

4-1-2018

## A Randomized Controlled Dosing Study of Iyengar Yoga and Coherent Breathing for the Treatment of Major Depressive Disorder: Impact on Suicidal Ideation and Safety Findings

Maren Nyer

Patricia Gerbarg  
*New York Medical College*

Marisa M. Silveri

Jennifer Johnston

Tammy M. Scott

*See next page for additional authors*

Follow this and additional works at: [https://touro scholar.touro.edu/nymc\\_fac\\_pubs](https://touro scholar.touro.edu/nymc_fac_pubs)



Part of the [Psychiatry and Psychology Commons](#)

---

### Recommended Citation

Nyer, M., Gerbarg, P., Silveri, M., Johnston, J., Scott, T., Nauphal, M., Owen, L., Nielsen, G., Mischoulon, D., Brown, R., Fava, M., & Streeter, C. (2018). A Randomized Controlled Dosing Study of Iyengar Yoga and Coherent Breathing for the Treatment of Major Depressive Disorder: Impact on Suicidal Ideation and Safety Findings. *Complementary Therapies in Medicine*, 37, 136-142. <https://doi.org/10.1016/j.ctim.2018.02.006>

This Article is brought to you for free and open access by the Faculty at Touro Scholar. It has been accepted for inclusion in NYMC Faculty Publications by an authorized administrator of Touro Scholar. For more information, please contact [touro.scholar@touro.edu](mailto:touro.scholar@touro.edu).

---

**Authors**

Maren Nyer, Patricia Gerbarg, Marisa M. Silveri, Jennifer Johnston, Tammy M. Scott, Maya Nauphal, Liz Owen, Greylin H. Nielsen, David Mischoulon, Richard P. Brown, Maurizio Fava, and Chris C. Streeter

# A Randomized Controlled Dosing Study of Iyengar Yoga and Coherent Breathing for the Treatment of Major Depressive Disorder: Impact on Suicidal Ideation and Safety Findings

Maren Nyer, PhD<sup>1,2</sup>, Patricia L. Gerbarg, MD<sup>3</sup>, Marisa M. Silveri, PhD<sup>1,4,5</sup>, Jennifer Johnston, PhD<sup>4</sup>, Tammy Scott<sup>4, 5,6, 7</sup>, Maya Nauphal, BA<sup>2</sup>, Liz Owen, BArch<sup>4</sup>, Greylin H. Nieslen<sup>4</sup>, David Mischoulon, MD, PhD<sup>1,2</sup>, Richard P. Brown, MD<sup>9</sup>, Maurizio Fava, MD<sup>1,2</sup>, Chris C. Streeeter, MD<sup>1, 4, 5, 10, 11</sup>

<sup>1</sup>Department of Psychiatry, Harvard School of Medicine, Boston, MA

<sup>2</sup>Department of Psychiatry, Massachusetts General Hospital, Boston, MA

<sup>3</sup>Department of Psychiatry, New York Medical College, Valhalla, NY

<sup>4</sup>Department of Psychiatry, Boston University School of Medicine, Boston, MA

<sup>5</sup>Department of Psychiatry, Boston Medical Center, Boston, MA

<sup>6</sup>Tufts University School of Medicine, Department of Psychiatry, Friedman School of Nutrition Science and Policy, Boston, MA

<sup>7</sup>Tufts Medical Center, Department of Psychiatry, Boston, MA

<sup>8</sup>Department of Psychiatry, McLean Hospital, Belmont, MA

<sup>9</sup>Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY

<sup>10</sup>Department of Neurology, Boston University School of Medicine, Boston, MA

<sup>11</sup>Department of Psychiatry, Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA

Journal: *Complementary Therapies in Medicine*. 2018 Apr;37:136-142. doi: 10.1016/j.ctim.2018.02.006.

Depression Clinical and Research Program Corresponding Author:

Maren Nyer, PhD

One Bowdoin Square, 76<sup>th</sup> Floor

Boston, MA 02114

Email: [mnyer@partners.org](mailto:mnyer@partners.org)

Phone: 617-643-4897

**Financial Support:** This work was supported by NCCIH K23 AT008043 02 (MBN); R21AT004014 and R01AT007483 (CCS); M01RR00533 and U11RR025771 (General Clinical Research Unit at Boston University Medical Center).

## ABSTRACT

**Background:** Yoga interventions offer promise for the treatment of major depressive disorder (MDD), yet their safety and potential impact on suicidal ideation (SI) have not been well documented. This study evaluated the safety of a randomized controlled dose-finding trial of Iyengar yoga plus coherent breathing for individuals with MDD, as well as the potential effects of the intervention on SI without intent.

**Methods:** Participants with Beck Depression Inventory-II (BDI-II) scores  $\geq 14$  and a diagnosis of MDD (using DSM-IV criteria) were randomized to either a low dose group (LDG) or high dose group (HDG) and received a 12-week manualized intervention. The LDG included two

90-minute yoga classes plus three 30-minute homework sessions weekly. The HDG offered three 90-minute classes plus four 30-minute homework sessions weekly.

**Results:** Thirty-two individuals with MDD were randomized, of which 30 completed the protocol. At screening, SI without intent was endorsed on the BDI-II by 9 participants; after completing the intervention, 8 out of 9 reported resolution of SI. There were 17 adverse events possibly-related and 15 definitely-related to the intervention. The most common protocol-related adverse event was musculoskeletal pain, which resolved over the course of the study.

