves memory retention after learning tasks, including fear extinction. The authors report on the first controlled experiment to examine the memory-enhancing effects of posttraining methylene blue administration on retention of fear extinction and contextual memory following fear extinction training.

Method: Adult participants displaying marked claustrophobic fear were randomly assigned to double-blind administration of 260 mg of methylene blue (N=23) or administration of placebo (N=19) immediately following six 5-minute extinction trials in an enclosed chamber. Retesting occurred 1 month later to assess fear renewal as indexed by peak fear during exposure to a nontraining chamber, with the prediction that the effects of methylene blue would vary as a function of fear reduction achieved during extinction training. Incidental contextual memory was assessed 1 and 30 days after training to assess the cognitive-enhancing effects of methylene blue independent of its effects on fear attenuation.

Results: Consistent with predictions, participants displaying low end fear posttraining showed significantly less fear at the 1-month follow-up if they received methylene blue posttraining compared with placebo. In contrast, participants displaying moderate to high levels of posttraining fear tended to fare worse at the follow-up if they received methylene blue posttraining. Methylene blue's enhancement of contextual memory was unrelated to initial or posttraining claustrophobic fear.

Conclusions: Methylene blue enhances memory and the retention of fear extinction when administered after a successful exposure session but may have a deleterious effect on extinction when administered after an unsuccessful exposure session.

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Over the past four decades, research on exposure therapy has shifted from demonstrating therapeutic efficacy toward the study of change mechanisms and augmentation strategies to improve short-term efficacy and reduce the return of fear (1, 2). Significant advances in cognitive and behavioral neuroscience have led to a better understanding of fear extinction and have ushered in a new era of "translational" research focusing on the integration of findings from these basic science disciplines to improve extinction-based therapies for anxiety disorders (3, 4).

A recent development in exposure therapy research is the use of memory-enhancing pharmacological agents to boost fear extinction during exposure therapy. The most widely studied of these is D-cycloserine, an *N*-methyl-D-aspartate receptor co-agonist. Based on early preclinical data demonstrating that D-cycloserine enhances fear extinction in rats (5), a series of randomized clinical trials have examined the clinical efficacy of exposure therapy with D-cycloserine augmentation across a range of anxiety disorders (for a review, see reference 6). Overall, findings have been mixed, with some showing strong augmentation effects (7–10), others showing weak (11–13) or negligible effects (14–16), and one study showing detrimental effects (17).

Another promising pharmacological agent that has received significant support in preclinical studies is methylene blue. Available in every emergency department as an antidote against metabolic poisons, methylene blue has been used safely for well over 100 years (18). Methylene blue is a diamino phenothiazine drug that at low doses (0.5–4 mg/kg) has neurometabolic-enhancing properties (19). Preclinical research with rodents has shown that at low doses, methylene blue is a metabolic and cognitive enhancer that improves brain oxygen consumption, brain glucose uptake, cerebral blood flow, functional MRI (fMRI) responses, and memory consolidation by induction of cytochrome oxidase, the respiratory enzyme found within nerve cells (19–21). By enhancing cytochrome oxidase activity, methylene blue increases oxygen consumption and the amount of ATP available in neurons during memory consolidation. Although methylene blue has the potential to enter any nerve cell, it preferentially accumulates in neurons with higher energy demand, such as those involved in memory consolidation after extinction training

(22). Hence, by acting as a mitochondrial electron cycler and antioxidant, low-dose methylene blue increases cellular energy production and enhances memory consolidation in key brain regions associated with memory processing (19).

Posttraining administration of low doses of methylene blue in rodents has been shown to improve memory retention in a variety of tasks, including inhibitory avoidance (23, 24), spatial memory (24–27), discrimination learning (28), and, most relevant to the present study, retention of conditioned fear extinction (22, 29). The Gonzalez-Lima et al. research group (22, 29) found that memory retention of extinction after Pavlovian fear conditioning using an animal model could be improved with the administration of 4 mg/kg of methylene blue postextinction. Moreover, the rate of cytochrome c oxidation in brain homogenates of these animals showed a 38% increase in absolute brain metabolic activity, compared with that for a comparison group administered saline. Cytochrome oxidase histochemistry revealed the largest effect on the prefrontal cortex (22), a brain region that is clearly implicated in fear extinction (30–32).

