ORIGINAL RESEARCH

Psychotherapy Treatment of Generalized Anxiety Disorder Improves When Conducted Under Narrow Band Green Light

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Background and Goals: Psychotherapy is one of the most highly recommended and practiced approaches for the treatment of Generalized anxiety disorder (GAD). Commonly defined as excessive worry that is uncontrollable, GAD is one of the most prevalent psychiatric disorders. Anxiety is also one of the most common associated symptoms of migraine. Exposing migraineurs to narrow band green light (nbGL) reduces their anxiety and anxiety-like physiological symptoms such as throat tightness, shortness of breath, and palpitations. Here, we sought to determine whether the reduced anxiety described by our patients was secondary to the reduced headache or independent of it. The goal of the current study was therefore to determine whether exposure to nbGL can reduce anxiety in GAD patients who are not migraineurs.

Patients and Methods: Included in this open-label, proof-of-concept, prospective study were 13 patients diagnosed with moderate-to-severe GAD. We used the State-Trait Anxiety Inventory Questionnaire (Y-1) to compare anxiety level before and after each 45-minutes psychotherapy session conducted in white light (WL) (intensity = 100 ± 5 candela/m^2) vs nbGL (wavelength = 520 ± 10nm (peak ± range), intensity = 10 ± 5 candela/m^2).

Results: Here, we show that psychotherapy sessions conducted under nbGL increase positive and decrease negative feelings significantly more than psychotherapy sessions conducted under regular room light ($\chi^2 = 0.0001$).

Conclusion: The findings provide initial evidence for the potential benefit of conducting psychotherapy sessions for patients suffering GAD under nbGL conditions. Given the absence of side effects or risks, we suggest that illuminating rooms used in psychotherapy with nbGL be considered an add-on to the treatment of GAD.

Keywords: photophobia, migraine, psychotherapy, GAD, retina, depression

Introduction

Migraine is a debilitating neurological disorder characterized by recurrent headaches often accompanied by throbbing, nausea, photophobia, phonophobia and various other abnormal sensory, autonomic, affective (eg, anxiety, depression) and cognitive functions.[1] Affecting about 15% of the US population[2,3] and worldwide, migraine is the 6th most common disease and the 2nd leading cause of years lived with disability.[4] The high prevalence of migraine (3-4-fold higher in women than in men)[5] and the $36 billion it costs the US annually explain its profound socioeconomic burden.[6–9]

Exacerbation of headache by light (photophobia) is experienced by 8/10 migraineurs with normal eyesight[10–12] and by visually impaired migraineurs.[13] Photophobia, although not as incapacitating as the headache, renders migraineurs dysfunctional as they are forced to quit their most fundamental daily tasks and seek the comfort of darkness. Because of the repetitiveness and frequency of the disease, migraineurs endure a significant hardship due to spending so much time in solitude during working hours or at times in which they must care for their family at home.[14] Historically, photophobia impact on migraine patients, although widely known, did not receive much attention. At one point, drugs could be approved for migraine pain without any demonstrated benefit on associated symptoms. Subsequently, the FDA decided

that migraine was a complex neurological disorder and that acute migraine treatments needed to improve more than the pain. That led the FDA to adapt the 4 coprimary solution whereby acute migraine treatments had to statistically separate from placebo on pain, nausea, photophobia and phonophobia.

Studying the neural mechanisms of photophobia, we found that blue and red light exacerbate migraine headache more than amber and white light, whereas a specific narrow band of green light (nbGL; wavelength = 520±10 nm) eases rather than worsens headache intensity.[15] Attempting to understand these unexpected psychophysical findings, we used electroretinography to record the electrical signals the eyes send to the brain in response to each color of light, and the signals they generate in the cortex (using visual evoked potential), and reported that in migraineurs, white and narrow bands of blue, amber, and red lights generate significantly larger electrical signals in the eye and cortex than nbGL.[15] In parallel pre-clinical studies, we also described a novel retino-thalamo-cortical pathway that allows brain areas that process vision to "talk" to brain areas that mediate the classical pain of migraine as well as some of its most commonly associated cognitive (eg, clarity of thinking, memory and attention), affective (eg, anxiety, irritability) and sensory (eg, photophobia, phonophobia, osmophobia) symptoms.[16] A few years later, an independent group described long-lasting antinociceptive effects of nbGL in different animal models of pain.[17,18]

