

RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

- | | |
|---|---|
| 1. Citation | Lam RW, Levitt AJ, Levitan RD, Michalak EE, Cheung AH, Morehouse R, Ramasubbu R, Yatham LN, Tam EM. Efficacy of Bright Light Treatment, Fluoxetine, and the Combination in Patients With Nonseasonal Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2016 Jan 1;73(1):56-63. |
| 2. Hypertext link to PDF of full article | http://www.ncbi.nlm.nih.gov/pubmed/26580307 |
| 3. First date published study available to readers | 01/01/2016 |
| 4. PubMed ID | 26580307 |
| 5. Nominated By | Other: Niladri Das |
| 6. Institutional Affiliation of Nominator | Other: |
| 7. Date Nominated | 12/16/2016 |
| 8. Identified Through | Other: TOC |
| 9. PURLS Editor Reviewing Nominated Potential PURL | Other: |
| 10. Nomination Decision Date | 01/07/2016 |
| 11. Potential PURL Review Form (PPRF) Type | |

12. Other
comments,
materials or
discussion

13. Assigned Potential
PURL Re-
viewer Gene Combs

14. Reviewer
Affiliation Other:

15. Date Re-
view Due 03/03/2016

16. Abstract

IMPORTANCE:

Bright light therapy is an evidence-based treatment for seasonal depression, but there is limited evidence for its efficacy in nonseasonal major depressive disorder (MDD).

OBJECTIVE:

To determine the efficacy of light treatment, in monotherapy and in combination with fluoxetine hydrochloride, compared with a sham-placebo condition in adults with nonseasonal MDD.

DESIGN, SETTING, AND PARTICIPANTS:

Randomized, double-blind, placebo- and sham-controlled, 8-week trial in adults (aged 19-60 years) with MDD of at least moderate severity in outpatient psychiatry clinics in academic medical centers. Data were collected from October 7, 2009, to March 11, 2014. Analysis was based on modified intent to treat (randomized patients with ≥ 1 follow-up rating).

INTERVENTIONS:

Patients were randomly assigned to (1) light monotherapy (active 10 000-lux fluorescent white light box for 30 min/d in the early morning plus placebo pill); (2) antidepressant monotherapy (inactive negative ion generator for 30 min/d plus fluoxetine hydrochloride, 20 mg/d); (3) combination light and antidepressant; or (4) placebo (inactive negative ion generator plus placebo pill).

MAIN OUTCOMES AND MEASURES:

Change score on the Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline to the 8-week end point. Secondary outcomes included response ($\geq 50\%$ reduction in MADRS score) and remission (MADRS score ≤ 10 at end point).

RESULTS:

A total of 122 patients were randomized (light monotherapy, 32; fluoxetine monotherapy, 31; combination therapy, 29; placebo, 30). The mean (SD) changes in MADRS score for the light, fluoxetine, combination, and placebo groups were 13.4 (7.5), 8.8 (9.9), 16.9 (9.2), and 6.5 (9.6), respectively. The combination (effect size $[d]=1.11$; 95% CI, 0.54 to 1.64) and light monotherapy ($d=0.80$; 95% CI, 0.28 to 1.31) were significantly superior to placebo in the MADRS change score, but fluoxetine monotherapy ($d=0.24$; 95% CI, -0.27 to 0.74) was not superior to placebo. For the respective placebo, fluoxetine, light, and combination groups at the end point, response was achieved by 10 (33.3%), 9 (29.0%), 16 (50.0%), and 22 (75.9%) and remission was achieved by 9 (30.0%), 6 (19.4%), 14 (43.8%), and 17 (58.6%). Combination therapy was superior to placebo in MADRS response ($\beta=1.70$; $df=1$; $P=.005$) and remission ($\beta=1.33$; $df=1$; $P=.02$), with numbers needed to treat of 2.4 (95% CI, 1.6 to 5.8) and 3.5 (95% CI, 2.0 to 29.9), respectively. All treatments were generally well tolerated, with few significant differences in treatment-emergent adverse events.

CONCLUSIONS AND RELEVANCE:

Bright light treatment, both as monotherapy and in combination with fluoxetine, was efficacious and well tolerated in the treatment of adults with nonseasonal MDD. The combination treatment had the most consistent effects.

17. Pending
PURL Review
Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study? light monotherapy = 32, fluoxetine mono therapy = 31, combinationn therapy = 29, placebo = 30