**Conclusions:** The Iyengar yoga plus coherent breathing intervention was associated with the resolution of SI in 8 out of 9 participants, with mild side effects that were primarily musculoskeletal in nature. This preliminary evidence suggests that this intervention may reduce SI without intent and be safe for use in those with MDD.

## INTRODUCTION

Major depressive disorder (MDD) is a common, recurrent, often chronic and disabling disorder<sup>(1)</sup>. Depression is globally responsible for more years lost to disability than any other disease<sup>(2)</sup>. Up to 40% of individuals with MDD treated with antidepressant medication do not achieve full remission<sup>(3)</sup>. Moreover, residual symptoms of depression are associated with increased risk of recurrence and relapse<sup>(4)</sup>. Data from randomized controlled trials (RCTs) indicate that yoga holds promise as an effective intervention for the treatment of depression<sup>(5-8)</sup>. However, the safety of yoga, including effects on suicidal ideation (SI), have not been well studied in individuals with MDD.

A meta-analysis and review of 12 RCTs ( $N=619$ ) using yoga for the treatment of depression found that yoga was significantly better than usual care, relaxation exercises, and aerobic exercise. However, this same review noted that there were no published reports of safety data from RCTs. In a recent meta-analysis of 92 RCTs across a broad range of conditions, yoga was not associated with increased frequency of intervention-related non-serious or serious adverse events compared to exercise or usual care. However, when compared to non-physical interventions, such as psychological or educational interventions, yoga was associated with increased frequency of intervention related non-serious adverse events; serious adverse events were rare<sup>(5)</sup>. There is a need for specific safety data for yoga-based interventions in MDD.

There are no known studies evaluating the use of an Iyengar yoga and coherent breathing intervention (yoga intervention) for SI. This manuscript presents a follow-up analysis of an RCT of a 12-week yoga intervention for individuals with MDD. The primary study found that both the low dose group (LDG; 2x weekly + homework) and high dose group (HDG; 3x weekly + homework) were associated with decreased Beck Depression Inventory-II (BDI-II) scores consistent with response (50% reduction in BDI-II scores) and remission (BDI-II < 14)<sup>(9)</sup>. This manuscript has two aims: 1) to evaluate the effects of the intervention on SI without intent in participants with MDD, and 2) to assess the safety of the intervention. Musculoskeletal AEs were anticipated based on previous reports<sup>(10,11)</sup>.

## MATERIALS AND METHODS

We present SI data and safety findings from a parent study described in a previous report<sup>(9)</sup>, conducted October 2013 - September 2015 at the Boston University Medical Center (BUMC), and approved by their Institutional Review Board (IRB). Recruitment was conducted in the community with flyers, newspaper advertisements, and the internet. Baseline data were collected prior to randomization. A rolling admissions design was utilized; participants entered the 12-week intervention to which they were randomized using a permuted block design ( $n=4$ ). A blinded statistician (with no participant contact) placed group assignments in sealed envelopes, sequentially opened when a participant was randomized.

Intervention: Participants were randomized to either a LDG or a HDG. The LDG was assigned two 90-minute classes and three 30-minute homework sessions per week. The HDG was assigned three 90-minute classes and four 30-minute homework sessions per week. Homework consisted of 15-minutes of Iyengar yoga followed by 15-minutes of coherent breathing. Each 90-minute class included approximately 60-minutes of Iyengar yoga postures, 10-minutes of transition including deep relaxation, and 20-minutes of coherent breathing, paced by a chime tone recording on a compact disc. Iyengar yoga emphasizes correct alignment while performing postures. Coherent breathing entails breathing through the nose with equal duration of inhalation and exhalation at a rate of 5 breaths per minute. These practices have been shown to optimize heart rate variability (HRV) and sympatho-vagal balance<sup>(12-14)</sup>. Further details of this same intervention were previously reported<sup>(9)</sup>.

Instructor Training and Intervention Fidelity: All instructors completed an Iyengar Introductory Level II certification exam ( $\geq 2$  years of study), had  $>5$  years teaching experience, used the intervention manual, received training in coherent breathing, were assessed quarterly by the Principal Investigator (PI) using a protocol compliance fidelity instrument. There were 15 fidelity assessments on 5 instructors that documented fidelity to the assessment categories. Instructors were trained and allowed to modify the sessions to meet the needs of the participants, which included the use of props (e.g., blocks, blankets, and straps). The protocol encouraged instructors to modify the classic postures such that participants could be successful in their attempts while also minimizing injuries.

Instruments: The *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)* was used at screening to confirm the diagnosis of MDD and assess for other Axis I disorders<sup>(15)</sup>. The *Beck Depression Inventory-II (BDI-II)*, a 21-item, self-rated questionnaire, measured depressive symptoms<sup>(16)</sup>. Scoring criteria: minimal depression 0-13, mild depression 14-19, moderate depression 20-28, and severe depression 29-63. BDI-II question #9 assessed SI with the following response options: 0) I don't have any thoughts of killing myself; 1) I have thoughts of killing myself, but I would not carry them out; 2) I would like to kill myself; and 3) I would kill myself if I had the chance.

The *Columbia-Suicide Severity Rating Scale (C-SSRS)* is a clinician-administered assessment<sup>(17)</sup>. At screening, the C-SSRS form was used for two time frames: 1) "lifetime", and 2) "last year" (rather than the standard time frame of "past month"). At weeks 4, 8, and 12, a "since the last visit" time frame was used. The C-SSRS SI section uses the following items: 1) wish to be dead, "Have you wished you were dead or wished you could go to sleep and not wake up?"; 2) non-specific active suicidal thoughts, "Have you actually had any thoughts of killing yourself?"; 3) active suicidal ideation with any method (not plan) without intent to act, "Have you been thinking about how you might do this?"; 4) active suicidal ideation with some intent to act; without specific plan; and 5) active suicidal ideation with specific plan and intent. Affirmative answers to items 4 or 5 during screening were exclusionary.