While studying the effects of colors on migraine patients, we took note of patients who found blue, red, and amber lights extremely unpleasant even when their headache intensity did not increase. After studying these patients more carefully, we reported that exposure to blue, red, amber, and white lights during migraine can be aversive as these colors of light increase anxiety level and trigger anxiety-like symptoms such as chest and throat tightness, shortness of breath, fast breathing, palpitations, dizziness, nausea, and lightheadedness by activating hypothalamic neurons that regulate pre-ganglionic sympathetic and parasympathetic neurons in the thoracic spinal cord and brainstem superior salivatory nucleus, respectively.[19] Unexpectedly, we found that exposure to nbGL replaced patients' perception of anxiety with the perception of feeling calm, relaxed, and happy.[19]

As the number of migraine patients who choose to use the lamp that emits the nbGL (Allay Lamp) for alleviating their headache increases, the number of subjects reporting that nbGL also reduces their anxiety rises. Given that nbGL encompasses only a small fraction of the full human visible light spectrum (380–700 nm), it is considered less than minimal risk by IRBs. As such, we sought to determine if the use of this non-invasive, risk-free lamp to illuminate rooms in which people diagnosed with moderate-to-severe generalized anxiety disorder (GAD) undergo psychotherapy could improve within-session treatment outcome as determined by comparing anxiety levels before and immediately after sessions conducted in regular "white" room light vs nbGL. Our lead hypothesis was that nbGL ability to reduce anxiety is not unique to the anxiety that migraine patients feel during acute attack. Rather, that it is achieved through nbGL ability to foster calmness in GAD patients who are excessively worried and anxious about work, school, home, and social performances[20] – possibly through the unique ability of this light to reduce cortical excitability, responsivity and sensitivity,[14] and hypothalamic activation of the sympathetic nervous system.[19]

Design/Methods

The findings reported in this study were collected between April and December 2021 from moderate-to-severe GAD subjects undergoing in-person psychotherapy sessions at the Delray Center for Healing (a comprehensive mental health treatment clinic in Florida). Institutional Review Board (IRB) approval for the conduct of human subject research was obtained from the Ethics and Human Research Protection Program of Florida Health (Federal Wide Assurance # 00004682). The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. ClinicalTrial.gov identifier: NCT04871087

Study Design

The overall goal of this prospective, open-label, proof-of-concept study was to evaluate effects of conducting psychotherapy sessions under regular room light (ie, white) vs nbGL on subjects undergoing repeated psychotherapy treatment sessions for the management of their anxiety. Patients of the Delray Center were presented with the option to participate in this study by their therapists. Those who signed the informed consent were instructed to mark the answers that best reflected their feelings on each of the 20 items in the State-Trait Anxiety Inventory Questionnaire
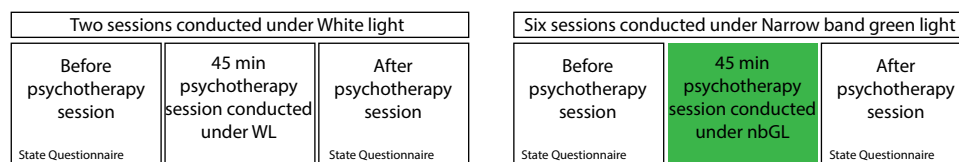
Figure 1 Experimental design.
Abbreviations: WL, White Light; nbGL, Narrow band green light.

(STAI Y-1) at the beginning and end of each 45-min therapy session with their regular psychotherapist. To complete the study, each participant had to attend a total of 8 sessions (Figure 1). Of these, 2 sessions were conducted in regular (intensity reflecting from the walls and floor and reaching the patient's eyes was measured at 100 ± 5 candela/m^2) white light (a standard mixture of the visible spectrum – wavelengths 380–750 nm), and 6 sessions were conducted in nbGL [wavelength: 520 ± 10 nm (peak±range), intensity reflecting from the walls and floor and reaching the patient's eyes was measured at 10 ± 5 candela/m^2, delivered by Allay Lamp, USA]. We chose this narrow band of green light as it allows 90% of the light to be distributed within a range that is least likely to activate the blue and red sensing retinal cones, and nearly maximally likely to activate the green sensing cones.

Intervention
Consistent with all our previous studies,[15,19,21,22] the device emitting the nbGL (Allay Lamp) was the only source of light in the rooms in which the 45-min psychotherapy sessions were conducted. To illuminate the entire room, the lamp was placed on a high shelf and set at an intensity that allowed the therapist and the patient to see effortlessly during the session (measured at 10 ± 5 candela/m^2).

