# TECHNICAL COMMENTARY

## Bright light therapy

NeuRA Discover. Conquer. Cure.
BIPOLAR DISORDERS LIBRARY

### Introduction

Light therapy, also called phototherapy, involves the use of a bright artificial light to improve depressive mood. It has long been used in psychiatric practice, usually for the treatment of seasonal affective disorder. The mechanism by which light therapy regulates mood is unclear. It has been suggested to have modulating effects on serotonin and melatonin and on the synchronisation of circadian rhythms, which is why it is often accompanied by sleep deprivation. This topic assesses the use of bright light therapy for depressive symptoms of bipolar disorder.

### Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results for people with a diagnosis of bipolar or related disorders. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

### Results

We found six systematic reviews that met our inclusion criteria[3-8].

- Moderate to high quality evidence finds a medium-sized improvement in depression symptoms with bright light therapy compared to placebo. There was no increased risk of shifting to a manic state with bright light therapy.
- Moderate quality evidence finds a small effect of increased response rate with bright light therapy compared to placebo. There were no differences in rates of remission.
- Moderate quality evidence finds greater improvements in depression symptoms in



Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

studies using <10 hours compared to >10 hours of bright light therapy, in studies using morning plus night exposure compared to morning exposure only, and in studies with adjunctive sleep deprivation and/or lithium. There were no differences in studies with or without other psychotropic medications, in studies using colour temperature < vs. >4500k, in studies using light intensity < vs. >5000lux, or in studies using white or green light therapy.



Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

*Dallaspezia S, Benedetti F*

## Antidepressant light therapy for bipolar patients: A meta-analyses

**Journal of Affective Disorders 2020; 274: 943-8**

View review abstract online

| | |
|---|---|
| **Comparison** | **Bright light therapy for people with bipolar depression vs. placebo.** |
| **Summary of evidence** | **Moderate to high quality evidence (small sample, consistent, precise, direct) finds a medium-sized improvement in depression symptoms after bright light therapy compared to placebo.** |

**Depression**

**Measured on the Hamilton Depression rating scale, Beck Depression Inventory, or Hamilton Depression Scale With Atypical Depression Supplement**

*A medium-sized improvement in depression symptoms after bright light therapy (vs. placebo);*

5 RCTs, N = 109, $g$ = -0.501, 95%CI - 0.777 to -0.225, $p < 0.001$, $I^2 = 34\%$

*A large improvement in depression symptoms after bright light therapy (pre-post);*

11 studies, N = 196, $g$ = -1.46, 95%CI -1.68 to -1.24, $p < 0.001$, $I^2 = 73\%$

Meta-regression showed more days in treatment resulted in greater improvement in depression symptoms in the pre-post analysis but not the analysis comparing bright light therapy with placebo.

Increased bright light intensity resulted in greater improvement in depression symptoms in the comparison with placebo but not in the pre-post analysis.

| | |
|---|---|
| **Risks** | Authors report that the treatment was mostly well-tolerated. |
| **Consistency**‡ | Inconsistent for the pre-post analysis, consistent for the placebo analysis. |
| **Precision**§ | Precise |
| **Directness**‖ | Direct |

*Hirakawa H, Terao T, Muronaga M, Ishii N*

## Adjunctive bright light therapy for treating bipolar depression: A systematic review and meta-analysis of randomized controlled trials