The *Weekly Safety Form* contained the following questions: 1) “Are you feeling more depressed?”; 2) “Are you feeling suicidal?”; 3) “Mark your level of depression in the last week – response options: none, mild, moderate, severe”; 4) “Have you had any muscle soreness?”; and 5) “Have you had any other adverse events this week? (Adverse events are new or worsening medical problems.) If so, please list them.” Participants returned completed Weekly Safety Forms at the beginning of each calendar week of the intervention. As the 12-week intervention could occur over 13 calendar weeks, each participant could complete a maximum of 13 Weekly Safety Forms.

Clinical evaluations by a psychiatrist (PI) at baseline and a psychiatrist (PI) or clinical psychologist at weeks 4, 8, and 12 included a review of Weekly Safety Forms, BDI-II, and C-SSRS. Additional clinical assessments by a psychiatrist or clinical psychologist were triggered by any 4-point increase on BDI-II, worsening depression or suicidality on the Weekly Safety Forms, staff observations of participant distress, or participant reports of distress. The BDI-II was only given during assessment visits, when the participant also had a clinical and safety assessment. Adverse events (AEs) were defined as new or worsening medical problems that increased by one level of severity. Severity level of AEs was rated: 1) mild - does not have a major impact on the participant, 2) moderate - causes some minor inconveniences, and 3) severe - causes substantial disruption to the participant. Adverse event relationship to study was rated: 1) definitely-related, 2) possibly-related, and 3) not related. Pre-existing conditions that continued in the pre-existing pattern were not considered AEs. All subjects had depression at baseline, and depression was not reported as an AE unless a patient changed one level of AE severity rating from their pre-existing baseline condition. Severity of AE and relationship to study was determined by the study PI, a board-certified psychiatrist and neurologist.

Original Inclusion and Exclusion Criteria: Participants met the following criteria: 18 to 55 years of age, current SCID diagnosis of MDD, and at least mild depression based on BDI-II total score of 14-27 ( $\geq 28$  indicates severe depression). Co-morbid anxiety disorders that would not interfere with study participation were allowed. The following items were exclusionary: treatment with antidepressants; psychotherapy for depression within 3 months of screening; more than 6 one-hour sessions of mind-body practices in the last 6 months; current prayer practice ( $>2$  hours per week), as this could be similar to meditation; diagnosis of bipolar illness or psychosis; lifetime history of a suicide attempt or SI with or without intent within the last year (using C-SSRS criteria); current alcohol or substance abuse or dependence; and inability to complete the study protocol.

Adjusted Inclusion and Exclusion Criteria: After the enrollment of 16 of the 32 participants, the inclusion and exclusion criteria were liberalized because no serious AEs were observed, and individuals who could potentially safely benefit from the intervention were being excluded by restrictive eligibility criteria. The inclusion criteria were expanded to: 1) remove the BDI-II total score upper limit ( $<28$ ) to include individuals with more severe depressive symptoms; 2) increase the age limit from 55 to 65; and 3) include participants on stable doses of antidepressant medications for at least three months with no anticipated dosage change during the study. Exclusion criteria were expanded to allow SI without intent, while still excluding SI with intent within the past year. This particular exclusion criterion was liberalized consistent with the 2008-2012 US National Survey on Drug Use and Health, that found past-month suicide attempts were far less common in those adults reporting SI without a plan in the past 12-months compared to those who reported SI with a plan (3.7% to 37.0%, respectively)<sup>(18)</sup>.

Statistical Methods: Study data were collected using Research Electronic Data Capture (REDCap). Data were analyzed using SPSS version 24. *P* values for all statistical tests were two-tailed, using an alpha of .05 for statistical significance, unless otherwise noted. Pearson Chi-Square tests were used to compare LDG and HDG across categorical variables, such as SI vs. no SI, race, ethnicity, and gender. Independent-Samples *T*-Tests were conducted to compare continuous demographic variables (e.g., age). If Levene’s Test for the Equality of Variances was violated, the degrees of freedom and *p*-values were reported for equal variances not assumed and noted as such. Bivariate correlations were used to

explore the relationship between total numbers of adverse events and age. AEs were not compared between the LDG and HDG, because there were multiple AEs within participants, such that a discrete denominator for the appropriate statistical test (i.e., generalized linear model [binomial model] allowing multiple events within a single subject) could not be calculated.

## RESULTS

Telephone screening yielded 265 participants; 86 participated in a screening visit, 32 were randomized, and 30 completed the intervention (LDG:  $n=15$ ; HDG:  $n=15$ ). Subject flow chart was previously provided<sup>(9)</sup>. Only adverse events in participants who were randomized were reported. Two participants (1 per arm) were lost to follow-up prior to the week-4 evaluation; they did not complete a BDI-II or C-SSRS after screening and were not included in the analyses.

**Baseline Demographics and Yoga Dose:** There were no statistically significant differences in baseline demographics (See Table 1). As reported in the primary manuscript<sup>(9)</sup>, compliance with total assigned class and homework minutes did not differ between groups ( $p=0.77$ ): LDG  $84\% \pm 19\%$  and HDG  $87\% \pm 28\%$ . As expected, the HDG had significantly greater total (in class + homework time) yoga minutes ( $4,075 \pm 1,314$ ) compared to the LDG ( $2,737 \pm 625$ ;  $p < 0.001$ ).