Recruitment and Data Collection
Recruited to this study were men and women fulfilling diagnostic criteria for Generalized Anxiety Disorder (GAD) as defined in the DSM-5.[23] As part of the inclusion criteria, we required participants to be able to communicate in English and answer each of the 20 questions in the STAI Y-1 form, and be between the ages of 18–75. Since each patient provided answers before and after exposure to white light and nbGL, thus allowing us to conduct within-subject analysis, no exclusion criteria were implemented.

Data Analysis
In this within-subject (repeated measures) study design comparing the effects of conducting 2 psychotherapy sessions under white light (WL) and 6 sessions under nbGL, GAD patients provided self-evaluation using the State part of the State-Trait Anxiety Inventory questionnaire to choose one answer (out of 4 options) to 10 questions that reflect positive feelings and 10 questions that reflect negative feelings at the beginning and end of each psychotherapy session. The 4 options for each question were: (1) Not at all; (2) Somewhat; (3) Moderately so; (4) Very much so. The 10 positive-worded questions were: (1) I feel calm, (2) I feel secure, (3) I feel at ease, (4) I feel satisfied, (5) I feel comfortable, (6) I feel self-confident, (7) I am relaxed, (8) I feel content, (9) I feel steady, (10) I feel pleasant. The 10 negative-worded questions were: (1) I am tense, (2) I feel strained, (3) I feel upset, (4) I am presently worrying, (5) I feel frightened, (6) I feel nervous, (7) I am jittery, (8) I feel indecisive, (9) I am worried, (10) I feel confused.

To determine improvement per light condition, we averaged the scores that each question was given before the 2 sessions under white light, and after the 2 sessions under white light. A positive question that scored higher and a negative question that scored lower after the session (compared to before) were marked as improvement and received a score of 1. Next, we added the number of questions that improved in each patient based on responses to all positive and all negative questions (these numbers appear in each row in Table 1). This process was repeated for the 6 sessions in which psychotherapy was conducted under nbGL conditions. The results obtained from each of the 13 participants who completed the 2 WL and 6 nbGL sessions were computed and the sums of all improved positive and negative items were compared using Chi square.

Table 1 A Summary of All 13 Patients' Improved Responses to All 20 Questions Before and After the 2 Sessions in WL and 6 Sessions in the nbGL

	Positive Items Improved		Negative Items Improved	
	White Light	**Green Light**	**White Light**	**Green Light**
Patient 1	0	2	3	5
Patient 2	3	2	4	4
Patient 3	3	7	2	6
Patient 4	7	8	2	7
Patient 5	1	2	0	4
Patient 6	0	9	1	6
Patient 7	2	2	0	5
Patient 8	5	7	7	7
Patient 9	1	7	4	7
Patient 10	2	1	2	3
Patient 11	4	10	6	8
Patient 12	6	8	4	6
Patient 13	1	6	6	4
Total	**35**	**71**	**41**	**72**

To determine the predictive power of each item (and to make the process simpler and more user-friendly), we counted the number of times each question received a score of 1 (ie, reflecting improvement after the treatment session as compared to before) among all 13 participants and compared values obtained under white light vs nbGL. The questions in which the improvement was more than 50% under nbGL as compared to WL were considered the most predictive items and were, therefore, used in our final analysis.

The overall effectiveness of all psychotherapy sessions conducted under white and nbGL was analyzed using patients' responses to 3 positive-worded and 4 negative-worded items (as explained above). Values were tested for normality, presented as median and interquartile range, and compared using the non-parametric Wilcoxon signed-rank test.

Data and Materials Availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Database

Thirteen participants diagnosed with GAD provided data for this study at the beginning and end of 104 psychotherapy sessions. They were 18–62 y/o male (n = 7) and female (n = 6) subjects with >2 years history of disease. Each dataset consists of participants' answers of 20 questions. A total of 4160 answers (2080 answers collected before treatment session and 2080 collected after treatment session) were analyzed. Of the 4160 questions/answers, 2080 were related to positively worded symptoms and 2080 to negatively worded symptoms.