**Brain and Behavior 2020; 10: e01876**

| | |
|---|---|
| View review abstract online | |
| **Comparison** | **Bright light therapy for people with bipolar depression vs. placebo.** |
| **Summary of evidence** | **Moderate quality evidence (small sample, consistent, imprecise, direct) finds a small effect showed increased response rate with bright light therapy compared to placebo. There were no differences in rates of remission.** |
| **Depression**<br>**Measured on the Hamilton Depression rating scale, Hamilton Depression Scale With Atypical Depression Supplement, Montgomery–Åsberg Depression Rating Scale, or the 16-item Quick Inventory of Depressive Symptomatology Self-report** | |
| *A small effect showed increased response rate with bright light therapy compared to placebo;*<br>4 RCTs, N = 190, RR = 1.78, 95%CI 1.24 to 2.56, $p$ = 0.002, $I^2$ = 17%<br>*There were no differences in rates of remission;*<br>RR = 2.03, 95%CI 0.48 to 8.59, $p$ = 0.34, $I^2$ = 67%<br>None of the articles reported any serious adverse effects. Manic switch rate was 1.1% in the light therapy group and 1.2% in the control group. | |
| **Risks** | Authors report no differences in rates of mania switching and no serious adverse effects. |
| **Consistency** | Consistent for response, inconsistent for remission. |
| **Precision** | Imprecise |
| **Directness** | Direct |

*Lam RW, Teng MY, Jung YE, Evans VC, Gottlieb JF, Chakrabarty T, Michalak EE, Murphy JK, Yatham LN, Sit DK*

## Light Therapy for Patients With Bipolar Depression: Systematic Review and Meta-Analysis of Randomized Controlled Trials

**Canadian Journal of Psychiatry 2020; 65: 290-300**

View review abstract online

| | |
|---|---|
| **Comparison** | **Bright light therapy for people with bipolar depression vs. placebo.** |
| **Summary of evidence** | **Moderate quality evidence (medium-sized sample, unable to assess consistency, some imprecision, direct) suggests a** |

| | |
|---|---|
| | **medium-sized effect of improved depression following light therapy, with no increased risk of polarity shifting.** |
| **Depression**<br>**Measured on the Hamilton Depression rating scale** | |
| *A medium-sized effect showed light therapy was associated with a significant improvement in Hamilton Depression Rating Scale score;*<br>7 RCTs, N = 259, SMD = 0.43, 95%CI 0.04 to 0.82, *p* = 0.03<br>*There was also a significant difference in favor of light therapy for clinical response;*<br>OR = 2.32, 95%CI 1.12 to 4.81, *p* = 0.024<br>There were no differences in remission rates.<br>Authors report that study limitations included different light treatment parameters, small sample sizes, short treatment durations, and variable quality across trials. | |
| **Risks** | Authors report no differences in rates of polarity shifting in patients receiving light therapy and those receiving control conditions. |
| **Consistency** | Unable to assess ($I^2$ not reported). |
| **Precision** | Precise for SMD, imprecise for OR. |
| **Directness** | Direct |

*Takeshima M, Utsumi T, Aoki Y, Wang Z, Suzuki M, Okajima I, Watanabe N, Watanabe K, Takaesu Y*

## Efficacy and safety of bright light therapy for manic and depressive symptoms in patients with bipolar disorder: A systematic review and meta-analysis

**Psychiatry and Clinical Neurosciences 2020; Jan: doi/10.1111/pcn.12976**

View review abstract online

| | |
|---|---|
| **Comparison** | **Bright light therapy for people with bipolar disorder vs. various control conditions (dim light therapy, low-density negative air ionization, or standard care).** |
| **Summary of evidence** | **Moderate to low quality evidence (medium-sized sample, inconsistent, imprecise, indirect) suggests no differences between groups.** |
| **Depression** | |

| Hamilton Depression rating scale, Structured Interview Guide for the Hamilton Depression Rating Scale with atypical depression supplement or with seasonal affective disorder supplement, Montgomery–Åsberg Depression Rating Scale, Quick Inventory of Depressive Symptomatology Self-Report | |
|---|---|
| *There were no significant differences between groups for the following outcomes;*<br>Depressive symptoms: 4 RCTs, N = 165, SMD = -0.25, 95%CI -0.74 to 0.23, $p$ = 0.30, $I^2$ = 56%<br>Remission rates: 5 RCTs, N = 199, RR = 1.81, 95%CI 0.43 to 7.64, $p$ = 0.42, $I^2$ = 92%<br>Subgroup analyses of higher quality studies, and studies with a shorter duration (≤ 2 weeks) found a significant increase in remission rates with bright light therapy. There were no moderating effects of intervention type (different light intensities or colours). | |
| **Risks** | Authors report no differences in rates of polarity shifting. |
| **Consistency** | Inconsistent |
| **Precision** | Imprecise |
| **Directness** | Indirect (mixed control conditions). |