Based on these preclinical studies, we sought to test whether postextinction methylene blue administration enhances the retention of pathological fear attenuation in individuals with claustrophobia receiving extinction training. Given recent findings suggesting that the facilitative effects of other cognitive enhancers, such as D-cycloserine (33) and yohimbine (34), may depend on the posttraining clinical status of the patient, we hypothesized that methylene blue would enhance fear extinction retention at the 1-month follow-up in participants who achieved low levels of fear at posttraining. In contrast, we predicted that methylene blue would be less effective than placebo at follow-up in participants who continued to display higher levels of fear at posttraining.

A second aim of this experiment was to address a significant limitation of all previous studies of cognitive enhancers and exposure therapy, namely, the lack of indexing cognitive enhancement independent of differences in fear responding. Toward this aim, we administered an episodic contextual memory test, with incidental encoding and free recall, 1 and 30 days after completion of extinction training. We predicted that participants who were administered methylene blue would display enhanced memory performance compared with those receiving placebo, irrespective of clinical status at posttraining.

Method

Participants

Participants (N=42) reporting marked claustrophobic fear (peak fear score >50 on a 100-point scale) while performing two consecutive behavioral approach tests and meeting DSM-IV criteria for claustrophobia (excluding the requirement of functional impairment, criterion E) were recruited from a large participant pool of undergraduate students (N=1,163) through a two-stage screening process. Detailed information on exclusion criteria is presented in the data supplement accompanying the online version of this article.

Randomly assigned participants ranged in age from 18 to 36 years (mean age=19.3 years [SD=1.46]) and were predominantly female (82%), white (76.19%), and non-Hispanic (71.43%). A detailed description of the sample characteristics is presented in Table 1 (35, 36).

Study Design and Procedures

Potential study participants completed a brief online assessment of claustrophobia (stage 1). Those reporting marked fear of enclosed spaces were invited to the laboratory for a face-to-face screening visit (stage 2), which also served as their formal pretreatment assessment. This consisted of 1) the Structured Clinical Interview for DSM-IV Axis I Disorders (37), 2) completion of self-report patient-rating scales, and 3) behavioral approach tests involving exposure to two distinct claustrophobia chambers. Eligible participants were stratified on gender and pretreatment claustrophobia severity and randomly assigned in double-blind fashion to one of two treatment arms: extinction training plus postsession methylene blue or extinction training plus postsession placebo. All extinction training was completed in one session and was identical in the two treatment arms. Ratings of peak fear and end fear after each of six 5-minute exposure trials were obtained. Outcome assessments identical to the pretreatment assessment were obtained immediately after extinction training and at a 1-month follow-up visit (for a graphical depiction of the experimental design and participant flow chart, see Figure S1 in the online data supplement). All study procedures were approved by the institutional review board at the University of Texas at Austin.

Extinction Training Paradigm

The extinction training paradigm we utilized has been used in several published basic studies evaluating the mechanisms of change in exposure therapy (38–42). In brief, the paradigm consists of the following elements: brief education about the nature of claustrophobia; presentation of a therapy rationale emphasizing the fear-reducing effects of direct confrontation with the feared target; six 5-minute in vivo exposure trials in which the participant enters a tightly enclosed wooden chamber and remains inside in a supine position for a duration of 5 minutes; and completion of self-report rating scales after each exposure trial.