Analysis of participants' responses to all 20 (questions) items: In 6 (46%) patients, improvement in psychotherapy sessions conducted under nbGL was shown by their answers to both the positive and negative questions (Figure 2A). In 5 (38%) patients, improvement under nbGL was shown by their answers to the positive but not

negative questions, or vice-versa by their answers to the negative but not positive questions (Figure 2B and C). In 2 (15%) patients, responses to positive or negative questions reflected no improvement with the nbGL (Figure 2D). A summary of all 13 patients' improved responses to all 20 questions before and after the 2 sessions in WL and 6 sessions in the nbGL is shown in Table 1. Under nbGL, patients reported increased positive feeling plus decreased negative feeling significantly more frequently than under WL (positively worded: WL = 35 vs nbGL = 71 times, χ^2 = 0.000005, DF = 1; negatively worded: WL = 41 vs nbGL = 72 times, χ^2 = 0.0001, DF = 1).

Individual Questions Analysis

Analysis of the frequency of improved individual question (defined in Methods) under WL vs nbGL conditions identified 7 items (3 positively worded items = calm, secure, and steady; and 4 negatively worded items = tense, nervous, worried, and confused) where improvement under nbGL was >50% higher than under WL (Figure 3). All other 13 items showed no difference or <50% difference in frequency of improvement under nbGL.

Effectiveness of Psychotherapy Sessions Conducted Under nbGL vs WL

Analysis of the 3 most predictive positively worded items showed that psychotherapy sessions conducted under WL were less effective (before session: 2.5 [1.5–3.0] median [IQR] vs after session: 2.0 [1.5–2.5] p = 0.07 Wilcoxon) than sessions conducted under nbGL (before session: 2.1 [1.5–2.6] vs after session: 2.3 [1.6–2.8] p = 0.002 Wilcoxon) (Figure 4A and B). Analysis of the 4 most predictive negatively worded items showed that psychotherapy session conducted under WL was less
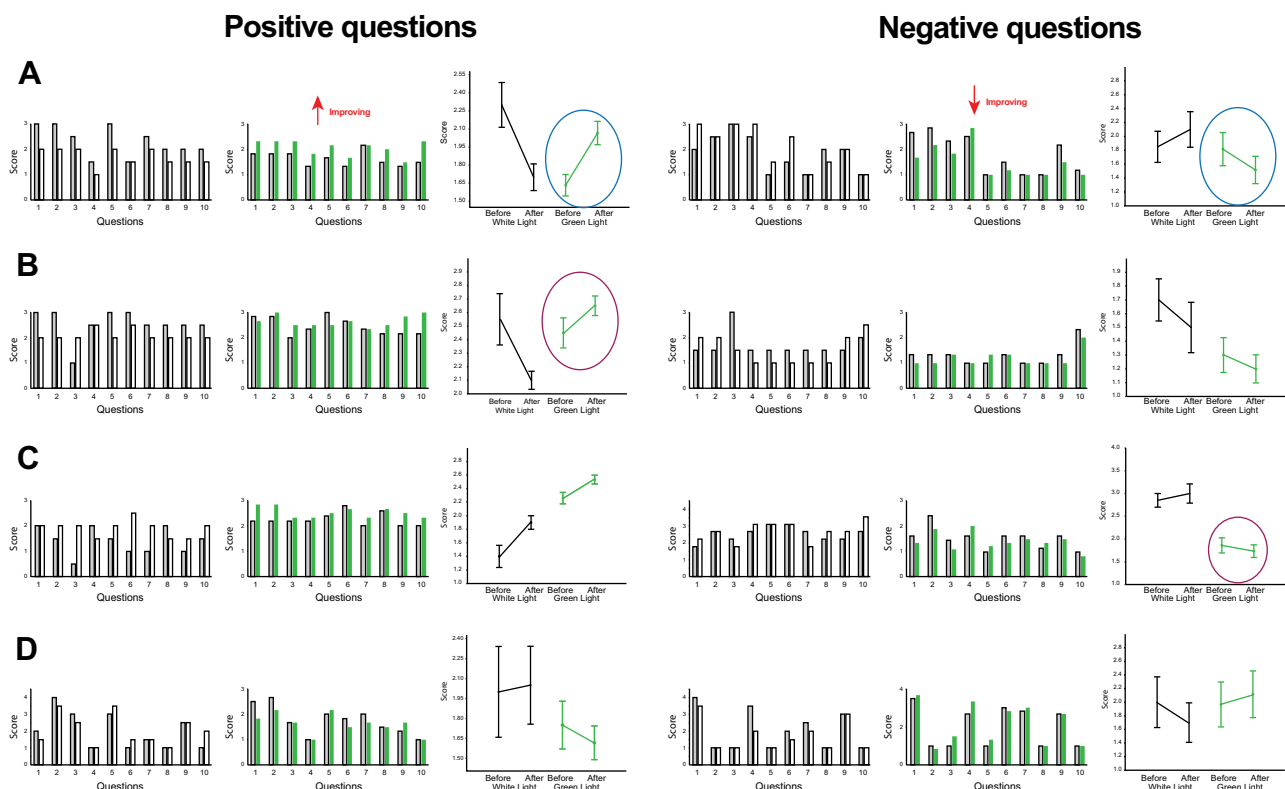