*Tseng PT, Chen YW, Tu KY, Chung W, Wang HY, Wu CK, Lin PY*

## Light therapy in the treatment of patients with bipolar depression: A meta-analytic study

**European Neuropsychopharmacology 2016; 26: 1037-47**

View review abstract online

| | |
|---|---|
| **Comparison 1** | **Pre-post assessment of bright light therapy for depression, with or without additional sleep deprivation or medication.**<br>**Light therapy consisted of 7 to 56 days of 150 to 10,000 light intensity using primarily white or green light.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of improved depression following light therapy, with no increased risk of polarity shifting. This effect was not influenced by medication status, sleep deprivation techniques, intensity or colour of light therapy, patient age, sex, or age at illness onset.** |
| **Depression**<br>**Measured on the Beck Depression Inventory or the Hamilton Depression rating scale** | |

| | |
|---|---|
| *A significant, medium-sized effect of improved depression following light therapy;*<br>11 studies, N = 567, *g* = -0.69, 95%CI -0.90 to -0.48, *p* < 0.001, $I^2$ = 70%, *p* < 0.001<br>Meta-regressions and subgroup analyses showed no differences in the results according to; medication status; if sleep deprivation was included or not; different intensity of light therapy; different colour of light therapy; patient age, sex, or age at illness onset.<br>Authors report evidence of publication bias. | |
| **Comparison 2** | **Light therapy in addition to sleep deprivation and/or medication compared to placebo, medication, and/or sleep deprivation.**<br>**Light therapy consisted of 7 to 28 days of 150 to 7,000 light intensity using primarily white or green light.** |
| **Summary of evidence** | **Moderate to low quality evidence (medium-sized sample, inconsistent, precise, indirect) suggests a medium-sized effect of improved depression following light therapy plus sleep deprivation and/or medication compared to controls, with no increased risk of polarity shifting.** |
| **Depression**<br>**Measured on the Beck Depression Inventory** | |
| *A significant, medium-sized effect of improved depression in the adjunctive light therapy group;*<br>4 studies, N = 225, *g* = 0.51, 95%CI 0.18 to 0.84, *p* = 0.002, $I^2$ not reported | |
| **Risks** | Authors report no differences in rates of polarity shifting in patients receiving light therapy and those receiving other treatments. |
| **Consistency** | Inconsistent for pre-post assessment, unable to assess for controlled analysis. |
| **Precision** | Precise |
| **Directness** | Direct for pre-post assessment, indirect for controlled assessments (mixed control conditions). |