**Table 1.** Participant demographics

Demographic	LDG ( $n=15$ )	HDG ( $n=15$ )	t-test or $\chi^2$	p-value
Age (years)	$34.7 \pm 10.4$	$38.4 \pm 15.1$	$t(24.84) = -0.79^*$	0.44
Gender (female/male)	12/3	13/2	$\chi^2(1) = 0.24$	0.62
Years of Education	$16.7 \pm 2.2$	$16.3 \pm 2.2$	$t(28) = 0.51$	0.62
Ethnicity			**n/a	**n/a
Hispanic	0/15	0/15		
Race			$\chi^2(2) = 3.40$	0.18
Caucasian	13/15	10/15		
African American	2/15	2/15		
Asian	0/15	3/15		

\*Violated Levene's Test for Equality of Variances, reported for unequal variances.

\*\* Could not complete statistical test due to zero participants per group.

LDG: Low Dose Group (two 90-minute yoga classes plus three 30-minute homework sessions weekly)

HDG: High Dose Group (three 90-minute classes plus four 30-minute homework sessions weekly)

This report focuses on AEs possibly- or definitely-related to the protocol. There were 17 individuals responsible for the 32 possibly- or definitely-related mild AEs (See Table 2). The most common study related AE, musculoskeletal pain, was anticipated and resolved during the study. Musculoskeletal pain was reported in 16 out of 30 (53%) of participants: 12 reports were possibly-related and 13 were definitely-related to the intervention. Table 2 provides a list of the participants who accounted for the related AEs. Other than musculoskeletal pain, AEs possibly-related to the intervention included

headaches, dizziness, and a nose bleed. One participant reported headaches when classes were held in a room with a carpet. One participant had a nose bleed that did not require medical intervention, which was likely an exacerbation of an existing condition due to inversions. Definitely-related AEs other than musculoskeletal pain, included a headache and increased negative/ruminative thoughts associated with use of the at home coherent breathing CD. The homework protocol was modified for this participant to include 30-minutes of postures without breathing exercises, which resolved the ruminative thoughts.

**Table 2:** Adverse events (AEs) possibly- and definitely-related to the study intervention

AE Number	Subject	Dose	Musculoskeletal Adverse Events	Localization	Other Adverse Event
<b>Possibly Related</b>					
1	1	Low	Musculoskeletal Pain	Calf	
2	1	Low	Musculoskeletal Pain	Left hip	
3	1	Low	Musculoskeletal Pain	Midback	
4	1	Low	Musculoskeletal Pain	Low back	
5	2	Low	Musculoskeletal Pain	Low back & left groin	
6	2	Low	Musculoskeletal Pain	Right shoulder	
7	2	Low	Musculoskeletal Pain	Right groin	
8	3	High	Musculoskeletal Pain	Neck	
9	3	High	Musculoskeletal Pain	General	
10	4	High	Musculoskeletal Pain	Left hip	
11	5	High	Musculoskeletal Pain	Low back	
12	6	High	Musculoskeletal Pain	Neck	
13	7	Low			Headache
14	7	Low			Headache
15	7	Low			Headache
16	1	Low			Dizziness
17	8	High			Nose bleed
<b>Definitely-Related</b>					
18	9	Low	Musculoskeletal Pain	Low back	
19	9	Low	Musculoskeletal Pain	Low back	
20	9	Low	Musculoskeletal Pain	Low back	
21	10	Low	Musculoskeletal Pain	General	
22	10	Low	Musculoskeletal Pain	General	
23	11	Low	Musculoskeletal Pain	Arm	
24	8	High	Musculoskeletal Pain	Low back	
25	12	High	Musculoskeletal Pain	General	



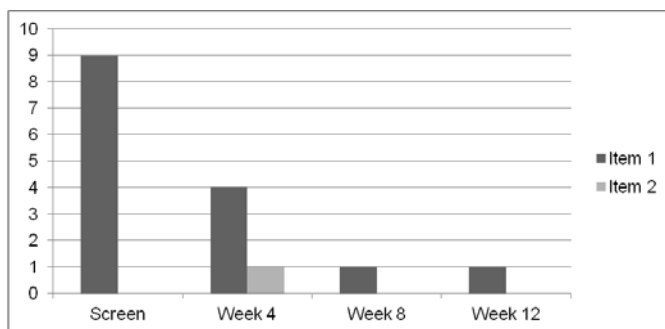
26	13	High	Musculoskeletal Pain	Ankle	
27	14	Low	Musculoskeletal Pain	General	
28	15	High	Musculoskeletal Pain	Arms and Hamstrings	
29	16	Low	Musculoskeletal Pain	Hamstrings	
30	17	High	Musculoskeletal Pain	Low back	
31	5	High			↑ Negative thoughts
32	5	High			Headache

Out of a possible maximum of 390 Weekly Safety Forms (30 participants completing up to 13 forms each), 366 (94%) were collected. The missing 6% occurred because some participants completed only 12 forms or did not turn in all scheduled forms. Twenty-three reports of worsening depression were identified by the Weekly Safety Forms (“Are you feeling more depressed?”). Thirteen individuals were responsible for the 23 reports of worsening depression. No subjects had an increase in the severity level of their depressive symptoms using AE criteria. Accordingly, none of the problem endorsements of worsening depression on the Weekly Safety forms were considered AEs based on the severity level of AEs (defined in the Method Section). No evaluations found increased risk of self-harm, or worsening functional impairment. No participants were withdrawn or referred for conventional treatment during the study.