Figure 2 Analysis of participants' responses to all 20 items in the State-Trait Anxiety Inventory (STAI Form Y-1). Histograms illustrate the score each item received before (gray bar) and after psychotherapy sessions conducted under white light (white bars) and narrow band green light (green bars). Answers to positively worded questions are shown on the left, and answers to negatively worded questions are shown on the right. Positively worded questions included: 1. I feel calm, 2. I feel secure, 3. I feel at ease, 4. I feel satisfied, 5. I feel comfortable, 6. I feel self-confident, 7. I am relaxed, 8. I feel content, 9. I feel steady, 10. I feel pleasant. Negatively worded questions included: 1. I am tense, 2. I feel strained, 3. I feel upset, 4. I am presently worrying over possible misfortunes, 5. I feel frightened, 6. I feel nervous, 7. I am jittery, 8. I feel indecisive, 9. I am worried, 10. I feel confused. Each question was scored as follows: 1 - not at all, 2 - somewhat, 3 - moderately so, 4 = very much so. Line plots illustrate mean ± SD of scores each subject provided for all 10 positively worded and all 10 negatively worded items before and after the 2 sessions in white light and 6 sessions in nbGL. (**A**) Example of a patient in which improvement in psychotherapy sessions conducted under nbGL was shown by the answers to both positive and negative questions (circled). (**B**) Example of a patient in which improvement under nbGL was shown by the answers to the positive (circled) but not negative questions. (**C**) Example of a patient in which improvement under nbGL was shown by the answers to the negative (circled) but not positive questions. (**D**) Example of a patient in which responses to positive or negative questions reflected no improvement under nbGL.
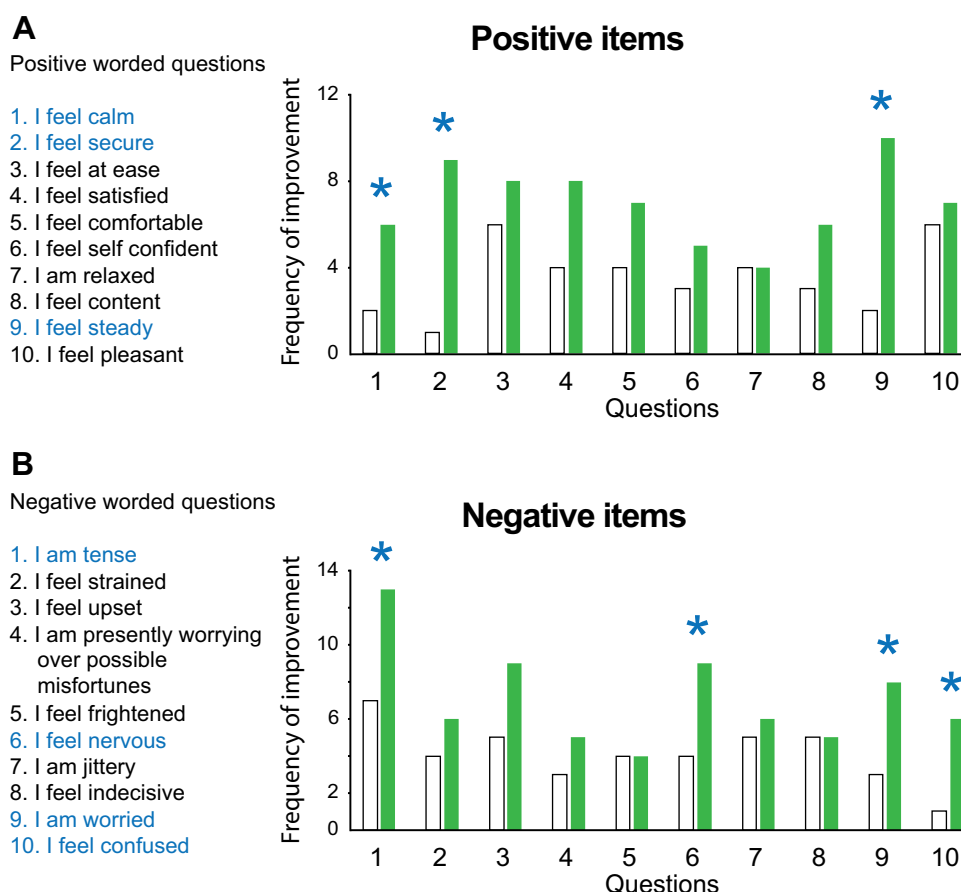
A