*Wang S, Zhang Z, Yao L, Ding N, Jiang L, Wu Y*

**Bright light therapy in the treatment of patients with bipolar disorder: A systematic review and meta-analysis**

**PLoS ONE 2020; 15: e0232798**

View review abstract online

| | |
|---|---|
| **Comparison** | **Bright light therapy for bipolar depression vs. placebo, sleep deprivation, and/or medication.** |
| **Summary of evidence** | **Moderate quality evidence (large samples, consistent, some imprecision, indirect) finds a medium to large effect of improved depression following bright light therapy. The effect was greater in studies using <10 hours compared to >10 hours of bright light therapy. The effect was greater in studies using morning plus night exposure compared to morning exposure only. The effect was greater in studies using adjunctive sleep deprivation and/or lithium compared to no adjunctive treatments. There were no effects of other adjunctive psychotropic medications, colour temperature (< vs. >4500k), light intensity (< vs. >5000lux), or white or green light therapy.** |
| **Depression**<br>**Measured on the Hamilton Depression rating scale, the Inventory of Depressive Symptomatology Clinician Rating, or the Structured Interview Guide for the HDRS** | |
| *Medium to large effects of improved depression following bright light therapy;*<br>5 RCTs, N = 237, SMD = -0.43, 95%CI -0.73 to -0.13, $p$ = 0.005, $I^2$ = 20%<br>7 cohort studies, N = 1,200, SMD = -2.12, 95%CI -2.3 to -1.94, $p$ < 0.00001, $I^2$ = 26%<br>The pooled effect size in studies without adjunctive psychotropic medications were similar to the pooled effect sizes reported above (SMD -0.60 in RCT and -1.99 in cohort studies).<br>There was a smaller pooled effect size in studies using >10 hours of bright light therapy (SMD -0.41) compared to studies using <10 hours of bright light therapy (SMD -1.88).<br>There was a smaller pooled effect size in studies using morning exposure (SMD -0.41) compared to studies using morning plus night exposure (SMD -2.10).<br>There was a smaller pooled effect size in studies with no auxiliary measures (SMD -0.42) compared to studies with auxiliary measures (SMD -2.16). Auxiliary measures included sleep deprivation and/or lithium.<br>The pooled effect size in studies using colour temperature greater than 4500k (SMD -2.06) were similar to the pooled effect size in studies using colour temperature less than 4500k (SMD -1.74).<br>The effect sizes in studies using white light therapy (SMD -0.56 in RCT to -2.17 in cohort studies) were similar to the effect sizes in studies using green light therapy (SMD -0.70 in RCT to -1.92 in cohort studies).<br>The effect sizes in studies using light intensity greater than 5000lux (SMD -0.38 in RCT to -2.17 in cohort studies) were similar to the effect sizes in studies using light intensity less than 5000lux (SMD -1.92 in cohort studies). | |
| **Risks** | Not reported |
| **Consistency** | Consistent for main analyses |
| **Precision** | Precise in RCT analysis only |



Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

| | |
|---|---|
| **Directness** | Indirect; mixed control conditions |

## Explanation of acronyms

CI = confidence interval, *g* = Hedges g, standardised mean difference, $I^2$ = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, SMD = standardised mean difference, vs. = versus

## Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[9].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardsed mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[9].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[10]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often



Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. $I^2$ is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. $I^2$ can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[9];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[11].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

## References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Tseng PT, Chen YW, Tu KY, Chung W, Wang HY, Wu CK*, et al.* (2016): Light therapy in the treatment of patients with bipolar depression: A meta-analytic study. *European Neuropsychopharmacology* 26: 1037-47.
4. Lam RW, Teng MY, Jung YE, Evans VC, Gottlieb JF, Chakrabarty T*, et al.* (2019): Light Therapy for Patients With Bipolar Depression: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Canadian Journal of Psychiatry* 65: 290-300.
5. Takeshima M, Utsumi T, Aoki Y, Wang Z, Suzuki M, Okajima I*, et al.* (2020): Efficacy and safety of bright light therapy for manic and depressive symptoms in patients with bipolar disorder: A systematic review and meta-analysis. *Psychiatry and clinical neurosciences* Jan: doi/10.1111/pcn.12976.
6. Dallaspezia S, Benedetti F (2020): Antidepressant light therapy for bipolar patients: A meta-analyses. *Journal of Affective Disorders* 274: 943-8.
7. Hirakawa H, Terao T, Muronaga M, Ishii N (2020): Adjunctive bright light therapy for treating bipolar depression: A systematic review and meta-analysis of randomized controlled trials. *Brain and Behavior* 10: e01876.
8. Wang S, Zhang Z, Yao L, Ding N, Jiang L, Wu Y (2020): Bright light therapy in the treatment of patients with bipolar disorder: A systematic review and meta-analysis. *PLoS ONE* 15: e0232798.
9. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
10. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
11. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*