**Reports of SI:**

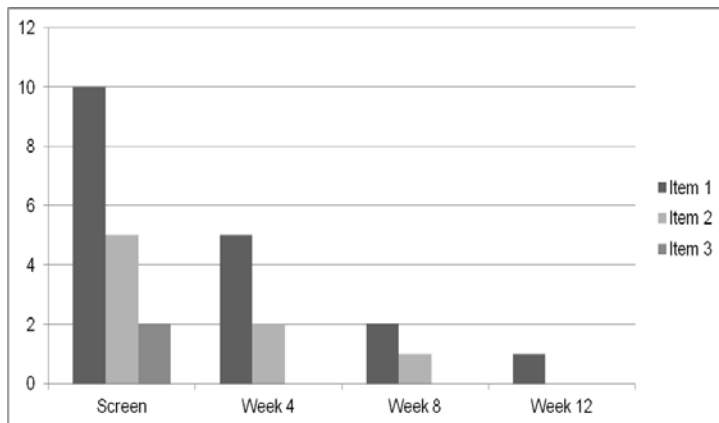
*BDI-II:* BDI-II question #9, item 1 (I have thoughts of killing myself, but I would not carry them out) was endorsed by 9 participants at screening (4 LDG, 5 HDG), 4 at week-4 (2 LDG, 2 HDG), 1 at week-8 (1 HDG), and 1 at week-12 (1 HDG). At week-4, 1 participant (1 HDG) endorsed item 2 (I would like to kill myself). This person was evaluated and found to have SI without intent (See Figure 1). Pearson Chi-Square revealed no differences at screen between the LDG and HDG on BDI-II item #9 zero versus non-zero responses ( $\chi^2(1)=.159, p=0.690$ ).

**Figure 1:** Comparative number of participants endorsing suicidal ideation on Question #9 items 1 and 2 of the Beck Depression Inventory-II



Legend: BDI-II question #9 assessed suicidal ideation severity:  
 Item 1) *I have thoughts of killing myself, but I would not carry them out;*  
 Item 2) *I would like to kill myself.*

**Figure 2:** Suicidal ideation severity on the Columbia-Suicide Severity Rating Scale (CSSR-S)

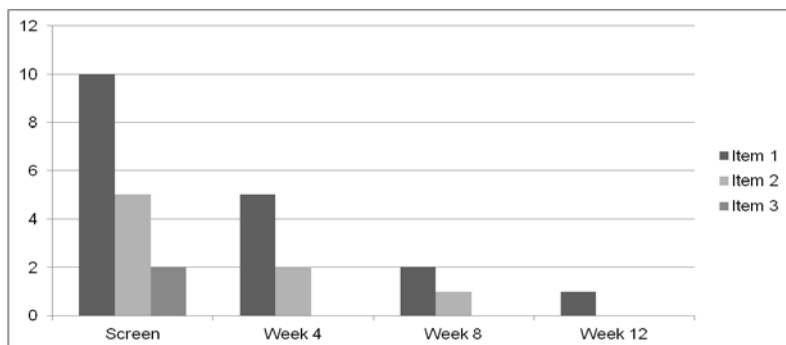


Legend: 1) wish to be dead; item 2) non-specific active suicidal thoughts; item 3) active suicidal ideation with any method (not plan) without intent to act.

Note: The total number of participants endorsing suicidality at each time point is equal to the total number for item 1. All participants who endorsed item 2 also endorsed item 1; all participants who endorsed item 3 also endorsed items 1 and 2.

C-SSRS: The C-SSRS item 1 (passive SI) was endorsed by 10 participants at screening (5 LDG, 5 HDG), 5 at week-4 (1 LDG, 4 HDG), 2 at week-8 (2 HDG), and 1 at week-12 (1 HDG). Item 2 (SI without intent) was endorsed by 5 participants at screening (3 LDG; 2 HDG), 2 at week-4 (2 HDG), 1 at week-8 (1 HDG), and 0 at week 12. Item 3 (SI with any method without intent to act) was endorsed by 2 participants at screening (2 HDG). Participants who endorsed items greater than 1 also endorsed lower item numbers as well, therefore the total number of participants reporting SI in any form equals the number of participants endorsing item 1 (See Figure 2). Pearson Chi-Square revealed no differences between the LDG and HDG at screen on C-SSRS passive SI responses (within the past year) when comparing zero versus non-zero responses ( $\chi^2(1)=.000, p=1.000$ ).

**Figure 2:** Suicidal ideation severity on the Columbia-Suicide Severity Rating Scale (CSSR-S)



Legend: 1) wish to be dead; item 2) non-specific active suicidal thoughts; item 3) active suicidal ideation with any method (not plan) without intent to act.

Note: The total number of participants endorsing suicidality at each time point is equal to the total number for item 1. All participants who endorsed item 3 also endorsed items 1 and 2.

One participant at screening and one at week-8 endorsed SI on the CSSR-S but not on the BDI-II. The CSSR-S at screen covered a longer time frame (“within the last year”) compared to the BDI-II (two-weeks). Also, the BDI-II only evaluated thoughts of killing oneself, whereas the CSSR-S has a more nuanced evaluation of passive SI (i.e., thought of falling asleep and not waking up).