Positive worded questions

1. I feel calm
2. I feel secure
3. I feel at ease
4. I feel satisfied
5. I feel comfortable
6. I feel self confident
7. I am relaxed
8. I feel content
9. I feel steady
10. I feel pleasant

B

Negative worded questions

1. I am tense
2. I feel strained
3. I feel upset
4. I am presently worrying over possible misfortunes
5. I feel frightened
6. I feel nervous
7. I am jittery
8. I feel indecisive
9. I am worried
10. I feel confused

Figure 3 Item-by-item analysis: (**A**) Analysis of the frequency of positive items showing improvement under WL (white bars) as compared to nbGL (green bars) conditions. (**B**) Analysis of the frequency of negative items showing improvement under WL (white bars) as compared to nbGL (green bars) conditions. Asterisks depict items where improvement under nbGL was >50% higher than under WL.

effective (before session: 2.2 [1.5–3.5] median [IQR] vs after session: 2.5 [1.5–3.3] p = 0.83 Wilcoxon) than sessions conducted under nbGL (before session: 2.1 [1.5–3.0] vs after session: 1.9 [1.3–2.7] p = 0.0002 Wilcoxon) (Figure 4C and D).

Discussion

Psychotherapy is one of the most highly recommended and practiced approaches for the treatment of GAD.[24] It is most commonly practiced at regular (white) room light. In this open-label, proof-of-concept, prospective study, we show that psychotherapy sessions conducted under a specific narrow band of green light improves treatment outcome as judged by changes in level of anxiety after, as compared to before a 45-min treatment session by licensed therapists. Given the non-invasive nature of nbGL, its affordability, and the absence of adverse events, we suggest that illuminating rooms used in psychotherapy with nbGL be considered an affordable add-on to the treatment of GAD. The nature of this study, the small number of participants, and the findings justify carrying out a large-scale, double-blind, randomized controlled trial.