Medication

United States Pharmacopeia-grade methylene blue powder (ScienceLab, Houston) was put into gelatin capsules, which were identical in appearance to the placebo capsules that contained food dye indigo carmine powder (FD&C blue no. 2, ScienceLab, Houston). Capsules were provided to each participant in a sealed, numbered envelope prepared by an unblinded pharmacist at the University of Texas at Austin. All other study personnel were blind to the drug condition. The 260-mg methylene blue dose corresponds to the 4-mg/kg dose shown to be effective in previously published preclinical studies of object recognition memory and fear extinction (22, 24, 29). Methylene blue and placebo were administered on three occasions, at a dose of one 86.66-mg capsule each. One capsule was administered immediately following the completion of extinction training. The participants were instructed to take the second capsule before going to bed that night (6–10 hours later) and to take the last capsule after waking up (another 6–10 hours later). This divided dosing schedule was intended to reduce possible urinary tract irritation sometimes associated with methylene blue excretion through the urine. Participants were instructed to take the capsules with a large glass of water in order to further minimize the chance of urinary tract irritation and to reduce the intensity of urine discoloration. Since

TABLE 1. Baseline Characteristics of Participants With Claustrophobic Fear

Variable	Methylene Blue Plus Extinction Training (N=23)		Placebo Plus Extinction Training (N=19)	
	Mean	SD	Mean	SD
Claustrophobia Questionnaire score[a]	70.91	10.64	68.42	12.88
Claustrophobic Concerns Questionnaire score[b]				
Training context	78.26	16.71	79.47	12.71
Generalization context	72.50	20.31	71.45	14.89
Behavioral Approach Task (peak fear) score				
Training context	77.39	17.38	68.95	16.96
Generalization context	66.09	16.72	63.68	15.35
Age (years)	19.04	1.46	19.58	3.66
	N	%	N	%
Gender				
Male	5	21.74	5	26.32
Female	18	78.26	14	73.68
Race/ethnicity				
White	17	73.91	15	78.95
African American	1	4.35	0	0.00
Asian	5	21.70	3	15.79
Native Hawaiian/Pacific Islander	0	0.00	1	5.26
Other	0	0.00	0	0.00
Hispanic	7	30.43	5	26.32

[a] The total and subscale scores (i.e., suffocation and restriction) for the Claustrophobia Questionnaire (see reference 35) are reported in Table S2 of the online data supplement.
[b] The data represent total scores for the Claustrophobic Concerns Questionnaire (see reference 36).

the average half-life for urinary excretion of methylene blue is 6.6 hours (43), our administration procedure served to maintain methylene blue in the circulation throughout the critical memory consolidation period following extinction training.

Twenty-four hours after completing extinction training, participants were administered a telephone interview to assess medication adherence and side effects.

Measures

In vivo fear responding to behavioral approach tests. Two behavioral approach tests were performed at each of the three assessment points (preextinction training, postextinction training, and 1-month follow-up). These tests were procedurally identical but used different stimuli (claustrophobia chambers), both of which were located in a darkened room in our laboratory. As reported elsewhere, participants' fear responding 1 month later when placed inside the nontraining chamber (generalization context) served as the primary index of clinical efficacy. More detailed information on the behavioral approach tests is presented in the online data supplement.

Assessment of fear extinction. Every 5 minutes during extinction training, participants rated their peak fear on the same 0- to 100-point scale used during the behavioral approach tests. Consistent with our previous research (33), fear ratings obtained at the conclusion of the final exposure trial served as the primary index of fear extinction, with lower ratings indicating greater, and higher ratings indicating less, extinction learning success.

Assessment of episodic contextual memory. Inside the extinction training chamber and secured at each corner of the inner upper surface of the door were four 2-inch single-digit glow-in-the-dark numbers positioned in direct sight of the participants as they lay on their back inside the chamber. These numbers and their locations served as the target stimuli for our context memory test. Memory encoding of the numbers was incidental. No instructions were provided to participants to attend to the numbers, nor did the experimenter make reference to the numbers during extinction training. One and 30 days after completing extinction training, participants were provided a sheet of paper with a proportionally equivalent outline of the chamber and were asked to recall and record the numbers in their correct locations. The number of correct responses, defined as the sum of correctly recalled numbers in their correct locations, served as the primary index of contextual memory. Similar tasks have been used to investigate contextual memory deficits in depression (44), dyslexia (45), and Williams syndrome (46).