## DISCUSSION

This study evaluated changes in SI without intent and overall safety of a LDG and HDG 12-week yoga intervention for adults with MDD. As reported previously, the intervention was associated with significantly decreased BDI-II total scores, demonstrating large effect sizes for both the LDG (Cohen’s  $d = -1.89$ ) and HDG (Cohen’s  $d = -2.81$ ) with a significant correlation in the expected direction between total number of yoga minutes and decreases on the BDI-II total score<sup>(9)</sup>. Overall, SI resolved in all but one participant and the intervention appeared to be tolerable, with musculoskeletal pain being the most common AE, which resolved and was mild in nature. There were no serious adverse events related to the protocol, nor did any subject need to be hospitalized or removed from the protocol due to worsening depressive symptoms or SI.

Suicidal Ideation: Intervention participation was associated with decreases in SI for 8 of the 9 participants who reported SI without intent at screening. Out of the 30 participants, only one reported a transient increase in rating of SI at week 4 (Figure 1). Decreased depressive symptoms and resolution of suicidality were seen in all but one participant (HDG) who continued to endorse SI on BDI-II and C-SSRS at week-12, while showing a decrease in BDI-II total score from 36 (severe depression) to 15 (mild depression).

While there is an assumed relationship between depressive symptoms and the presence of SI, there is a need for explicit evaluations of the effect of treatments on SI<sup>(19)</sup>. A systematic review and meta-analysis of RCTs in patients with MDD treated with serotonin selective reuptake inhibitors (SSRIs), with a secondary outcome measures of suicide, suicide attempts, and SI did not find a significant differences between participants randomized to placebo versus a SSRI for suicide (6 RCTs), suicide attempts (8 RCTs) or SI (11 RCTs)(20).

The lack of compelling evidence that RCTs of SSRIs decrease suicide ideation is in contrast to the findings of this study. These promising results need replication, given that this is the only study, to date, documenting reductions in SI associated with a yoga-based intervention in an MDD population.

Safety/Adverse Events: Safe and effective alternatives to antidepressant medications are sorely needed, given the significant AEs associated with antidepressant medications, such as: 1) the potential for the exacerbation of suicidality(21,22); 2) the induction of agitated and/or mixed manic and depressive states(23); 3) the burdensome common side effects (e.g., weight gain, sexual dysfunction, fatigue)(24); and 4) the potential for medication misuse in suicide attempts. The purpose of this paper was to understand what kind of AEs are common in a yoga-based intervention for depression and whether these AEs would involve a clinician’s immediate attention or would cause worsening psychiatric symptomatology. AEs in this study were mild with no serious intervention-related AEs; none of which were present in this study. Based on the Weekly Safety Forms and clinician evaluations of adverse events at weeks 4, 8, and 12 and the two-week follow-up phone call, all AEs were mild and all but one possibly-related back pain resolved by the two-week follow-up. The most common AE, musculoskeletal pain, was anticipated. There did not appear to be differences in musculoskeletal pain

between the LDG or HDG (though we were not able to conduct statistical tests on these data; please see Method Section), consistent with previous reports of dosage not being a determining factor in increased adverse events in yoga trials(11). No participants dropped out of the study due to musculoskeletal pain or any other AEs. Results indicated that yoga seemed tolerable to this population of individuals with MDD and did not worsen suicidality or depression, but was associated with decreased SI and depressive symptoms.

**Strengths:** Studies using yoga to treat depression have been limited by a lack of manualized yoga-based protocols(25), treatment fidelity monitoring(25), and insufficient reporting of safety findings<sup>(6)</sup>. This randomized dosing study used a manual-driven protocol that was first applied to healthy controls(10) and was then revised by the addition of the coherent breathing practice when tested in participants with MDD<sup>(9)</sup>. The yoga instructors attended study meetings to ensure consistency of delivery, used the manual to conduct each class, and received quarterly compliance feedback from the PI<sup>(9)</sup>. The teacher training and protocol policy of modifying yoga poses to a participant's physical abilities could contribute to the infrequent occurrence and mild nature of study AEs. SI was measured by two validated and commonly used scales, the BDI-II and C-SSRS. Participants were monitored for safety by a psychiatrist or clinical psychologist throughout the study. The procedures to maintain fidelity, execute safety protocols, and capture AEs in this study were clearly documented.

**Limitations:** The lack of a control group was a limitation, which should be addressed in future RCTs. The small sample size ( $N=30$ ) limits generalizability. Physical fitness was not evaluated prior to randomization such that the effect of physical fitness on AEs could not be evaluated. The findings cannot be generalized to individuals with more severe depression (BDI-II >40), SI with intent, or a history of suicide attempts within the past year. Finally, as with previously reported yoga studies(26,27), the majority of participants were white, educated females; future research would benefit from engaging more diverse populations.

## **CONCLUSIONS**

In adults with MDD, a 12-week Iyengar yoga plus coherent breathing intervention was associated with robust reductions in depressive symptoms and SI without intent on the BDI-II suicide item and C-SSRS in both the LDG and HDG. The intervention had a mild side effect profile, good tolerability, and a high level of adherence. The most common AE was musculoskeletal pain. This study provides preliminary data concerning the safety and efficacy of for yoga-based interventions as a potential treatment for individuals with MDD and SI without intent. However, larger RCTs with a longer duration are indicated to validate and extend these preliminary findings.

## **Acknowledgements**

We would like to acknowledge Patricia Walden for her assistance in the development of the protocol and assistance with the manuscript. We would like to acknowledge the contribution of J. Eric Jensen who passed away after the completion of this study.