Generalized anxiety disorder, commonly defined as excessive worry that is uncontrollable, is one of the most prevalent psychiatric disorders.[25,26] It affects more women than men,[27] mostly those younger than 50 y/o, and it carries with it a high burden of illness.[28,29] Pathophysiologically, it is thought to be maintained by cognitive biases toward events/stimuli that are potentially threatening or worrisome and the development of overly cautious behavior aimed at avoiding autonomic arousal,[30,31] somatic anxiety symptoms such as palpitations, dizziness, nausea, and muscle tension, and psychological symptoms such as nervousness, insomnia, and constant worry.[32] To date, most experts advocate psychotherapy, pharmacotherapy, or both, for the treatment of anxiety and its somatic and psychological symptoms. While the proven efficacy of anxiolytic drugs such as the benzodiazepines define a gold standard for pharmacotherapy, risky side effects, development of dependence and the introduction of withdrawal
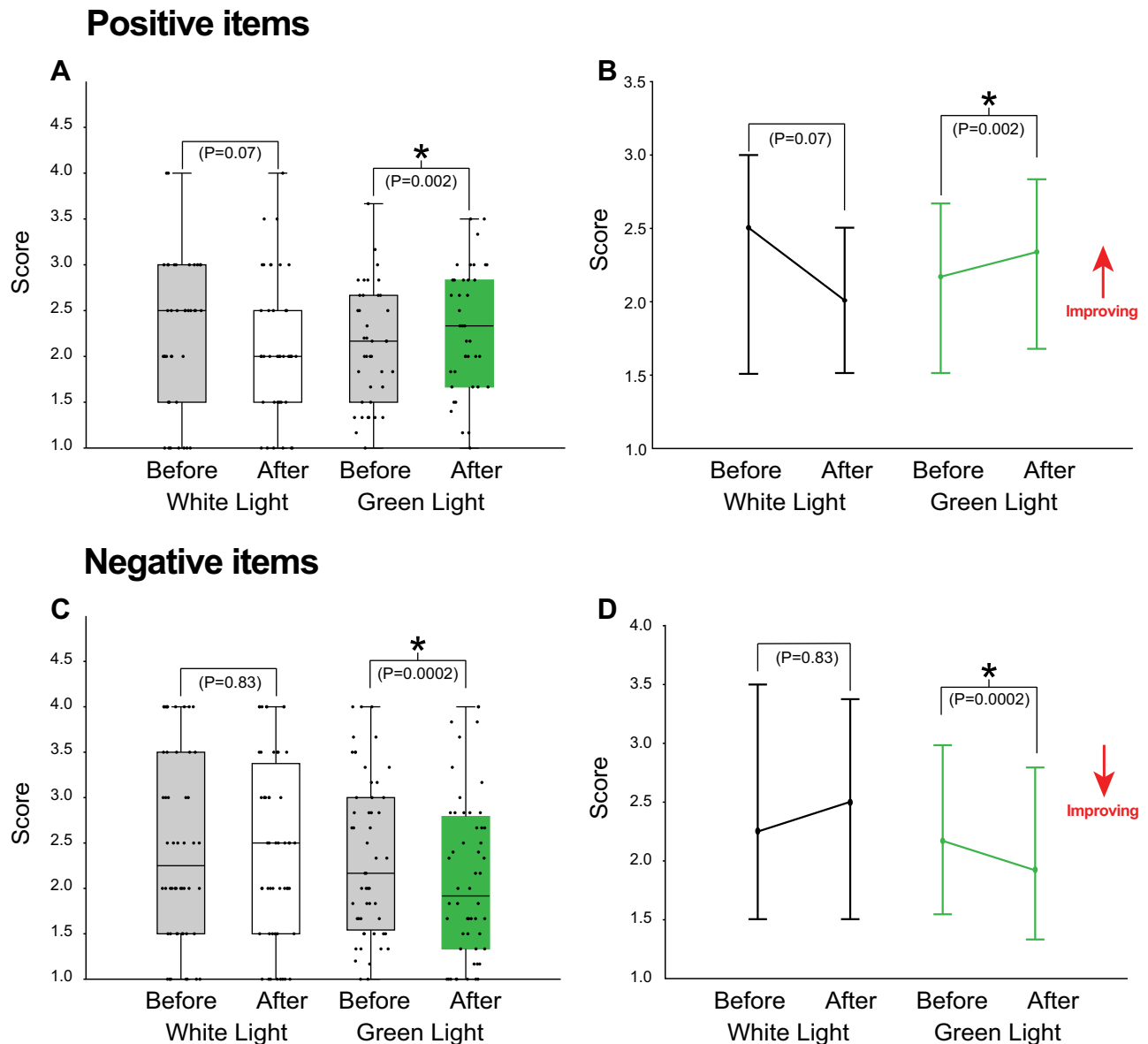
Most predictive items only

Positive items

Negative items

Figure 4 Effectiveness of psychotherapy under nbGL vs WL. (**A**) Analysis of the 3 most predictive positively worded items. In the scatograms, each of the 39 dots represents the average of the scores given by each of the 13 patients to each item before and after exposure to white (average of 2 sessions) and nbGL (average of 6 sessions) lights. The Boxplots show median and IQR. (**C**) Analysis of the 4 most predictive negatively worded items. In the scatograms, each of the 52 dots represents the average of the scores given by each of the 13 patients to each item before and after exposure to white (average of 2 sessions) and nbGL (average of 6 sessions) lights. The Boxplots show median and IQR. (**B** and **D**) Line plots of median and IQR show direction of improvement. Asterisks depict significant difference p<0.05 Wilcoxon signed rank test.

syndrome have led patients and health-care providers to seek alternative, less harmful treatment approaches. According to the European Study of the Epidemiology of Mental Disorders (ESEMeD), psychotherapy is one of the more commonly used alternative and/or complementary approaches to the treatment of GAD.[27,33,34] In spite of being highly recommended by the World Health Organization trials portal, the use of psychotherapy is challenged by methodological issues used to estimate magnitude of effect (as the use of placebo is difficult to establish), and by high rates of patient-initiated premature termination.[35–39] One of the many recognized causes of patient-initiated premature termination of psychotherapy[35] is loss of motivation,[40] possibly due to lack of immediate benefit (ie, potential to decrease anxiety level within a single psychotherapy session) to the patient. The current study

raises the possibility that motivation to continue with psychotherapy may be enhanced by conducting sessions under conditions of nbGL illumination as it increases patients' perception of within-session benefit of reduced level of anxiety (ie, immediate reward).