Data Analysis

Consistent with recommendations outlined by Kraemer et al. (47) for testing putative moderators in clinical trials, we performed a multiple regression analysis in which peak fear at the 1-month follow-up was predicted by drug condition (methylene blue compared with placebo), end fear (fear level at the last exposure trial), and their interaction. To enhance confidence that end fear was responsible for this effect and not other third variables associated with end fear, we followed the suggestions of Steiner et al. (48) and controlled for other relevant variables that may be related to both end fear and peak fear at follow-up. These control variables were initial fear at the first exposure trial, postexposure fear in the generalization context, and the presence (at baseline) of other axis I disorders.

To test the hypothesis that methylene blue would enhance contextual memory at the 1-month follow-up, we performed two additional regression analyses in which drug condition (methylene blue compared with placebo) was the predictor of participants' scores on our context memory index (modeled separately for posttest and follow-up). For consistency with our analyses of peak claustrophobic fear at follow-up, the presence of another axis 1 disorder was dichotomously coded and included as a covariate in the model.

Results

Effects of Methylene Blue on Fear Extinction

The mean fear level was 73.0 (SD=20.0; range: 20–100) at the first exposure and 23.5 (SD=23.3; range: 0–90) at the last exposure (end fear). As hypothesized, there was a significant drug condition-by-end fear interaction (b=−0.74; t=2.71, df=34, p=0.01; Cohen's d=0.93). We probed this interaction using procedures recommended by Aiken and West (49). This entailed two follow-up analyses, with end fear centered alternatively at low (end fear=0; 1 standard deviation below the mean) and high (end fear=47; 1 standard deviation above the mean) levels of fear. These analyses showed that for participants with low end fear (end fear=0), those given methylene blue had significantly lower levels of fear at the 1-month follow-up (peak fear=10.7) compared with those given placebo (peak fear=29.8) (b=19.2; t= 2.21, df=34, p=0.04; Cohen's d=0.76) (Figure 1). For those with higher levels of end fear, the opposite finding was observed; those given methylene blue had marginally higher levels of fear at the 1-month follow-up (peak fear=33.0) compared with those given placebo (peak fear=17.4) (b=−15.6; t=1.78, df=32, p=0.08; Cohen's d=0.63).

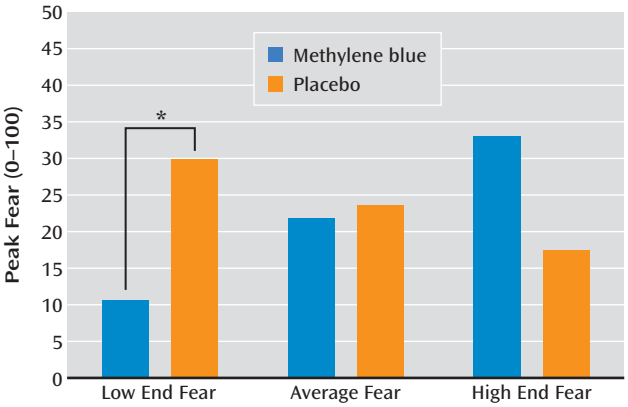
We used this same procedure to examine the model-based relation between end fear at the last exposure trial and peak fear at the 1-month follow-up for those given methylene blue compared with those given placebo. For those who received methylene blue, end fear at the last exposure trial significantly predicted peak fear at the 1-month follow-up (b=0.48; t=2.43, df=32, p=0.02; Cohen's d=0.86), with higher end fear associated with higher fear 1 month later. However, for those who received placebo, there was no significant relationship between end fear and peak fear at the 1-month follow-up (b=−0.27) (t=1.10, df=32, p=0.28; Cohen's d=0.39).

Effects of Methylene Blue on Contextual Memory

We also hypothesized that scores on our incidental contextual memory test given at the 1-day and 1-month follow-up assessments would reveal enhanced performance for those who received methylene blue compared with placebo. Although those in the methylene blue group did not have greater recall 1 day after completing extinction training (p=0.40), they did demonstrate better free recall performance at the 1-month follow-up (recall score=1.4) compared with those in the placebo group (recall score=0.7) (b=0.69; t=2.06, df=37, p<0.05; Cohen's d=0.68) (Figure 2).