2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	<p>INCLUSION: 19 to 60 YO, DSM IV-TR Dx of Major Depressive Disorder as assessed by board-certified psychiatrists and confirmed with the MINI, 20 or higher on HAM-D at screening and at baseline, psychotropic medicine free for 2 weeks prior to baseline visit.</p> <p>EXCLUSION: seasonal pattern, bipolar and psychotic disorders, substance abuse or dependence within the past year, serious suicidal risk, unstable medical illness, pregnancy, breastfeeding, treatment resistance during the current episode, use of other concurrent treatment—including psychotherapy.</p>								
3. Intervention(s) being investigated?	Bright-light therapy, fluoxetine, light-fluoxetine combination. (all for their effect on non-seasonal Major Depressive Disorder.								
4. Comparison treatment(s), placebo, or nothing?	Sham (fake ion generator) plus placebo fluoxetine.								
5. Length of follow up? Note specified end points e.g. death, cure, etc.	8 weeks.								
6. What outcome measures are used? List all that assess effectiveness.	<p>Primary outcome = change in score on the MADRS from baseline to 8-week endpoint.</p> <p>Secondary outcomes = response ($\geq 50\%$ reduction in MADRS score) and remission (MADRS score ≤ 10 at end point)</p>								
7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.	<table border="0" style="width: 100%;"> <tr> <td>Combination - mean change (SD) in MADRS score</td> <td>16.9 (9.2)</td> </tr> <tr> <td>Fluoxetine - “ “ “ “ “ “ “</td> <td>8.8 (9.9)</td> </tr> <tr> <td>Bright light - “ “ “ “ “ “ “</td> <td>13.4 (7.5)</td> </tr> <tr> <td>Placebo - “ “ “ “ “ “ “</td> <td>6.5 (9.6)</td> </tr> </table> <p>The combination (effect size $[d]=1.11$; 95% CI, 0.54 to 1.64) and light monotherapy ($d=0.80$, 95% CI, 0.28 to 1.31) were significantly superior to placebo in the MADRS change score. Combination therapy was superior to placebo in response and remission, with numbers needed to treat of 2.4 (95% CI, 1.6 to 5.8) and 3.5 (95% CI, 2.0 to 29.9) respectively.</p>	Combination - mean change (SD) in MADRS score	16.9 (9.2)	Fluoxetine - “ “ “ “ “ “ “	8.8 (9.9)	Bright light - “ “ “ “ “ “ “	13.4 (7.5)	Placebo - “ “ “ “ “ “ “	6.5 (9.6)
Combination - mean change (SD) in MADRS score	16.9 (9.2)								
Fluoxetine - “ “ “ “ “ “ “	8.8 (9.9)								
Bright light - “ “ “ “ “ “ “	13.4 (7.5)								
Placebo - “ “ “ “ “ “ “	6.5 (9.6)								
8. What are the adverse effects of intervention compared with no intervention?	none								
9. Study addresses an appropriate and clearly focused question - select one	<p><input checked="" type="checkbox"/> <input type="checkbox"/> Well covered</p> <p>Adequately addressed</p> <p>Poorly addressed</p> <p>Not applicable</p>								
10. Random allocation to comparison groups	<p>Comments:</p> <p><input checked="" type="checkbox"/> Well covered</p> <p>Adequately addressed</p> <p>Poorly addressed</p> <p>Not applicable</p> <p>Comments:</p>								

- 11.** Concealed allocation to comparison groups
- X** Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments:
- 12.** Subjects and investigators kept “blind” to comparison group allocation
- X** Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments:
- 12.** Comparison groups are similar at the start of the trial
- X** Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments:
- 14.** Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.
- X** Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments:
- 15.** Were all relevant outcomes measured in a standardized, valid, and reliable way?
- X** Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments:
- 16.** Are patient oriented outcomes included? If yes, what are they?
- Not exactly. MADRS is not self-report, I don't think.
- 17.** What percent dropped out, and were lost to follow up? Could this bias the results? How?
- 13% dropout
 4% lost to followup
 It was already an underpowered study.
- 18.** Was there an intention-to-treat analysis? If not, could this bias the results? How?
- Yes.
- 19.** If a multi-site study, are results comparable for all sites?
- The authors say they are comparable.

- 20.** Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity? Lead author appears to be a big pharma KOL. However, it's hard to see how that would influence the current study.
- 21.** To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized. Adults with non-seasonal Major Depressive Disorder.
- 22.** In what care settings might the findings apply, or not apply? General outpatient practice
- 23.** To which clinicians or policy makers might the findings be relevant? Anyone treating people with non-seasonal Major Depressive Disorder

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
 Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009. {search date}

1. DynaMed excerpts

2. DynaMed citation/access date Title. Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: . Accessed

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

4. UpToDate excerpts

5. UpToDate citation/access date

Unipolar depression in adults and initial treatment: Investigational approaches. Gitlin M & Ciechanowski In: Basrow, DS, ed. UpToDate; 2016. [database online]. Available at: <http://www.uptodate.com>. Last updated: Jan 06, 2016. Accessed Feb 2, 2016.

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Bright light therapy is generally not used as initial treatment of unipolar major depression. Although there is evidence that light therapy is efficacious for treating nonseasonal depression, the studies are difficult to interpret due to methodologic problems, such as small sample sizes, inclusion of bipolar patients, inadequate blinding and control conditions, inconsistencies in the timing and dose of therapy.

7. PEPID PCP excerpts
www.pepidonline.com
username: fpinauthor
pw: pepidpcp

8. PEPID citation/access data

Author. Title. In: PEPID [database online]. Available at: <http://www.pepidonline.com>. Last updated: . Accessed

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic? **Perhaps**
Yes, there is important evidence or recommendations that are missing
No, this topic is current, accurate and up to date.
If yes, which PEPID Topic, Title(s): **Depression: Adults**

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (Ei) that should be updated on the basis of the review?
Yes, there is important evidence or recommendations that are missing
No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):

10. Other excerpts (USPSTF; other guidelines; etc.)

11. Citations for other excerpts

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
1 2 3 4 5 6 7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

The fact that fluoxetine showed no difference vs placebo is interesting.

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
1 2 3 4 5 6 7

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)
1 2 3 4 5 6 7

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

Bright light treatment, both as monotherapy and in combination with fluoxetine, is efficacious and well tolerated in the treatment of adults with moderate to severe nonseasonal Major Depressive Disorder.

7. Applicability to a Family Medical Care Setting:

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

Give one number on a scale of 1 to 7
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)

1 2 3 4 5 6 7

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation?

Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)

1 2 3 4 5 6 7

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

1 2 3 4 5 6 7

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

13. In your opinion, is this a Pending PURL?
Criteria for a Pending PURL:

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
1 2 3 4 5 6 7

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

14. Comments on your response in 4.13

It is a single study on a rather small cohort.