The discovery that low-intensity nbGL reduces anxiety is relatively new.[18,19,41] It originated in a series of studies that initially attempted to understand how light exacerbates migraine headache. These studies have led to the discovery of 3 novel neural pathways by which color/light can alter sensory, physiological, cognitive, and emotional states. The first, called the retino-thalamo-cortical pathway, allows nbGL to reduce the perception of pain and headache, abnormal sensitivity to light, and, surprisingly, transient impairment in cognitive functions such as clarity of thinking, memory and attention[13,15,16] - symptoms commonly described during migraine.[1] The second, called the retino-hypothalamic-sympathetic pathway, allows nbGL to reduce somatic anxiety symptoms such as chest and throat tightness, shortness of breath, fast breathing, and palpitations by activating hypothalamic neurons that regulate sympathetic outflow,[19] and the third, called the retino-hypothalamic-parasympathetic pathway, allows nbGL to reduce the perception of dizziness, nausea, and lightheadedness by activating different classes of hypothalamic neurons that regulate parasympathetic outflow.[19] While the exact mechanism by which nbGL reduces overall brain excitability is not fully understood, human electrophysiological studies show that compared to red and blue lights, nbGL generates significantly smaller electrical signals in the retina (measured by electroretinography recording) and cortex (measured by recording visual evoked potentials). Thus, it is reasonable to propose that the anxiolytic effects of nbGL may be achieved by its ability to (a) reduce neuronal excitability and responsivity in cortical (eg, prefrontal cortex) and subcortical (eg, amygdala) areas involved in the pathophysiology of GAD,[42–46] (b) alter autonomic responses to negative emotions such as stress, fear, and anxiety,[47] and (c) stimulate hypothalamic neurons that release chemicals such as oxytocin, dopamine, and GABA.[19,48]

Conclusions

The findings provide initial evidence for the potential benefit of conducting psychotherapy sessions with patients suffering GAD under dim nbGL conditions. The lamp that emits this specific band of green light (the Allay Lamp) is affordable, non-invasive, and risk-free. Future randomized controlled trials are needed to evaluate the use of this nbGL as an add-on tool to increase patients' perception that each psychotherapy session reduces their anxiety. If successful, such confirmation can reduce patient-initiated premature termination due to lack of immediate gratification – a common expectation since the ubiquitous embrace of the internet.

Caveats: (a) As with all small, prospective, open-label, proof-of-concept studies, the findings must be interpreted with caution as only an appropriately powered, multi-center, randomized controlled trial can provide the strength of evidence needed to recommend the use of this intervention. (b) Whereas the intensity of the regular (white) room light was 100 candela/m^2, the intensity of the nbGL was 10 ± 5 candela/m^2. This difference raises the possibility that the improved outcome seen during the session conducted under nbGL (as compared to regular room light) may be attributed to the intensity of the light rather than the color. Our previous studies[15,19] refute this possibility. By showing that white light is aversive to the extent that it exacerbates the headache at intensities as low as 1, 5, and 20 candela/m^2 (eg, see Figure 1A and B in reference 6), while nbGL alleviates the headache and its aversive aspects at low (1 and 5 candela/m^2), medium (20 candela/m^2) and high (50 candela/m^2) intensities, we concluded that the therapeutic effects of nbGL are achieved due to its ability to activate retinal cones that are most sensitive to wavelengths of the green light and least sensitive to retinal cones that detect wavelengths of the red and blue lights (ie, the color effect), rather than the intensity on the these lights. (7) Given that symptoms such as fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance are common in both migraine and GAD, and that excessive worry about when the next attack will commence can give rise to anxiety in those experiencing frequent migraine attacks, electrophysiological and neuroimaging studies that focus on nbGL effects on brain areas involved in anxiety and migraine, anxiety but not migraine and migraine but not anxiety are needed to determine whether the mechanism by which nbGL reduce anxiety differ when patients experience GAD but no headache or headache and anxiety.

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