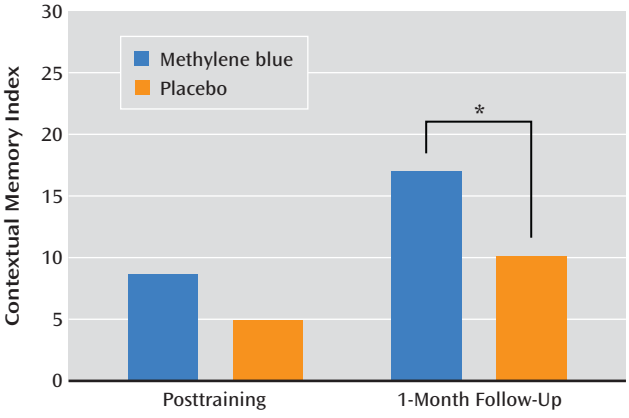
We next attempted to verify that recall assessed by our incidental context memory recall index was not merely a result of lower fear among participants in the methylene blue group. We found that peak fear at posttreatment was unrelated to incidental recall at posttreatment and at follow-up, across drug conditions (all p values >0.26) and within drug conditions (all p values >0.12). Similarly, peak fear at follow-up was unrelated to free recall at follow-up, both across drug conditions (all p values >0.57) and within each drug condition (all p values >0.23). The reverse possibility also received no support, since incidental recall at posttreatment was unrelated to peak fear at follow-up, both across (p=0.88) and within (all p values >0.33) drug conditions.

FIGURE 1. Effects of Methylene Blue on Peak Fear at the 1-Month Follow-Up Moderated by End Fear at the Last Extinction Trial[a]



[a] The graph shows the effects of methylene blue on peak fear in the generalization context at the 1-month follow-up in participants with low (end fear=0), average (end fear=23.5), and high (end fear=47) end fear levels at the last extinction trial. For participants with low end fear, those who received methylene blue had significantly lower levels of fear at the follow-up than those who received placebo (p=0.04). For those with higher levels of end fear, those who received methylene blue tended to show marginally significant higher levels of fear at the follow-up compared with those who received placebo (p=0.08). *p<0.05.

FIGURE 2. Effects of Methylene Blue on Contextual Memory Performance at Posttraining and the 1-Month Follow-Up[a]



[a] The graph shows the effects of methylene blue on contextual memory performance at posttraining and at the 1-month follow-up. Memory index scores depicted on the y-axis were derived by summing the total number of items for which participants correctly recalled both the number and its location (in the surface of the chamber). As shown, participants who received methylene blue posttraining demonstrated significantly better contextual memory performance at the 1-month follow-up (p<0.05) but not at the posttreatment assessment. *p<0.05.

TABLE 2. Reported Side Effects for Each Drug Condition

Side Effect	Methylene Blue Group		Placebo Group	
	Reporting Side Effect (%)	Mean Severity (Range: 0–4)	Reporting Side Effect (%)	Mean Severity (Range: 0–4)
Urine discoloration	95.6	3.3	21.1	2.9
Fecal discoloration	4.3	3.0	15.8	3.0
Increased frequency of urination	21.7	2.6	10.5	3.0
Indigestion	13.0	2.0	5.3	2.0
Diarrhea	8.7	2.5	0.0	—
Vomiting	4.3	2.0	0.0	—
Headache	13.0	2.0	21.1	2.3
Heart racing	4.3	1.0	0.0	—
Stomach cramps	0.0	—	5.3	3.0
Sensitivity to light	0.0	—	5.3	1.0
Trouble sleeping	8.7	1.5	0.0	—
Dizziness	17.4	2.0	0.0	—
Bladder irritation	4.3	2.0	0.0	—

Furthermore, because incidental recall could be associated with overall memory functioning and hence could be related to emotional memory of end fear at the last exposure trial, we investigated whether memory recall moderated the effect of end fear on peak fear at follow-up (i.e., end fear could be highly related to peak fear at follow-up for those with greater recall but less related to peak fear for those with poor recall). No evidence was found for this possibility (all p values >0.24). Thus, it appears that the memory facilitation effects of methylene blue at follow-up were independent of any differential changes in fear between the methylene blue and placebo groups.