This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

### **Conflict of Interest**

Drs. Brown and Gerbarg teach Breath-Body-Mind workshops that include coherent breathing. Dr. Streeter is certified to teach Breath-Body-Mind. Dr. Mischoulon has received research support from Nordic Naturals, Methylation Sciences, Inc. (MSI), and PharmorX Therapeutics. He has provided unpaid consulting for Pharmavite LLC and Gnosis USA, Inc. He has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy. He has received royalties from Lippincott Williams & Wilkins for published book "Natural Medications for Psychiatric Disorders: Considering the Alternatives."

All disclosures for Dr. Fava can be view on line at: [http://mghcme.org/faculty/faculty-detail/maurizio\\_fava](http://mghcme.org/faculty/faculty-detail/maurizio_fava)

Research Support: Abbott Laboratories; Acadia Pharmaceuticals; Alkermes, Inc.; American Cyanamid; Aspect Medical Systems; AstraZeneca; Avanir Pharmaceuticals; AXSOME Therapeutics; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon; Cerecor; Clintara, LLC; Covance; Covidien; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; FORUM Pharmaceuticals; Ganeden Biotech, Inc.; GlaxoSmithKline; Harvard Clinical Research Institute; Hoffman-LaRoche; Icon Clinical Research; i3 Innovus/Ingenix; Janssen R&D, LLC; Jed Foundation; Johnson & Johnson Pharmaceutical Research & Development; Lichtwer Pharma GmbH; Lorex Pharmaceuticals; Lundbeck Inc.; Marinus Pharmaceuticals; MedAvante; Methylation Sciences Inc; National Alliance for Research on Schizophrenia & Depression (NARSAD); National Center for Complementary and Alternative Medicine (NCCAM); National Coordinating Center for Integrated Medicine (NiiCM); National Institute of Drug Abuse (NIDA); National Institute of Mental Health (NIMH); Neuralstem, Inc.; NeuroRx; Novartis AG; Organon Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; Pharmacia-Upjohn; Pharmaceutical Research Associates., Inc.; Pharmavite® LLC; PharmorX Therapeutics; Photothera; Reckitt Benckiser; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Sanofi-Aventis US LLC; Shire; Solvay Pharmaceuticals, Inc.; Stanley Medical Research Institute (SMRI); Synthelabo; Taisho Pharmaceuticals; Takeda Pharmaceuticals; Tal Medical; VistaGen); Wyeth-Ayerst Laboratories

Advisory Board/ Consultant: Abbott Laboratories; Acadia; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Avanir Pharmaceuticals; AXSOME Therapeutics; Bayer AG; Best Practice Project Management, Inc.; Biogen; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon, Inc.; Cerecor; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DiagnoSearch Life Sciences (P) Ltd.; Dinippon Sumitomo Pharma Co. Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; ePharmaSolutions; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; Forum Pharmaceuticals; GenOmind, LLC; GlaxoSmithKline; Grunenthal GmbH; Indivior; i3 Innovus/Ingenix; Intracellular; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc.; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; Marinus Pharmaceuticals; MedAvante, Inc.; Merck & Co., Inc.; MSI Methylation Sciences, Inc.; Naurex, Inc.; Nestle Health Sciences; Neuralstem, Inc.; Neuronetics, Inc.; NextWave Pharmaceuticals; Novartis AG; Nutrition 21; Orexigen Therapeutics, Inc.; Organon Pharmaceuticals; Osmotica; Otsuka Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; PharmaStar; Pharmavite® LLC.; PharmorX Therapeutics; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc.; PPD; Puretech Ventures; PsychoGenics; Psylin Neurosciences, Inc.; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Rexahn Pharmaceuticals, Inc.; Ridge Diagnostics, Inc.; Roche; Sanofi-Aventis US LLC.; Sepracor Inc.; Servier Laboratories; Schering-Plough Corporation; Shenox Pharmaceuticals; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Synthelabo; Taisho Pharmaceuticals; Takeda Pharmaceutical

Company Limited; Tal Medical, Inc.; Tetragenex; Teva Pharmaceuticals; TransForm Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; Vanda Pharmaceuticals, Inc.; VistaGen

Speaking/Publishing: Adamed, Co; Advanced Meeting Partners; American Psychiatric Association; American Society of Clinical Psychopharmacology; AstraZeneca; Belvoir Media Group; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Cephalon, Inc.; CME Institute/Physicians Postgraduate Press, Inc.; Eli Lilly and Company; Forest Pharmaceuticals, Inc.; GlaxoSmithKline; Imedex, LLC; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier; Novartis AG; Organon Pharmaceuticals; Pfizer Inc.; PharmaStar; United BioSource, Corp.; Wyeth-Ayerst Laboratories.

Stock/Other Financial Options: Equity Holdings: Compellis; PsyBrain, Inc.

Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US\_7840419, US\_7647235, US\_7983936, US\_8145504, US\_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US\_9546401, US\_9540691).

Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Lippincott, Williams & Wilkins; Wolters Kluwer; World Scientific Publishing Co. Pte.Ltd.