Side Effects and Adverse Reactions

The frequency and mean severity of side effects reported during the study are summarized in Table 2. Minor side effects were reported in each drug condition. The three most commonly reported side effects in the methylene blue group were urine discoloration, increased frequency of urination, and dizziness, whereas the three most common side effects in the placebo group were urine discoloration, headache, and fecal discoloration. These side effects were generally mild, and no serious adverse reactions were observed. No problems with medication adherence were reported.

Discussion

Based on a fundamental assumption that the outcome of administering a memory-enhancing agent in combination with psychotherapy depends on what is learned during therapy, we hypothesized that methylene blue, compared with placebo, would promote the retention of fear extinction at a 1-month follow-up in individuals achieving marked fear attenuation during extinction training. In contrast, we hypothesized that for those showing minimal or no fear attenuation during training, methylene blue would show a less favorable outcome at the 1-month follow-up, compared with placebo, because of the potential strengthening of threat associations.

As predicted, end fear at posttraining significantly moderated the effects of methylene blue on claustrophobic fear in the nontrained, generalization context at follow-up. Specifically, participants displaying low end fear at posttraining showed significantly less fear at follow-up if they received methylene blue posttraining. The opposite pattern was observed for those displaying high levels of posttraining fear; that is, participants with high posttraining fear who received methylene blue posttraining tended to fare worse at follow-up compared with those who received placebo. These findings are consistent with preclinical studies in which methylene blue administered after fear extinction improved the retention of extinguished fear memories (22) and with later clinical studies using other cognitive enhancers, such as D-cycloserine (33), glucocorticoids (50), and yohimbine (34). Although the implications for those achieving average posttraining reduction in fear are less clear, the data underscore the importance of considering individual differences in patients' response to exposure therapy as an important factor in deciding when to use cognitive-enhancing agents in combination with psychotherapy.

Consistent with previous preclinical studies in rodents (19, 22–24, 27–29), our findings provide the first demonstration, to our knowledge, that low-dose methylene blue administration improves memory retention in humans. To determine whether the enhanced context memory performance observed in participants receiving methylene blue was a consequence of lower fear levels or differences on other clinical status variables (e.g., presence of comorbid axis I pathology), we controlled for these variables when testing the effects of drug condition on context memory performance. Results showed that the increased memory retention among methylene blue-treated participants was unrelated to individual differences in fear responding or history of other axis I disorders and thus supports the direct memory-enhancing effects of methylene

blue. There is no literature indicating whether the efficacy of methylene blue is affected by age or physical activity or by other factors affecting neurobiological oxygen uptake. However, the neurobiological efficacy of methylene blue has been demonstrated in both normoxia and hypoxia conditions in vivo (21).

We also considered the possibility that methylene blue's enhancement of contextual memory could have detrimental effects on later fear responding by enhancing the context dependency of fear extinction learning. For example, if the contextual associative links formed in the extinction context are especially strong, methylene blue augmentation could serve to circumscribe the inhibition of fear to select extinguished contexts (51, 52). However, our results suggest that the opposite occurs. Methylene blue appears to promote generalization of the learning that occurs during extinction training, for better or for worse, depending on the degree of in-session fear attenuation.

We assessed the effects of methylene blue on contextual memory independent of participants' fear responding. As mentioned, previous investigations of cognitive-enhancing agents in combination with exposure-based treatments have inferred cognitive enhancement based on greater symptom improvement among those receiving the cognitive enhancer compared with those receiving placebo. However, if the goal for using a cognitive enhancer with exposure therapy is to facilitate memory-related neuroplasticity so as to facilitate neural adaptations brought about by new learning occurring during exposure therapy (53), it is reasonable to expect enhancement of memory for context-relevant information unrelated to emotional responding. Thus, incorporating contextual memory tests, which have special relevance for fear extinction learning, provides an independent corroboration that memory-related neuroplasticity has indeed been enhanced.

Our findings should be interpreted in light of the neuropharmacological mechanisms governing the metabolic enhancement effects of methylene blue (19). Methylene blue enhances brain energy metabolism in two ways. The first mechanism is global. Methylene blue produces a global increase in brain cytochrome oxidase activity above baseline levels, which leads to enhanced capacity for oxidative energy production (22). This global action has been confirmed by increased baseline glucose uptake and cerebral blood flow using positron emission tomography and fMRI (20). However, this global effect is widespread and nonspecific. The second mechanism shows regional activational specificity. That is, methylene blue selectively potentiates cytochrome oxidase activity and evoked fMRI responses in brain regions activated by a specific task or stimulus (21, 22). Relative to the global effects of methylene blue, this activational effect is more pronounced and is specific to the neural networks demanding more energy utilization. In the case of fear-related neural networks, for example, memory for fear expression in humans activates a network that includes the amygdala and the dorsal anterior cingulate cortex, whereas memory for fear extinction activates a different network involving the ventromedial prefrontal cortex and hippocampal formation (31, 32). Therefore, among participants with high fear expression at the end of training, methylene blue would be expected to facilitate the "fear-expression network"; whereas in participants displaying marked fear extinction, methylene blue would be expected to facilitate the "fear-extinction network." Thus, administering methylene blue at the conclusion of exposure therapy may lead to opposite psychological outcomes depending on whether fear-expression or fear-extinction neural networks are potentiated. In contrast, since all participants were exposed to the same claustrophobia chamber, they may have shown the same contextual memory-enhancing effect from methylene blue irrespective of their level of fear activation because of the more global brain action of methylene blue, a hypothesis consistent with knowledge of the wide distribution of neural networks involved in context memory (51, 54, 55).

Study Limitations

Our study includes some limitations. First, our sample was relatively small and largely comprised of young, female university students. Thus, replication with a larger, more diverse sample is warranted. Second, conclusions as to whether methylene blue enhances exposure therapy in other anxiety disorders await further investigation. Third, single-item fear ratings (i.e., self-reported subjective units of distress) are a ubiquitous measure of fear responding in the phobia treatment literature. However, additional indices of fear, including physiological measurements, would have strengthened conclusions drawn from the present findings. Fourth, extinction training was delivered in a single session. Although single-session extinction-based treatments have been shown to be efficacious (42, 56), it remains unclear as to whether methylene blue enhances exposure therapy when delivered in a multisession treatment format. Fifth, a 4-mg/kg posttraining dosing strategy was selected because it has been shown to be the most reliable in rats for enhancing posttraining fear extinction memory retention (22, 29), as well as long-term behavioral habituation and object memory recognition (24). Future studies are needed to determine the optimal methylene blue dosing strategies for enhancing exposure therapy. Finally, given the small sample size, it is unclear how effectively the control variables corrected the potential differences between groups and between participants with varying levels of end fear.

Clinical Implications

Our findings have several implications for clinical practice. First, because methylene blue appears to strengthen the memory for fear extinction learning (or lack thereof) that occurs during exposure therapy, administration of methylene blue at the beginning of a therapy session should be avoided, given the inability to predict whether a session will be successful. Second, our findings suggest

that postsession methylene blue administration should be done judiciously, after careful consideration of the patient's level of fear attenuation achieved insession. Based on our findings, patients who continue to show moderate to high levels of fear at the conclusion of an exposure therapy session may have their fear inadvertently strengthened by methylene blue administration, thus leading to a less favorable therapeutic outcome. Finally, these findings highlight the need for research on the development of empirically based decision rules for administering methylene blue and other cognitive enhancers in the context of exposure therapy.

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