## REFERENCES

1. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, et al. Sequenced treatment alternatives to relieve depression (STAR\*D): rationale and design. *Control Clin Trials*. 2004 Feb 1;25(1):119–42.
2. Smith K. Mental health: a world of depression. *Nature*. 2014 Nov 13;515(7526):181.
3. Thase ME, Nierenberg AA, Vrijland P, Oers HJ van, Schutte A, Simmons JH. Remission with mirtazapine and selective serotonin reuptake inhibitors: a meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression. *Int Clin Psychopharmacol*. 2010 Jul 1;25(4):189–98.
4. Judd LL, Schettler PJ, Rush AJ, Coryell WH, Fiedorowicz JG, Solomon DA. A New Empirical Definition of Major Depressive Episode Recovery and Its Positive Impact on Future Course of Illness. *J Clin Psychiatry*. 2016 Aug;77(8):1065–73.
5. Pilkington K, Kirkwood G, Rampes H, Richardson J. Yoga for depression: the research evidence. *J Affect Disord*. 2005 Dec;89(1–3):13–24.
6. Cramer H, Lauche R, Langhorst J, Dobos G. Yoga for Depression: A Systematic Review and Meta-Analysis. *Depress Anxiety*. 2013 Nov 1;30(11):1068–83.
7. Uebelacker LA, Broughton MK. Yoga for Depression and Anxiety: A Review of Published Research and Implications for Healthcare Providers. *R I Med J* 2013. 2016 Mar 1;99(3):20–2.
8. Cramer H, Anheyer D, Lauche R, Dobos G. A systematic review of yoga for major depressive disorder. *J Affect Disord*. 2017 Apr 15;213:70–7.
9. Streeter CC, Gerbarg PL, Whitfield TH, Owen L, Johnston J, Silveri MM, et al. Treatment of Major Depressive Disorder with Iyengar Yoga and Coherent Breathing: A Randomized Controlled Dosing Study. *J Altern Complement Med*. 2017 Feb 16;23(3):201–7.
10. Streeter CC, Whitfield TH, Owen L, Rein T, Karri SK, Yakhkind A, et al. Effects of yoga versus walking on mood, anxiety, and brain GABA levels: a randomized controlled MRS study. *J Altern Complement Med*. 2010;16(11):1145–1152.
11. Cramer H, Ward L, Saper R, Fishbein D, Dobos G, Lauche R. The Safety of Yoga: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Am J Epidemiol*. 2015 Aug 15;182(4):281–93.

12. Brown RP, Gerbarg PL, Muench F. Breathing practices for treatment of psychiatric and stress-related medical conditions. *Psychiatr Clin North Am.* 2013;36(1):121–140.
13. Gerbarg P, Brown R. Breathing techniques in psychiatric treatment. In: Gerbarg P, Brown R, Muskin P, editors. *Complementary and Integrative Treatments in Psychiatric Practice.* Washington, DC: American Psychiatric Association Publishing.; 2017.
14. Khattab K, Khattab AA, Ortak J, Richardt G, Bonnemeier H. Iyengar yoga increases cardiac parasympathetic nervous modulation among healthy yoga practitioners. *Evid-Based Complement Altern Med ECAM.* 2007 Dec;4(4):511–7.
15. First M, Gibbon M, Spitzer R, Williams J, Benjamin L. *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP).* New York State Psychiatric Institute. New York State Psychiatric Institute; 1997. New York, NY.
16. Beck A, Steer R, Brown G. *Beck Depression Inventory Manual.* 2nd ed. San Antonio, TX: Psychological Corporation; 1996.
17. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. *Am J Psychiatry.* 2011 Dec 1;168(12):1266–77.
18. Han B, Compton WM, Gfroerer J, McKeon R. Prevalence and correlates of past 12-month suicide attempt among adults with past-year suicidal ideation in the United States. *J Clin Psychiatry.* 2015 Mar;76(3):295–302.
19. Linehan MM. Suicide intervention research: a field in desperate need of development. *Suicide Life Threat Behav.* 2008 Oct;38(5):483–5.
20. Jakobsen JC, Katakam KK, Schou A, Hellmuth SG, Stallknecht SE, Leth-Møller K, et al. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry.* 2017 Dec 1;17(1):58.
21. Antonuccio D, Healy D. Relabeling the Medications We Call Antidepressants. *Scientifica [Internet].* 2012 [cited 2017 Nov 20];2012. Available from: /pmcc/articles/PMC3820604/?report=abstract
22. Brent DA. Antidepressants and Suicidality. *Psychiatr Clin North Am.* 2016 Sep;39(3):503–12.
23. Pompili M, Serafini G, Innamorati M, Ambrosi E, Giordano G, Girardi P, et al. Antidepressants and Suicide Risk: A Comprehensive Overview. *Pharmaceuticals.* 2010 Aug 30;3(9):2861–83.
24. Cassano P, Fava M. Tolerability issues during long-term treatment with antidepressants. *Ann Clin Psychiatry Off J Am Acad Clin Psychiatr.* 2004;16(1):15–25.
25. Uebelacker LA, Epstein-Lubow G, Gaudio BA, Tremont G, Battle CL, Miller IW. Hatha yoga for depression: critical review of the evidence for efficacy, plausible mechanisms of action, and directions for future research. *J Psychiatr Pract.* 2010 Jan;16(1):22–33.
26. Saper RB, Eisenberg DM, Davis RB, Culpepper L, Phillips RS. Prevalence and patterns of adult yoga use in the United States: results of a national survey. *Altern Ther Health Med.* 2004;10(2):44–9.
27. Birdee GS, Legedza AT, Saper RB, Bertisch SM, Eisenberg DM, Phillips RS. Characteristics of Yoga Users: Results of a National Survey. *J Gen Intern Med.* 2008 Oct 1;23(10):1653–8.